RESEARCH REPORT

TRADE-OFFS BETWEEN BENEFITS AND HARMS OF DRUGS: A STATED PREFERENCE STUDY WITH ADULT PATIENTS WITH CANCER IN EUROPE

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
Agency / EMA	European Medicines Agency
AIC	Akaike information criteria
BIC	Bayesian information criteria
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CDRH	Center for Devices and Radiological Health
DCE	Discrete choice experiment
FDA	Food and Drug Administration
HTA	Health technology assessment
IRB	Institutional review board
LC	Latent class
MCDA	Multiple criterion decision analysis
MNL	Multinomial logit
MM	Multiple myeloma
NSCLC	Non-small cell lung cancer
OMEP	Orthogonal main effect plan
PAG	Patient advocacy group
PP	Patient preference
PFS	Progression free survival
PRO	Patient-reported outcome
QALY	Quality-adjusted life year
QoL	Quality of life
RPL	Random parameter logit
SAP	Statistical analysis plan
SW	Swing weighting
TTO	Time-trade off

3 EXECUTIVE SUMMARY

Cancer is the second most significant cause of non-communicable disease deaths globally, with approximately 9 million deaths annually. Europe bears a quarter of the global cancer burden, accounting for around 1.9 million deaths from cancer in 2018. Female breast, colorectal, lung, and prostate cancers are the most prevalent types in Europe, accounting for half of the overall cancer cases. Many novel drug therapies for cancer have improved survival outcomes, but their high toxicity may come at a cost of severe side effects and short- and long-term impacts on patients' quality of life. Decision-making around the benefits and harms of novel drug therapies should consider the patient's voice, which is not currently integrated into regulatory approval processes. Although studies of patient preferences demonstrate that most cancer patients favour increased survival outcomes from treatments, decision-making can become more complex in cases where the survival benefit is modest and high levels of toxicity are faced. Patient preference (PP) research, which asks patients to make choices between alternative outcomes/treatments and reflect on the potential consequences of these choices, can be useful in decision-making, particularly during the medical product life cycle.

This study had two phases aimed at gathering patient preferences. The first phase was qualitative and involved a targeted literature review and qualitative interviews with cancer patients to generate evidence. The second phase was quantitative and involved an online survey that included demographic and clinical background questions, as well as three preference elicitation exercises. The preference elicitation exercises consisted of a discrete-choice experiment (DCE) followed by either a time-trade off (TTO) or a swing-weighting (SW) exercise.

Based on the literature review, it was found that efficacy and progression-free survival (PFS) are important treatment attributes for cancer patients when making treatment decisions. However, patient preferences related to side effects and toxicity, as well as other treatment attributes, were also commonly assessed and found to be significant factors in patients' preferences.

In addition, preference heterogeneity was found to be a common theme in studies examining patient preferences for cancer treatments across different cancer types. Socio-demographic and health characteristics were found to be important factors that influenced preferences in these studies. Therefore, it was recommended to collect relevant socio-demographic and health characteristics of patients when eliciting patient preferences for cancer treatments, to assess factors that are likely to contribute to preference heterogeneity.

The targeted literature review was also used to develop interview guides for the qualitative interviews, which included the development of vignettes for cognitive debriefing.

Based on the recommendations from the qualitative evidence generation phase, the vignettes used in the quantitative phase were updated to clarify that information on progression free survival was a key attribute of the treatment and not information provided by a physician. Additionally, most treatment attributes, patient and treatment characteristics, and other factors that may

influence preference heterogeneity were already mentioned spontaneously by participants during the qualitative interviews. Therefore, the attributes identified during the targeted literature review and by The Agency were deemed sufficient for the quantitative phase.

The quantitative phase of the study had a final sample of 603 respondents who met inclusion criteria and completed the survey. The mean age of patients was 54 years old. 54% of patients had stage I early-stage cancer and 46% had stage II, III, IV, stage III multiple myeloma, or chronic lymphocytic leukaemia. About 42% of respondents were currently receiving cancer treatment and 61% had received cancer treatment in the past.

The study's analysis revealed that patients prioritize the impact of side effects on quality of life, followed by changes in time until disease progression, treatment administration, and location of treatment. However, only changes between severe and moderate side effects and between severe side effects and mild and moderate side effects were statistically significant.

The study also examined differences in preferences among subgroups based on cancer stage, education, comprehension of the DCE exercise, cancer relapse, and current living situation. Only subgroups based on cancer stage, education, and comprehension of the DCE exercise showed statistically significant differences in preferences. Patients with Stage I cancer did not have a significant preference for changes in time until disease progression, treatment administration, and location of treatment. However, those with Stage II, III, IV, stage III multiple myeloma, or chronic lymphocytic leukaemia had significant preferences for changes in the time until disease progression. Patients with lower educational qualifications did not have statistically significant preferences for any changes in time until disease progression, treatment administration, and location of treatment.

The small sample size of some subgroups may have influenced the ability to detect significant differences between attribute levels. Exploratory analysis using a latent class (LC) approach revealed three classes of respondents with systematic differences in preferences across the three countries. Class 1 valued changes in the time until disease progression from 12 months to 3 months followed by the impact of side effects on quality of life. Class 2 was risk averse and focused on the impact of side effects on quality of life followed by changes in the time until disease progression from 12 months to 3 months. Finally, Class 3 was more risk averse and more concerned about the impact of side effects on quality of life, followed by changes in the time until disease progression from 12 months to 3 months, and then treatment administration and location of treatment.

According to the TTO results, scenario 1, which involved a trade-off between 12 months without progression but with moderate side effects and approximately 8 months without progression but with mild treatment side effects, had lower utility scores compared to scenario 2. Scenario 2 involved a trade-off between 12 months without progression but with severe side effects and approximately 10 months without progression but with moderate treatment side effects. These results were somewhat consistent with the DCE results.

The regression analysis revealed that, for scenario 1, having Stage 1 cancer and comprehending the DCE choice questions had a statistically significant impact on the mean utility for TTO. However, for scenario 2, only having Stage 1 cancer had a statistically significant impact on the mean utility.

The SW utility score gave higher values for certain attributes, including time until progression of disease and treatment administration. When using time until progression of disease as a reference, the study found that the stage of cancer and comprehension of the DCE choice task had a statistically significant effect on the utility for the impact of side effects on quality of life.

All three methods showed a statistically significant impact of both the stage of cancer and the comprehension of the DCE choice task on the utility.

Overall, the DCE and TTO results were comparable, while SW results were not. It is important to note that while these methods are used to measure patient preferences in healthcare, their results should not be viewed as interchangeable.

The study's findings suggest that cancer treatment preferences are influenced by factors such as disease-stage and individual perspectives. The research also highlights that there can be variation between patient preferences and conventional endpoints used in clinical trials. The study provides valuable insights into what cancer patients consider important when choosing a treatment. However, it's important to note that different preference methods used in the study may have limitations, and their results should be interpreted carefully. Nevertheless, any additional insights obtained from each preference method could potentially inform regulatory decision-making processes.

4 INTRODUCTION

Cancers are the second highest cause of noncommunicable disease deaths globally, estimated to kill 9 million people each year.[1] Europe has approximately a quarter share of the global cancer burden, with an estimated 1.9 million deaths from cancer in Europe in 2018.[2] The most common cancers in Europe are female breast, colorectal, lung and prostate cancers. These 4 cancers represent half of the overall cases of cancer in Europe, but around 21 other major cancers and other rarer types of cancer contribute to the epidemiology of cancer across Europe as well.[2]

The introduction of novel drug therapies for cancer has improved survival outcomes for cancers dramatically. However, due to the high toxicity of many novel drug therapies, improved survival outcomes may come at a cost of severe side effects and/or short- and long-term impacts on patient's quality of life (QoL). Short and long term toxicities are well-documented in cancers such as breast cancer, liver cancer, multiple myeloma, advanced non-small cell lung cancer (NSCLC) and chronic lymphocytic leukaemia (CLL).[3–5] Some short and long term toxicities could be life threatening such as cardiac toxicities, respiratory failure and increased risk of secondary primary malignancies, while others not life threatening can have a substantial impact on QoL; such as fatigue, nausea, neuropathy, osteoporosis and infertility. There is also not enough integration of the patient's voice and their preferences around the benefits and harms of new novel drug therapies when receiving drug approval. Therefore, the benefits and harms of new novel drug therapies and the patient's voice needs to be further considered. Benefits and harms of novel drug therapies are currently considered in a clinical context during regulatory approval, but information about how patients with cancer assess benefits and harms of treatments while of notable interest to regulators, are also not currently routinely considered.

While some novel drug therapies lead to complete remission, other recently approved drugs may only increase survival by several months.[6,7] Studies of PP in cancer demonstrate that the majority of patients with cancer favour increased survival outcomes from treatments, however in cases where survival benefit is considered modest, and high levels of toxicity are faced, decision making may become more complex.[8] Studies looking at preferences of healthcare professionals and regulators have also demonstrated that while there is a trade-off between overall survival and toxicity, the majority of stakeholders also attach the most weight to overall survival.[9–11] A recent systematic review of the literature on QoL verses length of life (LoL) preferences of patients with cancer between 1942 and 2018, concluded that age, future expectations and better or poorer health were all key determinants of whether patients would prioritise QoL over LoL. Generally, those who were older or in poorer health were more likely to prioritise QoL.[12]

Patient preference (PP) refers to an individual's evaluation of priorities for dimensions of health outcomes and treatment attributes, which may in part influence health care choices.[13] Rooted in economic theory and cognition, patients are asked to make choices between alternative outcomes/treatments and reflect on potential consequences of these choices. A common use for stated PP work, and often considered by Health Technology Assessment (HTA) bodies and for

pricing negotiation once a drug has been approved by regulatory bodies, has been the elicitation of utilities for the eventual purpose of modelling cost per Quality-Adjusted Life Year (QALY). Common to the distinct QALY evaluation methods are that they examine the effect of an intervention and the decision-making rule to optimize effect per cost. In cost-effectiveness analysis, the effect is a one-dimensional measure such as blood pressure, whereas in cost-utility analysis (CUA) it is a multidimensional measure in which the quality of the life year gained (i.e., QALY) is taken into consideration. An important feature of these health outcomes is that they only allow for health-related preference-based outcome measures, meaning that only health-related measures of benefits are considered.[14]

At present, stated preference studies are not systematically carried out within the context of drug development. In 2016, the Food and Drug Administration (FDA) Centre for Devices and Radiological Health (CDRH) developed a patient-focused guidance document, with a focus on the inclusion of PP research into decision making. The FDA guidance defines PP as “a statement of the relative desirability or acceptability to patients of specified alternatives or choice among outcomes or other attributes that differ among alternative health interventions”.[15] The guidance makes the distinction between Patient-Reported Outcome (PRO) research and PP research, as “PRO instruments are designed to measure a patient’s perceptions of health status before, during, and after therapy, while PP studies are designed to measure what specified type of therapy or attributes of a given therapeutic or diagnostic strategy a patient might prefer”.[15]

Recently, the Innovative Medicines Initiative Patient preference (IMI-PREFER) project has developed recommendations for how and when it is best to perform and include patient preferences in decision making during the medical product life cycle. [16] This project supports the development of guidelines for structured patient input into decision making for the pharmaceutical industry, regulatory authorities, HTA bodies and reimbursement agencies and has received a positive qualification opinion from the Europeans Medicines Agency (EMA) committee responsible for human medicines.

Patient preference research has traditionally been the domain of health/behavioural economists, epidemiologists, and market researchers, with the intended use for HTA drug or medical device approvals, and clinical practice guideline development. A recent draft guidance from the FDA[17] supports the notion that patient experience data can be interpreted as information that captures patients’ experiences, perspectives, needs, and priorities related to but not limited to (1) symptoms of their condition and its natural history; (2) impact of the conditions on their functioning and quality of life; (3) their experience with treatments; (4) input on which outcomes are important to them; (5) their preferences for outcomes and treatments; and (6) the relative importance of any issue as defined by patients. Numbers one and 2 are traditionally captured through PROs; number 4 and 5 through PP research, and number 3 through both. This guidance has explicitly opened the door for the inclusion of PP research in the context of drug development. More explicitly, PP research can provide additional insight on the benefits patients seek and how this information can be used to inform decision making across the drug development lifecycle.

Previous studies conducted by the EMA elicited individual PP on 3 generic attributes: overall survival, long term moderate toxicity and severe toxicity using multi-criteria decision analysis (SW).[18] This was later followed by a larger online survey based on SW and swing-weighting methods to elicit stated preferences for similar attributes in patients with multiple myeloma.[10] However, how patient, treatment and disease characteristics are associated with preferences of patients with cancer remains largely unknown as cultural, demographic, clinical and psychological characteristics may influence preferences in certain subsets of patients with cancer. It is therefore important to explore the heterogeneity of preferences for different novel cancer treatments. Different subsets of patients with cancer may have different treatment choices, which could inform policy and clinical practice.

5 STUDY OVERVIEW

This study was a patient preference study consisting of 2 phases to meet the study objectives. The study included a qualitative evidence generation phase which then informed a quantitative evidence generation phase. Qualitative evidence generation consisted of a targeted literature review and qualitative interviews with cancer patients. Quantitative evidence generation phase included an online survey which had a combination of demographic and clinical background questions as well as 3 preference elicitation exercises (a discrete choice experience [DCE] followed by either a time-trade off [TTO] or a swing-weighting [SW] exercise). Both qualitative and quantitative evidence generation methodologies are further detailed in Sections 6.1and 6.2 respectively.

5.1 Study Goals and Objectives

The objectives of this study were to describe stated preferences regarding benefits and harms of novel cancer treatments of patients with cancer in Europe and to understand the heterogeneity in treatment preferences. To achieve this, there were 3 main key objectives outlined in the study:

5.1.1 Primary Objectives

1. To identify and describe PP relating to benefits and harms of cancer drugs in patients with both common and rare cancer types
2. To identify and describe the PP towards key endpoints used traditionally to assess the efficacy and safety of oncology drugs in patients with both common and rare cancer types

5.1.2 Secondary Objectives

1. To determine the extent to which patients' heterogeneous characteristics are associated with stated preferences

5.1.3 Exploratory Objectives

1. To compare preference weights and patient characteristics with stated preferences using different stated preference methods (DCE/TTO/SW), within the context of the use of these methodologies for regulatory use.

5.2 Study Procedures

Full study procedures are outlined in the study protocol that was delivered to the Agency on

8 December 2022. Key procedures around data management, ethical and regulatory requirements and protection of participants are summarised in the sections below.

5.2.1 Data Management, Arching and Storage

IQVIA were responsible for the data management of this study, including quality checking of the quantitative data and management of audio-recordings for qualitative interviews and subsequent transcriptions and translations. IQVIA will comply with procedures regarding archiving and record management.

5.2.2 Ethical and regulatory obligations

This study was reviewed and approved for exemption by the WCG Institutional review board (IRB) based in USA. In Europe there were no central or local IRB requirements for this type of study in participating countries (Spain, Italy, and Croatia).

In accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki, all patients had to provide informed consent, or agreement to a data protection notice before participating in the study.

In the qualitative phase, all patients were asked to provide verbal consent to participate in the interview. In the quantitative online survey phase, patients provided their consent prior to being enrolled in the survey. Patients were provided study information in advance and provided adequate time to consider study information and ask questions before proving consent to any phase of this study.

5.2.3 Protection of participants

To maintain patient confidentiality, patients in the qualitative interviews and the quantitative survey were assigned a unique identifier upon study enrolment. This identifier was used for the purpose of data analysis and reporting. All parties ensured the protection of personal data and did not include names on any study forms, reports, publications, or in any other disclosures. Patients were informed about data handling procedures and asked for their consent. Data protection and privacy regulations were observed in capturing, forwarding, processing, and storing patient data. Patient information was kept in a separate and encrypted database only accessible to the research team for the purposes of scheduling patient interviews and analysis.

6 METHODS

6.1 Qualitative evidence generation

6.1.1 Literature review

A targeted literature review was conducted to identify different treatment attributes of current marketed treatments in oncology. A range of rare and more common cancers in adult patients were selected for inclusion to allow for a more manageable targeted literature review, including late-stage NSCLC, breast cancer, liver cancer, Multiple Myeloma (MM), and CLL. The targeted literature review aimed to identify the attributes related to oncology treatments in each identified cancer and the language used by patients and oncologists when treating patients. The literature review also aimed to identify key characteristics of the patient population, such as age, disease severity, family background, health awareness and literacy, and prior disease history, as potential covariates to examine preference heterogeneity.

The attributes from the literature review were then compared to key endpoints typically used for consideration in the approval of novel cancer therapies by regulatory authorities. A final list of attributes and attributes-levels were identified to develop a survey assessing cancer treatment preferences and the potential trade-offs made when considering the approval of oncology drugs. The attributes from the literature review were used to develop a conceptual model summarising the attributes and levels identified in the literature as well as the key endpoints and their potential attributes and associated levels.

6.1.2 Qualitative Interviews

Qualitative interviews consisted of one-to-one semi-structured concept elicitation (identification of new attributes and levels) and cognitive debriefing interviews (discussing the vignettes and available survey questions) with 30 patients with cancer, such as patients with late-stage non-small cell lung cancer (NSCLC), breast cancer, liver cancer, multiple myeloma (MM), or chronic lymphocytic leukaemia (CLL) from Spain and Croatia The interview guide was aimed at understanding the factors patients take into account when assessing their preferences and satisfaction with available treatment options provided by their physicians (See **Appendix 1: Qualitative interview guide** for full interview guide). The interview guide used a “think aloud” framework designed to encourage patients to verbalize their thought processes and provide input when presented with the vignettes, in accordance with the Professional Society for Health Economics and Outcomes Research (ISPOR) recommendations and good practices. [22, 23]

The attributes identified in the literature review were used to create clinical vignettes to be presented to patients in qualitative interviews. The vignettes were developed to represent the different hypothetical patient profiles based on a range of common and rare cancer types. The

vignettes contained a written description of a patient's cancer experience and detailed treatment-related characteristics and health outcomes/endpoints of interest corresponding to each patient profile. These characteristics were defined by the endpoints, their potential attributes, and associated levels resulting from the targeted literature review. The vignettes included different combinations of trade-offs and their levels to describe the endpoints and disease-related characteristics. A total of 6 vignettes were developed for the qualitative interviews; all 6 vignettes are included in Section 8.2.7. A full listing of the vignettes can also be found in **Appendix 2: Full list of vignettes**

Eligible patients were identified from a screener and if they met the criteria and were interested in taking part, they then received a link prior to the interview and were asked to join an online conference platform to conduct their interview. All patients provided verbal consent to take part in the qualitative interview guides and were provided opportunity to ask any questions concerned the study prior to taking part. The moderators were trained on the study protocol and interview guide prior to interviewing any patients. Interviews lasted approximately 45 minutes to 1hr and were conducted in local language.

Further detail on the qualitative interview procedures followed for this study can be found in the Study Protocol Sections 4.1.1.2 and 4.1.1.3 (*EMA patient preferences on benefits and harms of cancer drugs Protocol 6 December 2021).* Findings from the qualitative evidence generation phrase were presented to The Agency and used to inform the final list of attributes and levels to be included in the quantitative evidence generation phase.

6.2 Quantitative evidence generation

6.2.1 Development of the survey

The attributes and associated levels most relevant to patients when making a treatment decision, as validated during the qualitative interviews, were incorporated into a web-based survey. The survey was programmed online using Confirmit Horizons™ software. The Agency reviewed and agreed on the contents of the survey prior to recruitment being initiated. The full survey can be found in the final survey document (*EMA patient preference survey 1.1 29Sept2022-clean*).

6.2.2 Pilot/feasibility phase

After the experimental design of the choice sets and draft survey, a pilot/feasibility phase was conducted with the first 20 patients to assess the comprehension of the choice sets and to identify any issues encountered during completion of the quantitative survey, such as clarity of the questions, understanding of the different choice tasks and what can be improved. This feedback was reported through open-ended questions at the end of the survey and provided the study team with some early insights into how the survey was being understood by patients prior to survey deployment. Feedback from the open-ended questions indicated no refinements required to the

survey, and therefore the survey was deployed to the full population after the first 20 patient pilot was complete.

6.2.3 Overview of quantitative methodologies

Given the novel application of the use of PP information for regulatory context use, this study aimed at eliciting both the PP on the trade-offs between the benefits and risks of oncology drugs, but also trying to understand whether a methodology is superior to another in this novel context. All surveys included a DCE task as the leading/primary methodology. In addition, patients were also randomly assigned to either an additional TTO or SW task. The order of tasks was randomly presented to patients i.e. some patients were presented the DCE first, followed by the TTO or SW task, and other patients were presented the TTO or SW task first, followed by the DCE and the order was also be randomized equally across participants. The web-based survey was estimated to take approximately 20 minutes to complete. DCE, TTO and SW methodology are summarised in the sections below, for further detail on the background, use and context of these methods refer to the Study Protocol Sections 4.1.2.3 (DCE), 4.1.2.4 (TTO), 4.1.2.5 (SW) (*EMA patient preferences on benefits and harms of cancer drugs Protocol 6 December 2021).*

6.2.4 Discrete choice experiment

A DCE is a quantitative technique based on random utility theory used to elicit individual preferences for different hypothetical alternatives for treatment. The assumption of a DCE is that choices among sets of alternative profiles are motivated by differences in the levels of the attributes that define the profiles. [24, 27] A DCE allows researchers to quantify the impact of changes in attribute levels on choice and to understand the strength of preference for changes in attribute-level. The DCE method also allows for hypothetical choices to be incorporated in multiple attributes and levels to be used in simulated realistic scenarios. For example, a patient or patient must weigh both efficacy and side effects simultaneously.

Respondents evaluate trade-offs when deciding about different treatment options, each consisting of numerous attributes, as it is done in the real-world setting. The design of a DCE usually consists of a choice-based task that enables the simultaneous assessment of multiple attributes and levels to be presented and assessed. During the DCE, patients were presented with a pairwise choice set in the form of 2 alternative profiles. The choice set compromised of all attributes and associated attribute levels finalized from the qualitative evidence generation and quantitative pilot phase. The levels of the attributes vary in each choice set of the DCE. Patients were asked to choose a preferred choice set out of the 2 alternatives. Patients were presented with an illustrative example of a pairwise choice set as well as definitions of all attributes and associated attribute levels, before being asked to state their preferences (see an example from the DCE in **Appendix 3: Discrete choice experiment example**). The selection of choice sets that each patient completed were determined via experimental design.

For this study design, an orthogonal main effect plan (OMEP) was used. In an OMEP design, all main effects are unrelated to each other and are optimal for main effects linear statistical models. The factorial model consisted of 2 alternative profiles with variations of the levels of each attribute, where the patient traded-off combinations of the attributes from a choice set. The combinations of the vignettes across the choice sets were randomized.

6.2.5 Time-Trade Off Analysis

A TTO methodology is a direct preference elicitation technique which result directly in patient utility scores for the attribute levels. The utility scores can be used for weighing life years gained for the calculation of QALYs on a scale where '0' represents 'being dead' and '1' represents the 'ideal health' state.

In this study 'ideal health' states were represented by the alternative treatment options (scenarios) delineated in the survey questionnaire. Therefore, in this study the TTO method elicited preferences for time until progression of disease (progression free survival) by letting a patient imagine living a defined number of months with treatment side effects. The patient then indicated the number of months he/she was willing to trade-off such that the respondent was indifferent between the longer period of treatment side effects and the shorter period until progression of disease.

The point at which a respondent was comfortable to trade-off time for a preferred set of options for treatment was used to establish a value of the selected treatment option.[19] Normalizing the value of full health to 1 provides the value of the side effects being represented by the ratio of the 2 periods, i.e., the amount of time left in which more time until progression of disease is delivered against the amount of time with treatment side effects. An example of the TTO exercise patients completed for this study is shown in **Appendix 4: Time-trade off example**.

6.2.6 Swing-Weighting Analysis

Swing-weighting is a preference elicitation method that obtains respondents' trade-offs for changes between attributes. The trade-offs are elicited directly from individuals in a format, which enables the analysis of individual-level preferences. This contrasts with some other preference elicitation methods such as DCEs, which elicit preference statements that are used as inputs to a preference model, which then provides the trade-offs as outputs (i.e., trade-offs are elicited indirectly) and may not allow for as precise individual-level analyses.[20]

The typical swing-weighting procedure consists of 2 stages. In the first stage, respondents are asked to rank importance of changes in attributes (i.e., 'swings') from the highest to the lowest. In the second stage, respondents are asked to judge the relative value of the attribute swings. The most common method is by assigning a value of 100 to the highest ranked attribute, and then

asking respondents to express the value (between 0 and 100) of the second highest ranked attribute swing as compared to the highest ranked swing. The process is then repeated for all attributes and the resulting weights normalized to sum to a constant, typically 1 or 100, to obtain trade-off weights that express the relative importance of attribute scale swings.

The basic swing-weighting procedure only captures the trade-offs respondents make between attributes. It is often paired with a scoring procedure to capture preferences for changes within attributes.

In this study, respondents were asked to imagine that they are being offered a new treatment that has different impacts on their treatment experience based on the 4 attributes. An example of the SW task patients completed for this study is shown in **Appendix 5: Swing weighing example**

6.2.7 Variables

The web-based survey included the following sections and variables:

- A DCE exercise to evaluate PP and estimate utilities.
- A short TTO exercise to evaluate health valuation utilities (subset of patients).
- A SW exercise to evaluate PP and estimate utilities (subset of patients).
- A ranking exercise in which respondents will be asked to rank order the attributes.
- A set of questions regarding:
  - Respondents' socio-demographics, clinical (. e. diagnosis, cancer stage, number of previous treatments), self-assessed health status, constructs related to choices that may explain heterogeneity (i.e., age, disease severity, family background, patient's understanding of the disease, health awareness and literacy);
  - Question to assess respondents' level of understanding of the DCE, SW/TTO tasks.
  - Question to assess how difficult respondents found to complete the DCE, SW/TTO tasks.

6.3 Sample

6.3.1 Eligibility Criteria

Patients were required to meet all of the following eligibility criteria in order to take part in the qualitative and quantitative evidence generation phases of this study:

6.3.1.1 Qualitative Evidence Generation

- Patient is ≥18 years of age
- Patient has a self-confirmed diagnosis of cancer

- Patient lives in a European country
- Patient has access to an internet browser or application to participate in the interview
- Patient can read and write in country-specific main language
- Patient can provide an email address and click on an invitation to participate in the interview
- Patient provides informed consent to take part in the study

6.3.1.2 Quantitative Evidence Generation

- Patient is ≥18 years of age
- Patient has a self-confirmed diagnosis of cancer
- Patient lives in a European country
- Patient has access to an internet browser or application to complete the online survey
- Patient can read and write in country-specific main language
- Patient can provide an email address and click on an invitation to participate in the online survey
- Patient provides informed consent to take part in the study

6.3.2 Sample Size

6.3.2.1 Qualitative Evidence Generation

Approximately 30 adult patients with cancer will be recruited to participate in the qualitative interviews for evidence generation of the attributes and review of the vignettes. To participate in this part of the study, patients must meet all of the eligibility criteria.

6.3.2.2 Quantitative Evidence Generation

This study aimed to recruit approximately 900 adult patients with cancer to participate and complete a web-based preference survey to understand their treatment choices and treatment heterogeneity. Sample size recommendations depend on the number of attributes and levels of each attribute included.[20] Johnson and Orme suggest that the sample size required for assessing main effects depends on the number of choice tasks (*t*), number of alternatives (*a*) and the number of analysis cells (*c*) equal to the largest number of levels for any of the attributes: N >500*c* / (*t* x *a*). Recently findings show that precision of preference estimates increase at sample sizes just below 150 respondents.[21] Most studies estimating PP include approximatively 100 – 250 respondents per country.[20] Given the number of attributes and the potential interactions to examine differences in task and heterogeneity in this study, a larger sample size is warranted. It was estimated that a sample size of approximately 600 patients would be sufficient to estimate

preferences and to account for heterogeneity.

6.3.3 Participant Recruitment

6.3.3.1 Qualitative Evidence Generation

This study aimed to recruit approximately 30 adult patients with cancer to participate in the qualitative interviews via patient panels. IQVIA worked with Global Perspectives, an external patient recruitment partner, to recruit potential eligible patients to participate in the qualitative evidence generation phase of the study. The panel teams are from different sources, including marketing campaign targeting, social media, or through a referring process (such as by physicians or patients directly). Patients who request to join patient panels are requested to complete a profiling survey including several socio-demographic and healthcare questions so that the panel can pre-target patients as having a certain condition (e.g., NSCLC) and being part of a certain socio-demographic background.

Global Perspectives invited potential eligible patients to participate in the qualitative evidence generation phase of the study. To do this, a screener was developed by IQVIA to help identify eligible patients. Patients who were eligible based on the completion of the screener and agreed to participate were contacted to obtain consent and will consequently have an interview scheduled.

6.3.3.2 Quantitative Evidence Generation

This study aimed to recruit approximately 900 adult patients with cancer to participate in the quantitative phase of the study using a combination of both patient panels and patient advocacy groups (PAGs). A full description of the proposed approach is outlined in the Study Protocol (*EMA patient preferences on benefits and harms of cancer drugs Protocol 6 December 2021).*

In the patient panel approach, IQVIA worked with Global Perspectives to recruit potential eligible patients with cancer to participate in the quantitative phase of the study. Similar to the qualitative evidence generation phase, patients who request to join patient panels are requested to complete a profiling survey where they will be asked several socio-demographic and healthcare questions so the panel can pre-target the patients as having a certain condition (e.g., NSCLC) and being part of a certain socio-demographic background. A sample size of 300 patients with cancer was proposed from Western Europe (e.g., Spain) and Eastern Europe (e.g., Poland) (total = 600 patients) to have a better balance of different regions of Europe that may differ in terms of oncology treatment practices and ensure heterogeneity in patients with cancer from different parts of Europe. The final sample size and distribution of patients are included in Section 8.3.1.

Global Perspectives invited potential eligible patients to participate in the qualitative and quantitative phases of the study. A screener was developed by IQVIA to help identify eligible patients. Patients who were eligible based on the completion of the screener and agreed to participate were sent a link via email to the survey. Once patients completed the survey the

anonymized data was automatically saved to the data management platform.

The Agency later made the decision not to implement the PAG approach due to logistical concerns, therefore the PAG method of recruitment was not utilised to recruit patients in this study and therefore is not described in this report. As this method of recruitment was not utilised, the study was unable to recruit the additional n=300 participants that were intended via this approach.

7 STATISTICAL ANALYSIS

7.1 Qualitative Evidence Generation Analyses

To assess the face and content validity of the survey, vignettes, attributes and associated levels, the data obtained from the interviews and the pilot was assessed and coded thematically for analysis, and issues arising in relation to vignette content or format were extracted and used for revision towards the final survey. Patient verbatim was coded to examine comprehension, relevance, and ease or difficulty of selecting a response. The overall goal of coding these data was to facilitate the identification of concepts that are most important and relevant to patients. The coding process identified and categorised patient concept expressions. Coders reviewed each transcript to identify text that included concept expressions and tagged selected text with a code. The codes were organized within a coding framework, which was established at the beginning of the process and refined/expanded throughout the coding process. Once the coding process has been completed, outputs were generated and summarised for presentation to The Agency in a PowerPoint report. All interview transcripts (PDF format) are provided as supplemental electronic files to this final report. Content within and between vignettes was compared and examined for comprehension and ease or difficulty of selecting a response. For the qualitative phase, all data was coded using Atlas.ti® version 8.

7.2 Quantitative Evidence Generation Analyses

The final analyses are fully described in the statistical analysis plan (SAP) (*EMA Stated Patient Preference SAP Final 08Dec*), analyses for primary, secondary, and exploratory objectives are summarised in the sections below. Continuous variables were described by mean, standard deviation (SD), 95% confidence intervals (CI), median, 25th and 75th percentiles, minimum and maximum. Categorical variables were described by frequencies and related percentages of the study population, and by subgroups.

7.2.1 Primary Analyses

The primary objective was aimed at identifying and describing the cancer PP on benefits and harms of cancer drugs and to understand the trade-offs between factors leading to PP using the main method, a DCE.

For the DCE, the analysis of the DCE data was initially be explored using a conditional multinomial logit (MNL) then the analysis proceeded using a random parameter logit (RPL) model assuming all random parameters were normally distributed and independent.

The DCE had 10 treatment-choice questions from the experimental design which were used to estimate main effects. Main effects included the preference weight for each attribute level

independent of the other attributes and levels included in the study. In the utility specification considered in the main analysis, all parameters were effects-coded as categorical values. In the RPL model specification, all parameters were assumed to be normally distributed.

Results from utility estimation allows for the estimation of coefficients for each attribute level, with a positive parameter in the model representing a positive utility associated with a particular attribute level, whereas a negative parameter in the model represents disutility associated with a particular attribute level.

7.2.2 Secondary Analyses

The secondary objective was to determine the extent to which patients' heterogeneous characteristics were associated with stated preferences. To explore variation in preferences for patient treatment based on patient given factors collected such as patient characteristics, or disease experience. A latent class (LC) and subgroup analyses were conducted to achieve this secondary objective.

For subgroup analysis, the RPL models were conducted with coefficients for attribute levels interacting with subgroup variables for the DCE methodology. Regression models were also conducted to examine the relationship between the utilities from the TTO and SW methods and patients' characteristics, using regression coefficients and 95% confidence intervals. Regression assumptions were assessed, and appropriate regressions models were based on the assumptions and data distributions of the utilities.

The RPL models were also used to control for differences in error variance and explore consistency of treatment choices for the DCE methodology. Random utility theory assumes that there may be an additional component of utility that is unobservable. Therefore, the utility function comprises of 2 elements: a deterministic component based on the participants' preferences for the observed attributes of the alternative, and random error associated with the alternative.[22]

7.2.3 Exploratory Analyses

An additional objective was to compare preference weights of patient associated with stated preference using different stated preferences methods. Preference weights estimated from the 3 methods and association between preferences and patients' characteristics were compared descriptively.

Patients were also asked about the level of difficulty completing each task (either DCE/SW or DCE/TTO). This question was asked at the end of the survey, and the data was compared descriptively.

For the quantitative phase, all computations and generation of tables, listings and data for figures were performed using Stata 17.

7.3 Changes to the Planned Analysis

The planned analyses in the SAP included using the RPL DCE results to calculate the marginal rates of substitutions, such as maximum acceptable risk or minimum acceptable benefit. In this study, the minimum acceptable benefit of time until progression of disease for changes in each attribute was to be explored. The minimum acceptable benefit is defined as the negative of the ratio between the marginal dis/utility of given changes in any of the attributes included in the DCE and the marginal utility of the increase in time until progression of disease. The minimum acceptable benefit was to be computed using the linear time until progression of disease coefficient as the denominator, using the effects-coded variables by assuming linearity of preference weights between each pair of levels included in the survey instrument. The RPL results showed that the most important attribute was the impact of side effects on QoL relative to other attributes included in the study. This result rendered the calculation of the minimum acceptable benefit of time until progression of disease for changes in each attribute not intuitive.

Another planned analysis was to use the preference weights from the RPL DCE to estimate the probability that an average respondent in the sample selects one treatment profile over another. The attribute levels used to characterize the treatment profiles were to be determined in collaboration with Agency. The predicted chance that a given treatment is selected is based on the differences in the levels of the attributes for each treatment alternative. Given the DCE results greatly skewed towards preference for the impact of side effects on QoL relative to other attributes included in the study, this additional analysis was considered not useful.

8 RESULTS

8.1 Targeted Literature Review

The full results from the targeted literature review can be found in the literature review report (*EMA Literature Review – Summary Report – v1.0 17June2021*), a summary of key results is included in the following section.

A total of 41 studies were included for review from the literature search. Studies included patients from USA (n=18, 44%), Europe (n=17, 41%), Australia (n=3, 17%) and Japan (n=2, 5%), with most studies including patients from the USA (n=18, 44%), UK (n=6, 15%) and Germany (n=5, 12%), 4 studies (10%) included patients from more than one country. Studies elicited preferences from patients with a wide range of cancers, including to lung cancer (n=11, 27%), melanoma (n=5, 12%), prostate (n=4, 10%), ovarian (n=3, 7%), breast (n=3, 7%), lymphoma (n=3, 7%), multiple myeloma (n=2, 5%), colorectal (n=2, 5%) and more. Of the 41 included studies, 11 (27%) elicited preferences in metastatic or advanced cancers. A wide range of patient preference methodologies were also demonstrated across the 41 included studies. Most studies included a DCE (n=25, 61%), other methods also included Multiple criterion decision analysis (MCDA) (n=3, 7%), value clarification (n=2, 5%), best-worst scaling (n=2, 5%), social media analysis (n=1, 2%), TTO (n=1, 2%) and willingness to pay (n=1, 2%). Around a quarter of studies identified utilised multiple patient preference methods as part of their study (n=10, 24%).

Most studies included attributes and levels relating to efficacy (n=34, 83%), side effects, adverse events and toxicity (n=32, 78%) and treatment characteristics (n=32, 78%). Nearly 40% of studies included attributes relating to impact on quality of life (n=16, 39%) and 4 studies included attributes relating to disease severity (10%). In studies that included attributes relating to efficacy, overall survival (n=22, 54%) and progression free survival (PFS) (n=21, 51%) were the most included attributes. A small number of studies included overall response rate (n=2, 5%), reduction in tumour size/growth (n=2, 5%), requiring/not requiring further follow up (n=2, 5%), complete remission (n=1, 2%), and time to response (n=1, 2%) as attributes. In total 29 different side effects/adverse events were used as attributes in the 41 included studies, the most used were fatigue (n=8, 20%), long term side effects (n=4, 10%) and cognition (memory/ “fogginess”) (n=4, 10%). The most common treatment characteristics included as attributes in the identified studies were mode of administration (n=11, 27%), out of pocket costs (n=11, 27%), frequency of administration (n=8, 20%) and travel distance/transport (n=5, 12%). A full list of attributes identified relating to side effects/toxicity and treatment characteristics can be found in the literature review report (*EMA Literature Review – Summary Report – v1.0 17June2021*).

The literature review also explored commonly assessed factors when aiming to capture preference heterogeneity. The most explored factors were age (n=11. 27%), sex (n=8, 20%), education level (n=7, 17%), employment status (n=7, 17%), income (n=5, 12%) and marital status (n=5, 12%). Around a third of studies assessed preference heterogeneity by patients’ health

characteristics, most commonly by type of treatment previously received (n=4, 10%), cancer type (n=3, 7%), risk category (n=3, 7%) and health insurance (n=3, 7%). A full list of factors assessed for preference heterogeneity in the 41 included studies can be found in the literature review report (*EMA Literature Review – Summary Report – v1.0 17June2021*).

8.1.1 Recommendations from the targeted literature review

- Efficacy and PFS have been well-documented as some of the most important treatment attributes to patients with different cancer types when making a treatment decision. Patient preferences relating to side effects and toxicity and treatment attributes were also commonly assessed and found to contribute to patient's preferences, therefore it was recommended to consider these attributes when eliciting patient preferences for cancer treatments.
- Several studies also considered preference heterogeneity when examining patient preferences for cancer treatment across different cancer types. When tested for preference heterogeneity, most studies found significant factors that influenced preferences based on socio-demographics and health characteristics. Therefore, it was recommended to consider collecting relevant socio-demographic and health characteristics of patients when eliciting patient preferences for cancer treatments, to be able to assess factors that are likely to contribute to preference heterogeneity.
- The findings from the targeted literature review were used to develop the interview guides for the qualitative interview guides, including the development of the vignettes for cognitive debriefing. Results of which are described in the next sections.

8.2 Qualitative Interviews

8.2.1 Demographics

Table 1 describes the 30 patients who took part in the qualitative interview phase of this study. Interviews included 15 patients from Spain and 15 from Croatia. Patients ranged between 27-78 yrs old, with an average age of 51yrs old. Most participants were above 40yrs old (n=28, 90%) and female (n=25, 83%). Half of patients were married, 20% were single and 17% were divorced, 40% had a university education. Most patients lived with their partner or family (n=20, 67%). Interviewees had a wide range of cancers. Just over a third of patients (n=11, 37%) had breast cancer. Other patients had lung cancer (NSCLC) (n=6, 20%), colorectal or stomach cancer (n=4, 13%), multiple myeloma (n=2, 7%), sarcoma or chondrosarcoma (n=2, 7%), one patient each respectively had CLL, endometrial cancer, melanoma of the eye, prostate cancer, and tonsil cancer.

Table 1. Interview population demographics

Demographics	Total (n=30)	%
Age		
Age (mean, yrs)	51	-
Range (yrs)	27-78	
<30 yrs old	1	3%
30-39 yrs old	1	3%
40-49 yrs old	3	10%
50-59 yrs old	12	40%
60-69 yrs old	7	23%
70+ yrs old	6	20%
Sex		
Female	25	83%
Male	5	17%
Country		
Spain	15	50%
Croatia	15	50%
Marital Status		
Married	15	50%
Single	6	20%
Divorced	5	17%
Co-habiting	2	7%
Widowed	1	3%
Not asked	1	3%

Demographics	Total (n=30)	%
Education		
University	12	40%
High school	6	20%
Higher education	2	7%
Not asked	10	33%
Living Situation		
Lives with partner or family	20	67%
Lives alone	4	13%
Lives with parents	2	7%
Lives with friends	1	3%
Not asked	3	10%
Type of Cancer		
Breast	11	37%
Lung cancer (NSCLC)	6	20%
Colorectal / stomach	4	13%
Multiple Myeloma	2	7%
Sarcoma / Chrondosarcoma	2	7%
CLL	1	3%
Endometrial	1	3%
Melanoma of the eye	1	3%
Prostate	1	3%
Tonsil	1	3%
Abbreviations: Yrs – Years, NSCLC – Non-small cell lung cancer, CLL – chronic lymphatic lymphoma,		

8.2.2 Experiences of Treatment

Patients were asked to describe their treatment experiences and were asked what they considered to the positive and negative parts of those experiences; their responses are outlined in Table 2. The majority of participants were able to describe positive experiences in relation to their treatment. Most participants described positive experiences related to how successful their treatment had been (n=21, 70%), some participants also described that they valued the good quality of life they had while on treatment (n=8, 27%). Quotes from patients describing positive experiences relating to treatment success and quality of life are included below.

Treatment Success*:*

> *"But well, when all is said and done, this was good for me because I was in very, very bad shape. They told me that if I had waited another week, I probably would have died. It went well for me. The treatment worked well for me. Comparing the good to the bad, I would say "It was worth going through all that hardship because I'm in complete remission instead of having to have a transplant" (P1, MM)*

Quality of Life:

> *"Very good. It's working and it allows me to have a moderately decent quality of life. It has side effects, but I know that from other girls. The [side effects] are muscle discomfort and some joint discomfort, but I have it under control with exercise. I have more control over it because I walk a lot" (P8, Breast)*

Three patients also mentioned the convenience of their treatment (10%) and 2 patients (7%) described how they had accepted their treatment and that this feeling of acceptance was a positive experience for them.

Where patients described negative experiences of treatment, this was most often related to side effects of treatment (n=15, 50%). Patients also described negative experiences of treatment related due to the impact of treatment on their mental health (n=3, 10%), sex life (n=2, 7%), their work/employment (n=2, 7%) and the number of treatment appointments associated with treatment (n=1, 3%). Ten patients did not consider any of their treatment experiences to be negative when asked (33%). Quotes from patients describing negative treatment experiences relating to side effects and work/employment are included below.

Side effects:

> *"I had a very bad experience. I guess because it was the first phase of treatment. I was emotionally depressed. I guess that also influences when you take this medication. Thalidomide gave me... I don't know what they're called... Finger cramps. They were getting stiff. I started to notice it on my fingertips, and I started to see that treatment was really harming me. A lot of fatigue. I guess that was everything. Everything. A combination of everything. I got into bed. I didn't leave the bed. I got into bed. I got into bed with the first treatment" (P9, MM)*

Work/Employment:

> *"I have changes in all the bones in my body and the cervical spine. I can no longer sit, and I was in front of a computer for 16 hours a day… I just took on a lot more than I could actually handle physically. And that's what I said, I said that I just can't. I started to have pain in my spine, my neck started hurting, you know, all those things in my everyday life and the way I… I am aware of it. Besides, people who have metastatic breast cancer are tired. We have to rest, sleep in the afternoon. I don't know who's able to go back. You never go back, because you can't" (P3, Breast)*

Table 2. Positive and negative experiences of treatment

Treatment experiences	Total (n=30)	%
Positive treatment experiences		
Success of treatment	21	70%
Quality of life	8	27%
Convenience of treatment	3	10%
Acceptance of treatment	2	7%
Not asked	1	3%
Not mentioned	1	3%
Negative treatment experiences		
Side effects	15	50%
Mental health	3	10%
Sex life	2	7%
Work / Employment	2	7%
Treatment appointments	1	3%
Not mentioned*	10	33%
Don't know / unsure	1	3%

Footnote: Participants had the opportunity to describe more than 1 positive or negative experience of treatment

** Negative experiences of treatment were not discussed by 10 participants. Participants were asked to describe their treatment experiences, and then discuss whether they perceived them as positive or negative. In these instances, participants did not consider any of their treatment experiences to be negative.*

8.2.3 Factors Considered When Making a Treatment Decision

8.2.3.1 Most Important Factors When Making A Treatment Decision (Spontaneous)

Patients were asked an open-ended question to describe what they considered to be the most important factors when making a treatment decision. Patients were able to discuss as many factors as they wanted in their response and all answers were spontaneous. In total, 17 different factors were described by patients, responses are listed in Table 3. Nearly half of patients (n=13, 43%) considered their physicians opinion to be one of the most important factors to consider when

making a treatment decision, these patients trusted their physician to make the best treatment decision for them. Survival was also mentioned by around a third of patients (n=9, 30%) as a priority, these participants wanted their treatment to extend life as much as possible. Quality of life (n=8, 27%) and side effects (n=7, 23%) were described similarly, in terms of whether patients were able to cope with the side effects of treatment or a poorer quality of life. Some patients also considered their children/grandchildren in their decision (n=4, 13%), wanting to live longer to support their children/grandchildren and also considering how treatment would impact their family. Quotes from patients describing these factors are included below.

Physician's opinion:

> *"I have obeyed the doctor, who said: "We're going to try this. The first line therapy to be a smart drug." I just followed. In this context, I trust the doctor, absolutely, as far as my illness is concerned." (P4, NSCLC)*

Survival:

> *"First and foremost, life. Wanting to live, wanting to fight, wanting... I don't know, for me, life is the most beautiful thing there is, so you grab onto anything. When they told me I had to undergo chemotherapy, I told them yes, the sooner the better." (P7, NSCLC)*

Side effects:

> *"Regarding the side effects, well if you find yourself unable to cope psychologically with them, then I would stop taking the treatment. So far, I'm trying to work with them in different ways, and I'm handling it, but yes. I think that if a treatment gives me terrible side effects and I'm not able to manage them emotionally or psychologically, I would stop it." (P12, Breast)*

Quality of life:

> *"Quality of life. Of course. Having a quality of life. They give you a treatment and I think the best thing is, even if you live less, but live better. It's not about living a bad life for many years. From my point of view." (P9, MM)*

Presence of children and family

> *It is necessary to live with this every day and I personally have a child that is minor, so that all this together must be taken into account, that you must prepare yourself and everyone around you to such a situation and state (P2, NSCLC)*

Table 3. Most important factors when making a treatment decision

Most important factors (spontaneous)	Total (n=30)	%
Physician's opinion	13	43%
Survival	9	30%
QoL	8	27%
Side effects	7	23%
Presence of children and family	4	13%
Efficacy of treatment	4	13%
Remission	4	13%
Feeling mentally prepared for treatment	3	10%
Impact of treatment on ability to work	2	7%
Mode of administration	2	7%
Overall health status	2	7%
Reputable hospital/doctors	2	7%
Cost of treatment	1	3%
Duration of treatment	1	3%
Previous treatment	1	3%
Understanding information around treatment	1	3%
Not asked	0	0%
Footnote: Participants had the opportunity to describe more than 1 most important factor when making a treatment decision		

8.2.3.2 Least Important Factors When Making A Treatment Decision (Spontaneous)

Patients were also asked to describe what they considered to be the least important factors when making a treatment decision, patients' responses are outlined in Table 4. Most participants either considered all factors to be important when making a treatment decision (n=8, 27%), or said that they did not know of any factors that were unimportant (n=6, 20%). Patients who were able to identify some factors that they considered to be least important in making a treatment decision described side effects of treatment (n=4, 13%), cost of treatment (n=2, 7%),travel to treatment (n=2, 7%), duration of treatment (n=1, 3%), mode of administration (n=1, 3%) and type of drug

molecule (n=1, 3%). One patient also described that they felt patients were not in control of treatment decisions and therefore was not able to identify any factors they should consider least important. Quotes illustrating patients discussing that all factors have some importance, and side effects are included below:

None (all factors have some importance): *"I don't know. Everything's important regarding treatment. Everything can affect you. [silence] I don't know, I don't know what you mean by not important. Everything's important regarding treatment." (P5, NSCLC)*

Side Effects: *"The only thing I wanted was to live. I would say, "Give me whatever you want, but I want to live even if I have side effects." It was all the same to me. At first you just wanted to live. You didn't want anything else. You didn't care about anything, really. Not the side effects, or if I vomited, or if my hair fell out. It didn't matter to me. It didn't matter as long as I lived." (P9, MM)*

Table 4. Least important factors when making a treatment decision

Least important factors (spontaneous)	Total (n=30)	%
None – all factors have some importance	8	27%
Don't know	6	20%
Side effects of treatment	4	13%
Cost of treatment	2	7%
Travel to treatment	2	7%
Duration of treatment	1	3%
Mode of administration	1	3%
Type of drug molecule	1	3%
None - patients not in control of decisions	1	3%
Not asked	7	23%
Not mentioned	1	3%
Footnote: Participants had the opportunity to describe more than 1 least important factor when making a treatment decision		

8.2.3.3 Most And Least Important Factors When Making A Treatment Decision (Probed)

After being asked to spontaneously describe factors they considered to be most important when making a treatment decision (see Section 8.2.3.1 above), patients were then presented with the

list of treatment factors provided in Table 5 and were asked to state which factors they thought were the most important and why. Nearly half of patients identified overall survival (n=14, 47%) and progression free survival (n=14, 47%) as the most important factors included in the list. Patients reported that they considered overall survival to be most important because ultimately, they wanted to live longer and gave reasons such as continuing to be able to spend time with loved ones. Progression free survival was considered important because patients associated stopping disease progression with longer overall survival (n=14, 47%). Quality of life was also mentioned by a third of patients (n=10, 33%) and was considered important because of the value they placed on high quality of life compared to longer life. Some participants also considered mode of administration (n=3, 10%), treatment regimen (n=3, 10%) and side effects (n=3, 10%) as most important factors when making a treatment decision. Quotes illustrating patients views on overall survival, progression free survival and quality of life are included below.

Overall survival:

> *"I guess overall survival… Because you think about your family. You have family, and to be with them. More time with them. The longer you have with them, the better for you. Of course. I say." (P9, MM)*

Progression free survival:

> *"You just want this progression not to occur, or worsening of the condition, so that you can move on, so that you stop it. That's why I find it important. To stop this progression, i.e., the current state if it is not very alarming and very bad. If you can stop it and continue to live with it in some way as a chronic disease, let's call it so.." (P2, NSCLC)*

Quality of life:

> *"Because I... personally... and I think many fellow patients in my support group share the same opinion. We don't want more life, but better quality of life. If we have to choose between living 10 years or longer and living a year to the fullest, we'd choose one year of life to the fullest than 10 sucky years. We don't want to live just for the sake of living. We want to live, not survive. (P12, Breast)*

In a similar fashion, patients were then asked to discuss which factors on the list presented they considered to be the least important when making a treatment decision and why, responses are also presented in Table 5. Nearly half of participants chose mode of administration as one of the least important factors (n=14, 47%), treatment regimen and side effects were also mentioned by a third of patients (n=10, 33% each respectively). Patients described considering these factors to be least important mainly by comparison to the factors they considered to be most important. While most patients thought that all factors had some importance, they considered the aforementioned factors to have lesser priority than others. Overall survival was mentioned by 2 participants (n=2, 7%), one considered overall survival as a statistic to not be very important, and the other considered progression free survival and quality of life to be more important than overall survival.

Table 5. Most important and least important factors when making a treatment decision (probed)

Most important factor (probed list)	Total (n=30)	%
Most important factors		
Overall survival	14	47%
Progression free survival	14	47%
Quality of life	10	33%
Mode of administration	3	10%
Treatment regimen	3	10%
Side effects	3	10%
Least important factors		
Mode of administration	14	47%
Treatment regimen	10	33%
Side effects	10	33%
Overall survival	2	7%
Participants had the opportunity to describe more than 1 most/least important factor		

8.2.4 Overall Survival vs Progression Free Survival

Patients were asked to consider overall survival and progression free survival and discuss which attribute was more important and why, results are described in Table 6. Responses near evenly split, just over half the sample considered overall survival to be more important than progression free survival (n=17, 57%). Those who considered overall survival to be more important described this was because they considered living for as long as possible to be their ultimate aim, including potential disease progressions. Examples of patients describing why they thought overall survival and progression free survival were the more important attributes are included below.

Overall survival:

> *"I prefer to have to go every 3 weeks to get the treatment, but let it be many weeks. That. For me, the important thing, as I told you, is to stay alive with or without the disease. I don't need...I don't need to be healthy to be happy." (P6, NSCLC)*

Those who considered progression free survival to be more important than overall survival (n=13, 43%), described that this was because progression free survival signified that their disease was under control

Progression free survival:

"Because it simply means that the overall condition in my body, that my condition is good. In the sense that the therapy is good and that I'm responding well to the treatment, while the disease is not spreading" (P11, Breast)

Table 6. Overall survival vs progression free survival

Which is more important?	Total (n=30)	%
Overall survival	17	57%
Progression free survival	13	43%
Footnote: Responses are mutually exclusive; patients were only allowed to select one answer for this question		

8.2.5 Quality of Life vs Side Effects

Patients were also asked to consider quality of life and side effects and discuss which attribute they considered to be more important and why, results are described in Table 7. Quality of life was considered to be the more important attribute by 83% of patients (n=25). Quality of life was considered to be more important by these patients because they considered side effects to be temporary and potentially manageable, compared to quality of life which was described as a longer-term issue. Some patients also stated that they considered these 2 attributes to be too similar to choose between and very much dependent on each other (n=2, 7%). Quotes illustrating patients discussions on quality of life and side effects are included below,

Quality of life:

"Side effects are temporary. Today you have them, tomorrow you don't, but quality of life means that you're still, how should I say, functional, what I've been trying to do the whole time, even with this diagnosis, is to live as if I didn't have it. (P5, NSCLC)

Quality of life and side effects considered the same:

"I think it's the same because quality of life will always be affected by the side effects of a treatment. If the effects are terrible, my quality of life is going to get worse. If I can control the side effects in some way, my quality of life is going to be much better. So, I think it's the same. I can't say that one is more important than the other. It's exactly the same for me." (P12, Breast)

Table 7. Quality of life vs side effects

Which is more important?	Total (n=30)	%
Quality of life	25	83%
Side effects	3	10%
Same importance	2	7%

8.2.6 Contributions to Decision Making

8.2.6.1 Most Important Patient/Treatment Characteristics That Contribute To Treatment Decision Making (probed)

Patients were asked to select which characteristics would have the most important contribution to treatment decision making for them from a list of factors shared on the screen during the interview. The list of characteristics and frequencies for which patients selected characteristics as most important are included in Table 8. Understanding treatment information (n=10, 33%) and patient health status (n=9, 30%) were considered as one of the most important contributions by around a third of patients respectively. Understanding treatment information was considered important because patients felt that understanding the treatment information was a key component of making a treatment decision. Health status was important because patients recognized health status as contributing to how well patients would be able to tolerate treatment, a similar description was also given around the importance of age (n=3, 10%). Whether or not patients had children was also considered as one of the most important contributions by 6 patients (20%). Productivity and sex (male or female) were not considered most important by any patients asked. Quotes from patients explaining why they chose understanding treatment, patient health status and having children as most important are included below.

Understanding treatment information:

> *"First, before I get a treatment, I want to have a good understanding of the treatment information, what I'm going to take, what the side effects are. All that. How I have to take it. All the information at that time… once you have all the treatment information, then you can make a decision" (P3, Breast)*

Patient health status:

> *"State of health, of course. This is very important. It depends on how you're doing, whether you're given one treatment or another. If you're in very poor health, there are treatments that you won't be able to handle. So, I think state of health, come on, that's very important" (P20, Breast)*

Having children:

> *"Having children…that's 10 out of 10. I think every mom would like to live, of course, those*

with children. That's it. This is the most important thing." (P30, Tonsil Cancer)

Table 8. Most important patient/treatment characteristics contributing to treatment decisions (probed)

Patient characteristics	Total (n=30)	%
Understanding treatment information	10	33%
Patient health status	9	30%
Having children	6	20%
Age	3	10%
Duration of treatment	3	10%
Cost of treatment	2	7%
Living situation *(social support)*	2	7%
All characteristics are important	1	3%
Marital status	1	3%
Previous treatments	1	3%
Travel to treatment	1	3%
Productivity	0	0%
Sex *(whether patient is male or female)*	0	0%
Patients had the opportunity to choose more than 1 most important contribution		

8.2.6.2 Least Important Patient/Treatment Characteristics Contributing to Treatment Decisions (probed)

Patients were then asked to select which characteristics they would consider to be the least important contributions to treatment decision making from the same list as in the previous section (Section 8.2.6.1). The list of characteristics and frequencies for which patients selected characteristics as least important are included in Table 9. Sex (male/female) (n=8, 27%), cost of treatment (n=5, 17%) and marital status (n=5, 17%) were most frequently considered least important characteristics by patients. Sex and marital status were both considered least important by patients because they were unable to think of any reasons why these characteristics would be important. Cost was considered to be not important because patients felt that the best treatment should be received regardless, or because they were not given this type of information to consider when receiving treatment. Age, productivity, travel to treatment were also considered least important by 4 patients each respectively (n=4, 13%). Health status and understanding treatment information were not considered to be one of the least important characteristics by any patients.

Quotes from patients discussing why they considered sex, cost of treatment, marital status and productivity to be least important are included below.

Sex:

> *"Because it's irrelevant which gender one is. I think that it's the same for both genders, for the treatment... Why was it put here? What's the difference, male and female? I believe they would equally agree to anything just to help themselves." (P28, Breast)*

Cost of treatment:

> *"To say which is the least important, well, the "treatment cost" is the least important. You're fighting. I don't know what else to choose." (P4, NSCLC)*

Marital status:

> *"Marital status. What difference does it make if you're single, married, or divorced? The important thing is to live. If you live for yourself, especially if you have children. Marital status compared to having children, has no influence. The least important thing, I think is marital status." (P10, Breast)*

Productivity:

> *""Work productivity"? I think that at the age of [age], you know? [laughter] I have worked a lot, too much. So, that's really not important to me. (P3, Breast)*

Table 9. Least important patient/treatment characteristics contributing to treatment decisions (probed)

Patient characteristics	Total (n=30)	%
Sex *(whether patient is male or female)*	8	27%
Cost of treatment	5	17%
Marital status	5	17%
Age	4	13%
Productivity	4	13%
Travel to treatment	4	13%
Duration of treatment	3	10%
Having children	1	3%
Living situation *(social support)*	1	3%
Previous treatments	1	3%
Patient health status	0	0%

Patient characteristics	Total (n=30)	%
Understanding treatment information	0	0%
Participants had the opportunity to choose more than 1 least important contribution		

8.2.7 Cognitive Debriefing of the Vignettes

Patients were presented with 5 vignettes during the patient interviews (see Section 6.1.2) and were asked to provide their insights on whether they thought the vignette was a good treatment option and why, whether the experiences in the vignette were similar to any of their treatment experiences, and whether information was relevant and sufficient to be able to make a treatment decision. Vignettes 1-5 and the feedback from each vignette are presented in the following sections.

8.2.7.1 Vignette 1 – Sara

Figure 1. Vignette 1 – Sara

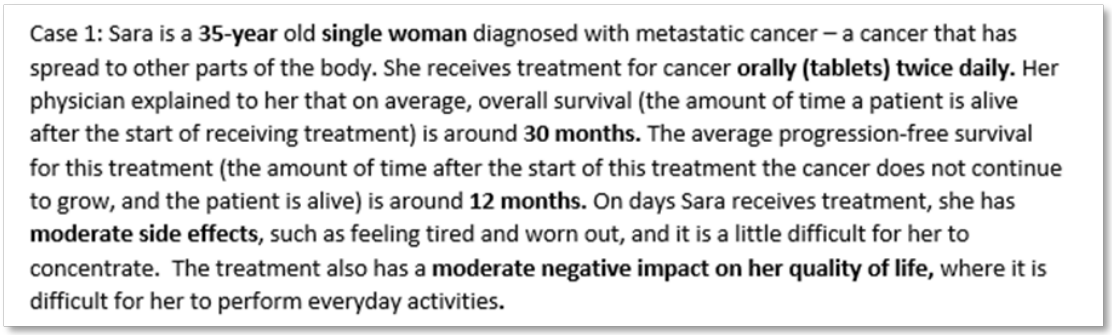

Case 1: Sara is a **35-year** old **single woman** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. She receives treatment for cancer **orally (tablets) twice daily.** Her physician explained to her that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **30 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **12 months.** On days Sara receives treatment, she has **moderate side effects**, such as feeling tired and worn out, and it is a little difficult for her to concentrate. The treatment also has a **moderate negative impact on her quality of life,** where it is difficult for her to perform everyday activities.

Table 10 outlines feedback from patients on Vignette 1. When presented with Vignette 1, just over half of patients thought that Vignette 1 presented a good treatment option (n=16, 53%). Patients who thought Vignette 1 presented a good treatment option attributed this to the moderate side effects and oral mode of administration. More than half of patients reported that Vignette 1 was similar (n=14, 47%) or somewhat similar (n=6, 20%) to their own experiences. Those who thought that Vignette 1 was not similar to their own experiences described that this was due to differences in information received (overall survival for example was not discussed), mode of administration and side effects. Patients were also asked about whether they considered the information in the vignette to be relevant and sufficient to make a treatment decision, 43% of patients thought that the information was relevant (n=13, 43%) and sufficient (n=12, 40%). Patients who thought that the information was not relevant or sufficient were seeking additional information relating to the type of cancer, more detail on side effects, or thought that some information already included was not relevant (such as overall survival as a statistic). Quotes illustrating these discussions are included below.

Good treatment option (mild side effects and oral mode of administration):

> *""If only I could have that! No way! Instead of being injected into your vein one day, and then having a week loaded up with toxicants in your body, [before] the toxicity level starts to go down. A week of rest and they give you [the same again] … I think it would be a little steadier, possibly a little more bearable. (P19, Stomach)*

Not similar to own experiences:

> "*Different. For example, I have never asked anyone nor has anyone told me what it would be like, what would happen without treatment, and how it would go. No one has ever mentioned any survival time. internet. My oncologist does not even mention such things (P14, Colon)"*

Information not relevant

> *"No. It tells me here that they are giving her this treatment, but since I don't really know what her cancer is, I don't know if there might be other possible treatment alternatives" (P6, NSCLC)*

Table 10. Patient feedback on Vignette 1

Vignette 1	Total (n=30)	%
Does Vignette 1 present a good treatment option?		
Good	16	53%
Don't know	8	27%
Not good	4	13%
Not asked	2	7%
Are the experiences similar to own experiences?		
Yes	14	47%
No	10	33%
Somewhat	6	20%
Not asked	0	0%
Is the included information relevant?		
Yes	13	43%
No	9	30%
Not asked	8	27%

Vignette 1	Total (n=30)	%
Is the included information sufficient?		
Yes	12	40%
No	13	43%
Not asked	5	17%
Footnote: Not asked – refers to when a participant was not asked the question, this may have been either due to time constraints or if responses to similar questions became repetitive, in this instances interviews would use their judgement as to whether any new information would arise from continued line of questioning. If not then interviewers ceased the line of questioning for the remaining vignettes.		

8.2.7.2 Vignette 2 – Bill

Figure 2 Vignette 2 – Bill

Case 2: Bill is a **45-year** old **single man** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. He receives treatment for cancer **orally (tablets) once daily.** His physician explained to him that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **18 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **9 months.** On days Bill receives treatment, he has **mild side effects**, such as feeling a little tired and slightly worn out. When receiving his treatment, Bill does not have difficulty with his concentration. The treatment also has **no negative impact on his quality of life.**

Table 11 outlines feedback from patients on Vignette 2. Half of the patients interviewed thought that Vignette 2 presented a good treatment option (n=15, 50%), and a third were unsure (n=9, 30%). Patients who thought Vignette 2 presented a good treatment option thought so because of the mild side effects and oral mode of administration, similarly to Vignette 1. Nearly half of patients felt that Vignette 2 was not similar to their own experiences, while around a third (n=9, 30%) of patients did think that Vignette 2 was similar to their experiences. Patients that thought Vignette 2 was not similar to their own experiences stated this was due to differences in treatment mode and side effects, again similarly to feedback on Vignette 1. Around a third of patients stated that the information in Vignette 2 was relevant (n=9, 30%) while approximately another third felt the information was not relevant (n=11, 37%). Patients who stated that the information was not sufficient or relevant wanted additional information such as cancer type and location of the tumour(s) or felt that included information such as overall survival was not relevant. The feedback regarding sufficient/relevant information in Vignette 2 was overall very similar to feedback on Vignette 1. Quotes illustration why some patients thought Vignette 2 was a good treatment option, and why some information was not relevant and sufficient are included below.

Good treatment option – mild side effects:

"Well I'm jealous because of the mild side effects and that there is no negative impact on his quality of life… Well, I wish all medications were like that. Wonderful!." (P12, Breast)

Information not relevant:

"Maybe I would omit the life expectancy, the references to 18 months or nine months, because I value quality of life more. So, perhaps, from my point of view, and of course, this is my personal opinion, I would appreciate it more if they told me [quality of life]" (P19, Stomach)

Information not sufficient:

"It's super important for any treatment. The initial cancer and where it has metastasized. I think the rest is fine. Those two pieces of information, I see them as super important. " (P20, Breast)

Table 11. Patient feedback on Vignette 2

Vignette 2	Total (n=30)	%
Does Vignette 2 present a good treatment option?		
Good	15	50%
Don't know	9	30%
Not good	2	7%
Not asked	4	13%
Are the experiences similar to own experiences?		
Yes	9	30%
No	14	47%
Somewhat	6	20%
Not asked	1	3%
Is the included information relevant?		
Yes	9	30%
No	11	37%
Not asked	10	33%
Not mentioned	0	0%
Is the included information sufficient?		

Vignette 2	Total (n=30)	%
Yes	7	23%
No	17	57%
Not asked	6	20%

Footnote: Not asked – refers to when a participant was not asked the question, this may have been either due to time constraints or if responses to similar questions became repetitive, in this instances interviews would use their judgement as to whether any new information would arise from continued line of questioning. If not then interviewers ceased the line of questioning for the remaining vignettes.

8.2.7.3 Vignette 3 – Pat

Figure 3. Vignette 3– Pat

Case 3: Pat is a **55-year** old **married woman** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. She receives treatment for cancer **directly into a vein (intravenous) once a week.** Her physician explained to her that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **24 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **6 months.** On days Pat receives treatment, she has **moderate side effects**, such as feeling tired and worn out, and it is a little difficult for her to concentrate. The treatment also has a **mild negative impact on her quality of life,** where it is a little difficult for her to perform everyday activities.

Table 12 outlines patient feedback on Vignette 3. Just under half of patients thought that Vignette 3 presented a good treatment option (n=14, 47%). These patients thought that Vignette 3 presented a good treatment option because of the treatment regimen and moderate side effects. Around a third of patients thought that Vignette 3 was somewhat similar to their own experiences (n=11, 37%), those who stated that Vignette 3 was not similar to their own experiences mainly stated this was due to difference in the mode of administration (IV) (n=6, 20%). A third of patients stated that the information in Vignette 3 was not relevant (n=10, 33%), whereas around a quarter of patients stated that the information was relevant (n=8, 27%). Nearly half of patients stated that the information in the vignette was not sufficient alone to make a treatment decision, while around a quarter thought that the information provided was sufficient (n=8, 27%). Patients who stated information was not relevant or sufficient, similarly to previous vignettes generally wanted additional information such cancer type, duration of treatment and specific side effects. Quotes illustrating patients views on which information was relevant/sufficient and why they thought Vignette 3 was a good treatment option and similar to their own views are included below.

Good treatment option:

"Yes. It is a good option. At that point, yes. It's good, it's easy to bear. Once-weekly treatment is far more bearable than once-monthly. I tell you the body can withstand and resist it much better. You'll have a couple of bad days, but otherwise, you are very tied to the hospital." (P21, Breast)

Similar to own experiences:

"I feel identified… because I've had intravenous treatment, side effects, yes, I felt... I have told you, before, in my first treatment, tired and exhausted. Concentration, well, the effects that... One of the side effects is Chemo brain. Memory, well... yes, I can see myself reflected in my first treatment!." (P10, Breast)

Information not sufficient:

"It is [relevant], except this part that's missing in all, which type of cancer it is and to which parts of the body it has spread." (P15, Melanoma of the eye)

Table 12. Patient feedback on Vignette 3

Vignette 3	Total (n=30)	%
Does Vignette 3 present a good treatment option?		
Good	14	47%
Don't know	8	27%
Not good	3	10%
Not asked	5	17%
Are the experiences similar to own experiences?		
Yes	8	27%
No	6	20%
Somewhat	11	37%
Not asked	5	17%
Is the included information relevant?		
Yes	8	27%
No	10	33%
Not asked	12	40%
Is the included information sufficient?		
Yes	8	27%
No	14	47%
Not asked	8	27%

Footnote: Not asked – refers to when a participant was not asked the question, this may have been either due to time constraints or if responses to similar questions became repetitive, in this instances interviews would use their judgement as to whether any new information would arise from continued line of questioning. If not then interviewers ceased the line of questioning for the remaining vignettes.

8.2.7.4 Vignette 4 – George

Figure 4. Vignette 4 – George

Case 4: George is a **65-year old married man** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. He receives treatment for cancer **directly into a vein (intravenous) every 2 weeks.** His physician explained to him that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **12 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **6 months.** On days George receives treatment, he has **mild side effects,** such as feeling a little tired and slightly worn out. When receiving his treatment, George does not have difficulty with his concentration. The treatment also has a **mild negative impact on his quality of life,** where it is a little difficult for him to perform everyday activities.

Table 13 outlines patient feedback on Vignette 4. Just under half of patients thought that Vignette 4 presented a good treatment option (n=13, 43%). Patients thought Vignette 4 was a good treatment option because of the mild side effects mild negative impact on quality of life. Twelve patients thought that Vignette 4 was either similar or somewhat similar to their experiences (n=12, 40%), those who thought Vignette 4 was similar to their experiences mainly stated that this was due to similarities in mode of administration and side effects. Around a quarter of patients stated that the information in Vignette 4 was relevant (n=7, 23%) (note that >50% of patients were not asked if information was relevant in Vignette 4). Similar numbers of patient's information included in Vignette 4 was sufficient (n=8, 27%) and not sufficient (n=9, 30%) (note that >40% of patients were not asked if information was relevant in Vignette 4). Patients who stated information was not relevant or sufficient had similar feedback to previous vignettes, that they wanted additional information on cancer type and specific side effects, or felt that some included information was not relevant. Quotes from patients illustrating why they thought Vignette 4 presented a good treatment option and why they considered information included not to be sufficient are included below.

Good treatment option

> *"Well, I'd consent to this one too. Well, six months, there are no serious side effects here. He may have some support, has no concentration issue, and there's a mild negative effect on his quality of life. Every two weeks, most probably when he gets it, he feels sick, and the rest, or the next day, so generally one or two days every two weeks.." (P5, NSCLC)*

Information not sufficient

> *"Man, none of the profiles say what type of cancer they have. Normally, when cancer metastasizes, whatever it is, you aren't offered any treatment other than [treatment]." (P23, Chondrosarcoma)*

Table 13. Patient feedback on Vignette 4

Vignette 4	Total (n=30)	%
Does Vignette 4 present a good treatment option?		
Good	13	43%
Don't know	6	20%
Not good	3	10%
Not asked	8	27%
Are the experiences similar to own experiences?		
Yes	6	20%
No	10	33%
Somewhat	6	20%
Not asked	8	27%
Is the included information relevant?		
Yes	7	23%
No	4	13%
Not asked	19	63%
Is the included information sufficient?		
Yes	8	27%
No	9	30%
Not asked	13	43%

Footnote: Not asked – refers to when a participant was not asked the question, this may have been either due to time constraints or if responses to similar questions became repetitive, in this instances interviews would use their judgement as to whether any new information would arise from continued line of questioning. If not then interviewers ceased the line of questioning for the remaining vignettes.

8.2.7.5 Vignette 5 – Kate

Figure 5. Vignette 5 – Kate

Case 5: Kate is a 75-year old **widowed woman** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. She receives treatment for cancer **through an injection (subcutaneous) every two weeks.** Her physician explained to her that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **36 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **12 months.** On days Kate receives treatment, she has **severe side effects**, such as feeling very tired and worn out, and it is a very difficult for her to concentrate. The treatment also has a **moderate negative impact on her quality of life,** where it is difficult for her to perform everyday activities.

Table 14 outlines patient feedback on Vignette 5. A third of patients thought that Vignette 5 presented a good treatment option, while another third were unsure (n=9, 30% both respectively). Patients thought that Vignette 5 was a good treatment option considering the age of the patient in the vignette and the survival time. Nearly half of patients felt that Vignette 5 was not similar to their own experiences (n=13, 43%). These patients felt the vignette was not similar to their experience because of the age of the patient and the presence of severe side effects. Around a third of participants stated that the information in Vignette 5 was relevant (n=9, 30%) (note that >60% were not asked if information was relevant in Vignette 5), similar numbers of patients thought that the information included in Vignette 5 was sufficient vs not sufficient (both n=8, 27% respectively). Where patients stated that information was not relevant or sufficient, this was due to wanting similar additional information to the previous vignettes such as other treatment options and specific side effects, or feeling that some included information was not relevant to making a treatment decision. Quotes illustrating why patients thought Vignette 5 was a good treatment option, and why some information was not sufficient are included below.

Good treatment option

> *"I see that this is a new typology, through a subcutaneous injection, less invasive, non-aggressive, even if the side effects are serious, I would tell you that they can be dealt with, and that it's also offering greater overall survival than the others. 36 months. At 75 years, you get a 36-month survival to metastatic cancer that only requires a subcutaneous injection. Come on! Welcome! Where to sign?" (P17, CLL)*

Information not (all) sufficient

> *"This is missing here as with all previous, whether there is some other option except these subcutaneous injections every 2 weeks. It was the same with me, nobody ever offered me any options, no. That was missing, that someone would explain all the possibilities that exist." (P14, Colon)*

Table 14. Patient feedback on Vignette 5

Vignette 5	Total (n=30)	%
Does Vignette 5 present a good treatment option?		
Good	9	30%
Don't know	9	30%
Not good	2	7%
Not asked	10	33%
Are the experiences similar to own experiences?		
Yes	4	13%
No	13	43%
Somewhat	6	20%
Not asked	7	23%
Is the included information relevant?		
Yes	9	30%
No	2	7%
Not asked	19	63%
Is the included information sufficient?		
Yes	8	27%
No	8	27%
Not asked	14	47%

Footnote: Not asked – refers to when a participant was not asked the question, this may have been either due to time constraints or if responses to similar questions became repetitive, in this instances interviews would use their judgement as to whether any new information would arise from continued line of questioning. If not then interviewers ceased the line of questioning for the remaining vignettes.

8.2.7.6 Vignette 6 – Charlie

Figure 6. Vignette 6 – Charlie

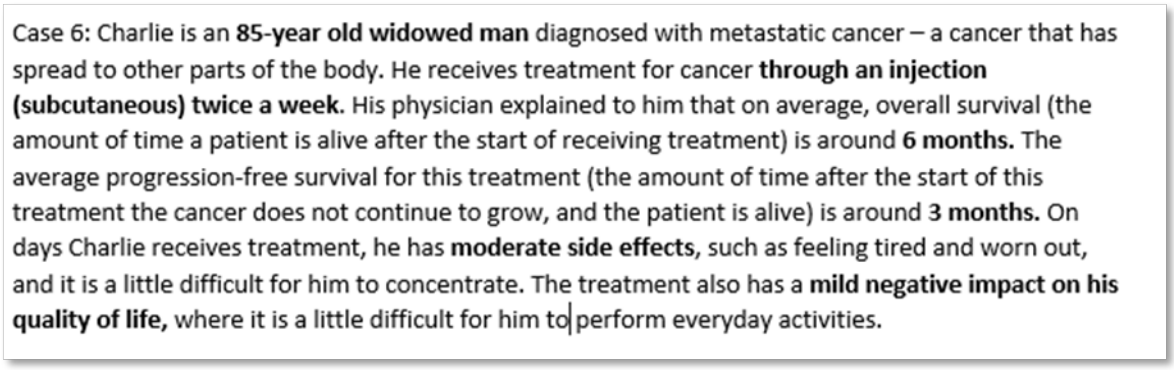


Table 15 outlines patient feedback on Vignette 6. Around a third of patients thought that Vignette 6 presented a good treatment option (n=11, 37%), whereas around a quarter thought that Vignette 6 was not a good treatment option (n=7, 23%). Patients who thought that Vignette 6 was a good treatment option attributed this mainly to the mild impact on quality of life. Patients who thought that Vignette 6 was not a good treatment option mainly attributed this to the patients' age. Half of patients felt that Vignette 6 was not similar to their own experiences (n=15, 50%), those who thought Vignette 6 was not similar to their own experiences mainly stated this was due to the age of the patient and short overall survival. Around a third of patients stated that the information in Vignette 6 was relevant (n=10, 33%), (note that > 60% of patients were not asked if information was relevant in Vignette 6). Similar numbers of patients thought that information included in Vignette 6 was sufficient (n=9, 30%) verses not sufficient (n=7, 23%) (note that >40% of patients were not asked if information was relevant in Vignette 6). Similarly to previous vignettes, patients who stated information was not relevant or sufficient thought further information on specific treatments and cancer type, or thought that some included information (such as marital status and overall survival) were not relevant. Quotes illustrating why patients thought Vignette 6 was or was not a good treatment information, and why some information was not relevant are included below.

Good treatment option:

> *"Because he is so old and has metastatic cancer, and they give him about 6 months after the start of treatment. It is better for him to have mild side effects and [impact on] his quality of life. So, a less invasive treatment that doesn't have a large negative effect is better. " (P1, MM)*

Not a good treatment option:

> *"No, it seems awful to me. A 85-year-old man, getting a treatment twice a week to live 3 or 6 months. It seems terrible to me. Anyway, I'm reading here... there are no cancer treatments that are given twice a week." (P8, Breast)*

Information not (all) relevant:

> *"To me, being a widower is still unnecessary, and we're missing information on the cancer. I mean, the primary [cancer] and where it's metastasized. It's still unnecessary, like… It really rubs me the wrong way when a doctor tells you that, "This treatment will only be effective for three months, and then we'll see." Every time, it really rubs me the wrong way. I don't know if all the people that you interview feel the same, but you know that thing about the treatment seriously bugs the crap out of me " (P20, Breast)*

Table 15. Patient feedback on Vignette 6

Vignette 6	Total (n=30)	%
Does Vignette 6 present a good treatment option?		
Good	11	37%
Don't know	6	20%
Not good	7	23%
Not asked	6	20%
Are the experiences similar to own experiences?		
Yes	1	3%
No	15	50%
Somewhat	3	10%
Not asked	11	37%
Is the included information relevant?		
Yes	10	33%
No	2	7%
Not asked	18	60%
Is the included information sufficient?		
Yes	9	30%
No	7	23%
Not asked	14	47%
Footnote: Not asked – refers to when a participant was not asked the question, this may have been either due to time constraints or if responses to similar questions became repetitive, in this instances interviews would use their		

Vignette 6	Total (n=30)	%
judgement as to whether any new information would arise from continued line of questioning. If not then interviewers ceased the line of questioning for the remaining vignettes.		

8.2.7.7 Additional feedback from qualitative interviews

The majority of participants (n=19) also spontaneously mentioned either that physicians would not typically discuss the treatment's OS/PFS, or that a physician discussing the OS/PFS of a treatment would be perceived negatively and de-moralising to patients. Some patients were aware that OS/PFS is an average number and therefore does not apply to individual cases. Illustrative quotes are provided below.

> *"Overall survival and progression-free survival, I don't think they're that important when taking a treatment. I do see it as a bit negative to tell this to patients because if you give them a treatment, you give it to them to see whether it works or not. I don't think you can tell patients with certainty that something or another will end up like this." (P1, MM)*
>
> *"For me, this information, this "The physician explained that the overall survival time is around 30 months on average. The average progression-free survival time for this type of treatment lasts for around 12 months." For me, it's "unnecessary". We don't know that. She is 35 years old, and most people are older than 35, this analysis is made for people who are maybe 70. Therefore, it's unnecessary information. And it's what burdens me the most" (P5, NSCLC)*

8.2.8 Recommendations for quantitative evidence generation phase

Following the qualitative evidence generation phase, the following considerations were made for the quantitative evidence generation phase:

- Vignettes for the quantitative phase were updated to state that information on progression free survival was a key attribute of the treatment and not information that was given by a physician.
- Most treatment attributes, patient and treatment characteristics, and other factors that may influence preference heterogeneity that were planned for the final survey were mentioned spontaneously by participants when discussing important factors in treatment decision making at the beginning of the interviews (progression free survival, quality of life, mode of administration, side effects, for example). The results of the qualitative phase confirmed that the attributes and characteristics earlier identified during the targeted literature review and by The Agency provide sufficient conceptual coverage and there are not any attributes missing.
- Feedback from patients in the quantitative phase was used to further contextualize results

of the quantitative phase in the discussion section of this report.

8.3 Quantitative evidence generation

8.3.1 Descriptive analysis

8.3.1.1 Data Collection and Statistical Analysis

For the Spain study, Global Perspectives invited potential respondents via e-mail to participate in an online survey through Global Perspectives' partner panels. Of those respondents who were eligible, 253 consented to participate and were included in the final sample.

For the Italy study, Global Perspectives invited potential respondents via e-mail to participate in an online survey through Global Perspectives' partner panels. Of those respondents who were eligible, 250 consented to participate and were included in the final sample.

For the Croatia study, Global Perspectives invited potential respondents via e-mail to participate in an online survey through Global Perspectives' partner panels. Of those respondents who were eligible, 100 consented to participate and were included in the final sample.

To be eligible for inclusion in the study, respondents had to meet the following criteria as stated in section 6.3.1.

Table 16 presents the respondents' demographic characteristics. The final sample included 603 respondents who met the inclusion criteria, provided informed consent, and whose surveys were considered complete. The mean patient age was 54 years, 54% had stage I early-stage cancer where the tumour has not grown deeply into nearby tissues, and 46% were stage II, III, IV and Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia. Approximately, 42% of the respondents were currently receiving treatment for their cancer, while approximately 61% of the respondents had received treatment for cancer in the past (for more details on sample composition, see **Appendix 6: Demographic Characteristics of Respondents in Spain, Italy, and Croatia**

Table 16: Demographic Characteristics of Respondents (N = 603)

Characteristic	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
Age, Mean (SD)	53 (12.4)	55 (12.17)	55 (13.86)	54.3 (12.55)
Stage of cancer				
Stage I - Early-stage cancer where the tumour has not grown deeply into nearby tissues	159 (62.85%)	132 (52.80%)	35 (35.00%)	326 (54.06%)
Stages II & III – Larger cancers where the tumour has grown more deeply into nearby tissue and may have spread to lymph nodes, but not to other parts of the body	76 (30.04%)	101 (40.40%)	39 (39.00%)	216 (25.82%)
Stage IV – Advanced or metastatic cancer, where cancer has spread to other parts of the body	15 (5.93%)	16 (6.40%)	23 (23.00%)	54 (8.96%)
Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia	3 (1.19%)	1 (0.40%)	3 (3.00%)	7 (1.16%)
Do you currently receive treatment for cancer?				
Yes	100 (39.53%)	93 (37.20%)	60 (60.00%)	253 (41.96%)
No	153 (60.47%)	156 (62.40%)	40 (40.00%)	349 (57.88%)
Have you received any previous treatments for cancer since you were first diagnosed?				
Yes	135 (53.36%)	154 (61.60%)	76 (76.00%)	365 (60.53%)
No	118 (46.64%)	95 (38.00%)	24 (24.00%)	237 (39.30%)

SD = standard deviation.

8.3.2 Primary Analyses

8.3.2.1 Model Specification

The Spain, Italy and Croatia DCE data were analysed using an RPL model that relates respondents' choices to the differences in the attribute levels across the alternatives in each choice question[23]. The RPL model mitigates potential estimation bias from unobserved preference heterogeneity among respondents by estimating a distribution of preferences for each

mean preference parameter[24,25].

An RPL model requires a large sample size. We analysed country-specific preference data and then explored the possibility of pooling Spain (N=253), Italy (N=250) and Croatia (N = 100) preference data to have a larger sample size. Before combining the 3 data sets, we tested whether data from each country could be pooled into one larger data set.

A procedure to test whether preference data from different sources could be combined, known as Swait and Louviere test [26] was used. The Swait and Louviere (1993) test assumes that data are analysed using a conditional MNL model for the different countries; therefore, the analysis does not account for heterogeneity in preferences across respondents. Based on this assumption, we analysed the Spain, Italy and Croatia preference data using the MNL models to test (1) whether preferences were similar, followed by a heteroscedastic MNL model for the combined data set that tested (2) whether scale heterogeneity existed across the 3 country data sets. The Swait and Louviere (1993) test results found no statistically significant difference in preferences across Spain, Italy and Croatia and no scale heterogeneity across countries. The results suggested that preference data from Spain, Italy and Croatia could be pooled together.

Following this procedure, we then estimated an RPL model for Spain (N=253), Italy (N=250) and Croatia (N = 100) preference data with a larger sample size (N=603).

To further explore preference heterogeneity and differences in preferences among respondents with different characteristics in the pooled sample for the 3 countries, we conducted additional exploratory analyses using the modelling approach. The LC model is an extension of the MNL that identifies classes of respondents based on unobserved or “latent” heterogeneity in preferences [27]. The researcher assumes a discrete, rather than a continuous, mixing distribution to describe preference heterogeneity among respondents in the sample. The statistical analysis of the DCE data was conducted following good research practice guidelines published by ISPOR [23]. The analyses were performed in STATA 17 (StataCorp; College Station, Texas).

The results reported in this report are for the combined preference data from Spain (N=253), Italy (N=250) and Croatia (N = 100), estimated using an RPL model.

Table 17 summarizes the variables in the RPL model, which include a variable for each attribute level. All the levels in each attribute are effects-coded. With effects coding, 0 indicates the mean effect across all attribute levels rather than the omitted level, as in dummy coding [28]. This procedure produces parameter estimates for all levels of an attribute, where the parameter on the omitted level is the negative sum of the parameters on the included levels. The resulting log odds parameter estimates from the RPL model can be interpreted as preference weights that indicate the relative strength of preferences for each attribute level. The delta method was used to calculate standard errors for the preference weight for each omitted attribute level [28].

Table 17: Model Variables for Estimating Preference Weights

Variable Label	Variable Definition
TIM1 TIM2 TIM3 TIM4	Effects-coded variables for **Time until progression of disease** (the amount of time after the start of this treatment the disease is under control) [TIM1 = 3 months; TIM2 = 6 months; TIM3 = 9 months; and TIM4 = 12 months]. TIM1 was omitted for model identification.
ADMIN1 ADMIN2	Effects-coded variables for **Treatment administration** (how the treatment is administered) (ADMIN1 = Oral (pill/tablet); ADMIN2 = Non-oral). ADMIN1 was omitted for model identification.
LOC1 LOC2	Effects-coded variables for **Location of treatment** (where the treatment is taken, for instance at a hospital/clinic or at home*)* (LOC1 = At home; LOC2 = At hospital / clinic). LOC1 was omitted for model identification.
SIDEEF1 SIDEEF2 SIDEEF3	Effects-coded variables for **Impact of side effects on quality of life** (the severity of the impact of treatment side effects on daily activities) (SIDEEF 1 = Mild side effects (e.g., feeling a little tired, some hair loss, etc.) that do not limit everyday activities (preparing meals, shopping for groceries or clothes, using the telephone, managing money); SIDEEF 2 = Moderate side effects (e.g., feeling tired, hair loss, a little nausea and diarrhea, etc.), with occasional limits on everyday activities (difficulty with preparing meals, shopping for groceries or clothes, using the telephone, managing money); and SIDEEF 3 = Severe side effects but are not life threatening (e.g., feeling very tired, hair loss, vomiting and diarrhea, appetite loss, flu-like symptoms, pain, etc.), with some limits on everyday activities (difficulty with preparing meals, shopping for groceries or clothes, using the telephone, managing money) and self-care (bathing, dressing, taking medication). SIDEEF1 was omitted for model identification.

Based on the specification assumed for each attribute, the following preference model was estimated:

Eq (1) $V = \beta_{TIM1} \times TIM1 + \beta_{TIM2} \times TIM\ 2 + \beta_{TIM3} \times TIM\ 3 + \beta_{TIM4} \times TIM\ 4 +$

β_{ADMIN1} x ADMIN1 + β_{ADMIN2}× ADMIN2 +

$\beta_{LOC1} \times$ LOC1 + $\beta_{LOC2} \times$ LOC +

$\beta_{SIDEEF1} \times$ SIDEEF1 + $\beta_{SIDEEF2} \times$ SIDEEF2 + $\beta_{SIDEEF3} \times$ SIDEEF3,

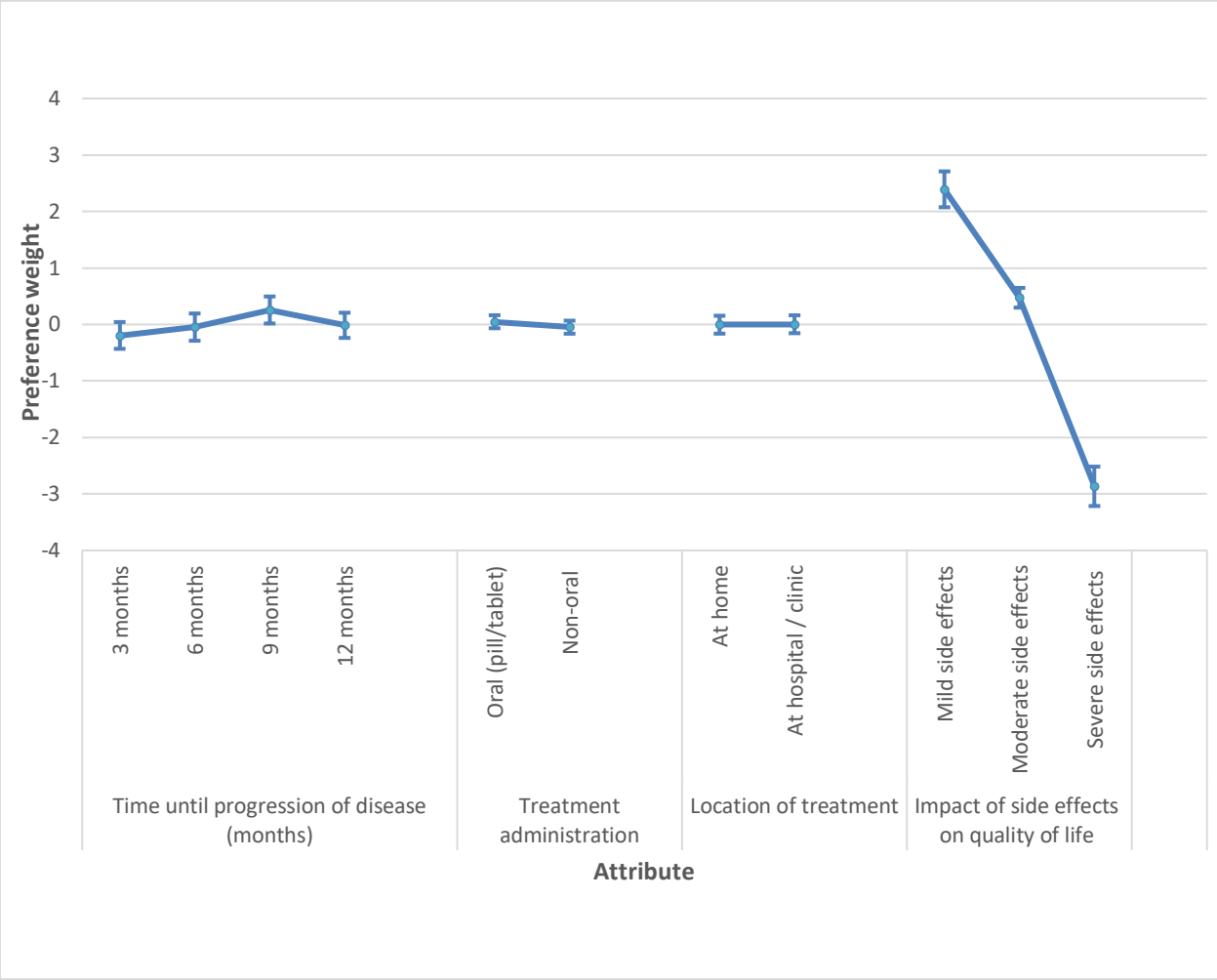
where *V* is the systematic indirect utility for a treatment profile (specified as a function of the attributes as in equation 1), β is a parameter estimate for each attribute level. A Wald χ^2 test was used to determine the statistical significance of differences between adjacent attribute levels for each attribute. A *p* value less than or equal to 0.05 was considered statistically significant. The results are reported using the 95% confidence interval, and the results with confidence intervals that include 0 are not statistically significant.

8.3.2.2 Preference Weights

Using the results from the RPL model, preferences for attribute levels were ordered as expected, with better levels being preferred to worse levels. Respondents preferred treatment with less impact of side effects on quality of life (severity of the impact of treatment side effects on daily activities); treatment with more time in months until progression of disease (the amount of time after the start of this treatment the disease is under control); treatment that is oral (pill/tablet) compared with non-oral treatment; and location of treatment (at home or at hospital/clinic), in that order. A Wald χ^2 test was used to determine the statistical significance of differences between adjacent attribute levels. Most of the levels within each attribute were not statistically different from one another (p <0.05), except for the difference between time in months until progression of disease of 9 months and 3 months (p <0.027) and the difference between the impact of side effects on quality of life of severe side effects and moderate side effect; severe side effects and mild side effects; and moderate side effects and mild side effects (p <0.001).

Figure 7 shows the normalized mean preference weight estimates for each attribute level (the estimated preference weight values from the RPL model are the log odds and are presented in Table 18. The vertical bars around each mean parameter estimate represent the 95% confidence interval. The preference weights indicate the ranking of levels within each attribute (i.e., a higher preference weight indicates that a level is more preferred).

Figure 7: Attribute Preference Weights for Respondents (N = 603)



Note: The vertical bars surrounding each mean preference weight denote the 95% confidence interval of the point estimate (preference weights computed by the delta method for the level omitted in estimation for each attribute; see Table 17).

The change in utility associated with a change in the levels of each attribute is represented by the difference between the preference weights for those levels (Table 18). Larger differences between preference weights indicate that respondents viewed the change as having a relatively greater effect on overall utility. For example, Table 18 shows that treatment with less impact of side effects on quality of life from severe side effects and moderate side effects yielded a change in utility of approximately 3.338; severe side effects and mild side effects had a utility of 5.257; and moderate side effects and mild side effects yielded a change in utility of approximately 1.919. The change in impact of side effects on quality of life from moderate to mild side effects was approximately 2.7 times as important as the change in impact of side effects on quality of life from severe to mild side effects.

The relative importance of the change in impact of side effects on quality of life is mostly larger than the relative importance of changes in other attributes across the full range of levels presented for each attribute.

Changing a treatment from non-oral to oral (pill/tablet) yielded a change in utility that was approximately 0.097; and a change in location of treatment from hospital/clinic to home yielded a utility of approximately −0.008, albeit not statistically significant (p = 0.408 and 0.958, respectively).

Table 18: Attribute Relative Importance Changes (N = 603)

Attributes	From Level	To Level	Change in Utility (Difference Calculation)	P Value
Time until progression of disease (months)	6 months	3 months	−0.147	0.375
	9 months	3 months	−0.45	0.027
	12 months	3 months	−0.179	0.411
	9 months	6 months	−0.304	0.183
	12 months	6 months	−0.033	0.868
	12 months	9 months	0.271	0.077
Treatment administration	Non oral	Oral (pill/tablet)	0.097	0.408
Location of treatment	At hospital/clinic	At home	−0.008	0.958
Impact of side effects on quality of life	Moderate side effects	Mild side effects	1.919	<0.001
	Severe side effects	Mild side effects	5.257	<0.001
	Severe side effects	Moderate side effects	3.338	<0.001

8.3.2.3 Conditional Relative Attribute Importance

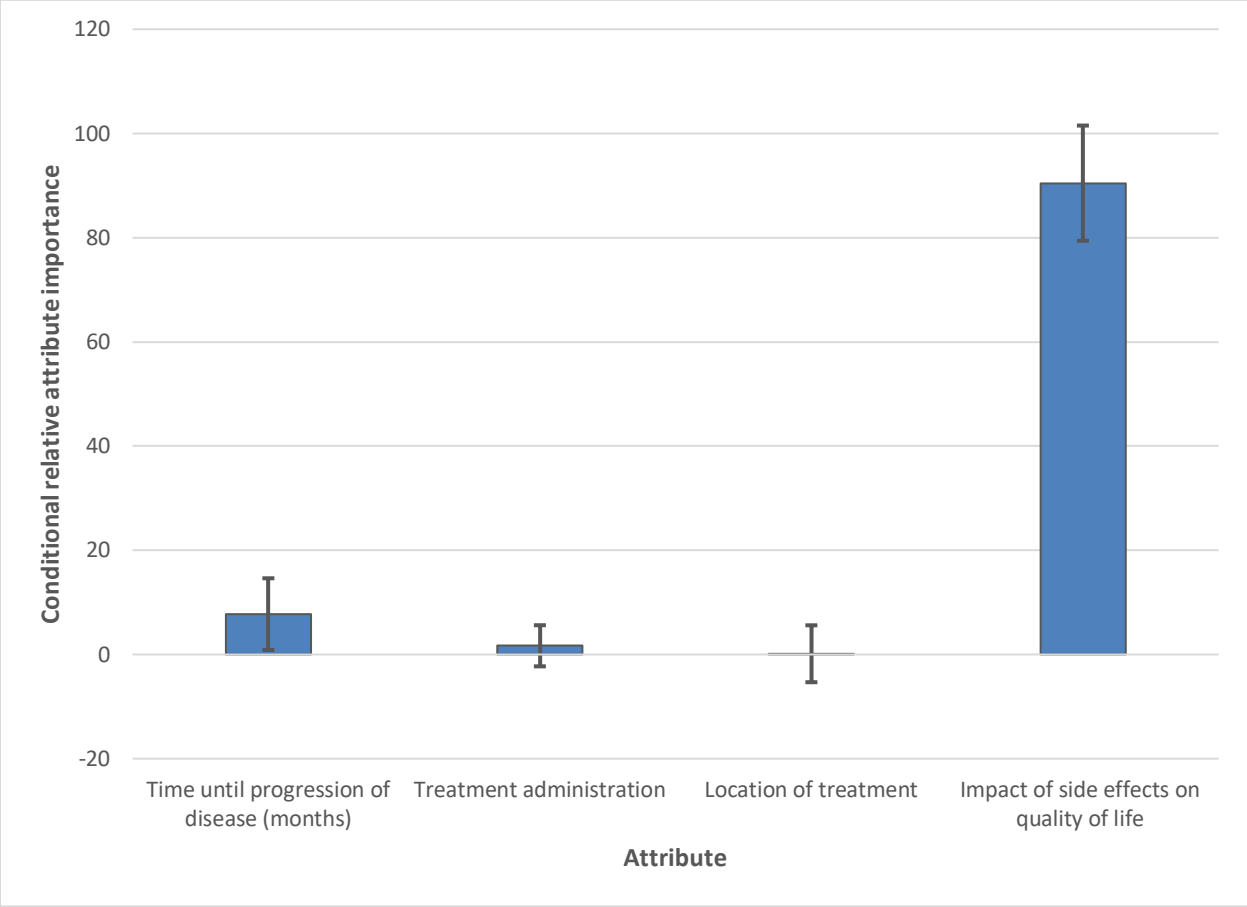
The conditional relative importance for an attribute is calculated as the difference between the preference weights for the most- and least-preferred levels for that attribute. The difference between the most-preferred and least-preferred levels of an attribute is a measure of the overall importance of that attribute relative to the other attributes in the study across the full range of levels for each attribute.

All estimates were reported with 95% confidence intervals.

Figure 8 shows the conditional relative attribute importance of changing each attribute from the least-preferred level to the most-preferred level (similar to the calculations in Table 18). These

differences are summed across attributes and the sum is scaled to 100. Over the ranges presented in the survey, the change in impact of side effects on quality of life from severe to mild side effects yielded the largest change in utility of approximately 5.257, as shown in Figure 8. This was followed by treatment with more time in months until progression of disease (the amount of time after the start of this treatment the disease is under control); treatment that is oral (pill/tablet) compared with non-oral treatment; and location of treatment (at home or at hospital/clinic), in that order. As noted earlier, only the difference between time in months until progression of disease of 9 months and 3 months (p <0.027) and the difference between the impact of side effects on quality of life of severe side effects and moderate side effect; severe side effects and mild side effects; and moderate side effects and mild side effects (p <0.001) were estimated to be statistically significantly different.

Figure 8: Conditional Relative Attribute Importance for Respondents (N = 603)



Note: The conditional relative importance is the difference between the preference weights on the most influential attribute level and the least influential attribute level. These differences are summed across attributes and the sum is scaled to 100. The conditional importance of each attribute is a percentage of this total. The vertical bars surrounding each relative importance weight estimate denote the 95% CI around the point estimate (computed by the delta method).

8.3.3 Secondary Analyses

8.3.3.1 Latent Class Model

As noted in the previous section, the RPL model did not test for systematic differences in preferences among Spain, Italy and Croatia respondents and does not provide information about the correlation between preference heterogeneity and observed characteristics of the respondents in these countries. To further explore preference heterogeneity and differences in preferences among respondents with different characteristics in the 3 countries, we conducted additional exploratory analyses using the LC modelling approach [27]. The first step in conducting an LC analysis is to determine the optimal number of preference classes for the data. Information criteria based on maximizing the log-likelihood of the model and minimizing the number of parameters to be estimated should be used in determining the optimal number of preference classes in the data. We considered the following information criteria to determine the appropriate number of preference classes: the Bayesian information criteria (BIC) [29], the Akaike information criteria (AIC) [30], and the AIC3, which is a variation of the AIC that penalizes more for the number of parameters used in estimation [31]. A 3-class LC model was the optimal level based on the BIC. In general, the literature suggests the use of the BIC as a good indicator for class enumeration for LC modelling over the other information criteria [32]. Accordingly, a 3-class LC model was considered optimal for this data set.

Preference weights for each attribute level and conditional relative importance estimates for all attributes are presented in Figure 9 and Figure 10, respectively. The difference in the preference estimates for each class in the 3-class LC model and the probability that any individual in the sample is in each class can be summarised as follows:

Class 1 (blue, 14.5%): strongly valued changes in months of time until progression of disease from 12 months to 3 months followed by impact of side effects on quality of life

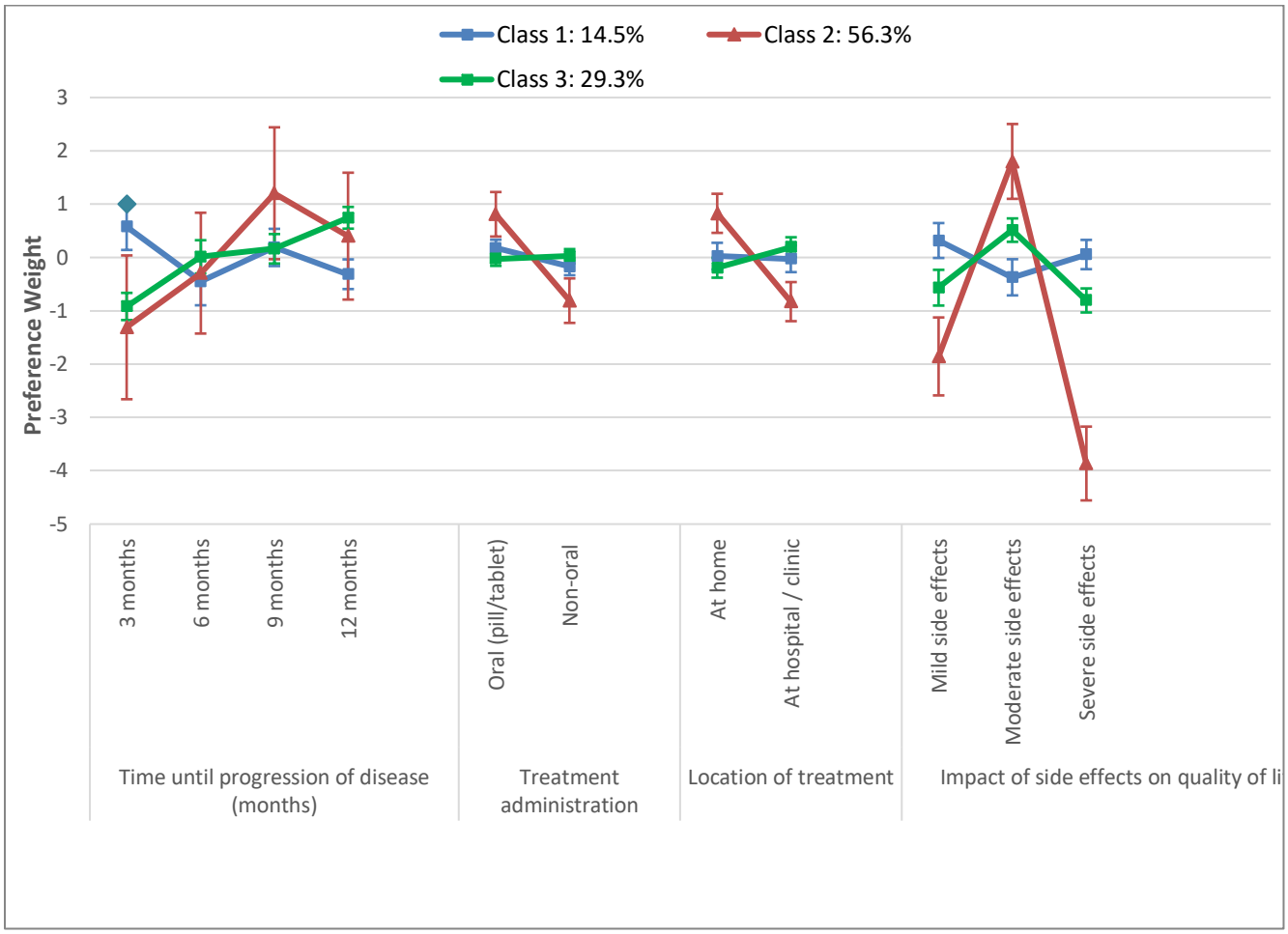
Class 2 (orange, 56.3%): was risk averse, concerned with the impact of side effects on quality of life followed by changes in months of time until progression of disease from 12 months to 3 months

Class 3 (green, 29.3%): was more risk averse, more concerned with the impact of side effects on quality of life followed by changes in months of time until progression of disease from 12 months to 3 months.

It can be noted in Figure 9 that class 1 respondents had preferences for 3 months as time until progression of disease over any longer periods. This could perhaps be that respondents did not fully understand the attribute as suggested in Table 19 that respondents who found the survey relatively more difficult were more likely to be in class 1 compared to class 2.

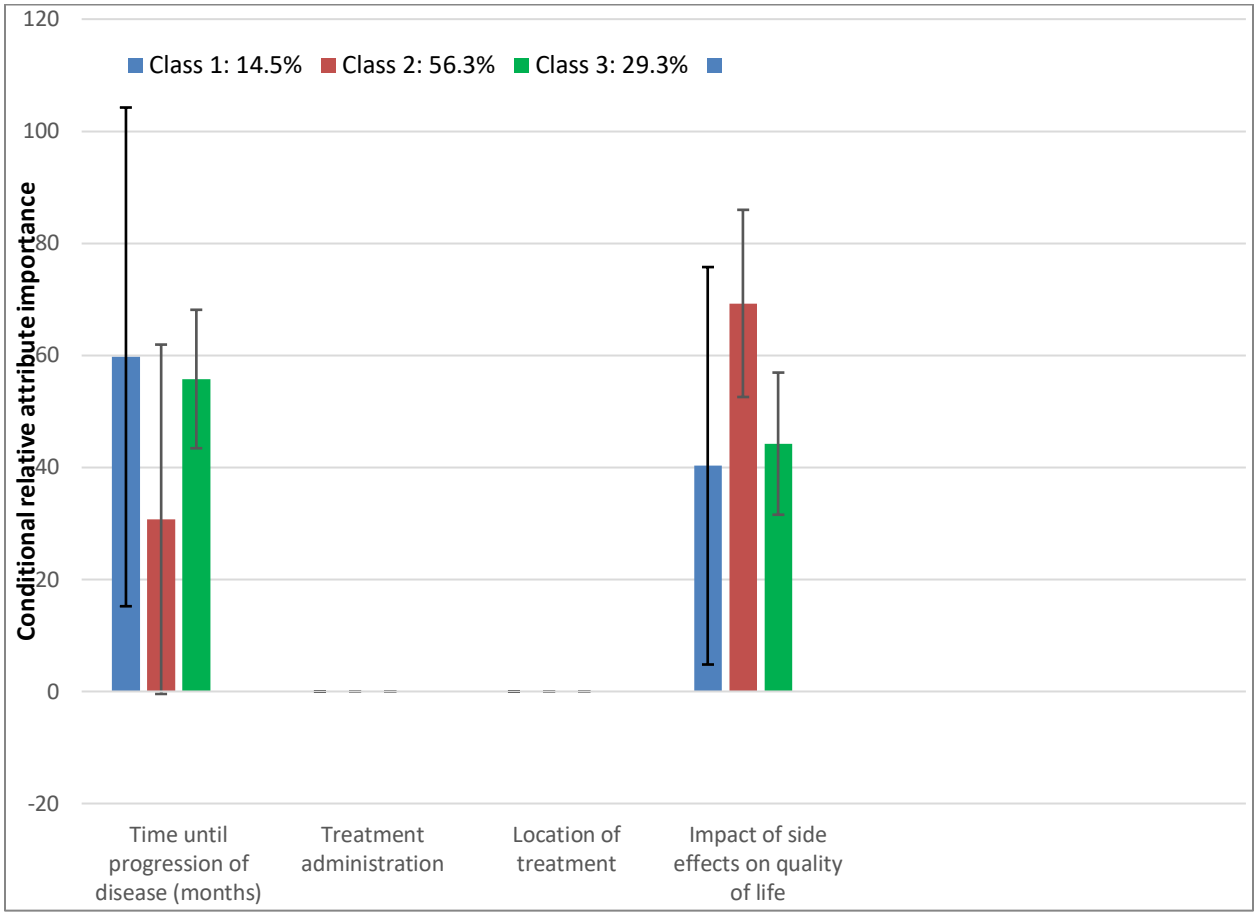
All individuals in each of the 3 classes were not concerned with how the treatment was administered or location of treatment.

Figure 9: Attribute Relative Importance Changes (N=603)



Note: The vertical bars surrounding each mean preference weight denote the 95% confidence interval of the point estimate (preference weights computed by the delta method for the level omitted in estimation for each attribute; see Table 17)

Figure 10: Conditional Relative Importance (N=603)



Note: The conditional relative importance is the difference between the preference weights on the most influential attribute level and the least influential attribute level. These differences are summed across attributes and the sum is scaled to 100. The conditional importance of each attribute is a percentage of this total. The vertical bars surrounding each relative importance weight estimate denote the 95% CI around the point estimate (computed by the delta method).

8.3.3.2 Modeling the Probability of Class Membership

We conducted an additional analysis to include covariates in the class membership probability function of the LC model to explore the relationship between respondent characteristics and the probability of being in each of the three preference classes. However, because of the collinearity of some of the data in the survey questions and the fact that preference heterogeneity may have many possible causes, finding the correct model specification to predict the probability of class membership is not always straightforward and often requires testing different combinations of explanatory variables. When modeling the probability of class membership, the model estimates preference weights of each class and the probability of class membership simultaneously; therefore, small differences between the preference weight results and class membership probabilities estimated with and without including covariates to explain class membership are

possible. We explored whether the variables that defined the prespecified subgroup pairs used in the RPL subgroup analysis were statistically significant predictors of class membership.

The results of the analysis of class probability as a function of the prespecified subgroup pairs used in the RPL subgroup analysis are presented in Table 19, in which each covariate included to explain the class membership is associated with a γ estimate.

Table 19: Membership Probability Model for Class 1 and Class 2 Over Class 3 in the Latent Class Main-Effects Model, Including Patient Characteristics Used for the Subgroup Analysis (N = 603)

	Class 1		Class 2	
Covariate	γ Estimate	*P* Value	γ Estimate	*P* Value
Constant	−1.335	0.001	−0.518	0.064
Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	**Reference**		**Reference**	
Stage I	0.893	0.004	0.720	0.001
Under/postgraduate qualification	**Reference**		**Reference**	
Secondary/high school/trade qualification	0.236	0.442	0.182	0.400
Neither easy nor difficult, somewhat difficult, very difficult	**Reference**		**Reference**	
Easy, somewhat easy	0.118	0.691	1.054	<0.001
No cancer relapse	**Reference**		**Reference**	
Cancer relapse	−0.216	0.566	−0.227	0.388
Couple with/without children, other	**Reference**		**Reference**	
Single person/parent	0.342	0.327	0.368	0.150

For the model to be identified, class 3 is omitted and is the reference for the model estimates. Therefore, a positive and significant γ estimate for the constant and each covariate in the class membership probability model is interpreted as increasing the probability that a respondent with this characteristic will be in class 1 or class 2 rather than class 3, compared with the baseline respondent (for which each covariate is equal to 0). Covariates such as cancer stage, and

comprehension of the DCE tasks (included in Table 19), were significantly different from 0, meaning that these respondent characteristics explained the class membership probability. However, it is also possible that we do not have enough power in the data to identify the small effect on the membership probability.

Several interesting significant coefficients are observed in the covariates used for the class membership probability model. Respondents with stage I disease are significantly likely to be in class 1 and class 2 (strongly valued changes in months of time until progression of disease from 12 months to 3 months and risk averse, concerned with the impact of side effects on quality of life. Respondents who understood the DCE tasks are likely to be in class 2 (risk averse, concerned with the impact of side effects on quality of life followed by changes in months of time until progression of disease from 12 months to 3 months).

8.3.3.3 Subgroup analyses

Although the RPL model controls for unobserved preference heterogeneity among respondents in the sample, it does not identify observable characteristics that may be systematically associated with such differences in preferences. We explored preferences across the following five mutually exclusive groups to test for systematic difference in attribute preferences (all variables are self-reported):

1. Cancer stage I versus stage II, III, IV and Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia
2. Education (secondary/high school/trade versus under/postgraduate)
3. Comprehension of the DCE exercise (Easy, somewhat easy versus neither easy nor difficult, somewhat difficult, very difficult)
4. Cancer relapse versus no cancer relapse
5. Current living situation (single person/parent versus couple with/without children, other)

Subgroups were analysed using an RPL model with the same specification as the full sample model. For each mutually exclusive set of subgroups in the sample, we created a dummy variable that was equal to 1 if the respondent belonged to the subgroup and interacted the dummy variable with each of the explanatory variables in equation 1. Each interaction term is the product of the dummy-coded variable and one of the treatment attribute-levels in equation 1. The parameter on each of these interaction terms can be interpreted as the difference between the subgroup and the corresponding attribute level. Equation 2 shows the preference model for any subgroups (S):

Eq (2) $V = \beta_{TIM1} \times TIM1 + \beta_{TIM2} \times TIM2 + \beta_{TIM3} \times TIM3 + \beta_{TIM4} \times TIM4 +$

$\beta_{ADMIN1} \times ADMIN1 + \beta_{ADMIN2} \times ADMIN2 +$

$\beta_{LOC1} \times LOC1 + \beta_{LOC2} \times LOC2 +$

$\beta_{SIDEEF1} \times SIDEEF1 + \beta_{SIDEEF2} \times SIDEEF2 + \beta_{SIDEEF3} \times SIDEEF3 +$

$\beta_{TIM1} \times TIM1 \times S + \beta_{TIM2} \times TIM2 \times S + \beta_{TIM3} \times TIM3 \times S + \beta_{TIM4} \times TIM4 \times S +$

$\beta_{ADMIN1} \times ADMIN1 \times S + \beta_{ADMIN2} \times ADMIN2 \times S +$

$\beta_{LOC1} \times LOC1 \times S + \beta_{LOC2} \times LOC2 \times S +$

$\beta_{SIDEEF1} \times SIDEEF1 \times S + \beta_{SIDEEF2} \times SIDEEF2 \times S + \beta_{SIDEEF3} \times SIDEEF3 \times S,$

where *V* is the systematic indirect utility for a treatment profile (specified as a function of the attributes as in equation 2), β is a parameter estimate for each attribute level, and S is the dummy variable equal to 1 if the respondent is a part of the subgroup. Preference weights for subgroups represented by the interaction terms are calculated as the sum of estimated parameters for the baseline and interaction term parameters. For all subgroups, we estimated equation 2.

Differences in preferences between subgroups were tested through a log-likelihood χ^2 test of joint statistical significance of all the interaction terms (p <0.05). A Wald χ^2 test was used to determine the statistical significance of differences between adjacent attribute levels (p <0.05) for each attribute.

8.3.3.4 Subgroups Preference Weights

We tested for differences in preferences by stage of cancer, respondents' education, whether respondents understood the DCE exercise, whether their cancer has ever relapsed and their current living situation. Of these 5 subgroups, only the differences between stage of cancer, respondents' education, and whether respondents understood the DCE exercise were statistically significantly different. For the subgroups in which no difference in preferences was detected, the test may indicate that there was indeed no difference, or the sample size of the subgroups may have been too small to detect differences in preferences. The sample size of respondents who had cancer relapsed (n = 114) was smaller than that of those who had cancer not relapsed (n = 479). The sample size of respondents who were single persons or parent (n = 149) was smaller than that of those were a couple with or without children/other (n = 449). These small sample sizes for the subgroup pairs may have influenced the ability to detect significant differences between attribute levels.

Table 20 presents the 5 subgroups tested with the P values from the log-likelihood χ^2 test of joint statistical significance.

Table 20: Descriptions of the Subgroups Analysed (N = 603)

Subgroup Pair	Subgroup Description	Sample Size	*P* Value[a]
Self-reported cancer stage	Stage I	326	0.0027
	Stage II, III, IV and Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia	277	
Education [b]	Secondary school/high school/trade	348	0.0180
	Under/postgraduate	249	
Comprehension of the DCE exercise	Easy, somewhat easy	379	0.0002
	Neither easy nor difficult, somewhat difficult, very difficult	224	
Cancer relapse	Relapsed	114	0.2170
	Not relapsed	479	
Current living situation	Single person/parent	149	0.1670
	Couple with/without children, other	449	

[a] *P* values from the log-likelihood χ^2 test of joint statistical significance.

[b] 6, 10 and 5 respondents were not included in the education, cancer relapse and current situation subgroups analysis, respectively because they did not indicate their responses (missing values).

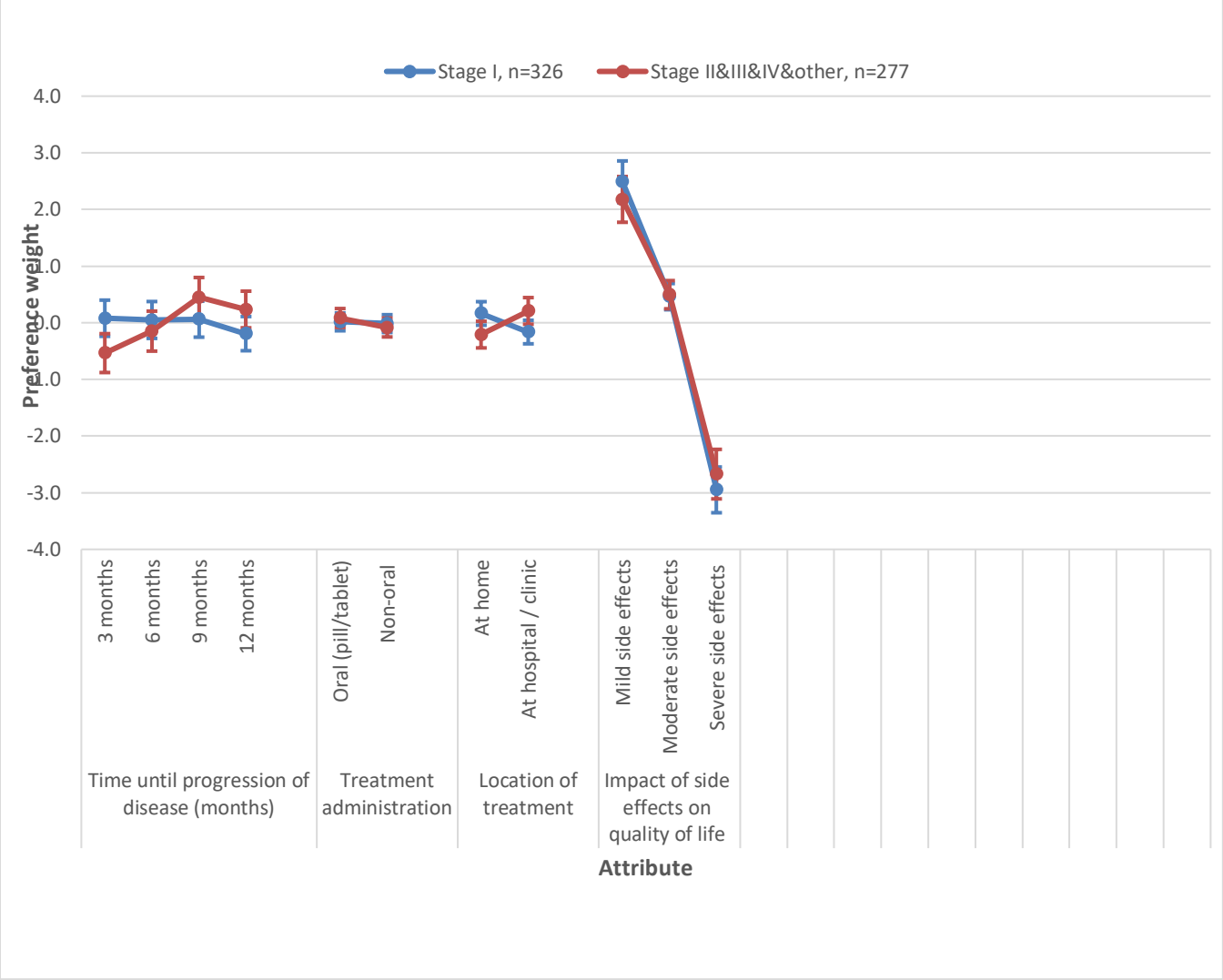
Respondents With Stage I Cancer Versus Respondents with Stage II, III, IV and Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia

Respondents were asked to state the stage of cancer they are currently diagnosed with. A total of 326 respondents indicated that they had Stage I – early-Stage cancer where the tumour has not grown deeply into nearby tissues, while 216 respondents indicated that they had Stages II and III – larger cancers where the tumour has grown more deeply into nearby tissue and may have spread to lymph nodes, but not to other parts of the body. Fifty-four respondents reported that their cancer was Stage IV – advanced or metastatic cancer, where cancer has spread to other parts of the body, and 7 respondents had Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia. Figure 11 shows the normalized mean preference weights for each attribute level for the 2 cancer stage subgroups. The test for joint significance of the interaction terms was statistically significant ($p = 0.0027$), indicating that respondents who had Stage I cancer had statistically systematically different preferences compared with those who had Stage II, III, IV and Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia.

Both sets of respondents wanted to avoid any level of impact of side effects on quality of life and statistically significant differences were observed between wanting to avoid severe and moderate side effects. Respondents with Stage I cancer had no statistically significant differences in changes between time until progression of disease (months); treatment administration; and location of treatment whereas respondents with Stage II, III, IV and Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia had statistically significant differences for changes in time until progression of disease (months) from 9 months to 3 months and 12 months to 3 months.

Estimated preference weight values from the RPL model based on this subgroup analysis is presented in Table 21.

Figure 11: Attribute Relative Importance Changes (N=603)



Note: The vertical bars surrounding each mean preference weight denote the 95% confidence interval of the point estimate (preference weights computed by the delta method for the level omitted in estimation for each attribute)

Table 21: Preference Weights for Cancer Stage I versus Stage II, III, IV and stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia

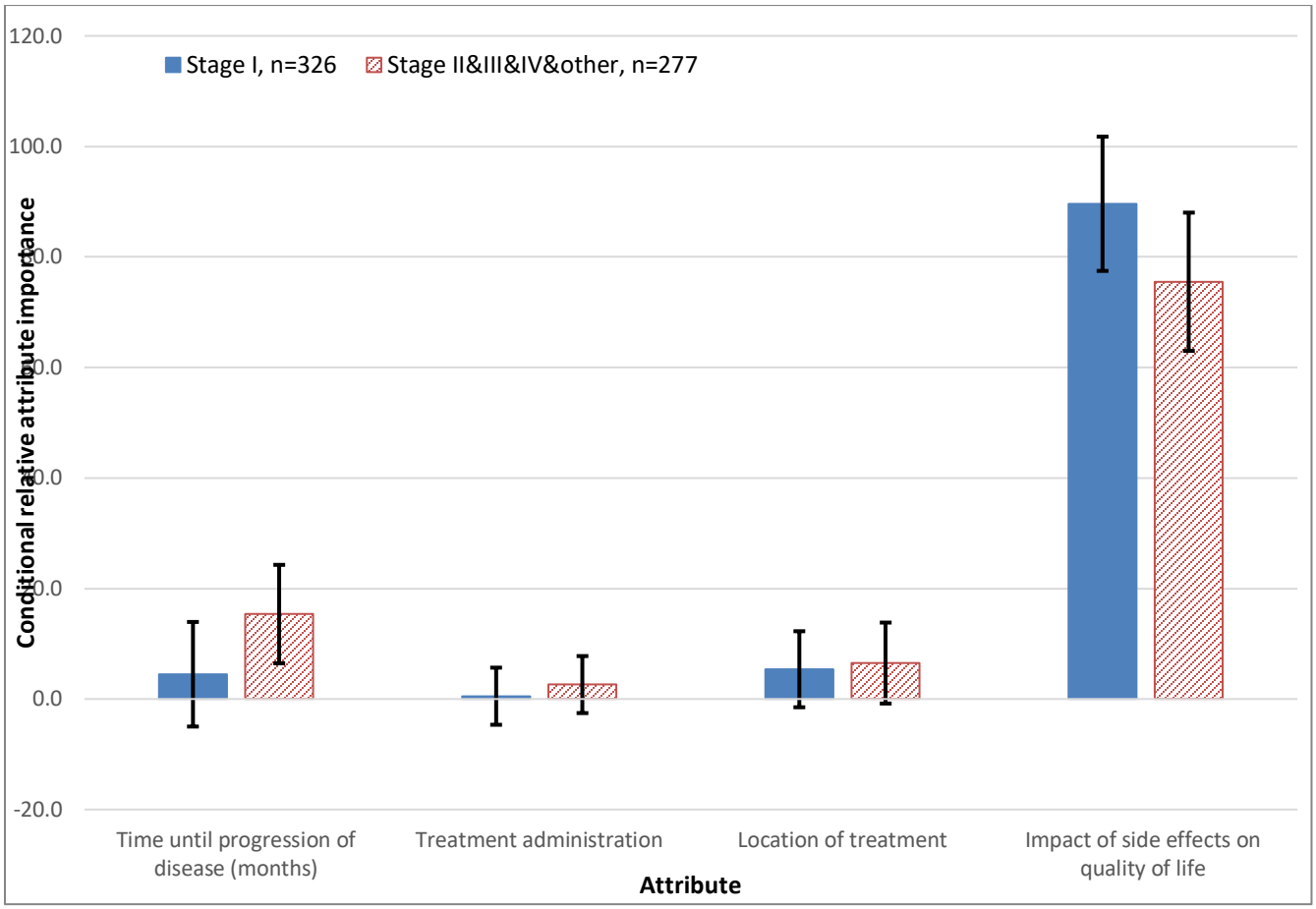
Attributes	From Level	To Level	Change in Utility (Difference Calculation)	*P* Value
Cancer Stage 1				
Time until progression of disease (months)	6 months	3 months	0.031	0.889
	9 months	3 months	0.017	0.951
	12 months	3 months	0.272	0.353
	9 months	6 months	−0.014	0.964
	12 months	6 months	0.242	0.371
	12 months	9 months	0.255	0.204
Treatment administration	Non oral	Oral (pill/tablet)	0.031	0.849
Location of treatment	At hospital/clinic	At home	0.327	0.125
Impact of side effects on quality of life	Moderate side effects	Mild side effects	2.027	<0.001
	Severe side effects	Mild side effects	5.438	<0.001
	Severe side effects	Moderate side effects	3.411	<0.001

Attributes	From Level	To Level	Change in Utility (Difference Calculation)	*P* Value
Cancer Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia				
Time until progression of disease (months)	6 months	3 months	−0.388	0.112
	9 months	3 months	−0.987	0.001
	12 months	3 months	−0.77	0.015
	9 months	6 months	−0.599	0.075
	12 months	6 months	−0.382	0.176
	12 months	9 months	0.216	0.339
Treatment administration	Non oral	Oral (pill/tablet)	0.168	0.321
Location of treatment	At hospital/clinic	At home	−0.418	0.082
Impact of side effects on quality of life	Moderate side effects	Mild side effects	1.682	<0.001
	Severe side effects	Mild side effects	4.849	<0.001
	Severe side effects	Moderate side effects	3.167	<0.001

Both sets of respondents placed the most relative importance on the impact of side effects on quality of life from severe to mild side effects. However, the impact of side effects on quality of life were more important to respondents with Stage II, III, IV and Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia relative to the other attributes than for respondents with Stage I disease.

Figure 12 below present the conditional relative attribute importance of changing each attribute from the least-preferred level to the most-preferred level. Comparing the height of the bars for each subgroup in Figure 12 provides an estimate of the relative importance of one attribute compared with the other attributes for the subgroup.

Figure 12: Conditional Relative Importance for Cancer Stage I versus Stage II, III, IV and stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia (N=603)



Note: The conditional relative importance is the difference between the preference weights on the most influential attribute level and the least influential attribute level. These differences are summed across attributes and the sum is scaled to 100. The conditional importance of each attribute is a percentage of this total. The vertical bars surrounding each relative importance weight estimate denote the 95% CI around the point estimate (computed by the delta method).

Respondents With Secondary School, High School/Trade Qualifications Versus Respondents With Undergraduate/Postgraduate Qualifications

In the full sample (n=603), 348 respondents indicated that they had secondary school/high school/trade qualifications and 249 respondents indicated that they had either an undergraduate or a postgraduate qualification. Figure 13 shows the normalized mean preference weights for each attribute level for the 2 subgroups related to respondents' education. The interaction terms were jointly statistically significant ($p = 0.0180$), indicating that respondents with secondary school/high school/trade qualifications had statistically systematically different preferences compared with those of respondents with either an undergraduate or a postgraduate qualification.

Both sets of respondents wanted to avoid severe and moderate impact of side effects on quality of life with statistically significantly different preferences between severe and moderate side effects, severe and mild side effects, and between moderate and mild side effects.

Respondents with secondary school/high school/trade qualifications did not have statistically significant preferences for any changes in time until progression of disease (months), treatment administration, and location of treatment whereas respondents with an undergraduate or postgraduate qualification had statistically significant differences in preferences for changes in time until progression of disease (months) from 6 months to 3 months, 9 months to 3 months and 12 months to 3 months. Table 22 below shows the estimated preference weight values from the RPL model based on this subgroup analysis. The results are also presented in Figure 13 and Figure 14.

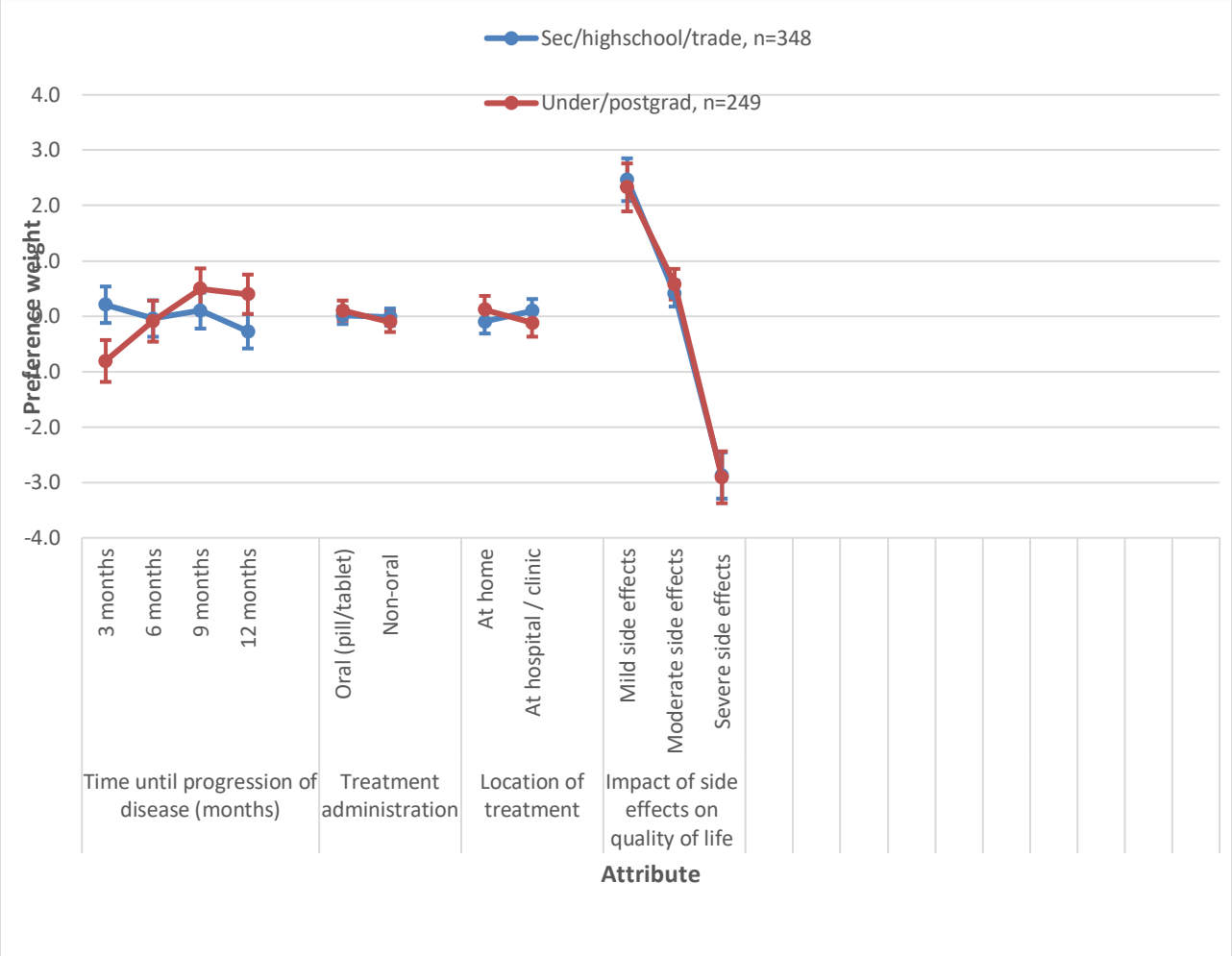
Table 22: Respondents With Secondary School/High School/Trade Qualifications Versus Respondents With Undergraduate/Postgraduate Qualifications (N=603)

Attributes	From Level	To Level	Change in Utility (Difference Calculation)	*P* Value
Secondary school/high school/trade				
Time until progression of disease (months)	6 months	3 months	0.249	0.267
	9 months	3 months	0.105	0.709
	12 months	3 months	0.481	0.112
	9 months	6 months	−0.144	0.644
	12 months	6 months	0.232	0.397
	12 months	9 months	0.375	0.068
Treatment administration	Non oral	Oral (pill/tablet)	0.028	0.861
Location of treatment	At hospital/clinic	At home	−0.193	0.38
Impact of side effects on quality of life	Moderate side effects	Mild side effects	2.058	<0.001
	Severe side effects	Mild side effects	5.343	<0.001
	Severe side effects	Moderate side effects	3.284	<0.001

Attributes	From Level	To Level	Change in Utility (Difference Calculation)	*P* Value
Under/postgrad				
Time until progression of disease (months)	6 months	3 months	−0.719	0.005
	9 months	3 months	−1.303	<0.001
	12 months	3 months	−1.205	0.001
	9 months	6 months	−0.584	0.094

Attributes	From Level	To Level	Change in Utility (Difference Calculation)	*P* Value
Under/postgrad				
	12 months	6 months	−0.486	0.117
	12 months	9 months	0.098	0.675
Treatment administration	Non oral	Oral (pill/tablet)	0.208	0.258
Location of treatment	At hospital/clinic	At home	0.242	0.336
Impact of side effects on quality of life	Moderate side effects	Mild side effects	1.748	<0.001
	Severe side effects	Mild side effects	5.237	<0.001
	Severe side effects	Moderate side effects	3.488	<0.001

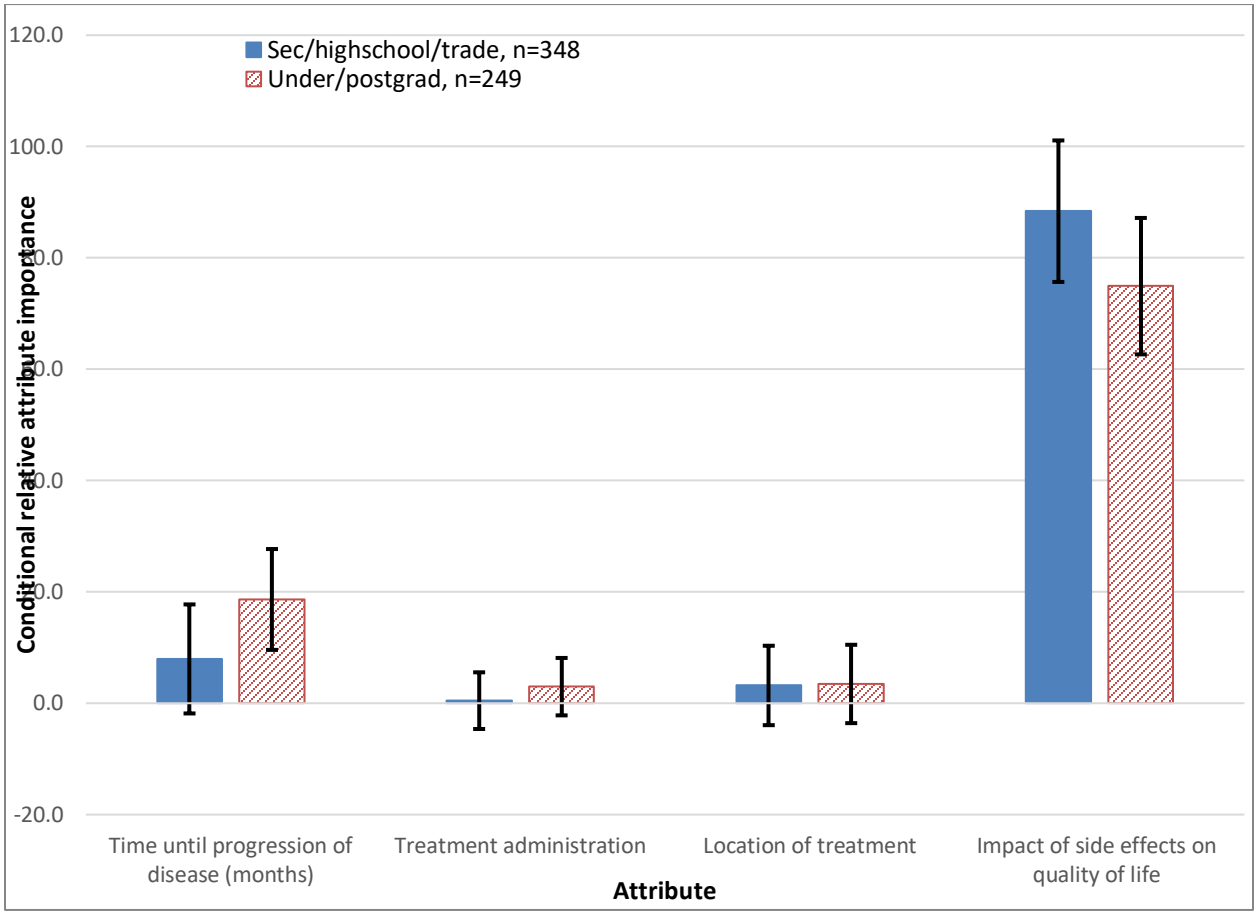
Figure 13: Attribute Relative Importance Changes for Respondents With Secondary School/High School/Trade Qualifications Versus Respondents With Undergraduate/Postgraduate Qualifications (N=603)



Note: The vertical bars surrounding each mean preference weight denote the 95% confidence interval of the point estimate (preference weights computed by the delta method for the level omitted in estimation for each attribute)

Both sets of respondents placed the most relative importance on the impact of side effects on quality of life from severe to mild side effects. However, the impact of side effects on quality of life were more important to respondents with secondary school/high school/trade qualification relative to the other attributes than for respondents with undergraduate/postgraduate qualification. Respondents with secondary school/high school/trade qualification considered time until progression of disease as the second most important attribute relative to the other attributes while respondents with undergraduate/postgraduate qualification considered time until progression of disease attribute as the least important attribute relative to the other attributes included in the study.

Figure 14: Conditional Relative Importance for Respondents With Secondary School/High School/Trade Qualifications Versus Respondents With Undergraduate/Postgraduate Qualifications (N=603)



Note: The conditional relative importance is the difference between the preference weights on the most influential attribute level and the least influential attribute level. These differences are summed across attributes and the sum is scaled to 100. The conditional importance of each attribute is a percentage of this total. The vertical bars surrounding each relative importance weight estimate denote the 95% CI around the point estimate (computed by the delta method).

Respondents Who Indicated That the DCE Tasks Were Easy or Somewhat Easy Versus Those Who Indicated That the DCE Tasks Were Neither Easy nor Difficult, Somewhat Difficult, or Very difficult

In the full sample (n=603), 379 respondents indicated that the DCE tasks were easy or somewhat easy and 224 respondents indicated that they found the DCE tasks to be neither easy nor difficult, somewhat difficult, or very difficult. Figure 15 shows the normalized mean preference weights for each attribute level for the 2 subgroups related to respondents' assessment of how easy or difficult the DCE tasks were. The interaction terms were jointly statistically significant ($p = 0.0002$), indicating that respondents who indicated that the DCE tasks were easy or somewhat easy had statistically systematically different preferences compared with those of respondents who

indicated that they found the DCE tasks to be neither easy nor difficult, somewhat difficult, or very difficult.

Both sets of respondents wanted to avoid severe and moderate impact of side effects on quality of life with statistically significantly different preferences between severe and moderate side effects, severe and mild side effects, and between moderate and mild side effects.

Respondents who indicated that the DCE tasks were easy or somewhat easy did not have statistically significant preferences for any changes in treatment administration, and location of treatment and time until progression of disease (months) except for changes from 12 months to 9 month whereas respondents who indicated that they found the DCE tasks to be neither easy nor difficult, somewhat difficult, or very difficult had no statistically significant differences in preferences for changes in time until progression of disease (months), treatment administration, and location of treatment. Table 23 below shows the estimated preference weight values from the RPL model based on this subgroup analysis. The results are also presented in Figure 15 and Figure 16.

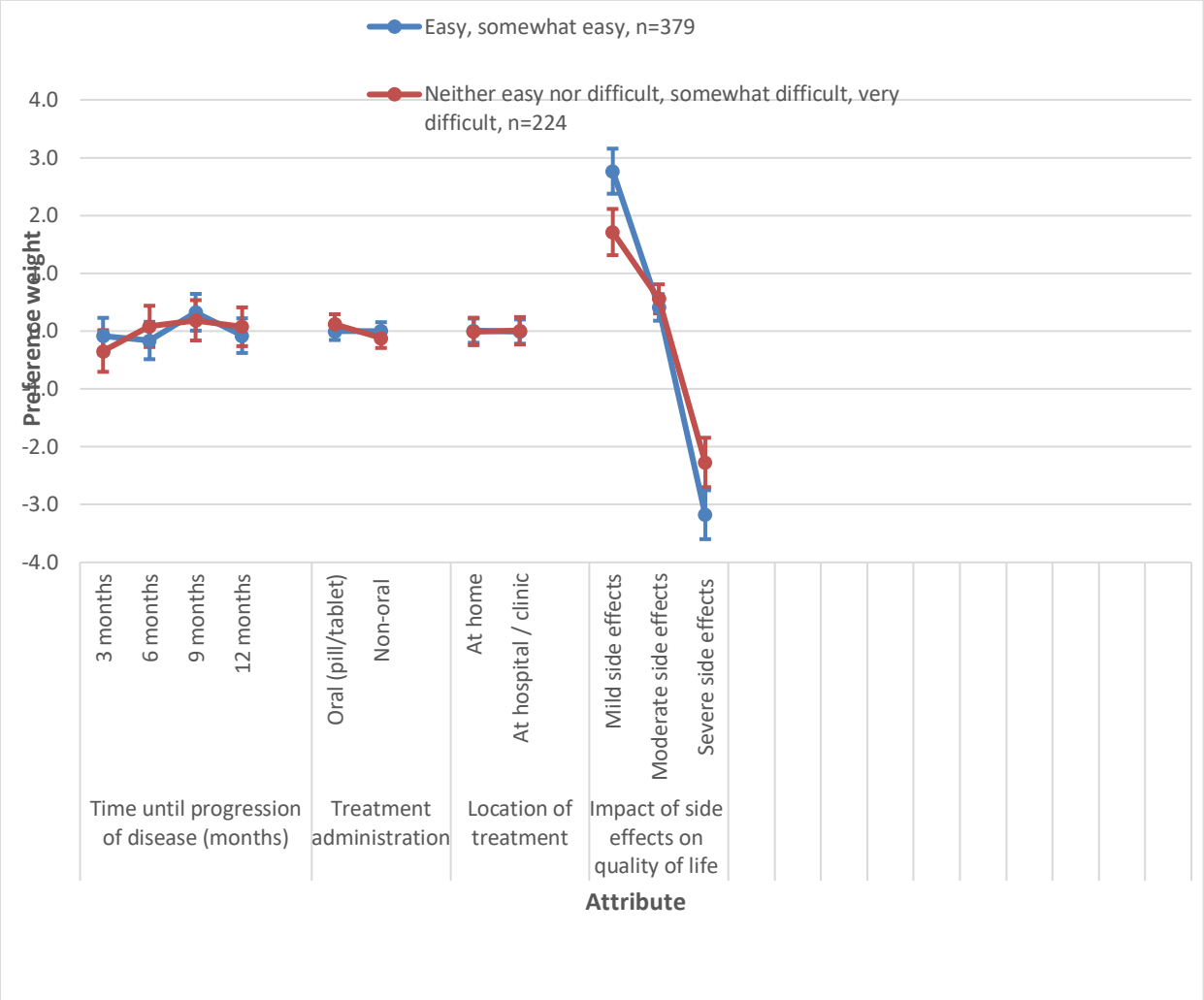
Table 23: Respondents Who Indicated That the DCE Tasks Were Easy or Somewhat Easy Versus Those Who Indicated That the DCE Tasks Were Neither Easy nor Difficult, Somewhat Difficult, or Very difficult (N=603)

Attributes	From Level	To Level	Change in Utility (Difference Calculation)	*P* Value
Easy, somewhat easy				
Time until progression of disease (months)	6 months	3 months	0.077	0.728
	9 months	3 months	−0.412	0.13
	12 months	3 months	−0.008	0.977
	9 months	6 months	−0.489	0.108
	12 months	6 months	−0.085	0.749
	12 months	9 months	0.404	0.048
Treatment administration	Non oral	Oral (pill/tablet)	−0.002	0.988
Location of treatment	At hospital/clinic	At home	0.016	0.94
	Moderate side effects	Mild side effects	2.357	<0.001

Attributes	From Level	To Level	Change in Utility (Difference Calculation)	*P* Value
Easy, somewhat easy				
Impact of side effects on quality of life	Severe side effects	Mild side effects	5.941	<0.001
	Severe side effects	Moderate side effects	3.584	<0.001

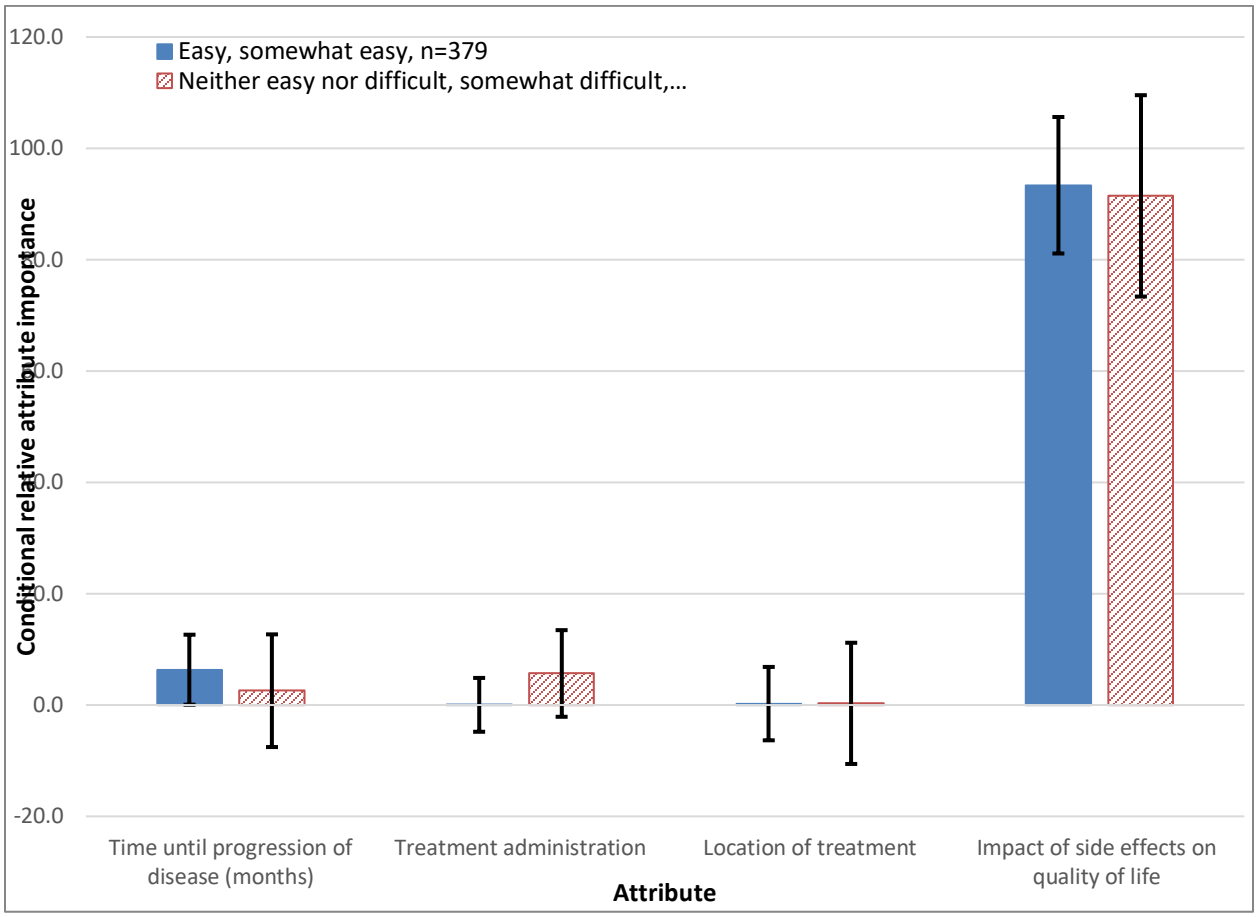
Attributes	From Level	To Level	Change in Utility (Difference Calculation)	*P* Value
Neither easy nor difficult, somewhat difficult, very difficult				
Time until progression of disease (months)	6 months	3 months	−0.426	0.088
	9 months	3 months	−0.531	0.081
	12 months	3 months	−0.419	0.203
	9 months	6 months	−0.105	0.754
	12 months	6 months	0.007	0.981
	12 months	9 months	0.112	0.619
Treatment administration	Non oral	Oral (pill/tablet)	0.247	0.153
Location of treatment	At hospital/clinic	At home	−0.013	0.958
Impact of side effects on quality of life	Moderate side effects	Mild side effects	1.155	<0.001
	Severe side effects	Mild side effects	3.985	<0.001
	Severe side effects	Moderate side effects	2.83	<0.001

Figure 15: Attribute Relative Importance Changes for Respondents Who Indicated That the DCE Tasks Were Easy or Somewhat Easy Versus Those Who Indicated That the DCE Tasks Were Neither Easy nor Difficult, Somewhat Difficult, or Very difficult (N=603)



Note: The vertical bars surrounding each mean preference weight denote the 95% confidence interval of the point estimate (preference weights computed by the delta method for the level omitted in estimation for each attribute)

Figure 16: Conditional Relative Importance for Respondents Who Indicated That the DCE Tasks Were Easy or Somewhat Easy Versus Those Who Indicated That the DCE Tasks Were Neither Easy nor Difficult, Somewhat Difficult, or Very difficult (N=603)



Note: The conditional relative importance is the difference between the preference weights on the most influential attribute level and the least influential attribute level. These differences are summed across attributes and the sum is scaled to 100. The conditional importance of each attribute is a percentage of this total. The vertical bars surrounding each relative importance weight estimate denote the 95% CI around the point estimate (computed by the delta method).

Both sets of respondents placed the most relative importance on the impact of side effects on quality of life from severe to mild side effects. However, the impact of side effects on quality of life was more important to respondents who indicated that the DCE tasks were easy or somewhat easy relative to the other attributes than for respondents who indicated that they found the DCE tasks to be neither easy nor difficult, somewhat difficult, or very difficult. Respondents who indicated that they found the DCE tasks to be neither easy nor difficult, somewhat difficult, or very difficult considered treatment administration and time until progression of disease as the next important attributes, in that order, relative to the other attributes included in the study.

8.3.4 Exploratory Analyses

8.3.4.1 Comparison of preference weights from a DCE, TTO and SW

An additional objective was to compare preference weights of patient associated with stated preference using different stated preferences methods.

Time-Trade Off Results

Each respondent was given 2 scenarios with 2 hypothetical treatment options. The first scenario had 15 choice questions (TTO-A1 to TTO-A15) with 2 hypothetical treatment options as follows:

1. Treatment option 1: time *t* without progression but with mild treatment side effects *x* with *t* given in months as time with lower hypothetical progression time (Treatment A)
2. Treatment option 2: time *s* as 12 months without progression but with moderate treatment side effects (Treatment B).

The second scenario had 15 choice questions (TTO-B1 to TTO-B15) with 2 hypothetical treatment options as follows:

1. Treatment option 1: time *t* without progression but with moderate treatment side effects *x* with *t* given in months as time with lower hypothetical progression time (Treatment A)
2. Treatment option 2: time *s* as 12 months without progression but with severe treatment side effects (Treatment B).

The TTO scores for each patient for each hypothetical scenario were calculated using a scale from 0 and 1.

For each scenario, the TTO score was calculated at the point of indifference between the 2 options after an iterative' process and the score, v(x) was calculated as follows:

- *tv(x* mild treatment side effect for the first scenario or moderate treatment side effect for the second scenario*)* = sv (12 months without progression but with moderate treatment side effects for the first scenario or 12 months without progression but with severe treatment side effects for the second scenario.

Therefore, *v(x) = t/s.* Table 24 below presents the mean TTO score.

Table 24: The mean TTO score

Country	TTO (mean score, SD)	
	Scenario 1	Scenario 2
Mean point of indifference in months	**8.07**	**9.63**
Spain	0.78 (0.33)	0.85 (0.30)
Italy	0.70 (0.37)	0.80 (0.32)
Croatia	0.38 (0.39)	0.69 (0.38)
All countries	0.68 (0.38)	0.80 (0.32)

SD=standard deviation

The results show that for scenario 1, a trade-off against 12 months without progression but with moderate side effects with approximately 8 months without progression but with mild treatment side effects for has lower utility scores (0.68) compared with scenario 2 (0.80), where a trade-off against 12 months without progression but with severe side effects with approximately 10 months without progression but with moderate treatment side effects. These results are somewhat consistent with the DCE results.

Further analysis of the TTO included using a logistic regression to examine the impact of the same covariates used in the DCE subgroup analysis on the TTO utility score:

- Cancer Stage I versus Stage II, III, IV and Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia
- Education (secondary/high school/trade versus under/postgraduate)
- Comprehension of the DCE exercise (Easy, somewhat easy versus neither easy nor difficult, somewhat difficult, very difficult)
- Cancer relapse versus no cancer relapse
- Current living situation (single person/parent versus couple with/without children, other)

The following in Table 25 are the descriptive statistics in terms of mean TTO score for these subgroups for scenario 1 and scenario 2.

Table 25: Descriptive statistics for the subgroup covariates for the TTO

All countries	N	TTO (mean score, SD) Scenario 1	TTO (mean score, SD) Scenario 2
Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	123	0.57 (0.41)	0.75 (0.35)
Stage I	153	0.77 (0.34)	0.85 (0.29)
Couple with/without children, other	216	0.70 (0.38)	0.81 (0.32)
Single person/parent	57	0.65 (0.40)	0.78 (0.34)
Under/postgraduate qualification	110	0.69 (0.37)	0.79 (0.34)
Secondary/high school/trade qualification	163	0.68 (0.39)	0.81 (0.31)
No cancer relapse	220	0.68 (0.39)	0.81 (0.32)
Cancer relapse	52	0.66 (0.38)	0.77 (0.34)
Neither easy nor difficult, somewhat difficult, very difficult	105	0.61(0.40)	0.78 (0.34)
Easy, somewhat easy	171	0.73 (0.36)	0.82 (0.32)

SD=standard deviation

Stage I respondents had the highest utility (0.77) in a trade-off against 12 months without progression but with moderate side effects with approximately 8 months without progression but with mild treatment side effects. This was followed by respondents who understood the DCE task (0.73).

The regression results show that, for scenario 1 (a trade-off against 12 months without progression but with moderate side effects with approximately 8 months without progression but with mild treatment side effects), having Stage 1 cancer and comprehending the DCE choice questions had a statistically significant impact on the mean utility.

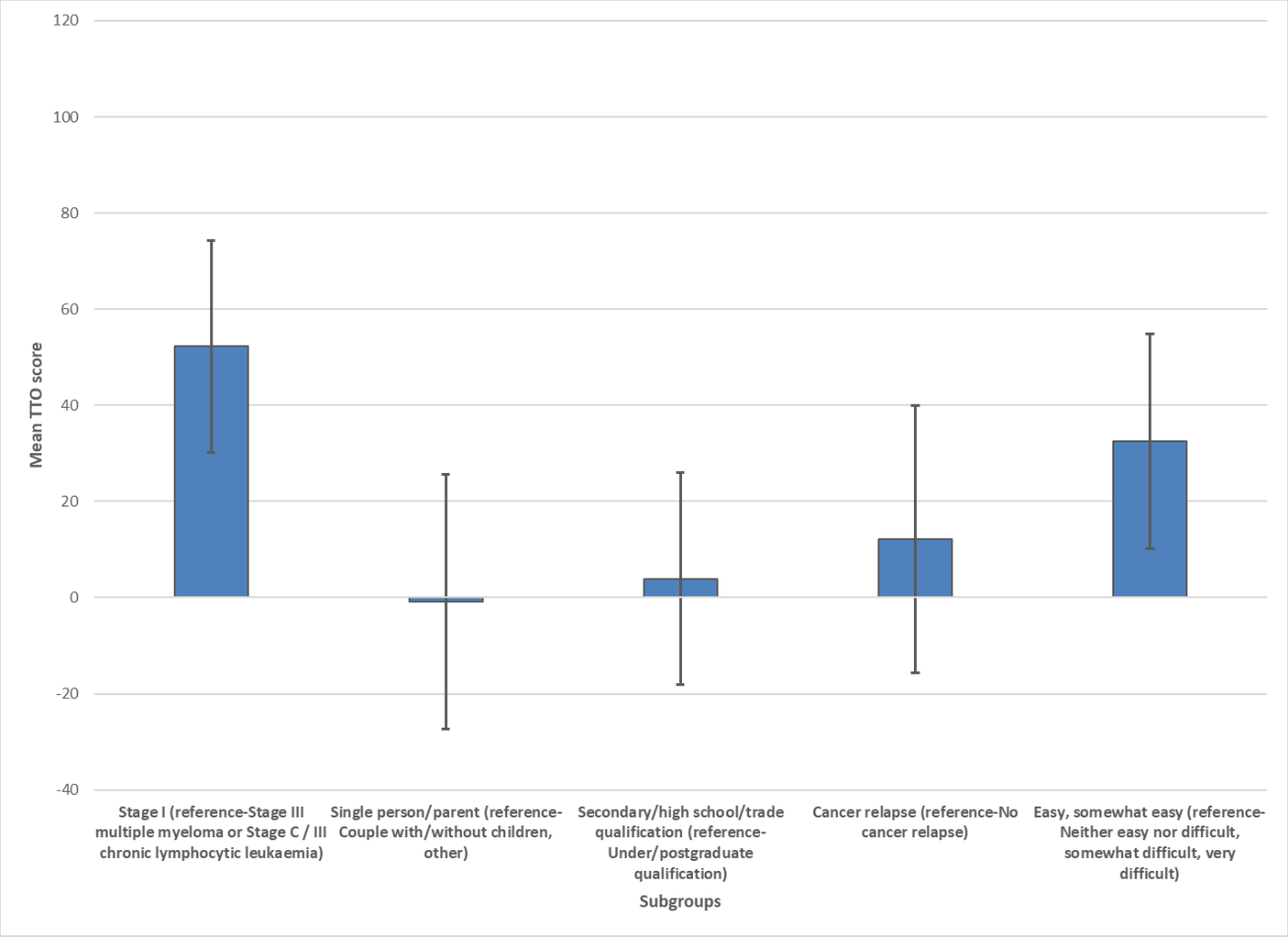
For scenario 2 (a trade-off against 12 months without progression but with severe side effects with approximately 10 months without progression but with moderate treatment side effects), only having Stage 1 cancer had a statistically significant impact on the mean utility. below presents a summary of the regression analysis results.

Table 26: The mean TTO score and subgroup covariates for the TTO

All countries	TTO (mean score, *p* value)	
	Scenario 1	Scenario 2
Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	Reference	Reference
Stage I	0.22 (*p*<0001)	0.12 (*p*=0.005)
Couple with/without children, other	Reference	Reference
Single person/parent	−0.003 (*p*=0.952)	−0.003 (*p*=0.994)
Under/postgraduate qualification	Reference	Reference
Secondary/high school/trade qualification	0.02 (*p*=0.725)	0.04 (*p*=0.286)
No cancer relapse	Reference	Reference
Cancer relapse	0.05 (*p*=0.392)	0.004 (*p*=0.942)
Neither easy nor difficult, somewhat difficult, very difficult	Reference	Reference
Easy, somewhat easy	0.13 (*p*<0001)	0.05 (*p*=0.257)

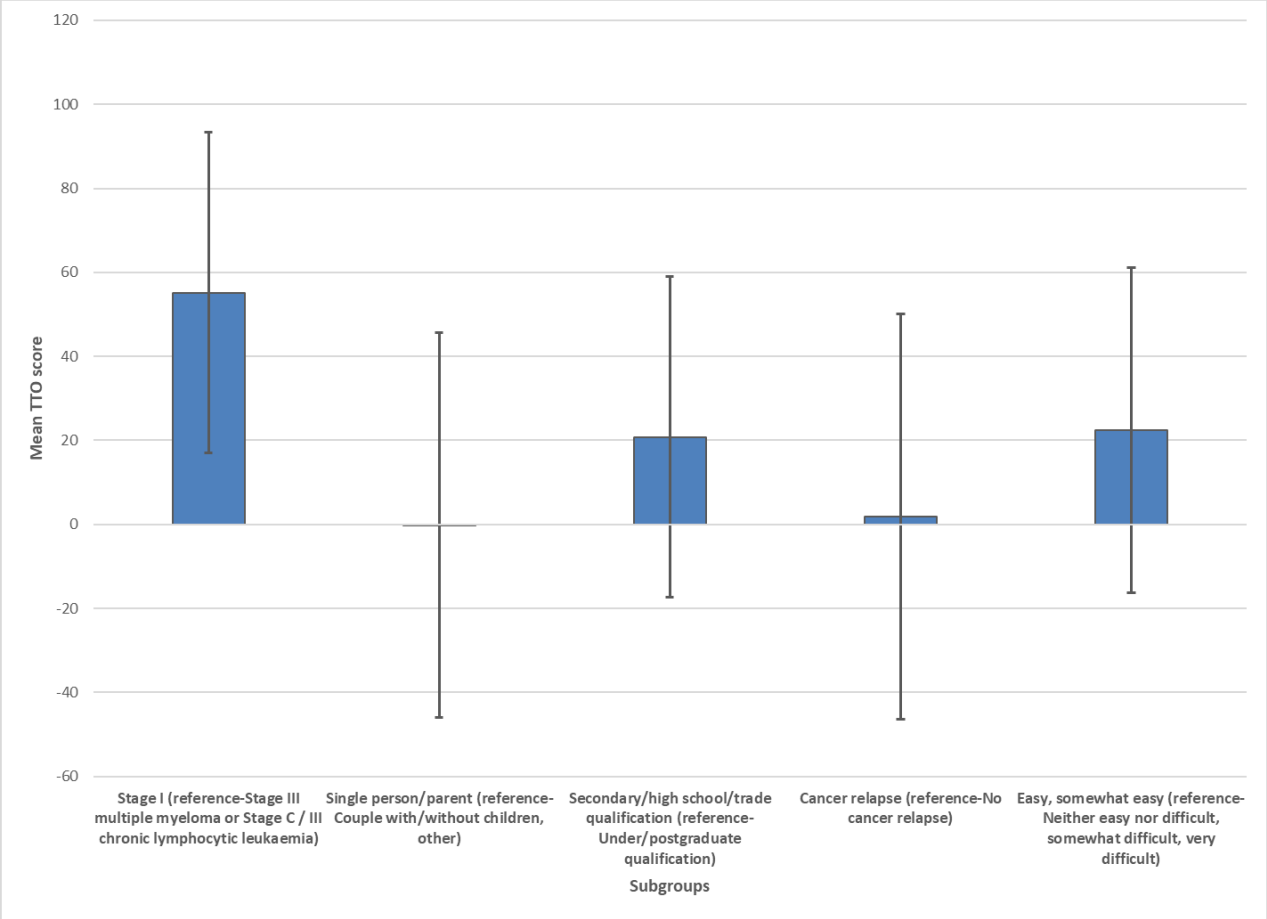
The results above are presented in Figure 17 and Figure 18 below:

Figure 17: The mean TTO score and subgroup covariates for scenario 1



Note: The mean TTO scores is scaled to 100. The mean TTO score of each covariate is a percentage of this total. The vertical bars surrounding each mean TTO score estimate denote the 95% CI around the point estimate (computed by the delta method).

Figure 18: The mean TTO score and subgroup covariates for scenario 2



Note: The mean TTO scores is scaled to 100. The mean TTO score of each covariate is a percentage of this total. The vertical bars surrounding each mean TTO score estimate denote the 95% CI around the point estimate (computed by the delta method).

8.3.4.2 Swing-weighting Results

Swing-weighting approach estimated the trade-offs directly from individuals and provided individual-level preferences. The Swing-weighting technique allowed making a systematic comparison of the 4 attributes against the one deemed to be the most important by respondents. The swing consisted of 2 general activities:

1. Rank ordering attributes according to the relative importance of incremental changes in attribute values considering the full range in levels.
2. Selecting the most important attribute as a reference point. Respondents selected the most important attribute as a reference point and assigned it a fixed score of 100 points. Any attribute could assume the role of reference attribute.

3. Assessing how much more or less important the other attributes are with respect to the reference point. This step involved the calculation of attribute weights as the ratio of points assigned to an attribute to the total points assigned to all attributes. Given a fixed reference attribute, respondents were asked to estimate how much less important the remaining attributes are with respect to the reference attribute. For example, if the most important attribute was used as the reference point with a reference score of 100 points, respondents made a judgement of how many points should be allocated to each remaining attribute with respect to this reference attribute in a relative sense (e.g., 10 less points) or an absolute sense (e.g., 90 points).
4. Calculating the preference weights using the point scores assigned to each of the attributes in elicitation step 2 and 3. This was done by normalizing each attribute score against the total score among all the 4 attributes. Table 27 below presents the utility score results.

Table 27: Swing-Weighting Utility Scores

Attributes	Spain (mean, SD)	Italy (mean, SD)	Croatia (mean, SD)	All (mean, SD)
T**ime until progression of disease** would change from **3 months** to **12 months**	0.27 (0.18)	0.27 (0.18)	0.29 (0.13)	0.28 (0.17)
Treatment Administration (how the treatment is administered) would change from **non-oral treatment (injectable / intravenous)** to **oral (pill/tablet)**	0.26 (0.13)	0.25 (0.12)	0.28 (0.14)	0.26 (0.12)
Location of treatment (where the treatment is taken, for instance at a hospital/clinic or at home) would change from **at the hospital / clinic** to **at home**	0.22 (0.11)	0.24 (0.13)	0.22 (0.09)	0.23 (0.12)
Impact of side effects on quality of life would change from **severe** to **mild side effects** (e.g., feeling a little tired, some hair loss, e.g.) that do not limit everyday activities (preparing meals, shopping for	0.24 (0.15)	0.24 (0.14)	0.20 (0.14)	0.24 (0.15)

Attributes	Spain (mean, SD)	Italy (mean, SD)	Croatia (mean, SD)	All (mean, SD)
groceries or clothes, using the telephone, managing money)				

SD=standard deviation

Compared with the DCE results, the SW utility score was higher for time until progression of disease, followed by treatment administration, impact of side effects on quality of life, and location of treatment, in that order.

Further analysis for the SW approach used a Dirichlet regression to model the distribution of the individual-level preference weights for the attributes to that of the sample population. Dirichlet regression model controlled for the effects of the same covariates used in the subgroup analysis for the DCE on the attribute preference weights.

Table 28 below presents the descriptive statistics of the covariates and Table 29 presents the results of the Dirichlet regression model.

Table 28: Descriptive statistics for the subgroup covariates for the Swing Weighting

All countries	Covariates	N	Mean utiity SD)
Time until progression of disease			
	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	144	0.29 (0.18)
	Stage I	158	0.26 (0.16)
	Couple with/without children, other	214	0.27 (0.18)
	Single person/parent	86	0.28 (0.15)
	Under/postgraduate qualification	129	0.28 (0.16)
	Secondary/high school/trade qualification	170	0.28 (0.18)
	No cancer relapse	240	0.27 (0.17)
	Cancer relapse	56	0.27 (0.14)
	Neither easy nor difficult, somewhat difficult, very difficult	107	0.28 (0.16)
	Easy, somewhat easy	195	0.27 (0.17)
Treatment Administration			

	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	144	0.27 (0.14)
	Stage I	158	0.25 (0.11)
	Couple with/without children, other	214	0.26 (0.13)
	Single person/parent	86	0.27 (0.11)
	Under/postgraduate qualification	129	0.25 (0.11)
	Secondary/high school/trade qualification	170	0.27 (0.13)
	No cancer relapse	240	0.26 (0.13)
	Cancer relapse	56	0.25 (0.12)
	Neither easy nor difficult, somewhat difficult, very difficult	107	0.27 (0.13)
	Easy, somewhat easy	195	0.26 (0.12)
Location of treatment			
	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	144	0.22 (0.12)
	Stage I	158	0.23 (0.11)
	Couple with/without children, other	214	0.23 (0.11)
	Single person/parent	86	0.22 (0.11)
	Under/postgraduate qualification	129	0.22 (0.11)
	Secondary/high school/trade qualification	170	0.23 (0.11)
	No cancer relapse	240	0.23 (0.12)
	Cancer relapse	56	0.23 (0.11)
	Neither easy nor difficult, somewhat difficult, very difficult	107	0.25 (0.13)
	Easy, somewhat easy	195	0.22 (0.10)

Time Impact of side effects on quality of life			
	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	144	0.22 (0.14)
	Stage I	158	0.25 (0.15)
	Couple with/without children, other	214	0.24 (0.15)
	Single person/parent	86	0.22 (0.13)
	Under/postgraduate qualification	129	0.25 (0.15)
	Secondary/high school/trade qualification	170	0.23 (0.14)
	No cancer relapse	240	0.23 (0.14)
	Cancer relapse	56	0.25 (0.15)
	Neither easy nor difficult, somewhat difficult, very difficult	107	0.21 (0.12)
	Easy, somewhat easy	195	0.25 (0.16)

SD=standard deviation

It can be noted from the descriptive statistics in Table 28 that the utility associated with respondents with stage III multiple myeloma or stage C / III chronic lymphocytic leukaemia was higher for time until progression of disease (0.29) compared with those with stage I disease (0.26) and the utility associated with treatment administration (0.27 for respondents with stage III multiple myeloma or stage C / III chronic lymphocytic leukaemia compared with 0.25 for stage I disease respondents).

Table 29: Results of the Dirichlet regression model

Attribute	Covariates	Utility	*p* Value
Treatment Administration			
	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	Reference	
	Stage I	0.07	0.454
	Couple with/without children, other		
	Single person/parent	−0.01	0.936
	Under/postgraduate qualification	Reference	

Attribute	Covariates	Utility	*p* Value
	Secondary/high school/trade qualification	0.11	0.251
	No cancer relapse	Reference	
	Cancer relapse	−0.04	0.766
	Neither easy nor difficult, somewhat difficult, very difficult	Reference	
	Easy, somewhat easy	0.09	0.384
Location of treatment			
	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	Reference	
	Stage I	0.19	0.062
	Couple with/without children, other	Reference	
	Single person/parent	−.10	0.342
	Under/postgraduate qualification	Reference	
	Secondary/high school/trade qualification	0.06	0.555
	No cancer relapse	Reference	
	Cancer relapse	−0.02	0.880
	Neither easy nor difficult, somewhat difficult, very difficult	Reference	
	Easy, somewhat easy	0.00	0.972
Impact of side effects on quality of life			
	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	Reference	
	Stage I	0.24	0.016
	Couple with/without children, other	Reference	
	Single person/parent	−0.10	0.352
	Under/postgraduate qualification	Reference	
	Secondary/high school/trade qualification	−0.06	0.517
	No cancer relapse	Reference	
	Cancer relapse	0.09	0.496
	Neither easy nor difficult, somewhat difficult, very difficult	Reference	
	Easy, somewhat easy	0.20	0.050

Using time until progression of disease as a reference proportion for the attributes, stage I disease and easy or somewhat easy comprehension of the DCE choice task had a statistically significant

effect on the utility for the impact of side effects on quality of life (p=0.016 and p=0.050, respectively).

An exploratory analysis further conditioned only one covariate at a time using a Dirichlet regression to model the distribution of the individual-level preference weights for each attribute. Table 30 below shows the results of this analysis.

Table 30: Results of the Dirichlet regression model for Each Covariate

Attribute	Covariates	Utility	*p* Value
Treatment Administration	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	Reference	
	Stage I	0.10	0.272
Location of treatment	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	Reference	
	Stage I	0.21	0.035
Impact of side effects on quality of life	Stage III multiple myeloma or Stage C / III chronic lymphocytic leukaemia	Reference	
	Stage I	0.26	0.008
Treatment Administration	Couple with/without children, other	Reference	
	Single person/parent	0.00	0.984
Location of treatment	Couple with/without children, other	Reference	
	Single person/parent	-–0.09	0.402
Impact of side effects on quality of life	Couple with/without children, other	Reference	
	Single person/parent	-–0.09	0.412
Treatment Administration	Under/postgraduate qualification	Reference	
	Secondary/high school/trade qualification	0.09	0.355
Location of treatment	Under/postgraduate qualification	Reference	

Attribute	Covariates	Utility	*p* Value
Impact of side effects on quality of life	Secondary/high school/trade qualification	0.04	0.678
	Under/postgraduate qualification	Reference	
	Secondary/high school/trade qualification	-–0.10	0.316
Treatment Administration	No cancer relapse	Reference	
	Cancer relapse	-–0.07	0.593
Location of treatment	No cancer relapse	Reference	
	Cancer relapse	-–0.06	0.655
Impact of side effects on quality of life	No cancer relapse	Reference	
	Cancer relapse	0.03	0.760
Treatment Administration	Neither easy nor difficult, somewhat difficult, very difficult	Reference	
	Easy, somewhat easy	0.10	0.325
Location of treatment	Neither easy nor difficult, somewhat difficult, very difficult	Reference	
	Easy, somewhat easy	0.01	0.946
Impact of side effects on quality of life	Neither easy nor difficult, somewhat difficult, very difficult	Reference	
	Easy, somewhat easy	0.26	0.013

Using time until progression of disease as a reference proportion for the attributes, stage I disease had a statistically significant effect on the utility for the location of treatment and impact of side effects on quality of life (p=0.035 and p=0.008, respectively). Easy or somewhat easy comprehension of the DCE choice task had a statistically significant effect on the utility for the impact of side effects on quality of life (p=0.013).

We further compared the RPL model results of the DCE to the Dirichlet distribution of the SW approach by using individual preference weights using ternary diagrams. Ternary diagrams can be used to represent the individual-level preference weights assigned by respondents to different attributes or levels. [33] In this case, the ternary diagrams are restricted to show the ratios of three variables (preference weights): time until progression of disease in months, impact of side effects on QoL, and location and treatment administration summed together.

Figure 19 and Figure 20 below show ternary diagrams of the distribution of the individual preference weights from a DCE (absolute weights) and SW, respectively.

Figure 19: Ternary Plot for the RPL model

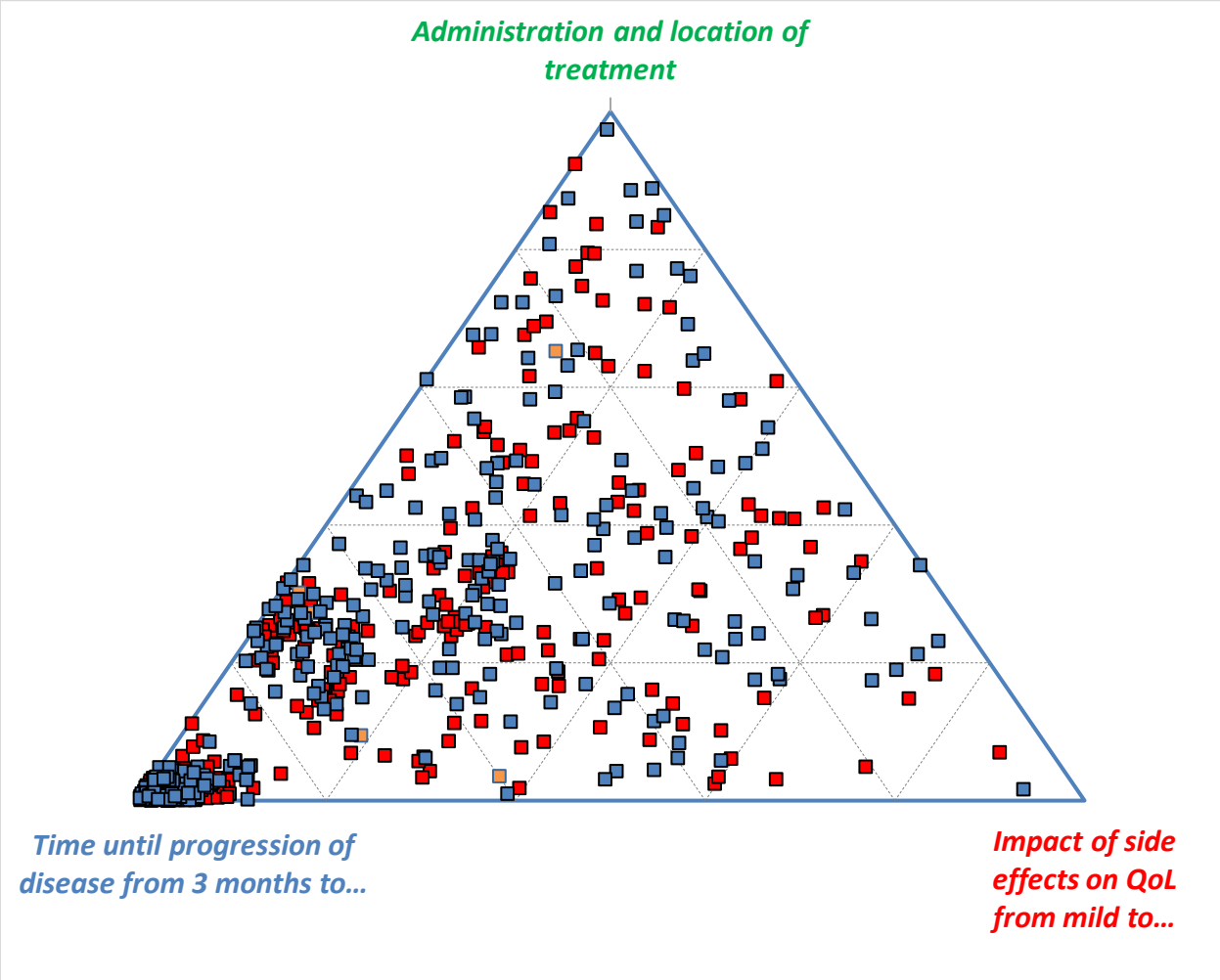
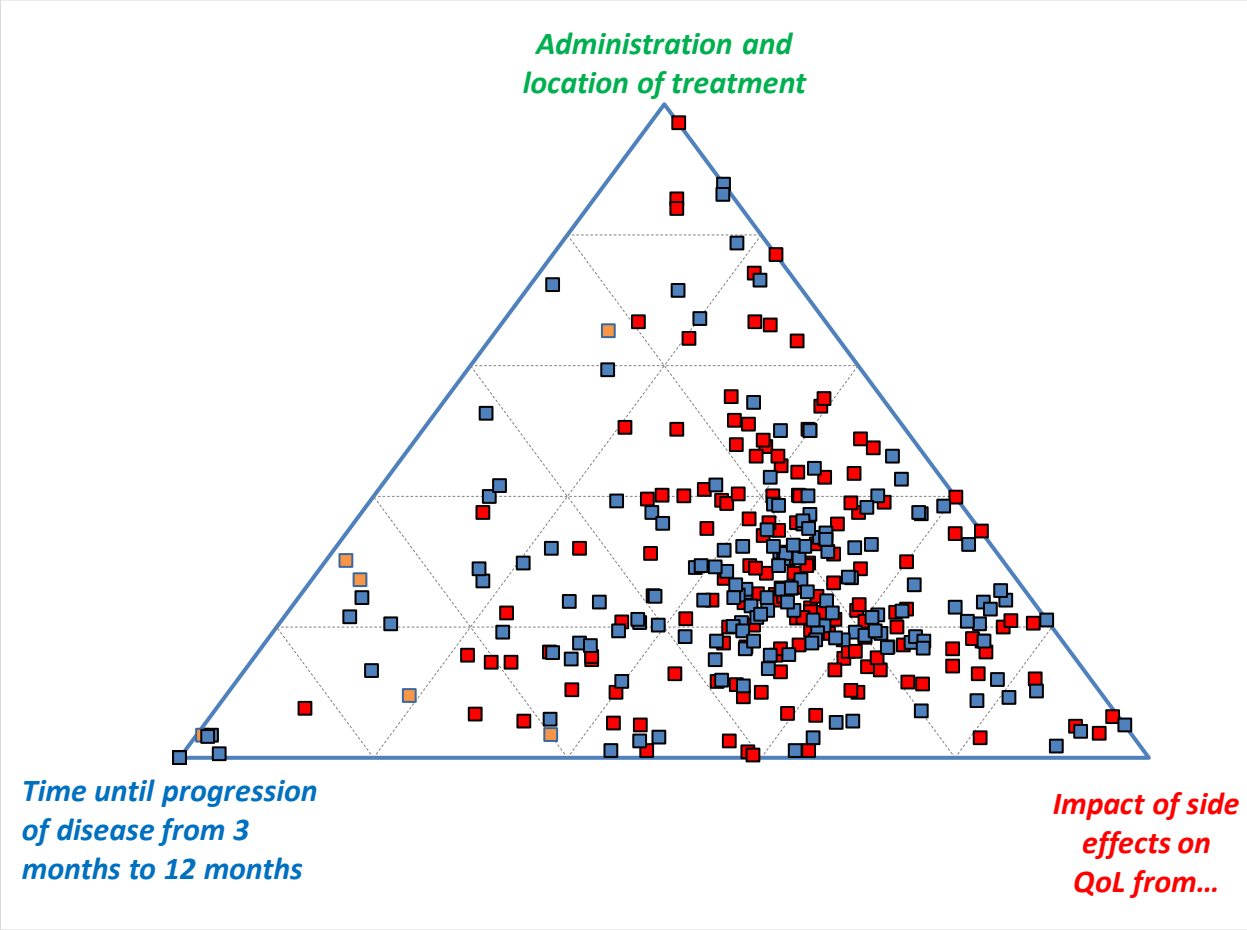


Figure 20: Ternary Plot for the Dirichlet Model



It can be seen from the diagrams that samples drawn from the RPL and Dirichlet models have relatively different spreads over the preference space. The RPL model has a dispersion towards time until progression while the Dirichlet model seems to have a dispersion towards impact of side effects on QoL.

9 DISCUSSION

This report summarises the results of a DCE survey conducted among cancer patients in Spain, Italy, and Croatia to determine their preferences regarding treatment attributes. Initially, a separate analysis for each country was carried out, which revealed that respondents across all 3 countries had similar preferences. Therefore, the data were pooled for a global analysis using a Random Parameters Logit (RPL) model to control for any potential differences in preferences. The DCE survey focused on the following attributes: time until progression of disease (in months), treatment administration, location of treatment, and the impact of side effects on quality of life.

The analysis revealed that patients attach the most importance to the impact of side effects on quality of life, followed by changes in the time until progression of the disease, treatment administration, and location of treatment. However, only changes between severe and moderate side effects and between severe side effects and mild and moderate side effects were statistically significant.

The study also tested for differences in preferences among several subgroups based on cancer stage, education, comprehension of the DCE exercise, cancer relapse, and current living situation. Only subgroups based on cancer stage, education, and comprehension of the DCE exercise showed statistically significant differences in preferences.

Patients with Stage I cancer had no significant preference for changes in time until progression of the disease, treatment administration, and location of treatment. However, those with Stage II, III, IV, stage III multiple myeloma, or chronic lymphocytic leukaemia had significant preferences for changes in the time until progression of the disease.

Patients with lower educational qualifications (respondents with secondary school/high school/trade qualifications) did not have statistically significant preferences for any changes in time until progression of disease (months), treatment administration, and location of treatment whereas respondents with an undergraduate or postgraduate qualification had statistically significant differences in preferences for changes in time until progression of disease (months) from 6 months to 3 months, 9 months to 3 months and 12 months to 3 months. Both sets of respondents wanted to avoid severe and moderate impact of side effects on quality of life with statistically significantly different preferences between severe and moderate side effects, severe and mild side effects, and between moderate and mild side effects.

In terms of comprehension of the DCE exercise, both respondents who found it easy or somewhat easy and those who found it neither easy nor difficult, somewhat difficult, or very difficult wanted to avoid severe and moderate impact of side effects on quality of life with statistically significantly different preferences between severe and moderate side effects, severe and mild side effects, and between moderate and mild side effects. Respondents who indicated that the DCE tasks were easy or somewhat easy did not have statistically significant preferences for any changes in treatment administration, and location of treatment and time until progression of disease (months) except for changes from 12 months to 9 month whereas respondents who indicated that they

found the DCE tasks to be neither easy nor difficult, somewhat difficult, or very difficult had no statistically significant differences in preferences for changes in time until progression of disease (months), treatment administration, and location of treatment.

It should be noted that the small sample size of some subgroups, such as those with cancer relapse or those who were single persons or parents, may have influenced the ability to detect significant differences between attribute levels.

Exploratory analysis using a LC approach revealed 3 classes of respondents with systematic differences in preferences across the 3 countries. Class 1 valued changes in the time until progression of the disease from 12 months to 3 months followed by the impact of side effects on quality of life. Class 2 were risk averse and focused on the impact of side effects on quality of life followed by changes in the time until progression of the disease from 12 months to 3 months. Finally, Class 3 were more risk averse and more concerned about the impact of side effects on quality of life, followed by changes in the time until progression of the disease from 12 months to 3 months, and then treatment administration and location of treatment. A further LC analysis with subgroups used as covariates for the class membership probability model showed that respondents with stage I disease are significantly likely to be in class 1 and class 2 (strongly valued changes in months of time until progression of disease from 12 months to 3 months and risk averse, concerned with the impact of side effects on quality of life. Respondents who understood the DCE tasks are likely to be in class 2 (risk averse, concerned with the impact of side effects on quality of life followed by changes in months of time until progression of disease from 12 months to 3 months).

According to the TTO results, scenario 1, which involved a trade-off between 12 months without progression but with moderate side effects and approximately 8 months without progression but with mild treatment side effects, had lower utility scores (0.68) compared to scenario 2 (0.80). Scenario 2, on the other hand, involved a trade-off between 12 months without progression but with severe side effects and approximately 10 months without progression but with moderate treatment side effects. These results were consistent with the DCE results.

The regression analysis revealed that, for scenario 1, having Stage 1 cancer and comprehending the DCE choice questions had a statistically significant impact on the mean utility. However, for scenario 2, only having Stage 1 cancer had a statistically significant impact on the mean utility.

In comparison to the DCE results, the SW utility score demonstrated higher values for time until progression of disease, followed by treatment administration, impact of side effects on quality of life, and location of treatment, in that order. The comparison between the DCE model results and the Dirichlet model results using the ternary plots show that samples drawn from the RPL and Dirichlet models have relatively different spreads over the preference space. The RPL model has a dispersion towards time until progression while the Dirichlet model seems to have a dispersion towards impact of side effects on QoL.

When using time until progression of disease as the reference proportion for the attributes, it was found that the stage of cancer and comprehension of the DCE choice task had a statistically

significant effect on the utility for the impact of side effects on quality of life (p=0.016 and p=0.050, respectively).

All 3 methods showed a statistically significant impact of both the stage of cancer and the comprehension of the DCE choice task on the utility.

Overall, DCE results and those of TTO were comparable. Compared with DCE results, SW results were not comparable. It is important to note that while DCE, TTO, and swing-weighting approaches are all methods used to measure patient preferences in health care, these methods differ in their approach and the type of information they provide. DCE provides information on the relative importance of different treatment attributes at sample level. Time-trade off provides information on the value that patients place on different health states (in this study-scenarios), and swing-weighting provides information on the relative importance of different treatment attributes and is used to quantify individual/patient preferences for each attribute.

9.1 Study Limitations

The results of the DCE survey should be considered within the limitations related to the survey instrument and sample. Developing a DCE survey instrument involves a trade-off between providing a detailed description of the treatment and ensuring that respondents can comprehend and complete the survey without difficulty. This study aimed to connect the benefits and risks described in the survey with clinical data, which constrained the set of potential attributes. The attributes and types of treatments were described in a neutral, accurate, and concise manner, and the survey text was reviewed by experts and pretested with patients. However, there are several limitations to consider when interpreting the results. Firstly, all data were self-reported, and respondents may have had difficulty understanding the attributes. Additionally, the study used a convenience sample that may not be representative of all cancer patients, and the final survey was administered online. While online surveys have been found to produce results that are not statistically different from those obtained through face-to-face interviews [34,35], the online setting may have influenced respondents' choices.

For the TTO and SW, one notable limitation was that not all respondents were presented with the TTO and SW questions. Some respondents were presented the DCE first, followed by the TTO or SW task (approximately 50%), and other respondents were presented the TTO or SW task first, followed by the DCE (approximately 50%). This approach may have had implications on sample sizes; hence caution should be exercised when comparing results of the 3 methods.

9.2 Study Strengths

Despite these limitations, the DCE survey has several strengths. The survey was carefully designed and pretested with patients in all study countries, and it used an experimental design that adheres to good research practices [36]. The treatment-choice data were analysed using advanced RPL methods that prevent estimation bias from unobserved variation in preferences

across the sample and within-sample correlation in the choice sequence for each respondent [23].

10 CONCLUSIONS

Overall, the findings indicate that preferences for cancer treatments vary by individuals and disease-stage. There is considerable variation in cancer treatment preferences between the perspective of patients themselves and the conventional endpoints in cancer clinical trials. The findings from this study provide insights into which features patients with cancer consider important for cancer treatments.

The results obtained by these different approaches should be interpreted with caution from a regulatory perspective knowing that these methods are different from each other in their utility elicitation process. Any additional insight obtained from each preference method could add to the regulatory decision process.

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12 APPENDICES

Appendix 1: Qualitative interview guide

Treatment Decisions for Novel Cancer Treatments - Patient Interviews

Patient Interview Guide – v1.0

Summer 2021

TITLE	Interview Guide: Semi-structured Qualitative Interviews with Patients with Cancer
VERSION	V1.0
SPONSOR	EMA
CONDUCTED BY	IQVIA

Background and Methods

Interviews will be performed individually with each patient and are anticipated to take approximately **45 minutes**. Interviews will be performed in local language by Global Perspectives, and moderators will be trained on the study protocol and interview guide by IQVIA's research professionals prior to interviewing any patients.

Interviews will be audio recorded for note-taking purposes only. Transcripts from each interview will be developed.

Note: All scripted text in this discussion guide is in *italics*. This text is meant to serve as guidance for moderators, rather than as word-for-word recitation.

Introduction (5 minutes)

[Start with greeting and thank the participant for partaking in this study. Introduce yourself and your affiliation]

Before we start the introduction, do you have any remaining questions about the study or the consent information?

To set the scene, the purpose of this discussion (approximately 45-minutes) is to understand your experience of receiving treatment for cancer and what factors you take into account when making a treatment decision.

We plan to record this conversation today, so that we accurately capture everything you say and represent your views accurately in our report. With that being said, confidentiality is very important to us, so please try not use your name or the names of any clinic/facility personnel in any of your responses during the interview. This will help keep the interview as anonymous as possible. Your personal information will not be included in any of the reports that result from these interviews, which means that those who read any of the reports would not know that any responses came from you.

In addition to ourselves, we also have someone from Global Perspectives who is present to set up this call using this platform and will stay on during the call-in case we need any technical help.

Are you comfortable to continue with us recording the interview?

[If Yes - Start recording]

The recording has started. Please can you reconfirm that you have agreed to be recorded; and that you have consented to participate in the study?

If you are not familiar with it, 'PSL' (the platform we are currently using for this call) is a program that allows us to participate in a private online session so that I can show you material on your computer screen. You should be able to see the material I am sharing at the moment.

Can you see my screen clearly? The screen says [describe what is visible on the screen]

[Trouble shoot if answer is no, then ask again]

Patient Background (3 minutes)

1. Demographics
    a. *Could you please start by telling me your:*
        i. *Age*
        ii. *Sex*
        iii. *Ethnicity*
        iv. *Immediate family composition / living situation*
        v. *Employment status*
        vi. *Highest level of education*
        vii. *Marital status*

Concept elicitation (10 minutes)

In this section I want to talk about your treatment experiences including the factors you take into consideration when making a treatment decision and your satisfaction with available treatment options provided to you.

First of all,

1. Can you please tell me a bit about your experience with receiving treatment for [cancer type]?

2. For each concept mentioned in the previous question ask the following questions:

a. Can you please elaborate on [concept in patients' words]?
b. What impact does [concept in patients' words] on your day-to-day life?
c. Do you view this part of cancer treatment positively or negatively?
    i. Can you please explain why you view it this way?
    ii. *[if negative]* On a scale of 0 to 10, with 0 being not disturbing at all and 10 being the most disturbing, how disturbing was [concept in patients' words] when it was occurring?

iii. *[if positive]* On a scale of 0 to 10, with 0 being neutral and 10 being the very positive, how positive was [concept in patients' words] when it was occurring?

3. What would you say are the most important factors you take into consideration when making a treatment decision?

a. Why are these factors the most important?

4. What other factors you would take into consideration when making a treatment decision ?

5. Are there any factors that you think are not so important when making a treatment decision?

a. Why are these factors the least important?

6. Out of the following factors, which would you say is the most important when making a treatment decision in cancer? **(share list on slide)**

a. Overall survival (the amount of time a patient is alive after the start of receiving treatment)
b. Progression-free survival (the amount of time after the start of treatment the cancer does not continue to grow)
c. Side effects
d. Mode of treatment administration
e. Treatment regimen
f. Expected quality of life from treatment

a. Why?

7. Out of the following factors, which would you say is the least important when making a treatment decision in cancer? **(share list on slide)**

a. Overall survival (the amount of time a patient is alive after the start of receiving treatment)

b. Progression-free survival (the amount of time after the start of treatment the cancer does not continue to grow)
c. Side effects
d. Mode of treatment administration
e. Treatment regimen
f. Expected quality of life from treatment

a. Why?

8. When compared, which of these two factors would you consider to be more important when making a treatment decision in cancer? **(share list on slide)**

a. Overall survival (the amount of time a patient is alive after the start of receiving treatment)
b. Progression-free survival (the amount of time after the start of treatment the cancer does not continue to grow)

a. Why?

9. When compared, which of these two factors would you consider to be more important when making a treatment decision in cancer? **(share list on slide)**

a. Side effects
b. Expected quality of life from treatment

a. Why?

10. How do you think the following characteristics contribute to making a treatment decision in cancer? **(share list on slide; probe only characteristics not previously mentioned)**

a. Age
b. Sex
c. Marital Status

d. Presence of children

e. Travel associated with treatment

f. Current health status (excellent, good, fair, poor)

g. Number of previous treatments

h. Duration of treatment

i. Understanding of treatment information

j. Cost of treatment

k. Work productivity

l. Living situation

11. Out of the listed characteristics, which would you consider to be the most important characteristic to contribute to making a treatment decision in cancer?

a. Why?

12. Out of the listed characteristics, which would you consider to be the least important characteristic to contribute to making a treatment decision in cancer?

a. Why?

Vignettes testing (25 min)

Individual Vignettes

First, I am going to show you six profiles, one at a time about a fictional patient who has cancer requiring treatment. We want to understand how well you understand the descriptions of the patient in each profile, if they include the relevant information required for you to make a treatment decision, your satisfaction with the available options provided, and whether you think the descriptions accurately portray a typical patient experience.

[Show each vignette one at a time through slides and ask the patient to read the vignettes out loud. For each vignette, ask the following questions:]

1. Was the profile clear as you read it?
    a. Were there any characteristics you thought were confusing?
    b. Would you change the wording of the profile to make it clearer?

2. Would you say that the information in this profile is in any way similar to your own experience?
    a. Please elaborate. In what ways is it similar? In what ways is it different?
3. What do you think of the treatment option presented in this profile? Do you think it is a good option for [name] or not?
    a. If good, why?
    b. If not, why?
4. Is all of the information in the profile relevant to make a treatment decision?
    a. If no, which information is not relevant?
5. Does the profile provide sufficient information to make a treatment decision?
    a. If not, what information is missing?

[once all six vignettes have been discussed, move on to section B]

Overall Vignettes

1. Was it clear to you that the profiles described different versions of a similar experience?
2. Was there one profile that you thought was clearly better compared to the others?
    a. If Yes:
        i. Why this profile?
        ii. If no: Move to next question
3. Was there one profile you thought was clearly worse compared to the others?
    a. If Yes:
        i. Why this profile?
        ii. If no: Move to next question
4. What, if anything, would make a big enough difference among the profiles for you to choose one over the other?
5. Overall, which characteristics included in the patient profiles did you consider to be most important?
6. Overall, which characteristics included in the patient profiles did you consider to be least important?

Closing (2 minutes)

We have reached the end of our discussion today.

Is there anything that we did not discuss that would add to our understanding of the patient experience of receiving treatment for cancer that we did not discuss today?

Thank you very much for your time today.

Appendix 2: Full list of vignettes (utilized in the qualitative interviews)

Case 1: Sara is a **35-year-old single woman** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. She receives treatment for cancer **orally (tablets) twice daily.** Her physician explained to her that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **30 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **12 months.** On days Sara receives treatment, she has **moderate side effects**, such as feeling tired and worn out, and it is a little difficult for her to concentrate. The treatment also has a **moderate negative impact on her quality of life,** where it is difficult for her to perform everyday activities**.**

Case 2: Bill is a **45-year-old single man** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. He receives treatment for cancer **orally (tablets) once daily.** His physician explained to him that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **18 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **9 months.** On days Bill receives treatment, he has **mild side effects**, such as feeling a little tired and slightly worn out. When receiving his treatment, Bill does not have difficulty with his concentration. The treatment also has **no negative impact on his quality of life.**

Case 3: Pat is a **55-year**-old **married woman** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. She receives treatment for cancer **directly into a vein (intravenous) once a week**. Her physician explained to her that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **24 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **6 months.** On days Pat receives treatment, she has **moderate side effects**, such as feeling tired and worn out, and it is a little difficult for her to concentrate. The treatment also has a **mild negative impact on her quality of life,** where it is a little difficult for her to perform everyday activities**.**

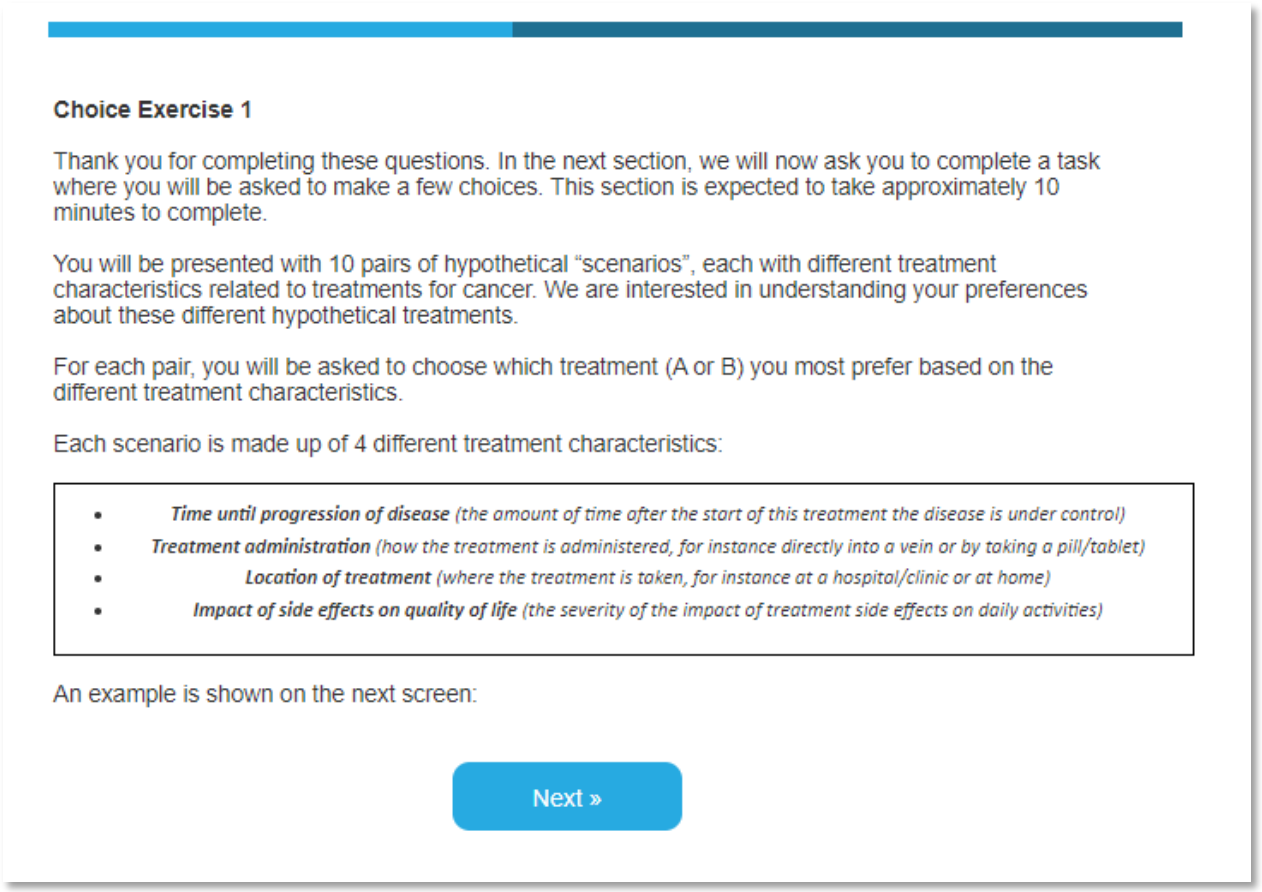
Case 4: George is a **65-year-old married man** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. He receives treatment for cancer **directly into a vein (intravenous) every 2 weeks**. His physician explained to him that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **12 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **6 months.** On days George receives treatment, he has **mild side effects**, such as feeling a little tired and slightly worn out. When receiving his treatment, George does not have difficulty with his concentration. The treatment also has a **mild negative impact on his quality of life,** where it is a little difficult for him to perform everyday activities.

Case 5: Kate is a 75-year-old **widowed woman** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. She receives treatment for cancer **through an injection (subcutaneous) every two weeks**. Her physician explained to her that on average, overall

survival (the amount of time a patient is alive after the start of receiving treatment) is around **36 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **12 months.** On days Kate receives treatment, she has **severe side effects**, such as feeling very tired and worn out, and it is a very difficult for her to concentrate. The treatment also has a **moderate negative impact on her quality of life,** where it is difficult for her to perform everyday activities.

Case 6: Charlie is an **85-year-old widowed man** diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. He receives treatment for cancer **through an injection (subcutaneous) twice a week**. His physician explained to him that on average, overall survival (the amount of time a patient is alive after the start of receiving treatment) is around **6 months.** The average progression-free survival for this treatment (the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive) is around **3 months.** On days Charlie receives treatment, he has **moderate side effects**, such as feeling tired and worn out, and it is a little difficult for him to concentrate. The treatment also has a **mild negative impact on his quality of life,** where it is a little difficult for him to perform everyday activities.

Appendix 3: Discrete choice experiment example



Choice Exercise 1

Thank you for completing these questions. In the next section, we will now ask you to complete a task where you will be asked to make a few choices. This section is expected to take approximately 10 minutes to complete.

You will be presented with 10 pairs of hypothetical "scenarios", each with different treatment characteristics related to treatments for cancer. We are interested in understanding your preferences about these different hypothetical treatments.

For each pair, you will be asked to choose which treatment (A or B) you most prefer based on the different treatment characteristics.

Each scenario is made up of 4 different treatment characteristics:

- ***Time until progression of disease*** *(the amount of time after the start of this treatment the disease is under control)*
- ***Treatment administration*** *(how the treatment is administered, for instance directly into a vein or by taking a pill/tablet)*
- ***Location of treatment*** *(where the treatment is taken, for instance at a hospital/clinic or at home)*
- ***Impact of side effects on quality of life*** *(the severity of the impact of treatment side effects on daily activities)*

An example is shown on the next screen:

Next »

1 of 10.

When making your treatment choice, please note the following definitions for side effects:

Mild side effects: For example, feeling a little tired, some hair loss. These are side effects that do not limit everyday activities like preparing meals, shopping for groceries or clothes, using the telephone, managing money.

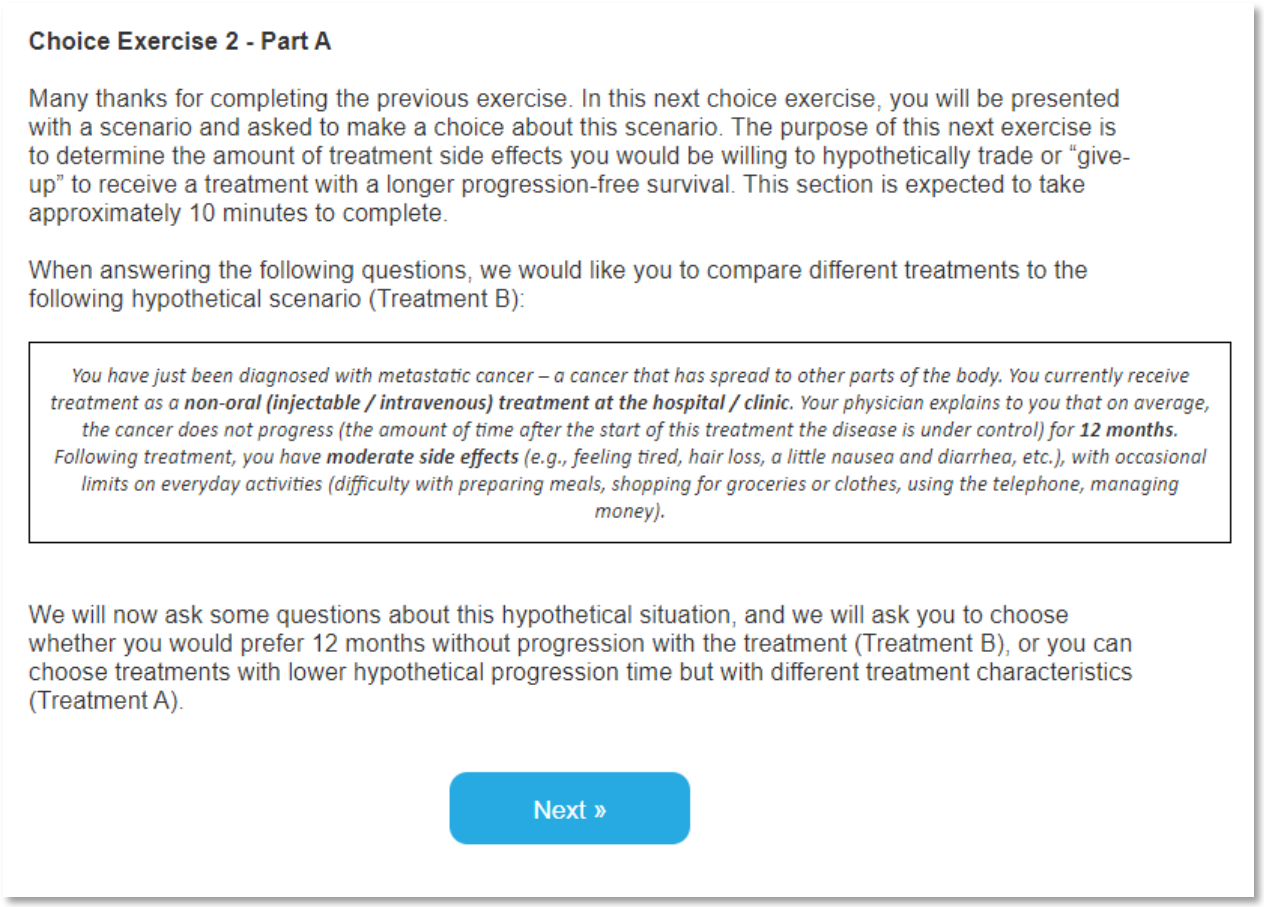
Moderate side effects: For example, feeling tired, hair loss, a little nausea and diarrhea. These are side effects with occasional limits on everyday activities, like difficulty with preparing meals, shopping for groceries or clothes, using the telephone, managing money.

Severe side effects: For example, feeling very tired, frequent vomiting and diarrhea, appetite loss, feeling like having the flu, severe pain. These are side effects that limit some everyday activities, like difficulty with preparing meals, shopping for groceries or clothes, using the telephone, managing money, and limit self-care, like bathing, dressing, taking medication, but are not life-threatening.

Attribute	Treatment B	Treatment A
Location of treatment (where the treatment is taken, for instance at a hospital/clinic or at home)	At home	At hospital / clinic
Impact of side effects on quality of life (the severity of the impact of treatment side effects on daily activities)	**Moderate side effects**	**Mild side effects**
Treatment administration (how the treatment is administered)	Non-oral	Oral (pill/tablet)
Time until progression of disease (the amount of time after the start of this treatment the disease is under control)	3 months	6 months
Please choose your preferred treatment:	○	○

Next »

Appendix 4: Time-trade off example



Choice Exercise 2 - Part A

Many thanks for completing the previous exercise. In this next choice exercise, you will be presented with a scenario and asked to make a choice about this scenario. The purpose of this next exercise is to determine the amount of treatment side effects you would be willing to hypothetically trade or "give-up" to receive a treatment with a longer progression-free survival. This section is expected to take approximately 10 minutes to complete.

When answering the following questions, we would like you to compare different treatments to the following hypothetical scenario (Treatment B):

You have just been diagnosed with metastatic cancer – a cancer that has spread to other parts of the body. You currently receive treatment as a ***non-oral (injectable / intravenous) treatment at the hospital / clinic****. Your physician explains to you that on average, the cancer does not progress (the amount of time after the start of this treatment the disease is under control) for* ***12 months****. Following treatment, you have* ***moderate side effects*** *(e.g., feeling tired, hair loss, a little nausea and diarrhea, etc.), with occasional limits on everyday activities (difficulty with preparing meals, shopping for groceries or clothes, using the telephone, managing money).*

We will now ask some questions about this hypothetical situation, and we will ask you to choose whether you would prefer 12 months without progression with the treatment (Treatment B), or you can choose treatments with lower hypothetical progression time but with different treatment characteristics (Treatment A).

Next »

When making your treatment choice, think about the following definitions of side effects:

Mild side effects: (e.g., feeling a little tired, some hair loss, etc.) that do not limit everyday activities (preparing meals, shopping for groceries or clothes, using the telephone, managing money)

Moderate side effects: (e.g., feeling tired, hair loss, a little nausea and diarrhea etc.), with occasional limits on everyday activities (difficulty with preparing meals, shopping for groceries or clothes, using the telephone, managing money)

Attribute	Treatment A	Treatment B
Progression *(the amount of time after the start of this treatment the cancer does not continue to grow, and the patient is alive)*	6 months	12 months
Impact of side effects on quality of life *(the severity of the impact of treatment side effects on daily activities)*	With mild side effects	With moderate side effects

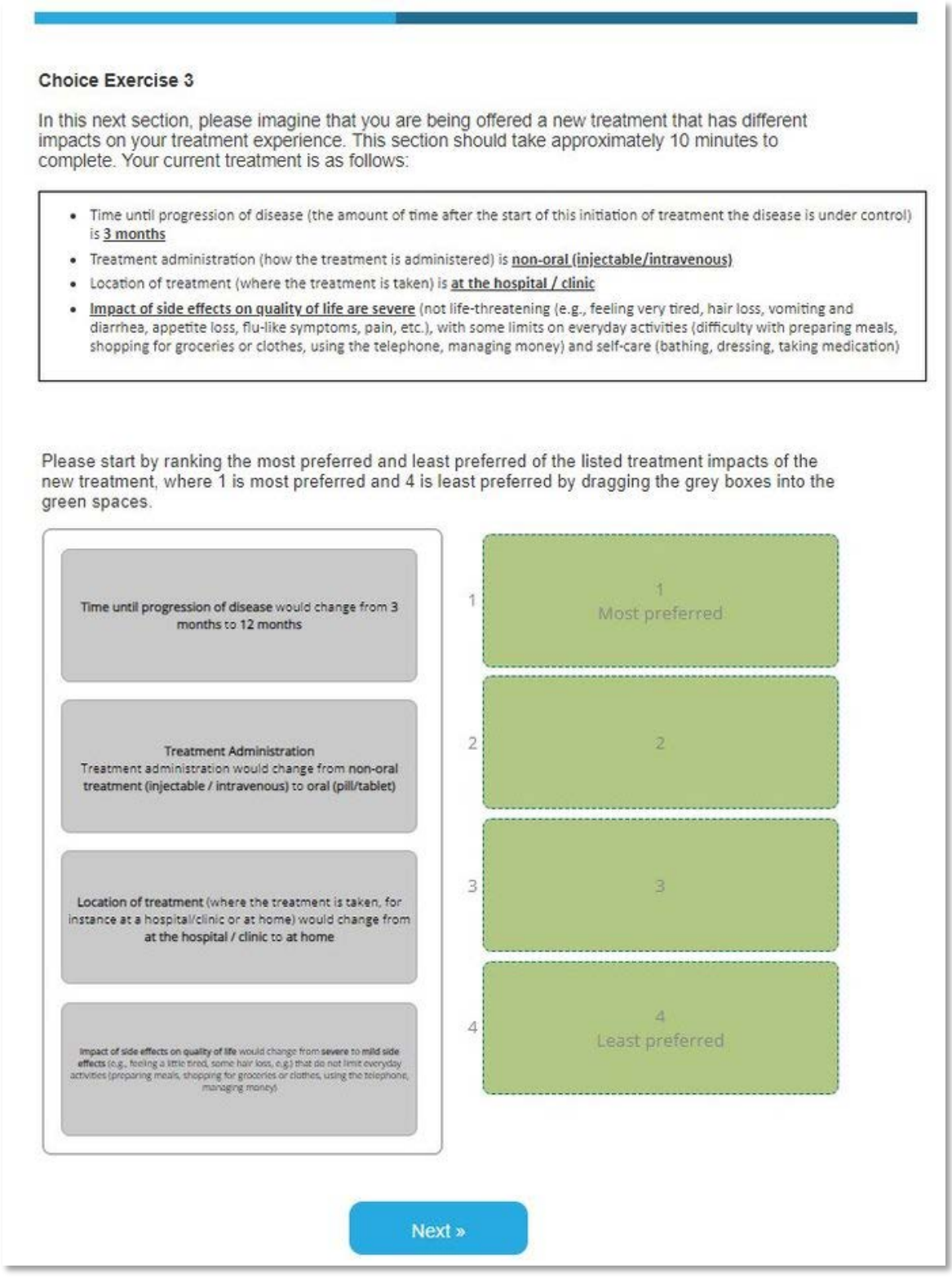
Please choose your preferred treatment:

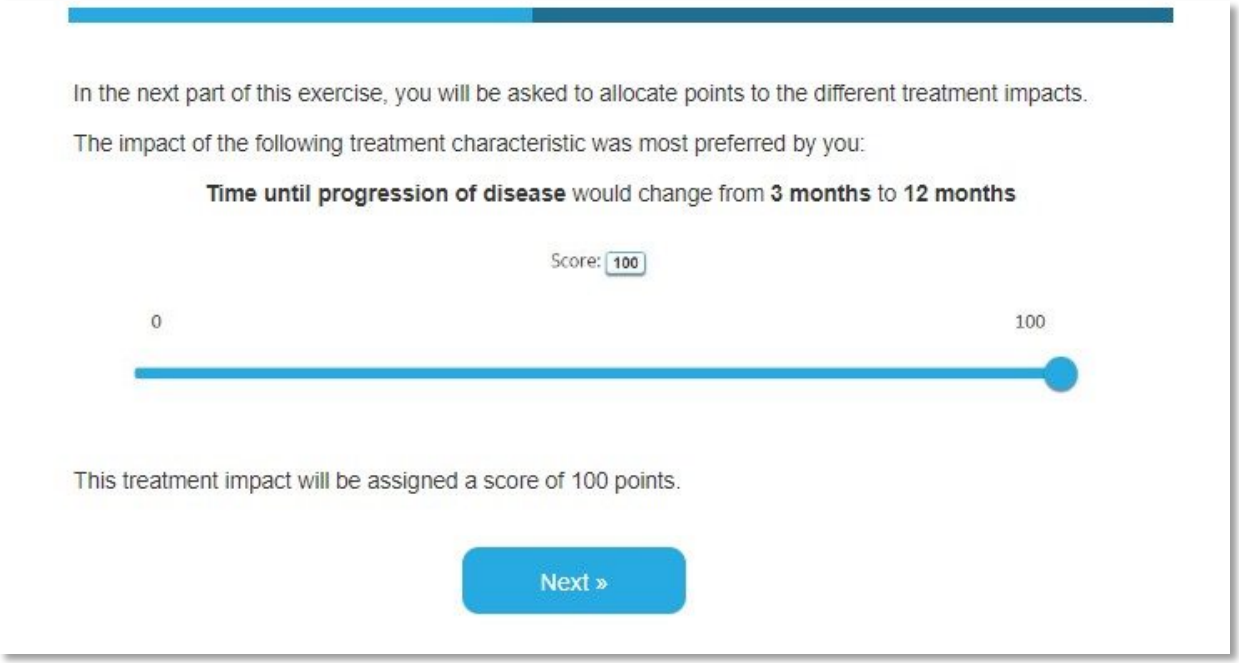
○ Treatment A

○ Treatment B

Next »

Appendix 5: Swing weighing example




In the next part of this exercise, you will be asked to allocate points to the different treatment impacts.
The impact of the following treatment characteristic was most preferred by you:
Time until progression of disease would change from 3 months to 12 months
Score: 100
0
100
This treatment impact will be assigned a score of 100 points.
Next »

Appendix 6: Demographic Characteristics of Respondents in Spain, Italy, and Croatia

Question	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
All respondents				
What is your current age? (years)				
Mean (SD)	53 (12.4)	55 (12.17)	55 (13.86)	54.3 (12.55)
Median	54.0	56	56	55
Min, max	18, 82	23, 84	19, 83	18, 84
What is your sex?				
Male	102 (40.32%)	68 (27.20%)	18 (18.00%)	188 (31.18%)
Female	151 (59.68%)	182 (72.80%)	82 (82.00%)	415 (68.82%)
Other	0	0	0	0
Prefer not to answer	0	0	0	0
What country do you live in? Please select only one option.				
UK	1 (0.40%)	0	1 (1.00%)	2 (0.33%)
Italy	0	250 (100%)	0	250 (41.46%)
Spain	232 (91.70%)	0	0	232 (38.47%)
Croatia	0	0	99 (99.00%)	99 (16.42%)
Other	0	0	0	0
Missing	20 (7.91%)	0	0	20 (3.32%)
What is your current living situation?				

Question	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
Single person	36 (14.23%)	50 (20.00%)	21 (21.00%)	107 (17.74%)
Single parent	21 (8.30%)	11 (4.40%)	10 (10.00%)	42 (6.97%)
Couple with no children	40 (15.81%)	49 (19.60%)	8 (8.00%)	97 (16.09%)
Couple with children	134 (52.96%)	121 (48.40%)	45 (45.00%)	300 (49.75%)
Other (please explain):	20 (7.91%)	16 (6.40%)	16 (16.00%)	52 (8.62%)
Prefer not to answer	2 (0.79%)	3 (1.20%)	0	5 (0.83%)
What is your current employment status?				
Working (full-time)	102 (40.32%)	78 (31.20%)	42 (42.00%)	222 (36.82%)
Working (part-time)	19 (7.51%)	37 (14.80%)	2 (2.00%)	58 (9.62%)
Self-Employed	13 (5.14%)	18 (7.20%)	1 (1.00%)	32 (5.31%)
Not working / unemployed	45 (17.79%)	43 (17.20%)	12 (12.00%)	100 (16.58%)
Retired	66 (26.09%)	65 (26.00%)	39 (39.00%)	170 (28.19%)
Other	8 (3.16%)	9 (3.60%)	4 (4.00%)	21 (3.48%)
Prefer not to answer	0	0	0	0
What type of location do you live in?				
Urban / city / metro	198 (78.26%)	149 (59.60%)	69 (69.00%)	416 (68.99%)
Suburban / regional	33 (13.04%)	51 (20.40%)	21 (21.00%)	105 (17.41%)
Rural	22 (8.7%)	49 (19.60%)	10 (10.00%)	81 (13.43%)
Prefer not to answer	0	1 (0.40%)	0	1 (0.17%)

Question	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
What is your highest level of education?				
Secondary education (pre-high school)	33 (13.04%)	29 (11.60%)	56 (56.00%)	118 (19.57%)
High school	45 (17.79%)	102 (40.80%)	5 (5.00%)	152 (25.21%)
Trade / technical vocational training	45 (17.79%)	26 (10.40%)	7 (7.00%)	78 (12.94%)
Undergraduate education (Bachelor's degree)	93 (36.76%)	56 (22.40%)	24 (24.00%)	173 (28.69%)
Postgraduate education (Masters, PhD)	35 (13.83%)	35 (14.00%)	6 (6.00%)	76 (12.60%)
Prefer not to answer	2 (0.79%	2 (0.80%)	2 (2.00%)	6 (1.00%)
What is your current marital status?				
Single (never married)	41 (16.21%)	47 (18.80%)	17 (17.00%)	105 (17.41%)
Married or civil partnership	161 (63.64%)	157 (62.80%)	54 (54.00%)	372 (61.69%)
Married but separated	9 (3.56%)	13 (5.20%)	2 (2.00%)	24 (3.98%)
Widowed and not remarried	12 (4.74%)	9 (3.60%)	11 (11.00%)	32 (5.31%)
Divorced and not remarried	29 (11.46%)	22 (8.80%)	14 (14.00%)	65 (10.78%)
Prefer not to answer	1 (0.4%)	2 (0.80%)	2 (2.00%)	5 (0.83%)

Max = maximum; min = minimum; SD = standard deviation.

Note: The percentage totals may not sum to exactly 100% because of rounding.

[a] Respondents could provide multiple responses to some questions. Therefore, the totals may exceed the total number of respondents.

Appendix 7: Summary of Respondents' Experiences with Cancer and Cancer Treatments

Question	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
All respondents				
Have you been diagnosed with cancer by a qualified health care provider? Please select only one option.				
Yes	253 (100%)	250 (100%)	100 (100%)	603 (100%)
No	0	0	0	0
What type of cancer are you currently diagnosed with? [a]				
Bladder Cancer	9 (3.56%)	10 (4.00%)	0	19 (3.15%)
Brain cancer	2 (0.79%)	1 (0.40%)	0	3 (0.50%)
Breast Cancer	70 (27.67%)	87 (34.80%)	34 (34.00%)	191 (31.67)
Colon or Rectal Cancer (Colorectal)	26 (10.28%)	13 (5.20%)	7 (7.00%)	46 (7.63%)
Endometrial Cancer	12 (4.74%)	7 (2.80%)	3 (3.00%)	22 (3.65%)
Kidney Cancer	7 (2.77%)	6 (2.40%)	0	13 (2.16%)
Liver Cancer	2 (0.79%)	3 (1.20%)	0	5 (0.83%)
Lung Cancer	14 (5.53%)	10 (4.00%)	22 (22.00%)	46 (7.63%)
Melanoma	16 (6.32%)	20 (8.00%)	3 (3.00%)	39 (6.47%)
Multiple Myeloma	0	0	2 (2.00%)	2 (0.33%)
Lymphoma including Non-Hodgkin Lymphoma	6 (2.37%)	4 (1.60%)	9 (9.00%)	19 (3.15%)
Leukaemia (including chronic lymphocytic or myelogenous leukaemia)	5 (1.98%)	2 (0.80%)	4 (4.00%)	11 (1.82%)
Ovarian Cancer	9 (3.56%)	9 (3.60%)	1 (1.00%)	19 (3.15%)
Pancreatic Cancer	1 (0.4%)	4 (1.60%)	0	5 (0.83%)

Question	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
Prostate Cancer	28 (11.07%)	16 (6.40%)	2 (2.00%)	46 (7.63%)
Thyroid Cancer	19 (7.51%)	22 (8.80%)	1 (1.00%)	42 (6.97%)
Other	27 (10.67%)	36 (14.40%)	12 (12.00%)	75 (12.44%)
When were you diagnosed with cancer? Years ago (SD)	6.4 (10.14)	6.9 (9.96)	4.2 (5.99)	6.2 (9.53)
What stage of cancer are you currently diagnosed with?				
Stage I - Early-stage cancer where the tumour has not grown deeply into nearby tissues	159 (62.85%)	132 (52.80%)	35 (35.00%)	326 (54.06%)
Stages II & III – Larger cancers where the tumour has grown more deeply into nearby tissue and may have spread to lymph nodes, but not to other parts of the body	76 (30.04%)	101 (40.40%)	39 (39.00%)	216 (25.82%)
Stage IV – Advanced or metastatic cancer, where cancer has spread to other parts of the body	15 (5.93%)	16 (6.40%)	23 (23.00%)	54 (8.96%)
Stage III multiple myeloma OR Stage C / III chronic lymphocytic leukaemia	3 (1.19%)	1 (0.40%)	3 (3.00%)	7 (1.16%)
When were you first diagnosed with cancer?				
Less than 1 year ago	22 (8.7%)	29 (11.60%)	19 (19.00%)	70 (11.61%)
Between 1 and 5 years ago	123 (48.62%)	98 (39.20%)	46 (46.00%)	267 (44.28%)
More than 5 years ago	108 (42.69%)	122 (48.80%)	35 (35.00%)	265 (43.95%)

Question	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
Prefer not to answer	0	1 (0.40%)	0	1 (0.17%)
Have any of your relatives also been diagnosed with this type of cancer?				
Yes	77 (30.43%)	58 (23.20%)	24 (24.00%)	159 (26.37%)
No	176 (69.57%)	189 (75.60%)	76 (76.00%)	441 (73.13%)
Prefer not to answer	0	3 (0.99%)		3 (0.50%)
If yes, were the relative(s) diagnosed with this type of cancer first, second- or third degree relatives? (Select all that apply)	n=77	n=58	n=24	n=159
First degree relative (Parents, siblings or children)	45 (17.79%)	39 (15.60%)	13 (13.00%)	97 (16.09%)
Second degree relative (Grandparents, grandchildren, uncles, aunts, nephews, nieces, and half-siblings)	32 (12.65%)	24 (9.60%)	15 (15.00%)	71 (11.77%)
Third degree relative (First cousins, great-grand parents, great-aunt/uncle)	11 (4.35%)	7 (2.80%)	1 (1.00%)	19 (3.15%)
Other	2 (0.79%)	1 (0.40%)	1 (1.00%)	4 (0.66%)
All respondents				
Do you currently receive treatment for cancer?				
Yes	100 (39.53%)	93 (37.20%)	60 (60.00%)	253 (41.96%)
No	153 (60.47%)	156 (62.40%)	40 (40.00%)	349 (57.88%)

Question	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
Prefer not to answer	0	1 (0.40%)	0	1 (0.17%)
If yes, what type of treatment have you received in the last month? (Choose all that apply)[a]	n=100	n=93	n=60	n=253
Chemotherapy - in the hospital	31 (12.25%)	19 (7.60%)	16 (16.00%)	66 (10.95%)
Chemotherapy - at home	8 (3.16%)	3 (1.20%)	7 (7.00%)	18 (2.99%)
Hormonal treatment	42 (16.60%)	45 (18.00%)	19 (19.00%)	106 (17.58%)
Radiotherapy	13 (5.14%)	9 (3.60%)	3 (3.00%)	25 (4.15%)
Surgery	12 (4.74%)	15 (6.00%)	1 (1.00%)	28 (4.64%)
Other	18 (7.11%)	20 (8.00%)	19 (19.00%)	57 (9.45%)
Prefer not to answer	2 (0.79%)	1 (0.40%)	0	3 (0.50%)
When did you start receiving this treatment?				
Less than 1 year ago	35 (13.83%)	27 (10.80%)	26 (26.00%)	88 (14.59%)
Between 1 and 5 years ago	52 (20.55%)	47 (18.80%)	30 (30.00%)	129 (21.39%)
More than 5 years ago	13 (5.14%)	19 (7.60%)	4 (4.00%)	36 (5.97%)
Prefer not to answer	0	0	0	0
How often do you currently receive treatment?				
More than once every week	40 (15.81%)	39 (15.60%)	31 (31.00%)	110 (18.24%)
Once every week	13 (5.14%)	10 (4.00)	3 (3.00%)	26 (4.31%)
Once every 2 weeks	7 (2.77%)	11 (4.40%)	4 (4.00%)	22 (3.65%)
Once every 3 weeks	18 (7.11%)	16 (6.40%)	13 (13.00%)	47 (7.79%)
Less than once every 3 weeks	20 (7.91%)	13 (5.20%)	9 (9.00%)	42 (6.97%)
Prefer not to answer	2 (0.79%)	4 (1.60%)	0	6 (1.00%)

Question	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
All respondents				
Have you received any previous treatments for cancer since you were first diagnosed?				
Yes	135 (53.36%)	154 (61.60%)	76 (76.00%)	365 (60.53%)
No	118 (46.64%)	95 (38.00%)	24 (24.00%)	237 (39.30%)
Prefer not to answer	0	1 (0.40%)	0	1 (0.17%)
If yes, what type of treatments have you previously received? (More than 1 month ago) (Choose all that apply) [a]	n=135	n=154	n=76	n=365
Chemotherapy - in the hospital	59 (23.32%)	72 (28.80%)	57 (57.00%)	188 (31.18%)
Chemotherapy - at home	7 (2.77%)	4 (1.60%)	9 (9.00%)	20 (3.32%)
Hormonal treatment	27 (10.67%)	36 (14.40%)	10 (10.00%)	73 (12.11%)
Radiotherapy	60 (23.72%	68 (27.20%)	35 (35.00%)	163 (27.03%)
Surgery	82 (32.41%)	92 (36.80%)	34 (34.00%)	208 (34.49%)
Other	15 (5.93%)	11 (4.40%)	11 (11.00%)	37 (6.14%)
Prefer not to answer	1 (0.40%)	0	0	1 (0.17%)
All respondents				
Has your cancer ever relapsed (where cancer returns after treatment)?				
Yes	49 (19.37%)	40 (16.00%)	25 (25.00%)	114 (18.91%)

Question	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
No	202 (79.84%)	206 (82.40%)	71 (71.00%)	479 (79.44%)
Prefer not to answer	2 (0.79%)	4 (1.60%)	4 (4.00%)	10 (1.66%)
Do you feel you have enough information about your cancer diagnosis, the available services and treatment options to manage your cancer?				
Yes	185 (73.12%)	204 (81.60%)	55 (55.00%)	444 (73.63%)
No	37 (14.62%)	10 (4.00%)	19 (19.00%)	66 (10.95%)
I don't know	30 (11.86%)	36 (14.40%)	26 (26.00%)	92 (15.26%)
Prefer not to answer	1 (0.40%)	0	0	1 (0.17%)
Apart from your cancer diagnosis, how would you classify your current health today?				
Excellent	19 (7.51%)	11 (4.40%)	3 (3.00%)	33 (5.47%)
Very good	45 (17.79%)	34 (31.60%)	17 (17.00%)	96 (15.92%)
Good	88 (34.78%)	91 (36.40%)	31 (31.00%)	210 (34.83%)
Fair	79 (31.23%)	94 (37.60%)	40 (40.00%)	213 (35.32%)
Poor	22 (8.70%)	20 (8.00%)	9 (9.00%)	51 (8.46%)
Prefer not to answer	0	0	0	0

SD = standard deviation.

Note: The percentage totals may not sum exactly to 100% because of rounding.

[a] Respondents could provide multiple responses to these questions. Therefore, the totals may exceed the total number of respondents.

Appendix 8: Summary of Responses to Comprehension Questions Among Respondents

Questions	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
DCE questions				
How easy or difficult was it to choose between the 2 scenarios in the previous section?				
Very easy	51 (20.16%)	55 (22.00%)	15 (15.00%)	121 (20.07%)
Somewhat easy	120 (47.43%)	109 (43.60%)	29 (29.00%)	258 (42.79%)
Neither difficult or easy	60 (23.72%)	59 (23.60%)	26 (26.00%)	145 (24.05%)
Somewhat difficult	20 (7.91%)	26 (10.40%)	26 (26.00%)	72 (11.94%)
Very difficult	2 (0.79%)	1 (0.40%)	4 (4.00%)	7 (1.16%)
How well did you understand the scenarios in the previous section?				
Fully understood the scenarios	161 (63.64%)	117 (46.80%)	67 (67.00%)	345 (57.21%)
Somewhat understood the scenarios	88 (34.78%)	130 (52.00%)	31 (31.00%)	249 (41.29%)
Did not understand the scenarios	4 (1.58%)	3 (1.20%)	2 (2.00%)	9 (1.49%)
Time until progression of disease (the amount of time after initiation of treatment the disease is under control)				
Fully understood this characteristic	175 (69.17%)	122 (48.80%)	62 (62.00%)	359 (59.54%)

Questions	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
Somewhat understood this characteristic	70 (27.67%)	120 (48.00%)	33 (33.00%)	223 (36.98%)
Somewhat misunderstood this characteristic	3 (1.19%)	6 (2.40%)	5 (5.00%)	14 (2.32%)
Did not understand this characteristic	5 (1.98%)	2 (0.80%)	0	7 (1.16%)
Treatment administration (how the treatment is administered, for instance directly into a vein or by taking a pill/tablet)				
Fully understood this characteristic	210 (83.0%)	178 (71.20%)	94 (94.00%)	482 (79.93%)
Somewhat understood this characteristic	37 (14.62%)	64 (25.60%)	5 (5.00%)	106 (17.58%)
Somewhat misunderstood this characteristic	2 (0.79%)	5 (2.00%)	1 (1.00%)	8 (1.33%)
Did not understand this characteristic	4 (1.58%)	3 (1.20%)	0	7 (1.16%)
Location of treatment (where the treatment is taken, for instance at a hospital/clinic or at home)				
Fully understood this characteristic	214 (84.58%)	193 (77.20%)	94 (94.00%)	501 (83.08%)
Somewhat understood this characteristic	35 (13.83%)	51 (20.40%)	5 (5.00%)	91 (15.09%)
Somewhat misunderstood this characteristic	1 (0.40%)	5 (2.00%)	1 (1.00%)	7 (1.16%)
Did not understand this characteristic	3 (1.19%)	1(0.40%)	0	4 (0.66%)

Questions	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
Impact of side effects on quality of life (the severity of the impact of treatment side effects (fatigue, nausea, hair loss, pain, etc.), on daily activities)				
Fully understood this characteristic	196 (77.47%)	161 (64.40%)	87 (87.00%)	444 (73.63%)
Somewhat understood this characteristic	50 (19.76%)	84 (33.60%)	12 (12.00%)	146 (24.21%)
Somewhat misunderstood this characteristic	2 (0.79%)	5 (2.00%)	1 (1.00%)	8 (1.33%)
Did not understand this characteristic	5 (1.98%)	0	0	5 (0.83%)
Time until progression of disease. Please select the situation that best describes time until progression of disease:				
Time until the disease spreads, and the disease becomes worse	82 (32.41%)	67 (26.80%)	79 (79.00%)	228 (37.81%)
Time until the disease reduces or disappears, and the disease gets better	72 (28.46%)	92 (36.80%)	5 (5.00%)	169 (28.03%)
Time until the disease becomes less severe	22 (8.70%)	14 (5.60%)	6 (6.00%)	42 (6.97%)
Time until the disease does not require any treatment anymore	57 (22.53%)	77 (30.80%)	10 (10.00%)	144 (23.88%)
Missing	20 (7.91%)	0	0	20 (3.32%)
TTO Questions				

Questions	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
How easy or difficult was it to complete the choice exercise 2, where you were asked to make trade-offs with different treatment scenarios?				
Very easy	17 (6.72%)	26 (10.40%)	6 (6.00%)	49 (8.13%)
Somewhat easy	56 (21.34%)	54 (21.60%)	12 (12.00%)	122 (20.23%)
Neither difficult or easy	34 (13.44%)	28 (11.20%)	10 (10.00%)	72 (11.94%)
Somewhat difficult	20 (7.91%)	15 (6.00%)	14 (14.00%)	49 (8.13%)
Very difficult	0	1 (0.40%)	8 (8.00%)	9 (1.49%)
Missing	126 (49.80%)	126 (50.40%)	50 (50.00%)	302 (50.08%)
How well did you understand the choice exercise 2, where you were asked to make understood the exercise with different treatment scenarios?				
Fully understood the exercise	69 (27.27%)	51 (20.40%)	35 (35.00%)	155 (25.70%)
Somewhat understood the exercise	54 (21.34%)	63 (25.20%)	13 (13.00%)	130 (21.56%)
Somewhat misunderstood this exercise	2 (0.79%)	10 (4.00%)	1 (1.00%)	13 (2.16%)
Did not understand the exercise	2 (0.79%)	0	1 (1.00%)	3 (0.50%)
Missing	126 (49.80%)	126 (50.40%)	50 (50.00%)	302 (50.08%)
Swing-Weighting Questions				

Questions	Spain All Respondents N = 253	Italy All Respondents N = 250	Croatia All Respondents N = 100	All Countries All Respondents N=603
How easy or difficult was it to complete the choice exercise 3, where you were asked to provide points to different treatment impacts?				
Very easy	23 (9.09%)	17 (6.80%)	5 (5.00%)	45 (7.46%)
Somewhat easy	50 (19.76%)	42 (16.80%)	4 (4.00%)	96 (15.92%)
Neither difficult or easy	34 (13.44%)	45 (18.00%	21 (21.00%)	100 (16.58%)
Somewhat difficult	13 (5.14%)	17 (6.80%)	14 (14.00%)	44 (7.30%)
Very difficult	6 (2.37%)	5 (2.00%)	6 (6.00%)	17 (2.82%)
Missing	127 (50.20%)	124 (49.60%)	50 (50.00%)	301 (49.92%)
How well did you understand the choice exercise 3, where you were asked to provide points to different treatment impacts?				
Fully understood the exercise	56 (22.13%)	29 (11.60%)	17 (17.00%)	102 (16.92%)
Somewhat understood the exercise	58 (22.92%)	65 (26.00%)	25 (25.00%)	148 (24.54%)
Somewhat misunderstood the exercise	10 (3.95%)	28 (11.20%)	6 (6.00%)	44 (7.30%)
Did not understand the exercise	2 (0.79%)	4 (1.60%)	2 (2.00%)	8 (1.33%)
Missing	127 (50.20%)	124 (49.60%)	50 (50.00%)	301 (49.92%)

Note: The percentage totals may not sum exactly to 100% because of rounding.