1. SYNOPSIS/ABSTRACT

Title

Survey to evaluate the effectiveness of risk minimization measures for atezolizumab use in the European Union.

Keywords

Post-authorization study, cross-sectional survey, safety messages, Tecentriq®, risk minimization, atezolizumab.

Rationale and Background

Tecentriq® (atezolizumab) is an Fc-engineered, humanized, monoclonal antibody targeting human programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells and tumor cells. Tecentriq® received marketing authorization from the European Commission in September 2017 for the treatment of locally advanced or metastatic urothelial carcinoma (UC) and locally advanced or metastatic non-small cell lung cancer (NSCLC) patients.

The following important immune-related adverse drug reactions (irADRs) associated with the use of Tecentriq® were identified to require additional risk minimization measures (aRMMs): immune-related pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis and infusion related reactions (IRRs). The aim of the Tecentriq® aRMMs (healthcare professional (HCP) Guide and patient alert card (PAC)) is to minimize the consequences of these adverse reactions by increasing the physician´s awareness of irADRs to facilitate early detection and prompt treatment.

The MAH proposed a physician survey to the EMA to assess receipt of, understanding and use, knowledge and behavior outlined in the aRMMs among physicians and to assess whether the aRMMs are effective in informing physicians to recognize and manage irADRs.

Research Question and Objectives

The primary objective of this study was to assess receipt of the Tecentriq® HCP Guide and PAC for the target physician population and to assess the level of knowledge of key messages related to irADRs outlined in the Tecentriq® HCP Guide and PAC.

The secondary objectives of this study were to assess:

- Self-reported understanding of key messages related to irADRs outlined in the Tecentriq® HCP Guide
- Use of the Tecentriq® HCP Guide and PAC
- Behavior consistent with key messages related to irADRs outlined in the Tecentriq® HCP Guide and PAC
- Knowledge according to receipt and use of the Tecentriq® aRMMs

- Behavior consistent with key message, according to receipt and use of the Tecentriq® aRMMs

Amendment and Updates to Protocol

None.

Study Design

This was a multi-country, one-wave, cross-sectional physician survey using stratified random sampling from panels of physicians within each participating country.

Setting

Oncologists, urologists and pulmonologists in Denmark, Germany, Italy, Spain, Sweden and the United Kingdom.

Subject and study size (including dropouts)

Physicians who prescribed or managed at least one patient with Tecentriq® in their routine clinical practice provided data in each country within 9 to 18 months of each country-specific launch.

The total target study population was 300 evaluable physicians across the participating countries and a minimum of 10 evaluable physicians in any country but varying numbers of oncologists, pulmonologists and urologists across the countries based on clinical practice. The total sample of 300 physicians allowed precision of ±5.8% to ±3.6% for correct responses ranging from 50% to 90%, respectively.

Variables and Data Sources

A network of registered physicians (panel) was used to identify oncologists, pulmonologists and urologists to participate in the survey who prescribed or managed Tecentriq® in routine clinical practice. The survey was conducted through an on-line questionnaire consisting of multiple-choice questions.

The main questionnaire domains and calculations were:

- Receipt: Percentage of respondents that reported having received the HCP Guide and PAC.
- Knowledge: awareness, identification, monitoring and management of irADRs and awareness of the need to report them. Percentage of respondents that correctly answered each knowledge question. An individual physician score (0 – 100) was calculated from the proportion of all knowledge questions with correct responses.
- Self-reported understanding of key messages in the HCP Guide. Percentage of respondents that reported having understood the HCP Guide.

- Use of the HCP Guide and PAC, i.e. whether physicians read and refer to the HCP Guide, inform patients of the risks associated with Tecentriq®, complete and hand out the PAC to patients. Percentage of respondents that reported having read or used the HCP Guide and PAC. An individual physician score was calculated as the proportion of all use questions with correct responses.
- Behavior related to the identification, monitoring and management of irADRs. Percentage of respondents that correctly answered each behavior question. An individual physician score (0 – 100) was calculated from the proportion of all behavior questions with correct responses.

Statistical analyses were descriptive. Continuous variables were described by number, mean, standard deviation, median, interquartile range, minimum and maximum. Categorical variables were described as the total number and relative percentage per category. Confidence intervals of 95% were calculated, where relevant. Pre-specified subgroup analyses were conducted by country, physician specialty and time since last contact with a patient on Tecentriq®. Knowledge and behavior by receipt and non-receipt of the HCP guide and PAC were calculated. The percentages with correct responses ≥70% for each domain were calculated. Missing values were not included in the denominators for proportions and no imputation was performed for the main analyses. Sensitivity analyses were conducted assuming missing to be incorrect responses.

Results

The analyzable study population consisted of 313 physicians and was selected through the following process:

- *The Study Population* (invited =6881) included all physicians (oncologist, pulmonologists, and urologist) in the panel database in the participating countries who were invited.
- *The Evaluable Set* (responders=760) consisted of all physicians who were successfully contacted and provided information sufficient to assess their eligibility for the study.
- *The Eligible Set* (=378) consisted of all physicians among responders who fulfilled all the inclusion and none of the exclusion criteria.
- *The Enrolled Set* (=371) consisted of all eligible physicians who accessed the eCRF to answer the online self-administered questionnaire.
- *The Full Analysis Set* (=313) included all enrolled physicians who completed the online self-administered questionnaire, and for whom at least one response was available to questions, not including the HCP profile questions.
- Participation rates were 11.0% (760/6881) among responders/invited and 82.8% (313/378) for analyzed/eligible.

The distribution of the 313 physicians varied by:

- Country (N; %): Denmark (11; 3.5%), Germany (91; 29.1%), Italy (88; 28.1%), Spain (47; 15.0%), Sweden (13; 4.2%) and the UK (63; 20.1%).

- Specialty (N; %): oncologists (255; 81.6%), urologists (28; 9.0%) and pulmonologists (30: 9.6%).
- Gender: females comprised 26.8% and males 73.2%
- Age group (years): less than 30 years (1.0%), 30-45 years (47.3%), 46-65 years (50.8%) and greater than 65 years (1.0%).
- Type of setting: office based (14.4%), hospital-based (72.8%), office and hospital-based (12.8%).
- Experience (years) in managing oncology patients: less than 3 years (0.3%), 3-5 years (4.5%), 6-10 years (17.0%) and greater than 10 years (78.3%).
- Time since last contact with a patient using Tecentriq®: 0-3 months (89.1%) and more than 3 months (10.9%).

Receipt was reported by 77.4% (240/310) for the HCP Guide and 74.2% (230/310) for the PAC. Receipt of the HCP Guide varied by:

- Country: Denmark (81.8%), Germany (71.1%), Italy (80.5%), Spain (78.3%), Sweden (84.6%) and the UK (79.4%).
- Specialty: oncologists (80.6%), urologists (59.3%) and pulmonologists (66.7%).
- Time since last contact with a patient using Tecentriq®: 0-3 months (76.8%) and more than 3 months (82.4%).

Reported receipt of the PAC varied by:

- Country: Denmark (72.7%), Germany (63.3%), Italy (85.1%), Spain (73.9%), Sweden (69.2%) and the UK (76.2%).
- Specialty: oncologists (77.8%), urologists (51.8%) and pulmonologists (63.3%).
- Time since last contact with a patient using Tecentriq®: 0-3 months (73.5%) and more than 3 months (79.4%).

The sources of receipt or access to the materials were: pharmaceutical representative (81.6%), congress/symposia (37.6%), pharmaceutical company website (36.4%), regulatory authority/formulary website (30.1%), regular post (28.9%), colleagues (27.2%) and e-prescribing prompts (17.2%).

For **knowledge,** the average score for overall correct responses (across all questions in the knowledge domain) was 63.9 (SD: 15.9) and 39.4% of physicians had correct knowledge scores ⩾70. There were no notable differences in these results across the pre-specified subgroups. Knowledge scores of the materials varied by:

- Country: Denmark (74.5), Germany (60.7), Italy (62.6), Spain (65.0), Sweden (62.5) and the UK (67.9).
- Specialty: oncologists (64.9), urologists (60.4) and pulmonologists (58.1).
- Time since last contact with a patient using Tecentriq®: 0-3 months (64.0) and more than 3 months (62.8).

The average overall correct knowledge scores by reported receipt of materials were: 66.8 (SD 13.9) for receiving both the HCP Guide and PAC, 59.4 (SD 15.9) for one of the materials, and 60.8 (SD 16.9) for having received none of the materials.

The percentage of physicians who had average correct knowledge scores ⩾70 by reported receipt of materials were: 43.8% for receiving both the HCP Guide and PAC, 28.1% for one of the materials, and 37.5% for having received none of the materials.

For **self-reported understanding**, the overall average score for the response to self-reported understanding (calculated from the ordinal responses to the one question about self-reported understanding, with the response ´I do not remember´ treated as missing) was 96.0. There were 89.0% of physicians who had correct self-reported understanding scores ≥70. Overall, 85.4% (146/171) of physicians who had read the HCP Guide reported having ´completely understood´ it, 1.2% did not understand most of the information, 9.4% found it too difficult to understand and 0.0% did not understand it at all. The figures were similar in pre-specified subgroups.

The percentage for complete understanding of the HCP Guide varied by:

- Country: Denmark (87.5%), Germany (83.3%), Italy (81.3%), Spain (88.9%), Sweden (88.9%) and the UK (89.5%).
- Specialty: oncologists (87.3%), urologists (72.7%) and pulmonologists (72.7%).
- Time since last contact with a patient using Tecentriq®: 0-3 months (86.4%) and more than 3 months (79.2%).

For **Usage**, among the 267 physicians who received the materials, 71.3% had read the HCP Guide and 31.6% reported that they referred to it frequently. Overall, the average correct usage score (calculated across all questions in the domain) was 69.5, and 57.1% of physicians had scores ≥70.

These average scores for correct usage were similar in most of the pre-specified subgroups.

- Country: Denmark (55.9), Germany (70.8), Italy (72.4), Spain (62.1), Sweden (69.7) and the UK (70.8).
- Specialty: oncologists (69.3), urologists (70.9) and pulmonologists (69.6).
- Time since last contact with a patient using Tecentriq®: 0-3 months (68.4) and more than 3 months (77.1).

The reasons given by the 17 physicians who reported not providing the PAC to patients were: ´Somebody else is responsible for handing it out´ (35.3%), ´I have not had time to hand it out´ (11.8%), ´I forgot to hand it out´(17.7%), ´It is not useful´(11.8%), and ´I don´t remember´(35.3%).

Reasons given by the 28 physicians who reported not completing their contact details on the PAC at all were: ´Somebody else is responsible for handing it out´ (35.7%), ´I have not had time´ (14.3%), ´I forgot´(17.9%), ´It is not useful´(17.9%), ´other´(3.6%) and ´I don´t remember´(28.6%).

For **behavior,** the average score for overall correct responses (across all questions in the behavior domain) was 78.9, and 74.8% of physicians had behavior scores ≥70.

The average overall correct behavior scores of the aRMMs were broadly similar across the pre-specified subgroups:

- Country: Denmark (83.6), Germany (78.7), Italy (77.9), Spain (76.5), Sweden (81.5) and the UK (81.0).
- Specialty: oncologists (79.2), urologists (77.0) and pulmonologists (77.9).
- Time since last contact with a patient using Tecentriq®: 0-3 months (79.4) and more than 3 months (74.7).

The average correct behavior scores by reported receipt of materials were: 79.0 (SD 18.0) for receiving both the Guide and PAC, 76.9 (SD 18.6) for one of the materials and 81.5 (SD 20.5) for having received none of the materials.

The percentage of physicians who had average behavior scores ≥70 by reported receipt of materials were: 74.9% for receiving both the HCP Guide and PAC, 73.4% for one of the materials and 74.9% for having received none of the materials.

92.9% of physicians had counselled their last patient about the signs and symptoms of irADRs associated with Tecentriq® and 94.5% had counselled their last patient to contact their treating doctor immediately if they were to experience symptoms of irADRs.

Among 230 physicians who received the PAC, 54.8% provided them to all patients and 30.4% to most patients. Counselling all patients to carry the PAC at all times was done by

57.0% of physicians and to most patients by 26.5% of physicians. Completion of the PAC with contact details was done completely by 57.8% and partially by 25.7% of physicians.

Discussion

The planned target number of participants for analysis was achieved within the planned timeframe of the study with oncologists, pulmonologists and urologists in panels in Denmark, Germany, Italy, Spain, Sweden and the UK in the 9 to 18-month period after the launch of Tecentriq® in each country. Participation rates based on enrolment/eligible exceeded 80%, suggesting that physicians in the current study are representative of those in the panel from which they were sampled.

The proportion of physicians who reported to have received the HCP Guide and the PAC exceeded the pre-specified threshold of 70%. Over 70% of physicians who received the materials read them, although the actual use of these materials in practice appears limited. While most physicians who read the materials reported understanding them, the overall mean knowledge score did not reach the pre-specified target of ≥70. Knowledge scores and behavior scores were similar regardless of whether physicians received the materials or not, with behavioral scores exceeding the pre-specified threshold.

All results are based on self-report. While physicians who responded to the survey may be representative of the panel from which they were sampled, physicians who agree to participate in the panel may represent a self-selected group relative to the underlying general population of all physicians in each country. Low knowledge scores may be affected by a number of factors including potentially increased difficulty with identifying “false” risks (e.g., NOT amnesia) relative to “true positive” risks, or conflicting messages from other materials as well as exposure and impact from other materials on the market. Furthermore, different irADRs are listed for different immunotherapies on the market. Under-usage of materials may be due to physicians utilizing other materials or resources outside of the Tecentriq® HCP Guide and PAC including resources as well as primarily referring to the SmPC.

As these materials represent guidance for treatment, physicians in the real-world setting may only refer to them when they feel they need to. Access to resources outside of the current materials may also contribute to the high behavioral score and may explain the potential lack of difference in knowledge score associated with the current materials.

Conclusion

The educational materials reached over 70% of target physicians, 57.1% of whom reported using them. Despite demonstrating knowledge scores below the threshold, physicians reported scores for understanding and behavior that exceeded the threshold.

Thus, it appears that the additional risk minimization measures may not impact knowledge nor change physician behavior related to irADRs for Tecentriq®.

Marketing Authorization Holder(s)

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Roche was the MAH which oversaw MAH activities and Competent Authority submissions.

The MAH representative for this study was OXON Epidemiology, a Clinical Research Organization (CRO) delegated to serve as the study coordinating center. OXON Epidemiology conducted the study on behalf of Roche.

The MAH representative was responsible for overall conduct, deliverables and timelines for the study and communication with Roche.

Names and affiliations of principal physicians

Not applicable.