SYNOPSIS OF RESEARCH REPORT
(PROTOCOL ML28446)

NAME OF SPONSOR/COMPANY: F. Hoffmann-La Roche Ltd. NAME OF STUDY TREATMENT: Bevacizumab (RO4876646) TRADENAME: Avastin®	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY	An Indian Multicentric, Open Label, Prospective, Phase IV Study of Bevacizumab in the Front Line Management of Advanced/Metastatic Epithelial Ovarian Cancer, Fallopian Tube Cancer or Primary Peritoneal Cancer in Real-Life Clinical Practice.
NUMBER OF STUDY CENTERS AND COUNTRIES	This study was conducted at 13 center(s) in India.
PUBLICATIONS (IF ANY)	Not Applicable.
STUDY PHASE	Phase IV
STUDY PERIOD	First participant enrolled: 23-Dec-2021 Data cutoff: 30-Jul-2025 Last participant last visit: 18-Jun-2025
METHODOLOGY	This was a Phase IV, single-arm, open-label, prospective, multicenter study evaluating the safety and efficacy of bevacizumab in combination with standard chemotherapy (carboplatin and paclitaxel) for front-line treatment of advanced/metastatic epithelial ovarian, fallopian tube, or primary peritoneal cancer (FIGO Stage IIIB–IV) in the Indian population. A total of 100 patients were enrolled over approximately 12 months. The study included a Screening Phase, a Treatment Phase, and a Post-Treatment Follow-Up Phase.

<table>
<tr><td></td><td>During treatment, patients received five cycles of bevacizumab 15 mg/kg concurrently with six cycles of standard chemotherapy (paclitaxel and carboplatin) every three weeks (q3w), followed by extended cycles of bevacizumab 15 mg/kg q3w as a single agent for an additional 16 cycles. A total of 21 cycles of bevacizumab were administered in the study, with the first cycle of bevacizumab administered concurrently on Cycle 2 of the standard chemotherapy. Treatment continued until completion of planned cycles, disease progression, unacceptable toxicity, or death.</td></tr>
<tr><td>NUMBER OF PARTICIPANTS (PLANNED AND ANALYZED)</td><td>Planned: 100 patients across multiple study centers in India.

Analyzed: A total of 104 patients were screened for participation in the study. Of these, 100 patients (96.2%) were enrolled based on eligibility criteria. Among the enrolled patients, 98 patients (94.2% of those screened) received at least one dose of the study drug and were included in the Safety Population. The Efficacy Population comprised 94 patients (90.4% of those screened) who met all inclusion criteria, received at least one dose of Bevacizumab, and had at least one post-baseline efficacy assessment available.

Overall, 45 patients (45.0%) completed the study, while 55 patients (55.0%) discontinued early due to various reasons, including adverse events, withdrawal of consent, disease progression, or loss to follow-up.

<table>
<tr><th>Population</th><th>Statistics n(%)</th></tr>
<tr><td>Screened</td><td>104 (100%)</td></tr>
<tr><td>Enrolled</td><td>100 (96.2)</td></tr>
<tr><td>Safety Population</td><td>98 (94.2)</td></tr>
<tr><td>Efficacy population</td><td>94 (90.4)</td></tr>
<tr><td>Completed the study</td><td>45 (45.0)</td></tr>
<tr><td>Discontinued the study</td><td>55 (55.0)</td></tr>
</table>
</td></tr>
<tr><td>DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION</td><td>Patients with Advanced/Metastatic Epithelial Ovarian Cancer, Fallopian Tube Cancer or Primary Peritoneal Cancer were enrolled in Study ML28446.
Key inclusion criteria are provided below:
• Female subjects ≥18 years of age
• Subjects signed informed consent
• Subjects who were prescribed to receive bevacizumab for advanced/metastatic epithelial</td></tr>
</table>

	ovarian cancer, fallopian tube cancer or primary peritoneal cancer (FIGO Stage IIIb, IIIc and IV) according to the routine clinical practice. • Women of childbearing potential who agreed to use adequate contraception (per institutional standard of care) during treatment and until 6 months after the last administration of bevacizumab. Key exclusion criteria are provided below: • Subjects who were considered not eligible to receive bevacizumab for advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc and IV) according to the local prescribing information and investigator's discretion were not enrolled in the study.
STUDY TREATMENTS, DOSE, MODE OF ADMINISTRATION	The investigational medicinal product (IMP) for this study was Bevacizumab. The non-investigational therapies administered concurrently were Paclitaxel and Carboplatin. During the treatment phase, patients received Bevacizumab in combination with Paclitaxel and Carboplatin chemotherapy followed by Bevacizumab monotherapy. Bevacizumab 15 mg/kg was administered intravenously every 3 weeks for five cycles concurrently with six cycles of standard chemotherapy (Paclitaxel and Carboplatin). Thereafter, patients continued to receive Bevacizumab 15 mg/kg every 3 weeks as a single agent for up to 16 additional cycles or until disease progression or death, whichever occurred earlier. A total of 21 cycles of Bevacizumab were planned in this study. Paclitaxel and Carboplatin were administered according to locally approved prescribing information. All dose modifications, interruptions, and discontinuations were managed as per protocol and local label recommendations, with corresponding documentation in the eCRF. Medication errors or overdoses, along with any related adverse events, were reported according to pharmacovigilance procedures.
DURATION OF STUDY PARTICIPATION	**During Concurrent cycles:** • Patients received six cycles of paclitaxel and carboplatin: on Day 1 of Cycle 1 to Cycle 6, as per local prescribing information, q3w. • And, five cycles of bevacizumab: on Day 1 of Cycle 2 to Cycle 6, as 15 mg/kg q3w.

	During Extended cycles: • Patients received sixteen cycles of bevacizumab: on Day 1 of Cycle 7 to Cycle 22, as 15 mg/kg q3w. The duration of each cycle was 21 days (every three weeks). The end of this study was defined as the date when the last patient's last visit occurred, which was anticipated to be the timepoint at which all patients enrolled in the study either had at least 2 years of follow-up from the time of the treatment-completion visit or had discontinued the study.

SUMMARY OF OBJECTIVES, ENDPOINTS/ESTIMANDS, AND STATISTICAL METHODS

Study ML28446 evaluated the safety and efficacy of Bevacizumab in the Front Line Management of Advanced/Metastatic Epithelial Ovarian Cancer, Fallopian Tube Cancer or Primary Peritoneal Cancer in Real-Life Clinical Practice. Objectives and endpoints of the study are outlined in Table 1.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the safety profile (all grade 3 and above) of bevacizumab when added to standard chemotherapy (carboplatin and paclitaxel) in front line advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV) in Indian population.	• Incidence of adverse events (AEs) of Grade 3 and above as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 • Incidence of serious adverse events (SAEs) as per NCI-CTCAE, version 4.03 • Incidence of adverse events of special interest (AESI) • Laboratory results abnormalities
Secondary	
To assess the efficacy of Bevacizumab Based on below parameters. • Progression-free survival (PFS) • Overall survival (OS)	• Progression-free survival, defined as the time from enrollment to the first radiographically documented disease progression as determined by the investigator using Response Evaluation

Objectives	Endpoints
• Overall response rates (ORR; complete response [CR] + partial response [PR]) • Clinical benefit response rates (CR + PR + stable disease [SD])	Criteria in Solid Tumors (RECIST) criteria, version 1.1, or death from any cause, whichever occurs first. • Overall Survival, defined as the time from the date of enrollment to the date of death, regardless of the cause of death. • Overall response rate (CR + PR), determined by the investigator using RECIST criteria v1.1. Overall response rate is defined as the best response recorded from the start of study treatment until disease progression/recurrence or death and confirmed ≥4 weeks later. • Clinical benefit response rates (CR + PR + SD)

AE = adverse event; AESI = adverse event of special interest; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; FIGO = International Federation of Gynecology and Obstetrics; NCI = National Cancer Institute; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE = serious adverse event; SD = stable disease.

SUMMARY OF RESULTS AND CONCLUSIONS

DISPOSITION OF PARTICIPANTS

A total of 104 subjects were screened, of whom 100 (96.2%) were enrolled. Four subjects (3.8%) failed screening. Among enrolled subjects, 98 (94.2% of those screened) received at least one dose of study medication and were included in the Safety Population, while 94 subjects (90.4%) with post-baseline efficacy assessments comprised the Efficacy Population. Of the 100 enrolled subjects, 98 (98.0%) initiated treatment, and 41 (41.0%) completed the full course of bevacizumab therapy. Overall, 45 subjects (45.0%) completed the study (treatment plus follow-up), while 55 subjects (55.0%) discontinued early.

The primary reasons for discontinuation were withdrawal of consent (18 subjects; 32.7%), lost to follow-up (14; 25.5%), and death (12; 21.8%). Other reasons included investigator discretion (4; 7.3%), adverse events (2; 3.6%), and disease progression or recurrence (5; 9.1%). No discontinuations were due to sponsor-related reasons.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All 98 treated subjects were female (100%) and not Hispanic or Latino (100%). The mean age was 52.9 years (range 26-74), and the mean BMI was 23.0 kg/m². Most subjects (96; 98.0%) were not of childbearing potential.

Among treated subjects, the majority had advanced/metastatic epithelial ovarian cancer (89; 90.8%), followed by primary peritoneal cancer (5; 5.1%) and fallopian tube cancer (4; 4.1%); one subject (1.0%) had papillary adenocarcinoma, and one had dual ovarian and fallopian tube involvement.

By FIGO stage, Stage IIIc was most common (51; 52.0%), followed by Stage IV (28; 28.6%) and Stage IIIb (19; 19.4%). Prior surgery occurred in 77 subjects (78.6%), and cancer therapy in 56 (57.1%); none received radiotherapy.

EXPOSURE

A total of 98 patients received Bevacizumab, with a mean treatment duration of 44.8 weeks (SD 21.73; range 0.1-78.7) and a median of 56.3 weeks. Across all patients, 1,426 cycles were administered, with an average of 14.6 cycles per patient (SD 7.03; range 1-21). The majority (41 patients; 41.8%) completed the maximum 21 cycles, while others received 1-20 cycles, most commonly between 1 and 13. No infusion modifications were required; all patients completed infusions as scheduled. All calculations were based on the Safety Population, with treatment duration defined as the interval between first and last dose plus one day.

EFFICACY RESULTS

This clinical study report (CSR) presents the final efficacy results based on the last patient last visit (LPLV) 18-Jun-2025 data cut-off of 30-Jul-2025. The study was non-randomized and single-arm, designed to assess the safety and efficacy of Bevacizumab in combination with standard chemotherapy in patients with advanced or metastatic epithelial ovarian, fallopian tube, or primary peritoneal cancer. An overview of key efficacy results is provided in Table 2.

Primary Efficacy Endpoint

Overall Survival (OS)

At data cut-off, among 94 patients in the efficacy population, 11 patients (11.7%) experienced an OS event (death), while 83 patients (88.3%) were censored. The median OS was not estimable (95% CI: 36.60, NE), with the first quartile (Q1) at 36.60 months. The Kaplan-Meier estimated OS rate remained high through early follow-up, with 98.9% at Months 3 and 6, 96.3% at Month 12, and 87.8% at Month 24, gradually declining to 72.2% at Month 39.

When analyzed by baseline ECOG performance status, median OS was not estimable for either subgroup (ECOG 0 or 1–2). OS rates remained ≥94.4%

through Month 39 for ECOG 0, and ≥86.2% through Month 24 for ECOG 1–2, with no statistically significant difference between groups (p = 0.3703).

Key Secondary Efficacy Endpoint

Progression-Free Survival (PFS)

In the efficacy population (N = 94), 19 patients (20.2%) experienced a PFS event (disease progression or death), while 75 patients (79.8%) were censored. The median PFS was 23.85 months (95% CI: 15.77, 30.75). PFS rates were 97.8% at Month 3, 85.6% at Month 12, and 13.6% at Month 36.
When analyzed by ECOG performance status, the median PFS was not estimable (95% CI: 15.60, NE) for ECOG 0 and 23.85 months (95% CI: 15.77, 30.75) for ECOG 1–2, with no statistically significant difference (p = 0.4636).

Other Secondary Efficacy Endpoints

Overall Response Rate (ORR)

The ORR (CR + PR) was 24.5% (95% CI: 16.2-34.4), including 6 patients (6.4%) with a complete response (CR) and 17 patients (18.1%) with a partial response (PR), per RECIST v1.1 criteria.

Clinical Benefit Rate (CBR)

The CBR (CR + PR + SD) was 47.9% (95% CI: 37.5-58.4), comprising 23 patients (24.5%) with an overall response and 22 patients (23.4%) with stable disease (SD). Responses were confirmed ≥4 weeks later as per RECIST v1.1.

Table 2 Efficacy Summary

Endpoint	Parameter/ Statistic	Result (Bevacizumab)	95% Confidence Interval (CI)
Overall Survival (OS)	Number of events (deaths), n (%)	11 (11.7%)	–
	Median OS (months)	NE	(36.60, NE)
	OS rate at 12 months	96.3%	(0.9, 1.0)
	OS rate at 24 months	87.8%	(0.8, 0.9)
Progression-Free Survival (PFS)	Number of PFS events (progression or death), n (%)	19 (20.2%)	–
	Median PFS (months)	23.85	(15.77, 30.75)
	PFS rate at 12 months	85.6%	(0.8, 0.9)

	PFS rate at 24 months	40.8%	(0.1, 0.7)
Overall Response Rate (ORR)	CR + PR, n (%)	23 (24.5%)	(16.2, 34.4)
	Complete Response (CR), n (%)	6 (6.4%)	(2.4, 13.4)
	Partial Response (PR), n (%)	17 (18.1%)	(10.9, 27.4)
Clinical Benefit Rate (CBR)	CR + PR + SD, n (%)	45 (47.9%)	(37.5, 58.4)
ECOG 0 vs 1–2 (OS)	Median OS (months)	NE (ECOG 0) vs NE (ECOG 1–2)	–
ECOG 0 vs 1–2 (PFS)	Median PFS (months)	NE (ECOG 0) vs 23.85 (ECOG 1–2)	(15.77, 30.75)

AE = Adverse Event; CBR = Clinical Benefit Rate; CI =Confidence Interval; CR = Complete Response; ECOG = Eastern Cooperative Oncology Group; KM = Kaplan–Meier; NE = Not Estimable; ORR = Overall Response Rate; OS = Overall Survival; PFS = Progression-Free Survival; PR = Partial Response; SD = Stable Disease

SAFETY RESULTS

Overall Safety Summary

Bevacizumab was generally well tolerated in the study population (N=98). The overall safety profile was consistent with the known risks of bevacizumab and its pharmacologic class. No new or unexpected safety signals were identified during the study. Adverse events (AEs) were largely manageable with standard supportive care and dose modifications where applicable.

A total of 606 AEs were reported, with 94 subjects (95.9%) experiencing at least one AE. Most AEs were of Grade 1-2 intensity (81.6% and 74.5%, respectively), while Grade ≥3 AEs occurred in 39.8% of patients (95% CI: 30.0-50.0%). Treatment-related AEs were reported in 18 subjects (18.4%). Most AEs did not lead to discontinuation or modification of bevacizumab treatment. AEs resolved or were resolving in the majority of cases (93.9% resolved; 10.2% resolving). One fatal event (1.0%) was reported. An overview of the key safety results is provided in Table 3.

Commonly Reported Adverse Events

The most frequently reported AEs (≥10% of patients) were:

- Gastrointestinal disorders: 57.1% (abdominal pain, vomiting, nausea, diarrhoea)
- General disorders and administration site conditions: 46.9% (pyrexia, fatigue, asthenia)

- Nervous system disorders: 41.8% (peripheral neuropathy, headache, vertigo)
- Blood and lymphatic system disorders: 39.8% (anaemia, thrombocytopenia)
- Skin and subcutaneous tissue disorders: 32.7% (alopecia, rash, pruritus)
- Musculoskeletal and connective tissue disorders: 26.5% (pain in extremity, back pain, arthralgia)

Less frequent AEs (<10%) included infections, vascular disorders (notably hypertension in 15.3%), and metabolic disturbances such as hypomagnesaemia or hyperglycemia.

Table 3 Safety Summary

Parameter	**Statistics**	**Bevacizumab (Safety Population) (N=98)**
Total number of patients with at least one AE	n (%)	94 (95.9%)
Total number of AEs	E	606
Total number of patients with		
Grade ≥3 AE	n (%)	39 (39.8%)
Related AE	n (%)	18 (18.4%)
Serious AE	n (%)	17 (17.3%)
Serious AE related to study drug	n (%)	1 (1.0%)
AE leading to study drug discontinuation	n (%)	10 (10.2%)
AE leading to any study drug withholding	n (%)	14 (14.3%)
AE leading to infusion delay	n (%)	10 (10.2%)
AE leading to infusion interruption	n (%)	1 (1.0%)
AE leading to fatal outcome (Grade 5)	n (%)	1 (1.0%)

CONCLUSIONS

- Treatment with bevacizumab plus standard chemotherapy followed by bevacizumab monotherapy demonstrated favorable overall survival (OS) and durable disease control in Indian patients with advanced/metastatic ovarian, fallopian tube, or primary peritoneal cancer.
- Median OS was not reached, and median PFS was approximately 24 months, consistent with the known efficacy profile of bevacizumab in this indication.
- The safety profile of bevacizumab was manageable and predictable, with most adverse events (AEs) of low to moderate intensity.

- Serious or treatment-limiting toxicities were infrequent, and the incidence of Grade ≥3 and serious AEs was within the expected range for bevacizumab-treated populations.
- PFS outcomes in Indian patients were consistent with those observed in pivotal global trials and real-world studies.
- The toxicity profile mirrored the established global experience, with no new concerns identified in the Indian clinical setting.
- The study provides important local evidence supporting the integration of bevacizumab into front-line therapy for advanced/metastatic ovarian cancer in India.
- The results reinforce the favorable risk-benefit profile of bevacizumab when patients are appropriately selected and toxicities proactively managed.
- In conclusion, this Phase IV study met its regulatory objective, confirming that bevacizumab is both effective and safe in Indian patients with advanced/metastatic ovarian cancer and supports its role as a standard component of front-line therapy in this population.

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