BMC Cancer

RESEARCH

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Final analysis of the phase 3 randomized clinical trial comparing HD201 vs. referent trastuzumab in patients with ERBB2-positive breast cancer treated in the neoadjuvant setting

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Abstract

Background The TROIKA trial established that HD201 and trastuzumab were equivalent in terms of primary endpoints (total pathological complete response) following neoadjuvant treatment. The objective of the present analysis was to compare survival outcomes and final safety.

Methods In the TROIKA trial, patients with ERBB2-positive early breast cancer were randomized and treated with either HD201 or the referent trastuzumab. Eligible patients received 8 cycles of either HD201 or referent trastuzumab (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) every 3 weeks in combination with 8 cycles of chemotherapy (4 cycles of docetaxel, 75 mg/m^2, followed by 4 cycles of epirubicin, 75 mg/m^2, and cyclophosphamide, 500 mg/m^2) in the neoadjuvant setting. The patients then underwent surgery followed by 10 cycles of adjuvant HD201 or referent trastuzumab according to their initial randomization to complete one year of trastuzumab-directed therapy. Event-free and overall survival rates were calculated using Kaplan–Meier analysis. The hazard ratio for event-free survival was estimated by Cox proportional hazards regression.

Results The final analysis was performed after all patients completed the study at a median follow-up of 37.7 months (Q1-Q3, 37.3–38.1 months). A total of 502 randomized patients received either HD201 or the referent trastuzumab, and 474 (94.2%) were eligible for inclusion in the per-protocol set. In this population, the 3-year event-free survival rates were 85.6% (95% CI: 80.28–89.52) and 84.9% (95% CI: 79.54–88.88) in the HD201 and referent trastuzumab groups, respectively (log rank $p=0.938$) (HR 1.02, 95% CI: 0.63–1.63; $p=0.945$). The 3-year overall survival rates were comparable between the HD201 (95.6%; 95% CI: 91.90–97.59) and referent trastuzumab treatment groups (96.0%, 95% CI: 92.45–97.90) (log rank $p=0.606$). During the posttreatment follow-up period, adverse events were reported for 64 (27.4%) and 72 (29.8%) patients in the HD201 and the reference trastuzumab groups, respectively. Serious adverse events were rare and none of which were related to the study treatment.

Conclusions This final analysis of the TROIKA trial further confirms the comparable efficacy and safety of HD201 and trastuzumab.

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Trial registration ClinicalTrials.gov identifier: NCT03013504.

Keywords Trastuzumab, Biosimilar, HD201, Breast cancer, Neoadjuvant, HER2, ERBB2

Introduction

In the primary analysis of the prospective, randomized, multicenter phase 3 TROIKA study, HD201, a trastuzumab biosimilar, was shown to be equivalent to the referent trastuzumab in patients with ERBB2-positive early breast cancer (EBC) based on the primary endpoints of locally assessed total pathologic complete response (tpCR) [1].

The relationship between tpCR status and survival has been extensively debated following a meta-analysis indicating that tpCR status predicts survival outcome in patients with ERBB2-positive EBC [2]. Regulatory agencies have acknowledged this relationship by authorizing several compounds on this early criterion for activity [3–7]. The neoadjuvant setting can be definitively considered the new era for development in ERBB2-positive breast cancer [8]. It remains reassuring that in most cases, the conclusion derived from the early criteria of pathologic complete response (pCR) has been confirmed by survival outcome analysis [9–11]. In this final analysis of the TROIKA study, we report the long-term efficacy and safety outcomes at 3 years of follow-up.

Methods

Study design and patients

TROIKA (NCT03013504) was a multicenter, randomized, phase 3 trial previously detailed in the publication reporting the primary analysis [1]. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approval of the study protocol and all accompanying documents provided to the patients was obtained from independent ethics committees at participating institutions, and all patients provided voluntary written informed consent. Key eligibility criteria were age $\geq$ 18 years; ERBB2-positivity; new diagnosis; unilateral, operable breast cancer; and a baseline left ventricular ejection fraction $\geq$ 55%.

Patients were enrolled and randomized using a block of 8 in a ratio of 1:1 to receive either HD201 or referent trastuzumab (loading dose: 8 mg/kg; maintenance dose: 6 mg/kg) every 3 weeks, administered concurrently with 8 cycles of chemotherapy (4 cycles of docetaxel [75 mg/m^2], followed by 4 cycles of epirubicin [75 mg/m^2]/cyclophosphamide [500 mg/m^2]) in the neoadjuvant setting. After surgery, patients received an additional 10 cycles of HD201 or referent trastuzumab in the adjuvant setting according to the previous allocation.

Outcomes

Secondary objectives included evaluation of event-free survival (EFS) (defined as the time from randomization to the first observation of disease progression, including local and distant recurrence, second primary cancer, or death due to any cause), overall survival (OS) (defined as the time from randomization to death), safety, and immunogenicity. Exploratory analyses were conducted for EFS including locally assessed tpCR and bpCR as covariates.

Statistical analysis

Target sample sizes and statistical power calculations for the primary analysis have been reported previously [1]. Statistical analyses were performed with SAS (version 9.4; SAS Institute Inc., NC, USA). Kaplan–Meier analysis was used to estimate EFS and OS rates. Cox proportional hazards regression analyses providing hazard ratios (HRs) and 95% confidence intervals (95% CIs) for EFS adjusted for region, stage, and tumor hormonal receptor status are presented. Survival analyses were conducted in the per-protocol set (PPS), including all patients who received the study treatment (without a major protocol deviation affecting the primary efficacy assessment) and who underwent surgery after the completion of neoadjuvant treatment or did not undergo surgery because of lack of efficacy, and analysis was also performed in the modified full analysis set (mFAS), including all patients who received at least 1 dose of study medication (Fig. 1). Safety analyses were descriptive and conducted in all patients who received at least one dose of treatment. Adverse events (AEs) and serious AEs (SAEs) were recorded and graded per standard common technology criteria for adverse events (CTCAE).

Results

Patient population

This analysis was performed after all patients completed the study at a median follow-up of 37.7 months (Q1-Q3, 37.3–38.1 months). The mFAS comprised 502 randomized and treated patients, among whom 250 (49.8%) were in the HD201 group and 252 (50.2%) were in the referent trastuzumab group and were included between February 19 and September 21, 2018, across 70 centers in 12 countries. A total of 28 patients with mFAS were excluded from the PPS (12 patients in the HD201 treatment group and 16 patients in the referent trastuzumab group). The PPS thus comprised 238 patients in the HD201 treatment group and 236 patients in the referent trastuzumab treatment group. Baseline demographics

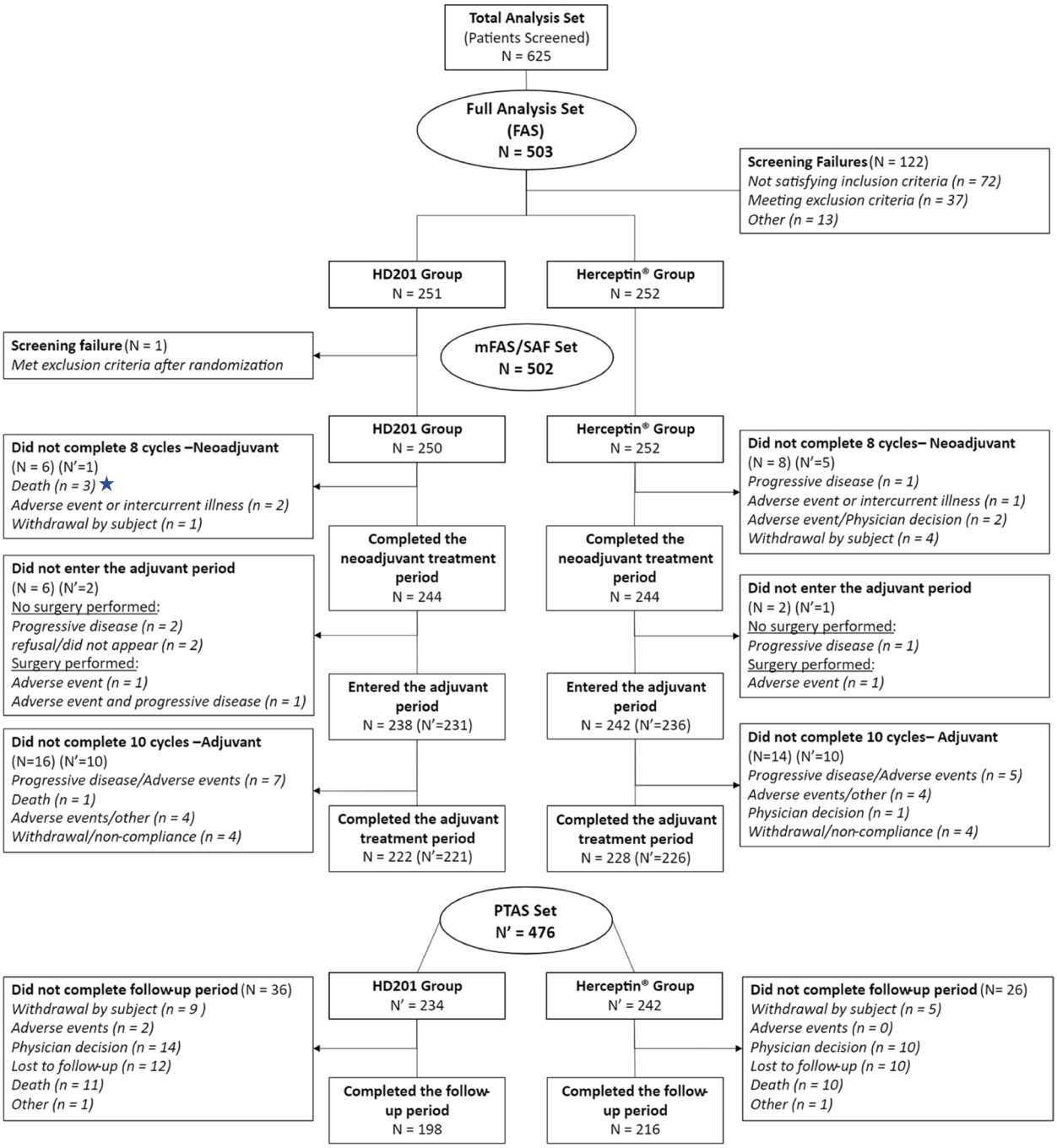

Fig. 1 Patient distribution: CONSORT diagram

and disease characteristics were well balanced between the study arms as reported previously [1].

Efficacy

In the PPS, the 3-year EFS rates were 85.6% (95% CI: 80.28–89.52) and 84.9% (95% CI: 79.54–88.88) in the HD201 and referent trastuzumab groups, respectively (log rank $p=0.938$) (Fig. 2A). The Cox proportional HR adjusted for region, stage, and tumor hormonal receptor status was 1.02 (95% CI: 0.63–1.63; $p=0.945$) (Fig. 2A). The 3-year OS rates were comparable for the HD201 (95.5%; 95% CI: 91.90–97.59) and referent trastuzumab treatment groups (96.0%, 95% CI: 92.45–97.90) (log rank $p=0.606$) (Fig. 2B). These results for EFS and OS were similar to those in the mFAS population (Figs. 2E and F). The sensitivity analysis searching heterogeneity of

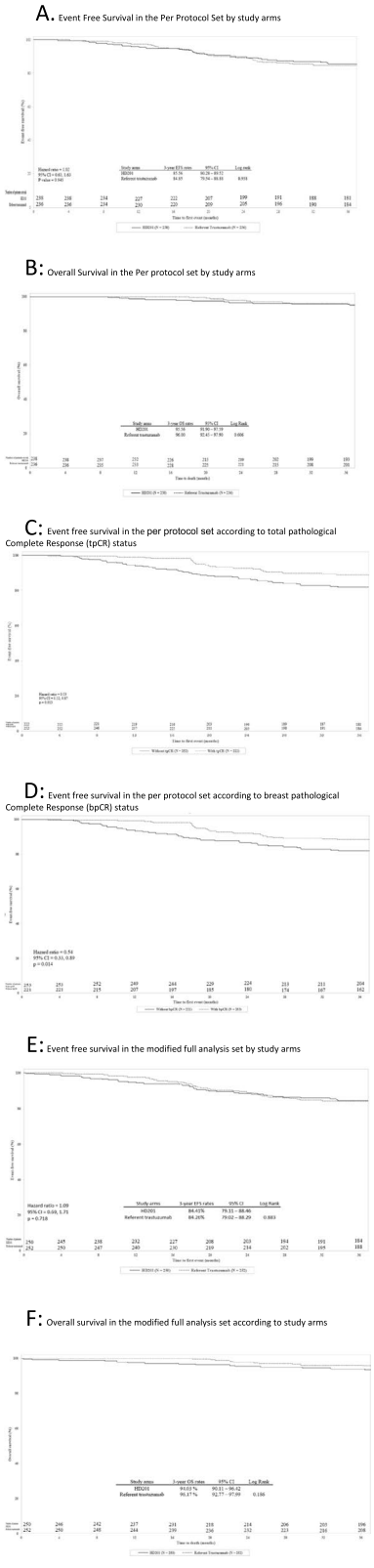

Fig. 2 Event-Free Survival and Overall Survival in the Per Protocol set (PPS) and in the modified Full Analysis set (mFAS). **A** EFS by study arm in the PPS. **B** OS by study arm in the PPS. **C** EFS by tpCR status in the PPS. **D** EFS by bpCR status in the PPS. **E** Event free survival in the mFAS. **F** Overall survival in the mFAS. bpCR, breast pathologic complete response; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; PPS, per protocol set; OS, overall survival; pCR, pathologic complete response; tpCR, total pathologic complete response

treatment effect according to the disease characteristics did not observed any discordances between the two arms in terms of survival outcomes.

Locally assessed pCR and long-term efficacy

In the PPS, in both treatment arms, 3-year EFS was more better for patients achieving a tpCR (locally assessed) than for those with residual disease, with 10.8% (24/222) versus 17.9% (45/252) of patients with events counting for EFS, respectively (HR 0.53, 95% CI 0.32–0.87; $p=0.013$) (Fig. 2C). Similarly, 3-year EFS was more favorable for patients achieving a bpCR (locally assessed) than for those without (HR 0.54, 95% CI 0.33–0.89; $p=0.014$) (Fig. 2D).

Long-term safety

During the posttreatment follow-up period, PTAEs were reported for 64 (27.4%) and 72 (29.8%) patients in the HD201 and the referent trastuzumab groups, respectively (Table 1). PTAEs with severity grade 3 or higher were reported for 7 (3.0%) patients and 13 (5.4%) patients, and serious PTAEs were reported for 4 (1.7%) patients and 5 (2.1%) patients, respectively. No serious PTAEs related to

Table 1 Safety results for the post treatment period

	HD201 ***N*** **= 234**	**Herceptin®** ***N*** **= 242**
Patients presenting with ANY	*n* (%)	*n* (%)
PTAE	64 (27.4%)	72 (29.8%)
PTAE Related to Study Treatment	21 (9.0%)	23 (9.5%)
PTAE ≥ Grade 3	7 (3.0%)	13 (5.4%)
Serious PTAE	4 (1.7%)	5 (2.1%)
Serious PTAE Related to Study Treatment	0 (0.0)	0 (0.0)
PTAE of Special Interest	35 (15.0%)	40 (16.5%)
PTAE by Preferred Term		
Cardiac disorders	19 (8.1%)	27 (11.2%)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	16 (6.8%)	14 (5.8%)
Blood and lymphatic system disorders	12 (5.1%)	10 (4.1%)
PTAEs related to study treatment by preferred term		
Cardiac disorders	12 (5.1%)	11 (4.5%)
Blood and lymphatic system disorders	6 (2.6%)	1 (0.4%)

PTAE Post treatment Adverse Event

study treatment were reported during the posttreatment follow-up period. Overall, no noteworthy differences were found between the two groups.

Discussion

The phase 3 TROIKA study in patients with ERBB2-positive EBC is the conclusive step in the investigation of HD201 and the referent trastuzumab in the extensive comparison of the two supporting the development of the biosimilar candidate [1]. Analysis of the secondary long-term efficacy endpoints, EFS and OS, after 3 years of follow-up continues to support the equivalence of HD201 to referent trastuzumab established by the primary analysis based on the tpCR criterion. Most recurrent events in ERBB2-positive breast cancer have been reported to occur within 3 years, and this duration appears sufficient to provide adequate evidence to support efficacy and safety conclusions [12–14]. Achieving tpCR was associated with longer EFS in both treatment arms, and these results were consistent with those observed in other studies assessing neoadjuvant trastuzumab [9–11, 14].

The overall safety profile of HD201 and trastuzumab at the 3-year follow-up remains consistent with the safety profiles observed in previous studies, post-treatment adverse events are unrelated or unlikely to the study drug, and rarely, events related to the study drug occurred in the post-treatment follow-up period.

Limitations of the study include the use of newer anti-HER2 agents, which could impact survival in patients with relapse and were not assessed in this study. In addition, subgroup analyses are limited by their small and unbalanced sample sizes.

Conclusions

This final analysis of TROIKA further supports the comparability of the efficacy and safety of HD201 and the referent trastuzumab.

Acknowledgements

Nothing

Authors' contributions

Dr. Pivot had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Pivot, Kaufman. Acquisition, analysis, or interpretation of data: Pivot, Dzagnidze, Georgeivich, Shamrai, Fen, Kaewkangsadan, Petrelli, Villanueva, Kim, Pradhan, Jaison, Feyaerts, Kaufman, Derde, Deforce, Cox. Drafting of the manuscript: Pivot, Derde. Critical revision of the manuscript for important intellectual content: Pivot, Georgeivich, Fen, Kaewkangsadan, Petrelli, Villanueva, Kim, Pradhan, Jaison, Feyaerts, Kaufman, Derde, Deforce, Cox. Statistical analysis: Pivot, Kaufman, Derde, Deforce, Cox. Administrative, technical, or material support: Kim, Pradhan, Jaison, Feyaerts, Supervision: Pivot, Feyaerts. All author read and accept the final manuscript.

Funding

Funding/Support: This study was sponsored by Prestige Biopharma Ltd. Role of the Funder/Sponsor: The funding source validated the study as designed by the trial's steering committee, as well as subsequent amendments. The sponsor organized the management and the conduction of the study, including the collection of data. The data were analyzed by DICE with Drs Derde and Kaufman. The data were interpreted by the trial's steering committee, including Drs. Pivot, Cox, Deforce, Feyaerts, and Derde, independently from the sponsor. The preparation of the manuscript was performed by Drs. Pivot and Derde and reviewed and approved by all enclosed authors. The sponsor approved the manuscript and agreed to submit the manuscript for publication.

Availability of data and materials

Data types: Deidentified participant data.
How to access data: The application providing the project details should be submitted to Prestige Bio Pharma,(2 Science Park Dr, #04–13/14 Ascent Tower B, Singapore Science Park, Singapore 118,222) or by email at jamie.kim@prestigebio.com or x.pivot@icans.eu. Then the request need to be approved by the steering committee of the study before release the data.
Restriction: The steering committee of the trial approval based on the scientific assessment of the application is requested to release the data.

Declarations

Ethics approval and consent to participate

TROIKA trial (NCT03013504) that was reported according to the Enhancing the Quality and Transparency Of Health Research guidelines. The TROIKA trial was conducted according to the ethical principles of good clinical practice and was approved by ethics committees in each involved country. All patients signed an informed consent to participate in the trial which are available at request submitted to Prestige Bio Pharma, (2 Science Park Dr, #04–13/14 Ascent Tower B, Singapore Science Park, Singapore 118222). An independent monitoring committee monitored the study.
List of the ethics committees / institutional review board that approved the study.

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	458–003	Medical Research and Ethics Committee,	National Institutes of Health, Ministry of Health Malaysia, Block A, Level 2, No 1, Jalan Setia Murni U13/52, Seksyen U13, Setia Alam, 40170, Shah Alam, Selangor
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	380–005	Local	Comitato Etico dellÁrea Vasta Emilia Nord	Via G. Taberna, 49- Edificio 7 – Ingresso B, piano rialzato, 29121 Piacenza
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	380–015	Local	Comitato Etico IRCCS Di Candiolo Strada Provinciale 142	
	380–004	Central	00144 ROMA	via Chianesi, 53
	380–004	Central	143 ROMA	via Chianesi, 53
	380–005	Local	Comitato Etico dellÁrea Vasta Emilia Nord	Via G. Taberna, 49- Edificio 7 – Ingresso B, piano rialzato, 29121 Piacenza
	380–006	Local	Comitato Etico per le sperimentazioni cliniche della provincia de Vicenza	
	380–002	Local	Comitato Etico dell' Area Vasta Emilia Nord	Via del Pozzo, 71 – 41124 Modena
	380–013	Local	Comitato Etico Bergamo Piazza OMS	Organizzazione mondiale della sanita, 1
	380–015	Local	Comitato Etico IRCCS Di Candiolo	Strada Provinciale 142
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	616–002	Central	Komisja Bioetyezna przy Okregowej Lekarskiej w Lublinie	
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	724–001	Central	Research Ethics Committee Center of the Unversity Hospitals Virgen Macarena—Virgen del Rocio de Sevilla	
	724–004	Central	Autonomous Ethical Committee for Clinical Studies of Medicines and Health Products of the Valencian Community (CAEC)	

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France	ANSM	143/147, bd Anatole France, 93285 Saint Denis cedex Paris,
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Bulgaria	Bulgaria Drug Agency	8, Damyan Gruev Str., 1303 Sofia, Bulgaria

Country	Site Code	IEC
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	112–003	Ethics Committee of Mogilov Regional Oncological Dispensary, Academic Pavlova str., 2a, Mogilov, 212018
	112–004	Ethics Committee of Brest Regional Clinical Oncological Dispensary, Meditskinskaya str., Brest 224027
	112–005	Ethics Committee of N.N.Alexandrov national cancer center of Belarus, s. Lesnoy-2, Minsk, 223040
Georgia	268–001	Independent Ethics committee of "Unimedi Ajara" Ltd
	268–002	Ethical CommitteeS. Khechinashvili University Hospital
	268–003	Independent Ethics committee of "Unimedi AjaraOncology center", new name Independent Ethics committee of Evex Medical Corporation " oncology center (from 03 December 2018), new name Independent Ethics committee of "Evex Hospitals" oncology center (from May 2019)
	268–004	Ethics committee of Cancer center of Adjara Autonomous Republic LTD, new name Ethics committee of LTD "High Technology Hospital Medcenter (from 16 May 2018)

Country	Site Code	IEC
	268–005	Independent Ethics committee of ST NICHOLAS CENTER FOR SURGERY and ONCOLOGY" Ltd new name Independent Ethics committee JSC EVEX Medical Center (from 03 December 2018), from May 2019 new name Independent Ethics committee JSC EVEX Clinic
	268–006	Ethics committee of Research Institute of Clinical Medicine" Ltd
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	268–008	Independent Ethics committee of Multiprofile Clinic Consilium Medulla"
	268–009	Independent Ehics Committee of Cancer Research Center" Ltd
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	643–002	Independent Ethics Committee of State Budgetary Healthcare Institution Tambov Regional Oncology Clinical Dispensary
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	643–004	Local Ethics Committee of State Bugetary Healthcare institution "Leningrad Regional Oncology Dispensary", new name Local Ethics Committee State Bugetary Healthcare institution "Leningrad Regional Oncology Dispensary named after L.D. Roman"
	643–005	Ethica committe at "Republican Clinical Oncology Dispensary of Ministry of Health of Bashkortostan Republic"
	643–006	Ethics Committee of Moscow State Budgetary Healthcare Institution Moscow City Oncologic Hospital No. 62 of Moscow Healthcare Department. From 10/04/2019 Independent Inetrdisciplinary committee on Ethica Review of Clinical studies
	643–007	Local Ethics Committee of State Budgetary Healthcare Institution Orenburg Regional Clinical Oncologic Dispensary
	643–008	Local Ethics Committee of Ryazan State Medical University n.a. academician I.P.Pavlov" of the Ministry of Health of the Russian Federation
	643–009	Ethics Committee at State Budgetary Healthcare Institution of Ryazan Region Regional Clinical Oncology Dispensary
	643–010	Ethica committee at Budgetary Healthcare Institution of Omsk Region Clinical Oncologic Dispensary
	643–011	Ethics Committee at Saint Petersburg City Clinical Oncologic Dispensary
	643–012	Ethical Committee of Regional budgetary Healthcare institution Kursk Regional clinical oncology dispensary
	643–013	Ethics Committee of Limited Liability Company EVIMED
	643–014	Independent Ethics committee of MEDSI
	643–017	Local Ethics Committee of FGBOU VO North-Western State Medical University named after I.I. Mechnikov of the Ministry of Health of the Russian Federation
	643–018	The Ethics Committee of OOO Komanda
	643–019	The Local Ethics Committee of State Budgetary Healthcare Institution of Stavropol Region Pyatigorsk Interdistrict Oncologic Dispensary
	643–021	Ethics Committee of Limited Liability Company VitaMed
	643–022	Federal State Budgetary Institution National Medical Research Center of Oncology named after N.N. Petrov of the Ministry of Health of the Russian Federation
	643–023	Independent Ethics committee of MEDSI
	643–024	Independent Interdisciplinary Committee on Ethics Review of Clinical Studies
	804–001	Committee on Ethics at the MI "Dnipropetrovsk City multiprofile Clinical Hospital #4" of Dnipropetrovsk Regional Council*
	804–002	Committee on Bioethics and Deontology of SI "Zaytsev V.T. Institute of General and Urgent Surgery of NAMS of Ukraine"
	804–003	Committee on Ethics at the Zaporizhzhya Regional Clinical Oncology Dispensary of Zaporizhzhya Regional Council
Ukraine	804–004	Local Ethics Committee at "Lviv State Regional Oncology Treatment and Diagnostic Center"
	804–005	The Committee on Ethics at the "Volyn Regional Oncological Dispensary"
	804–006	The Committee on Ethics at the Central City Clinical Hospital of the City of Uzhgorod
	804–007	The Committee on Ethics at Podillya Regional Oncology Center
	804–008	The Committee on Ethics at MI KRC Kyiv regional oncology dispensary"

COUNTRY	NAME of the RA
Belarus	Ministry of Health of the Republic of Belarus
Georgia	State Regulatory Agency for Medical Activities of Ministry of labour, Health and Social Affairs of Georgia
Russia	Ministry of Health of Russian Federation
Ukraine	State Expert Center of Ministry of Health of Ukraine

COUNTRY	NAME of the RA	RA ADDRESS
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	764–004	IRB	Ethics Committee, National Cancer Institute	The IRB, Royal Thai Army Medical Department 317/5 Rajavithi Road, Rajathevee, Bangkok 10400, Thailand

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Malaysia	National Pharmaceutical Regulatory Agency (NPRA)	36, Jln Professor Diraja Ungku Aziz, Pjs 13, 46200 Petaling Jaya Selangor, Malaysia

Consent for publication
Not applicable.

Competing interests
Conflict of Interest Disclosures: Dr. Pivot reported being an unpaid adviser for Prestige Biopharma. Dr Dzagnidze reported personal fees from Khechinashvili University Hospital during the conduct of the study. Dr Kaewkangsadan reported grants from Prestige BioPharma during the conduct of the study. Drs Derde, Kaufman, and Deforce are/were employees of DICE Ltd. and had a memorandum of understanding with Prestige BioPharma Ltd. No other disclosures were reported.

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Received: 30 September 2022 Accepted: 23 January 2023

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