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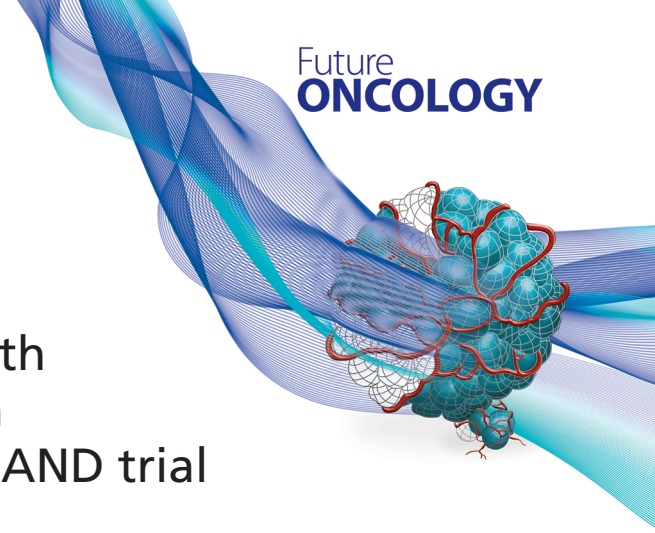

Atezolizumab and bevacizumab with transarterial chemoembolization in hepatocellular carcinoma: the DEMAND trial protocol

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The combination of the anti-PD-L1 antibody atezolizumab and the anti-VEGF bevacizumab is the first approved immunotherapeutic regimen for first-line therapy in patients with unresectable hepatocellular carcinoma (HCC), currently approved in more than 80 countries. The efficacy and tolerability of this regimen suggest that the use of atezolizumab + bevacizumab could be extended to the treatment of patients with intermediate-stage HCC in combination with transarterial chemoembolization (TACE). The authors describe the rationale and design of the DEMAND study. This investigator-initiated, multicenter, randomized phase II study is the first trial to evaluate the safety and efficacy of atezolizumab + bevacizumab prior to or in combination with TACE in patients with intermediate-stage HCC. The primary end point is the 24-month survival rate; secondary end points include objective response rate, progression-free survival, safety and quality of life.

Clinical Trial Registration: NCT04224636 (ClinicalTrials.gov).

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Liver cancer is the sixth most common malignancy worldwide with an increasing incidence in Europe and is one of the world's leading causes of cancer-related death [1–3]. Hepatocellular carcinoma (HCC) is the main cause of

liver cancer accounting for 90% of cases and, based on estimates from the WHO, more than 1 million people will die each year due to liver cancer by 2030 [4]. HCC primarily develops on the basis of chronic liver diseases such as hepatitis C (predominant etiology in Europe, America and Japan), hepatitis B (China), alcoholic liver disease and nonalcoholic fatty liver disease [5]. Treatment decisions for HCC are made based on tumor burden, liver function and patient's performance status as summarized in current guidelines [6]. Despite well-defined risk factors and established surveillance in patients with chronic liver disease, most patients with HCC are diagnosed in more advanced stages, where curative options (e.g., resection, ablation or liver transplantation) are no longer feasible. Patients with intermediate-stage HCC, or Barcelona Clinic Liver Cancer (BCLC) stage B, constitute a large subgroup accounting for 20–30% of cases [7,8]. Intermediate-stage HCC is defined as unresectable HCC without vascular invasion or extrahepatic spread in a patient with preserved liver function and good performance status. Transarterial chemoembolization (TACE) is the globally accepted standard of care in patients with intermediate HCC [6,9]. TACE consists of the intra-arterial administration of a cytotoxic agent (e.g., doxorubicin, irinotecan or other agents) into the feeding arteries of an HCC combined with embolization of the tumor vessels. Despite the improvement in patients' outcomes after the implementation of TACE, the median overall survival (OS) is limited to 19 months based on a large meta-analysis [10]. TACE is considered a palliative treatment because of the high occurrence of TACE-refractory disease defined by the failure of TACE to control liver lesions or extrahepatic spread. Furthermore, liver function is a major determinant of survival in patients with HCC and repeated TACE can cause unintended collateral damage to the nontumor liver tissue with a deterioration of liver function in up to 30% of patients [11]. Several clinical studies have been conducted assessing the combination of TACE and systemic treatment to improve patient outcomes. Five randomized, placebo-controlled clinical trials with a total of approximately 2500 patients combining TACE and the multikinase inhibitors sorafenib [12–14], brivanib [15] or orantinib [16] failed to show a benefit for progression-free survival (PFS), OS or time-to-progression (TTP) over TACE alone. Effective treatment alternatives or combination partners to TACE are urgently needed to improve outcomes for patients with intermediate-stage HCC.

Immunotherapy in the treatment of hepatocellular carcinoma

Checkpoint inhibitor (CPI)-based immunotherapy marked a breakthrough in the treatment of a wide range of cancer entities, including HCC. CPIs are monoclonal antibodies that enhance the antitumor immune response by blocking the signaling mediated by PD-1 and its ligand PD-L1, or CTLA-4 [17,18]. The binding of PD-1 on immune cells to PD-L1 on cancer cells or other cells in the tumor microenvironment (TME) strongly inhibits immune-mediated tumor cell killing. The anti-PD-L1 targeting antibody atezolizumab as well as the anti-PD-1 antibodies nivolumab and pembrolizumab have shown promising results in early-phase clinical trials of advanced HCC with durable responses in 15–20% of patients [19–21]. However, CPI monotherapy with nivolumab and pembrolizumab showed very limited benefit in the respective phase III trials over the standard of care in the first-line or second-line setting [22,23]. As single-agent CPIs only elicited moderate antitumor immune responses, studies of CPI-based combination regimens have been designed to foster synergistic activity and further increase the efficacy of immune cells in killing HCC. Cotargeting of immune checkpoints and VEGF recently emerged as a promising strategy. VEGF can act as a strong immunosuppressive molecule by recruitment and activation of immature dendritic cells, Tregs and myeloid-derived-suppressor cells (MDSCs) to the tumor site (Figure 1) [24]. Furthermore, VEGF inhibits the migration of antitumor lymphocytes via downregulation of adhesion molecule expression on the neovascular endothelium [25]. The anti-VEGF antibody bevacizumab can reverse VEGF-mediated immunosuppression by decreasing the abundance of MDSCs and Tregs and promoting the maturation of dendritic cells [26–29]. Based on this rationale and encouraging results from a phase Ib study of atezolizumab + bevacizumab in patients with unresectable HCC showing an objective response rate of 37% [21], Finn and colleagues assessed and recently reported the groundbreaking results of the IMbrave150 trial [30].

The phase III study, IMbrave150, randomized patients with unresectable HCC in a 2:1 ratio to combined atezolizumab + bevacizumab or sorafenib. IMbrave150 patients had received no prior systemic therapy and were characterized by Child-Pugh class A liver function and a good performance status. Atezolizumab + bevacizumab markedly improved the coprimary end points of PFS and OS in the intention-to-treat population compared with sorafenib, with a median PFS of 6.8 months versus 4.3 months (hazard ratio [HR]: 0.59; 95% CI: 0.47–0.76, $p < 0.001$) and a median OS of not reached versus 13.2 months (HR: 0.58; 95% CI: 0.42–0.79, $p < 0.001$) [30]. An update of the trial yielded a median OS of 19.2 months for atezolizumab and bevacizumab versus 13.4 months

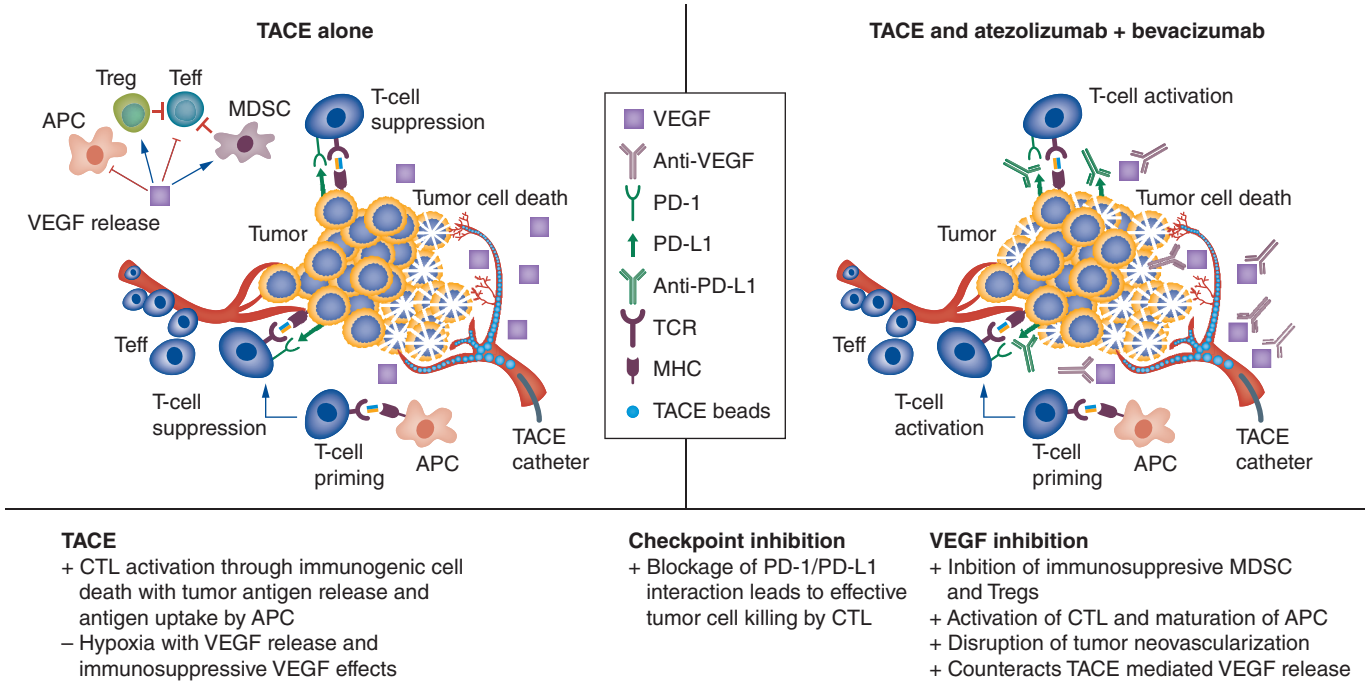

Figure 1. Combination of atezolizumab and bevacizumab plus transarterial chemoembolization in the treatment of hepatocellular carcinoma.
APC: Antigen-presenting cell; CTL: Cytotoxic T lymphocyte; HCC: Hepatocellular carcinoma; MDSC: Myeloid-derived suppressor cells; TACE: Transarterial chemoembolization; TCR: T-cell receptor; Teff: Effector T cell;.

for sorafenib (p = 0.0009) [31]. The objective response rate (ORR) assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) was 29.8% compared with 11.3% ($p < 0.001$) with 25 complete responses (CR) in the atezolizumab plus bevacizumab arm versus one CR in the sorafenib arm [31]. Disease control was achieved in 73.6% versus 55.3% ($p < 0.001$) of patients [30]. Based on these results, atezolizumab and bevacizumab was the first immunotherapeutic regimen to receive regulatory approval for the first-line treatment of unresectable HCC in the USA, Europe, China and Japan, and is currently approved in more than 80 countries.

Transarterial chemoembolization & immunotherapy

After uptake of cancer antigens by antigen-presenting cells (APCs) and presentation to immature T cells (T-cell priming), activated T cells can recognize the antigens on the tumor cell surface and eliminate cancer cells. Local treatments like TACE or radiofrequency ablation (RFA) result in immunogenic cell death and release of tumor neoantigens (Figure 1) with subsequent tumor infiltration by APCs and activation of tumor-specific T cells [32–34]. However, the limited outcomes of TACE show that immune activation via TACE may not be sufficient to control tumor growth and prevent HCC recurrence. A combination of TACE and CPI therapy may show synergistic effects in the treatment of HCC. In a pilot study by Duffy *et al.*, 39 patients with advanced HCC after progression on sorafenib were treated first with an anti-CTLA-4 antibody followed by TACE or RFA targeting one lesion [35]. The end points, feasibility and safety, defined by the frequency of adverse events (AEs), were met and an encouraging ORR of 26% with a median OS of 12.3 months was observed in this therapy-refractory population. Responses were assessed in tumors not treated locally. An increase in T cells invading the HCC nodules and circulating in the blood of patients was observed.

Transarterial chemoembolization & bevacizumab

TACE-induced ischemia of hypervascularized HCC and surrounding liver parenchyma is accompanied by hypoxia and release of the transcription factor HIF-1 leading to a release of proangiogenic cytokines like VEGF [36–38]. High levels of the immunosuppressive factor VEGF are associated with a poor prognosis in patients with HCC [39,40]. Moreover, high VEGF levels after TACE can predict treatment failure. Three clinical trials combining TACE and the anti-VEGF antibody bevacizumab have been conducted in patients with HCC. In a recent trial by Pinter *et al.*,

40 patients with HCC BCLC stage A or B and Child-Pugh class A or B were randomized to receive either TACE with bevacizumab (5 mg/kg of body weight every two weeks) or TACE with placebo [41]. After the first TACE, repeated TACE procedures were conducted in four-week intervals, if clinically indicated. A median of three TACE cycles (range: 1–6) were performed per patient with a median of 13 bevacizumab infusions (range: 1–23). Because of severe and even lethal septic and vascular AEs (variceal hemorrhage, sepsis, myocardial infarction, thrombosis) in the TACE/bevacizumab arm, the trial was stopped prematurely. Pinter and colleagues attributed the events to the use of bevacizumab and advised against bevacizumab as an adjuvant treatment to TACE. However, two other clinical trials investigating the combination of TACE and bevacizumab reported a favorable safety profile with a lower incidence of serious AEs, although bevacizumab was used at higher doses [42,43]. In a study by Britten and colleagues, patients with unresectable HCC (maximum lesion size: 15 cm, maximum number of lesions: 3; n = 30) and Child-Pugh class A or B were randomized to receive either TACE or TACE plus bevacizumab at 10 mg/kg of body weight every two weeks, beginning one week prior to TACE. TACE was performed on day 8 and at week 14 if needed [42]. The only clinically significant vascular AE occurred in the TACE-only arm (variceal hemorrhage). Buijs *et al.* conducted a single-arm phase II trial assessing the combination of TACE and bevacizumab in patients with HCC BCLC stage B or C and Child-Pugh class A or B liver function (n = 26) [43]. Patients were treated with bevacizumab every two weeks (10 mg/kg of body weight) and TACE at week three. The median number of TACE cycles was two (range: 1–3). Bevacizumab-attributed severe toxicities included four vascular events (grade 5: duodenal ulcer perforation; grade 3–4: variceal hemorrhage, stroke) and three infections (grade 3–4: cellulitis, cholangitis, *Clostridium difficile* enteritis). Both groups concluded that the combination of TACE and bevacizumab was safe and tolerable in patients with HCC. In addition to the differences in patient characteristics, it should be noted that the higher frequency of TACE cycles in the trial by Pinter and colleagues may have caused a higher incidence of AEs. A limitation of TACE sessions per lesion seems to be an important part of a strategy combining TACE and bevacizumab improving safety without compromising efficacy, considering that response to TACE decreases significantly after each TACE cycle performed, as shown in a large prospective observational study [11]. Furthermore, in the trials by Buijs and Britten, upper endoscopy was not mandatory to screen for esophageal varices. Because of the occurrence of variceal hemorrhage in these studies, endoscopic screening and management of gastroesophageal varices should be included in trials of the combination of TACE and bevacizumab in HCC.

Rationale for combining transarterial chemoembolization & atezolizumab plus bevacizumab

Adding the effective immunotherapeutic regimen of atezolizumab plus bevacizumab to TACE could provide a benefit in patients with intermediate-stage HCC. Synergistic effects through enhanced activation of antitumor immunity could lead to improvements in tumor control and reduce the rate of TACE-refractory disease. However, the optimal sequence of TACE and immunotherapy is unclear. Performing TACE first could enhance the effects of the following treatment with atezolizumab + bevacizumab by tumor necrosis and release of tumor antigens. On the other hand, there are important reasons in favor of starting with immunotherapy: patients responding to CPIs may achieve long-lasting disease control and survival [44]. In the IMbrave150 trial an ORR of 27.3% by RECIST v.1.1 and 33.2% by HCC-specific modified RECIST (mRECIST) translated into a duration of response of at least 6 months in 87.6% of patients [30]. Notably, Kudo *et al.* recently presented an exploratory analysis of the trial for patients with intermediate-stage HCC BCLC stage B treated with atezolizumab plus bevacizumab showing a best confirmed ORR of 43% per RECIST v1.1 (48% per mRECIST) and an OS of 25.8 months [45]. Initiation of immunotherapy prior to TACE may allow for early selection of responders, considering the time to response of 2.8 months in the IMbrave150 study [46]. Furthermore, liver function is an important factor influencing the survival of patients with HCC and repeated TACE can negatively impact the hepatic reserve [11]. Starting immunotherapy first and delaying TACE to the timepoint of progression will reduce the number of TACE cycles and the proportion of liver parenchyma exposed to the collateral damage potentially caused by TACE [47]. This could further improve patient outcomes. Moreover, upfront administration of immunotherapy leads to intratumoral CD-8$^+$ T-cell infiltration, as shown by Duffy *et al.* [35], may prevent vessel occlusion via TACE and facilitate lymphocyte and drug delivery into the tumor. However, progressive disease was observed in 20% of patients with unresectable HCC treated with atezolizumab and bevacizumab [30]. Resistance to cancer immunotherapy is mediated by immunosuppressive factors of the TME. The immunogenic effects of TACE on progression could switch on the antitumor response via tumor antigen release and restore sensitivity to checkpoint blockade.

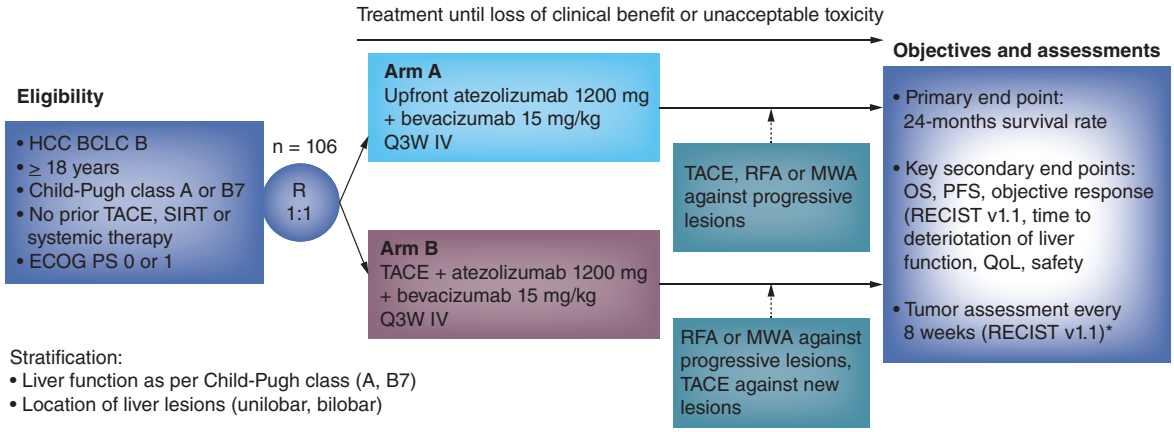

Figure 2. DEMAND study schema.
*6 weeks after treatment initiation and every 8 weeks thereafter.
BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HCC: Hepatocellular carcinoma; IV: Intravenous; MWA: Microwave ablation; OS: Overall survival; PFS: Progression-free survival; PS: Performance status; Q3W: Once every 3 weeks; QoL: Quality of life; R: Randomization; RECIST v1.1: Response evaluation criteria in solid tumors version 1.1; RFA: Radiofrequency ablation; SIRT: Selective internal radiation treatment; TACE: Transarterial chemoembolization.
Clinical trial registration: NCT04224636 (ClinicalTrials.gov).

Overall, the preclinical and clinical data presented provide a clear rationale to combine the established standard-of-care TACE with the CPI-based combination regimen atezolizumab plus bevacizumab in patients with intermediate HCC and to determine its safety and efficacy as well as its optimal sequence in a phase II clinical trial.

DEMAND Clinical Trial

The DEMAND clinical trial is an investigator-initiated multicenter, randomized, open-label, noncomparative, stratified phase II trial (NCT04224636) evaluating the efficacy and safety of either upfront atezolizumab and bevacizumab followed by sequential on-demand selective TACE upon detection of disease progression or of initial synchronous treatment with TACE and atezolizumab and bevacizumab in the treatment of patients with intermediate HCC (Figure 2).

Study design

A total of 106 patients with intermediate HCC (BCLC stage A not amenable to curative therapy or BCLC stage B) and preserved liver function of Child-Pugh class A or B7 will be randomized in a 1:1 ratio to sequential (arm A) or synchronous (arm B) treatment with atezolizumab + bevacizumab and TACE (Figure 2). In arm A, patients will receive upfront atezolizumab + bevacizumab. Upon detection of progressive hepatic lesions, sequential TACE will be performed while treatment with atezolizumab + bevacizumab is continued. In arm B, synchronous treatment with TACE against all viable tumor lesions will be performed followed by the first cycle of atezolizumab + bevacizumab. To standardize the synchronous therapy and to allow for sufficient tumor necrosis and antigen release, atezolizumab + bevacizumab will be administered within three days after TACE. If a second session of TACE is required to achieve complete treatment of the initial lesions, atezolizumab + bevacizumab may be initiated after the first session of TACE treatment. TACE will be performed against all viable lesions whenever selectively possible based on angiography examination. Since thermal ablation represents a frequently used treatment option in unresectable HCC [6] and a combined approach of TACE and ablation has shown efficacy [48–51], RFA or microwave ablation (MWA) are possible alternatives to TACE in both study arms for lesions that cannot be selectively targeted by TACE. Each lesion may be treated only once with TACE and RFA or MWA. To standardize the TACE procedure, only selective drug-eluting beads TACE (DEB-TACE) will be used in this trial. TACE can be divided into two treatment sessions in the case of multifocal disease if deemed appropriate by the interventional radiologist. However, each hepatic lesion may be treated with TACE only once. In case of a progressive hepatic lesion requiring more than one TACE or local treatment modalities other than RFA or MWA, study treatment with atezolizumab and bevacizumab will be stopped.

Randomization will be stratified by liver function as per Child-Pugh class (A, B7) and localization of liver lesions (unilobar, bilobar). Patients will be randomized separately for each stratum via a web-based tool according to a computer-generated randomization list prepared by the clinical research organization with no involvement in the recruitment process.

Atezolizumab will be administered at a dose of 1200 mg and bevacizumab at 15 mg per kilogram of body weight intravenously every 3 weeks. Patients will receive study treatment until loss of clinical benefit or unacceptable toxicity for up to 24 months. Dose modifications will not be permitted. Permanent discontinuation of one study drug will be allowed if clinically indicated. Atezolizumab treatment may be interrupted or permanently discontinued in patients experiencing AEs considered to be causally related, especially immune-related AEs (irAEs), based on the severity of the events. Management guidelines for irAEs have been designed in accordance with the recommendations from the European Society for Medical Oncology Practice Guidelines [52] and provided to the investigators. For example, in case of ≥grade 2 pneumonitis, colitis or myocarditis; ≥grade 3 skin toxicity and, for symptomatic endocrinopathies, atezolizumab should be withheld, followed by a diagnostic work-up, adequate immunosuppressive therapy, hormone substitution for endocrine side effects and close follow-up. Atezolizumab can be resumed, if the irAE resolves to grade 1 or better. If glucocorticoids are initiated for management of irAEs, they must be reduced to ≤10 mg once daily of oral prednisone or equivalent before atezolizumab can be resumed. Bevacizumab treatment may be withheld in patients experiencing toxicity, such as ≥grade 2 hypertension, ≥grade 3 venous thromboembolic events or in case of proteinuria >2 g per 24 h. Bevacizumab will be permanently discontinued in cases of severe toxicity, such as intestinal perforation, cerebral hemorrhage or arterial thromboembolic events, and interrupted prior and after operative procedures.

Treatment decisions will be made based on radiographic assessments by the investigator. Patients experiencing disease progression as defined by RECIST v1.1 may continue to receive atezolizumab + bevacizumab if the investigator ascertains continued clinical benefit from the study drugs. Loss of clinical benefit will be determined by the investigator after integrated assessment of the patient's clinical status (e.g., symptoms such as pain or decline of performance status due to progressive disease), biochemical (e.g., worsening of liver function) and radiological data.

Key eligibility criteria

Key inclusion and exclusion criteria are listed in Table 1. Briefly, eligible patients aged 18 years or older have histologically confirmed HCC without extrahepatic spread not amenable to curative resection or local ablation and measurable disease by computed tomography or MRI per RECIST v1.1 with a maximum of seven lesions, the largest lesion being <7 cm. Patients must have preserved liver function defined by a Child-Pugh Score of A–B7, adequate end-organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients may have received prior local ablation treatment but must not have received prior treatment with TACE, selective internal radiation therapy (SIRT) or systemic therapy. Patients with decompensated liver function as defined by ascites or hepatic encephalopathy as well as patients with esophageal varices with high risk for bleeding and patients with autoimmune disease will be excluded. A screening gastroscopy to assess for esophageal varices will be mandatory.

Objectives

The primary end point of the DEMAND trial is the 24-month survival rate of upfront atezolizumab + bevacizumab followed by sequential on-demand selective TACE and of initial synchronous treatment with TACE + atezolizumab and bevacizumab in the treatment of patients with unresectable, liver-limited HCC (Table 2). Secondary efficacy end points include PFS, ORR, disease control rate (DCR) per RECIST v1.1 assessed by investigators, OS, time to deterioration of liver function and time to first TACE (only in arm A). Safety end points are AEs and AEs of special interest, including irAEs. Other end points include objective response per HCC mRECIST by central review, patient-reported outcomes (PROs) and biomarker analyses in correlation with clinical outcomes (e.g., PD-L1 expression in tumor tissue; AFP, AFP-L3, PIVKA II in serum; diversity of gut microbiome).

Evaluations

Tumor response for secondary end points will be evaluated according to RECIST v1.1 by the local investigator and retrospectively by central review according to RECIST v1.1 and HCC-specific mRECIST. Radiographic tumor assessments (computed tomography or MRI of chest, abdomen, pelvis and any other sites of disease) are performed

Table 1. Key eligibility criteria for the DEMAND trial.

Inclusion criteria
• Patient signed informed consent • Age ≥18 years • HCC with a histologically confirmed diagnosis • Disease that is not amenable to curative resection and/or local ablation but eligible for TACE, with tumor burden below 50% of liver volume • At least one measurable (per RECIST version 1.1) untreated lesion • ECOG performance status of 0 or 1 • Child-Pugh class A or B7 • Adequate bone marrow function (absolute neutrophil count ≥1.5 × 109/l, lymphocyte count ≥0.5 × 109/l, platelet count ≥75 × 109/l, hemoglobin ≥90 g/l) • Adequate liver function (including ASAT, ALAT and AP ≤5 × ULN, bilirubin ≤3 × ULN, INR <1.25, ALB ≥28 g/l) • Adequate kidney function (creatinine ≤1.5 × ULN or creatinine clearance ≥50 ml/min calculated using Cockcroft-Gault formula, urine dipstick for proteinuria <2+) • If active HBV infection: HBV DNA <500 IU/ml and antiviral therapy
Exclusion criteria
• Diffuse HCC or presence of vascular invasion or extrahepatic spread (including extrahepatic lymph node affection or metastasis) or more than 7 lesions or at least one lesion ≥7 cm • Fibrolamellar or sarcomatoid HCC, or mixed CCC and HCC • Clinically relevant ascites • History or presence of hepatic encephalopathy • Coinfection of HBV and HCV (patients with active HCV only are eligible) • Patients actively listed for transplantation or who are not yet listed for transplantation but are potentially eligible by fulfilling the Milan criteria for liver transplantation • Prior systemic therapy for HCC • Prior treatment with TACE or SIRT • Patients who received prior local ablation treatment (e.g., RFA, MWA, brachytherapy) are eligible for the study provided that the target lesion(s) have not been previously treated with local therapy or the target lesion(s) within the field of local therapy have subsequently progressed • Major gastrointestinal bleeding within 4 weeks prior to randomization • Patients with untreated or incompletely treated varices with bleeding or high-risk for bleeding. Gastroscopy within 6 months prior to randomization mandatory • Active or history of autoimmune disease or immune deficiency. Patients with hypothyroidism, controlled Type 1 diabetes, eczema, psoriasis, lichen or vitiligo are eligible • Prior allogeneic stem cell or solid organ transplantation • History of pulmonary fibrosis • Significant cardiovascular or vascular disease • Inadequately controlled arterial hypertension • History of malignancy other than HCC within 5 years before enrollment, except adequately treated basal cell or squamous cell skin cancer, *in situ* cervical, breast or prostate cancer, stage I uterine cancer • Current use of acetylsalicylic acid (>325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel and cilostazol or use of full dose oral or parenteral anticoagulants or thrombolytic agents • Hypersensitivity to human or humanized antibodies • Treatment with systemic immunostimulatory agents or systemic immunosuppressive medication • Major surgical procedure within 28 days prior to randomization

CCC: Cholangiocellular carcinoma; ECOG: Eastern Cooperative Oncology Group; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; MWA: Microwave ablation; RECIST: Response evaluation criteria in solid tumors; RFA: Radiofrequency ablation; SIRT: Selective internal radiation treatment; TACE: Transarterial chemoembolization; ULN: Upper limit of normal.
Clinical trial registration: NCT04224636 (ClinicalTrials.gov).

Table 2. DEMAND trial end points.

Primary end point
• 24-months survival rate
Secondary end points
• OS • PFS, ORR, CRR, DCR according to RECIST version 1.1 by the investigator • Time to deterioration of liver function • Time to locally/locoregional untreatable progression • Time to BCLC C stage progression • Time to first TACE (only in arm A) • Patient-reported outcomes • Safety: AEs, and AEs of special interest (including irAEs)
Exploratory end points
• Efficacy (ORR, PFS, DCR, CRR) as determined by central review according to RECIST version 1.1 and modified RECIST • Biomarker analyses (e.g., PD-L1 expression in tumor tissue; AFP, AFP-L3, PIVKA II in serum; diversity of gut microbiome) and correlation with clinical outcomes

AE: Adverse events; BCLC: Barcelona Clinic Liver Cancer staging system; CRR: Complete response rate; DCR: Disease control rate; irAEs: Immune-related adverse events; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PIVKA II: Protein induced by vitamin K absence-II; RECIST: Response evaluation criteria in solid tumors; TACE: Transarterial chemoembolization.
Clinical trial registration: NCT04224636 (ClinicalTrials.gov).

at baseline, 6 weeks after treatment initiation and every 8 weeks thereafter until loss of clinical benefit or unacceptable toxicities for a maximum of 24 months. Patients will be followed up for 12 months after the last administration of study drugs. Safety evaluations include assessments of type, incidence and severity of AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5. As irAEs present a critical issue in CPI-based regimens, potential autoimmune toxicities are considered to be AEs of special interest (AESI). PROs are assessed using the questionnaire European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ-HCC18 at baseline and every 6 weeks until the end of treatment.

Translational analyses will be aimed at identifying predictive biomarkers by correlation with clinical outcomes. Biomarker analysis may include: Expression of PD-L1, immune cell infiltration and mutational load in tumor specimens; tumor markers (e.g., AFP, AFP-L3, PIVKA II), levels of VEGF and other circulating cytokines (e.g., IL-6, IL-8) and plasma genomics (circulating tumor DNA) in blood; diversity of gut microbiome in feces. Biomarkers to monitor treatment safety focus on liver function parameters (e.g., transaminases, alkaline phosphatase, bilirubin, coagulation panel) and liver function scores (e.g., Child-Pugh score, albumin-bilirubin [ALBI] grade).

Statistics

The full analysis set will be used to perform the intention-to-treat analysis including all randomized patients according to the arm to which they have been randomized. All patients receiving at least one dose of atezolizumab and/or bevacizumab form the safety population.

The 24-month survival rate is defined as the percentage of patients alive at 24 months after randomization. PFS is the time from randomization to first disease progression on radiographic assessment according to RECIST v1.1 or death from any cause. ORR consists of the proportion of patients with RECIST v1.1-defined CR or partial response (PR), DCR in the proportion of patients with CR, PR or stable disease. Time to deterioration of liver function is defined as the time from randomization to worsening of CTCAE grade of liver function tests (AST, ALT, bilirubin, ALB, prothrombin time international normalized ratio) persisting $\geq$30 days.

A total of 106 patients (53 patients per trial arm) are needed to assure 80% power to test the null hypothesis (24-month survival rate of TACE only $\leq$55% based on historical data from prior randomized studies such as TACE-2 [12], BRISK [15], SPACE [14]and the ORIENTAL trial [16]) against the alternative hypothesis (24-month survival rate $\geq$75%) at a two-sided significance level of 0.05, separately for each arm, assuming a noninformative dropout rate of 12%. An exact binomial test will be applied to the 24-month survival rate and Kaplan–Meier analysis will be used for OS and PFS. An efficacy interim analysis of OS is planned when 20 patients in each arm ($\sim$38% information fraction) will have received at least one dose of atezolizumab + bevacizumab. For additional safety monitoring, two safety interim analyses will be conducted once the first three and ten patients in each arm have completed six treatment cycles with the study drugs. Safety will be assessed by an independent Data Monitoring Committee (DMC) composed of oncologists, an interventional radiologist and a hepatologist.

Sites

Patients will be enrolled at 16 sites in Germany. The first patient was randomized in June 2020 and recruitment is ongoing.

Conclusion

Atezolizumab + bevacizumab has significantly prolonged OS and PFS in patients with unresectable HCC and has been approved for the therapy of patients with advanced or unresectable HCC who have not received prior systemic treatment. Patients with intermediate HCC represent a large disease subgroup. Combining TACE with agents targeting the immune checkpoint and VEGF pathway may represent an effective strategy to improve the limited outcomes of the current standard of care, TACE only. The DEMAND study is the first clinical trial to assess the safety, efficacy and optimal sequence of TACE and combined atezolizumab + bevacizumab. In addition to atezolizumab + bevacizumab, various clinical trials combining TACE and immunotherapy are being conducted for patients with intermediate HCC, including TACE and durvalumab + bevacizumab in the EMERALD I trial (NCT03778957) or TACE and lenvatinib + pembrolizumab in the LEAP-012 trial (NCT04246177). However, none of those studies includes an arm with upfront administration of immunotherapy followed by TACE upon progression. Enrollment in the DEMAND trial started in June 2020.

Executive summary

Background

- Hepatocellular carcinoma (HCC) is a common cause of cancer-related death and patients with intermediate-stage HCC constitute a large subgroup.
- Intermediate-stage HCC is defined as unresectable HCC without vascular invasion or extrahepatic spread in a patient with preserved liver function and good performance status.
- Transarterial chemoembolization (TACE) is the globally accepted standard of care in patients with intermediate HCC and is considered a palliative treatment with limited outcomes.
- Atezolizumab + bevacizumab is the first approved immunotherapeutic regimen for first-line treatment of patients with unresectable HCC.
- The efficacy and tolerability of this regimen suggest that its use could be extended to the treatment of patients with intermediate-stage HCC in combination with TACE.
- The effect of TACE combined with atezolizumab + bevacizumab could improve response and tumor control as well as prevent disease progression in nonresponders to TACE.
- Response to the early use of immunotherapy could also reduce the number and extent of TACE cycles needed to achieve tumor control, thereby contributing to the prevention of collateral damage to the liver parenchyma and preservation of liver function.
- Initiating immunotherapy first may also promote the access of circulating lymphocytes into tumor lesions.
- The DEMAND study was designed to investigate the efficacy, safety and ideal sequence of TACE and immunotherapy in intermediate-stage HCC.

DEMAND study design

- The DEMAND study (NCT04224636) is an investigator-initiated, multicenter, randomized, open-label, noncomparative, stratified phase II trial evaluating the efficacy and safety of either upfront atezolizumab + bevacizumab followed by sequential on-demand selective TACE upon detection of disease progression or of initial synchronous treatment with TACE and atezolizumab and bevacizumab in the treatment of patients with intermediate HCC.
- A total of 106 patients with intermediate HCC will be randomized in a 1:1 ratio to receive either upfront atezolizumab + bevacizumab followed by sequential on-demand selective TACE of progressive lesions (arm A: 53 patients) or atezolizumab + bevacizumab and initial synchronous treatment with TACE (arm B: 53 patients).
- Patients receive study treatment until loss of clinical benefit or unacceptable toxicity for up to 24 months.
- The use of local ablation is allowed for the treatment of lesions that cannot be sufficiently targeted selectively by TACE, or of *de novo* lesions.
- The primary end point is the 24-month survival rate; secondary end points include objective response rate, progression-free survival, safety and quality of life.

Eligibility

- Key inclusion criteria: Histologically confirmed HCC with Barcelona Clinic Liver Cancer stage A not amenable to curative therapy or B, Child-Pugh class A or B7 liver function, Eastern Cooperative Oncology Group performance status 0 or 1 and no prior TACE.
- Key exclusion criteria: Diffuse HCC or presence of vascular invasion or extrahepatic spread, patients actively listed for liver transplantation or potentially eligible for transplantation by fulfilling the Milan criteria, prior TACE; radioembolization or systemic therapy, untreated or incompletely treated varices with bleeding or high-risk for bleeding.

Conclusion

- A combination of TACE with agents targeting the immune checkpoint and VEGF pathway might represent an effective strategy to improve the limited outcomes by the current standard-of-care TACE only in patients with intermediate-stage HCC.
- The DEMAND study is the first clinical trial to assess safety, efficacy and optimal sequence of TACE and atezolizumab + bevacizumab in patients with intermediate-stage HCC.

Author contributions

All authors contributed to the literature review and search, writing, formatting and editing of the manuscript. N Ben Khaled designed the figures; N Ben Khaled and EN De Toni answered the questions of the peer reviewers' and replied to their comments with the approval of all authors. All authors approved the submitted manuscript.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The ethics review boards of all participating sites have approved the study protocol. The trial will be performed in accordance with the Declaration of Helsinki, Good Clinical Practice Standards and the applicable laws and regulations. All patients have to provide informed consent before any study-related procedures are conducted.

Data sharing statement

The sponsor of the DEMAND trial encourages additional scientific analyses based on the data collected. External data sharing requests will be considered for additional topics not already pursued by the investigators. Researchers can submit a request for individual participant data with a research proposal and a data-sharing agreement to the sponsor for review. All of the anonymized individual participant data collected during the trial can be shared. Data availability will begin one year and end five years after completion of the trial and publication of primary results. The study protocol, statistical analysis plan and informed consent form will also be made accessible.

Trial registration

The DEMAND clinical trial is registered at the US National Institutes of Health (ClinicalTrials.gov, NCT04224636) and the European Union Drug Regulating Authorities Clinical Trials Database (clinicaltrialsregister.eu, 2019-002430-36).

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Meta-Analysis

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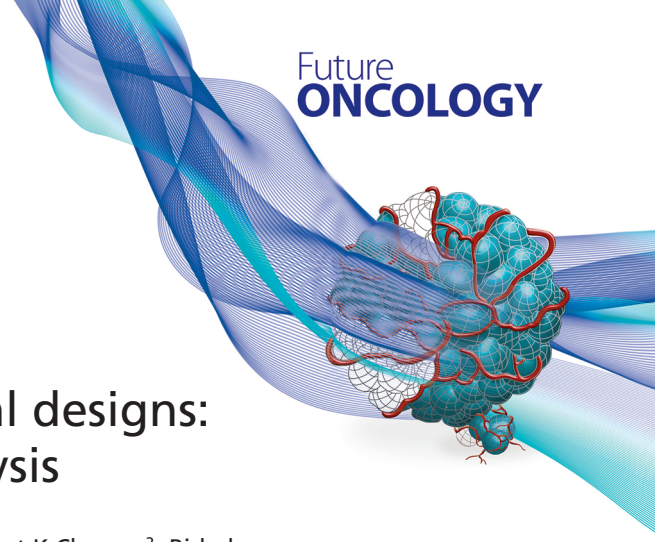

Comparison of tumor-agnostic and tumor-specific clinical oncology trial designs: a systematic review and meta-analysis

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Aim: To examine whether tumor-specific and tumor-agnostic oncology trials produce comparable estimates of objective response rate (ORR) in *BRAF*-altered cancers. **Materials & methods:** Electronic database searches were performed to identify phase I–III clinical trials testing tyrosine kinase inhibitors from 2000 to 2021. A random-effects model was used to pool ORRs. A total of 22 cohorts from five tumor-agnostic trials and 41 cohorts from 27 tumor-specific trials had published ORRs. **Results:** There was no significant difference between pooled ORRs from either trial design for multitumor analyses (37% vs 50%; p = 0.05); thyroid cancer (57% vs 33%; p = 0.10); non-small-cell lung cancer (39% vs 53%; p = 0.18); or melanoma (55% vs 51%; p = 0.58). **Conclusion:** For *BRAF*-altered advanced cancers, tumor-agnostic trials do not yield substantially different results from tumor-specific trials.

Plain language summary: Two types of studies were sought, including studies that measured health outcomes in patients who were selected to receive medicine based on the location of their cancer (tumor), called tumor-specific studies; and studies that measured health outcomes in patients who were selected to receive cancer medicine regardless of the location of their cancer (tumor), called tumor-agnostic studies. From the studies found, only the studies that tested a specific type of cancer medicine (called tyrosine kinase inhibitors) on cancers with a specific genetic alteration (called *BRAF*-altered cancers) were identified. These studies were included in the analysis. The goal of the analysis was to determine if the two types of studies gave similar estimates of response rate, which is a type of trial outcome that measures whether the cancer shrinks or disappears. To do this, the results from the tumor-specific studies were combined with the results of the tumor-agnostic studies. No meaningful differences in the results from the tumor-specific studies compared with the tumor-agnostic studies were found. This suggests that tumor-specific studies do not yield very different results from tumor-agnostic studies.

Tweetable abstract: For *BRAF*-altered advanced cancers, tumor-agnostic clinical trials do not yield substantially different results from tumor-specific studies and may offer a more efficient method for efficacy across multiple tumor types simultaneously, with less between-study heterogeneity.

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Keywords: *BRAF* • clinical trial • meta-analysis • tumor-agnostic • tumor-specific

Advancements in our understanding of the molecular basis of cancer have revealed new targets for cancer therapeutics. Relative to traditional cytotoxic agents that work to slow disease progression by killing cancerous cells in a nonspecific manner, targeted therapies act on specific cellular pathways to induce antitumor effects with greater efficacy and reduced toxicity. This has evolved into an interest in tumor-agnostic drug development, particularly for rare cancer mutations, where few patients meet both a histologic and molecular definition. In tumor-agnostic

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trials, classification by molecular alteration supersedes classification by tumor type, and patients are recruited into trials primarily by the presence of a specific molecular target [1]. Since 2017, three therapies have been approved for tumor-agnostic indications [2]. However, even for targeted therapy, the response may differ by histologic context [3,4]. For example, the efficacy of *BRAF* inhibitor monotherapy, such as vemurafenib, for *BRAF*-mutant melanoma is not consistent with the response seen in *BRAF*-mutant colorectal cancer for which efficacy is relatively poor [4]. Thus, given the importance of histological context in predicting the success of targeted therapy, the use of a tumor-agnostic approach in drug development has not been fully embraced, and the question of whether or not tumor-agnostic trials can offer comparable results to tumor-specific trials to support new drug development and approval has not been thoroughly investigated.

It is timely to understand the comparability of estimates of clinical efficacy for targeted agents using tumor-specific versus tumor-agnostic designs, and the relative importance of classifying patients by tumor type versus molecular alteration. Using two focused systematic reviews and meta-analyses (SRMAs), the current work was designed to compare clinical outcomes of published tumor-specific and tumor-agnostic clinical oncology trials to better understand how results compare across study designs and the potential implications for research and development of pharmaceuticals. This analysis focused solely on clinical trials of tyrosine kinase inhibitors (TKIs) in solid advanced cancers meeting one of two criteria: tumor-specific trials in *BRAF*-mutated cancer or tumor-agnostic trials in any molecular alteration. The comparison of tumor-specific and tumor-agnostic trials then focused on cohorts that had *BRAF*-mutated cancers, to allow for less heterogeneous comparisons. *BRAF* mutations were the focus of the analysis, as they occur across a broad group of human cancers and are common enough to provide sufficient sample sizes for data analysis.

Methods

The research question in this review differed from that of traditional SRMAs as it aimed to compare results from trial designs rather than clinical interventions. The comparison of interest in this meta-analysis occurred across trials, not within, and thus required some modifications to the traditional SRMA methodology. Nevertheless, the study followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) recommendations wherever possible and appropriate.

As the research question necessitated capturing two distinct trial designs, this qualitative comparison was conducted as two parallel SRMAs with independent eligibility criteria and search strategies for tumor-agnostic trials and tumor-specific trials. The search strategy and eligibility criteria for tumor-specific trials were limited to capturing only trials conducted in *BRAF*-mutated cancers. In comparison, the tumor-agnostic search strategy and criteria were broad enough to capture all tumor-agnostic trials across diverse molecular targets to provide a tumor-agnostic evidence base for future studies. However, this study focuses only on *BRAF*-mutated cohorts within tumor-agnostic trials to allow for less heterogenous comparisons between tumor-agnostic and tumor-specific trials. Thus, study selection occurred in two steps, with the first step being to screen for publications meeting overall eligibility criteria, and the second step being to identify publications that included *BRAF*-mutated trial populations or cohorts. This subset of trials containing *BRAF*-mutated cohorts was included in the descriptive analysis of trial/cohort characteristics and subsequent meta-analyses.

Eligibility criteria

To be eligible for inclusion, tumor-specific trials must have met the following criteria: phase Ib, phase I/II, phase II or phase III clinical trial; employed a tumor-specific trial design that recruited just one type of cancer; recruited patients with advanced cancer and a molecular alteration of the *BRAF* gene; experimental intervention included a TKI targeted to *BRAF* and/or *MEK* alterations; and had published results, including at least one of overall response rate (ORR), progression-free survival (PFS) or overall survival (OS).

Tumor-agnostic trials were eligible for inclusion if the publication met the following criteria: phase Ib, phase I/II, phase II or phase III clinical trial; employed a tumor-agnostic trial design that recruited across multiple cancer types; recruited patients with advanced cancer and a specific molecular alteration; experimental intervention was a TKI targeted to the molecular alteration for which patients were recruited; and had published results, including at least one of ORR, PFS or OS.

Although not part of the screening criteria, the tumor-agnostic trials included in this analysis were limited to those that included *BRAF*-mutated cancer cohorts and reported those results separate from other mutations. Both tumor-agnostic and tumor-specific trials were also excluded if they met any of the following additional exclusion

criteria: included pediatric tumors where results for adult tumors were not presented separately; did not include solid tumors; included only early-stage cancers; or if the experimental arm included treatments other than a TKI alone (e.g., TKI and monoclonal antibody combination therapy).

Information sources & search strategy

Electronic systematic literature searches were performed in PubMed/MEDLINE and EMBASE via the Ovid interface to identify trial publications from 1 January 2000, to 23 September 2021. The reference lists of key studies were reviewed for additional publications and hand searches of other search engines including ClinicalTrials.gov and Google Scholar were also conducted to identify potential additional studies not captured in the search strategies.

Separate search strategies were developed for tumor-specific and tumor-agnostic trials (Supplementary Tables 1 & 2). As the tumor-agnostic trial design is a relatively new phenomenon in the history of oncology clinical trials, the search was restricted to only trials published after the year 2000. Upon reviewing the distribution of publication years, trials published in 2010 or more recently were screened, to keep the time period as comparable as possible between the tumor-agnostic and tumor-specific trials. Abstracts were also excluded during study selection as they are not peer-reviewed publications and are unlikely to contain sufficient information to assess the risk of bias.

Study selection, evaluation & data extraction

Two independent reviewers conducted two levels of screening. Titles and abstracts for all trials were screened by both reviewers independently in Level 1 to determine which articles potentially met eligibility for inclusion. Full-text articles for all trials screened for inclusion in Level 1 were then screened in Level 2 by both reviewers independently. A third reviewer was consulted as necessary to resolve any disagreements between reviewers and reach a consensus. Kappa statistics were calculated to determine the level of agreement between the two independent reviewers.

Data extraction followed a uniform data extraction form that was common to both the tumor-agnostic and tumor-specific publications. Data extracted for each study included: study details such as study name/clinical trial ID, full citation, study design, study phase, blinding, number of centers and number of treatment arms; baseline characteristics such as geographic trial location(s), primary patient definition (histological vs molecular), eligibility criteria, sample size, age, sex, solid cancer type(s), primary tumor location(s) and genetic alteration characteristics; intervention and comparator characteristics such as experimental and comparator treatment regimen(s); and efficacy outcomes including PFS, ORR and OS.

Study evaluation

In addition to the data items just described, the methodological quality of the studies was assessed using the Cochrane Collaboration's Risk of Bias tool. This tool was used to assess the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias. The risk of bias was rated as 'high', 'low' or 'uncertain'. Heterogeneity between studies was also assessed using the I^2 value, with 0–40% indicating low heterogeneity, 30–60% indicating moderate heterogeneity and 50% or greater indicating substantial heterogeneity [5].

Data analysis

Analyses were focused on *BRAF*-mutated cohorts only. Multiple cohorts could be included from a single trial (e.g., results reported separately for different TKI interventions or clinical subgroups). Some trials also had results published across multiple articles, with separate publications from the same trial typically being for separate cohorts (e.g., separate tumor cohorts from tumor-agnostic trials), separate clinical subgroups (e.g., patients with brain metastases) or different time points (e.g., extended follow-up). All available data for all eligible cohorts were extracted, ensuring that patients were not double-counted across multiple cohorts, subgroups or time points. Where the same results were published for the same patients across multiple articles, the most recent publication was used.

Multiple meta-analyses were conducted for tumor-agnostic and tumor-specific trials, pooling ORRs across cohorts from tumor-agnostic trials and tumor-specific trials, respectively. ORR was the only outcome meta-analyzed, as it was the most consistently and uniformly reported compared with PFS and OS, for which reporting was more variable. ORR was pooled across multiple tumor types, creating one multitumor pooled ORR each from tumor-agnostic trials and tumor-specific trials. Results were then pooled within tumor types, creating single-tumor pooled ORRs for both tumor-agnostic trials and tumor-specific trials. Finally, results were pooled by intervention type received (e.g., *BRAF* inhibitors and *BRAF*/*MEK* inhibitors). This stepwise approach to the analysis, with each step limiting meta-analyses to a certain factor, such as tumor type or intervention type, was intended to simulate

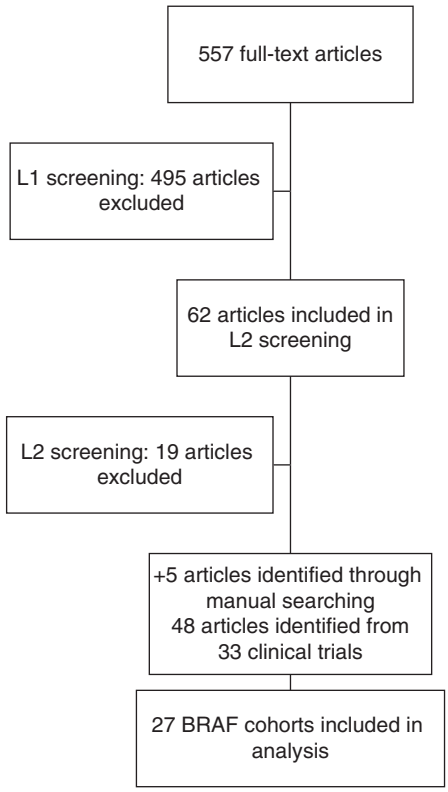

Figure 1. Flowchart of tumor-specific trials and cohorts included in final analysis.
L1: Level 1; L2: Level 2.

controlling for extraneous variables beyond trial design that would differ between the two groups of trials, to increase confidence that observed differences in pooled effect sizes and heterogeneity were at least partly attributable to differences in trial design. The clinical characteristics of the patient populations and methodological differences in the trials were also described qualitatively to further contextualize the differences observed in pooled results from the respective meta-analyses.

As considerable between-study heterogeneity was expected due to variability in populations, intervention and time periods, a generalized linear mixed-effects model [6] was used to pool effect sizes, and a maximum likelihood estimator was used to calculate the heterogeneity variance τ^2. A Knapp-Hartung adjustment [7–9] was also applied to the mixed-effects model to calculate the 95% CIs around the pooled effect sizes. Analyses were conducted in R software, version 4.1.1 [10] using the 'meta' [11] and 'forestplot' [12] packages. For all meta-analyses, results are reported as pooled ORR (95% CI) and statistical heterogeneity of the estimate (I^2). Comparison of pooled ORRs (i.e., tumor-specific vs tumor-agnostic) was performed using the $\chi 2$ test of independence, with exact p-values reported to describe the statistical significance of the comparison. Other descriptive characteristics are summarized as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables and frequency and proportion (%) for categorical variables.

Results

Study selection

The electronic database search for tumor-specific trials returned a total of 1372 citations. Of these, 557 were peer-reviewed, full-text articles that underwent title and abstract screening. A total of 495 articles were excluded from Level 1 screening and 62 articles underwent full-text screening. After the second-level screening, an additional 19 articles were excluded and 43 articles were considered eligible. An additional five articles were identified from hand-searching, resulting in a total of 48 tumor-specific publications eligible for inclusion, coming from 33 clinical trials (Figure 1). For tumor-agnostic trials, the electronic database search returned 8572 total citations, of which 2344 were peer-reviewed, full-text articles. Level 1 screening excluded 2300 of these articles, leaving 44 articles for Level 2 screening. A total of 18 articles were excluded during Level 2 screening and 26 were considered eligible. Hand-searching identified an additional six articles, resulting in 32 tumor-agnostic publications coming from 25 clinical trials (Figure 2). The vast majority of articles that were excluded at each phase of screening, for both tumor-

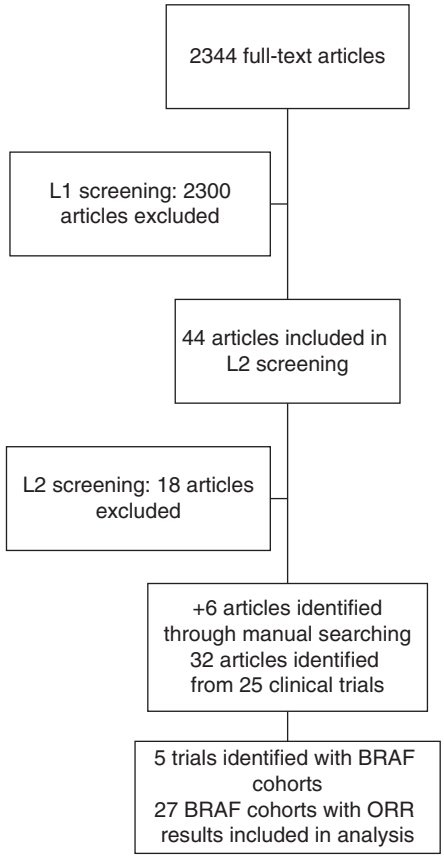

Figure 2. Flowchart of tumor-agnostic trials and cohorts included in final analysis.
L1: Level 1; L2: Level 2; ORR: Objective response rate.

agnostic and tumor-specific trials, met multiple exclusion criteria, the most common being that the experimental intervention included a non-TKI and/or the intervention was tested in an all-comer population (i.e., not targeted to a specific molecular alteration).

For both search strategies, the overall Kappa statistic for the inter-rater agreement was 0.57, indicating moderate agreement. However, this was mostly attributable to the iterative nature of refining inclusion criteria given the extensive scope of literature captured. That is, most disagreements between raters were due to novel publication or trial characteristics that had not been considered during protocol development. All disagreements were easily resolved through discussion of the specific citation, and any decisions made were then consistently applied to the screening of all other citations.

Study characteristics of publications included in meta-analyses

Publications from tumor-agnostic trials

Of the 25 tumor-agnostic trials identified in the initial step of study selection, 5 were identified as recruiting patients with targetable *BRAF* alterations and had published ORR results available. Four of the five trials were phase II trials, and one was a phase I/II trial. All trials were single-arm, multicenter and open-label. All five trials recruited patients from the United States, but three trials recruited patients internationally as well. All five trials were judged to have a high risk of bias.

Among the five tumor-agnostic trials, there were 22 distinct *BRAF*-mutated cohorts spanning the following tumor types: colorectal, non-small-cell lung (NSCLC), biliary tract, ovarian, bladder, pancreatic, uterine, salivary gland, small intestine, prostate, unknown primary and 21 other tumor types not further specified. Further cohorts were defined based on criteria such as prior treatment exposure. All TKI interventions were *BRAF* and/or *MEK* inhibitors, including vemurafenib, cobimetinib, trametinib, encorafenib, binimetinib and dabrafenib. Sample sizes of the cohorts ranged from 7 to 230. The proportion of males in each cohort ranged from 25% to 73%, and with the exception of one cohort, all cohorts had a median age over 50 years old. The vast majority included patients with any *BRAF V600* mutation, though two cohorts recruited only *V600E* mutations and one cohort recruited only

fusions in the *BRAF* gene or non-*V600* mutations. Tumor-agnostic trial and cohort characteristics are described in detail in Supplementary Tables 3 & 4, respectively, and PFS and OS are described in Supplementary Table 5.

Publications from tumor-specific trials

Of the 33 tumor-specific clinical trials identified in step one of study selection, 27 were identified with published ORR results for meta-analysis. Of the trials, 14 (51.6%) were phase II; 7 (25.9%) were phase III; and the remaining six were phase I/II or phase Ib (22.2%). Three studies used a single-blind or double-blind design and the rest were open-label. Seventeen (63.0%) were single-arm trials, with the remaining ten (37.0%) testing two or more treatment arms. A total of 24 (88.9%) were multicenter, 16 of which recruited patients internationally. Three (11.1%) trials were single-center trials, one taking place in the United States and another in Australia, with no location specified for the last trial. Twenty-five (92.6%) of the tumor-specific trials were conducted on melanoma, with the other two trials conducted in NSCLC and thyroid cancer, respectively. Twenty-one trials were judged to have a high risk of bias, three were low risk and three had an unclear risk of bias.

Among the 27 tumor-specific trials conducted in *BRAF*-mutated cancers, there were 41 distinct *BRAF*-mutated cohorts. Although each tumor-specific trial was conducted in a prespecified tumor type, there could be multiple cohorts per trial for different interventions (e.g., monotherapy vs *BRAF* and *MEK* inhibitor combination therapy), different dosing (e.g., intermittent vs continuous) or different clinical subgroups (e.g., with vs without brain metastases or pretreated vs treatment-naive). TKI interventions included the following *BRAF* and/or *MEK* inhibitors: vemurafenib, cobimetinib, trametinib, encorafenib, binimetinib and dabrafenib. Sample sizes of the cohorts ranged from 9 to 856 patients, and the proportion of males in each cohort ranged from 35% to 75%. All cohorts had a median age between 52 and 66 years old. Of the 41 cohorts, 17 (41.5%) cohorts included *V600E* or *K* mutations only, 14 (34.1%) included any *V600* mutation, six (14.6%) included *V600E* only, with the remaining four (9.8%) requiring other specifications of *BRAF* mutations or alterations. Tumor-specific trial and cohort characteristics are described in detail in Supplementary Tables 6 & 7, respectively, and PFS and OS are described in Supplementary Table 8.

Meta-analysis

Multitumor pooled ORRs

The multitumor meta-analysis for tumor-agnostic trials included 23 cohorts and 554 patients. The following cancer cohorts were represented: colorectal (n = 2), ovarian (n = 1), thyroid (n = 3), NSCLC (n = 4), melanoma (n = 3), head and neck (n = 1), Erdheim–Chester disease (ECD) and Langerhans cell histiocytosis (LCH; n = 2), cholangiocarcinoma (n = 2), glioma (n = 1), cancer of unknown primary (n = 1) and multicancer cohorts not further specified (n = 3). The pooled ORR was 37% (27–49%) with 55% heterogeneity. The multitumor meta-analysis for tumor-specific trials included 44 cohorts and 4891 patients. The meta-analysis included melanoma cohorts (n = 39), thyroid cancer (n = 2) and NSCLC (n = 3). There were no tumor-specific trials in colorectal cancer that met the eligibility criteria and reported ORR. The pooled ORR was 50% (43–57%) with 90% heterogeneity. The difference between the pooled ORRs for tumor-agnostic versus tumor-specific trials did not reach significance (p = 0.05; Figure 3).

Pooled ORRs by tumor type

Thyroid cancer

There were three cohorts totaling 24 patients from tumor-agnostic trials that reported results only for thyroid cancer. The pooled ORR from thyroid cohorts from tumor-agnostic trials (n = 3) was 57% (12–93%) with 32% heterogeneity. For tumor-specific trials, the pooled ORR from thyroid cohorts (n = 2) was 33% (1–96%) with 0% heterogeneity. There was no significant difference in effect size between the two pooled ORRs (p = 0.10; Figure 4).

Non-small-cell lung cancer

There were four NSCLC cohorts from tumor-agnostic trials with a pooled ORR of 39% (25–55%) and 0% heterogeneity. In comparison, the pooled ORR from tumor-specific trials (n = 3) was 53% (19–84%) with 85% heterogeneity. There was no significant difference in effect size between the two pooled ORRs (p = 0.18; Figure 5).

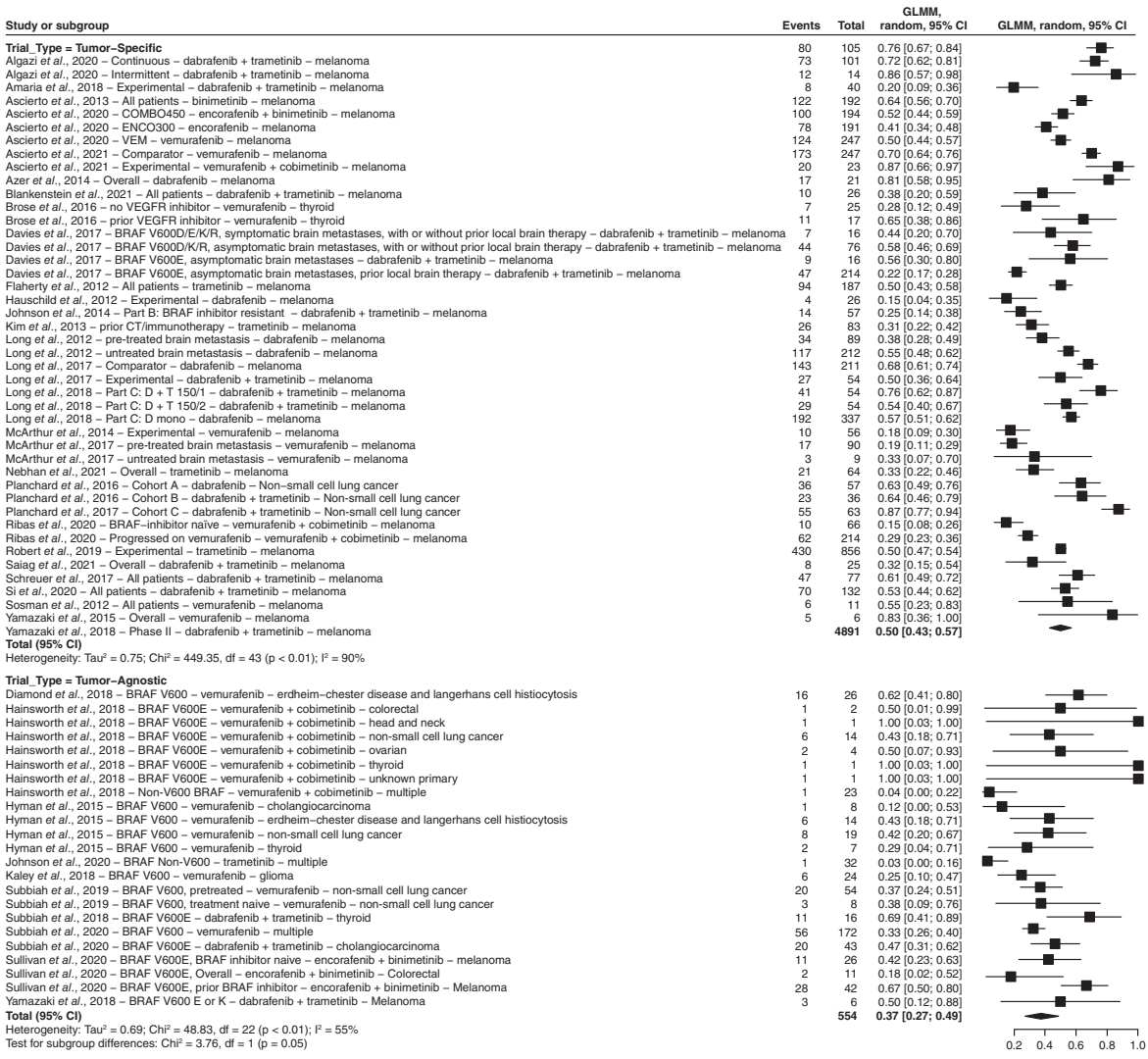

Figure 3. Pooled objective response rates for thyroid cancer.
GLMM: Generalized linear mixed model.

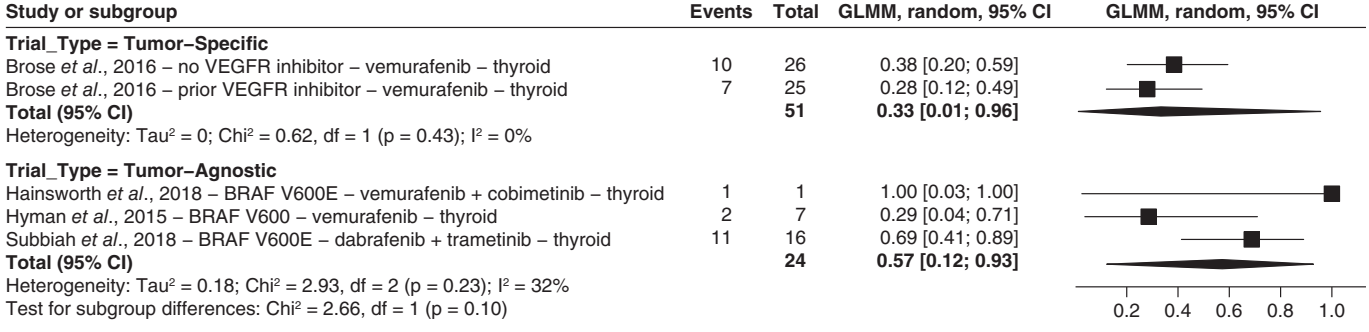

Figure 4. Pooled objective response rates for non-small-cell lung cancer.
GLMM: Generalized linear mixed model.

Melanoma

The pooled ORR for melanoma cohorts from tumor-agnostic trials (n = 3) was 55% (24–83%) with 49% heterogeneity. Most cohorts from tumor-specific trials were melanoma cohorts (n = 39), with a pooled ORR of

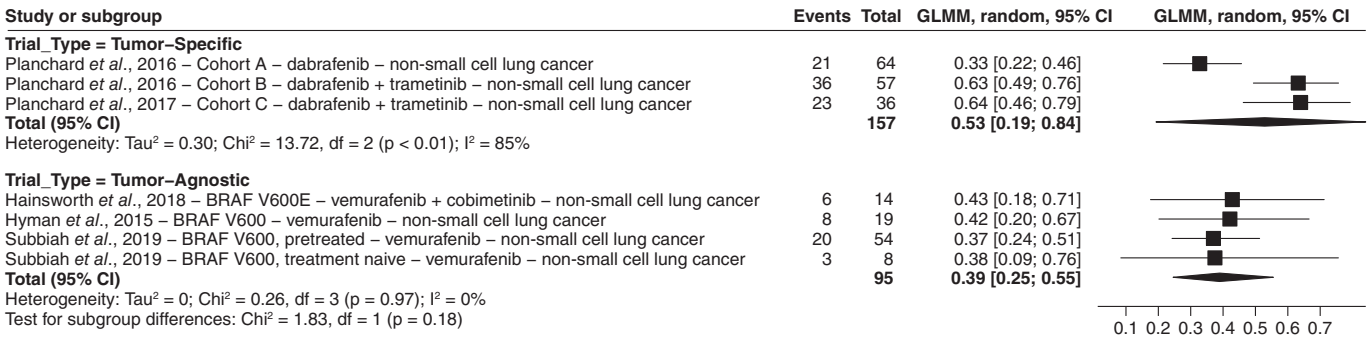

Figure 5. Pooled objective response rates for melanoma.
GLMM: Generalized linear mixed model.

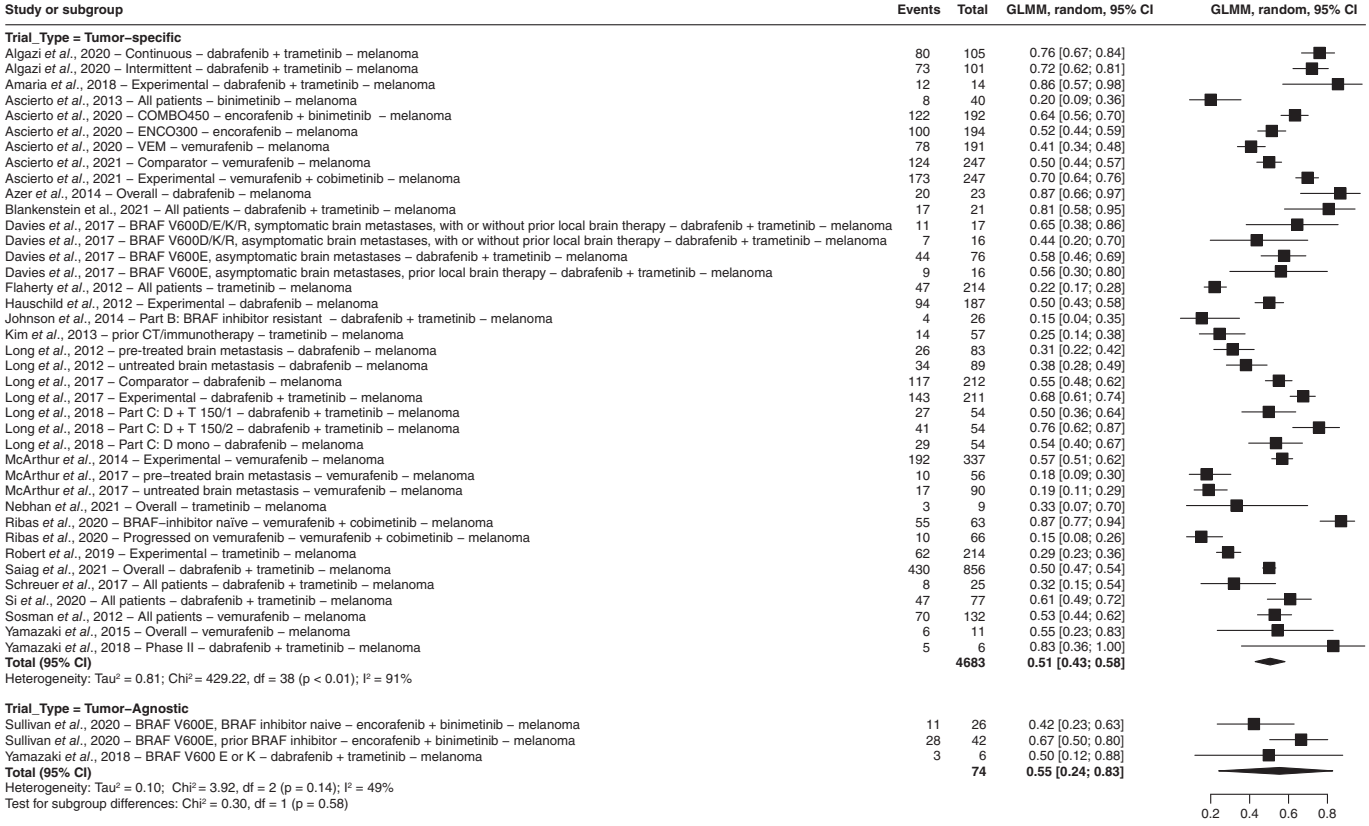

Figure 6. Pooled objective response rates, stratified by intervention type.
GLMM: Generalized linear mixed model.

51% (43–58%) and 91% heterogeneity. There was no significant difference in effect size between the two pooled ORRs (p = 0.58; Figure 6).

Pooled ORRs by intervention type

BRAF inhibition

Nine cohorts from tumor-agnostic trials received treatment with *BRAF* inhibitor monotherapy, specifically vemurafenib. Cohorts treated with vemurafenib included the following tumor types: ECD and LCH (n = 2), cholangiocarcinoma (n = 1), NSCLC (n = 3), thyroid cancer (n = 1), glioma (n = 1) and multitumor not otherwise specified (n = 1). The pooled ORR was 36% (29–45%) with 29% heterogeneity. Among tumor-specific trials, 17 cohorts comprised of melanoma (n = 14), NSCLC (n = 1) or thyroid tumor types (n = 2) had received

treatment with *BRAF* inhibitor monotherapy, either vemurafenib, encorafenib or dabrafenib. The pooled ORR was 44% (36–52%) with 84% heterogeneity. There was no significant difference in the two pooled effect sizes (p = 0.17; Supplementary Figure 1).

BRAF + *MEK* inhibition

Thirteen cohorts from tumor-agnostic trials received treatment with a combination of a *BRAF* and a *MEK* inhibitor, specifically one of the following regimens: vemurafenib plus cobimetinib, dabrafenib plus trametinib or encorafenib plus binimetinib. The tumor cohorts treated included colorectal (n = 2), head and neck (n = 1), NSCLC (n = 1), ovarian (n = 1), thyroid (n = 2), melanoma (n = 3), cholangiocarcinoma (n = 1), multitumor (n = 1) and unknown primary tumor (n = 1). The pooled ORR was 46% (29–63%) with 42% heterogeneity. There were 22 cohorts from tumor-specific trials, all melanoma, that were treated with either dabrafenib plus trametinib or vemurafenib plus cobimetinib. The pooled ORR was 61% (52–70%) with 87% heterogeneity. There was no significant difference in the two pooled effect sizes (p = 0.10; Supplementary Figure 2).

Discussion

To our knowledge, this is the first study to assess the comparability of tumor-agnostic and tumor-specific methodologies and outcomes, with implications for future trial design and targeted therapy development. To create a focused, less heterogenous comparison, we isolated cohorts of patients with *BRAF* alterations receiving treatment with TKIs, pooled their ORRs by trial design (tumor-specific vs tumor-agnostic), then applied stratifications for tumor type and intervention type to qualitatively understand how clinical results compare between the two trial design groups. We also aimed to understand the extent to which potential observed differences in clinical results can be attributed to trial design versus other clinical factors.

We captured a larger number of cohorts from tumor-specific trials than tumor-agnostic trials and with a larger number of patients. This is not surprising given the relatively recent advent of tumor-agnostic trials, and that a larger proportion of the tumor-specific trials were phase III. Comparisons of the two trial groups were unable to detect a statistically significant difference in pooled effect sizes for the comparison pooling across multiple tumor cohorts, or when stratified by tumor type and intervention types. Tumor-specific trials showed numerically higher ORRs for most meta-analyses, with the exception of those for thyroid cancer and melanoma. However, there was almost always more heterogeneity in the estimates from tumor-specific trials than tumor-agnostic trials, and often by a considerable margin. While this study limited its scope to *BRAF*-mutated cancers, this novel application of the SRMA methodology sets the stage for similar comparisons in other molecular cancer subtypes.

The results of these meta-analyses highlight important considerations in evaluating tumor-agnostic versus tumor-specific trial designs. Although both designs yielded consistent estimates of the outcome, there was typically less heterogeneity for meta-analyses of cohorts from tumor-agnostic trials than those of tumor-specific trials. This could be interpreted as more consistency in trial design, as cohorts of different tumor types are all exposed to the same overall trial design in a tumor-agnostic trial, while variability between trials conducted in separate tumor types introduces increased heterogeneity. Some of this heterogeneity was reduced when the meta-analyses were conducted within a single tumor type, suggesting some heterogeneity in the multitumor analyses is attributable to the range of tumor types included. However, if tumor type explained most of the heterogeneity observed, one would expect heterogeneity to be greater for the analysis of tumor-agnostic cohorts, which pooled at least 31 tumor types compared with just three tumor types from tumor-specific trials. Further, this pattern of lower heterogeneity across tumor-agnostic trials was also consistent within the meta-analyses for NSCLC and melanoma, increasing confidence that variability in trial design between tumor-specific trials is at least partly responsible for heterogeneity in corresponding effect sizes. Although differences in patient characteristics could create heterogeneity, the characteristics of patients in the two groups of trials were ultimately very similar: cohorts from both groups recruited patients of similar age, with comparable variability in trial location and, by extension, patient ethnicity. Both sets of trials included mostly patients with advanced cancer, with comparable proportions of males versus females. Both tested the same TKIs and combination therapies, mostly targeted to *V600* mutations. Though trials showed differences in the range of tumor types that were recruited, with most tumor-specific trials being in melanoma relative to a more diverse mix from tumor-agnostic trials, results were still consistent when meta-analyses were stratified by tumor type.

While it has already been shown that not all genomic and immunological targets are created equally, and histological context will be more important in evaluating efficacy for some targets than others, it is not well

understood how trial design itself may contribute to trial outcomes, particularly in this new age of tumor-agnostic trial design. While the current results indicated that tumor-specific trials may show slightly increased effect sizes, they also showed substantial heterogeneity across trials that was not observed to the same extent across tumor-agnostic trials, potentially attributable to inconsistent trial design. In comparison, tumor-agnostic trials offer the advantage of applying a single, consistent trial design to multiple tumor cohorts simultaneously, which may serve to increase confidence that variability in results between cohorts is due to true differences in efficacy rather than artifacts of trial design. Subsequently, a tumor-agnostic trial design need not imply a tumor-agnostic interpretation of results. As demonstrated in this analysis, effect sizes from both tumor-specific and tumor-agnostic studies may vary by tumor type, with some tumor types showing better efficacy than others despite a common mutation. However, it is with a tumor-agnostic trial design that one can best check for this complexity in certain molecular alterations. That is, the ability to compare efficacy across multiple tumor types with a common target, within a single trial rather than across multiple independent trials, may enable researchers to recognize the importance of histological context for a specific target much earlier and with greater confidence. This advantage goes beyond that of tumor-agnostic trials that have already been documented, including the ability to expand clinical trials and streamline regulatory approvals more efficiently, particularly for rarer cancers [1,3].

Limitations

This study has some limitations. First, the scope of this analysis was limited to statistical comparisons of separate meta-analyses conducted within the tumor-agnostic and tumor-specific trial groups, rather than tests of noninferiority or equivalence, limiting the ability to make definitive claims that results from the two trial designs were equivalent. However, the aim of this study was not necessarily to determine equivalence, but rather to explore the comparability of estimates produced from tumor-agnostic and tumor-specific trial designs, and perhaps develop hypotheses for further research. This analysis was also limited to ORR as it was the most uniformly reported variable across cohorts. However, ORR is not necessarily correlated with survival and thus may not be as important to patients and clinicians as outcomes such as PFS, OS or health-related quality of life. That said, the objective of this analysis was not to assess the efficacy of any given treatment regimen but rather to comment on the comparability of outcomes between trials of different designs and inform clinical trial design. While comparability of outcomes may differ for other survival-based outcomes and may represent an important area for future research, this analysis of ORR still provides a first look at the variability in outcomes between and across tumor-agnostic and tumor-specific trials.

The lack of statistical significance between pooled ORR estimates from tumor-agnostic and tumor-specific trials does not necessarily imply clinically meaningful equivalence. We recognize that the p-value depends on various factors such as sample size and contend that the results should be interpreted with ample consideration of these elements, (e.g., small sample size for some analyses, underpowered study). In the future, as tumor-agnostic trials become more common and bolster sample sizes for analysis, this will be an important area for future research. That is, will more favorably powered analyses, or alternative tests such as noninferiority and equivalence tests, show consistent results with those observed in this analysis?

Further, although we attempted to simulate control of factors other than trial design, either through stratified analysis or qualitative review of patient characteristics, it is still possible that between-study heterogeneity beyond overall trial design could have produced biased pooled results. However, we argue that the degree of heterogeneity is itself an important finding, as we saw notable patterns in the degree of heterogeneity across tumor-specific trials versus tumor-agnostic trials, and this may have implications for how the results of these trials can be generalized to the real world. Nonetheless, different baseline characteristics of patients and trial design could still contribute to different baseline probabilities of response, which may partly explain observed differences or lack thereof.

Lastly, this study was restricted to trials in *BRAF*-altered cancers, and findings on the comparability of outcomes between trial designs may not generalize to other populations. That said, the framework developed in this study provides a template for future comparisons of trial design in oncology clinical trials of targeted therapies, where the analysis could be further expanded to additional molecularly defined populations. The results of this analysis suggest it is plausible that ORRs yielded from tumor-agnostic trials may not be different from their tumor-specific counterparts. Future research that tests this comparison between trials of more comparable designs and patient populations would lend additional confidence to these conclusions.

Conclusion

The results of these meta-analyses indicate that, for *BRAF*-altered advanced cancers, tumor-agnostic clinical trials do not yield substantially different results from tumor-specific studies and may offer a more efficient method of studying efficacy across multiple tumor types simultaneously with less between-study heterogeneity.

Summary points

- Given the increasing interest in tumor-agnostic drug development, it is timely to understand the comparability of estimates of clinical efficacy for targeted agents using tumor-specific versus tumor-agnostic designs.
- Two systematic reviews and multiple meta-analyses were conducted to examine whether tumor-specific and tumor-agnostic clinical oncology trials produce comparable estimates of objective response rate (ORR) in *BRAF*-altered cancers.
- Tumor-specific trials had to recruit patients with advanced *BRAF*-altered cancer and tumor-agnostic trials had to recruit patients with a molecular alteration across multiple advanced cancer types. Approximately 8% of tumor-specific and 1.5% of tumor-agnostic publications screened met eligibility criteria.
- A total of 22 cohorts from five tumor-agnostic trials and 41 cohorts from 27 tumor-specific trials had published ORRs available for meta-analysis. There were no significant differences between pooled ORR estimates from tumor-agnostic and tumor-specific trials for multitumor analyses.
- Effect sizes also did not differ when stratified by intervention type.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0974

Author contributions

All authors contributed to the conception and design of the study and analysis, as well as the results interpretation and the drafting, editing and/or approval of the final manuscript.

Financial & competing interests disclosure

This study was sponsored by Hoffmann-La Roche Limited, for which IQVIA Canada provided consulting services. The authors have the following conflicts of interest to report: PK Cheema has received advisory board honorarium from AstraZeneca, Amgen, Hoffman La Roche Limited, Bristol Myers Squibb, Merck, Janssen, EMD Serono, Novartis and BeiGene. B Gyawali has received consulting fees from Vivo Health. HJ Conter and M Farid-Kapadia are employees and shareholders of Hoffman La Roche Limited. M Barton and Z Bider-Canfield are employees of Hoffman La Roche Limited. NM Nightingale and L Latifovic are employees of IQVIA and provided consulting services to Hoffman La Roche Limited through their positions at IQVIA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study did not require any ethical approval as the information included was freely available in the public domain, where the data were properly anonymized and informed consent was obtained at the time of original data collection.

Data sharing statement

All data supporting the findings of this study, which is a secondary analysis of clinical trial data, are available in the public domain.

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Short Communication

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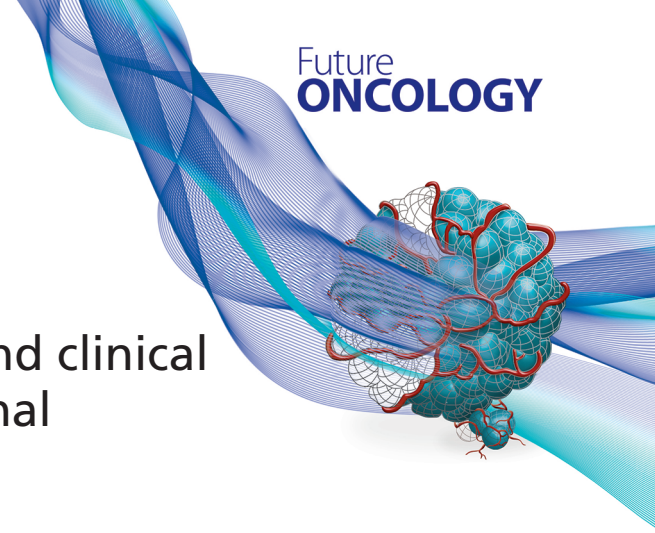

Overall survival in the real-world and clinical trials: a case study validating external controls in advanced melanoma

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Aims: We assessed the suitability of real-world data (RWD) as an external control for analysis of overall survival (OS) compared with clinical trial data (CTD) in advanced melanoma. **Methods:** OS among adults receiving ipilimumab for advanced melanoma was compared between trials (CTD group) and the Flatiron Health database (RWD group) using Cox models. Adjusted analyses accounted for differences in baseline factors; missing data were addressed through multiple imputation. **Results:** After adjusting for baseline factors and accounting for missingness, OS was similar in the CTD (n = 241) versus RWD groups (n = 816; hazard ratio: 0.98; 95% CI: 0.75–1.26). **Conclusion:** Flatiron Health data is suitable to construct external control groups for OS in advanced melanoma trials after adjusting for baseline factors and missing data.

Plain language summary: Clinical trials are the gold standard for measuring the efficacy and safety of new treatments. Comparisons between clinical trials and external controls drawn from real-world data are potentially valuable – especially when randomized trials are not available or feasible – but carry important risks of bias stemming from differences across populations, care settings and measurement of patient characteristics and outcomes. As a case study, we assessed the suitability of a particular real-world database (the Flatiron Health Database) for analyzing overall survival among patients in clinical trials of treatments for metastatic melanoma. Challenges included differences in patient baseline prognostic factors across populations, including high proportions with missing information in real-world data. After accounting for these differences, we observed similar survival between patients receiving ipilimumab monotherapy in clinical trials and in real-world data. We conclude that real-world external controls can be suitable for metastatic melanoma.

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Keywords: clinical trial data • external control • melanoma • methods • real-world data • survival

Real-world data (RWD) have the potential to improve our understanding of novel oncology treatments by serving as an external control group for comparisons with clinical trial data (CTD) [1,2]. A clinical regulatory evaluation may, for example, compare outcomes of patients receiving an investigational agent in a single-arm trial with those of patients receiving standard of care in a real-world population. In this way, RWD may be used to contextualize trial outcomes, augment a smaller randomized comparator arm, provide a pivotal or supportive comparator group, or provide a reference group for long-term extension data after internal controls have crossed over to active therapy [3–5]. Comparisons between CTD and RWD, if deemed reliable, could be used to inform a multitude of decisions, including new drug approvals, indication or population expansions, economic analyses and health technology appraisals. The potential value of RWD is heightened when the gold standard of a randomized, blinded, parallel-group trial is considered unfeasible or unethical. This situation often arises for drug development in late-stage oncology indications, rare conditions, precision medicine subpopulations and accelerated regulatory approvals, or when invasive treatment administration renders blinding unfeasible.

The promise of RWD in these settings, however, is appropriately limited by the substantial and well-recognized risks of bias that are inherent in any comparison across different data sources and across nonrandomized treatment groups. Differences in patient populations, background therapies, outcome assessments and many other factors can lead to unbounded risks of statistical bias when comparing treatment outcomes across groups [6,7]. Furthermore, missing data can be extensive in RWD, raising questions about how it can be accounted for, if at all.

Compounding the risks of confounding bias and missing data are practical challenges in the prespecification of analytical methods for external controls based on RWD. Prespecification is preferred [7]. However, the complexity of RWD, arising from diverse and nonprotocol-driven care settings, can frustrate prespecification. Patterns of missingness, irregular timing of assessments, and variations in clinical assessment methodology give rise to a multitude of study design choices. There is a tension between the value of preinspection of the RWD to inform these study design choices and the value of prespecification to guard against overinterpretation.

Prescriptive guidance for comparisons of RWD and CTD is limited, but there is a wealth of historical and emerging guidance from regulators, as well as evolving precedents. The integration of RWD and CTD has been deemed informative in some regulatory evaluations (e.g., tisagenlecleucel's EMA submission in the indications of diffuse large B-cell lymphoma and acute lymphoblastic leukemia) and uninformative in others (e.g., selinexor's US FDA submission for the indication of multiple myeloma) [6–10]. A series of workshops organized by Friends of Cancer Research brought together stakeholders including data sources, academic centers and pharmaceutical and biotechnology companies to perform a collaborative assessment of the consistency of outcomes across different data sources [11,12]. All of these sources indicate that RWD can differ from protocol-driven data collected through clinical trials and that standardized approaches are needed to reduce or manage potential biases [13].

In this spirit, and to inform the future use of RWD as external controls in clinical trials, we assessed the performance of specific data sources and statistical approaches applied to comparisons of CTD and RWD in advanced (stage III or IV) melanoma. Specifically, we compared the overall survival (OS) among patients receiving ipilimumab monotherapy in RWD from the US nationwide Flatiron Health electronic health record-derived, deidentified database (Flatiron Health data) versus CTD from later-phase clinical trials of the same patient population. We quantified the difference in OS across these data sources and assessed the extent to which statistical approaches, including adjustment for patient characteristics and handling of missing data, could mitigate any differences in OS.

This analysis serves as a 'negative control' for the use of Flatiron Health data as an external reference group for OS in advanced melanoma. Negative controls, which are widely used in laboratory research, are experimental units subjected as closely as possible to all experimental procedures except for the factor under investigation. In a typical application, a null finding in the negative control group is necessary to a successful experiment and provides confidence in any positive findings in the exposed groups. In contrast, if the negative control shows non-null results, the investigator may conclude that contamination renders the overall experiment unreliable.

Similarly, the use of negative controls has been advocated in retrospective epidemiological research to help guard against contamination due to confounding factors [14,15]. In the present study of advanced melanoma, the comparison of OS between Flatiron Health data and CTD serves as a negative control. Consistency in OS between Flatiron Health data and CTD patient groups would provide greater confidence in future comparisons of CTD for a novel therapy versus a reference group derived from Flatiron Health data using the same statistical methods. Conversely, if OS outcomes are inconsistent across data sources, the findings will illustrate the likely magnitude and direction of bias that would need to be accounted for when interpreting a future comparison with an external control group derived from Flatiron Health data in advanced melanoma.

Patients & methods

Patients

Clinical trial data

Data from two phase II and one phase III randomized clinical trials including ipilimumab (3 mg/kg) for the treatment of stage III or IV (advanced) unresectable melanoma were utilized. Among the phase II trials, one enrolled treatment-naive patients and one enrolled both treatment-naive and previously treated patients [16,17]. The phase III trial enrolled previously treated patients [18]. Enrollment for all three trials occurred within the years 2004–2008 and included patients aged 18 years or older with baseline Eastern Cooperative Oncology Group

Table 1. PICOS description of the study design.

Population	Adult patients in the Flatiron database with advanced melanoma representative of those enrolled in the studied clinical trials (NCT00289640, NCT00261365 and NCT00094653)
Intervention	Initiation of ipilimumab 3 mg/kg
Comparison	Difference between the settings of RWD and CTD
Outcome	OS
Settings	RWD and CTD

CTD: Clinical trial data; OS: Overall survival; PICOS: Population Intervention Comparison Outcomes Study/Setting; RWD: Real-world data.

(ECOG) performance status of 0 or 1. All patients randomized to receive 3 mg/kg ipilimumab monotherapy in these trials were included in the present study.

Real-world data

RWD were drawn from the Flatiron Health database for advanced melanoma (January 2011–April 2019). The Flatiron Health database is a longitudinal database comprising deidentified US patient-level structured and unstructured data, curated via technology-enabled abstraction [19]. Patients included in the present study were diagnosed with advanced (stage III or IV) melanoma and subsequently initiated ipilimumab (3 mg/kg) monotherapy in either the first- or later-line setting. Ipilimumab initiation, which was predefined within the database by an algorithm drawing on orders and administration records, served as the index date. Patients were eligible for inclusion if they were aged 18 years or older and had ECOG scores of 0 or 1 at the index date.

Outcomes

The primary outcome in this analysis was OS. In the CTD, OS was defined as the time from randomization until death from any cause, with censoring implemented as defined in underlying trial documentation. In the RWD, OS was defined as the time from the index date (i.e., ipilimumab initiation) until death from any cause, with deaths coded by a pre-existing algorithm in the Flatiron Health database drawn from medical records and national death records. For patients in the RWD group without a recorded death, OS was censored at the last recorded activity in the database (e.g., clinic visit, medication order).

Baseline characteristics & subsequent therapies

The selection of patient characteristics to be included in the analysis was guided by clinical associations with OS in advanced melanoma and data availability in CTD and RWD. Included baseline characteristics were age, sex, race, BMI, LDH levels, disease stage, ECOG score, time from advanced melanoma diagnosis to ipilimumab initiation, number of prior systemic therapies and presence of any prior immunotherapy. Factors of potential clinical interest that were not consistently recorded in the CTD or RWD and were thus not available for the present study included tumor measurements (e.g., depth and thickness), numbers and locations of metastases, $BRAF_{V600}$ mutation status and metastasis (M) stage (see Supplementary Table 1 for available data on $BRAF_{V600}$ mutation status and M stage). Calendar years at ipilimumab initiation were also summarized for the CTD and RWD groups.

In the CTD group, baseline characteristics were assessed at baseline visit of each trial. In the RWD group, baseline characteristics were assessed as the closest recorded value to the index date during a time window spanning 3 months before to 1 month after the index date. This time window was selected based on an assessment of data availability and clinical advice. Baseline characteristics that were unavailable within this time window were treated as missing.

Statistical analyses

The primary comparison in this study was between OS in the RWD and CTD groups. For clarity, the Population Intervention Comparison Outputs Study (PICOS) description of this study's design is presented in Table 1. Baseline characteristics, use of subsequent therapies and rates of missing data were summarized for each data source. OS was summarized for the CTD and RWD groups using Kaplan–Meier analyses. An unadjusted hazard ratio (HR) and its 95% CI comparing OS between the CTD and RWD were estimated using a Cox proportional hazards model.

To assess the extent to which differences in baseline characteristics between CTD and RWD might explain differences in OS, adjusted HRs were estimated using multivariable Cox proportional hazards models. All afore-

mentioned baseline characteristics were included in the adjusted analysis except for year of ipilimumab initiation, because the CTD and RWD represented nonoverlapping time periods.

Four separate approaches were applied to address missing baseline data in the RWD. First, as a reference point, a complete case analysis was conducted, including only the subset of patients with complete baseline data for all covariates in the multivariable Cox model. Complete case analysis is a convenience approach that is often used but widely deprecated due to loss in efficiency and unrepresentativeness of the target population, especially when attrition due to missing data is substantial [20]. Complete case analysis also makes the strong assumption that missing data are missing completely at random – an unlikely prospect for clinical assessments in RWD, given that a physician's decision to make a particular assessment (e.g., order new laboratory values) will depend on guidelines and on their overall knowledge of the patient's clinical status.

Second, to include all patients while accounting for missingness, a missing indicator method was applied. In this approach, missing baseline values were treated as a separate category for each covariate such that a separate coefficient for the effect of missingness was included for each variable in the Cox model [21].

Third, a regression prediction approach was applied. In this approach, the multivariable Cox proportional hazards model for OS was fitted to the RWD only, with missing values handled using the missing indicator method. The fitted model, together with a Breslow estimate of the baseline hazard, was then used to predict OS for a population with the same profile of average baseline characteristics observed in the CTD group; thus the predicted OS represented RWD outcomes adjusted to the CTD population. The adjusted RWD OS and observed CTD OS were compared, and an adjusted HR and 95% CI were estimated using a meta-analysis approach [22].

Finally, multiple imputation was implemented using the multivariate imputation by chained equations (MICE) approach with 200 imputations [23]. The MICE approach sequentially imputes missing data for each variable based on iterative regressions of that variable's observed data on the composite of observed and imputed values of other variables. In this way, MICE aims to preserve multivariable patterns of association among the baseline characteristics, while gaining efficiency by using all of the available data. MICE assumes that data are missing at random; that is, given the observed data there is no association between missingness and underlying values – a weaker assumption than missing completely at random.

Among the approaches applied to handle missing data, MICE is the preferred approach based on published simulation studies [24] and is presented as our primary adjusted analysis. Missing indicator methods, which are commonly used and included here as reference points, have performed poorly in simulations compared with multiple imputation – particularly when missingness is related to the exposure under investigation [21].

Results

The CTD group included all 241 patients who received ipilimumab monotherapy 3 mg/kg in the three clinical trials. The RWD group included 816 patients selected from the Flatiron Health database (Figure 1). The majority of patients in both data sources were white (96% in the CTD group and 89% in the RWD group) and male (64 and 67%, respectively; Table 2). Compared with the CTD group, patients in the RWD group were on average older (mean age: 65 vs 57 years) and had longer times from diagnosis of advanced disease to ipilimumab initiation (mean time: 8.5 vs 7.5 months). A higher proportion of patients in the RWD group compared with the CTD group received ipilimumab monotherapy as first-line treatment (74 vs 5%). The calendar years of ipilimumab initiation ranged from 2004 to 2008 in the CTD group and from 2011 to 2019 in the RWD group. The proportion of patients receiving subsequent therapy was higher in the RWD group compared with the CTD group (46 vs 27%; Supplementary Table 2). Among patients with subsequent treatments, 22 and 73% received immunotherapy in the CTD and RWD groups, respectively. In the RWD group, the median time from the index date to the first subsequent therapy was 10.7 months. Starting dates for subsequent therapies were not available in the CTD.

Among the 241 patients in the CTD group, 234 had complete data for the studied baseline characteristics (i.e., no missing data for age, sex, race, BMI, LDH, disease stage at ipilimumab initiation or ECOG score at ipilimumab initiation during the baseline period). Missingness was more common in the RWD group. Overall, 721 of 816 patients in the RWD group (88%) had missing data for at least one of the studied baseline characteristics. Baseline disease stage was missing for 46% and ECOG score was missing for 59% in the RWD group (Table 2).

OS was significantly shorter in the CTD group compared with the RWD group, with an unadjusted HR of 1.36 (95% CI: 1.14–1.62) and medians of 10.1 and 16.0 months, respectively, based on Kaplan–Meier analyses (Figure 2). Adjusted HRs and their corresponding CIs, based on multivariable models and four different approaches to handling missing data, are summarized in Figure 3. The adjusted HR from the complete case analysis was similar

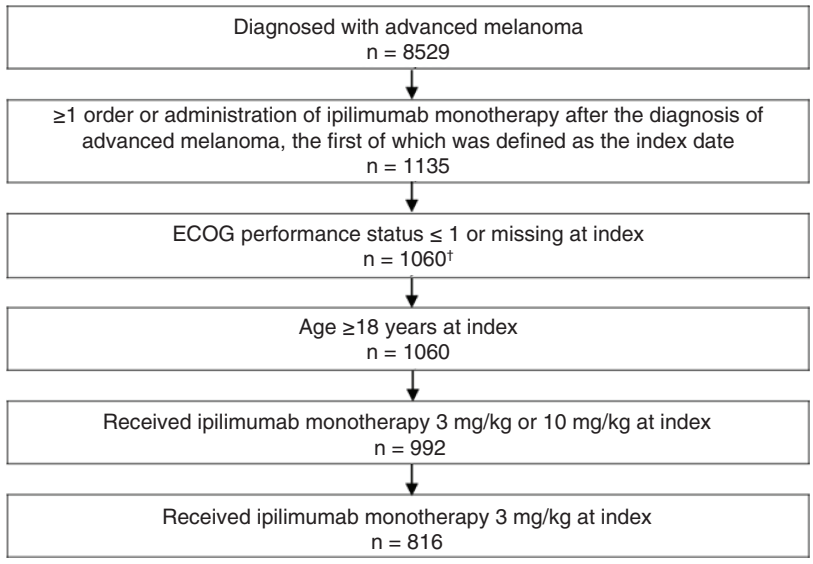

Figure 1. Sample selection in the Flatiron Health Database.
†ECOG performance status at the index date was defined as the closest measure to the index date within a time window spanning 3 months prior and 1 month after; 336 patients had ECOG performance status of 0 or 1 and 480 patients were missing this measure during the specified time window.
ECOG: Eastern Cooperative Oncology Group.

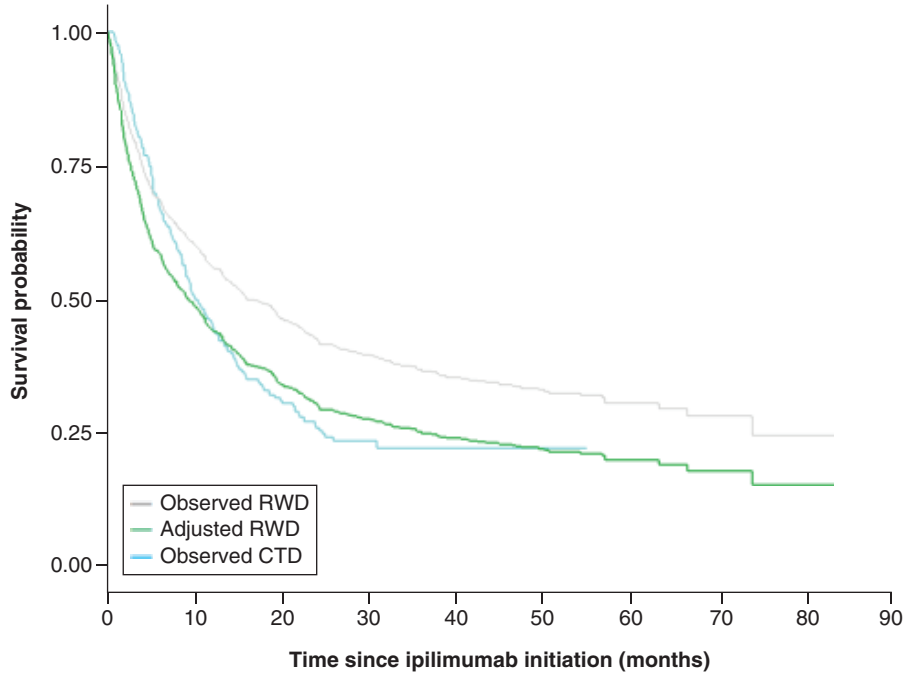

Figure 2. Overall survival in the clinical trial data and real-world data.
CTD: Clinical trial data; RWD: Real-world data.

Table 2. Baseline characteristics.

Characteristic	Clinical trial data n = 241	Real-world data (Flatiron)† n = 816
Age (years), mean ± SD	57.2 ± 13.2	64.8 ± 12.8
Male, n (%)	153 (63.5)	548 (67.2)
Race, n (%)		
White	232 (96.3)	722 (88.5)
Non-white	9 (3.7)	51 (6.3)
Missing	0 (0.0)	43 (5.3)
BMI (kg/m^2), n (%)		
BMI ≤25	76 (31.5)	215 (26.3)
BMI >25	159 (66.0)	537 (65.8)
Missing	6 (2.5)	64 (7.8)
LDH, n (%)		
LDH > ULN	96 (39.8)	182 (22.3)
LDH ≤ ULN	144 (59.8)	356 (43.6)
Missing	1 (0.4)	278 (34.1)
Time from advanced diagnosis to ipilimumab initiation (months), mean ± SD	7.5 ± 14.2	8.5 ± 11.6
Disease stage, n (%)		
Stage III	6 (2.5)	206 (25.2)
Stage IV	235 (97.5)	232 (28.4)
Missing	0 (0.0)	378 (46.3)
ECOG performance status, n (%)		
0	140 (58.1)	180 (22.1)
1	101 (41.9)	156 (19.1)
Missing	0 (0.0)	480 (58.8)
Number of prior systemic therapies, n (%)		
0	11 (4.6)	605 (74.1)
1	85 (35.3)	158 (19.4)
≥2	145 (60.2)	53 (6.5)
Prior immunotherapy, n (%)		
Yes	111 (46.1)	83 (10.2)
– Pembrolizumab	0 (0.0)	25 (3.1)
– Nivolumab	0 (0.0)	24 (2.9)
– Ipilimumab	0 (0.0)	2 (0.2)
– Interferon	83 (34.4)	42 (5.1)
– Interleukin	67 (27.8)	0 (0.0)
– Investigational immunotherapy	11 (4.6)	0 (0.0)
No	130 (53.9)	733 (89.8)
Year of ipilimumab initiation, n (%)		
2004–2006	125 (51.9)	0 (0.0)
2007–2008	116 (48.1)	0 (0.0)
2011–2013	0 (0.0)	242 (29.7)
2014–2016	0 (0.0)	503 (61.6)
2017–2019	0 (0.0)	71 (8.7)

†BMI, LDH and ECOG values in the real-world data were assessed as the closest measure to the index date within a time window spanning 3 months prior and 1 month after, and were treated as missing if no such assessment was available.
ECOG: Eastern Cooperative Oncology Group; SD: Standard deviation; ULN: Upper limit of normal.

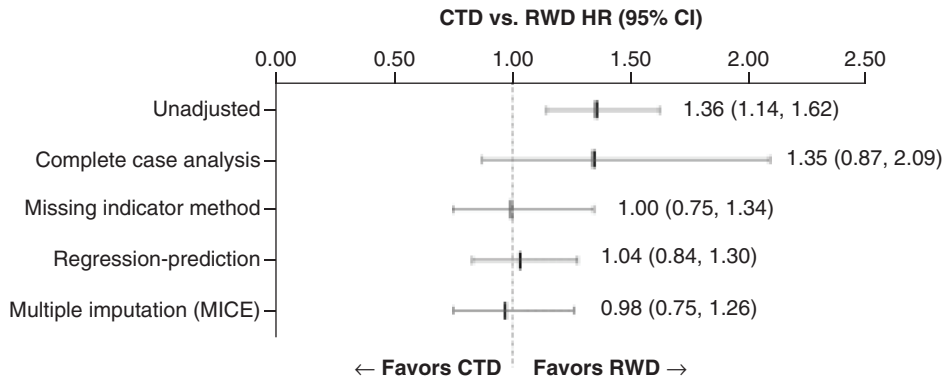

Figure 3. Hazard ratios and 95% CIs based on different methodological approaches. Except for the unadjusted analysis, all results are adjusted for the following baseline characteristics: age, sex, race, BMI, LDH levels, disease stage, Eastern Cooperative Oncology Group score, time from advanced melanoma diagnosis to ipilimumab initiation, number of prior systemic therapies and presence of any prior immunotherapy.
CTD: Clinical trial data; HR: Hazard ratio; MICE: Multivariate imputation by chained equations; RWD: Real-world data.

Table 3. Multivariable Cox proportional hazards model for overall survival in the clinical trial data and real-world data.

Baseline characteristic	Hazard ratio (95% CI)
CTD vs RWD	0.98 (0.75–1.26)
Age (years)	1.00 (0.99–1.01)
Male vs female	1.07 (0.90–1.27)
White race vs other	0.96 (0.66–1.38)
Disease stage III vs IV	0.52 (0.39–0.69)†
ECOG performance status 0 vs 1	0.65 (0.51–0.82)†
BMI ≤25 vs >25	1.15 (0.96–1.37)
LDH ≤ ULN vs > ULN	0.56 (0.46–0.68)†
Time from advanced diagnosis to ipilimumab initiation (months)	1.00 (0.99–1.01)
Received ≤1 prior systemic therapy	0.76 (0.59–0.99)†
Received prior immunotherapy	0.93 (0.73–1.20)

Results based on multiple imputation via multivariate imputation by chained equations.
†$p < 0.05$.
CTD: Clinical trial data; ECOG: Eastern Cooperative Oncology Group; RWD: Real-world data; ULN: Upper limit of normal.

to the unadjusted HR. In contrast, the missing indicator method, regression prediction (Supplementary Table 3) and MICE-based multiple imputation all resulted in estimated HRs close to 1 (Figure 3), representing no evidence of a difference in OS between CTD and RWD. The width of the 95% CIs may be informally interpreted as the range of plausible OS differences between CTD and RWD. Thus, based on the MICE approach, for example, we can be 95% confident that an interval spanning HRs of 0.75–1.26 covers the true HR for CTD versus RWD.

Significant predictors of longer OS were disease stage III versus IV, ECOG score 0 versus 1, LDH < upper limit of normal and receipt of no more than one line of prior therapy, based on the multivariable Cox model and multiple imputation (all $p < 0.05$; Table 3). The proportional hazards assumption was not violated globally, or for any predictor, based on an analysis of the Scheonfeld residuals. Adjusted RWD OS, based on the regression prediction approach, is also depicted in Figure 2 (median OS: 10.3 months).

Discussion

The findings of this study support use of the Flatiron Health database to construct external comparator groups for OS for clinical trials in advanced melanoma. When subjected to similar inclusion criteria and adjusted for multiple baseline prognostic factors, and when employing standard methods for handling missingness, we found that OS rates in the Flatiron Health database group were comparable to those in clinical trials for patients receiving ipilimumab. No statistically significant differences in OS were observed between CTD and RWD; HRs representing differences in magnitude of up to ±25% were excluded with 95% confidence. Thus this study serves as a successful

test case – a negative control – for comparisons of Flatiron Health data and CTD in advanced melanoma. Should similar analyses be applied in the future to compare OS between a novel clinical trial and Flatiron Health data, the consistency observed here for ipilimumab outcomes will lend credence to the new comparison.

Prior to adjustment for differences in baseline characteristics, OS was significantly longer in the RWD group compared with the CTD group. However, baseline adjustment addressed the higher prevalence of favorable prognostic factors in the RWD group relative to the CTD group, including more patients with normal LDH, more patients in the first-line setting and more patients with stage III melanoma, as well as substantial proportions with missing ECOG and other data. The success of regression adjustment in mitigating OS differences in this study may be due to the wealth of well-recognized and recorded prognostic factors in advanced melanoma and the relatively short follow-up time. For example, only eight patients remained at risk in the CTD group by month 40, limiting the power to detect longer-term differences in OS. Had robust sample sizes been available for 5 or 10 years of follow-up, it is possible that differences in longer-term OS would have emerged due to differences in the availability of effective subsequent therapies between the time periods represented by the CTD (2004–2008) and RWD (2011–2019). Indeed, a number of studies have documented improvements in OS among RWD patients with metastatic melanoma over the studied time period, largely attributed to increased use of novel effective therapies in the first and later lines [25–29].

It is noteworthy that the complete case approach to handling missing data (i.e., excluding patients with missing data) was not successful in mitigating OS differences between CTD and RWD, whereas missing indicator methods and multiple imputation were all similarly successful. These findings highlight the importance of adjusting for known baseline prognostic factors and utilizing preferred approaches to handling missing data.

While these results are supportive of using data from the Flatiron Health database to construct external controls in advanced melanoma, we emphasize that any future applications would need to be evaluated on a case-by-case basis. The results of the present study are most directly generalizable to comparisons of OS during the studied time periods. Because this is a nonrandomized study, we cannot entirely rule out bias, but we can conclude that any sources of bias had a minimal net impact on OS differences between the RWD and CTD groups observed here. We also emphasize that the results are not necessarily generalizable to other indications or outcome measures beyond OS in advanced melanoma or to other databases beyond Flatiron Health; additional research with different indications, treatments, outcomes or data sources would be necessary to assess generalizability. For these reasons, the negative control provided by the present study design is not as definitive as negative controls used in bench research; that is, not all conditions will be identical between the present analyses and a future externally controlled study in advanced melanoma that involves novel treatments and new clinical trials. However, we propose that the present results should greatly increase confidence in future use of Flatiron Health data and the studied statistical methods for RWD external controls in advanced melanoma, and can inform prespecification, study planning and interpretation. In addition, the template of this study could be applied to develop negative controls for other RWD and CTD data sources, treatments and disease settings.

This study has several important limitations. The effects of subsequent therapies were not studied because data on the timing of subsequent therapies were not available in the CTD. In addition, it was not possible to adjust for the year of ipilimumab initiation without extrapolation and other strong assumptions, because of the nonoverlap of years between the CTD and RWD sources. Finally, we considered only a Cox proportional hazards model, as it is a commonly used first choice for OS outcomes. Parametric survival models, accelerated failure time models, or piece-wise or spline-based models for the hazard could be evaluated in future studies.

Conclusion

The overall promise of RWD in drug evaluations is supported by the 21st Century Cures Act (2016) in the USA, which has spurred an increased need for understanding and evaluating appropriate uses of RWD in regulatory decision-making [2,3] and an emerging framework for doing so [8,30]. Representatives of the EMA and the Organisation for Economic Co-operation and Development have also highlighted the importance of RWD or natural history data for drug evaluation [31–33]. However, use of RWD for external controls will always be fraught with risks of bias. Data quality and similarity across data sources must be evaluated on a case-by-case basis using both clinical and statistical judgement. Negative controls, as presented in the current study, can provide empirical evidence for or against the suitability of a RWD source for external controls and can therefore substantially contribute to a rigorous evaluation.

In conclusion, the use of RWD as an external control group for clinical trials is feasible in some instances. Adjustment for baseline prognostic factors and sufficiently accounting for missing data are important when constructing the external control groups with RWD.

Summary points

- This study examined whether real-world data (RWD) from the Flatiron Health database could serve as an external control group for clinical trial data (CTD) to assess overall survival (OS) among patients with advanced melanoma.
- OS among adults receiving ipilimumab 3 mg/kg for the treatment of advanced melanoma was compared between clinical trials (CTD group) and the Flatiron Health database (RWD group).
- Adjusted analyses accounted for differences in baseline prognostic factors using a multivariable Cox proportional hazards model, with adjustment for age, sex, race, BMI, LDH levels, disease stage, performance status, time from advanced melanoma diagnosis, and prior therapies. Missing baseline data were addressed through multiple imputation.
- The CTD group included 241 patients from three clinical trials; the RWD group included 816 patients.
- Missing data were prevalent in the RWD, with 88% of patients missing at least one baseline prognostic factor.
- In the unadjusted analysis, patients in the CTD group had significantly shorter OS compared with those in the RWD group (hazard ratio: 1.36; 95% CI: 1.14–1.62).
- After adjusting for baseline prognostic factors and accounting for missing data, OS was similar in the CTD versus RWD groups (hazard ratio: 0.98; 95% CI: 0.75–1.26).
- These findings are supportive of use of the Flatiron Health database for external controls for OS in advanced melanoma, provided that adjustment is made for baseline prognostic factors and baseline missingness is well addressed.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-1054

Author contributions

All authors contributed to the conceptualization of the study and to reviewing and editing the manuscript. Data curation, formal analyses, investigation, software, resources, supervision, validation, visualization, the development of methodology and writing of the original draft were handled by J Signorovitch and J Zhao. Funding was procured by M Hamilton. Project administration was performed by M Hamilton and K Gooden.

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Statistical analysis was performed by L Yin of Analysis Group and J Li, formerly of Analysis Group, Inc. Medical writing was provided by S Batts of Analysis Group, Inc.

Financial & competing interests disclosure

Support for this study and medical writing assistance was provided by Bristol-Myers Squibb. A Moshyk, K Le, L Burns, K Gooden and M Hamilton are employees of Bristol-Myers Squibb and hold stock/options. J Signorovitch and J Zhao are employees of Analysis Group, Inc., which has received consulting fees from Bristol-Myers Squibb. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical conduct of research

This study used previously published data from clinical trials and deidentified electronic health record data; thus no institutional board review was required.

Data sharing statement

The real-world data used in this study are not available to share due to data agreements with Flatiron. The clinical trial data (CA184-022 (ClinicalTrials.org identifier: NCT00289640), CA184-004 (NCT00261365) and MDX010-20 (NCT00094653) are available by request from BMS via www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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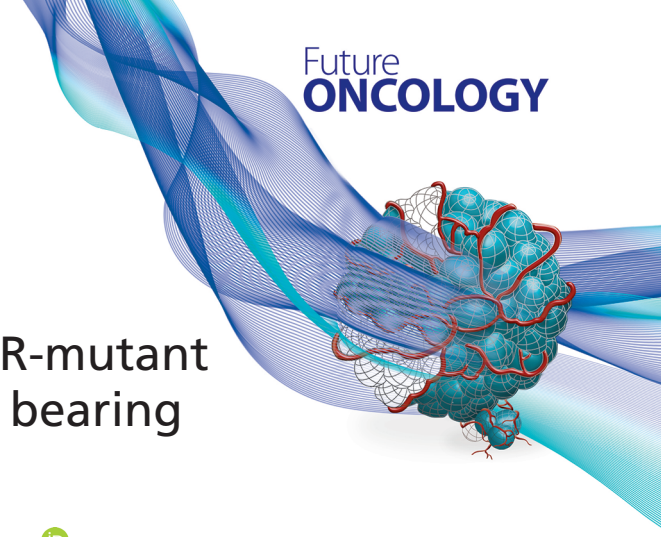

Continuation of osimertinib in EGFR-mutant non-small-cell lung cancer patients bearing CNS metastasis (EPONA study)

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The patients harboring EGFR-mutated non-small-cell lung cancer, treated with EGFR tyrosine kinase inhibitor will lead to longer survival than those having non-small-cell lung cancer (NSCLC) patient who do not harbor EGFR mutations. This ongoing clinical trial is to investigate the secondary chemoprevention effect of osimertinib from CNS with platinum doublets chemotherapy in patients who had progressive disease outside of CNS lesions. The aim of this randomized, phase II trial is to evaluate platinum and pemetrexed chemotherapy followed by pemetrexed maintenance with or without continuation of osimertinib for secondary CNS prevention in patients with brain metastatic NSCLC with EGFR mutation, with other than CNS lesions, but no progressive disease in the CNS lesion after osimertinib. The primary end point is to assess progression-free survival by investigator assessment. The key secondary end points are overall survival, response rate, time to CNS controlling, time to whole-brain irradiation and safety.

Clinical trial registration: Japan Registry of Clinical Trials (jRCT), Japan (jRCTs071200029)

Plain language summary: The authors are conducting a clinical trial aimed at improving treatment for individuals diagnosed with non-small-cell lung cancer, a specific type of lung cancer. In some cases, this cancer can spread to the brain. This study focuses on patients whose cancer is stable in the brain but progressing in other parts of the body. The study is comparing two different treatment approaches. One involves a combination of two drugs, platinum and pemetrexed, while the other combines these drugs with a third one called osimertinib. The main objective is to determine if continuing osimertinib treatment benefits these patients. The authors are evaluating the time it takes for the cancer to start growing again, known as progression-free survival, to identify the most effective treatment. Progression-free survival represents the duration that patients live without their disease worsening. This study, the EPONA study, will provide valuable insights into optimizing the treatment of this type of cancer.

Tweetable abstract: This randomized, phase II study is evaluating chemotherapy +/- the continuation of osimertinib for EGFR-mutant non-small-cell lung cancer patients bearing CNS metastasis and having systemic progressive disease outside of brain metastasis.

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Keywords: brain metastasis • CNS • EGFR mutation • intergroup study • non-small-cell lung cancer • osimertinib

Future Medicine

Activating EGFR mutations are key drivers in metastatic non-small-cell lung cancer (NSCLC) in approximately 10–15% of Western patients and 30–35% of Asian patients [1]. The key drug for metastatic EGFR-mutation-positive NSCLC is EGFR tyrosine kinase inhibitors (TKI) [2]. Currently, osimertinib is the *de facto* standard of care (SOC) for metastatic EGFR-mutation-positive NSCLC in previously untreated patients and T790M-positive NSCLC in those previously treated with first-/second-generation EGFR-TKIs. Robustly, the median progression-free survival (PFS) of metastatic NSCLC patients with EGFR mutations is 9–13 months with first-/second-generation EGFR-TKIs [2,3] and 18.9 months with osimertinib [4]. After failure of osimertinib, the SOC is platinum-doublets chemotherapy [5,6], and the later lines of the armamentarium for cytotoxic chemotherapy in patients with metastatic NSCLC are currently increasing [7–9].

In that concept, the IMPRESS study, which is gefitinib adding-on platinum-doublets chemotherapy comparing platinum-doublets chemotherapy was achieved; however, the survival benefit was not verified (hazard ratio [HR]: 0.86 [95% CI: 0.65–1.13]) [10] and the combination was worse in overall survival (OS; HR: 1.44 [95% CI: 1.07–1.94]). In the subgroup analysis, the CNS metastasis subgroup demonstrated an equivalent survival benefit in PFS (HR: 0.66 [95% CI: 0.40–1.10]) but PFS was 0.84 (0.60–1.16) in the absence of brain metastasis.

Osimertinib has confirmed high CNS activity *in vivo* [11] and clinically in comparison with other EGFR inhibitors [12]. Therefore, the authors hypothesize the additional effect of osimertinib, higher CNS control and good tolerability can be verified in the patients controlled by osimertinib but having progressed lesions in the other organ lesion outside of the CNS. By changing the subsequent chemotherapy, the CNS control can be 'unlocked'.

In this EPONA (Efficacy of osimertinib with Platinum and pemetrexedin EGFR mutant non-small cell lung cancer patients bearing CNS metastasis,and have systemic progression but stable intracranial disease on OsimertiNib resistAnce), we will confirm whether such a situation is present and CNS secondary chemoprevention by additional osimertinib continuation over platinum doublet chemotherapy for the patients harboring EGFR-mutation with brain metastasis regardless of the history of local treatment for CNS.

Objectives

In this study, the authors will determine the efficacy of the additional effect of osimertinib on platinum/pemetrexed for the PFS of patients with EGFR-mutant-bearing CNS metastasis and systemic progression but stable intracranial disease on osimertinib as the secondary CNS chemoprevention.

The primary end point is the PFS to evaluate by the investigators' assessment for the EGFR-mutation-positive NSCLC patients with more than 32 weeks' osimertinib treatment with a history of CNS metastasis regardless of local treatment and progressed lesion outside of the CNS. The secondary end points are OS, response rate, time to CNS controlling, time to whole-brain irradiation and safety. These end points will be assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [13]. The test for OS will be performed if PFS is statistically significant, since the true end point for this population is OS.

Trial design

This study is a randomized, multicenter, phase II study evaluating platinum/pemetrexed with or without continuation osimertinib as the SOC arm or experimental arm, respectively (Figure 1). This study is in accordance with the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group's guidance on clinical trial design for the systemic treatment of patients with solid tumors with brain metastases for study end points, eligibility and exclusion criteria [14]. The authors aim to overcome biases [15] observed in previous studies, where small brain metastatic lesions were often disregarded as nontargeted lesions. By focusing on tumors in both the brain and the body, this study strives to reduce bias and provide a comprehensive evaluation. This study is active and recruiting participants, with planned enrollment at approximately 60 sites across regional cooperative groups in Japan.

Methods

Study setting

Continuing osimertinib with chemotherapy after progression with osimertinib will benefit patients who are at a higher risk of having CNS metastasis. Patients who have CNS metastasis before starting systemic treatment have an increased risk of CNS progression [4]. Approximately 13% of patients (32% of patients with baseline CNS metastasis)

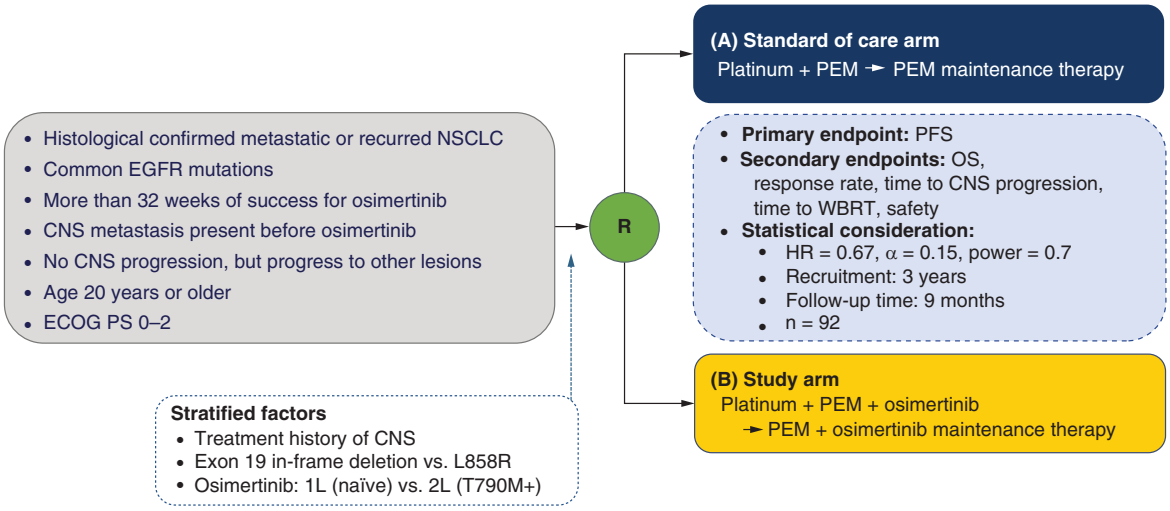

Figure 1. Randomized, phase II, open-label, multicenter study: EPONA study. Design schema.
ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growith factor receptor; HR: Hazard ratio; NSCLC: Non-small cell lung cancer; OS: Overall survival; PEM: Pemetrexed; PFS: Progression-free survival; PS: Performance status; WBRT: Whole brain radiotherapy.

will have CNS progression during osimertinib and will gain no benefit from continuing osimertinib after the progression. The authors hypothesize that those patients bear brain metastasis at the initiation of osimertinib. The patients has systemic progression other than CNS lesions at osimertinib resistance will have better CNS control with continuing osimertinib alongside chemotherapy.

Eligibility criteria

Patients must meet all of the following inclusion criteria and none of the exclusion criteria to be eligible for this study. NSCLC patients harboring common EGFR mutations with CNS metastasis regardless of local treatment at baseline and progressed targeted lesion based on the RECIST criteria outside of stable CNS by osimertinib more than 32 weeks' treatment success will be included. The selection of the 32-week cutoff was determined based on the 95% lower limit observed in the AURA-3 study [16]. The eligibility and exclusion criteria are based on the RANO-BM guidance [14,15].

Key eligibility criteria are summarized in Table 1. Eligible participants must have pathologically confirmed, previously osimertinib-treated nonsquamous NSCLC harboring common EGFR mutation with stage IV had metastasis previously to CNS but well controlled by osimertinib but progressed lesion outside of CNS with an Eastern Cooperative Oncology Group performance status of 0–2. The previous history of local treatment for brain metastasis is not always required by surgery or radiotherapy but progressed other organs with measurable lesion(s) in RECIST, version 1.1. Eligible patients will have molecularly harbored EGFR mutations (exon 19 deletion or exon 21 L858R). Patient must have been successfully treated with osimertinib for more than 32 weeks. Acquired resistance with T790M-positive mutation is permitted if the patients have been treated with first-/second-generation EGFR-TKIs. No progressive disease (PD) or clinical exacerbation of lesions outside of the CNS lesion after complete respnse (CR)/partial response (PR)/stable disease (SD) when the patients treated with osimertinib. Additionally, patients will be excluded if the uncontrollable complication is higher than grade 2 or they have a history of interstitial pneumonia.

Treatments under the protocol (control & intervention)

Investigator's choice of platinum agent or a dose of osimertinib reflecting the prior treatment must be declared prior to randomization. The enrolling patients will be randomly assigned into one of the two arms:

- Arm A: Pemetrexed (500 mg/m^2 intravenous) plus the following platinum administered, followed by pemetrexed maintenance therapy
  - Four cycles of carboplatin (area under the concentration 5) or cisplatin (75 mg/m^2 intravenous) every 3 weeks

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Table 1. Inclusion and exclusion criteria for the EPONA study.

Inclusion criteria	Exclusion criteria
1. Pathologically confirmed non-squamous cell non-small-cell lung cancer (excluding large cell neuroendocrine carcinoma) and not otherwise specified having clinical stage IIIB/C-IV or post status of recurrence in curative-intent radiotherapy or postoperative recurrence 2. The patients had metastasis prior to CNS metastasis but was well controlled by osimertinib. The previous history of local treatment of brain metastasis is not always required by surgery or radiotherapy. 3. The patients had molecularly harbored sensitizing EGFR mutations (exon 19 deletion or exon 21 L858R) by biopsy, surgical specimen, or blood sample. 4. The patient succeeded in treating osimertinib with/without antiangiogenic agents for more than 32 weeks. 5. Acquired resistance with exon 20 T790M-positive mutation is permitted if the patients have been treated with gefitinib, erlotinib, afatinib or dacomitinib. 6. Adults aged 20 years and older 7. Eastern Cooperative Oncology Group performance status of 0–2 8. Measurable lesion(s) in Response Evaluation Criteria in Solid Tumors, version 1.1 9. No prior chemotherapy; postoperative patients who were treated with platinum doublets chemotherapy permitted after 48 weeks 10. No progressive disease (PD) or clinical exacerbation of lesions outside of CNS lesion after complete response (CR)/partial response (PR)/ stable disease (SD) when the patients treated with osimertinib. However, no CNS exacerbation. 11. The patients treated with stereotactic radiotherapy in any lesions can be enrolled. 12. Adequate organ function with 14–28 days before registration, including CNS lesions 13. Signed, written, informed consent to participate in the study 14. Prognosis expected more than 12 weeks.	1. The uncontrollable complication is higher than grade 2, including uncontrolled diabetes mellitus with adequate treatments, including insulin injection, and hypertension. 2. The patient has a history of interstitial pneumonia or evidence of interstitial lung disease found on chest radiography. 3. Asymptomatic associated with CNS metastasis, including brain metastasis or carcinomatous meningitidis. 4. The patients treated with strong induced agents by CYP3A4, or herbs, or who cannot terminate defined drugs in the protocol. 5. The patients have risk of electrocardiogram QT-corrected interval prolongation or increased arrhythmic events, such as low serum potassium, magnesium, calcium, congenital long QT syndrome, and sudden death of unknown cause or Torsades de Pointes. 6. Active concurrent cancers within 5 years but completed cancers in the early stages are admitted, to be specified in the protocol. 7. Infectious diseases requiring systemic treatment. 8. Unable to take medications with or without refractory nausea and vomiting. Also, patients with the post status of bowel resection or chronic gastrointestinal diseases interfere with the proper absorption of osimertinib. 9. The patients required systemic steroid more than physiological dose or treated with continuous immune-suppressive agents 10. Serious illness or medical condition with unstable angina within 3 weeks or old myocardial infarction less than 6 months

CR: Complete response; PD: Progressive disease; PR: Partial response; SD: Stable disease.

- Arm B: Pemetrexed plus above platinum, followed by pemetrexed maintenance therapy as the same dosing with the Arm A and scheduling and continuous osimertinib at the dose of 40 or 80 mg/day

The treatment will begin at randomization and continue until disease progression or unacceptable toxicities. Patients who have undergone a dose reduction of osimertinib are allowed to receive a dosage of 40 mg/day. Additionally, these patients will initiate platinum and pemetrexed at a reduced dosage level (-1 level). If the study treatment is well tolerated, the dose of osimertinib may be escalated to 80 mg/day during the treatment period.

Statistical setting & sample size

The primary aim of this study is to show the superiority of osimertinib with chemotherapy versus chemotherapy alone in terms of PFS. Assuming median PFS of chemotherapy alone as 6 months [10], a total of 62 PFS events (92 patients) are required to detect a hazard ratio (HR) of 0.67, with 70% power and a one-sided 15% significance level of alpha. The expected HR of 0.67 was determined based on the IMPRESS study, which reported that adding gefitinib to chemotherapy for patients with baseline CNS metastasis resulted in a gain of PFS (HR: 0.66; 95% CI: 0.40–1.10) compared with chemotherapy alone [17]. The authors of the current study may lower the HR to 0.6, since there was no OS benefit even in this population. The PFS of the SOC arm is assumed to be 6 months. When PFS is significant in the intention-to-treat population, OS analysis will be formally performed. The use of fixed sequence testing requires no adjustment of significance level.

Randomization will be 1:1, and patients will be stratified by prior local therapy to CNS lesion, EGFR-mutation subtypes (exon 19 vs exon 21) and osimertinib (naive vs T790 acquired mutation).

Follow-up & clinical assessments

The investigators will assess radiologically at baseline whether contrasted computed tomography of the chest and abdomen every 8 weeks and MRI as for the brain until progressive disease (PD). The response and PFS will be evaluated according to RECIST, version 1.1.

Ethics & dissemination

This study will be conducted in compliance with the Declaration of Helsinki and the International Council for Harmonization for Good Clinical Practice Guidelines. The central institutional review board of the Clinical

Research Network Fukuoka Certified Review Board (CRB7180004) approved the study protocol and registered in the Japan Registry of Clinical Trials (jRCT), Japan (jRCTs071200029).

Conclusion

Currently, there is a paucity of clinical evidence regarding the benefit of adding osimertinib continuation after PD when the patients initiate platinum-doublets chemotherapy. In the IMPRESS study, gefitinib continuation in combination with platinum-doublets chemotherapy demonstrated no improvement in PFS and OS [10,17]; however, the subgroup analysis suggested the potential benefits of additional gefitinib continuation on the platinum-doublets chemotherapy for patients bearing CNS metastases. In the NEJ009 trial [18], gefitinib, carboplatin and pemetrexed combination therapy was not seen to be statistical significant; however, long OS was observed. As for osimertinib, the FLAURA2 study (NCT04035486), which will compare first-line osimertinib with osimertinib plus platinum-doublets chemotherapy, and the COMPEL study (NCT04765059) of continued osimertinib or placebo with chemotherapy after first-line osimertinib with CNS-specific outcomes will answer the clinical question, which it remains unclear if the results of IMPRESS study should be extrapolated to patients with disease that progresses on first-line osimertinib. Furthermore, the COMPEL study aims to determine the incidence of CNS progression (either with new or progressive brain metastasis) and its correlation with the administration of osimertinib in combination with chemotherapy. In the adjuvant setting of the ADAURA trial, osimertinib was demonstrated to be a good CNS control, including CNS-related disease or death [19]. Therefore, our study will confirm the potential activity for EGFR-mutation-positive patients bearing CNS metastasis; however, the patients are quite limited and have difficulty in the accrual for this clincial trial. However, the clinical impact will be strong; the good CNS control of osimertinib frequently results in durable control of brain metastases, even in the face of systemic progression outside of the CNS, in contrast to gefitinib in the IMPRESS study. Our study answers the clinical question for patients with baseline CNS metastases that remain controlled on osimertinib at the time of systemic progression outside of the CNS. We consider osimertinib continuation with second-line, platinum-based chemotherapy.

Regarding significant adverse effects, grade 3 and 4 leukocytopenia, thrombocytopenia and anemia were observed in the FLAURA2 study [20], LOGIK1604/NEJ032A study [21] and NEJ032C/LOGIK1801 (OPAL) study [22]. Other toxicities rated higher than grade 3 included skin rash, nausea, diarrhea, constipation, paronychia and fatigue.

Currently, clinical trials are under way to overcome the resistant mechanism for post-osimertinib, such as C797S ([BLU-945] [HARMORNY; NCT05153408] [SYMPHONY; NCT04862780], allosteric EGFR inhibitor and anti-EGFR antibodies), MET amplification (NCT05015608; NCT05261399) and unknown status (COMPEL study [NCT04765059]). This study will clarify the availability of post-osimertinib treatment strategies for those who have not acquired resistance and have no targeted therapy.

Executive summary

Significance of CNS protection in non-small-cell lung cancer

- CNS protection is a crucial strategy for the long-term survival of patients with non-small-cell lung cancer.

Overview of the EPONA study

- This randomized, phase II study will evaluate platinum and pemetrexed with or without the continuation of osimertinib for EGFR-mutant non-small-cell lung cancer patients bearing CNS metastasis and having systemic progression but stable intracranial disease on osimertinib resistance (EPONA study [TORG 1938]); based on tumor heterogeneity, subsequent chemotherapy does not always maintain control of CNS lesions.

Study end points

- The primary end point is progression-free survival to assess the continuous effect of osimertinib after progression other than to the CNS. The secondary end points are overall survival, response rate, time to CNS progression, time to whole-brain irradiation and safety.

Evaluation of efficacy

- This trial evaluates the efficacy of platinum and pemetrexed treatment, followed by pemetrexed maintenance with or without continuation of osimertinib for secondary CNS prevention.

Eligibility criteria & study design

- Key eligibility criteria are as follows: Eastern Cooperative Oncology Group performance status 0–2 and nonsquamous histology. Patients are required to succeed for at least 32 weeks; 94 patients will be randomized across treatment arms, stratified by previous treatment history for CNS metastases, EGFR-mutated subtypes and osimertinib naive versus T790M. The results of this trial are expected by 2025.

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Author contributions

All the authors listed in the manuscript have sufficiently contributed to the project to be included as authors, and all those who are qualified as authors are listed in the author byline. The first draft of the manuscript was written by Y Okuma. All the co-authors have read the final version of the manuscript and have agreed to its submission.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Clinical Trial Protocol

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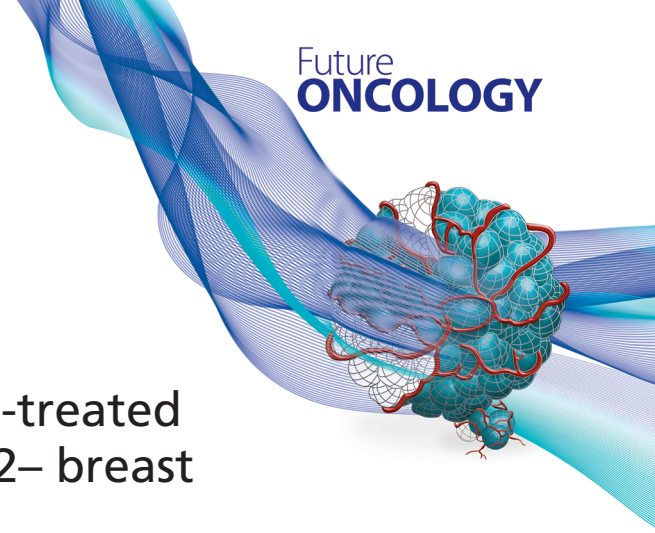

TROPION-Breast01: Datopotamab deruxtecan vs chemotherapy in pre-treated inoperable or metastatic HR+/HER2– breast cancer

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Improving the prognosis for patients with metastatic HR+/HER2- breast cancer remains an unmet need. Patients with tumors that have progressed on endocrine therapy and/or are not eligible for endocrine therapy had limited treatment options beyond chemotherapy. Antibody-drug conjugates are a novel and promising treatment class in this setting. Datopotamab deruxtecan (Dato-DXd) consists of a TROP2-directed humanized IgG1 monoclonal antibody attached *via* a serum-stable cleavable linker to a topoisomerase I inhibitor payload. TROPION-Breast01 is an ongoing phase 3 study that is evaluating the efficacy and safety of Dato-DXd compared with investigator's choice of standard-of-care chemotherapy in patients with inoperable or metastatic HR+/HER2- breast cancer who have received one or two prior lines of systemic chemotherapy in the inoperable or metastatic setting.

Clinical Trial Registration: NCT05104866 (ClinicalTrials.gov)

Plain language summary: Antibody-drug conjugates are a type of drug with two parts: an antibody that directs the drug to the cancer cells and a cancer-cell killing toxic payload. By binding to cancer cells before releasing the payload, treatment is directed to the site of action so there are fewer side effects in the rest of the body. Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugates made up of datopotamab (antibody) and DXd (payload) which are joined together *via* a stable linker. Datopotamab binds to a protein found on cancer cells called TROP2; it then goes inside and releases the DXd payload to kill the tumor cells. DXd may leak out to surrounding cancer cells and kill those as well. The TROPION-Breast01 study is comparing Dato-DXd with standard-of-care chemotherapy. Around 700 patients will take part, who have:

- Tumors that cannot be surgically removed.
- Tumors that are hormone receptor-positive and do not have HER2 overexpression.
- Had one or two lines of previous chemotherapy (after the tumor could not be surgically removed, or had spread).
- Had tumor growth despite hormonal therapy or are ineligible for hormonal therapy.

Patients who meet the entry criteria will be randomly assigned to a treatment group in equal numbers to either Dato-DXd or an appropriate chemotherapy, out of four options chosen by the treating doctor. At the end of the study, researchers will look at whether the patients who receive Dato-DXd live longer without their breast cancer getting worse, compared with patients who receive chemotherapy. This study is also looking at how the treatment affects patients' quality of life.

Tweetable abstract: Dato-DXd is a novel TROP2-directed ADC, which has demonstrated significant efficacy in phase 1/2 clinical trials. TROPION-Breast01 is the phase 3 clinical trial investigating Dato-DXd versus standard chemotherapy for patients with metastatic HR+ breast cancer in 2L (and plus) setting. This manuscript describes the study design of the clinical trial @FutureOncol_FSG.

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Keywords: antibody-drug conjugate (ADC) • datopotamab deruxtecan (Dato-DXd) • HR-positive/HER2-negative • inoperable breast cancer • metastatic breast cancer • Trophoblast cell surface antigen 2 (TROP2)

Breast cancer is the most frequently diagnosed cancer in the world (representing 11.7% of all new cancers) and the leading cause of cancer-related death among women, with an estimated 2.26 million new cases and 684,996 deaths annually [1]. Despite advances in diagnosis and treatment, around 6–10% of women diagnosed with breast cancer present with metastatic disease at time of diagnosis, and up to 30% of women with early-stage non-metastatic breast cancer will subsequently develop metastatic disease [2]. While treatment options are available for metastatic breast cancer, the prognosis remains limited, with a median overall survival (OS) of around 3 years and a ~30% 5-year survival rate [3,4]. However, breast cancer is a heterogenous disease and 4-year survival rates in patients with metastatic disease vary between different subtypes: estrogen receptor and/or progesterone receptor (hormone-receptor)-positive (HR+) / human epidermal growth factor receptor 2 negative (HER2-) 35.9%, HR+/HER2+ 45.5%, HR-/HER2+ 33.9% and triple-negative breast cancer (TNBC) 11.2% [5].

The most common breast tumors are those that are HR+ and HER2- per American Society of Clinical Oncology/College of American Pathologists guidelines (ASCO/CAP) guidelines [6,7]. In patients with metastatic HR+/HER2- breast cancer, the preferred cornerstone of treatment is endocrine therapy, given either alone or in combination with targeted therapies such as cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, phosphatidylinositol-3-kinase (PI3-K) inhibitors, and mammalian target of rapamycin (mTOR) inhibitors [8,9]. Of these, CDK4/6 inhibitors as a class have demonstrated progression-free survival (PFS) and OS benefits with manageable toxicity in combination with endocrine therapy versus endocrine therapy alone in this setting [10–16].

In patients for whom endocrine therapy is no longer an option either due to disease progression or ineligibility, chemotherapy is a standard of care, with sequential single-agent chemotherapy (such as eribulin mesylate, capecitabine, gemcitabine, vinorelbine) generally preferred over combination therapy [8]. However, survival outcomes in such patients are limited, representing an area of considerable unmet need. For example, in patients with locally recurrent or metastatic breast cancer and 2–5 prior chemotherapy regimens who received single-agent eribu-

lin mesylate in the phase 3 EMBRACE study, a median OS of 13.1 months (95% CI: 11.8–14.3) was reported [17]. A pooled analysis of patients with ER+/HER2- locally-advanced/metastatic breast cancer reported a median PFS of 4.1 months and a median OS of 15.7 months in patients receiving eribulin mesylate [18]. Moreover, chemotherapy is associated with significant toxicities, including hematologic adverse effects, gastrointestinal toxicities such as diarrhea, and skin reactions, which can have a significant impact on patient quality of life [19,20], particularly for incurable metastatic cancer. Consequently, novel treatments for patients with metastatic HR+/HER2- breast cancer are needed to improve prognosis, achieve long-term disease control and prevent symptoms while minimizing toxicity and improving quality of life.

Background & rationale

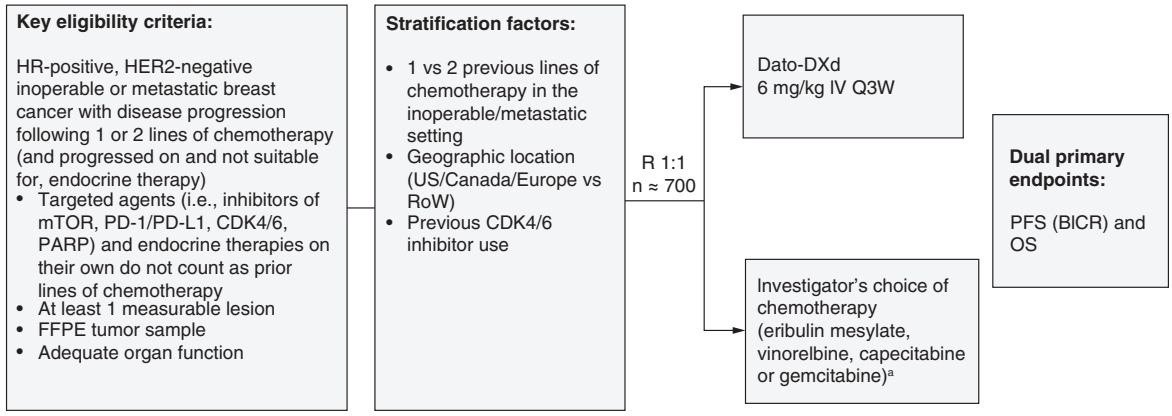
Trophoblast cell surface antigen 2 (TROP2) is a transmembrane protein involved in the mitogen-activated protein kinase and phosphatidylinositol 3-kinase (PI3K)/AKT intracellular signaling pathways that is broadly expressed in various solid tumor types [21,22], including breast cancer. TROP2 expression has been associated with increased tumor aggressiveness and shortened survival [21,23–25]. Expression of TROP2 has been recorded across a wide range of breast cancer subtypes [24] and therefore represents a promising antigen for appropriately directed anticancer therapies [26].

Antibody-drug conjugates (ADC) are an emerging class of potent anticancer drugs that combine an antibody conjugated with a cytotoxic drug *via* a linker to target specific antigens that are typically overexpressed or exclusively expressed on tumor cells [26–28]. ADCs are administered intravenously and bind to the target surface antigen to form an ADC-antigen complex [26]. This complex is then internalized *via* receptor-mediated endocytosis and the cytotoxic payloads released, ultimately resulting in cancer cell death [26,27]. By specifically binding to antigens that are overexpressed or exclusively expressed on tumor cells, ADCs may reduce the systemic toxicity associated with unselective cytotoxic agents [29,30]. However, the safety and efficacy profiles of ADCs are dependent on the different features of the drug components. For example, the selection of payload, linker, and drug-to-antibody ratio may affect overall efficacy of treatment, and the selected linker may also affect toxicity and certain pharmacokinetic characteristics [31–33].

Datopotamab deruxtecan (Dato-DXd) is an ADC consisting of a humanized immunoglobulin G1 (IgG1) monoclonal antibody, designed with a tumor-selective, serum-stable, tetrapeptide-based cleavable linker to deliver a potent, cytotoxic topoisomerase I (Topo-I) inhibitor payload into tumor cells expressing TROP2 [26,29]. The DXd ADC platform has a payload with a short systemic half-life to reduce systemic toxicity and possesses bystander tumor effect by efflux of the payload [34–38]. Using the example of Dato-DXd and another ADC, sacituzumab govitecan, that have the same target but distinct cleavable linker technologies (one chemical and one enzyme), the hydrolysable chemical linker of sacituzumab govitecan has a lower serum stability leading to an increased likelihood of extracellular payload release around the tumor site [39,40], while the peptide-based linker of Dato-DXd has a high serum stability and a low level of released payload in plasma [26].

The unique attributes of the DXd platform have already demonstrated practice-changing results in breast cancer [41–44]. This is exemplified by the US FDA approval of anti-HER2 ADC trastuzumab deruxtecan in patients with HR+/HER2- low breast cancers who have received a prior chemotherapy in the metastatic setting or disease recurrence during or within 6 months of adjuvant chemotherapy [45]. Furthermore, there is a strong rationale for TROP2-directed therapy with the FDA approval of anti-TROP2 ADC sacituzumab govitecan in both TNBC and in patients with unresectable locally advanced or metastatic HR+/HER2- breast cancer after endocrine-based therapy and ≥2 additional systemic therapies in the metastatic setting [46]. Indeed, recent data on the use of sacituzumab govitecan in patients with metastatic HR+/HER2- breast cancer versus control chemotherapy showed a 34% reduction in risk of progression or death (hazard ratio [HR] 0.66 [95% CI: 0.53–0.83]; p = 0.0003) and a median PFS of 5.5 versus 4.0 months in the sacituzumab and chemotherapy arms, respectively [44], as well as a statistically significant improvement in median OS (14.4 vs 11.2 months; HR: 0.79 [95% CI: 0.65–0.96]; p = 0.02) [47].

In the preclinical setting, Dato-DXd demonstrated potent antitumor activity against TROP2-expressing tumors and an acceptable safety profile [26]. Recent clinical data for Dato-DXd efficacy and safety in patients with metastatic HR+/HER2- breast cancer from the ongoing phase 1 TROPION-PanTumor01 study (NCT03401385) have shown a manageable safety profile and encouraging antitumor activity with high disease control in heavily pre-treated patients [48]. In these patients (n = 41), who had received 3–10 prior treatment regimens in the advanced setting and 95% of whom had received prior CDK4/6 inhibitors, the objective response rate (ORR) was 27% (11



[a]Chemotherapy will be administered at the following doses: eribulin mesylate: 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle via IV infusion; vinorelbine: 25 mg/m^2 on day 1 and 8 of a 21-day cycle via IV infusion; capecitabine: 1000 or 1250 mg/m^2 po BID on days 1 to 14 of a 21-day cycle; gemcitabine: 1000 mg/m^2 on days 1 and 8 of a 21-day cycle

BICR: Blinded independent central review; BID: Twice daily; CDK4/6: Cyclin-dependent kinase 4/6; Dato-DXd: Datopotamab deruxtecan; DoR: Duration of response; FFPE: Formalin-fixed paraffin-embedded; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; IV: Intravenous; mTOR: Mechanistic target of rapamycin; OS: Overall survival; PARP: Poly-ADP ribose polymerase; PD-1: Programmed death-1; PD-L1: programmed death ligand-1; PFS: Progression-free survival; po: Oral; Q#W: every # weeks; R: randomization; RoW: rest of world; TTR: Time to response.

Figure 1. TROPION-Breast01 study design.

confirmed partial responses [PR]) and the disease control rate (complete response + PR + stable disease) was 85%. There were also durable tumor responses with median PFS by Blinded Independent Central Review (BICR) of 8.3 months (95% CI 5.5–11.1 months). Most frequent treatment-emergent adverse events were stomatitis (83%), nausea (56%), fatigue (46%), and alopecia (37%), primarily Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2. Five patients discontinued treatment due to keratitis (n = 1), keratopathy (n = 1), stomatitis (n = 1) and pneumonitis (n = 2). However, it should be noted that this cohort of patients in the phase 1 study did not include the toxicity management guidelines for Dato-DXd that have been incorporated into protocols for later studies, such as strongly recommended mouthwash for all patients to ameliorate rates of mucositis.

Together with promising data from the TROPION-PanTumor01 study in patients with advanced/metastatic TNBC (ORR of 44% in topoisomerase-I inhibitor-naïve patients) [49] and the BEGONIA platform study of Dato-DXd combined with an immune checkpoint inhibitor in patients with previously untreated TNBC (confirmed ORR of 74%) [50], these results indicate that Dato-DXd has promising efficacy in breast cancer, even among patients who are heavily pre-treated. In terms of the safety profile, while manageable, newer phase 3 randomized studies of Dato-DXd have incorporated improved toxicity management guidelines with the aim of improving the safety profile for patients. Here, we outline the clinical trial design of one such study – TROPION-Breast01.

TROPION-Breast01

TROPION-Breast01 (NCT05104866) is an ongoing phase 3 study that is evaluating the safety and efficacy of Dato-DXd when compared with investigator's choice of standard-of-care single-agent chemotherapy (ICC) in patients with inoperable or metastatic HR+/HER2- breast cancer who have received one or two prior lines of systemic chemotherapy. TROPION-Breast01 is sponsored by AstraZeneca, in collaboration with Daiichi-Sankyo.

Planned sample size & study period

The planned sample size was approximately 700 patients. The study enrolled the first patient in October 2021 and all patients have now been randomized.

Study design

TROPION-Breast01 is a global, phase 3, open-label, randomized study (Figure 1). Eligible patients were randomized to receive either Dato-DXd or ICC (eribulin mesylate, capecitabine, vinorelbine, or gemcitabine) as outlined in Figure 1. Treatment will be administered until Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) defined radiological progression (as determined by the investigator), unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met. Randomization was stratified by previous lines of chemotherapy in the inoperable/metastatic setting (1 vs 2), geographic location (USA/Canada/Europe vs rest of world) and previous CDK4/6 inhibitor use (yes vs no). The study is being performed in accordance with ethical

principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation/Good Clinical Practice, and applicable regulatory requirements. All study participants provided written informed consent before any study-specific procedures were performed.

Eligibility criteria

Key eligibility criteria for TROPION-Breast01 are shown in Box 1. In brief, patients were eligible if they had: inoperable or metastatic HR+/HER2- breast cancer (per ASCO/CAP guidelines [6]), progressed on and were not eligible for endocrine therapy, and received 1 or 2 lines of prior chemotherapy in the inoperable/metastatic setting. Patients must have had a measurable lesion per RECIST 1.1. Clinically inactive brain metastases were permitted.

Box 1. TROPION-Breast01 study key inclusion & exclusion criteria

Inclusion criteria

- Documented informed consent.
- Aged ≥18 years at screening; male or female.
- Inoperable or metastatic HR-positive, HER2-negative breast cancer (per ASCO/CAP guidelines, on local laboratory results); i.e., is documented as HR-positive (either ER and/or PgR positive [ER or PgR ≥1%]) and HER2-negative.
- Progressed on and not suitable for endocrine therapy per investigator assessment, and treated with 1 to 2 lines of prior standard-of-care chemotherapy in the inoperable/metastatic setting. Documented progression on the most recent line of chemotherapy.
- Eligible for one of the chemotherapy options listed as ICC (capecitabine, gemcitabine eribulin mesylate, vinorelbine), per investigator assessment.
- ECOG PS of 0 or 1, with no deterioration over the previous 2 weeks prior to day of first dosing.
- At least 1 measurable lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion at baseline that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have short axis ≥15 mm) with CT or MRI, and is suitable for repeated measurements.
- Patients with previously treated neoplastic spinal cord compression, or clinically inactive brain metastases, requiring no treatment with corticosteroids or anticonvulsants, may be eligible. The patient must have recovered from the acute toxic effects of radiotherapy and last received radiotherapy ≥2 weeks prior to study enrollment.
- Adequate organ and bone marrow function within 7 days before day of first dosing.
- LVEF ≥50% by either an echocardiogram or MUGA within 28 days of first dosing.
- Undergone adequate treatment washout period before Cycle 1 Day 1.
- FFPE tumor sample at the time of screening.
- Minimum life expectancy of 12 weeks at screening.
- Willing to use an adequate method of contraception throughout the study.
- Negative serum pregnancy test for women of childbearing potential.

Exclusion criteria

- As judged by the investigator, any evidence of disease which, in the investigator's opinion, makes it undesirable for the participant to participate in the study, or that would jeopardize compliance with the protocol.
- History of another primary malignancy, except for malignancy treated with curative intent with no known active disease within 3 years before the first dose of study intervention and of low potential risk for recurrence.
- Bone-only metastases.
- Persistent toxicities caused by previous anticancer therapy (excluding alopecia), not yet resolved to CTCAE Version 5.0 grade ≤1 or baseline. Participants may be enrolled with some chronic, stable grade 2 toxicities (defined as no worsening to grade >2 for at least 3 months prior to first dosing and managed with standard-of-care treatment) which the investigator deems related to previous anticancer therapy.
- Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; suspected infections (e.g., prodromal symptoms); or inability to rule out infections.
- Known active or uncontrolled hepatitis B or C infection.
- Known HIV infection that is not well controlled.
- Known active tuberculosis infection.
- Uncontrolled or significant cardiac disease.
- Investigator judgement of ≥1 of the following: mean resting corrected QTcF interval >470 ms; history of QT prolongation associated with other medications that required discontinuation of that medication, or any current concomitant medication known to prolong the QT interval and cause Torsades de Pointes; congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives.
- History of (non-infectious) ILD/pneumonitis that required steroids, current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
- Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses.
- Leptomeningeal carcinomatosis.

10.2217/fon-2023-0188

- Clinically significant corneal disease.
- Any prior treatment (including ADC) containing a chemotherapeutic agent targeting topoisomerase I, TROP2-directed therapy, or prior treatment with same ICC agent.
- Any concurrent anticancer treatment, excluding bisphosphonates or denosumab for the treatment of bone metastases.
- Concurrent use of systemic hormonal replacement therapy.
- Major surgical procedure or significant traumatic injury within 3 weeks of the first dose of study intervention, or an anticipated need for major surgery during the study.
- Receipt of live, attenuated vaccine within 30 days prior to the first dose of study treatment.
- Previous treatment in the present study.
- Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 4 weeks prior to first dosing, randomization into a prior Dato-DXd or T-DXd study, or concurrent enrolment in another clinical study, unless it is an observational clinical study or during the follow-up period of an interventional study.
- Known hypersensitivity to Dato-DXd, or any of the excipients of the product.
- Known history of severe hypersensitivity reactions to other monoclonal antibodies.

ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists; ADC: antibody-drug conjugate; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; Dato-DXd: datopotamab deruxtecan; ECOG PS: Eastern Cooperative Oncology Group Performanc Status; ER: Estrogen receptor; FFPE: Formalin-fixed, paraffin-embedded; HER2: Human epidermal growth factor receptor 2; HIV: Human immunodeficiency virus; HR: Hormone receptor; ICC: Investigator's choice of chemotherapy; ILD: Interstitial lung disease; IV: Intravenous; LVEF: Left ventricular ejection fraction; ms: Milliseconds; MUGA: Multigated acquisition scan; PgR: Progesterone receptor; QTcF: Corrected QT interval formula; RECIST: Response Evaluation Criteria in Solid Tumors; TROP2: Trophoblast cell surface antigen 2; T-DXd: Trastuzumab deruxtecan.

Outcome measures/end points

The study will assess the efficacy of Dato-DXd compared with ICC for the dual primary end points of PFS (defined as time from randomization until progression per RECIST 1.1, as assessed by BICR, or death due to any cause) and OS (defined as time from randomization until the date of death due to any cause). Secondary end points include health-related quality of life, safety and tolerability, pharmacokinetics (PK) and immunogenicity (Box 2). Exploratory end points include assessment of TROP2 expression *via* immunohistochemical analysis and exposure/efficacy relationship. Similar assessment will be undertaken for HER2 expression.

Study procedures

Tumor assessments are being conducted using CT as the preferred method or MRI of the chest, abdomen, and pelvis. Tumor assessments are being performed every 6 or 9 weeks until RECIST 1.1 disease progression (as assessed by the investigator), regardless of start of subsequent anticancer therapy, with a follow-up scan after disease progression. Screening/baseline imaging should have been performed no more than 28 days before randomization. An MRI or CT of the brain was also collected for all participants during screening; any patients randomized with stable brain metastases at baseline have mandatory follow-up brain scans per the above RECIST 1.1 schedule. Following objective progression (or treatment discontinuation for OS assessments), additional assessments of progression status (per local standard clinical practice) and survival will be performed every 3 months to assess PFS2 and OS, respectively. Participants will be followed up for survival status until death, withdrawal of consent, or the end of the study.

Safety and tolerability are being assessed continuously from screening and up to 28 days after the last dose of study drug. For patients who develop ILD/pneumonitis, the safety follow-up will continue until the resolution of ILD/pneumonitis. All patients are given a mandatory proactive oral care plan for stomatitis prophylaxis; for those receiving Dato-DXd, steroid-containing mouthwash is highly recommended and prophylactic cryotherapy during Dato-DXd infusion or other prophylactic regimens as per local/institutional guidelines should also be considered. To prevent nausea, it is recommended that patients receive prophylactic anti-emetic agents prior to infusion of Dato-DXd and on subsequent days as needed. Adverse events are treated according to the Dato-DXd toxicity management guidelines and will usually be graded by CTCAE Version 5.0. Information on ECOG PS, vital signs, body weight, and physical examinations are being collected and assessments including laboratory, ophthalmologic, and cardiac testing will be undertaken.

Patient reported outcomes using the tools listed in Box 2 and blood samples for PK and immunogenicity analysis are being collected at various time points throughout the study.

Box 2. TROPION-Breast01 study end points

Primary end points

- PFS, defined as time from randomization until progression per RECIST 1.1, as assessed by BICR, or death due to any cause.
- OS, defined as time from randomization until the date of death due to any cause.

Secondary end points

- ORR, defined as the proportion of participants who have a confirmed CR or PR, as determined by BICR/investigator assessment, per RECIST 1.1.
- DoR, defined as the time from the date of first documented confirmed response until date of documented progression per RECIST 1.1, as assessed by BICR/investigator assessment or death due to any cause.
- PFS (investigator assessed).
- DCR at 12 weeks, defined as the percentage of patients who have a confirmed CR or PR or who have SD, per RECIST 1.1, as assessed by BICR and investigator.
- TTD in pain, physical functioning and in global health status/QoL, defined as the time from the date of randomization to the date of deterioration as measured by EORTC QLQ-C30.
- TFST, defined as the time from randomization until the start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death due to any cause.
- TSST, defined as the time from randomization until the start date of the second subsequent anticancer therapy after discontinuation of first subsequent treatment, or death due to any cause.
- PFS2, defined as the time from randomization to the earliest progression event (following initial progression), subsequent to first subsequent therapy, or death.
- Pharmacokinetics.
- Immunogenicity, as determined by the presence or absence of anti-drug antibodies.
- Safety and tolerability.

Exploratory end points

- Patient-reported outcomes:
  - Global impression of change in health status as measured by PGIC.
  - Global impression of severity of overall cancer symptoms as measured by PGIS.
  - Patient-reported symptomatic AEs and treatment tolerability per selected items from the PRO-CTCAE and EORTC item library, and overall tolerability per the PGI-TT.
  - Symptoms, functioning and health-related QoL as measured by EORTC QLQ-C30.
  - TTD in breast and arm symptoms as measured by EORTC QLQ-BR45/IL116.
  - Health status as measured by change in VAS score from baseline and 5-dimension scores as measured by EQ-5D-5L.
- Association of TROP2 or other tumor-derived biomarkers with clinical response (BOR, DoR, PFS, OS and other relevant efficacy end points) and tolerability to Dato-DXd and ICC.
- Association of exploratory biomarkers in tumor, plasma, whole blood, or serum collected before, during treatment or at disease progression with disease status and/or response and tolerability to Dato-DXd.
- Assessment of ctDNA levels and mutational status of cancer-associated genes in ctDNA and correlation with clinical response on Dato-DXd and ICC, and correlation of gene expression and cancer gene mutational profile with clinical response.
- Impact of treatment and disease on healthcare resource used.

AE: Adverse event; BICR: Blinded independent central review; BOR: Best overall response; CR: Complete response; CTCAE: Common Terminology Criteria for Adverse Events; ctDNA: Circulating tumor deoxyribonucleic acid; Dato-DXd: Datopotamab deruxtecan; DCR: Disease control rate; DoR: Duration of response; EORTC: European Organisation for Research and Treatment of Cancer; ICC: Investigator's choice of chemotherapy; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PFS2: Second progression-free survival; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impressions scale; PGI-TT: Patient Global Impression of Treatment Tolerability; PR: Partial response; PRO: Patient-reported outcome; QLQ: Quality of life questionnaire; QoL: Quality of life; RECIST: Response Evaluation Criteria In Solid Tumors; SD: Stable disease; TFST: Time to first subsequent treatment; TROP2: Trophoblast cell surface antigen 2; TSST: Time to second subsequent treatment; TTD: Time to deterioration; VAS: Visual analog scale.

Statistical methods

Approximately 1000 participants were enrolled to achieve ~700 patients randomly assigned (1:1) to a treatment group; a 30% screen failure rate was assumed. Primary efficacy analyses for the dual primary end points (PFS by BICR and OS) will be performed in the intention-to-treat population (consisting of all randomly-assigned patients) and analyzed by treatment group. The primary, final analysis of PFS will be performed when approximately 419 PFS events by BICR occur (60% data maturity). Assuming a true PFS HR of 0.55 for Dato-DXd versus ICC, this yields >99% power to demonstrate statistical significance at the 1.0% level (using a 2-sided test). The final

10.2217/fon-2023-0188

analysis of OS will be performed when approximately 444 OS events have occurred across the Dato-DXd and ICC treatment groups (63% maturity). PFS and OS will be analyzed using a log-rank test stratified by number of previous lines of chemotherapy, geographic region and prior use of CDK4/6 inhibitors. The effect of Dato-DXd versus ICC will be estimated by the HR together with its corresponding CI and p-value, and Kaplan-Meier plots will be presented by treatment group. The study will be considered positive if either the PFS analysis results and/or the OS analysis results are statistically significant.

Safety will be assessed in the safety analysis set, which will consist of all randomized patients who received treatment (Dato-DXd or ICC). Safety data will be summarized according to the treatment received. ORR will be assessed in the response-evaluable population (all randomized patients with measurable disease at baseline) and will be evaluated between groups *via* either logistic regression or Cochran-Mantel-Haenszel test. DoR will be assessed in all patients with a response *via* Kaplan-Meier methodology. TFST, TSST, and PFS2 will be analyzed as per the PFS methods. PK results for the Dato-DXd treatment arm will be summarized by visit and nominal sample time using standard PK summary statistics. A summary will be provided of the number and percentage of participants who develop detectable anti-Dato-DXd antibodies (ADA) using the ADA evaluable set (patients in the safety analysis set with a baseline and $\geq$1 post-baseline Dato-DXd ADA result). Patient-reported/HRQL outcomes and other exploratory end points will be summarized descriptively. Exploratory TROP2 IHC expression and exposure/efficacy relationship will be reported, with similar analysis for HER2 expression. An independent data monitoring committee will periodically review safety and efficacy data to determine whether the study should continue as is, be amended, or stopped.

Conclusion

In patients with HR+/HER2- metastatic breast cancer for whom endocrine therapy is no longer an option, the current standard of care in much of the world only includes chemotherapy, which is associated with limited survival outcomes, representing a significant unmet need. However, there is a new role for TROP2-directed ADCs in this setting. Interim findings from the TROPION-PanTumor01 study [48,49] indicate that Dato-DXd provides promising antitumor activity and a manageable safety profile in patients with metastatic HR+/HER2- breast cancer. The ongoing, global, phase 3 TROPION-Breast01 study is evaluating the efficacy and safety of Dato-DXd when compared with ICC in patients with inoperable or metastatic HR+/HER2- breast cancer who have received one or two prior lines of systemic chemotherapy. This study complements a number of other ongoing evaluations of Dato-DXd in breast cancer, including the TROPION-Breast02 (NCT05374512), BEGONIA (arm 7; NCT03742102), and the recently initiated TROPION-Breast03 (NCT05629585) studies in patients with varying stages of TNBC. The results of TROPION-Breast01 will help define the role of Dato-DXd among patients with metastatic HR+/HER2- breast cancer and potentially offer a new treatment option over traditional chemotherapy.

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Manuscript writing: all Authors.

Final approval of manuscript: all authors.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Data sharing statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Executive summary

Background

- Female breast cancer is the most frequently diagnosed cancer in the world and the leading cause of cancer-related death among women.
- For patients who are diagnosed with metastatic estrogen receptor and/or progesterone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer and who have progressed on endocrine therapy and/or are ineligible for standard-of-care endocrine therapy, there were limited treatment options available beyond chemotherapy.
- Antibody drug conjugates, which interact with specific antigens that are overexpressed or exclusively expressed on tumor cells, are a promising alternative to chemotherapy in this setting and may avoid the systemic toxicity associated with unselective cytotoxic agents.
- Datopotamab deruxtecan (Dato-DXd), consists of a humanized IgG1 monoclonal antibody for trophoblast cell surface antigen 2 (TROP2) attached *via* a stable cleavable linker to a topoisomerase I inhibitor payload. In a phase 1 study (TROPION-PanTumor01), Dato-DXd demonstrated potent antitumor activity and an acceptable safety profile in advanced, heavily pre-treated breast cancer.

TROPION-Breast01 (NCT05104866)

- TROPION-Breast01 is an ongoing, global, open-label, randomized, phase 3 study that is evaluating the efficacy and safety of Dato-DXd when compared with investigator's choice of single-agent chemotherapy (ICC) in patients with inoperable or metastatic HR+/HER2- breast cancer who have received one or two prior lines of systemic chemotherapy.
- Approximately 700 eligible patients with inoperable or metastatic HR+/HER2- breast cancer will be randomized 1:1 to receive either Dato-DXd or ICC.

Outcomes

- The dual primary end points are progression-free survival (per Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST 1.1]; as assessed by blinded independent central review) and overall survival.

Conclusion

- The results of the phase 3 TROPION-Breast01 study will help define the role of Dato-DXd in the metastatic HR+/HER2- breast cancer setting in patients who have progressed on, or are ineligible for, endocrine therapy, and after chemotherapy.

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