IMbrave 151: a randomized phase II trial of atezolizumab combined with bevacizumab and chemotherapy in patients with advanced biliary tract cancer

Stephen P. Hack [iD] **, Wendy Verret, Sohail Mulla, Bo Liu, Yulei Wang, Teresa Macarulla, Zhenggang Ren, Anthony B. El-Khoueiry and Andrew X. Zhu**

Abstract

Background: Biliary tract cancers (BTCs) are heterogenous, highly aggressive tumors that harbor a dismal prognosis for which more effective treatments are needed. The role of cancer immunotherapy in BTC remains to be characterized. The tumor microenvironment (TME) of BTC is highly immunosuppressed and combination treatments are needed to promote effective anticancer immunity. Vascular endothelial growth factor (VEGF) drives immunosuppression in the TME by disrupting antigen presentation, limiting T-cell infiltration, or potentiating immune-suppressive cells. Many VEGF-regulated mechanisms are thought to be relevant to repressed antitumor immunity in BTC, making dual targeting of VEGF and programmed cell death protein 1 (PD-1)/PD-L1 pathways a rational approach. Gemcitabine and Cisplatin (Gem/Cis) can also modulate anticancer immunity through overlapping and complementary mechanisms to those regulated by VEGF. Anti-PD-L1/VEGF inhibition, coupled with chemotherapy, may potentiate antitumor immunity leading to enhanced clinical benefit.

Methods: IMbrave 151 is a randomized, double-blind, placebo-controlled, multicenter, international phase II study to evaluate atezolizumab (a PD-L1 inhibitor) in combination with chemotherapy (gemcitabine and cisplatin) and bevacizumab (an anti-VEGF monoclonal antibody) as a first-line treatment for advanced BTC. Approximately 150 patients with previously untreated, advanced BTC will be randomized to either Arm A (atezolizumab + bevacizumab + Gem/Cis) or Arm B (atezolizumab + placebo + Gem/Cis). Randomization is stratified by the presence of metastatic disease, primary tumor location, and geographic region. The primary efficacy endpoint is investigator-assessed progression-free survival (PFS) per RECIST 1.1. Secondary endpoints include objective response rate (ORR), duration of response (DoR), disease control rate (DCR), overall survival (OS), and safety and patient reported outcomes (PROs). Tissue, blood, and stool samples will be collected at baseline and on-treatment in order to perform correlative biomarker analyses.

Discussion: IMbrave 151 represents the first randomized study to evaluate combined PD-L1/VEGF blockade on a chemotherapy backbone in BTC.

Trial registration: NCT identifier: NCT04677504; EUDRACT number: 2020-003759-14

Correspondence to:
Stephen P. Hack
Genentech, Inc, 1 DNA
Way, South San Francisco,
CA 94080, USA
hack.steve@gene.com

Wendy Verret
Bo Liu
Yulei Wang
Genentech, South San
Francisco, CA, USA

Sohail Mulla
Hoffmann-La Roche
Limited, Mississauga, ON,
Canada

Teresa Macarulla
Department of Medical
Oncology, Vall d'Hebron
University Hospital,
Barcelona, Spain

Zhenggang Ren
Zhongshan Hospital,
Fudan University,
Shanghai, China

Anthony B. El-Khoueiry
USC Norris
Comprehensive Cancer
Center, University of
Southern California, Los
Angeles, CA, USA

Andrew X. Zhu
Massachusetts General
Hospital Cancer Center,
Boston, MA, USA

Jiahui International
Cancer Center, Jiahui
Health, China

Background

Biliary tract cancer (BTC) comprises a group of rare, anatomically distinct epithelial tumors arising in the biliary tree. Based on their anatomical location, BTCs are classified as gallbladder carcinoma (GBC), intrahepatic cholangiocarcinoma (iCCA), or extrahepatic cholangiocarcinoma (eCCA).[1–3] In addition, eCCA can be further divided into perihilar (pCCA) and distal (dCCA), depending on origination above or below the cystic duct.[1] Anatomical subtypes possess distinct demographics, natural history, clinical presentations, risk factors, molecular backgrounds, treatment options, and prognosis.[1,2,4,5] Inoperable, recurrent, or metastatic CCA and GBC are collectively referred to as advanced BTC. Despite being rare, BTCs are an important source of cancer-related mortality and harbor a dismal prognosis (3-year survival approximately 1% for patients with advanced disease).[4,6] iCCA is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC), comprising 10–20% of all newly diagnosed primary liver tumors and 3% of gastrointestinal cancers.[2,7] Approximately 50% of patients with iCCA have liver-only disease.[4] The incidence and mortality of iCCA has risen in most regions over recent years, whereas the incidence of eCCA and GBC has tended to decline.[8–12]

BTCs are often asymptomatic in their early stages and, as a result, are often first diagnosed when the tumor is at an advanced stage when therapeutic options are limited. Localized BTC can be managed with surgical resection and adjuvant chemotherapy,[13] however, only approximately 20% are eligible for curative resection at presentation and a significant number of initially resectable cases at diagnosis are subsequently found to be inoperable; local and distant relapses following surgery are frequent.[12,14] Most patients (approximately two thirds) initially present at an advanced stage when palliative chemotherapy is the only feasible treatment option.[15] The results of the phase III ABC-02 and Japanese BT22 phase II studies have established gemcitabine and cisplatin (Gem/Cis) doublet chemotherapy as the standard of care for the first-line management of advanced BTC.[16–18]

Targeted agents have been extensively investigated in BTC. Earlier studies targeting classical oncogenic pathways implicated in BTC carcinogenesis such as angiogenesis and epidermal growth factor receptor (EGFR) in unselected patient populations failed to show superiority to standard chemotherapy.[19–25]

With respect to antiangiogenesis, the addition of either cediranib [a vascular endothelial growth factor (VEGF) multikinase inhibitor] or ramucirumab (a VEGFR2 monocolonal antibody) to Gem/Cis as first-line treatment failed to improve PFS or survival.[20,21] The addition of bevacizumab (a VEGF monoclonal antibody) to gemcitabine/oxaliplatin demonstrated good tolerability and antitumor activity in advanced BTC in a single arm phase II trial.[26] In the second-line setting, regorafenib (a multikinase VEGF inhibitor) significantly improved PFS and disease control compared with best supportive care.[27] Based on improved understanding of the molecular basis of BTC, focus has shifted to 'precision medicine' strategies involving targeted therapies for use in biomarker-selected patient subgroups.[19,28–30] Inhibitors of fibroblast growth factor receptor (FGFR) fusions, isocitrate dehydrogenase 1 (IDH1/2) mutations, and BRAF[V600E] mutations, which are found almost exclusively in iCCA, represent the most promising targets to date.[28,31–34] The modest efficacy of chemotherapy (median survival ~12 months), coupled with the limited applicability of molecularly-targeted agents, emphasizes the urgent need to develop more effective treatments to improve patient outcomes.

Cancer immunotherapy (CIT) with immune checkpoint inhibitors (CPIs), most notably anti-PD-1/PD-L1 antibodies, has joined surgery, chemotherapy, targeted agents, and radiation therapy as a standard treatment modality for a variety of malignancies. PD-1 and PD-L1 inhibitors as monotherapies or in combination with other treatments are now considered mainstream treatments for lung cancer, melanoma, and hepatocellular carcinoma (HCC), as well as other malignancies.[35] For most cancers, only a minority of patients respond to PD-1/PD-L1 inhibitor monotherapy due to the immunosuppressive mechanisms operating in both the tumor and surrounding tumor microenvironment (TME) that result in primary and acquired resistance.[36,37] By identifying and therapeutically targeting resistance mechanisms, treatment regimens can be developed to improve clinical outcomes.[37]

PD-L1 expression in either tumor cells or infiltrating immune cells has been observed in up to 70% of BTCs[38,39] and high PD-L1 expression has been associated with poor prognosis, suggesting a potential role for PD-1/PD-L1 inhibition.[39] To date, however, clinical data for PD-1 or PD-L1 inhibitors in BTC are limited to small studies or sub analyses from basket trials focusing on

pre-treated patients.[40–42] The antitumor activity of single-agent anti-PD-1/PD-L1 antibodies, including atezolizumab, in BTC patients, is modest, and in most cases response rates have not exceeded 10%.[43–49] Consistent with other solid tumors, responses were durable in a small subgroup of responsive patients.[48] At present, anti-PD-1 treatment is indicated for approximately 2% of patients with CCA harboring DNA mismatch repair (MMR) defects or microsatellite instability (MSI).[1] Despite relatively low response rates, the quality and durability of responses to PD-1/PD-L1 inhibitors are similar to other tumor types, thereby warranting the development of combination treatment strategies to improve response rates and clinical outcomes.[47,48]

The goal of CIT combinations is to increase the potential of the immune system to eliminate cancer by disrupting immunosuppressive mechanisms in both the tumor and the TME.[50] In CCA, the TME is dominated by a desmoplastic stroma made up of a complex network of malignant cells, stromal cells, extracellular matrix components, and blood vessels, as well as immune cell subsets.[51] These components of the TME operate individually, or in combination, to directly or indirectly orchestrate tumor growth, treatment resistance, antitumor immunity, and sensitivity to CIT.[50,51] Therefore, drug combinations targeting immunosuppressive components of the TME represent a rational approach in BTC.

One way to target TME immunosuppression is to combine PD-1/PD-L1 inhibitors with chemotherapy and/or anti-angiogenics which both possess immunomodulatory capabilities.[50,52–54] In addition to its well characterized role in mediating angiogenesis, VEGF is a potent driver of tumor immune evasion.[54] The immunosuppressive effects of VEGF include inhibition of dendritic cell (DC) function and maturation, impaired $CD8^+$ T-cell infiltration and function, upregulation of inhibitory immune checkpoints, and the accumulation of immunosuppressive cell types such as tumor-associated macrophages (TAM), myeloid-derived suppressor cells (MDSC), and regulatory T cells (Treg).[53–56] Each of these mechanistic components provides a therapeutic target to reprogram an immunosuppressive TME. Preclinical and clinical studies have demonstrated that antiangiogenic drugs can revert VEGF-driven immunosuppression and augment the activity of PD-1 and PD-L1 inhibitors.[54] In the clinical setting, combinations of PD-1 or PD-L1 inhibitors,

along with anti-VEGF agents, (either multikinase inhibitors or monoclonal antibodies) have proven superior to standard treatments in non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and more recently HCC.[57–60] Similarly, multiple phase III studies have shown that PD-1 and PD-L1 inhibitors combined with chemotherapeutic regimens are superior to chemotherapy alone in a variety of solid tumors.[61–64] Triplet combination therapy with atezolizumab, bevacizumab, and platinum-based chemotherapy (carboplatin plus paclitaxel) has been evaluated in phase III studies in patients with advanced NSCLC (IMpower 150) and ovarian cancer (IMagyn050)[58,65] and is under investigation in multiple randomized studies across different cancer types with various chemotherapy backbones.[54] While this combination was found to be effective in NSCLC, it was not efficacious in ovarian cancer. These disparate findings suggest that response to this regimen may differ depending on the malignancy under study and it remains to be seen if the combination is effective in BTC. In both phase III studies, the toxicity of the triplet regimens were found to be tolerable and manageable with no new safety signals identified.[65,66] A detailed analysis of the safety data from IMpower 150 demonstrated that the addition of atezolizumab to bevacizumab and chemotherapy did not result in premature termination of chemotherapy and the adverse events associated with the triplet combination were mostly grade 1 or 2 and manageable.[66] In addition, the incidence of immune-related adverse events – mainly grade 1 or 2, was similar in the atezolizumab/chemotherapy and atezolizumab/bevacizumab/chemotherapy arms.[66]

Many of the critical immunosuppressive mechanisms identified in the BTC TME are regulated to some degree by VEGF, thereby providing justification to study dual PD-L1/VEGF blockade in this setting. Antitumor immunity can also be augmented with cytotoxic chemotherapies, including gemcitabine and cisplatin, through mechanisms complementary to those that are regulated by VEGF. Therefore, dual inhibition of PD-L1 and VEGF coupled with the immunomodulatory effects of Gem/Cis could create an immune-favorable TME in biliary cancers, leading to enhanced clinical benefit over and above standard of care Gem/Cis.

In this paper, we describe the design of IMbrave 151, a randomized phase II study, that will be the first trial to evaluate combined anti-PD-L1/VEGF

inhibition in tandem with chemotherapy in patients with advanced BTC. We also briefly discuss the scientific and clinical rationale for this combination approach in BTC.

Methods

Study design

IMbrave 151 is a randomized, double-blind, placebo-controlled multicenter phase II study designed to evaluate the efficacy and safety of atezolizumab with bevacizumab in combination with Cis/Gem, compared with atezolizumab plus Cis/Gem, in patients with advanced BTC (iCCA, eCCA, and GBC) who have not received systemic therapy for advanced disease.

The study will enroll approximately 150 patients who will be randomized, in a 1:1 ratio, to one of two treatments arms (see Table 1). Randomization will be stratified according to the anatomical location of the primary tumor (iCCA *versus* eCCA *versus* GBC), presence or absence of metastatic disease, and geographic region (Asia *versus* rest of world). The study design is shown in Figure 1. Recruitment will be competitive.

Study endpoints

The primary efficacy endpoint of IMbrave 151 is PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1[67] or death from any cause (whichever occurs first).

Secondary efficacy endpoints include OS, confirmed ORR, duration of response, and disease control rate according to investigator-assessed RECIST 1.1, time to confirmed deterioration (TTCD) in patient-reported physical functioning, role functioning, quality of life (QoL), and safety.

Exploratory endpoints include PFS and OS rates at specific timepoints, additional patient-reported outcomes (PROs), biomarkers, pharmacokinetics, and the evaluation of anti-drug antibodies (ADAs).

Key eligibility criteria

Key inclusion and exclusion criteria for IMbrave 151 are shown in Table 1. Briefly, IMbrave 151 will enroll patients aged 18 years or older with a histopathological or cytological diagnosis of advanced BTC (intrahepatic or extrahepatic cholangiocarcinoma), or gallbladder carcinoma. Patients with ampullary carcinomas are not eligible. Previous systemic treatment for locally advanced or metastatic disease is not allowed. Patients may have received neoadjuvant or adjuvant therapy provided that was completed at least 6 months prior to Day 1 of Cycle 1. All patients must have adequate biliary drainage with no evidence of ongoing infection. A baseline tumor specimen (accompanied by a pathology report) should be provided unless one is either unavailable or a biopsy is not clinically feasible. All patients at high risk of esophageal varices must undergo an esophagogastroduodenoscopy (EGD), either during screening or within 6 months of cycle 1/day 1. Variceal risk criteria are listed in the study protocol. Any varices must be assessed and treated per local standard of care prior to enrollment.

Study treatments. The study treatment schedule is shown in Table 2. During the induction phase, patients will receive up to 8 cycles of Cis/Gem in combination with either atezolizumab and bevacizumab (arm A) or atezolizumab plus placebo (arm B). Following the cessation of chemotherapy, atezolizumab and bevacizumab (arm A) or atezolizumab with placebo (arm B) will be continued until unacceptable toxicity, disease progression (per RECIST 1.1) or loss of clinical benefit.

In the absence of unacceptable toxicity, patients who meet criteria for disease progression while receiving atezolizumab alone or in combination with bevacizumab will be permitted to continue the study treatment if they meet all of the following criteria; evidence of clinical benefit, as determined by the investigator following a review of all available data, absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease, absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression, and the absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.

Study assessments

Patients will sign a written informed consent prior to any study related procedures. Screening

Table 1. Eligibility criteria.

Inclusion criteria

1. Signed Informed Consent Form

2. ⩾18 years old

3. Eligible to receive gemcitabine and cisplatin

4. Documentation of recurrent/metastatic or locally advanced unresectable BTC based on CT or MRI scans

5. Histologically or cytologically confirmed diagnosis of iCCA, eCCA, or GBC

6. No prior systemic therapy (including systemic investigational agents) for advanced BTC except for:
   - Prior chemotherapy or radiotherapy (with or without radiosensitizing chemotherapy) in the neoadjuvant or adjuvant setting provided this is completed at least 6 months prior to Day 1 of Cycle 1.
   - Prior treatment with gemcitabine administered as a radiation sensitizer in the neoadjuvant and adjuvant settings surrounding surgery, during and up to 4 weeks after radiation therapy is allowed, provided all toxicities have returned to baseline, or Grade 1 or better.
   - Previous use of herbal therapies and traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to Day 1 of Cycle 1.

7. At least one measurable untreated lesion (per RECIST v1.1)

8. Adequate biliary drainage with no evidence of ongoing infection
   - If applicable, treatable, and clinically relevant biliary duct obstruction must be relieved by internal endoscopic drainage/stenting at least 2 weeks prior to Day 1 of Cycle 1 or by palliative bypass surgery or percutaneous drainage prior to Day 1 of Cycle 1, and the patient has no active or suspected uncontrolled infection.
   - Patients fitted with a biliary stent should be clinically stable and free of signs of infection and have total bilirubin ⩽ 2 × ULN and AST/ALT ⩽ 5 × ULN for ⩾ 2 weeks prior to Day 1 of Cycle 1.
   - Patients with improving biliary function who meet all other inclusion criteria may be re-tested during the screening window.

9. Availability of a representative tumor specimen (with a pathology report):
   - A FFPE tumor specimen in a paraffin block (preferred) or at least 16 slides containing unstained, freshly cut, serial sections should be submitted within 4 weeks of randomization.
   - If FFPE specimens described above are not available, any type of specimen (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion], and lavage samples) are also acceptable.
   - If archival tissue is either insufficient or unavailable, a core-needle biopsy specimen should be collected during the screening period, if clinically feasible.
   - If archival tissue is either insufficient or unavailable and a fresh biopsy is not clinically feasible, the patient may still be eligible, upon discussion with the Medical Monitor.

10. Documented virology status of hepatitis, as confirmed by screening HBV and HCV tests
    - For patients with active HBV: HBV DNA < 500 IU/ml during screening, initiation of anti-HBV treatment at least 14 days prior to Day 1 of Cycle 1 and willingness to continue anti-HBV treatment during the study
    - Patients with HCV, either with resolved infection (as evidenced by detectable antibody) or chronic infection (as evidenced by detectable HCV RNA), are eligible

11. ECOG Performance Status of 0 or 1

12. Adequate hematologic and end-organ function, defined by laboratory test results

Exclusion criteria

1. Recurrent disease ⩽ 6 months after curative surgery or ⩽ 6 months after the completion of adjuvant therapy (chemotherapy and/or radiation)

2. Combined or mixed hepatocellular/cholangiocarcinoma

(continued)

Table 1. (continued)

3. NCI CTCAE Grade ≥ 2 peripheral neuropathy

4. Prior bleeding event due to untreated or incompletely treated esophageal and/or gastric varices within 6 months prior to Day 1 of Cycle 1
   - Patients with risk factors for esophageal varices must undergo an EGD, and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment.
   - Patients who have undergone an EGD within 6 months of Day 1 of Cycle 1 do not need to repeat the procedure.

5. Active or history of autoimmune disease or immune deficiency

6. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

7. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to Day 1 of Cycle 1, unstable arrhythmia, or unstable angina

8. History of malignancy other than BTC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma *in situ*, or Stage I uterine cancer

9. Severe infection within 4 weeks prior to Day 1 of Cycle 1

10. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to Day 1 of Cycle 1

11. Prophylactic antibiotics (e.g., to prevent a urinary tract infection or COPD exacerbation) are allowed

12. Prior allogeneic stem cell or solid organ transplantation or on the waiting list for liver transplantation

13. Co-infection with HBV and HCV

14. Prior treatment with CD137 agonists or immune checkpoint blockade therapies

15. Inadequately controlled arterial hypertension (systolic blood pressure > 150 mmHg and/or diastolic BP > 100 mmHg)

16. Anti-hypertensive therapy to achieve these parameters is allowed.

17. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1

18. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)

19. Current or recent (within 10 days prior to Day 1 of Cycle 1) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose

20. History of abdominal or tracheoesophageal fistula, GI perforation, or intra-abdominal abscess within 6 months prior to Day 1 of Cycle 1

21. Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture

22. Major surgical procedure within 4 weeks prior to Day 1 of Cycle 1 or anticipation of need for a major surgical procedure during the study

23. History of clinically significant and uncontrolled intra-abdominal inflammatory disease within 6 months prior to Day 1 of Cycle 1

24. Chronic daily treatment with a NSAID.

25. Occasional use for symptomatic relief of medical conditions such as headache or fever is allowed.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BTC, biliary tract carcinoma; COPD, chronic obstructive pulmonary disease; CT, computed tomography; eCCA, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; EGD, esophagogastroduodenoscopy; FFPE, formalin-fixed paraffin-embedded; GBC, gallbladder cancer; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; iCCA, intrahepatic cholangiocarcinoma; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drugs; OS, overall survival; ULN, upper limit of normal.
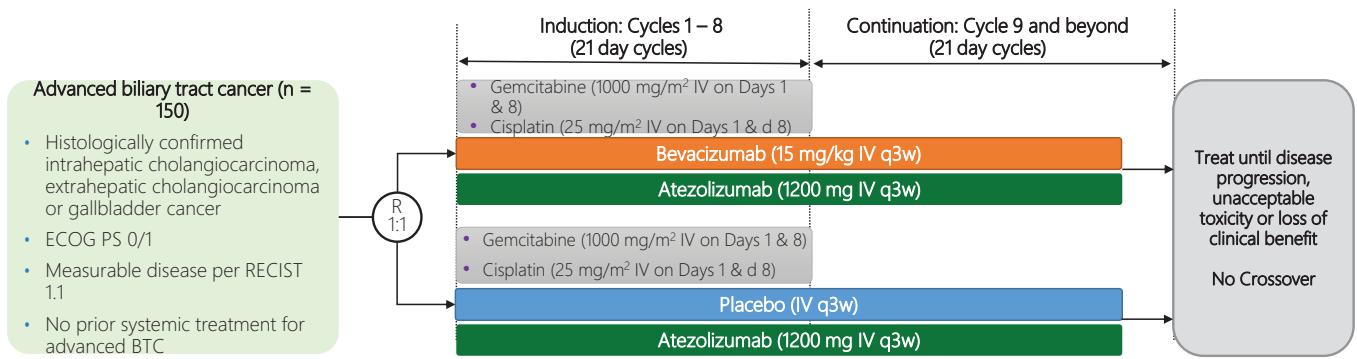
Figure 1. IMbrave 151 study design.

Table 2. Study treatments.

Arm	Dose, route, and regimen (drugs listed in order of administration)	
	Induction phase	**Continuation phase**
	Cycles 1–8 (21-day cycles)[a]	Cycles 9 + (21-day cycles)
A	Atezolizumab + Bevacizumab + CisGem • Atezolizumab 1200 mg IV on d1 • Bevacizumab 15 mg/kg IV on d1 • Cisplatin 25 mg/m² IV on d1 and d8 • Gemcitabine 1000 mg/m² IV on d1 and d8	Atezolizumab + Bevacizumab • Atezolizumab 1200 mg IV on d1 • Bevacizumab 15 mg/kg IV on d1
B	Atezolizumab + Placebo + CisGem • Atezolizumab 1200 mg IV on d1 • Placebo IV on d1 • Cisplatin 25 mg/m² IV on d1 and d8 • Gemcitabine 1000 mg/m² IV on d1 and d8	Atezolizumab + Placebo • Atezolizumab 1200 mg IV on d1 • Placebo IV on d1

[a]Treatment during the chemotherapy combination phase will be administered on a 21-day cycle until completion of eight cycles, loss of clinical benefit, or unacceptable toxicity, whichever occurs first.
Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin and gemcitabine; CIT, cancer immunotherapy; d, day; IV, intravenous; PBO, placebo.

evaluations, including medical history, physical examination, laboratory assessments, and ECG must be completed and reviewed to confirm that patients meeting all eligibility criteria prior to enrollment. Once enrolled and randomized, all patients will return to the clinic on day 1 and 8 of each 21-day cycle for the first 8 cycles, then on day 1 of each 21-day cycle thereafter for study treatment and assessments. Patients will undergo tumor assessments at baseline and every 9 weeks following treatment initiation until radiographic

disease progression per RECIST v1.1 or (for patients who continue atezolizumab plus bevacizumab or placebo, after radiographic disease progression) loss of clinical benefit, as determined by the investigator.

Patient reported outcomes. Patient experience with advanced BTC is complex and effected by both disease- and treatment-related symptoms. To this end, an innovative PRO endpoint strategy has been developed for this study and includes

using a digital platform to uniquely and directly capture the patient voice in a robust manner. The PRO assessments include the following questionnaires:

- European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) – a validated and reliable self-reported measure that assesses aspects of patient functioning, overall health, and generic cancer symptomatology, during the preceding week.[68]
- EORTC quality-of-life questionnaire for cholangiocarcinoma and cancer of the gallbladder (QLQ-BIL21) – a validated and reliable self-reported measure that assesses BTC specific symptomology during the preceding week.[69]
- Selected items from the EORTC Item Library (IL77) – a reduced version of the QLQ-C30 that was created for this study, and which assesses aspects of patient functioning and generic cancer symptomology.
- Patient Global Impression of Change and its Importance (PGI-CI) – a self-reported measure that was adapted for this study and which assesses patients' impression about changes to their overall health because of their cancer and the associated importance compared with when they began the study.
- Patient Global Impression of Severity (PGI-S) – a self-reported measure that was adapted for this study and which assesses patients' impression about how severely their overall health has been impacted because of their cancer during the preceding week
- Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) – a validated item bank of 78 patient-reportable symptomatic treatment toxicities from which four symptoms deemed most applicable to the treatments being evaluated for this study were selected.[70]

The PRO assessments will be completed before patients start treatment, at specified timepoints over the course of treatment, and at treatment discontinuation.

Translational research. An extensive program of translational research is planned, using both tissue, blood, and stool samples from enrolled patients in order to identify potential biomarkers (predictive and/or prognostic) and mechanisms of treatment resistance. Tissue (either archival or fresh), if available, will be collected at baseline with an option to provide an on-treatment tissue specimen. Given the challenges associated with tissue harvesting in BTC, the provision of tumor tissue is strongly encouraged, but not mandated in our study.[71]

Blood samples [serum, plasma, and peripheral blood mononuclear cells (PBMCs)] will be collected from enrolled patients at baseline, during treatment, and at disease progression. Patients will be given the option of consenting to provide stool samples that will be collected at baseline and at one additional timepoint between Cycle 2 and Cycle 3 of treatment.

All biomarker analyses are exploratory and will be performed retrospectively to assess their association with clinical endpoints in order to identify potential mechanisms of response and resistance to atezolizumab and bevacizumab combination therapy. Key translational science objectives of IMbrave 151 include:

- Evaluating the association between PD-L1 expression, tumor mutation burden (TMB), and MSI/MMR status and clinical outcomes.
- Exploring the relationship between genomic markers and clinical benefit.
- Studying the association between circulating biomarkers and clinical outcomes.

Key biomarker analyses are described below.

Tissue-based biomarker analysis
Achieved tumor tissue samples or fresh biopsies at baseline will be collected to assess PD-L1 expression levels on both tumor and immune cells by immunohistochemistry assay (SP263).

Whole exome sequencing (WES) will be performed to determine TMB, mismatch repair (MMR) deficiency, microsatellite instability (MSI), as well as frequent driver mutations found in BTC, such as IDH1/2 mutations and FGFR fusions. These genetic aberrations will be correlated with clinical outcomes in this trial to inform their potential roles in immunotherapy in BTC patients. Transcriptome analysis will be performed on tumor tissues by RNA sequencing. Gene expression signatures on T-effectors,

regulatory T cells, myeloid inflammation, and angiogenesis, as well as other immune subsets and biological pathways, will be evaluated and associated with clinical outcomes.

Blood-based biomarker analysis

Peripheral blood samples for exploratory biomarker studies are collected at baseline and at several time points during treatment (C2D1, C3D1, C4D1, C8D1, C12 D1, and C16D1) and at disease progression. Circulating tumor DNA (ctDNA) will be evaluated in the plasma by Signatera™ 16-plex multiplex PCR next-generation sequencing assay specific to each patient's tumor mutational signatures. Single cell RNA sequencing or Flow Cytometry panels will be performed in PBMC samples collected at baseline and post-treatment to explore the proportion and kinetics of different immune subsets and their association with responses to the treatment. Circulating cytokines and chemokines [i.e., interleukin-6 (IL6), interleukin-8 (IL8), and c-reactive protein(CRP)] will be evaluated by an ELISA-based immunoassay in the serum. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab in combination with bevacizumab.

Microbiome

Stool sample collection, in order to study the effect of the gut microbiome on treatment efficacy and safety, is optional for patients in IMbrave 151. The gut microbiome has been shown to be a key determinant of carcinogenesis and in anticancer immunity, in part by influencing T-cell driven anti-tumor responses.[72] The role of microbial dysbiosis in the development and immune regulation of hepatobiliary tumors is not well characterized.[73] Furthermore, antibiotic treatment, which is commonly used in BTC management, is associated with poor survival outcomes to anti-PD-1 therapy in a variety of solid tumors.[74] The effect of antibiotics on the microbiome of patients with BTC undergoing immunotherapy will be evaluated.

Statistics

The primary objective of this study is to estimate the treatment effect in each of the treatment arms. No formal hypothesis testing will be conducted. The primary efficacy endpoint is investigator-assessed PFS according to RECIST v1.1. A planned sample size of approximately 150 patients will be randomized at a 1:1 ratio to either arm A or arm B. The final PFS analysis will occur when approximately 90 events have been observed. The number of PFS events is deemed adequate to provide sufficient data and precision to estimate the PFS hazard ratio (HR) point estimate and its 95% confidence interval (CI).

Key secondary endpoints include OS, confirmed ORR, duration of response, and disease control rate according to investigator-assessed RECIST 1.1 and safety.

Efficacy analyses will be performed based on the intent-to-treat (ITT) principle stating that all randomized patients, regardless of whether they receive the assigned treatment or not, will be included and grouped according to the treatment assigned at randomization. All subjects who received any amount of study treatment will be included in the safety-evaluable population. HRs and associated 95% CIs for PFS and OS will be estimated by a stratified Cox proportional hazards regression model. The differences in PFS and OS between the two treatment arms will be further estimated by use of the stratified log-rank test. The Kaplan–Meier method will be used for computing medians for time-to-event endpoints including PFS, OS, DOR, and TTCD. The Brookmeyer–Crowley method will be used to calculate the 95% CI for each median time to event. Objective response and disease control rates will be calculated along with 95% CIs estimated by the Clopper–Pearson method. Safety analyses will be conducted using descriptive statistics. One interim analysis will be performed at the time once 100 randomized patients have been followed for at least 6 months.

Ethics

This study will be conducted in accordance with the 1964 Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. Patients will provide written informed consent for participating in the study and for allowing the collection of tissue and blood samples. This study is carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH-GCP). The study is under review by Institutional Review Board or Ethics Committee (IRB/EC) at participating institutions and, if applicable, an appropriate regulatory body.

Discussion

BTC is a highly lethal tumor, for which new and effective treatments, such as immunotherapies, are urgently needed. The role of CIT in the treatment of BTC is at a nascent stage, and, given the modest response rates reported with PD-1/PD-L1 antibodies, combination approaches are likely needed to unleash effective antitumor immunity in biliary tumors. IMbrave 151 seeks to build on the Gem/Cis regimen and will evaluate the efficacy and safety of atezolizumab combined with Gem/Cis with or without bevacizumab.

IMbrave 151 is a randomized phase II study with two parallel experimental arms. The study is not designed to directly compare the arms but rather to evaluate the efficacy of each arm independently in order to inform future phase III studies and/or novel combination regimens. We believe this design is justified and appropriate, in light of both the inherent complexity and heterogeneity of BTC, as well as the availability of relevant combination safety data from other advanced solid tumors. IMbrave 151 does not include a Gem/Cis treatment arm as the clinical outcomes for this standard regimen are well described in the literature.[4,16,17] The clinical and molecular heterogeneity of BTC make interpretation of data, especially time-to-event endpoints such as PFS, from single-arm studies challenging.[75] Historically, ORR, a typical phase I study efficacy endpoint, has proven to be an unreliable surrogate endpoint in BTC.[76,77] However, ORR and its association with PFS or OS has not yet been evaluated in the setting of immunotherapy where antitumor responses are often more durable than responses to chemotherapy or targeted agents. A randomized study design allows for stratification based on critical clinical parameters.[75] While the combination of atezolizumab, bevacizumab, and Gem/Cis has not been studied in BTC, similar combinations have been, or are currently being evaluated in phase III studies in other advanced solid tumors.[58,65]

The immune phenotype of tumors can be broadly characterized as immune inflamed ('hot'), immune-excluded or immune-desert according to the type, location, and density of the immune-cell infiltrate.[78–80] These frameworks can be used to predict the likelihood of response to a CPI and to guide combination treatment strategies.[78] Tumors harboring immune-excluded and immune-desert phenotypes are considered poorly responsive to PD1/PD-L1 blockade.[78] Relative to other cancers, the TME of BTC is not well characterized, but recent data indicate that the majority of CCAs harbor either immune-excluded (T-cell effectors confined to the tumor margin unable to penetrate the tumor bed) or immune-desert phenotypes (absence or scarce T-cell infiltration in the stroma and tumor bed).[81,82] Approximately 11% of both iCCA and eCCA harbor an immune-inflamed phenotype defined using integrative genomic analysis, which may portend to response to PD-1 or PD-L1 monotherapy.[29,82] TME composition is an important determinant of patient prognosis in BTC.[83–85] and the accumulation of immunosuppressive cell types e.g. tumor associated macrophages (TAMs) and regulatory T-cells (T-regs), poor infiltration of cytotoxic $CD8^+$ T-cells, or defective MHC class 1 expression is linked with poor prognosis as well as gemcitabine resistance.[83,84,86] Basic and clinical studies indicate that many of these immunosuppressive mechanisms within the TME of CCAs are subject to regulation by VEGF, or can be modulated with platinum-based chemotherapy, thereby providing a mechanistic rationale for IMbrave 151 (Table 3).

VEGF blockade can restrain the immune-suppressive effects of VEGF, which include inhibition of DC function and maturation, defective T-cell function and infiltration, the accumulation of immunosuppressive cells (TAMs, MDSCs and Tregs), as well as upregulated expression of PD-L1.[54] Known immunomodulatory effects of cisplatin and gemcitabine include increased MHC class 1 expression, recruitment and proliferation of immune effectors, increased PD-L1 expression, and downregulation of immune-suppressive cell types. VEGF inhibitors, gemcitabine, and cisplatin exhibit varied and overlapping immunomodulatory effects that may promote therapeutic synergy with anti-PD-L1 treatment (Table 3).

Clinical evidence from randomized trials has demonstrated the benefit of PD-1/PD-L1 inhibitors combined with anti-VEGF agents in both primary and secondary liver cancers.[57,98,99] Atezolizumab combined with bevacizumab significantly improved OS, PFS, and ORR compared with sorafenib in patients with unresectable HCC.[57] The combination of atezolizumab and bevacizumab was superior to atezolizumab alone in terms of PFS in a randomized unresectable HCC phase 1b cohort.[98] An exploratory analysis from this study demonstrated that PFS was

Table 3. Immunomodulatory effects of gemcitabine, cisplatin, and VEGF inhibitors.

	Immunogenic cell death	PD-L1 ↑	MDSC ↓	Treg ↓	TAMs ↓	MHC class I ↑	Dendritic cells (maturation and/ or function)	T-cell effectors ↑
Gemcitabine[87–89]	✗	✓	✓	✓	?	✓	✓	✓
Cisplatin[90–93]	?	✓	✓	✓	✗	✓	✓	✓
Anti-VEGF[53,55,94–97]	✗	✓	✓	✓	✓	✓	✓	✓

↑, increase; ↓, decrease;?, data mixed or inconclusive ✓, drug shown to modulate mechanism; ✗, drug does not modulate mechanism; MDSC, myeloid derived suppressor cell; MHC, major histocompatibility complex; PD-L1, programmed death ligand 1; TAM, tumor-associated macrophage; Treg, T-regulatory cell.

prolonged in patients with high expression of VEGR2, Treg, and myeloid inflammation signatures treated with atezolizumab and bevacizumab compared with atezolizumab alone.[100] Atezolizumab combined with bevacizumab and platinum-based chemotherapy significantly improved PFS, OS, and ORR in patients with NSCLC adenocarcinoma with liver metastases at baseline, whereas neither atezolizumab or bevacizumab in tandem with chemotherapy were effective in this subgroup.[99] Together, these data indicate that VEGF is an important driver of hepatic immunosuppression and dual VEGF PD-1/PD-L1 blockade can be exploited clinically to improve treatment outcomes. Although combined PD-1/PD-L1 and VEGF inhibition has proven effective in HCC and NSCLC, it failed in advanced ovarian cancer,[65] which suggests that tumor histology may be an important factor.

Therapeutic combinations of PD-1/PD-L1 antibodies with VEGF inhibitors or chemotherapy have not been well studied in BTC (Table 4). It should be noted that no study has yet evaluated all three treatment modalities in patients with BTC. In the first-line setting, doublet regimens comprising VEGF inhibitors and Gem/Cis have failed to demonstrate superiority to Gem/Cis;[20,21] while the efficacy of PD-1/PD-L1 blockade in tandem with chemotherapy is unclear (Table 4).

Overall, data for PD-1 and PD-L1 inhibitors in combination with Cis/Gem as a first-line treatment suggest encouraging response rates and manageable toxicity, but PFS and OS similar to that reported for Gem/Cis alone (Table 4).[46,49] Phase III studies are ongoing to evaluate PD-1 or PD-L1 antibodies in combination with Gem/Cis.[109,110]

To date, combined PD-1/VEGF inhibition has been evaluated in several small single-arm phase I and phase II studies in patients with previously treated advanced BTC with mixed results (Table 4).[108,111] These studies suggest that dual PD-1/VEGF blockade is clinically feasible in advanced BTC but the antitumor activity may be limited. Based on the limited clinical benefit seen so far with PD-1/PD-L1 antibodies in combination with either Gem/Cis or anti-VEGF agents, it is possible that these doublet combinations may be unable to sufficiently overcome immunosuppression in the TME to unleash an anticancer immune response. Given the overlapping and complementary immune-modulating effects of VEGF and chemotherapy, co-targeting of PD-L1 and VEGF pathways coupled with Gem/Cis, could unlock more effective antitumor immunity in BTC by more effectively targeting relevant immune mechanisms within the TME.

This proof-of-concept randomized, double-blind, placebo-controlled phase II study will investigate the efficacy and safety of atezolizumab in combination Gem/Cis chemotherapy with or without bevacizumab as first-line treatment for advanced BTC. The combination of atezolizumab, bevacizumab, and Gem/Cis is a unique combination approach in BTC and the results of IMbrave 151, along with the accompanying translational studies and other ongoing clinical trials with other checkpoint inhibitor combination regimens, will provide important insights into the role of immunotherapy in the treatment of BTC.

Funding

Table 4. Clinical data for PD-(L)1 antibodies combined with Gem/Cis or anti-VEGF agents in BTC.

Study design	Ueno *et al.*[46]	Feng *et al.*[49]	Oh *et al.*[101]	Sahai *et al.*[102]	Chen *et al.*[103]	Lin *et al.*[104]	Zhou *et al.*[105]	Zong *et al.*[106]	Villanueva *et al.*[107]	Arkenau *et al.*[108]
	Ph1b	Ph1b	Ph2	RPh2	Ph2	Ph1b	Ph1b	Ph2	Ph2	Ph1b
Treatment	Nivo + G/C	Nivo + G/C	Durva + G/C	Nivo + G/C or Nivo + Ipi	Cam + GEMOX	Pembro + Lenva	Anlotinib + TQB2450	Anlotinib + Sint	Pembro + Lenva	Pembro + Ramu
Patient population	First-line	First-line	First-line	First-line	First-line	Previously treated	Previously treated	Previously treated	Previously treated	Previously treated
Country	Japan	China	Korea	USA	China	China	China	China	Global	Global
Sample size	30	21	45	35*	54	32	25	17	31	26
Anatomic site										
iCCA	50%	34%	60%	63%*	NR	50%	32%	53%	NR	42%
eCCA	17%	47%	20%	17%*	NR	31%	32%	12%		35%
GBC	33%	19%	16%	20%*	41%	19%	36%	35%		15%
ORR	40%	62%	73%	NR	54%	25%	42%	40%	10%	4%
Median PFS	7.9 m	6.2 m	11 m	7.4 m	6.1 m	4.9 m	240 days	6.5 m	6.1 m	1.6 m
Median OS	15.4 m	8.6 m	18 m	10.6 m	11.8 m	11 m	NR	NR	8.6 m	6.4 m
DCR	97%	95%	100%	NR	89%	78%	75%	87%	68%	39%

*randomized to arm A (Nivo + G/C).
Cam, camrelizumab; DCR, disease control rate; eCCA, extrahepatic cholangiocarcinoma; G/C, gemcitabine/cisplatin; GBC, gallbladder cancer; GEMOX, gemcitabine/oxaliplatin; iCCA, intrahepatic cholangiocarcinoma; Ipi, ipilimumab; Lenva, lenvatinib; Nivo, nivolumab; NR, Not Reported; ORR, objective response rate; OS, overall survival; Pembro, pembrolizumab; PFS, progression-free survival; Ph1, phase 1b; Ph2, phase 2; Ramu, ramucirumab; RPh2, randomized phase 2; Sint, sintilimab.

ORCID iD
Stephen P. Hack https://orcid.org/0000-0002-0640-5709

References
1. Valle JW, Kelley RK, Nervi B, *et al.* Biliary tract cancer. *Lancet* 2021; 397: 428–444.

2. Banales JM, Marin JJG, Lamarca A, *et al.* Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020; 17: 557–588.

3. Khan AS and Dageforde LA. Cholangiocarcinoma. *Surg Clin N Am* 2019; 99: 315–335.

4. Lamarca A, Ross P, Wasan HS, *et al.* Advanced Intrahepatic Cholangiocarcinoma: post Hoc

analysis of the ABC-01, -02, and -03 clinical trials. *J Natl Cancer Inst* 2020; 112: 200–210.

5. McNamara MG, Lopes A, Wasan H, *et al.* Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer. *J Hepatol* 2020; 73: 1109–1117.

6. Zhu X, Zhang X, Hu X, *et al.* Survival analysis of patients with primary gallbladder cancer from 2010 to 2015: a retrospective study based on SEER data. *Medicine* 2020; 99: e22292.

7. Massarweh NN and El-Serag HB. Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Cancer Control* 2017; 24: 1073274817729245.

8. Bertuccio P, Malvezzi M, Carioli G, *et al.* Reply to: "Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma". *J Hepatol* 2019; 71: 1262–1263.

9. Saha SK, Zhu AX, Fuchs CS, *et al.* Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist* 2016; 21: 594–599.

10. Henley SJ, Weir HK, Jim MA, *et al.* Gallbladder cancer incidence and mortality, United States 1999-2011. *Cancer Epidemiol Biomarkers Prev* 2015; 24: 1319–1326.

11. Bridgewater JA, Goodman KA, Kalyan A, *et al.* Biliary tract cancer: epidemiology, radiotherapy, and molecular profiling. *Am Soc Clin Oncol Educ Book* 2016; 35: e194–e203.

12. Wu L, Tsilimigras DI, Paredes AZ, *et al.* Trends in the incidence, treatment and outcomes of patients with intrahepatic cholangiocarcinoma in the USA: facility type is associated with margin status, use of lymphadenectomy and overall survival. *World J Surg* 2019; 43: 1777–1787.

13. Shroff RT, Kennedy EB, Bachini M, *et al.* Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. *J Clin Oncol* 2019; 37: 1015–1027.

14. Akhoundova Sanoyan D, McNamara MG, Lamarca A, *et al.* Adjuvant chemotherapy in biliary tract cancer: state of the art and future perspectives. *Curr Opin Oncol* 2020; 32: 364–369.

15. Adeva J, Sangro B, Salati M, *et al.* Medical treatment for cholangiocarcinoma. *Liver Int* 2019; 39: 123–142.

16. Valle J, Wasan H, Palmer DH, *et al.* Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *New Engl J Med* 2010; 362: 1273–1281.

17. Valle JW, Furuse J, Jitlal M, *et al.* Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol* 2014; 25: 391–398.

18. Okusaka T, Nakachi K, Fukutomi A, *et al.* Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer* 2010; 103: 469–474.

19. Athauda A, Fong C, Lau DK, *et al.* Broadening the therapeutic horizon of advanced biliary tract cancer through molecular characterisation. *Cancer Treat Rev* 2020; 86: 101998.

20. Valle JW, Bai L-Y, Orlova R, *et al.* Ramucirumab (RAM) or merestinib (MER) or placebo (PL) plus gemcitabine (GEM) and cisplatin (CIS) as first-line treatment for advanced or metastatic biliary tract cancer (BTC): a randomized, double-blind, phase II study. *J Clin Oncol* 2020; 38: 477.

21. Valle JW, Wasan H, Lopes A, *et al.* Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. *Lancet Oncol* 2015; 16: 967–978.

22. Malka D, Cervera P, Foulon S, *et al.* Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. *Lancet Oncol* 2014; 15: 819–828.

23. Palmieri LJ, Lavolé J, Dermine S, *et al.* The choice for the optimal therapy in advanced biliary tract cancers: chemotherapy, targeted therapies or immunotherapy. *Pharmacol Ther* 2020; 210: 107517.

24. Santoro A, Gebbia V, Pressiani T, *et al.* A randomized, multicenter, phase II study of vandetanib monotherapy versus vandetanib in combination with gemcitabine versus gemcitabine plus placebo in subjects with advanced biliary tract cancer: the VanGogh study. *Ann Oncol* 2015; 26: 542–547.

25. Rimini M and Casadei-Gardini A. Angiogenesis in biliary tract cancer: targeting and therapeutic potential. *Expert Opin Investig Drugs* 2021; 30: 411–418.

26. Zhu AX, Meyerhardt JA, Blaszkowsky LS, *et al.* Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. *Lancet Oncol* 2010; 11: 48–54.

27. Demols A, Borbath I, Van Den Eynde M, *et al.* An exploratory analysis based on tumor location of REACHIN, a randomized double-blinded placebo-controlled phase II trial of regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced (nonresectable) and metastatic biliary tract tumors. *J Clin Oncol* 2019; 37: e15622.

28. Lamarca A, Barriuso J, McNamara MG, *et al.* Molecular targeted therapies: ready for "prime time" in biliary tract cancer. *J Hepatol* 2020; 73: 170–185.

29. Montal R, Sia D, Montironi C, *et al.* Molecular classification and therapeutic targets in extrahepatic cholangiocarcinoma. *J Hepatol* 2020; 73: 315–327.

30. Sipra QUAR and Shroff R. The impact of molecular profiling on cholangiocarcinoma clinical trials and experimental drugs. *Expert Opin Investig Drugs* 2021; 30: 281–284.

31. Abou-Alfa GK, Macarulla T, Javle MM, *et al.* Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; 21: 796–807.

32. Abou-Alfa GK, Sahai V, Hollebecque A, *et al.* Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol* 2020; 21: 671–684.

33. Hilmi M, Vienot A, Rousseau B, *et al.* Immune therapy for liver cancers. *Cancers (Basel)* 2019; 12. DOI: 10.3390/cancers12010077

34. Subbiah V, Lassen U, Élez E, *et al.* Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol* 2020; 21: 1234–1243.

35. Xin Yu J, Hodge JP, Oliva C, *et al.* Trends in clinical development for PD-1/PD-L1 inhibitors. *Nat Rev Drug Discov* 2020; 19: 163–164.

36. Sharma P, Hu-Lieskovan S, Wargo JA, *et al.* Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell* 2017; 168: 707–723.

37. Fares CM, Van Allen EM, Drake CG, *et al.* Mechanisms of resistance to immune checkpoint blockade: why does checkpoint inhibitor immunotherapy not work for all patients? *Am Soc Clin Oncol Educ Book* 2019; 39: 147–164.

38. Ahn S, Lee JC, Shin DW, *et al.* Author correction: high PD-L1 expression is associated with therapeutic response to pembrolizumab in patients with advanced biliary tract cancer. *Sci Rep* 2020; 10: 21552.

39. Ahn S, Lee Y, Kim J-W, *et al.* Programmed cell death ligand-1 (PD-L1) expression in extrahepatic biliary tract cancers: a comparative study using 22C3, SP263 and E1L3N anti-PD-L1 antibodies. *Histopathology* 2019; 75: 526–536.

40. Kelley RK, Bridgewater J, Gores GJ, *et al.* Systemic therapies for intrahepatic cholangiocarcinoma. *J Hepatol* 2020; 72: 353–363.

41. Vogel A, Bathon M and Saborowski A. Immunotherapies in clinical development for biliary tract cancer. *Expert Opin Investig Drugs* 2021; 30: 351–363.

42. Rizzo A, Ricci AD and Brandi G. Recent advances of immunotherapy for biliary tract cancer. *Expert Rev Gastroenterol Hepatol* 2021; 15: 527–536.

43. Yarchoan M, Cope L, Anders RA, *et al.* Abstract CT043: a multicenter randomized phase 2 trial of atezolizumab as monotherapy or in combination with cobimetinib in biliary tract cancers (BTCs): A NCI experimental therapeutics clinical trials network (ETCTN) study. *Cancer Res* 2020; 80: CT043.

44. Ioka T, Ueno M, Oh DY, *et al.* Evaluation of safety and tolerability of durvalumab (D) with or without tremelimumab (T) in patients (pts) with biliary tract cancer (BTC). *J Clin Oncol* 2019; 37: 387.

45. Kang J, Jeong JH, Hwang H-S, *et al.* Efficacy and safety of pembrolizumab in patients with refractory advanced biliary tract cancer: tumor proportion score as a potential biomarker for response. *Cancer Res Treat* 2020; 52: 594–603.

46. Ueno M, Ikeda M, Morizane C, *et al.* Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study. *Lancet Gastroenterol Hepatol* 2019; 4: 611–621.

47. Kim RD, Chung V, Alese OB, *et al.* A phase 2 multi-institutional study of nivolumab for patients with advanced refractory biliary tract cancer. *JAMA Oncol* 2020; 6: 888–894.

48. Piha-Paul SA, Oh DY, Ueno M, *et al.* Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: results from the KEYNOTE-158 and KEYNOTE-028 studies. *Int J Cancer* 2020; 147: 2190–2198.

49. Feng K, Liu Y, Zhao Y, *et al.* Efficacy and biomarker analysis of nivolumab plus gemcitabine and cisplatin in patients with unresectable or metastatic biliary tract cancers: results from a phase II study. *J Immunother Cancer* 2020; 8: e000367.

50. Murciano-Goroff YR, Warner AB and Wolchok JD. The future of cancer immunotherapy: microenvironment-targeting combinations. *Cell Res* 2020; 30: 507–519.

51. Høgdall D, Lewinska M and Andersen JB. Desmoplastic tumor microenvironment and immunotherapy in Cholangiocarcinoma. *Trends Cancer* 2018; 4: 239–255.

52. Bailly C, Thuru X and Quesnel B. Combined cytotoxic chemotherapy and immunotherapy of cancer: modern times. *NAR Cancer* 2020; 2: 1–20.

53. Fukumura D, Kloepper J, Amoozgar Z, *et al.* Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol* 2018; 15: 325–340.

54. Hack SP, Zhu AX and Wang Y. Augmenting anticancer immunity through combined targeting of angiogenic and PD-1/PD-L1 pathways: challenges and opportunities. *Front Immunol* 2020; 11: 598877.

55. Pinter M, Jain RK and Duda DG. The current landscape of immune checkpoint blockade in hepatocellular carcinoma: a review. *JAMA Oncol* 2021; 7: 113–123.

56. Chen DS and Hurwitz H. Combinations of bevacizumab with cancer immunotherapy. *Cancer J* 2018; 24: 193–204.

57. Finn RS, Qin S, Ikeda M, *et al.* Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *New Engl J Med* 2020; 382: 1894–1905.

58. Socinski MA, Jotte RM, Cappuzzo F, *et al.* Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *New Engl J Med* 2018; 378: 2288–2301.

59. Rini BI, Plimack ER, Stus V, *et al.* Pembrolizumab plus Axitinib versus Sunitinib for Advanced renal-cell carcinoma. *New Engl J Med* 2019; 380: 1116–1127.

60. Motzer RJ, Penkov K, Haanen J, *et al.* Avelumab plus Axitinib versus Sunitinib for advanced renal-cell carcinoma. *New Engl J Med* 2019; 380: 1103–1115.

61. Jiang T, Zhou C, Hu J, *et al.* Combination immune checkpoint inhibitors with platinum-based chemotherapy in advanced non-small cell lung cancer: what's known and what's next. *Transl Lung Cancer Res* 2019; 8: S447–S450.

62. Burtness B, Harrington KJ, Greil R, *et al.* Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 2019; 394: 1915–1928.

63. Horn L, Mansfield AS, Szczęsna A, *et al.* First-line Atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *New Engl J Med* 2018; 379: 2220–2229.

64. Galsky MD, Arija JÁA, Bamias A, *et al.* Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2020; 395: 1547–1557.

65. Moore KN, Bookman M, Sehouli J, *et al.* LBA31 primary results from IMagyn050/GOG 3015/ENGOT-OV39, a double-blind placebo (pbo)-controlled randomised phase III trial of bevacizumab (bev)-containing therapy +/− atezolizumab (atezo) for newly diagnosed stage III/IV ovarian cancer (OC). *Ann Oncol* 2020; 31: S1161–S1162.

66. Reck M, Wehler T, Orlandi F, *et al.* Safety and patient-reported outcomes of Atezolizumab plus chemotherapy with or without Bevacizumab versus Bevacizumab plus chemotherapy in non-small-cell lung cancer. *J Clin Oncol* 2020; 38: 2530–2542.

67. Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228–247.

68. Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European Organization for Research and Treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85: 365–376.

69. Kaupp-Roberts SD, Yadegarfar G, Friend E, *et al.* Validation of the EORTC QLQ-BIL21 questionnaire for measuring quality of life in patients with cholangiocarcinoma and cancer of the gallbladder. *Br J Cancer* 2016; 115: 1032–1038.

70. Basch E, Reeve BB, Mitchell SA, *et al.* Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst* 2014; 106. DOI: 10.1093/jnci/dju244

71. Lamarca A, Frizziero M, McNamara MG, *et al*. Clinical and translational research challenges in biliary tract cancers. *Curr Med Chem* 2020; 27: 4756–4777.

72. Routy B, Le Chatelier E, Derosa L, *et al*. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 2018; 359: 91–97.

73. Mima K, Nakagawa S, Sawayama H, *et al*. The microbiome and hepatobiliary-pancreatic cancers. *Cancer Lett* 2017; 402: 9–15.

74. Elkrief A, Derosa L, Zitvogel L, *et al*. The intimate relationship between gut microbiota and cancer immunotherapy. *Gut Microbes* 2019; 10: 424–428.

75. Gan HK, Grothey A, Pond GR, *et al*. Randomized phase II trials: inevitable or inadvisable? *J Clin Oncol* 2010; 28: 2641–2647.

76. Eckel F and Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *Br J Cancer* 2007; 96: 896–902.

77. Valle JW. BINGO: targeted therapy for advanced biliary-tract cancer. *Lancet Oncol* 2014; 15: 778–780.

78. Ochoa de Olza M, Navarro Rodrigo B, Zimmermann S, *et al*. Turning up the heat on non-immunoreactive tumours: opportunities for clinical development. *Lancet Oncol* 2020; 21: e419–e430.

79. Hegde PS, Karanikas V and Evers S. The where, the when, and the how of immune monitoring for cancer immunotherapies in the Era of checkpoint Inhibition. *Clin Cancer Res* 2016; 22: 1865–1874.

80. Galon J and Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. *Nat Rev Drug Discov* 2019; 18: 197–218.

81. Zhou G, Sprengers D, Mancham S, *et al*. Reduction of immunosuppressive tumor microenvironment in cholangiocarcinoma by ex vivo targeting immune checkpoint molecules. *J Hepatol* 2019; 71: 753–762.

82. Job S, Rapoud D, Dos Santos A, *et al*. Identification of four immune subtypes characterized by distinct composition and functions of tumor microenvironment in intrahepatic cholangiocarcinoma. *Hepatology* 2020; 72: 965–981.

83. Goeppert B, Frauenschuh L, Zucknick M, *et al*. Prognostic impact of tumour-infiltrating immune cells on biliary tract cancer. *Br J Cancer* 2013; 109: 2665–2674.

84. Kitano Y, Okabe H, Yamashita YI, *et al*. Tumour-infiltrating inflammatory and immune cells in patients with extrahepatic cholangiocarcinoma. *Br J Cancer* 2018; 118: 171–180.

85. Tariq NU, Vogel A, McNamara MG, *et al*. Biliary tract cancer: implicated immune-mediated pathways and their associated potential targets. *Oncol Res Treat* 2018; 41: 298–304.

86. Sabbatino F, Villani V, Yearley JH, *et al*. PD-L1 and HLA class I antigen expression and clinical course of the disease in Intrahepatic Cholangiocarcinoma. *Clin Cancer Res* 2016; 22: 470.

87. Peng J, Hamanishi J, Matsumura N, *et al*. Chemotherapy induces programmed cell death-ligand 1 overexpression via the Nuclear factor-κB to foster an immunosuppressive tumor microenvironment in ovarian cancer. *Cancer Res* 2015; 75: 5034–5045.

88. Galluzzi L, Buqué A, Kepp O, *et al*. Immunological effects of conventional chemotherapy and targeted anticancer agents. *Cancer Cell* 2015; 28: 690–714.

89. Di Caro G, Cortese N, Castino GF, *et al*. Dual prognostic significance of tumour-associated macrophages in human pancreatic adenocarcinoma treated or untreated with chemotherapy. *Gut* 2016; 65: 1710.

90. Bezu L, Gomes-de-Silva LC, Dewitte H, *et al*. Combinatorial strategies for the induction of immunogenic cell death. *Front Immunol* 2015; 6: 187–187.

91. Xue Y, Gao S, Gou J, *et al*. Platinum-based chemotherapy in combination with PD-1/PD-L1 inhibitors: preclinical and clinical studies and mechanism of action. *Expert Opin Drug Deliv* 2021; 18: 187–203.

92. de Biasi AR, Villena-Vargas J and Adusumilli PS. Cisplatin-induced antitumor immunomodulation: a review of preclinical and clinical evidence. *Clin Cancer Res* 2014; 20: 5384–5391.

93. Flieswasser T, Van Loenhout J, Freire Boullosa L, *et al*. Clinically relevant chemotherapeutics have the ability to induce immunogenic cell death in non-small cell lung cancer. *Cells* 2020; 9: 1474.

94. Liu X-D, Hoang A, Zhou L, *et al*. Resistance to antiangiogenic therapy Is associated with an immunosuppressive tumor microenvironment in metastatic renal cell carcinoma. *Cancer Immunol Res* 2015; 3: 1017–1029.

95. Terme M, Pernot S, Marcheteau E, *et al*. VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. *Cancer Res* 2013; 73: 539–549.

96. Huang Y, Yuan J, Righi E, *et al.* Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. *Proc Natl Acad Sci USA* 2012; 109: 17561–17566.

97. Wallin JJ, Bendell JC, Funke R, *et al.* Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. *Nat Commun* 2016; 7: 12624.

98. Lee MS, Ryoo B-Y, Hsu C-H, *et al.* Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. *Lancet Oncol* 2020; 21: 808–820.

99. Reck M, Mok TSK, Nishio M, *et al.* Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med* 2019; 7: 387–401.

100. Zhu AX, Guan Y, Abbas AR, *et al.* Abstract CT044: genomic correlates of clinical benefits from atezolizumab combined with bevacizumab vs. atezolizumab alone in patients with advanced hepatocellular carcinoma (HCC). *Cancer Res* 2020; 80: CT044.

101. Oh DY, Lee K-H, Lee D-W, *et al.* Phase II study assessing tolerability, efficacy, and biomarkers for durvalumab (D) ± tremelimumab (T) and gemcitabine/cisplatin (GemCis) in chemo-naïve advanced biliary tract cancer (aBTC). *J Clin Oncol* 2020; 38: 4520.

102. Sahai V, Griffith KA, Beg MS, *et al.* A multicenter randomized phase II study of nivolumab in combination with gemcitabine/cisplatin or ipilimumab as first-line therapy for patients with advanced unresectable biliary tract cancer (BilT-01). *J Clin Oncol* 2020; 38: 4582.

103. Chen X, Wu X, Wu H, *et al.* Camrelizumab plus gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer: a single-arm, open-label, phase II trial. *J Immunother Cancer* 2020; 8: e001240.

104. Lin J, Yang X, Long J, *et al.* Pembrolizumab combined with lenvatinib as non-first-line therapy in patients with refractory biliary tract carcinoma. *Hepatobiliary Surg Nutr* 2020; 9: 414–424.

105. Zhou J, Gong J, Cao Y, *et al.* Anlotinib plus TQB2450 in patients with advanced refractory biliary tract cancer (BTC): an open-label, dose-escalating, and dose-expansion cohort of phase Ib trial. *J Clin Oncol* 2021; 39: 292.

106. Zong H, Zhong Q, Zhao R, *et al.* Phase II study of anlotinib plus sintlimab as second-line treatment for patients with advanced biliary tract cancers. *J Clin Oncol* 2021; 39: 307.

107. Villanueva L, Lwin Z, Chung HC, *et al.* Lenvatinib plus pembrolizumab for patients with previously treated biliary tract cancers in the multicohort phase II LEAP-005 study. *J Clin Oncol* 2021; 39: 321.

108. Arkenau H-T, Martin-Liberal J, Calvo E, *et al.* Ramucirumab plus pembrolizumab in patients with previously treated advanced or metastatic biliary tract cancer: nonrandomized, open-label, phase I trial (JVDF). *Oncologist* 2018; 23: 1407.

109. Oh DY, Chen LT, He AR, *et al.* A phase III, randomized, double-blind, placebo-controlled, international study of durvalumab in combination with gemcitabine plus cisplatin for patients with advanced biliary tract cancers: TOPAZ-1. *Ann Oncol* 2019; 30: v319.

110. Valle JW, Kelley RK, Furuse J, *et al.* 78TiP KEYNOTE-966 trial in progress: Pembrolizumab plus gemcitabine and cisplatin for advanced biliary tract cancer. *Ann Oncol* 2020; 31: S270–S271.

111. Lin J, Shi W, Zhao S, *et al.* Lenvatinib plus checkpoint inhibitors in patients (pts) with advanced intrahepatic cholangiocarcinoma (ICC): preliminary data and correlation with next-generation sequencing. *J Clin Oncol* 2018; 36: 500.

Visit SAGE journals online
journals.sagepub.com/
home/tam

§SAGE journals