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Progress Report

Ipilimumab with atezolizumab-bevacizumab in patients with advanced hepatocellular carcinoma: The PRODIGE 81-FFCD 2101-TRIPLET-HCC trial

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ABSTRACT

A substantial proportion of patients with hepatocellular carcinoma have to face up, sooner or later, to systemic therapy. The current standards as first line systemic therapies are either atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF), or durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA-4). However, the median overall survival remains below 20 months, and a minority of patients become long-term survivors. Of interest in immune-oncology strategies for hepatocellular carcinoma, the objective response seems to be the most reliable surrogate marker of better overall survival.

TRIPLET-HCC (NCT05665348) is a multicentre, randomised, open-label phase II-III trial designed to evaluate efficacy and safety of the triple combination by the addition of ipilimumab (anti-CTLA-4) to atezolizumab/bevacizumab, versus the double atezolizumab/bevacizumab combination. The main inclusion criteria are histologically proven BCLC-B/C HCC without previous systemic therapy. The primary objective

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; DOR, duration of response; DSMB, data safety monitoring board; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; IO, immuno-oncology; ICI, immune-checkpoint inhibitors; irAE, immune-related adverse event; MIV, macrovascular invasion; mITT, modified intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD-L1, Programmed death-ligand 1; PD-1, Programmed cell Death protein 1; TKI, tyrosine kinase inhibitor; TTR, time to response; TTP, time to progression; TRAE, treatment-related adverse event; VEGF, Vascular Endothelial Growth Factor.

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of the phase II is the objective response rate in the triple arm, and OS in the triple versus double arms in the phase III. Secondary endpoints common to the phases II and III are the comparisons of progression-free survival, objective response rates, tolerance and quality of life. In addition, genetic and epigenetic studies from tissue and circulating DNA/RNA will be conducted to assess their prognostic or predictive value.

1. Background

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide, and the principal cause of cancer-related death. In France, its incidence is around 10,000 new cases per year [1,2]. Unfortunately, the diagnosis is frequently late while the tumour burden is large, multifocal within the liver with possible extension within the portal or hepatic veinous tract or spread as distant metastasis. Due to the high risk of tumour recurrence along the history of HCC patients, numerous are those who have to face up, sooner or later, to systemic therapies, even if initially treated by curative options such as surgical strategies or radiological percutaneous ablations. Cytotoxic chemotherapy and hormonotherapy have never demonstrated any benefit in phase III trials [3,4]. The first systemic therapy giving significant benefit on the outcome of HCC patients is sorafenib, a tyrosine kinase inhibitor (TKI) sharing anti-angiogenic and anti-proliferative properties [5]. However, sorafenib is a palliative option with poor objective response rate (ORR), the rarity of substantial down-staging, the absence of long-term survivors and of possible subsequent recovery. Some other TKIs such as regorafenib [6] or cabozantinib [7], validated for HCC in phases III after sorafenib failure, share the same characteristics than sorafenib as cited above. In contrast to the other TKIs cited, lenvatinib has shown a non-inferiority efficacy to sorafenib in overall survival (OS), but with higher ORR and substantial down-staging [8], however remaining strictly palliative with exceptional long-term survivors.

Immuno-oncology (IO) based on the use of immune checkpoint inhibitors (ICI) has revolutionized the paradigm of systemic therapy in advanced HCC. Indeed, in addition to increase the median OS, IO-based combinations are able to increase substantially ORR, to allow shrinkage of HCC tumors, long-term survival of tumour-responder patients and maybe recovery for some of them. IO monotherapies with ICI targeting the PD-1/PD-L1 axis (i.e. nivolumab and pembrolizumab) are in a way disappointing for HCC since they do not significantly improve median OS but allow long-term survival of the responders [9,10].

Some IO-based combinations have shown significant benefit on the outcome of HCC patients in phase III studies. The first of them is the combination of atezolizumab (PD-L1 inhibitor) plus bevacizumab (VEGF inhibitor), bevacizumab playing its own role on tumour anti-angiogenesis and silencing the immunosuppressive role of the tumour microenvironment [11,12]. Thanks to the IMbrave-150 trial, atezolizumab/bevacizumab has become the gold-standard of the first line systemic therapy of HCC [13,14]. Atezolizumab (1200 mg IV Q3W) plus bevacizumab (15 mg/kg IV Q3W) led to higher ORR (30% RECIST v1.1, 35% mRECIST), better OS vs sorafenib [19.2 mo (95% CI, 17.0–23.7) vs. 13.4 mo (95% CI, 11.4–16.9), HR 0.66, $P = 0.0009$], and better PFS [6.9 mo (95% CI, 5.7–8.6) vs. 4.3 mo (95% CI, 4.0–5.6), HR 0.65 (95% CI, 0.53–0.81), $P = 0.0001$], with long-term survivors and a median OS not reached for patients with tumour response. Of interest, the addition of bevacizumab did not increase the rate of immune-related adverse events caused by atezolizumab as demonstrated in the phase Ib GO30140 trial [15].

The second IO-based combination with significant benefit on outcome of HCC patients in a phase III trial is the association of durvalumab (PD-L1 inhibitor) plus tremelimumab (CTLA-4 inhibitor) in the HIMALAYA trial [16]. This combination allows to initiate the immune response as well as to enhance the anti-tumour activity of the CD8+ T-lymphocytes [17]. In HIMALAYA, durvalumab (1500 mg IV Q4W) plus one single injection of tremelimumab (300 mg IV) at day-1, was compared to sorafenib. Durvalumab/tremelimumab led to a substantial ORR per RECIT v1.1 (20.1%), and an increase of OS [16.4 mo (95% CI, 14.2–19.6) vs. 13.8 mo (95% CI, 12.3–16.1), HR 0.78, $P = 0.0035$], with long term survivors. Of interest, in all IO-based therapies for HCC, ORR seems to be so far the best surrogate marker of better OS for patients.

In the present TRIPLET-HCC study, we aim to improve IO-based combinations for HCC by adding ipilimumab (CTLA-4 inhibitor) to the standard atezolizumab/bevacizumab treatment. Ipilimumab will be used at the dose of 1 mg/kg per injection for the first four cycles only – i.e. the induction phase - as described in the phase Ib-II CheckMate-040 study [18]. The aim of TRIPLET-HCC is to assess the potential synergy between the anti-PD-L1 + anti-CTLA-4 + anti-VEGF to reach higher ORR and subsequently improved OS of patients in first line systemic therapy.

2. Study design

2.1. Population

The PRODIGE 81- FFCD 2101-TRIPLET trial is a prospective, multicentre, open-label, phase II-III trial randomizing the double atezolizumab/bevacizumab vs the triple ipilimumab/atezolizumab/bevacizumab combinations in first line systemic therapy of advanced HCC. This trial is funded and coordinated by the Fédération Francophone de Cancérologie Digestive (FFCD). All French centres affiliated to the PRODIGE group (Partenariat de Recherche en Oncologie DIGEstive) involving FFCD, UNICANCER-GI and GERCOR could participate to the study, as well as other European centres in the frame of a partnership with the FFCD group. Main inclusion criteria are patients $\geq$ 18 years of age, with histologically proven HCC, eligible to first line systemic treatment, WHO $\leq$ 1 and Child-Pugh A score (Table 1). The randomization (1:1 ratio) of patients is done according to the minimization technique and is stratified according to the following factors: i) Centre; ii) WHO 0 vs 1; iii) Presence of macrovascular invasion (MIV) or extrahepatic spread (EHS) vs absence; iv) Alpha Fetoprotein level $<$400 ng/ml vs $\geq$ 400 ng/ml. The study is open in January 2023 in about 50 centres in France and Belgium, and the end of inclusions is scheduled for end of 2025. This study (clinicaltrials.gov NCT05665348) is performed in accordance with the declaration of Helsinki and Good Clinical Practice Guidelines. The French ANSM (Agence nationale de sécurité du médicament et des produits de santé) and a French ethics committee approved the study. All patients have to provide written informed consent before entering the study.

2.2. Inclusion, treatment and follow-up

Clinical examination, laboratory tests and imaging should be performed within 28 days prior to randomisation (Table 2). Eligible patients will be randomised to be treated either in the ex-

Table 1
Main eligibility criteria.

Main inclusion criteria
• Age ≥ 18 years
• Histologically proven HCC
• At least one target lesion measurable according to RECIST v1.1 criteria
• WHO ≤ 1
• HCC not amenable to curative treatment by surgery, thermo-ablation or liver transplantation, or to the palliative trans-arterial chemoembolization for intermediate BCLC-B HCC
• Child-Pugh A liver functions if cirrhosis
• Adequate liver function tests: AST and ALT ≤ 5 x ULN, total bilirubin ≤ 35 µM/L, albumin ≥ 28 g/L
• No clinically evident ascites or history of clinical ascites, liver failure, encephalopathy
• Presence of esogastric varices with high risk of bleeding (esogastroscopy performed within the prior 6 months)
• Normal troponin-T value
• Patients with controlled cardiovascular disease for at least 6 months
• Adequate haematological and renal function (haemoglobin > 8.5 g/dL, platelets > 60 G/L, PNN > 1.5 G/L) and renal function (creatinine clearance ≥ 40 ml/min according to MDRD formula)
• Ability of the patient to understand, sign and date the informed consent form before randomisation
• Patient affiliated to a social security scheme
Main non-inclusion criteria
• Patients who have already received systemic therapy for HCC
• Bleeding related to portal hypertension in the last 6 months
• Patients on dual anti-platelet therapy
• Patients on chronic non-steroidal anti-inflammatory drugs (except aspirin)
• History of abdominal or oesophageal fistula, gastrointestinal perforation or intra-abdominal abscess, diverticulitis or colitis within 6 months prior to randomisation
• Other malignancies within the last 2 years, except for carcinoma in situ of the uterus or basal cell or squamous cell skin carcinoma or any other carcinoma in situ, considered as cured
• History of severe active life-threatening autoimmune disease
• Interstitial lung disease
• Chronic HBV infection with HBV load > 500 IU/ml, cirrhotic or not, should be treated with nucleotide/nucleoside analogues
• Known HIV infection
• Immunosuppression, including subjects with conditions requiring systemic corticosteroid treatment (>10 mg/day prednisone equivalent)
• History of organ transplantation
• Non-healing decaying wound, active ulcer or untreated bone fracture
• Proteinuria ≥ 2 g/24 h
• Medically uncontrolled arterial hypertension (systolic value > 150 mm Hg and/or diastolic value > 90 mm Hg)
• History of arterial aneurysm at high risk of bleeding
• Alive attenuated vaccine within 28 days prior to randomisation
• History of pericardial abnormalities possibly immune-related (pericarditis or cardiac tamponade)
• Patients with previous received external radiotherapy up to 1 month before the start of the study treatment, or 3 months before the start of the study treatment, in case of radio embolization
• Central nervous system metastases
• Patients with uncontrolled cardiovascular disease
• History of arterial thromboembolic events, including stroke, transient ischaemic attack and myocardial infarction, if less than 6 months old and unresolved.
• History of venous thromboembolic disease, if less than 6 months old
• Pregnant or breastfeeding women
• Person under guardianship, or person deprived of liberty.
• Inability to undergo the medical follow-up of the trial for geographical, social or psychological reasons

HCC: hepatocellular carcinoma; RECIST: response evaluation criteria in solid tumors; WHO PS: world health organization performance status; BCLC: Barcelona Clinic Liver Cancer staging classification; ULN: upper limit of normal; MDRD: modification of diet in renal disease: HBV: hepatitis B virus; HIV: human immunodeficiency virus.

perimental triple arm (ipilimumab 1 mg/kg for the first 4 cycles + atezolizumab 1200 mg + bevacizumab 15 mg/kg for 2 years) or the control double arm (atezolizumab 1200 mg + bevacizumab 15 mg/kg for 2 years). Cycles will be repeated every three weeks, up to radiological progression (confirmed one month later by a new imagery), unacceptable toxicity, refusal by the patient, withdrawal of consent, pregnancy or decision by the investigator. The maximal duration of treatment within the TRIPLET-HCC trial will be 2 years (i.e. 35 cycles) (Fig. 1).

Cycles of treatment will be administered in the absence of NCI-CTCAE 4.0 grade ≥ 2 toxicity (except for non-symptomatic hypertension, hypocorticism and hypothyroidism which do not resolve rapidly and are life-threatening). If a cycle cannot be performed on the theoretical date (+ 7 days allowed), it will be cancelled and the patient will move to the next cycle 3 weeks later. Radiological assessments must be carried out at the theoretical times. If immunotherapy (atezolizumab +/- ipilimumab) needs to be stopped, bevacizumab should also be stopped and carried over to the next cycle. If bevacizumab is discontinued, immunotherapy will be continued as per the protocol. In case of consecutive cancellations of three cycles, the protocol treatment will be stopped and the patient will be treated outside the TRIPLET-HCC protocol at the decision of the investigator. After discontinuation of the protocol treatment, further treatments will be at the discretion of the investigator. In all cases, the patient will continue to be followed up in the protocol according to the protocol rhythm.

2.3. Safety

Toxicities will be evaluated according to National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) scale. Immune-related adverse events (irAEs) may occur shortly after the first dose or several months after the last dose of atezolizumab +/- ipilimumab and may affect more than one body system simultaneously. Based on irAE severity, atezolizumab +/- ipilimumab will be withheld or permanently discontinued and corticosteroids will be administered. In addition, specific toxicity of bevacizumab will be monitored. In the phase II, a data safety monitoring board (DSMB) will be convened three weeks after the last cure of ipilimumab in the 5th and the 15th patient included in the triple arm. Thereafter, the DSMB will meet at least once a year or more regularly at its own request or at the request of the

Table 2
Main examination and follow-up schedule.

	SCREENING	DURING PROTOCOL TREATMENT		AFTER DISCONTINUATION OF THE PROTOCOL TREATMENT		
	28 days prior to randomisation	Before each cycle	At 6 weeks and then every 9 weeks (i.e. every 3 theoretical cycles)	Within 30 days	follow up / 9 weeks for other reason than radiological progression	Every 3 months for 2 years
Clinical and biological informed consent	X					
CLINICAL EXAMINATION						
Height	X					
Weight, WHO, blood pressure, temperature	X	X	X		X	
Child-Pugh, BCLC score	X					
Dental examination, cardiologic opinion (if < 1 year old) for patients with severe cardiac history	X					
Toxicity assessment NCI-CTCAE version 4.0		X		X	X	
Quality of life (QLQ-C30 and QLQ-HCC18)	X	X				
BIOLOGICAL TESTS						
Biological tests*	X	X**	X	X		
Pregnancy test for childbearing age women	X	X		X		
PARACLINICAL EXAMINATIONS						
Injected abdomino-pelvic MRI plus not injected chest CT, or injected thoraco-abdomino-pelvis CT if MRI is not possible***	X		X		X	
ECG	X	X (only before ipilimumab or cardiac symptoms apparition)				
ANCILLARY STUDIES						
Tumour and non-tumour liver biopsies	X (if no biopsy or biopsy > 2 years)					
Blood samples for tcDNA + serum for protein marker		X (until first radiological assessment)		X (with progression)		
Blood sample for leucocyte DNA		X (only before the 1st course)				
Circulating microRNA		X (until first radiological assessment)		X (with progression)		
Immuno-monitoring		X (until radiological assessment)		X (with progression)		
Stool sampling for microbiome analysis		X (only at week-0)	X (only at week-6)			
Quality of life questionnaires QLQ-C30 + QLQ-HCC 18	X	X	X			
Social Determinants Questionnaires (Social, Sarason and DipCare)	X					
Processing of subsequent lines, survival data and patient status to be completed in the e-CRF						X

* Urine dipstick for proteinuria: if ≥ 2+, perform 24-hour proteinuria. Count of blood cells/platelets, PT, INR, AST, ALT, alkaline phosphatases, GGT, bilirubin (total and conjugated), blood ionogram calcium, magnesium, creatinine, creatinine clearance MDRD albuminemia, fasting cortisol, lipase, TSH, T4 L, troponin-T, PKC, blood glucose or glycated haemoglobin (HbA1c) every 3 months for diabetic patients, alpha-fetoprotein.

** Urine dipstick for proteinuria: if ≥ 2+, perform the day's treatment but schedule 24-hour proteinuria before the next treatment, which can only be done if < 2 g per 24 h + Biological check-up*.

*** The type of imaging used for the first assessment should be the same for the others. Send an anonymised copy of the images to the KEOSYS IMAGYS platform.

sponsor following a pharmacovigilance alert for an event deemed significant by the DSMB or the sponsor. It is also convened at the end of the phase II in order to rule on the safety profile of the triple combination (atezolizumab-bevacizumab-ipilimumab) prior to the possible transition to the phase III. The objective is to ensure that there is no unexpected over-toxicity of the atezolizumab-bevacizumab-ipilimumab triple combination.

2.4. Endpoints and assessments

The primary objective of the phase II is to assess the percentage of patients with the best objective response (complete response or partial response) according to the investigator (RECIST v1.1) within the first 24 weeks (9 cycles) for both treatment arms. If radiological progression occurs within these 24 weeks, it will be necessary

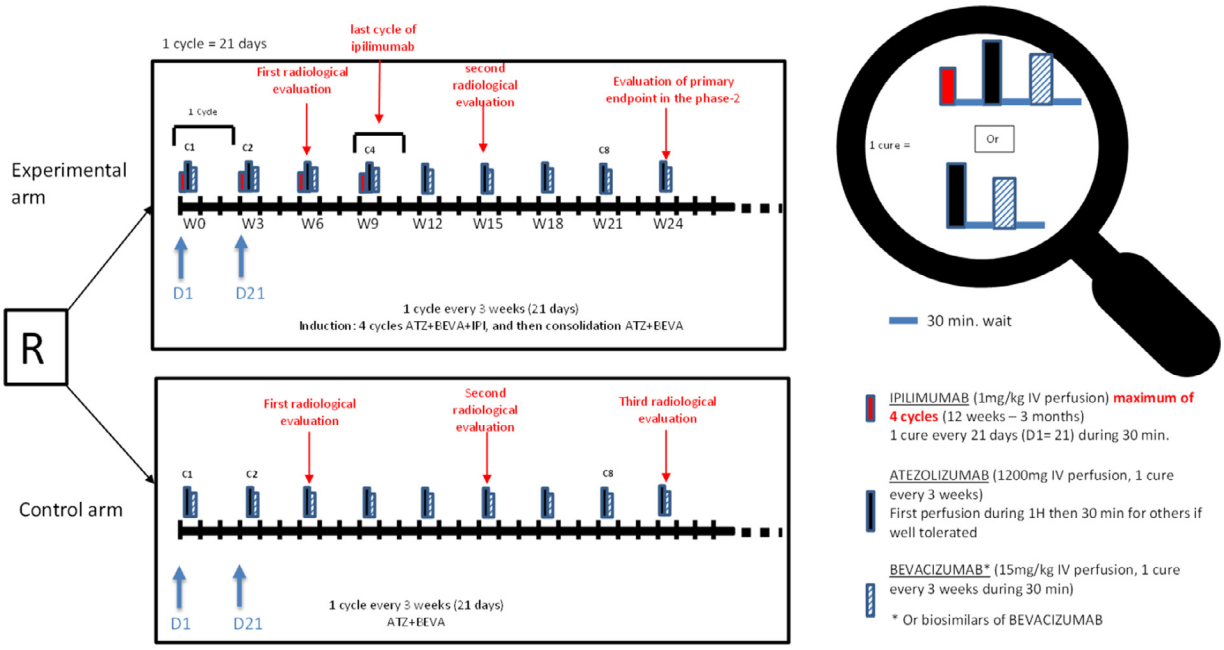

Fig. 1. Study design.

to confirm it 4 weeks later by another imaging before considering discontinuation of study treatment.

The primary objective of the phase III is to compare the median overall survival between the triple (atezolizumab-bevacizumab-ipilimumab) and the double arm (atezolizumab-bevacizumab). The patients from the phase II will be integrated into the phase III.

The secondary objectives, common to phases II and III, will be radiological progression-free survival (PFS), objective response rates (ORR), disease control rate (DCR), time to objective response (TTR), duration of response (DOR), time to progression (TTP), time to degradation of the WHO status > 2, tolerance of treatment (per NCI CTC v4.0, non-treatment-related and treatment-related adverse events [TRAE]), rate of trial withdrawal due to TRAE, quality of life according to the EORTC QLQ-C30 and its HCC supplement EORTC QLQ-HCC18 and time to deterioration of the quality of life scores. Radiological PFS, ORR, DCR, DOR, DCR, TTP and TTR will be assessed: i) per investigator according to RECIST v1.1 criteria; and ii) in centralized review, according to mRECIST and RECIST v1.1 criteria for phases II and III.

2.5. Statistical plan analysis

The clinical hypotheses for the phase II are: H_0, ORR of 25% in the triple arm within the first 24 weeks is considered insufficient; H_1, ORR is $\geq$ 35% in the triple arm. With an one-sided α-risk of 10%, a power of 81% and using the exact binomial method, 102 evaluable patients per arm are required. Allowing for a 10% rate of non-evaluable or lost to follow-up patients, 113 patients will be included per treatment arms (226 patients in total).

The clinical hypotheses for phase III are: H_0, no difference between arms in OS; H_1, a difference of 6 months in median OS in favour of the triple arm (from 19 months in the double arm to 25.1 months in the triple arm) is expected, giving an HR = 0,75. With an α-risk of 5% two-sided and a power of 80% and taking into account two intermediate analyses at 25% (98) and 50% (196) of the events (death from any cause), 392 events are required (according to the Schoenfeld method). Based on an inclusion period of 36 months, a follow-up of 24 months, 546 patients will be required. Taking into account a 5% drop-out rate, a total of 574 patients will be randomised (287 patients per arm). The patients from phase II will be integrated into phase III. Interim analyses are planned to provide early evidence of effectiveness (reject H_0) or futility (accept H_0). The p-values will be calculated with the O'Brien-Fleming function according to the actual number of events observed. Analyses will be performed on a modified intention-to-treat (mITT) basis on all randomised patients, regardless of eligibility, who received at least one dose of treatment (regardless of dose and treatment). Inclusion characteristics will be described for the whole population and by treatment arm. The description of inclusion characteristics and adverse events will be done using standard descriptive statistics: for quantitative variables: mean, standard deviation, median, interquartile range, minimum, maximum and for qualitative variables: frequencies and percentages (with confidence intervals). For the primary efficacy endpoint, a 90% confidence interval (two-sided) will be calculated. Survival analyses will be performed using the Kaplan-Meier method. For phase III, the two arms will be compared using a log-rank test. HRs will be calculated using Cox models (unadjusted or adjusted for stratification variables). For phase III, comparisons between the two arms will be made using Student's *t*-test, or Wilcoxon test (depending on the distribution of variables) for quantitative variables, and Chi^2 test, or Fischer Exact test for qualitative variables.

2.6. Ancillary studies

The objectives of the ancillary studies will aim at investigating predictive and prognostic factors for ORR, PFS and OS through analysis of: i) Tumour and non-tumour liver tissues; ii) Circulating protein biomarkers (sequential serum bio-banking will be performed at baseline and then at each treatment cycle until the first assessment and at radiological progression or 2 years of treatment in the absence of progression); iii) Circulating tumour DNA (correlate the presence of circulating tumour DNA and the type of mutations at baseline and then the outcome of patients); iv) Immunophenotyping of circulating immune cells; v) Circulating miRNAs profiles; vi) leucocyte DNA (identification of genetic variants that may be associated with the occurrence of adverse events and the outcome of patients); vii) Microbiota from stool samples will also be collected prospectively from all patients to al-

low for microbiota analysis (for identification of the bacteria making up the patients' gut microbiota); vii) Radiological ancillary study (explore the potential of early imaging response as a predictor of better overall imaging response and outcome); ix) Social ancillary study (describe the social determinants of patients and their relationship with treatment tolerance and quality of life).

3. Discussion

TRIPLET-HCC is a prospective, controlled, open-label, multicentre, randomised phase II-III trial, evaluating in patients with HCC eligible for first line systemic therapy, the addition of a CTLA-4 inhibitor (ipilimumab) to the gold-standard combining atezolizumab (PD-L1 inhibitor) and bevacizumab (VEGF inhibitor).

The combination of durvalumab (PD-L1 inhibitor) plus tremelimumab (CTLA-4 inhibitor) was safe in the HIMALAYA trial, and the addition of bevacizumab to atezolizumab (PD-L1 inhibitor) did not show any significant higher rate of immune-mediated toxicity in the phase Ib GO30140 comparing in one arm atezolizumab to the combination of atezolizumab plus bevacizumab [15,16]. Further, in the TRIPLET-HCC trial, we use ipilimumab at the lower dose (1 mg/kg per cycle for 4 cycles only), that showed the same ORR in the phase Ib-II CheckMate-040 trial by the comparison to ipilimumab at the dose of 3 mg/kg per cycle for 4 cycles (31% vs 32%), but giving lower incidence of treatment-related grade 3–4 adverse events (29% vs 53%) [18]. However, the potential difference of efficacy between the both doses of ipilimumab on OS could not be reliably assessed in the phase Ib-II study, but it is noticeable that in the melanoma paradigm for instance, the dose of ipilimumab of 1 mg/kg vs 3 mg/kg in the induction phase in addition to nivolumab does not change the patient median OS [19].

In conclusion, we expect that the addition of ipilimumab at the dose of 1 mg/kg in the induction phase to the standard atezolizumab plus bevacizumab combination will be safe and show acceptable toxicity, and will increase the ORR (primary end-point in the phase II part) and thereafter improve the outcome of patients as assessed by OS (primary endpoint in the phase III part) of the TRIPLET-HCC study.

Conflict of interest

• B.G. has participated in consulting and/or advisory boards for Roche, AstraZeneca, BMS, Bayer, Ipsen, and received research grant from Roche.

• C.C. has participated in consulting and/or advisory boards for Ipsen, Gilead, Abbvie, Intercept and received research grant from Gilead.

• D.T. has participated in consulting and/or advisory boards for AstraZeneca, Pierre Fabre, Ipsen, MSD, BMS, Servier, Sirtex Medical, Novartis and AMGEN

• E.A.: Consulting: BMS, AstraZeneca, Bayer, Roche, Ipsen, Incyte, Servier, Boston Scientific, AAA; Travel expense: IPSEN, MSD

• H.S. report lecture fee, board membership, or consultancy from Amgen, Fresenius, IPSEN, Actial, Astellas, Danone, THAC, Biose, BiomX, Eligo, Immusmol, Adare, Nestle, Ferring, MSD, Bledina, Pfizer, Biocodex, BMS, Bromatech, Gilead, Janssen, Mayoli, Roche, Sanofi, Servier, Takeda, Abbvie, has stocks from Enterome bioscience and is co-founder of Exeliom Biosciences.

• J.C.N. has received research grants from Ipsen and Bayer.

• J.E.: Consulting: MSD, Eisai, BMS, AstraZeneca, Bayer, Roche, Ipsen, Basilea, Merck Serono, Incyte, Servier, Beigene, Taiho, Boston Scientific; Travel expense: Amgen; Research funding (institutional): BMS, Beigene, Boston Scientific

• J.F.B.: Bayer, Ipsen, Esai, Astra-Zeneca, Roche, BMS, Servier, Incyte, Tahio Oncology

• J.M.P. has participated in consulting and/or advisory boards for Roche, AstraZeneca, Eisai, MSD, Bayer, Ipsen, Lilly

• K.L.M.: No conflict of interests

• M.A. has participated in consulting and/or advisory boards for AstraZeneca, Bayer and Roche.

• M.B. has participated in consulting and/or advisory boards for Bayer, AstraZeneca, Roche, Ipsen, MSD, BMS, Servier, Sirtex Medical, Eisai, Taiho

• M.G.: No conflict of interests

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