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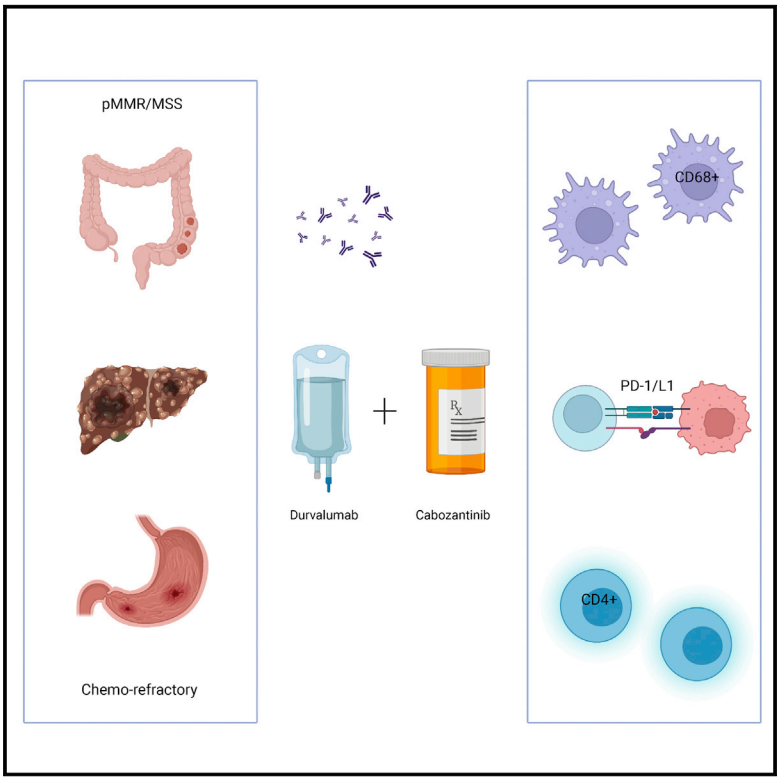
Cabozantinib plus durvalumab in advanced gastroesophageal cancer and other gastrointestinal malignancies: Phase Ib CAMILLA trial results

Graphical abstract



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In brief

Saeed et al. show that cabozantinib plus durvalumab is a safe, active, and potentially synergistic regimen in patients with advanced gastrointestinal malignancies with proficient mismatch repair or microsatellite stable tumors including colorectal cancer, who usually do not respond to immune checkpoint inhibitors. This regimen is being evaluated in larger, later phase trials.

Highlights

- Cabozantinib plus durvalumab has anti-tumor activity and potential synergy
- Toxicity is manageable and consistent with prior studies
- PD-L1 CPS of 5 or more is predictive of response
- Higher CD4 and lower CD68 infiltration correlate with longer progression-free survival

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Cabozantinib plus durvalumab in advanced gastroesophageal cancer and other gastrointestinal malignancies: Phase Ib CAMILLA trial results

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SUMMARY

This is the phase Ib part of the phase I/II CAMILLA trial evaluating cabozantinib plus durvalumab in advanced chemo-refractory proficient mismatch repair or microsatellite stable (pMMR/MSS) gastrointestinal malignancies including gastric/gastroesophageal junction/esophageal (G/GEJ/E) adenocarcinoma, colorectal cancer (CRC), and hepatocellular carcinoma (HCC). Thirty-five patients are enrolled. There are no observed dose-limiting toxicities during dose escalation. The overall grade 3/4 treatment-related adverse event rate is 34%. Among evaluable patients (n = 30), the objective response rate (ORR) is 30%, disease control rate (DCR) 83.3%, 6-month progression-free survival (PFS) 36.7%, median PFS 4.5 months, and median overall survival (OS) 8.7 months. Responses are seen in 4 of 17, 3 of 10, and 2 of 3 patients with CRC, G/GEJ/E adenocarcinoma, and HCC, respectively. Participants with a PD-L1 combined positive score (CPS) $\geq$5 have numerically higher ORR, PFS, and OS. Cabozantinib plus durvalumab demonstrates a tolerable safety profile and potential efficacy in previously treated advanced pMMR/MSS gastrointestinal malignancies.

INTRODUCTION

Gastrointestinal (GI) malignancies account for about 18% of all new cancer cases in the United States, among which the most common tumors are colorectal cancer (CRC), hepatocellular cancer (HCC), and gastric/gastroesophageal junction/esophageal (G/GEJ/E) adenocarcinoma.[1] Despite rapid advances in systemic treatment in advanced GI malignancies, prognoses of patients remain poor, as the median overall survival (OS) of patients with metastatic or advanced disease are approximately 2 years for HCC and CRC and 1 year for G/GEJ/E adenocarcinoma.[1–3] Thus, there is an area of unmet need for systemic treatment in advanced GI malignancies that warrants further investigation.

Immune checkpoint inhibitors (ICIs) that target PD-1 or PD-L1 have changed the paradigm of systemic therapy in advanced solid tumors including in GI malignancies. Anti-PD-1/PD-L1 agents have demonstrated durable responses in patients with metastatic G/GEJ/E adenocarcinoma and HCC.[4–6] However, therapeutic benefit is limited to a minority of patients with G/GEJC and HCC. Furthermore, most patients with metastatic CRC who harbor proficient mismatch repair or microsatellite stable (pMMR/MSS) tumors do not respond to ICI therapy.[7,8] Thus, unique approaches of potentiating or enhancing ICI therapies are needed. To this end, therapeutic combinations that incorporate ICI with targeted therapies is emerging as a promising option and is currently the most intense area of research.

Cabozantinib is an orally bioavailable, multi-tyrosine kinase inhibitor with activities against the tyrosine kinases VEGFR2, MET/HGF, AXL, MER, and TYRO3. It has broad single-agent activity across various solid tumors including metastatic CRC and HCC and has demonstrated potential anti-tumor activity in preclinical models of G/GEJ adenocarcinoma.[9,10] Moreover, the immunomodulatory effects of cabozantinib have been established in pre-clinical and clinical settings, which demonstrate its ability to counteract tumor-mediated immune suppression and potentiate innate and adaptive anti-tumor immune responses.[11–15] Thus, cabozantinib represents an attractive therapeutic partner to combine with ICI agents for the treatment of advanced GI malignancies.

Table 1. Baseline patient characteristics

Baseline characteristics	Overall (n = 35)
Gender, n (%)	
Female	14 (40)
Male	21 (60)
Median age, years (range)	53 (27–79)
>60 (%)	22 (63)
<60 (%)	13 (37)
ECOG PS, n (%)	
0	8 (23)
1	27 (77)
Race, n (%)	
White	31 (89)
African American	2 (6)
Hispanic	1 (3)
Asian	1 (3)
Tumor types, n (%)	
GEA	10 (29)
CRC	20 (58)
HCC	5 (14)
Prior lines of therapy	
Median	2
0	4 (11)
1	7 (20)
2	11 (31)
3	13 (37)
MMR status, n (%)	
MMR proficient	35 (100)
Patients with liver metastasis, n (%)	
GEA	4 (40)
CRC	15 (75)

Table 2. Summary of TRAEs

	Cabozantinib (Cabo) + durvalumab (Durva)
Parameter, n (%)	Overall (n = 35)
TRAEs (number of events)	313
TRAEs ≥ grade 3 (%)	32 (10)
TRAEs ≥ grade 3 (number of patients) (%)	12 (34)
Grade 3	9 (26)
*Immunotherapy-related events	*4 (11)
Grade 4	3 (9)
*Immunotherapy-related events	*1 (3)
Grade 5	0 (0)
Dose modifications	
Durva dose interruptions due to AEs	14 – Durva treatment delay/hold
Cabo dose interruptions or reductions due to AEs	14 – Cabo treatment delay/hold
Discontinuation of Cabo or Durva due to AEs	1 – Durva treatment discontinuation 2 – Cabo treatment discontinuation

Recently, both early and late phase clinical trials have studied anti-PD-1/PD-L1-based cabozantinib combinations in various advanced solid tumors.[16–21] In several clinical trials, cabozantinib has been combined with nivolumab (anti-PD-1) with or without ipilimumab (anti-CTLA-4) and with pembrolizumab (anti-PD-1) in metastatic renal cell cancer, urothelial cancer, and HCC and demonstrated an acceptable safety profile and promising efficacy.[20–22] Moreover, cabozantinib plus atezolizumab (anti-PD-L1) has been studied in metastatic renal cell carcinoma, urothelial cancer, and non-small cell lung carcinoma with encouraging safety and efficacy results.[16–19] Thus, we have conducted a phase I/II trial to evaluate the safety and potential efficacy of cabozantinib with durvalumab (anti-PD-L1) in patients with advanced GI cancers.

RESULTS

Study population and treatment

Overall, 35 patients (14 female, 21 male) were enrolled (Table 1). The patient population was predominantly White (89%) and had a median age of 53 (range: 27–79). Of these patients, 58% had CRC (20/35), 29% had G/GEJ/E adenocarcinoma (10/35), and 14% had HCC (5/35). All patients were confirmed to have pMMR/MSS tumors. Most patients had an ECOG status of 1 (77%). The median number of prior systemic therapies was 2 (range: 0–3) (Table 1). Five patients were not evaluable for dose-limiting toxicities (DLTs) or disease response: three patients in the dose-escalation phase were not evaluable due to missing more than 30% of DLT window doses, which were not related to DLTs, and two patients in the dose-expansion phase

Table 3. Most common TRAEs by preferred term and grade

	Cabo + Durva (n = 35)						
Preferred term, n (%)	Any grade (%)	G1	G2	Grade ≥ 3 (%)	G3	G4	G5
Fatigue	21 (60)	12	9	2 (6)	2	0	0
Hyperthyroidism	20 (57)	20	0	1 (3)	1	0	0
Nausea	18 (51)	17	1	1 (3)	1	0	0
Anorexia	14 (40)	10	4	0 (0)	0	0	0
Alanine aminotransferase increased	13 (36)	9	4	1 (3)	1	0	0
Diarrhea	13 (36)	10	3	0 (0)	0	0	0
Aspartate aminotransferase increased	12 (34)	9	3	0 (0)	0	0	0
Hypothyroidism	10 (29)	9	1	0 (0)	0	0	0
Weight Loss	10 (29)	1	9	2 (6)	2	0	0
Palmar-plantar erythrodysesthesia syndrome	9 (26)	3	6	1 (3)	1	0	0

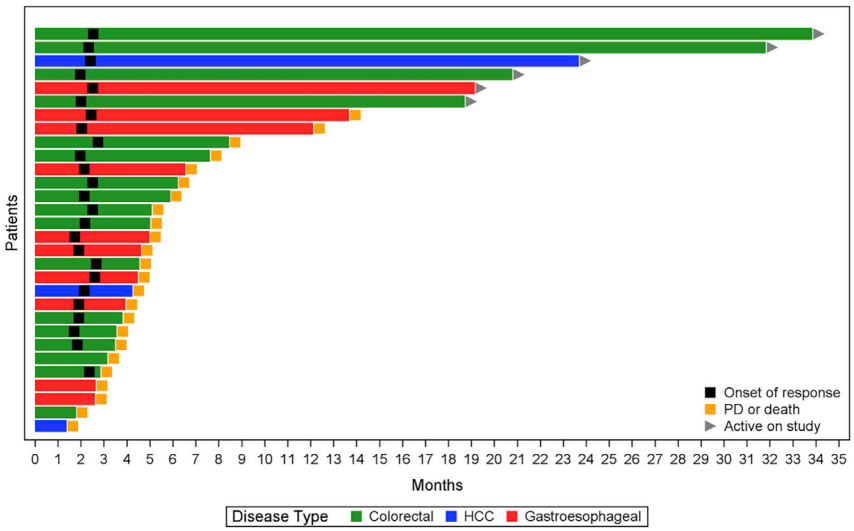

Figure 1. Swimmer plot showing the tumor response with duration by tumor type and month

were not evaluable due to withdrawal from the study with non-completion of at least a 14-day study drug exposure.

Safety and toxicity

During dose escalation (part 1), no DLTs were observed when cabozantinib was escalated from 20 to 60 mg daily. Dose interruptions due to adverse events for durvalumab were required in 14 out of 35 patients and for cabozantinib in 14 out of 35 patients (Table 2). Discontinuation due to treatment-related adverse events (TRAEs) associated with durvalumab was necessary in 1 patient with recurrent immunotherapy-related colitis post durvalumab rechallenge. Two patients required permanent discontinuation of cabozantinib, one due to esophageal perforation and the other patient due to recurrent bleeding from known esophageal varices. Overall, 11 out of 14 patients receiving cabozantinib 60 mg daily required dose reduction to 40 mg daily after the second cycle. The dose reductions were all attributable to accumulative fatigue, anorexia, and associated weight loss. However, no DLTs were reported within the 28-day DLT window. Grade 3 or 4 TRAEs occurred in 34% of patients. The most common any-grade TRAEs were fatigue, hyperthyroidism or hypothyroidism, nausea, anorexia, weight loss, ALT and AST elevations, diarrhea, and palmar-plantar erythrodysesthesia syndrome. The most common serious AEs were thromboembolic events, fatigue, weight loss, and abdominal pain (Tables 3 and S4).

Efficacy

In total, 30 patients were eligible for efficacy assessment. Among them, 17 patients had CRC (57%), 10 patients had G/GEJ/E adenocarcinoma (33%), and 3 patients had HCC (10%). Overall, the objective response rate (ORR) was 30% (9/30); disease control rate (DCR) was 83.33% (25/30) (90% confidence interval [CI], 68.1%–93.19%); median progression-free survival (PFS) was 4.5 months (90% CI, 3.7–6.2 months); 6-month PFS was 36.67% (11/30) (90% CI, 22.11%–53.31%); and median OS was 8.7 months (90% CI, 7.2–19.7 months) (Figures 1, 2, and 3; Tables 4 and S1). Of the 12 patients with a PD-L1 combined positive score (CPS) $\geq$5, ORR was 41.67% (5/12) (90% CI, 18.1%–68.48%); DCR was 91.67% (11/12) (90% CI, 66.13%–99.57%); median PFS was 6.1 months (90% CI, 3.7–not reached [NR] months); 6-month PFS was 50% (6/12) (90% CI, 24.53%–75.47%); and median OS was 14.4 months (6.1–NR months) (Tables 4 and S3). In patients with G/GEJ/E adenocarcinoma (n = 10), the ORR and DCR were 30% and 80% and mPFS and mOS were 4.6 and 7.2 months respectively. In patients with CRC (n = 17), the ORR and DCR were 23.5% and 88.2% and the median PFS (mPFS) and mOS were 4.6 and 9.6 months, respectively (Table S2). Among patients with HCC (n = 3), 2 patients had an objective response.

Immune correlates

Subgroup analysis showed patients with a PD-L1 CPS of 5 or higher had significantly improved OS (log rank test, p = 0.0616) and PFS (log rank test, p = 0.0462) (Figures S2 and S3). Cox proportional hazard (PH) analysis demonstrated that a PD-L1 CPS of 5 or higher (hazard ratio [HR] 0.406, 90% CI 0.188–0.875), less tumor-associated macrophages (TAMs) ($CD68^+$) (HR 0.368, 90% CI 0.158–0.855), and greater tumor-infiltrating CD4 T cells ($CD4^+$) (HR 0.420, 90% CI 0.189–0.932) as well as a lower ratio of TAMs/CD4 T cells (CD68/CD4) (HR 0.319, 90% CI 0.124–0.821) were associated with improved PFS (Figure S1).

DISCUSSION

This study demonstrates the tolerable safety profile and promising efficacy of cabozantinib plus durvalumab in patients with chemotherapy-refractory unresectable or metastatic GI malignancies including HCC, CRC, and G/GEJ/E adenocarcinoma. This study evaluates a cabozantinib-based ICI combination in patients with pMMR/MSS G/GEJ/E adenocarcinoma and CRC and highlights the regimen's potential efficacy in this otherwise ICI-resistant patient population. Furthermore, we demonstrate that PD-L1 CPS may be a potential predictive marker for this ICI-based combination therapy in this patient population.

Cabozantinib 40 mg daily was determined to be the recommended phase 2 dose (RP2D) instead of 60 mg daily, as most of the patients receiving the 60 mg daily dose required an early dose reduction. Grade 3 or 4 TRAEs were seen in 34% of patients treated with cabozantinib plus durvalumab, which is consistent with that observed for cabozantinib plus ICI combinations in prior studies such as in combination with anti-PD-1 (47%–60%) and with anti-PD-L1 (47%–71%).[17–22] Most TRAEs were manageable with dose interruptions, and almost every patient remained on treatment without discontinuation. The most common any-grade AEs and severe AEs were mainly

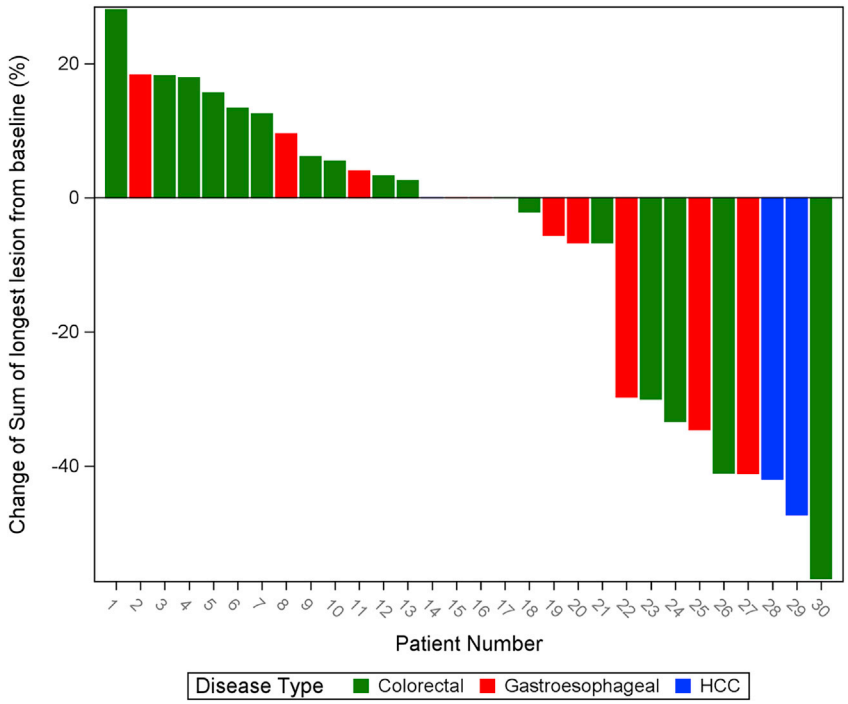

Figure 2. Waterfall plot showing the percentage of change from baseline to nadir in sums of diameters of target lesions

constitutional or GI, which is consistent with the known toxicities of cabozantinib. Overall, no new safety signals were identified, and the toxicity of cabozantinib plus durvalumab was tolerable and comparable to other studies in non-GI tumors.

The efficacy in our study population composed primarily of pMMR/MSS G/GEJ/E adenocarcinoma and CRC is promising as those tumor types are well known to have poor responses to ICI monotherapy.[23,24] The REGONIVO study, which was a phase I/II study conducted in Japan, showed that nivolumab plus regorafenib elicited an ORR of 36% and an mPFS of 7.9 months in patients with chemorefractory metastatic pMMR/MSS CRC. However, studies that were conducted subsequently showed that regorafenib plus nivolumab or pembrolizumab failed to replicate the anti-tumor activity in North American populations (ORR 0%–10%, mPFS 2–4.3 months).[25–28] However, more recent early phase studies conducted in North American populations such as the LEAP-005 trial that evaluated lenvatinib plus pembrolizumab showed an ORR of 22%, whereas the RIN study showed the regorafenib plus nivolumab and ipilimumab elicited an ORR of 27.6% in treatment-refractory CRC, suggesting that specific combinations of ICI plus TKI are active in pMMR/MSS CRC and that exploratory tumor molecular studies are needed to identify biomarkers of response and to help with future trials development in this space.[29,30] Of note, while one study demonstrated that single-agent cabozantinib has disease-stabilizing activity in patients with CRC, the depth and frequency of tumor responses were underwhelming, with only 1 out of 32 patients having achieved objective responses.[10] The tumor responses elicited by cabozantinib plus durvalumab suggest synergy between these agents and demonstrate that cabozantinib may potentiate ICIs' efficacy in these difficult-to-treat patients. The interim results of the phase II CRC cohort of the CAMILLA study presented at the GI ASCO 2022 symposium further validate the anti-tumor activity of cabozantinib plus durvalumab in these patients.[31]

Similarly, cabozantinib plus durvalumab also demonstrated promising efficacy in our pre-treated, advanced-stage, non-biomarker-selected G/GEJ/E adenocarcinoma population, which are also largely poorly responsive to single-agent ICI therapies.[32] The REGONIVO study had enrolled 25 patients with gastric cancer in parallel with the patients with CRC and demonstrated in this population that regorafenib plus nivolumab elicited an ORR of 44% and an mPFS of 5.6 months.[25] In addition, the phase II LENPEM study, which was conducted in Asia, demonstrated that lenvatinib plus pembrolizumab elicited an ORR of 69% and an mPFS of 7.1 months.[33] Recently, the standard-of-care first-line systemic therapy for patients with unresectable G/GEJ/E adenocarcinoma has changed with the approval of combination chemoimmunotherapy regimens with pembrolizumab or nivolumab.[34,35] These recent changes and the promising efficacy of cabozantinib plus durvalumab taken together warrant the evaluation of cabozantinib-based ICI combinations in the maintenance or second-line setting for metastatic pMMR/MSS G/GEJ/E adenocarcinoma. The phase III COSMIC-312 trial demonstrated that atezolizumab (anti-PD-L1) plus cabozantinib led to a PFS benefit over sorafenib but did not result in an OS benefit.[36] Nonetheless, the recent reporting of the phase III HIMALAYA study confirmed the superior OS of durvalumab plus tremelimumab (anti-CTLA-4) over standard-of-care sorafenib in first-line settings in advanced HCC. Interestingly, in this STRIDE regimen, only a single priming dose of tremelimumab was added to durvalumab, which was effective yet associated with less toxicity.[37] Based on these results, an additional phase II HCC cohort has been added to the CAMILLA trial and is enrolling patients to evaluate the triplet regimen of cabozantinib plus durvalumab plus tremelimumab.

Our study demonstrates that baseline PD-L1 CPS as well as tumor CD68 and CD4 protein levels via immunohistochemistry (IHC), which represent cell surface protein markers for TAMs and tumor-infiltrating CD4 T cells, respectively, are potential predictive markers for cabozantinib plus durvalumab. Notably, enrichment of tumors with subsets of TAMs characterized in part by CD68 expression have been associated with a lower complete response rate in patients with melanoma treated with anti-PD-1 therapy and with reduced OS in patients with head and neck cancer.[38] Thus, our findings warrant further evaluation of PD-L1 CPS as well as CD68 and CD4 levels and CD68/CD4

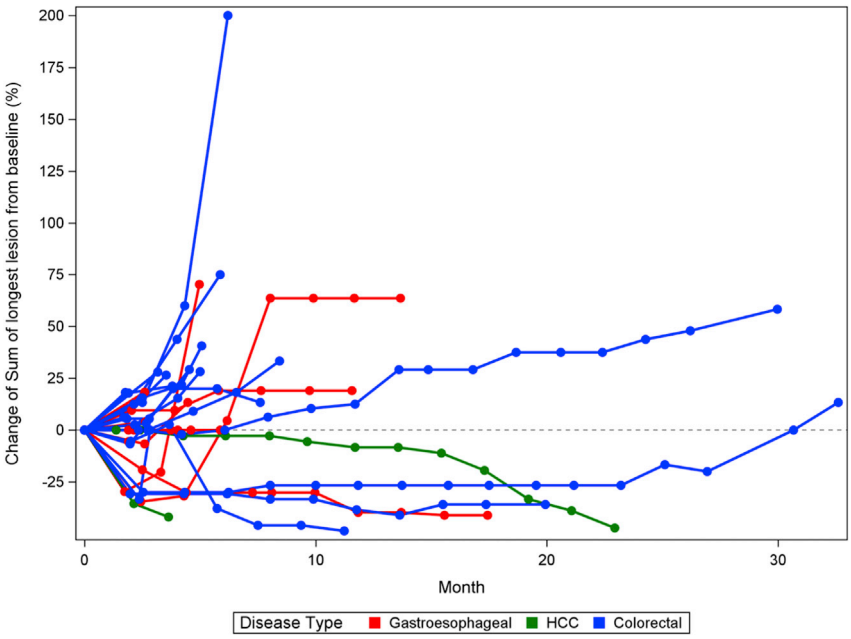

Figure 3. Spider plot showing the percentage of change from baseline in sums of diameters of target lesions over time

ratio as potential ICI biomarkers in patients with pMMR/MSS CRC, G/GEJC, and HCC in a larger trial population.

In conclusion, combined cabozantinib and durvalumab is fairly tolerated and has potential efficacy in treatment-refractory, unresectable, or metastatic pMMR/MSS GI malignancies. The multicohort phase II of the CAMILLA study is currently ongoing, with results anticipated soon.

Limitations of the study

There are several limitations to our study. First, given the nonrandomized, single-arm nature of the study, no within-study comparisons were made of cabozantinib plus durvalumab with established therapeutic agents for each tumor types in respective treatment settings or with cabozantinib or durvalumab alone. Second, the limited number of patients enrolled across the different tumor types limits the power of the study, and thus a p value cut-off of 0.10 was used to define significance. Evaluation of cabozantinib plus durvalumab in a larger population is therefore warranted.

Table 4. Key efficacy outcomes for the overall and PD-L1 CPS ≥5 population

	Overall	PD-L1 CPS ≥5
1. ORR	30% (16.63%, 46.51%), (9/30)	41.67% (18.1%, 68.48%), (5/12)
2. Disease control rate	83.33% (68.1%, 93.19%), (25/30)	91.67% (66.13%, 99.57%), (11/12)
3. Median PFS (months)	4.5 (3.7, 6.2)	6.1 (3.7, not estimable)
4. Median OS (months)	8.7 (7.2, 19.7)	14.4 (6.1, not estimable)
5. 6-month PFS rate	36.67% (22.11%, 53.31%), (11/30)	50% (24.53%, 75.47%), (6/12)

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrm.2023.100916.

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AUTHOR CONTRIBUTIONS

Conceptualization, A.S.; methodology, A.S., J.D., and M.P.; software, J.D. and M.P.; validation, all authors; formal analysis, A.S., J.D., and M.P.; investigation, all authors; resources, A.S.; data curation, J.D., M.P., K.M., M.S., J.F.-B., and J.R.; writing – original draft preparation, A.S., R.P., and M.P.; writing – review and editing, all authors; visualization, J.D. and M.P.; supervision, A.S.; project administration, A.S.; funding acquisition, A.S. All authors have read and agreed to the published version of the manuscript.

DECLARATION OF INTERESTS

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INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Biological samples		
Formalin-fixed paraffin-embedded archival tumor specimens	This manuscript	N/A
Chemicals, peptides, and recombinant proteins		
Cabozantinib	Exelixis (Alameda, CA, USA)	www.cabometyxhcp.com
Durvalumab	Astrazeneca (Cambridge, UK)	www.imfinzi.com
PD-L1 Rabbit mAb #13684	Cell Signaling Technology (Danvers, MA, USA)	www.cellsignal.com; RRID:AB_2687655
CD68 Rabbit mAb #76437	Cell Signaling Technology (Danvers, MA, USA)	www.cellsignal.com; RRID:AB_2799882
CD4 Rabbit mAb #48274	Cell Signaling Technology (Danvers, MA, USA)	www.cellsignal.com
Deposited data		
Patient data	This manuscript	N/A
Software and algorithms		
SAS software version 9.4	SAS institute, Cary, NC, USA	www.sas.com
R version 3.6.2	The R Foundation	www.r-project.org

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Anwaar Saeed (dranwaarsaeed1@gmail.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

All data reported in this paper and any additional information required to reanalyze the data will be shared by the lead contact upon reasonable request (Table S5). Specifically, de-identified individual patient level data such as baseline clinical variables, treatment outcomes including treatment response and survival, and incidence and grade of adverse events for each trial participant will be available upon request. Any additional information regarding individual participants that may result in breach of patient confidentiality will not be provided.

This publication does not generate new code.

Any additional information required to reanalyze the data reported in this work paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and local institutional review board at the participating site.

Human subjects

Patients with histologically confirmed hepatocellular carcinoma, gastric/gastroesophageal junction/esophageal adenocarcinoma, or colorectal cancer were enrolled in this study. Demographic information was provided in Table 1. All patients provided written consent prior to enrollment.

Patient eligibility

Patients 18 years or older with Eastern Cooperative Oncology Group (ECOG) performance status 0–1 with histologically confirmed advanced or locally advanced unresectable (stage IV or unresectable III) G/GEJ/E adenocarcinoma, CRC, or HCC with measurable

disease per modified RECIST (mRECIST) 1.1 were eligible for enrollment. Patients must have demonstrated progression or intolerance to at least 1 prior line of standard of care systemic therapy for patients with G/GEJC, at least 2 lines of therapy for patients with CRC, and 0 to 1 line of therapy for patients with HCC. Patients with RAS wild-type CRC must have demonstrated failure to anti-EGFR therapy. Patients with HER2 positive G/GEJ/E adenocarcinoma must have demonstrated failure to anti-HER2 therapy. Patients with prior exposure to anti PD-1/L1, or other co-inhibitory receptors such as CTLA-4 were excluded from enrollment, except for the HCC cohorts, as were patients with prior treatment with cabozantinib or monoclonal antibodies or tyrosine kinase Inhibitors (TKIs) against MET or MET/HGF. Patients with a history of autoimmune disorder or immune deficiency were also excluded from the study. Eligible patients must have an accessible primary or metastatic lesion for a required baseline biopsy.

Subject allocation

The phase Ib part of this trial reported here is a single arm study with no control group.

METHOD DETAILS

Study design

This is an ongoing non-randomized, open-label, phase I/II clinical trial registered at clinicaltrials.gov (NCT03539822). The trial consisted of an initial phase of dose limiting toxicities (DLT) evaluation (phase I) and a subsequent dose-expansion phase to better evaluate the regimen's safety profile at the Maximum Tolerated Dose (MTD). While the planned duration of therapy was 12 cycles per participant, treatment was continued until disease progression, unacceptable toxicity, patient desire to discontinue therapy, or whichever occurred first. The primary outcome of interest was the MTD defined as the highest dose studied for which the observed incidence of DLT is less than 33% as per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The MTD was used to inform the RP2D. Secondary outcomes were ORR defined as the proportion of patients achieving a complete response (CR) or partial response (PR), DCR defined as the proportion of patients achieving a CR, PR or stable disease (SD), PFS defined as the duration of time from start of treatment until objective tumor progression or death, OS defined as the duration of time from start of treatment to death, and proportion of participants with adverse events. DLT was evaluated at the end of cycle 1. Patients who did not complete cycle 1 and did not meet criteria for DLT were considered unevaluable.

Sample size estimation

The number of patients (n = 35) enrolled in this phase 1b study was justified according to the requirements of the 3 + 3 design (number of dose increments to find the MTD) followed by the dose expansion scheme consistent with the study protocol.

Drug administration

The phase I part was conducted in the classic 3 + 3 dose escalation design where participants received durvalumab 1500 mg every four weeks intravenously plus a starting dose of cabozantinib 20 mg daily per oral and titrated up to 40mg then 60 mg daily. Cabozantinib was administered daily throughout the 28-day cycles and durvalumab was administered intravenously on day 1 of every 28-day cycles. In part 2, patients were administered durvalumab 1500 mg every 28 days intravenously plus cabozantinib at the recommended phase II dose (RP2D).

Assessments

Treatment response was evaluated every 2 cycles using the mRECIST criteria version 1.1 and patients with at least two tumor imaging scans were eligible for assessment. mRECIST criteria version 1.1 allows patients with no clinical deterioration to continue trial therapy beyond first Progressive Disease (PD) on scans to assess for possibility of pseudoprogression. PD confirmatory scan was done at least 4 weeks from the first one.

QUANTIFICATION AND STATISTICAL ANALYSIS

- The observed TRAEs were summarized by type and severity according to the CTCAE 5.0. The research questions concerning primary, secondary and exploratory analyses required the use of several survival analyses methods. As this is a small sample study (N ranging from 24 to 26 for most analyses), results of all statistical tests were reported using 90% confidence intervals and p-values of statistical tests were assessed at the 10% level of significance. The primary outcomes of ORR, DCR and 6-month PFS rate were reported as proportions while PFS and OS was reported using median and the corresponding 90% confidence interval. For calculation of median PFS and median OS, all alive subjects (or no progression patients) were flagged as censored on 02/18/2022. Kaplan Meier curves for both OS and PFS were generated and a comparison of PD-L1 CPS levels ≥ 5 vs CPS <5 was made using a weighted log-rank test. As the research interest was focused on comparing long-term survivors in the two groups, the Fleming-Harrington (0,1) weights were used for this analysis. Additionally, a Cox proportional hazards (PH) model was used to compare PD-L1 CPS levels (≥ 5 vs CPS <5), CD68 levels (<5% vs $\geq$ 5%), CD4 levels ($\geq 10\%$ vs < 10%) and CD68/CD4 ratio (<1 vs $\geq$ 1) and results were reported using a forest plot. The proportional hazards assumption was validated using two methods – the log-log survival plot and the observed vs expected survival plot – and was found to be appropriate. Likewise, all exploratory molecular subgroup analyses were

conducted using the Cox PH model. Additional analyses included using the two-sample test for comparing survival rates for PD-L1 CPS levels ≥ 5 vs CPS <5 at the landmark times of 12 months and 24 months respectively. The median PFS and OS in these two groups was compared using the Chen test for small sample censored data to correct for the inflation in type I error emerging from the Brookmeyer and the Crowley method.[3]

ADDITIONAL RESOURCES

This study has been registered on clinicaltrials.gov (NCT03539822).