The LEAP program: lenvatinib plus pembrolizumab for the treatment of advanced solid tumors

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Tumor progression and immune evasion result from multiple oncogenic and immunosuppressive signals within the tumor microenvironment. The combined blockade of VEGF and inhibitory immune checkpoint signaling has been shown to enhance immune activation and tumor destruction in preclinical models. The LEAP clinical trial program is evaluating the safety and efficacy of lenvatinib (a multikinase inhibitor) plus pembrolizumab (a PD-1 inhibitor) across several solid tumor types. Preliminary results from ongoing trials demonstrate robust antitumor activity and durable responses across diverse tumor types with a manageable safety profile. Thus, lenvatinib plus pembrolizumab is anticipated to be an important potential new regimen for several solid cancers that currently have limited therapeutic options.

Clinical trial registration: NCT03884101, NCT03713593, NCT03820986, NCT03776136, NCT03797326, NCT03829319, NCT03829332, NCT03976375, NCT04428151, NCT04199104, NCT03898180, NCT04246177 (ClinicalTrials.gov).

Lay abstract: Over the last 20 years, several new drugs have been developed that have greatly improved outcomes for patients with cancer. However, some patients have tumors that do not respond or become unresponsive to treatment over time when a given drug is used as the sole treatment. To overcome this problem, combinations of drugs that attack the tumor in different ways are being studied. Here, we describe the rationale and design of the LEAP clinical trial program, which is investigating the combination of pembrolizumab and lenvatinib in patients with several solid tumor types who currently have limited available therapies. Pembrolizumab works with the patient's immune system to attack cancer cells whereas lenvatinib targets angiogenesis, a process that promotes tumor growth by supplying nutrients and oxygen. In early phase trials, the combination of pembrolizumab and lenvatinib has been shown to provide robust antitumor activity, durable responses and manageable safety.

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Advances in understanding immune regulation and cancer immunobiology have led to the development of novel agents targeting various immune checkpoint molecules including CTLA-4 and the PD-1/PD-L1 axis [1]. In addition, a number of tyrosine kinase inhibitors (TKIs) have been developed over the last two decades that target multiple signaling pathways [2]. Collectively, these developments have transformed the standard of care for several advanced cancers [3]. However, innate and acquired resistance to monotherapy with immune checkpoint inhibitors and TKIs remains a challenge [2,4,5]. Consequently, there is much interest in the use of combination therapies to simultaneously target multiple signaling pathways to overcome the mechanisms of resistance. The LEAP clinical trial program is designed to evaluate the safety and efficacy of the combination of lenvatinib, a multi-TKI and pembrolizumab, a PD-1 inhibitor, for a broad range of solid cancers. This combination therapy targets multiple

tumor intrinsic molecular abnormalities (excessive VEGF and FGF signaling) as well as immune inhibitory signaling through PD-1 [6,7]. Early results from a study investigating lenvatinib and pembrolizumab in combination have shown improved efficacy and response durability in several advanced solid tumors [8]. The combination of lenvatinib and pembrolizumab may provide clinical benefit to a broad patient population across multiple tumor types.

Lenvatinib

Lenvatinib is an oral small-molecule inhibitor of VEGFRs, FGFRs, PDGFR α , KIT and RET proto-oncogene [7,9]. Several of these receptor tyrosine kinases (RTKs) are overexpressed in multiple cancers [10]. In a preclinical investigation, lenvatinib inhibited VEGF- and FGF-driven angiogenesis and demonstrated antitumor activity in human xenograft tumor models [11].

In addition to antiangiogenic and antiproliferative activity, lenvatinib has shown immunomodulatory properties in preclinical models. In a syngeneic mouse tumor model, lenvatinib increased tumor infiltration of CD8⁺ T cells expressing granzyme B and IFN- γ , plasmacytoid dendritic cells and decreased tumor-associated macrophages (TAMs) [12]. TAMs, derived from blood monocytes, influence tumor cell survival, proliferation and dissemination and produce a range of molecules that attenuate the antitumor immune response [13,14].

VEGF signaling modulates the tumor microenvironment and also plays an important role in regulating T-cell activation. VEGF signaling in T-cells results in increased expression of multiple inhibitory immune checkpoint molecules including PD-1, CTLA-4, TIM-3 and LAG-3 [15]. High tumor expression of VEGF is also correlated with increased intratumoral Tregs [16]. Inhibition of VEGF signaling has been shown to decrease the number of intratumoral Tregs in patients with advanced renal cell carcinoma as well as preclinical mouse models [16]. FGFR1 signaling promotes the survival and migration of TAMs into tumors [17]. Therefore, inhibition of VEGFR and FGFR1 signaling by lenvatinib may lead to TAM depletion and promote antitumor immunological responses.

Lenvatinib is administered orally as monotherapy for the treatment of radioactive iodine-refractory differentiated thyroid cancer and for the first-line treatment of unresectable hepatocellular carcinoma (HCC) [7,18]. Lenvatinib plus everolimus is approved as a second-line therapy for advanced renal cell carcinoma following one prior anti-angiogenic therapy. Table 1 summarizes the indications approved by the US FDA for lenvatinib in the USA [7].

Pembrolizumab

Immunotherapies exploit the ability of the immune system to identify and eradicate tumors. PD-1 is a negative regulator of T-cell immunity, found primarily on the surface of activated T-cells [19]. On binding to its ligands PD-L1 or PD-L2, PD-1 can inhibit effector T-cell responses contributing to evasion of the antitumor immune response [20,21].

Pembrolizumab is a potent, highly selective, fully humanized monoclonal immunoglobulin G4 κ , anti-PD-1 antibody (mAb) that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2 [6]. PD-1 inhibition by pembrolizumab counteracts the downregulation of the antitumor immune response mediated by the PD-1 pathway [6]. Pembrolizumab is administered by intravenous infusion and is currently indicated for a broad spectrum of solid and hematologic cancers (Table 1) [6,22].

Rationale for lenvatinib plus pembrolizumab

Combination immunotherapies that modulate different aspects of tumor immunobiology may help to overcome primary and acquired resistance to immunotherapy and may offer improved efficacy across a broad range of cancers [23]. The combination of lenvatinib and pembrolizumab is based on a strong mechanistic rationale. In syngeneic CT26 CRC and Hepa1-6 HCC murine tumor models, the combination of lenvatinib and an anti-PD-1 antibody produced greater reduction in tumor volume and a higher response rate than either agent alone, including complete regression of tumors in some animals [12,24]. The combination showed immunomodulatory properties: increased tumor infiltration of effector CD8⁺ T cells and decreased monocytes and macrophages [24].

The maximum tolerated dose, recommended Phase II dose and preliminary antitumor activity of lenvatinib plus pembrolizumab are being studied in patients with selected solid tumors in a Phase Ib/II, open-label, single-arm trial (study 111/KEYNOTE-146; NCT02501096). In the Phase Ib dose-finding portion of the study, toxicities were manageable and a maximum tolerated dose for the combination was identified; this dose was considered as the recommended Phase II dose [8]. Analysis of the expansion phase of the study demonstrated robust antitumor activity and durable response across six tumor types – urothelial cancer, head and neck squamous cell carcinoma

Table 1. Indications as of 18 November 2020 for lenvatinib and pembrolizumab and lenvatinib in combination with pembrolizumab as approved by the US FDA.

Tumor type	Monotherapy/combination	Details of indication [†]
Lenvatinib		
DTC	Monotherapy	Locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC
RCC	Combination with everolimus	Advanced RCC following one prior anti-angiogenic therapy
HCC	Monotherapy	First-line treatment of unresectable HCC
Pembrolizumab		
Melanoma	Monotherapy	Unresectable or metastatic melanoma
	Monotherapy	Adjuvant treatment of melanoma with involvement of lymph node(s) following complete resection
NSCLC	Combination with pemetrexed and platinum chemotherapy	First-line treatment of metastatic nonsquamous NSCLC with no <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations
	Combination with carboplatin and either paclitaxel or nab-paclitaxel	First-line treatment of metastatic squamous NSCLC
	Monotherapy	First-line treatment of NSCLC expressing PD-L1 (TPS $\geq 1\%$) as determined by an FDA-approved test, with no <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations and is: stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic
	Monotherapy	Metastatic NSCLC tumors expressing PD-L1 (TPS $\geq 1\%$) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab
SCLC	Monotherapy	Metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy [‡]
HNSCC	Combination with platinum and FU	First-line treatment of metastatic or unresectable, recurrent HNSCC
	Monotherapy	First-line treatment of metastatic or unresectable, recurrent HNSCC tumors expressing PD-L1 (CPS ≥ 1) as determined by an FDA-approved test
	Monotherapy	Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy
cHL	Monotherapy	Adult patients with relapsed or refractory cHL
	Monotherapy	Pediatric patients with refractory cHL or cHL that has relapsed after two or more lines of therapy
PMBCL	Monotherapy	Adult and pediatric patients with refractory PMBCL, or who have relapsed after two or more prior lines of therapy (not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy)
Urothelial carcinoma	Monotherapy	Locally advanced or metastatic urothelial carcinoma not eligible for cisplatin-containing chemotherapy and with tumors expressing PD-L1 (CPS ≥ 10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status [‡]
	Monotherapy	Locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
	Monotherapy	BCG-unresponsive, high risk, nonmuscle invasive bladder cancer with carcinoma <i>in situ</i> with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy
MSI-H cancers	Monotherapy	Adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR: – Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options [‡] – CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan [‡] The safety and effectiveness of pembrolizumab in pediatric patients with MSI-H CNS cancers is not yet established
MSI-H or dMMR CRC	Monotherapy	First-line treatment of unresectable or metastatic MSI-H or dMMR CRC
Gastric cancer	Monotherapy	Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with tumors expressing PD-L1 (CPS ≥ 1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy [‡]

[†]Details taken from [6,7].[‡]This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.[§]This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.[¶]This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

BCG: Bacillus Calmette–Guérin; cHL: Classical Hodgkin lymphoma; CNS: Central nervous system; CPS: Combined positive score; CRC: Colorectal cancer; cSCC: Cutaneous squamous cell carcinoma; dMMR: Mismatch repair-deficient; DTC: Differentiated thyroid cancer; FU: Fluorouracil; HCC: Hepatocellular carcinoma; HNSCC: Head and neck squamous cell carcinoma; MSI-H: Microsatellite instability high; NSCLC: Non-small-cell lung cancer; PMBCL: Primary mediastinal large B-cell lymphoma; RCC: Renal cell carcinoma; SCLC: Small cell lung cancer; TMB-H: Tumor mutational burden high; TNBC: Triple-negative breast cancer; TPS: Tumor proportion score.

Reproduced with permission from [6,7].

Table 1. Indications as of 18 November 2020 for lenvatinib and pembrolizumab and lenvatinib in combination with pembrolizumab as approved by the US FDA (cont.).

Tumor type	Monotherapy/combination	Details of indication [†]
Esophageal cancer	Monotherapy	Recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus with tumors expressing PD-L1 (CPS ≥ 10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy
Cervical cancer	Monotherapy	Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy with tumors expressing PD-L1 (CPS ≥ 1) as determined by an FDA-approved test [‡]
HCC	Monotherapy	HCC previously treated with sorafenib [‡]
Merkel cell carcinoma	Monotherapy	Adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma [‡]
RCC	Combination with axitinib	First-line treatment of advanced RCC
TMB-H cancer	Monotherapy	Adult and pediatric patients with unresectable or metastatic TMB-H (≥ 10 mutations/megabase) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options [‡] The safety and effectiveness of pembrolizumab in pediatric patients with TMB-H CNS cancers is not yet established
cSCC	Monotherapy	Recurrent or metastatic cSCC that is not curable by surgery or radiation [‡]
TNBC	Combination with chemotherapy	Locally recurrent unresectable or metastatic TNBC with tumors expressing PD-L1 (CPS ≥ 10) as determined by an FDA-approved test [§]
Adult indications	Monotherapy	Use at an additional dosing regimen of 400 mg every 6 weeks for all approved adult indications [¶]
Lenvatinib and pembrolizumab		
Endometrial cancer	Combination	Advanced endometrial cancer that is not MSI-H or dMMR with disease progression following prior systemic therapy and who are not candidates for curative surgery or radiation [‡]

[†]Details taken from [6,7].[‡]This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.[§]This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.[¶]This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

BCG: Bacillus Calmette–Guérin; cHL: Classical Hodgkin lymphoma; CNS: Central nervous system; CPS: Combined positive score; CRC: Colorectal cancer; cSCC: Cutaneous squamous cell carcinoma; dMMR: Mismatch repair-deficient; DTC: Differentiated thyroid cancer; FU: Fluorouracil; HCC: Hepatocellular carcinoma; HNSCC: Head and neck squamous cell carcinoma; MSI-H: Microsatellite instability high; NSCLC: Non-small-cell lung cancer; PMBCL: Primary mediastinal large B-cell lymphoma; RCC: Renal cell carcinoma; SCLC: Small cell lung cancer; TMB-H: Tumor mutational burden high; TNBC: Triple-negative breast cancer; TPS: Tumor proportion score.

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(HNSCC), melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma and endometrial cancer (Table 2). Objective response rates ranged from 25 to 55% and median progression-free survival ranged from 4.7 to 11.7 months depending on the tumor type (Figure 1A & B) [8,25,26]. Final results from the cohort of patients with metastatic endometrial cancer showed that the combination of lenvatinib plus pembrolizumab showed encouraging antitumor activity, irrespective of tumor microsatellite instability (MSI) high or mismatch repair deficient (dMMR) status, providing further support for efficacy of this combination [26]. Results from another Phase Ib study (study 116/KEYNOTE-524) demonstrated encouraging antitumor activity with lenvatinib plus pembrolizumab in 100 patients with previously untreated and unresectable HCC, with 11% of patients showing a complete response by independent imaging review per modified RECIST (Table 2) [27].

Based on the results of the study 111/KEYNOTE-146 trial, the combination of lenvatinib plus pembrolizumab was approved by the FDA, the Australian Therapeutic Goods Administration and Health Canada for the treatment of patients with advanced endometrial carcinoma that is not MSI high or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiotherapy [28].

Safety considerations

In some cases, treatment combinations can result in additive or synergistic toxicities and severe adverse events arising from overlapping or unexpected toxicities [23]. However, the tolerability of lenvatinib–pembrolizumab combination therapy appears to be consistent with the safety of each individual agent.

Lenvatinib

Adverse events with lenvatinib monotherapy are comparable to those reported for other VEGFR targeting TKIs [29]. In a meta-analysis of lenvatinib clinical trials, encompassing 978 patients, the most frequent grade ≥ 3 treatment-related adverse events (AEs) were thrombocytopenia (25.4%), hypertension (17.7%), peripheral edema (15.5%)

Table 2. Preliminary findings of Phase I/II trials of lenvatinib + pembrolizumab in advanced solid tumors (study 111/KEYNOTE-146; study 116/KEYNOTE-524).

Tumor type	n	Line of therapy	Data cut-off	ORR % (95% CI)	Median DOR, months (95% CI)	Median PFS, months (95% CI)	Grade 3–4 TRAEs, n (%)	Grade 5 TRAEs, n (%)	Ref.
Advanced UC	20	Any	1 March 2018	25 (8.7–49.1) [†]	NE (6.5–NE)	5.4 (1.3–NE)	10 (50)	1 (5) [‡]	[8]
Metastatic NSCLC	21	Any	1 March 2018	33 (14.6–57.0) [†]	10.9 (2.4–NE)	5.9 (2.3–13.8)	12 (57)	1 (5) [§]	[8]
Metastatic HNSCC	22	Any	1 March 2018	46 (24.4–67.8) [†]	8.2 (2.2–12.6)	4.7 (4.0–9.8)	16 (73)	0 (0)	[8]
Unresectable HCC	100 [¶]	First line	31 October 2019	46 (36.0–56.3) [#]	8.6 (6.9–NE)	9.3 (5.6–9.7)	64 (64)	3 (3) ^{††}	[27]
Advanced melanoma	21	Any	1 March 2018	48 (25.7–70.2) [†]	12.5 (2.7–NE)	5.5 (2.6–15.8)	14 (67)	0 (0)	[8]
Advanced EC	108	Any	10 January 2019	39 (29.7–48.7) [†]	21.2 (7.6–NE)	7.4 (5.3–8.7)	83 (66.9)	2 (2) ^{‡‡}	[26]
Metastatic RCC	104	Any	9 April 2020	55 (45.0–65.0) ^{§§}	12 (9.0–18.0)	11.7 (9.4–17.7)	NR ^{¶¶}	2 (2) ^{##}	[25]

[†] Proportion of patients with confirmed complete or partial response by independent review per immune-related RECIST.

[‡] Gastrointestinal hemorrhage.

[§] Pulmonary hemorrhage.

[¶] Of 104 enrolled patients, 100 were included in first-line analysis.

[#] Proportion of patients with complete or partial response by independent imaging review per modified RECIST.

^{††} One patient died due to acute respiratory failure/acute respiratory distress; one died due to abnormal hepatic function and one due to intestinal perforation.

^{‡‡} One patient died due to sepsis caused by an *Escherichia coli* infection and one patient died due to intracranial hemorrhage.

^{§§} Proportion of patients with confirmed complete or partial response by investigator assessment per immune-related RECIST.

^{¶¶} Grade 3 TRAEs (hypertension, 19%; diarrhea 9%; proteinuria, 8%; fatigue, 5%; nausea 2%; arthralgia 1%); grade 4 TRAEs (increased lipase, diverticulitis, large intestine perforation and myocardial infarction).

^{##} One patient died due to upper gastrointestinal hemorrhage and one had sudden death.

DOR: Duration of response; EC: Endometrial carcinoma; HCC: Hepatocellular carcinoma; HNSCC: Head and neck squamous cell carcinoma; NE: Not estimable; NR: Not reported; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; PFS: Progression-free survival; RCC: Renal cell carcinoma; RECIST: Response Evaluation Criteria in Solid Tumors; TRAE: Treatment-related adverse event; UC: Urothelial carcinoma.

and increased aspartate aminotransferase (12.6%) [29]. AEs with lenvatinib monotherapy generally occur early and resolve with dose modifications, supportive care and concomitant medications [30]. In the Phase III SELECT trial assessing lenvatinib in radioactive iodine-refractory differentiated thyroid cancer, the most frequent AE was hypertension (68%) [31] and 47% of patients experienced the first occurrence of hypertension within the first cycle of treatment (28 days) [32]. Other common AEs were diarrhea (67%), fatigue, asthenia, malaise (each, 67%), proteinuria (32%), rash (23%) and palmar-plantar erythrodysesthesia syndrome (33%), which had a median time to onset ranging from 3.0 to 12.1 weeks [30]; the median time to resolution of these AEs ranged from 5.9 to 20.0 weeks.

Patients with short dose interruptions (<10% of total treatment duration) in the Phase III SELECT trial had a greater magnitude of progression-free survival benefit compared with those with longer dose interruptions [33]. This finding highlights the importance of closely monitoring patients for AEs to lenvatinib and timely implementation of dose interruptions, reductions or both to obtain optimum lenvatinib treatment benefit.

Pembrolizumab

The most frequent AEs (of any grade) associated with pembrolizumab monotherapy across clinical studies in approximately 5000 patients with cancer include fatigue (34.1%), rash (22.7%), nausea (21.7%), diarrhea (21.5%) and pruritus (20.2%) [34]. The combination of lenvatinib and pembrolizumab has demonstrated a manageable safety profile. In the Phase Ib/II study 111/KEYNOTE-146 trial involving patients with advanced solid tumors – metastatic renal cell carcinoma, endometrial cancer, HNSCC, melanoma, NSCLC or urothelial cancer – treatment-related AEs (TRAEs) with the combination were reported by 97% of patients; the most common being fatigue (58%), diarrhea (52%), hypertension (47%), hypothyroidism (42%) and decreased appetite (39%) [8]. Grade 3–5 TRAEs occurred in 67% of patients; most commonly hypertension, fatigue, diarrhea, proteinuria and increased lipase levels [8]. TRAEs led to discontinuation (12–15% pembrolizumab; 12–15% lenvatinib) or interruption/dose reduction (45–70% pembrolizumab; 63–85% lenvatinib) [8,25,26]. Six treatment-related deaths have occurred in this study: one patient with urothelial cancer with gastrointestinal hemorrhage, one patient with NSCLC with a pulmonary hemorrhage, two patients with metastatic clear cell renal cell carcinoma (one with gastrointestinal hemorrhage and one had sudden death) and two patients with endometrial cancer (one with sepsis caused by *Escherichia coli* infection and one with intracranial hemorrhage) (Table 2) [8,25,26]. The combination was also

Figure 1. Summary of efficacy outcomes with lenvatinib and pembrolizumab. (A) Objective response rate[†] and **(B)** median progression-free survival[†] in patients with advanced solid tumors enrolled in Phase I/II trials of lenvatinib + pembrolizumab (study 111/keynote-146; study 116/KEYNOTE-524) [8,25–27].

[†]By independent review per irRECIST for UC, NSCLC, HNSCC, MEL and EC; by investigator assessment per irRECIST for RCC; by independent imaging review per modified RECIST for HCC.

EC: Endometrial cancer; HCC: Hepatocellular carcinoma; HNSCC: Head and neck squamous cell carcinoma; irRECIST: Immune-related Response Evaluation Criteria in Solid Tumors; MEL: Melanoma; NSCLC: Non-small-cell lung cancer; PFS: Progression-free survival; RCC: Renal cell carcinoma; UC: Urothelial carcinoma.

considered tolerable in the Phase Ib study 116/KEYNOTE-524 trial in patients with previously untreated and unresectable HCC [27]. Grade 3 and 4 TRAEs occurred in 63 and 1% of patients, respectively, with hypertension being the most commonly reported grade 3 TRAE (17%) [27]. Three patients in this study have died due to TRAEs; one due to acute respiratory failure/acute respiratory distress syndrome, one due to intestinal perforation and one due to abnormal hepatic function [27]. No new safety signals emerged in studies evaluating the combination of lenvatinib and pembrolizumab [8,26,27].

LEAP clinical development program

The promising results from study 111/KEYNOTE-146 [8,25,26] and study 116/KEYNOTE-524 [27] led to the development of the LEAP program, which is currently evaluating the safety and relative efficacy of lenvatinib plus pembrolizumab with or without chemotherapy in several tumor types. The LEAP program involves a broad spectrum of tumors in a variety of settings where new treatment options are needed (Table 3): advanced endometrial

Table 3. LEAP program.

Trial number, Trial ID	Tumor type	Patient population	Treatment	Line of therapy	Primary end point(s)	Phase/n	Estimated study completion date	Notes on design
LEAP-001, NCT03884101	Endometrial carcinoma	Stage III, IV or recurrent endometrial carcinoma (prior radiation/chemoradiation/hormonal therapy permitted)	Arm 1: lenvatinib + pembrolizumab Arm 2: paclitaxel + carboplatin	1L	PFS OS	III/720	10 April 2023	- Active comparator - Randomized - International 31-months PFS/45-months OS - Imaging: Q9W; >54 weeks FU Q12W
LEAP-002, NCT03713593	HCC	Previously untreated advanced HCC, BCLC stage C disease or stage B disease refractory to locoregional therapy and not amenable to curative approach and Child-Pugh class A liver score	Arm 1: lenvatinib + pembrolizumab Arm 2: lenvatinib + placebo	1L	PFS OS	III/750	13 May 2022	- Active controlled - Randomized - International 44-months PFS/44-months OS - Imaging: Q9W
LEAP-003, NCT03820986	Melanoma	Previously untreated advanced (stage III/IV) melanoma	Arm 1: lenvatinib + pembrolizumab Arm 2: pembrolizumab + placebo	1L	PFS OS	III/660	6 April 2024	- Placebo controlled - Randomized - International 24-months PFS/24-months OS - Imaging: Q9W; >54 to <102 weeks FU Q12W; >102 weeks FU Q24W
LEAP-004, NCT03776136	Melanoma	Advanced (stage III/IV) melanoma that progressed following anti-PD-1/PD-L1 monoclonal antibody treatment as monotherapy or combination therapy	Arm 1: lenvatinib + pembrolizumab	≥2L	ORR	II/100	15 June 2021	- Single-arm - Open-label - International 36-months ORR - Imaging: Q9W; >54 to <102 weeks FU Q12W; >102 weeks FU Q24W
LEAP-005, NCT03797326	TNBC, ovarian cancer, gastric cancer, CRC, GBM, biliary tract cancer [†]	Select advanced solid tumors that progressed on or since last treatment	Arm 1: lenvatinib + pembrolizumab	≥2L	ORR (initial) ORR (expansion) AEs Discont due to AE	II/600	24 February 2024	- Single-arm - Open-label - International 60-months ORR by investigator/60-months ORR by BICR/60-months AEs/60-months discontinuation due to AEs - Imaging: Q9W; >54 to <102 weeks FU Q12W; >102 weeks FU Q24W
LEAP-006, NCT03829319	Non-squamous NSCLC	Previously untreated metastatic nonsquamous NSCLC	Arm 1: pemetrexed + platinum chemotherapy + pembrolizumab + lenvatinib Arm 2: pemetrexed + platinum chemotherapy + pembrolizumab + placebo	1L	Part 1: DLTs, AEs, discont. due to AEs Part 2: PFS, OS	III/726	21 June 2024	- Placebo controlled - Randomized - International - Part 1: 3-wk DLTs/27-months AEs - Part 2: 24-months PFS/60-months OS - Imaging: Q6W; >18 to <54 weeks FU Q9W; >54 weeks FU Q12W
LEAP-007, NCT03829332	NSCLC	Previously untreated, advanced (Stage IV), PD-L1 positive (TPS ≥1%) NSCLC	Arm 1: lenvatinib + pembrolizumab Arm 2: pembrolizumab + placebo	1L	PFS OS	III/620	8 March 2024	- Active controlled - Randomized - International 24-months PFS/60-months OS - Imaging: Q9W; >54 weeks FU Q12W

[†] Patients with additional malignancy such as basal cell carcinoma of skin, squamous cell carcinoma of the skin or *in situ* cervical cancer or *in situ* breast cancer that has undergone potentially curative therapy were allowed.

[‡] Investigator's choice of paclitaxel, docetaxel, cetuximab or capecitabine.

1L: First line; 2L: Second line; ≥2L: Second line or greater; AE: Adverse event; BCLC: Barcelona Clinic Liver Cancer; BICR: Blinded independent central review; CPS: Combined positive score; CRC: Colorectal cancer; discont: Discontinued; DLT: Dose-limiting toxicity; FU: Follow-up; GBM: Glioblastoma multiforme; HCC: Hepatocellular carcinoma; HNSCC: Head and neck squamous cell carcinoma; mo: Month; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PD: Progressive disease; PD-1: Programmed death 1; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; Q6W: Every 6 weeks; Q9W: Every 9 weeks; Q12W: Every 12 weeks; Q24 weeks: Every 24 weeks; RECIST 1.1: Response Evaluation Criteria in Solid Tumors, version 1.1; TACE: Transarterial chemoembolization; TNBC: Triple-negative breast cancer; yr: Year; TPS: Tumor proportion score; Wk: Week.

Table 3. LEAP program (cont.).

Trial number, Trial ID	Tumor type	Patient population	Treatment	Line of therapy	Primary end point(s)	Phase/n	Estimated study completion date	Notes on design
LEAP-008, NCT03976375	NSCLC	Metastatic NSCLC that progressed during/after platinum doublet chemotherapy or on treatment with anti-PD-1/PD-L1 monoclonal antibody as monotherapy or combination therapy	Arm 1: lenvatinib + pembrolizumab Arm 2: docetaxel Arm 3: lenvatinib	≥2L	PFS OS	III/405	23 February 2026	- Active comparators - Randomized - Open-label - International 48-months OS/36-months PFS - Imaging: Q6W; >36 to <54 weeks FU Q9W; >54 weeks FU Q12W
LEAP-009, NCT04428151	HNSCC	Recurrent/metastatic HNSCC of the oral cavity, oropharynx, hypopharynx and/or larynx that progressed during/after platinum chemotherapy with/without cetuximab and progressed during/after anti-PD-1/PD-L1 monotherapy or combination therapy	Arm 1: lenvatinib + pembrolizumab Arm 2: SOC chemotherapy [†] Arm 3: lenvatinib	≥2L	ORR	II/400	18 August 2024	- Active comparators - Open-label - Randomized - International 48-months ORR - Imaging: Q6W; >52 weeks FU Q9W
LEAP-010, NCT04199104	HNSCC	Recurrent/metastatic HSNCC of the oral cavity, oropharynx, hypopharynx, or larynx with PD-L1 CPS ≥1	Arm 1: lenvatinib + pembrolizumab Arm 2: pembrolizumab + placebo	1L	ORR PFS OS	III/500	13 April 2024	- Placebo controlled - Randomized - International 24-months ORR/30-months PFS/44-months OS - Imaging: Q6W; >48 weeks FU Q9W
LEAP-011, NCT03898180	Urothelial carcinoma	Previously untreated, advanced/unresectable or metastatic urothelial carcinoma that is ineligible for platinum-containing chemotherapy or cisplatin-ineligible with PD-L1 CPS ≥10	Arm 1: lenvatinib + pembrolizumab Arm 2: pembrolizumab + placebo	1L	PFS OS	III/694	30 December 2022	- Active controlled - Randomized - International 40-months PFS/40-months OS - Imaging: Q6W; >24 to <60 weeks FU Q9W; >60 weeks FU Q12W
LEAP-012, NCT04246177	HCC	Incurable, nonmetastatic, previously untreated HCC localized to the liver with Child–Pugh class A liver score	Arm 1: lenvatinib + pembrolizumab + TACE Arm 2: placebo + TACE	1L	PFS OS	III/950	31 December 2029	- Active controlled - Randomized - International 60-months PFS/60-months OS - Imaging: Q9W

[†]Patients with additional malignancy such as basal cell carcinoma of skin, squamous cell carcinoma of the skin or *in situ* cervical cancer or *in situ* breast cancer that has undergone potentially curative therapy were allowed.

[‡]Investigator's choice of paclitaxel, docetaxel, cetuximab or capecitabine.

1L: First line; 2L: Second line; ≥2L: Second line or greater; AE: Adverse event; BCLC: Barcelona Clinic Liver Cancer; BICR: Blinded independent central review; CPS: Combined positive score; CRC: Colorectal cancer; discont: Discontinued; DLT: Dose-limiting toxicity; FU: Follow-up; GBM: Glioblastoma multiforme; HCC: Hepatocellular carcinoma; HNSCC: Head and neck squamous cell carcinoma; mo: Month; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PD: Progressive disease; PD-1: Programmed death 1; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; Q6W: Every 6 weeks; Q9W: Every 9 weeks; Q12W: Every 12 weeks; Q24 weeks: Every 24 weeks; RECIST 1.1: Response Evaluation Criteria in Solid Tumors, version 1.1; TACE: Transarterial chemoembolization; TNBC: Triple-negative breast cancer; yr: Year; TPS: Tumor proportion score; Wk: Week.

cancer (first line); advanced HCC (first line); advanced melanoma (first line and ≥ second line); relapsed or refractory triple-negative breast cancer, advanced ovarian cancer, advanced gastric cancer, recurrent colorectal cancer, glioblastoma multiforme, biliary tract cancer (all ≥ second line); NSCLC (first and ≥ second line); HNSCC (first line and ≥ second line), urothelial cancer (first line); and HCC (Barcelona Liver Clinic Cancer stage C or stage B refractory to locoregional therapy) (first line). The LEAP program includes nine Phase III studies (LEAP-001, LEAP-002, LEAP-003, LEAP-006, LEAP-007, LEAP-008, LEAP-010, LEAP-011 and LEAP-012), each with planned enrollment between 405 and 950 patients; as well as three Phase II studies (LEAP-004, LEAP-005 and LEAP-009) (Table 3).

Conclusion

Based on the promising results from study 111/KEYNOTE-146 and Study 116/KEYNOTE-524, the combination of lenvatinib plus pembrolizumab or triple therapy with lenvatinib plus pembrolizumab plus chemotherapy is

anticipated to provide superior antitumor activity in the selected tumor types compared with either agent alone or standard of care. Interim results from study 111/KEYNOTE-146 has resulted in the combination of pembrolizumab plus lenvatinib being approved in the USA, Australia and Canada for the treatment of advanced endometrial carcinoma that is not MSI-H or dMMR, for patients who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiotherapy. In tumor types where lenvatinib or pembrolizumab is already approved as monotherapy, the combination may result in improved efficacy.

The safety profiles of lenvatinib and pembrolizumab are well established as monotherapies. The safety of the combination is consistent with the safety of each individual agent and there have been no new safety signals. Therefore, the combination of lenvatinib and pembrolizumab is expected to be tolerable in the LEAP program. As such, we anticipate that combination therapy with lenvatinib plus pembrolizumab will be an important potential new treatment regimen for several solid cancers where therapeutic options are currently limited.

Executive summary

- The development of immunotherapies and targeted agents has significantly improved outcomes in a number of cancers; however, innate and acquired resistance to these therapies remains a challenge.
- One strategy being investigated to overcome resistance is to use combination therapy, allowing multiple signaling pathways to be targeted simultaneously.
- The LEAP clinical trial program is designed to investigate the efficacy and safety of lenvatinib in combination with pembrolizumab in a range of solid tumors.

Lenvatinib

- Lenvatinib is a multitargeted kinase inhibitor that has activity against a number of angiogenic kinases, including VEGF and FGF receptors. Lenvatinib also has antiproliferative and immunomodulatory properties.
- Lenvatinib is approved by the US FDA for the treatment of radioactive iodine-refractory differentiated thyroid cancer, for first-line treatment of unresectable hepatocellular carcinoma, in combination with everolimus for second-line treatment of advanced renal cell carcinoma and in combination with pembrolizumab for second-line treatment of endometrial carcinoma that is not microsatellite instability high or mismatch repair deficient.

Pembrolizumab

- Pembrolizumab is an anti-PD-1 antibody that counteracts downregulation of the antitumor immune response mediated by the PD-1 pathway.
- Pembrolizumab is approved by the FDA for the treatment of a range of solid and hematologic malignancies.

Rationale for lenvatinib & pembrolizumab combination therapy

- In preclinical investigation, lenvatinib plus pembrolizumab produced greater reductions in tumor volume and higher response rates than either agent alone and had immunomodulatory properties that may enhance antitumor immune response.
- Preliminary results from ongoing Phase Ib/II studies investigating lenvatinib plus pembrolizumab have reported manageable toxicity, robust antitumor activity and durable responses across seven tumor types, with no new safety signals.

LEAP clinical trial program

- The promising results from the Phase Ib/II studies investigating lenvatinib plus pembrolizumab led to development of the LEAP clinical trial program.
- The LEAP program includes nine Phase III studies and three Phase II studies investigating lenvatinib plus pembrolizumab with or without chemotherapy in a range of solid tumor types including: endometrial cancer, hepatocellular carcinoma, melanoma, triple-negative breast cancer, ovarian cancer, gastric cancer, colorectal cancer, glioblastoma multiforme, biliary tract cancer, non-small cell lung cancer, head and neck squamous cell carcinoma and urothelial cancer.

Conclusion

- Based on promising preliminary results from several ongoing trials, it is expected that lenvatinib plus pembrolizumab or triple therapy with lenvatinib plus pembrolizumab and chemotherapy may potentially be important new regimens for several solid cancers that currently have limited therapeutic options.

Author contributions

Conception, design or planning of the study was performed by C Ductus, Y Funahashi, E Schmidt and M. Taylor. Acquisition of the data was performed by C Ductus, D Rasco, E Schmidt and M Taylor. Analysis of the data was performed by C Ductus, E Schmidt and M Taylor. Interpretation of the results was performed by C Ductus, G Lubiniecki, E Pinheiro, D Rasco, E Schmidt and M Taylor. Drafting of the manuscript was performed by Y Funahashi, E Schmidt and M Taylor. Critically reviewing or revising the manuscript

for important intellectual content was performed by C Ductus, G Lubiniecki, E Pinheiro, D Rasco, E Schmidt and M Taylor. All the authors reviewed the final version and agreed with the content and the decision to submit.

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