TPS743

Trials in progress: TAM kinase inhibitor PF-07265807 and sasanlimab plus axitinib in patients with advanced or metastatic renal cell carcinoma: a phase 1, open-label, pharmacokinetic, safety and tolerability study

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Objective

- This first-in-human study will assess the safety, tolerability, PK, and preliminary activity of PF-07265807 (ARRY-067) as monotherapy and in combination with sasanlimab with or without axitinib in participants with selected advanced or metastatic solid tumors.

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Background

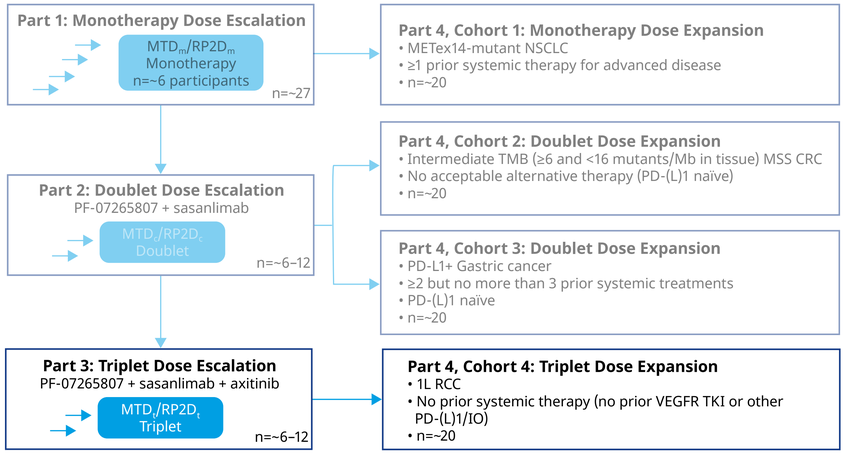
- AXL receptor tyrosine kinase (AXL) and Mer proto-oncogene tyrosine kinase (MERTK) are members of the tumor-associated macrophage kinases (TAMK) family and regulate key aspects of immune homeostasis and response to infection.
- TAMKs are expressed on dendritic cells and macrophages. TAMKs can also be expressed on tumor cells in the context of malignant transformation.[1]
- Inhibition of AXL and MERTK may lower the immune activation threshold and promote antitumor immunity.[2]
- PF-07265807, also known as ARRY-067, is a selective small-molecule inhibitor of MERTK and AXL showing potent activity against AXL and MERTK phosphorylation in vivo.[3]
- PF-07265807 demonstrated broad, potent immune-related antitumor activity in nonclinical immune-competent syngeneic models as monotherapy or in combination with anti-programmed cell death protein 1 (anti-PD-1) antibodies.[3]
  - PF-07265807 showed robust T cell–dependent antitumor immunity in multiple syngeneic tumor models.[3]
  - Tumor-bearing mice with complete responses upon treatment with PF-07265807 were resistant to subsequent rechallenge with the same syngeneic tumor, demonstrating AXL/MERTK inhibition led to the generation of long-term antitumor memory T cells.[3]
  - In the RENCA renal cell carcinoma (RCC) model, compared with a duplet therapy with vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors plus therapy targeting PD-1 or programmed death ligand PD-L1, a triplet therapy with added PF-07265807 showed survival benefits (data on file).
- Sasanlimab is a monoclonal antibody to PD-1 administered SC (300 mg every 4 weeks or equivalent) that has an acceptable safety profile[4,5] and is currently being evaluated in a phase 3 trial in non-muscle invasive bladder cancer (NCT04165317).
- Axitinib is a VEGFR inhibitor approved as a single agent and combined with anti-PD-(L)1 inhibitors to treat advanced RCC.
- This first-in-human, phase 1, open-label, multicenter study will evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of PF07265807 in patients with advanced or metastatic solid tumors as a single agent and in combination with sasanlimab with or without axitinib.
- The design of the PF-07265807 monotherapy dose escalation part (Part 1) of this study was presented at ASCO 2021 (TPS2671).[6] The designs of the doublet combination of PF-07265807 plus sasanlimab dose escalation (Part 2) and dose expansion (Part 4) parts of this study were presented at ASCO GI 2023.[7]
- We describe here the design of the dose escalation (Part 3) and dose expansion (Part 4) parts of this study for the triplet combination of PF-07265807 plus sasanlimab and axitinib.

Materials and Methods

STUDY DESIGN AND ELIGIBILITY CRITERIA

- This is a phase 1, open-label, multicenter, multiple-dose, dose-escalation, safety, PK, biomarker, and preliminary efficacy study (NCT04458259) of PF-07265807 in cohorts of adult participants with selected advanced or metastatic solid tumors.
- ~45–55 investigator sites will participate in this study globally.
- Participants will be enrolled into Part 1 monotherapy dose escalation, Part 2 doublet dose escalation with sasanlimab, Part 3 triplet dose escalation with sasanlimab plus axitinib, and Part 4 dose expansion cohorts (**Figure 1**).
- After dose-finding, safety, and PK data are obtained with single-agent PF-07265807 in Part 1, in combination with sasanlimab in Part 2, and in combination with sasanlimab plus axitinib in Part 3, the utility of PF-07265807 will be explored as monotherapy and in each combination in Part 4 (dose expansion).
  - The expansion cohorts in Part 4 may start independently of each other (eg, Part 4, Cohort 1 may start after Part 1 is completed; and Part 4, Cohorts 2 and 3 may start after Part 2 is completed) (**Figure 1**).

Figure 1: Triplet dose escalation and dose expansion for PF-07265807 and sasanlimab plus axitinib



1L=first-line treatment; CRC=colorectal cancer; IO=immunotherapy; METex14=splicing alteration resulting in skipping of the MET oncoprotein exon 14; MSS=microsatellite stable; MTD_m=maximum tolerated dose of PF-07265807 plus sasanlimab; MTD_m=maximum tolerated dose of PF-07265807 monotherapy; MTD_t=maximum tolerated dose of triplet therapy PF-07265807, sasanlimab, and axitinib; NSCLC=non–small-cell lung cancer; PD-1=programmed cell death protein 1; PD-L1=programmed cell death-ligand 1; PD-(L)1=programmed cell death protein 1 or programmed cell death-ligand 1; $RP2D_t$=recommended phase 2 dose of PF-07265807 plus sasanlimab; $RP2D_m$=recommended phase 2 dose of PF-07265807 monotherapy; $RP2D_t$=recommended phase 2 dose of triplet therapy PF-07265807, sasanlimab, and axitinib; RCC=renal cell carcinoma; TKI=tyrosine kinase inhibitor; TMB=tumor mutational burden; VEGFR=vascular endothelial growth factor

Table 1: Key eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Male or female patients aged ≥18 years	• Known active uncontrolled or symptomatic CNS metastases
• Participants with histologically or cytologically confirmed unresectable locally advanced or metastatic RCC with a clear cell component (Parts 3 and 4)	• Major surgery within 6 weeks or radiation therapy (except for palliative therapy) within 4 weeks before study entry
• Progressed following prior treatment and no satisfactory alternative treatment option is available (Part 3)	• Systemic anticancer therapy within 2 weeks or 5 half-lives (4 weeks or 5 half-lives for antibody therapies or investigational drugs taken on another study) before study entry
• Other tumor types may be allowed with prior approval by sponsor (only Part 3)	• Prior irradiation to >25% of bone marrow
• Intermediate and poor-risk RCC and no prior systemic therapy for metastatic disease (Part 4)	• Active or history of autoimmune disease requiring >10 mg/day prednisone or other concurrent immunosuppressive therapy
• Estimated creatinine clearance ≥30 mL/min and urinary protein <2+ or ≥2+ but 24-h urine protein:creatinine ratio <2 g/24 h	• Active, uncontrolled infection (controlled hepatitis B virus, hepatitis C virus, HIV/AIDS may be allowed) as defined in study protocol
• By RECIST v1.1, ≥1 measurable (Part 4) or non-measurable lesion(s) (Part 3) that has not been previously irradiated	• For Part 3, uncontrolled hypertension (BP >150/90 mmHg) despite optimal medical therapy; for Part 4, evidence of uncontrolled hypertension (BP >140/90 mmHg) as documented by 2 baseline BP readings taken ≥1 h apart (use of antihypertensive medications to control BP is allowed)
• ECOG performance status 0–2	• Inability to consume or absorb study drug
• Adequate bone marrow, renal, and liver function	• Known or suspected hypersensitivity to PF-07265807
• Resolved acute effects of any prior therapy	• Prohibited concomitant medications, as defined in the study protocol

BP=blood pressure; CNS=central nervous system; RCC=renal cell carcinoma

- For the triplet combination of PF-07265807 plus sasanlimab and axitinib (Part 3 dose escalation and Part 4 dose expansion), eligible participants are adults with:
  - Confirmed unresectable advanced or metastatic clear cell RCC.
    - Other tumor types may be allowed with prior sponsor's approval (only Part 3).
  - Estimated creatinine clearance ≥30 mL/min.
  - Urinary protein <2+ or ≥2+ but 24-h urine protein:creatinine ratio <2 g/24 h.
- Patients for Part 4 are required to have intermediate and poor-risk RCC and no prior systemic therapy for metastatic disease.
- Other key eligibility criteria are summarized in **Table 1.**
- Each cycle will be 21 days in duration. Initially, PF-07265807 will be administered once a day orally on a 14 days on/7 days off schedule.
  - In Part 3, the starting dose of PF-07265807 in combination with sasanlimab plus axitinib will not be higher than the maximum tolerated dose (MTD)/ recommended phase 2 dose (RP2D) for the combination of PF-07265807 and sasanlimab determined in Part 2.
  - The dose of sasanlimab will be 225 mg SC on Day 1 of each 21-day cycle. The provisional starting dose of axitinib will be the approved dose of 5 mg orally twice daily.
- Treatment with study drug will continue until disease progression, consent withdrawal, or unacceptable toxicity, whichever occurs first.
- The study began in late September 2020 and is currently recruiting patients. Informed consent will be obtained from all patients before enrollment.

ENDPOINTS AND ASSESSMENTS

- Primary endpoints of Part 3 will include the incidence of dose-limiting toxicities (DLTs) within first cycle; adverse event (AE) type, frequency, severity, timing, seriousness, and relationship to study therapy; and laboratory abnormalities.
- Secondary endpoints of Part 3 will include PK parameters for PF-07265807 and its metabolite AR00501994, the incidence and titer of anti-sasanlimab anti-drug antibody (ADA) response, objective response rate (ORR), disease control rate (DCR), and time-to-event endpoints, eg, duration of response (DoR).
- Primary endpoints of Part 4 will include ORR and complete response rate.
- Secondary endpoints of Part 4 will include DCR, time-to-event endpoints (eg, DoR and progression-free survival), AEs, laboratory abnormalities, PK parameters for PF-07265807 and its metabolite AR00501994 at selected time points, concentrations of sasanlimab and axitinib at selected time points, and incidence and titer of anti-sasanlimab ADA response.
- Exploratory endpoints of Part 3 and Part 4 will include changes in select biomarkers in blood (eg, soluble receptors, circulating tumor DNA, select immune cell populations) and tumor (eg, select immune cell populations), and correlation with efficacy outcomes of select biomarkers of tumor tissue (eg, PD-L1 protein expression, tumor mutational burden).
- Safety and tumor response will be assessed at specified time points.
  - AEs will be graded by the NCI CTCAE v5.0.
  - Tumor response will be assessed using RECIST v1.1.

TRIPLET DOSE ESCALATION AND STATISTICAL ANALYSIS

- ~6–12 participants will be enrolled in the triplet dose escalation part (Part 3), and ~20 participants with first-line RCC will be enrolled into the triplet dose expansion part (Part 4).
- There will be no formal hypothesis tested in this study.
- Triplet dose escalation will be guided by a Bayesian analysis of DLT data for PF-07265807 as triplet therapy with sasanlimab plus axitinib (Part 3) using the escalation with overdose control principle.[8]
  - A 10-parameter Bayesian logistic regression model will be used to model the toxicity relationship of PF-07265807 when given in combination with sasanlimab plus axitinib.
- The RP2D will then be determined via holistic data review with or without the MTD identification.
- The primary endpoint for dose expansion (Part 4) is ORR, which will be assessed using the response evaluable set and is defined as the percentage of participants with a best overall response of complete or partial response.
- Descriptive statistics will be provided for continuous endpoints. The rates of binary endpoints will be provided with the corresponding 2-sided exact 95% CIs.
- Time-to-event endpoints will be summarized using the Kaplan–Meier method. Median event times and 2-sided 95% CIs for each time-to-event endpoint will be provided.