1071TIP

Phase 1 Study of the Investigational CD228 x 4-1BB Costimulatory Antibody-Anticalin Bispecific SGN-BB228 (PF-08046049) in Advanced Melanoma and Other Solid Tumors

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Objective

- To evaluate the safety, tolerability, PK, and preliminary antitumor activity of PF-08046049/SGN-BB228 in patients with select advanced solid tumors.

Conclusions

- PF-08046049/SGN-BB228 is an investigational costimulatory antibody Anticalin® bispecific molecule directed to CD228 and 4-1BB.
- Enrollment of this study (NCT05571839) is ongoing in the USA, Canada, and Europe.

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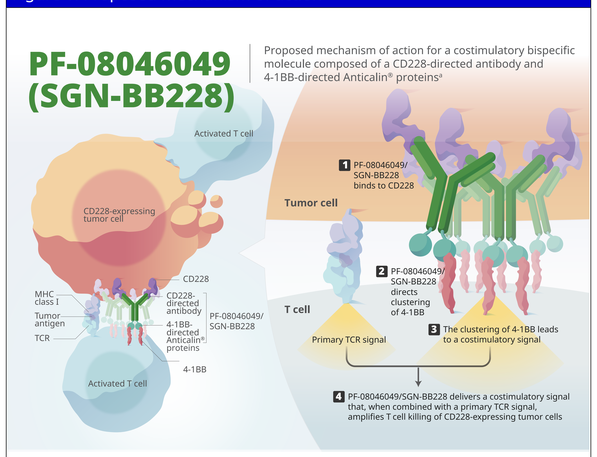
Background

- CD228 is a tumor antigen selectively expressed by multiple tumor types including melanoma, mesothelioma, and pancreatic, colorectal, breast, and lung cancers.[1]
- 4-1BB is an inducible costimulatory receptor expressed on activated T cells and other immune cell populations. Costimulation of 4-1BB has become a promising strategy for developing cancer immunotherapies.[2,3]
- Clinical development of 4-1BB agonists faces challenges achieving specificity and therapeutic effects without off-target activity or poor tolerability.[2,3]
- PF-08046049/SGN-BB228 is a CD228 directed, 4-1BB costimulatory bispecific designed to improve and localize T cell-mediated cytotoxicity in tumors.
- This agent is being investigated in a phase 1, open-label, multicenter study (NCT05571839)[4] in adult patients with metastatic or unresectable melanoma or other advanced solid tumors.

PROPOSED MECHANISM OF ACTION

- PF-08046049/SGN-BB228 is an investigational costimulatory bispecific molecule composed of a CD228-directed fully humanized antibody and 4-1BB-directed Anticalin® proteins designed to conditionally bridge tumor-reactive cytotoxic T cells and CD228-expressing tumor cells.
  - The 4-1BB component is designed to provide enhanced T cell activation, and the CD228 component is designed to provide a tumor-directed approach (**Figure 1**).
- In preclinical studies, PF-08046049/SGN-BB228 showed potent conditional 4-1BB stimulation and cytotoxic T cell activation, which was dependent on binding CD228, and a favorable safety profile.
  - 4-1BB costimulation enhances antitumor T cell activity by a mechanism distinct from but complementary to the blocking of inhibitory receptors.[5]

Figure 1: Proposed mechanism of action



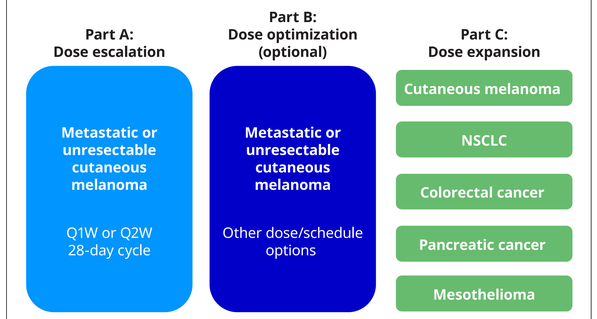
[a]PF-08046049/SGN-BB228 is an investigational agent, and its safety and efficacy have not been established. Other trademarks are property of their respective owner. CD=cluster of differentiation; MHC=major histocompatibility complex; TCR=T cell receptor

Methods

OVERALL STUDY DESIGN

- This study has dose-escalation, dose-optimization (optional), and dose-expansion parts (**Figure 2**).
  - The dose-expansion part will include multiple disease-specific cohorts.
    - Potential combination dosing cohorts may be enrolled in the future.
  - Up to approximately 275 patients may be enrolled.

Figure 2: Study schema



Part C will further characterize safety, tolerability, PK, and antitumor activity of PF-08046049/SGN-BB228 in disease-specific cohorts with potential for future combination dosing. Patients may continue on treatment until confirmed progressive disease per iRECIST, unacceptable toxicity, withdrawal of consent, initiation of subsequent therapy, or study termination, whichever occurs first.
NSCLC=non-small cell lung cancer; PK=pharmacokinetic; Q1W=once every week; Q2W=once every 2 weeks

OBJECTIVES AND ENDPOINTS

- This study aims to evaluate the safety, tolerability, pharmacokinetic (PK), and antitumor activity of PF-08046049/SGN-BB228 in adult patients with advanced melanoma and other solid tumors (**Table 1**).

Table 1: Objectives and endpoints

Primary Objectives	Primary Endpoints
• To evaluate the safety and tolerability of PF-08046049/ SGN-BB228	• Type, incidence, severity, seriousness, and relatedness of AEs and type, incidence, and severity of laboratory abnormalities
• To identify the MTD of PF-08046049/ SGN-BB228	• Incidence of DLTs
• To identify a recommended dose and schedule for PF-08046049/ SGN-BB228	• Incidence of DLTs and cumulative safety by dose level
Secondary Objectives	**Secondary Endpoints**
• To assess the immunogenicity of PF-08046049/SGN-BB228	• Incidence of ADAs
• To assess the PK of PF-08046049/ SGN-BB228	• Estimates of PK parameters including AUC, C_{max}, T_{max}, apparent terminal $t_{1/2}$, and C_{trough}. Additional analytes may be evaluated, as necessary
• To assess the antitumor activity of PF-08046049/SGN-BB228	• ORR (per RECIST v1.1), DOR, PFS, and OS

ADA=antidrug antibody; AE=adverse event; AUC=area under the curve; C_{max}=maximum serum concentration; C_{trough}=trough concentration; DLT=dose-limiting toxicity; DOR=duration of response; MTD=maximum tolerated dose; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; $t_{1/2}$=half-life; T_{max}=time to maximum serum concentration

ELIGIBILITY

KEY INCLUSION CRITERIA

- Adults aged ≥18 years with histologically or cytologically confirmed metastatic or unresectable advanced cutaneous melanoma (Parts A, B, C) or histologically or cytologically confirmed metastatic non-small cell lung cancer (NSCLC), colorectal cancer, pancreatic cancer, or mesothelioma (Part C only).
  - For Part A, consented patients may be enrolled to a biology backfill cohort with pre-treatment and on-treatment biopsies required.
  - For patients with cutaneous melanoma (Parts A, B, C):
    - Prior treatment with an anti-PD-1 or anti-PD-L1 agent is required.
    - Patients with a targetable *BRAF* mutation must have been treated with, intolerant of, or deemed ineligible to receive treatment with BRAF/MEK targeted therapy prior to study entry.
- Disease that is relapsed, refractory, or intolerant to standard-of-care therapies and no other therapeutic options known to provide clinical benefit, per investigator assessment.
- Eastern Cooperative Oncology Group performance status score of 0 or 1.
- Adequate organ function.

KEY EXCLUSION CRITERIA

- Acral, uveal, or mucosal melanoma.
- History of another malignancy within 3 years before the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy.
- Known active central nervous system metastases or leptomeningeal disease.
  - Patients with previously treated brain metastases may participate if they have been clinically stable for at least 4 weeks prior to study entry after brain metastasis treatment, have no new or enlarging brain metastases, and are off corticosteroids prescribed for a minimum of 7 days prior to the first dose of the study drug.
- Prior treatment with CD228 or 4-1BB-targeted drugs.
- Immunotherapy, biologics, and/or other approved or investigational antitumor treatment that is not completed 4 weeks prior to the first dose of study drug or within 2 weeks prior to the first dose of study drug if the underlying disease has progressed on treatment.

ASSESSMENTS

- Safety assessments include recording of adverse events, concomitant medications, physical examination findings, and laboratory tests, presented as descriptive statistics.
- Maximum tolerated dose and/or recommended dose of PF-08046049/ SGN-BB228 will be identified through the modified Toxicity Probability Interval design.[6]
- Response will be assessed by radiographic tumor evaluation at screening and every 6 weeks and at end of treatment, through progressive disease or initiation of subsequent therapy.
- Antitumor activity will be determined by objective response rate as defined by RECIST v1.1 and iRECIST.
  - Treatment decisions by the investigator will be based on iRECIST.
- Duration of response, progression-free survival, and overall survival will be estimated using the Kaplan–Meier method.
- Blood samples for PK and antidrug antibody analyses will be collected at protocol-defined time points for PK and immunogenicity assessments.
- Safety and antitumor activity will be summarized.