Category

Best Startup

Product/Solution Name

PRO1184 (rinatabart sesutecan, Rina-S)

Date of Approval

N/A

Indications

Not Applicable

Therapeutic Categories

Oncology; gynecologic oncology; breast cancer; lung cancer

Background information and need for solution/product

Epithelial ovarian cancer (EOC), including epithelial ovarian, fallopian tube, or primary peritoneal cancer, remains a highly lethal disease, despite the recent integration of PARP inhibitors and bevacizumab into its treatment armamentarium. Outcomes for patients with platinum resistant ovarian cancer (PROC) remain particularly poor, with low response rates to further chemotherapy (15-20%) and progression-free survival of only 3-4 months.1 Further, subsequent lines of systemic therapy are often associated with cumulative toxicities and limited tolerability for patients. Development of novel therapy with limited systemic toxicity for PROC is thus high unmet need.

Folate receptor alpha (FRa) is an attractive target for solid tumors owing to its overexpression in many tumor types, highly restricted expression in normal tissues, and inherent capacity to internalize large molecules.2 Mirvetuximab soravtansine (MIRV), a FRa-directed antibody-drug conjugate (ADC), recently received accelerated approval from FDA in patients with PROC,3 offering clinical proof-of-concept for FRa-directed cancer therapy. On the other hand, MIRV is built upon the first-generation ADC linker-drug platform (Sulfo-SPDB-DM4) that is associated with modest bystander effect (possibly due to its slow payload release), high susceptibility to efflux pumps, and a narrow therapeutic index.4,5 As a result, MIRV is only indicated in FRa-high patients which is a minor fraction (<35%) of the PROC population while carrying significant toxicity burden in ocular and other side effects.3,6,7 Novel ADC therapy that can broadly benefit the PROC patients with an improved therapeutic window is urgently needed.

History of the development of the solution/product

Historical studies in the ADC field have illustrated that the physiochemical properties of an ADC are key design attributes critically impacting on its stability and Pharmacokinetics (PK)/ pharmacodynamics (PD). Typically, ADCs with better hydrophilicity are less prone to aggregation and have lower systemic clearance hence greater anti-tumor activities and a larger therapeutic index. Yet lipophilic payloads are needed in order to mediate bystander effect in solid tumors. To resolve this conundrum and drawing on its deep expertise in ADC, ProfoundBio developed a suite of proprietary

and protease-cleavable hydrophilic linkers that offer effective masking on the highly lipophilic payloads. These novel linker-drugs (LDs) when conjugated to tool antibodies exhibited excellent physicochemical properties, PK/PD, anti-tumor activity, as well as tolerability, in preclinical models.8

Further proof-of-platform is provided via studies on PRO1102, a trastuzumab conjugate of LD038. LD038 is composed of ProfoundBio's novel hydrophilic linker and exatecan, a clinically validated payload that is not susceptible to efflux pumps, is highly membrane permeable thus conferring strong bystander effect, and is broadly active in many tumor types.9 In preclinical models, PRO1102 demonstrated superior efficacy compared to trastuzumab conjugates with contemporary or industry-leading LDs such as vedotin, emtansine, and deruxtecan with progressively larger margins in the HER2-low models. In a head-to-head comparison of LD038 vs. deruxtecan using a tool mAb in a cynomolgus monkey tolerability study, LD038 exhibited a more favorable toxicity profile compared to deruxtecan, suggesting an improved therapeutic index of the ProfoundBio platform compared to the deruxtecan platform.10,11

PRO1184 (rinatabart sesutecan, Rina-S) is a novel FRa-directed ADC that consists of a proprietary human anti-FRa IgG1 in conjugate with LD038. Rina-S demonstrated robust PK/PD and plasma stability in preclinical models. Rina-S produced superior anti-tumor activity compared to the MIRV analog in a broad range of cell-derived xenograft (CDX) and patient-derived xenograft (PDX) models that encompass diverse tumor types, histologies, and target expression levels. Specifically, Rina-S elicted profound tumor growth inhibition in all nine ovarian PDX models tested and was markedly more potent than the MIRV analog in FRa-low models. Rina-S was well-tolerated in the GLP toxicity study in monkeys at the HNSTD of 30 mg/kg with the principal toxicity (myelosuppression) being payload-driven. Of note, there were no histopathological findings in lung, suggesting Rina-S may be associated with lower risk of interstitial lung diseases (ILD) compared to the deruxtecan-based ADCs in the clinic.11,12 Rina-S is thus a very promising development candidate with best-in-class potential. A first in human phase 1/2 study of Rina-S in patients with advanced solid tumors (ovarian, endometrial, lung, breast cancer and beyond)13 is ongoing (NCT05579366); preliminary results demonstrate a promising clinical profile, with anti-tumor activity observed at tolerable dose levels.14

Attached Files:

- Abstract4021_Liu_Novel ADC Platform_poster.pdf
- Abstract5720_Wang_PRO1102_poster.pdf
- Abstract4320_Zhao_PRO1184_poster.pdf
- Abstract2637_Chen_PRO1184_poster_FINAL.pdf

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

Rina-S is a highly promising development candidate for ovarian cancer and multiple additional tumor types that are underserved. Its potent anti-tumor effect along with a well-tolerated and manageable toxicity profile also points to the potential of a cornerstone therapy in diverse combination settings and treatment lines. ProfoundBio is developing multiple novel ADCs that may address the unmet need in broad solid tumor indications, and the superior hydrophilic linker technology has enabled first-in-class or best-in-class potential for many promising tumor targets. Besides Rina-S, several other ProfoundBio ADC programs are either in first in human clinical study (PRO116014,15, a CD70-directed ADC [NCT05721222]) or in IND-enabling preclinical development (www.profoundbio.com). Effort and results from ProfoundBio's transformative research represent new directions and a major step forward toward

developing the next-generation ADCs that carry further improved physiochemical properties and expanded therapeutic index in the clinic.

Attached Files:

- Abstract4344_Wang_PRO1160_poster.pdf

Please provide appropriate references (ie Pubmed links)

1. Calo CA, et al., Expert Opin Biol Ther. 2021 Jul;21(7):875-887. https://pubmed.ncbi.nlm.nih.gov/32463296/
2. Scaranti M, et al., Nat Rev Clin Oncol. 2020 Jun;17(6):349-359. https://pubmed.ncbi.nlm.nih.gov/32152484/
3. Mirvetuximab soravtansine USPI. https://www.elahere.com/pdf/prescribing-information.pdf
4. Erickson HK, et al., Bioconjug Chem. 2010 Jan;21(1):84-92. https://pubmed.ncbi.nlm.nih.gov/19891424/
5. Tang R, et al., BMC Cancer. 2009 Jun 23;9:199. https://pubmed.ncbi.nlm.nih.gov/19549303/
6. Matulonis UA, et al., J Clin Oncol. 2023 Jan 30;JCO2201900. https://pubmed.ncbi.nlm.nih.gov/36716407/
7. Moore KN, et al., ESMO 2019 Congress. https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress/forward-i-gog-3011-a-phase-iii-study-of-mirvetuximab-soravtansine-a-folate-receptor-alpha-fra-targeting-antibody-drug-conjugate-adc-versus
8. Liu H, et al., Cancer Res (2022) 82 (12_Supplement): 1405. https://aacrjournals.org/cancerres/article/82/12_Supplement/1405/702987
9. Rowinsky EK., (2005). Book Chapter (Preclinical and Clinical Development of Exatecan (DX-951f)). https://link.springer.com/chapter/10.1385/1-59259-866-8:317
10. Wang L, et al., Cancer Res (2022) 82 (12_Supplement): 1758. https://aacrjournals.org/cancerres/article/82/12_Supplement/1758/701550/Abstract-1758-The-preclinical-pharmacology-of
11. Zhao B, et al., Cancer Res (2022) 82 (12_Supplement): 1085. https://aacrjournals.org/cancerres/article/82/12_Supplement/1085/701084
12. Wang L, et al., Cancer Res (2023) 83 (7_Supplement): 2637. https://aacrjournals.org/cancerres/article/83/7_Supplement/2637/720826
13. Call JA, et al., ASCO 2023. https://meetings.asco.org/abstracts-presentations/226614
14. https://en.prnasia.com/releases/global/profoundbio-announces-further-advancement-of-lead-programs-pro1184-rinatabart-sesutecan-and-pro1160-in-the-clinic-405542.shtml (Press Release, accessed on May 26, 2023)
15. Wang L, et al., Cancer Res (2022) 82 (12_Supplement): 1759. https://aacrjournals.org/cancerres/article/82/12_Supplement/1759/701549