A Phase 1/2a Dose Escalation and Expansion Study of 23ME-01473, an anti-ULBP6/2/5 Antibody, for Patients With Advanced Solid Malignancies

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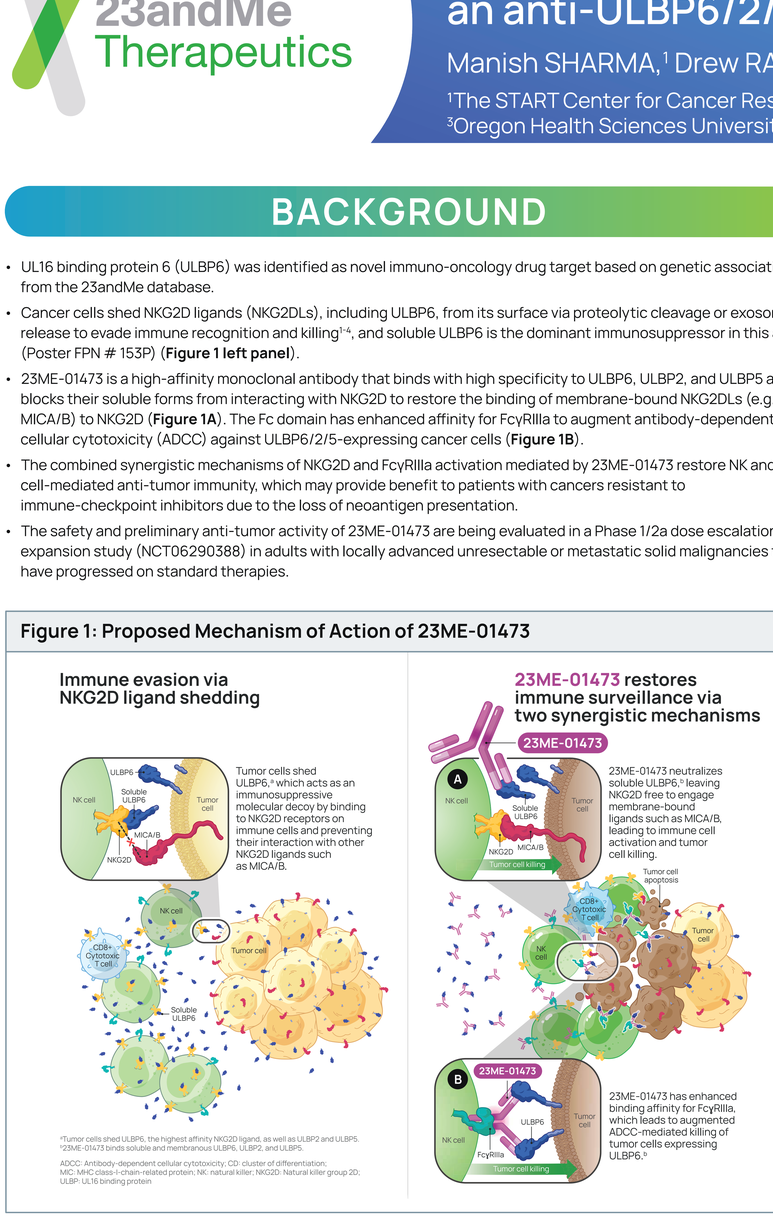
BACKGROUND

- UL16 binding protein 6 (ULBP6) was identified as novel immuno-oncology drug target based on genetic associations from the 23andMe database.
- Cancer cells shed NKG2D ligands (NKG2DLs), including ULBP6, from its surface via proteolytic cleavage or exosomal release to evade immune recognition and killing[1-4], and soluble ULBP6 is the dominant immunosuppressor in this axis (Poster FPN # 153P) (**Figure 1 left panel**).
- 23ME-01473 is a high-affinity monoclonal antibody that binds with high specificity to ULBP6, ULBP2, and ULBP5 and blocks their soluble forms from interacting with NKG2D to restore the binding of membrane-bound NKG2DLs (e.g. MICA/B) to NKG2D (**Figure 1A**). The Fc domain has enhanced affinity for FcγRIIIa to augment antibody-dependent cellular cytotoxicity (ADCC) against ULBP6/2/5-expressing cancer cells (**Figure 1B**).
- The combined synergistic mechanisms of NKG2D and FcγRIIIa activation mediated by 23ME-01473 restore NK and T cell-mediated anti-tumor immunity, which may provide benefit to patients with cancers resistant to immune-checkpoint inhibitors due to the loss of neoantigen presentation.
- The safety and preliminary anti-tumor activity of 23ME-01473 are being evaluated in a Phase 1/2a dose escalation and expansion study (NCT06290388) in adults with locally advanced unresectable or metastatic solid malignancies that have progressed on standard therapies.

Figure 1: Proposed Mechanism of Action of 23ME-01473



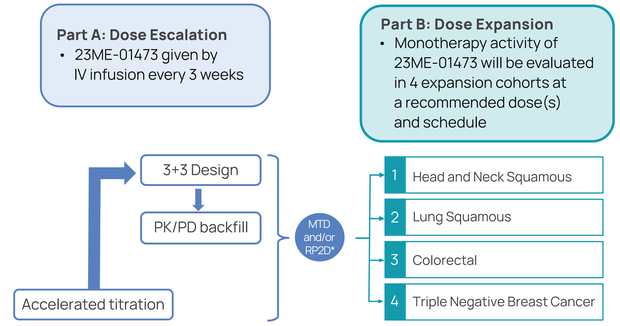
[a]Tumor cells shed ULBP6, the highest affinity NKG2D ligand, as well as ULBP2 and ULBP5.
[b]23ME-01473 binds soluble and membranous ULBP6, ULBP2, and ULBP5.

ADCC: Antibody-dependent cellular cytotoxicity; CD: cluster of differentiation; MIC: MHC class-I-chain-related protein; NK: natural killer; NKG2D: Natural killer group 2D; ULBP: UL16 binding protein

METHODS

Figure 2. 23ME-01473 Monotherapy Study Design in Patients With Advanced Solid Malignancies

Phase 1/2a dose escalation and expansion study evaluating 23ME-01473 in adults with locally advanced unresectable or metastatic solid malignancies who have progressed on standard therapies.



*Maximum Tolerated Dose; Recommended Phase 2 Dose

Key Inclusion Criteria

- Histologically-diagnosed locally advanced (unresectable), or metastatic carcinoma or sarcoma that has progressed after standard therapy
- Adults ≥ 18 years of age (Cohort 3 in expansion will allow adolescents ≥12 years of age)
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- For dose escalation, participants with evaluable disease are eligible regardless of tumor type, and RECIST v1.1 can be used to assess disease progression; for expansion cohorts, participants are required to have RECIST v1.1 measurable disease

Key Exclusion Criteria

- Immune-Related Medical History
  - Active autoimmune disease that has required systemic disease-modifying or immunosuppressive treatment within the last 2 years
  - Receipt of systemic immunosuppressive therapy (e.g. steroids) within 4 weeks prior to the start of study drug administration
  - History of idiopathic pulmonary fibrosis, interstitial lung disease, organizing pneumonia, non-infectious pneumonia that required steroids, or evidence of active, non-infectious pneumonitis
  - History of Grade ≥ 3 immune-mediated toxicity
- Prior allogeneic or autologous bone marrow transplant, or other solid organ transplant
- History of a positive test for:
  - Hepatitis C virus (HCV) infection[a]
  - Hepatitis B virus (HBV) infection[b]
  - Human Immunodeficiency Virus (HIV) infection[c]
- Prior anticancer therapy, including chemotherapy, targeted therapy, biological therapy or immune-checkpoint inhibitors within 4 weeks or 5 drug half-lives (whichever is shorter)
- History of another malignancy in the previous 2 years, unless cured by surgery alone and continuously disease free.
- Uncontrolled or symptomatic CNS metastases and/or carcinomatous meningitis

[a]Except for those who have completed curative therapy for HCV and have undetectable HCV RNA;
[b]Except for those who are receiving treatment with HBV-active nucleos(t)ide antiviral therapy at the time of study entry and have undetectable HBV DNA;
[c]Except those who meet the following criteria: CD4+ T cells ≥ 350 cells/μL, no history of Acquired Immunodeficiency Syndrome (AIDS)-defining opportunistic infections, HIV RNA < 50 copies/mL, and on a stable antiretroviral regimen for at least 3 months.

Primary Outcome Measures

Part A: Incidence and severity of dose-limiting toxicities, adverse events, and serious adverse events
Part B: Objective response rate based on investigator assessment against RECIST v1.1 criteria

Secondary Outcome Measures

Part A: Pharmacokinetic parameters, and prevalence and incidence of antidrug antibodies (ADA) to 23ME-01473
Part B: Objective response rate, duration of response, disease control rate, and progression-free survival

Exploratory Outcome Measures

Parts A and B:
- Objective response rate, duration of response, disease control rate, and progression-free survival against iRECIST
- Potential correlates of clinical activity of 23ME-01473
- Pharmacodynamic effects of 23ME-01473 in blood

Expansion Cohorts Prioritized Based Upon High ULBP6 Expression

Table 1: ULBP6/2/5 high tumors display MHC I pathway alterations and ICI sensitivity

	HNSCC	LUSC	CRC	TNBC
RAET1L (ULBP6) mRNA	+++	+++	+++	++
ULBP2/5 mRNA	+++	+++	+	++
Plasma sULBP6/2/5	+	+	++	TBD
MICA/B mRNA	++	++	+	+
KLRK1 (NKG2D) mRNA	++	+++	+	+++
ICI sensitivity[5]	++	++	+	++
MHC I alterations[6]	++	++	++	+

Data are categorized to overall range terciles (+/++/+++) based on the median expression or levels per tumor types using TCGA data from cBioPortal (n=19 tumor types evaluated). MSD assay (n=12), or reported metadata (n=14-28).

HNSCC

Advanced/metastatic HNSCC that has progressed following anti-PD-(L)1-based regimen and a platinum-based regimen. A minimum of 16 patients enrolled in this cohort will be HPV-positive based upon locally assessed HPV status using ACP guidelines

SqNSCLC

Advanced/metastatic, squamous non-small cell lung cancer that has progressed following anti-PD-(L)1-based regimen and a platinum-based regimen

CRC

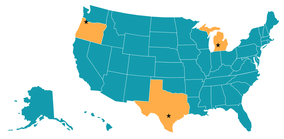
Advanced/metastatic colorectal cancer that has progressed following 5-fluororuacil based regimen, anti-vascular endothelial growth factor (VEGF) receptor antagonist (e.g. bevacizumab, regorafenib), and targeted therapy that are considered standard of care for participants with molecular alterations

TNBC

Advanced/metastatic triple breast cancer (TNBC) that has progressed following at least one systemic therapy in the metastatic setting, and targeted therapies that are considered standard of care

Current Status

Currently recruiting at the following sites: START Midwest in Grand Rapids, Michigan; Oregon Health and Science University in Portland, Oregon; START Center for Cancer Care in San Antonio, Texas.



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