



# 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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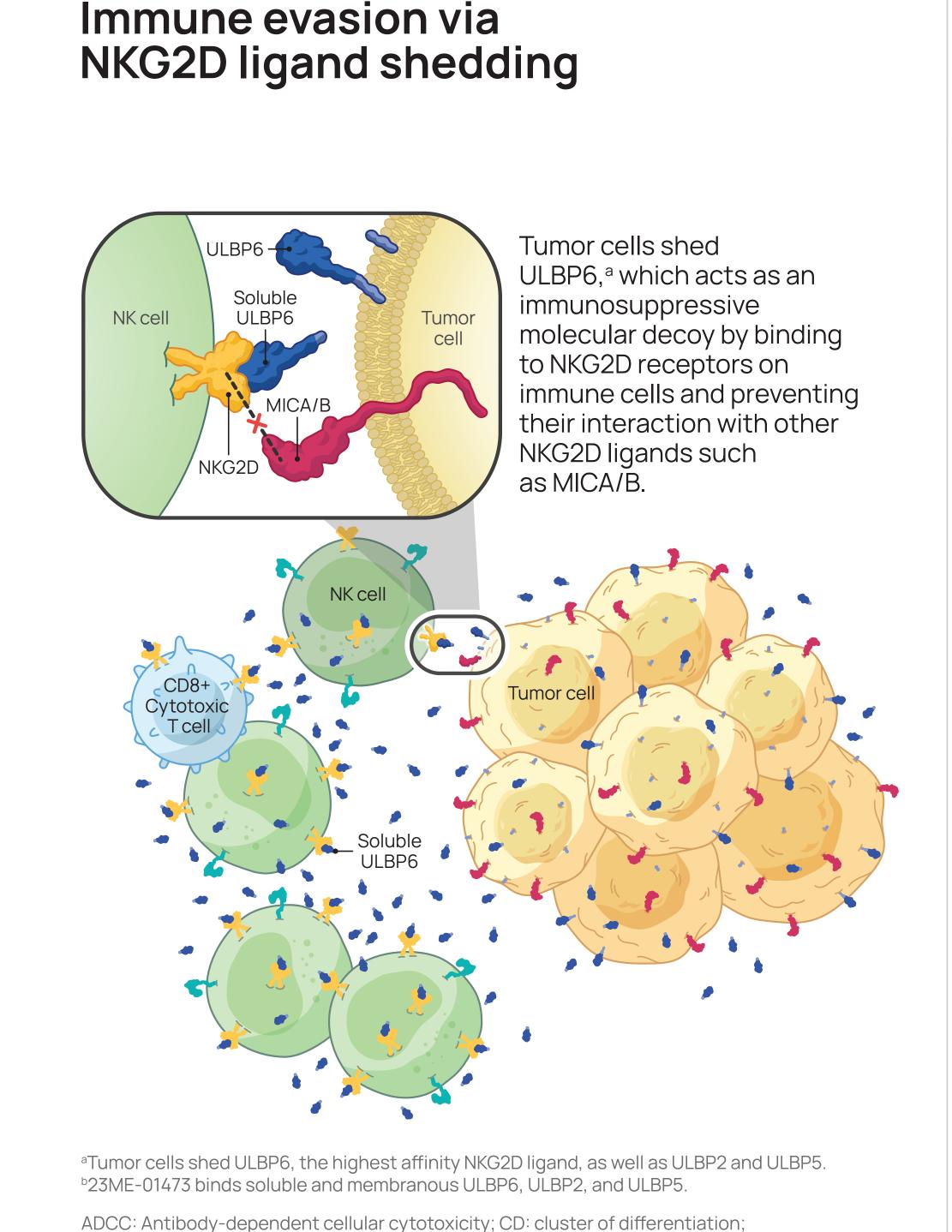


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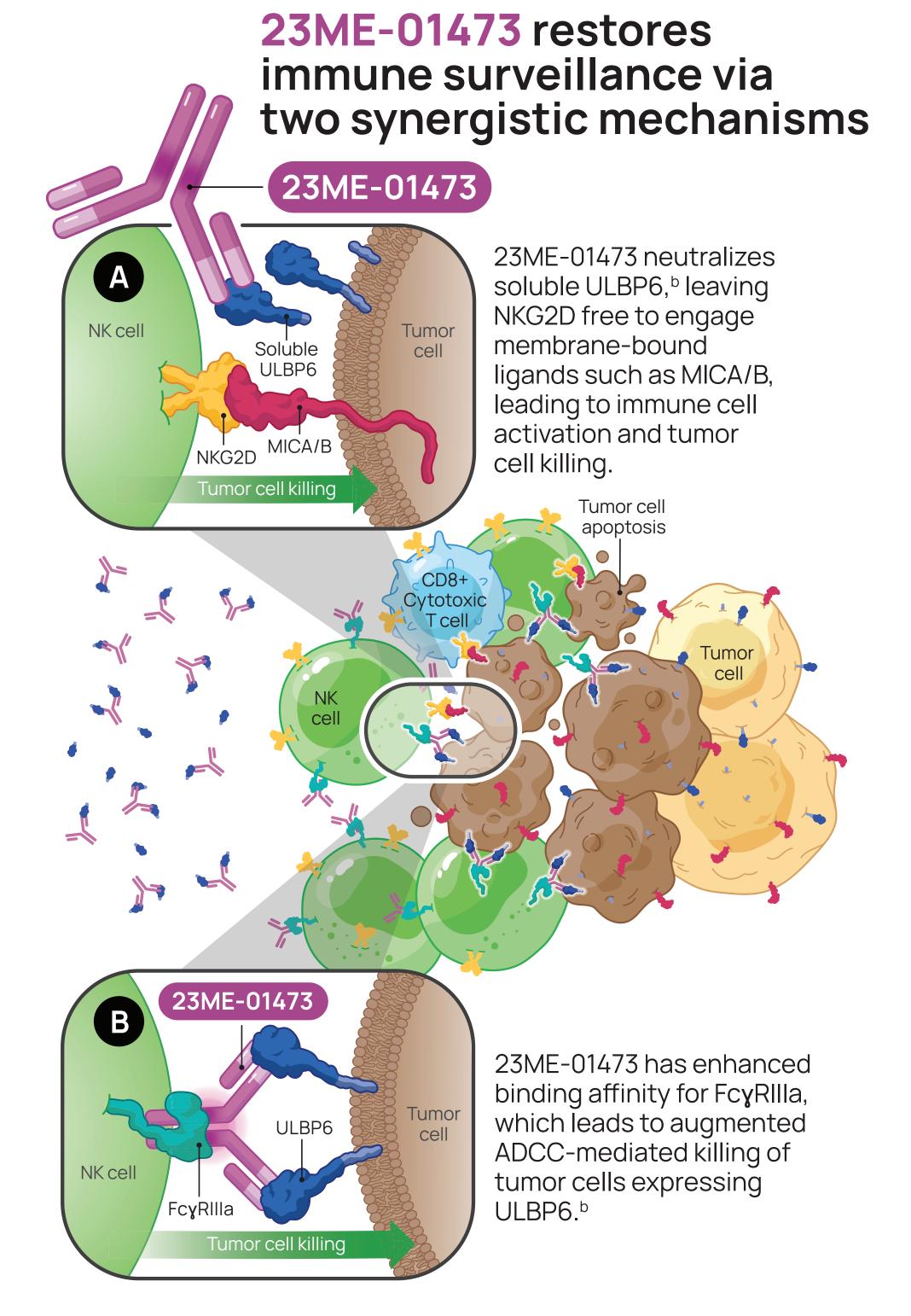
### BACKGROUND

- 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<sup>1-4</sup>, 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



MIC: MHC class-I-chain-related protein; NK: natural killer; NKG2D: Natural killer group 2D;



#### REFERENCES

1. Jinushi M, et al. J Hepatol. 2005;43(6):1013-20. 2. Groh V, et al. Nature. 2002;419(6908):734-8. 3. Song H, et al. Cell Immunol. 2006;239(1):22-30. 4. Zhang Y, et al. Oncol Lett. 2023;26(1):297. 5. Yarchoan M, et al. JCI Insight. 2019;4(6):e126908. 6. Dhatchinamoorthy K, et al. Front Immunol. 2021;12:636568.

Study sponsored by 23andMe, Inc.

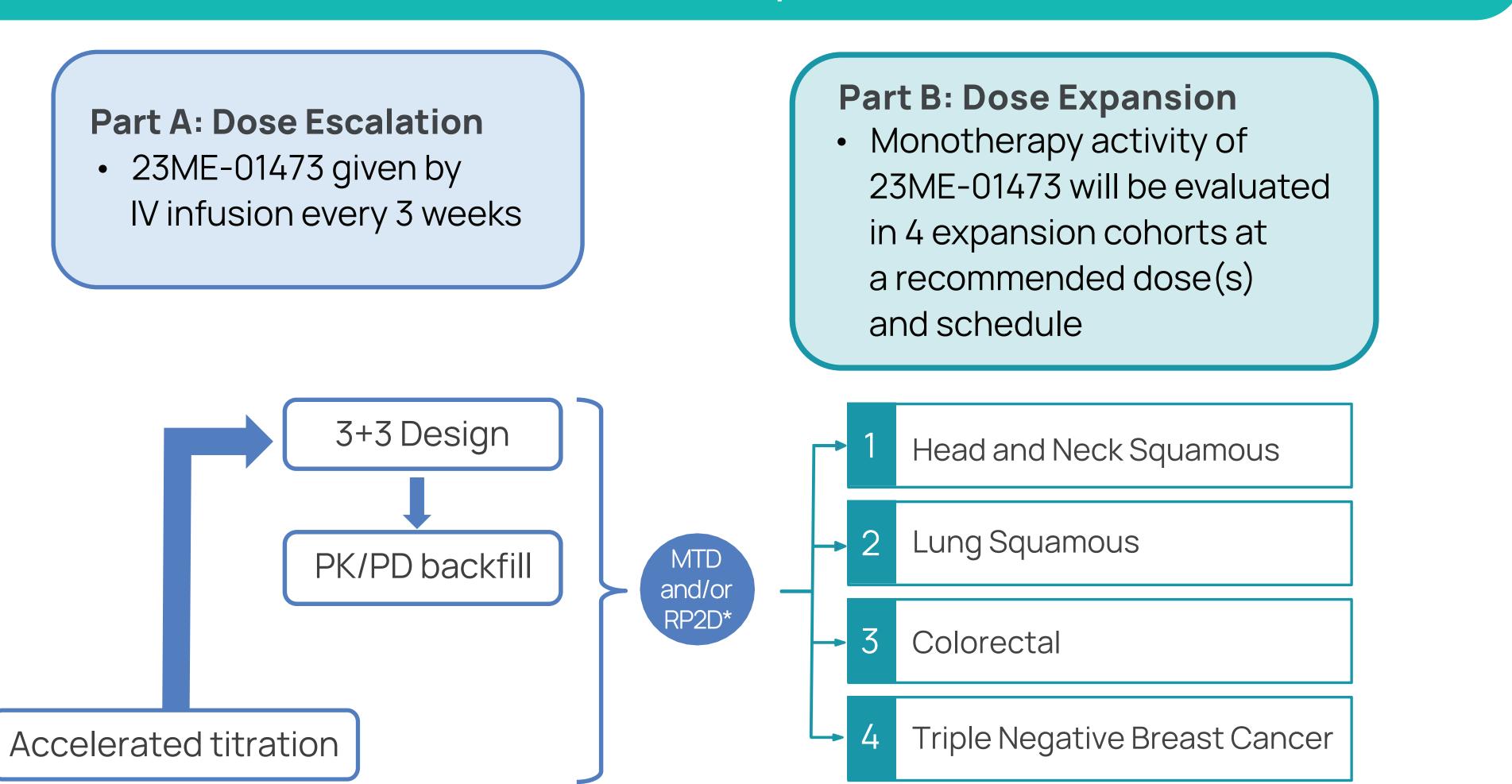
ULBP: UL16 binding protein

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## 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<sup>a</sup>
- Hepatitis B virus (HBV) infection<sup>b</sup>
- Human Immunodeficiency Virus (HIV) infection<sup>c</sup>
- 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

#### 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 <sup>5</sup>	++	++	+	++
MHC I alterations <sup>6</sup>	++	++	++	+

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

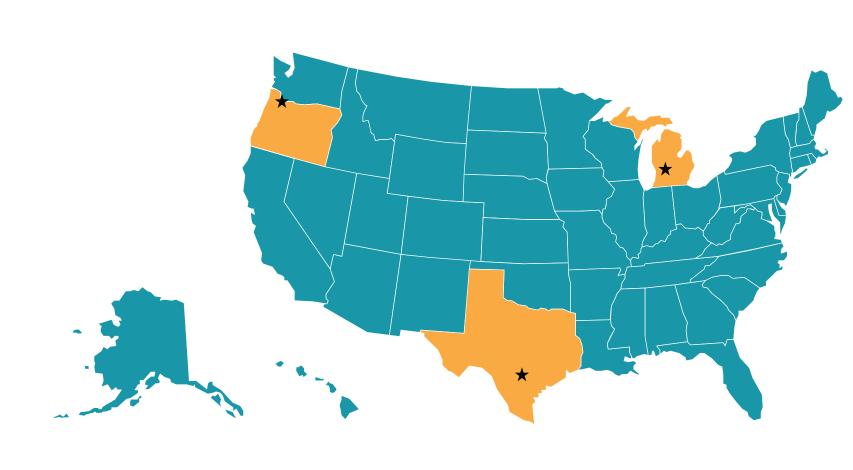
Advanced/metastatic colorectal cancer that has progressed following 5-fluororuacil based regimen, anti-vascular endothelial growth factor (VEGF) receptor antagonist (e.g. bevacizumab, regorafenib), and targeted therapy that are considered standard of care for participants with molecular alterations

#### 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.



<sup>a</sup>Except for those who have completed curative therapy for HCV and have undetectable HCV RNA; <sup>b</sup>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; 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.