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BASECAMP-1 is an efficient pre-screening study that identifies patients with HLA LOH and provides mutational, RNA-Seq, and microbiome data for precision logic-gated CAR T therapeutic trials

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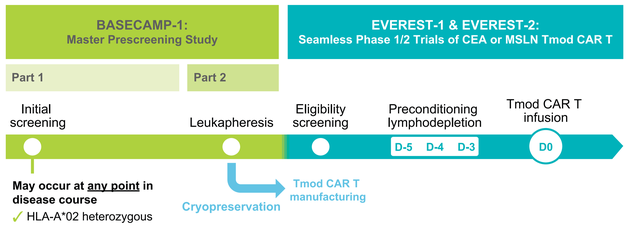
STUDY RATIONALE AND DESIGN

- Precision medicine studies must overcome the operational burden of prescreening patients, limited participant diversity due to racial or ethnic differences in target expression, and small cohort sizes for correlative studies
- BASECAMP-1 (NCT04981119) is an ongoing, master prescreening study (**Figure 1**) that uses a single next-generation sequencing (NGS) assay (Tempus AI Inc) to address these problems by:
  - Efficiently screening for tumor-associated human leukocyte antigen (HLA)-A*02 loss of heterozygosity (LOH) for subsequent trials of Tmod™ logic-gated chimeric antigen receptor T-cell (CAR T) therapy [1,2] (eg, EVEREST-1 [NCT05736731], EVEREST-2 [NCT06051695] [3,4])
  - Optimizing enrollment criteria to improve diversity
  - Providing a large dataset available for translational studies to augment statistical power of discovery analyses

Figure 1: BASECAMP-1 Study Schema



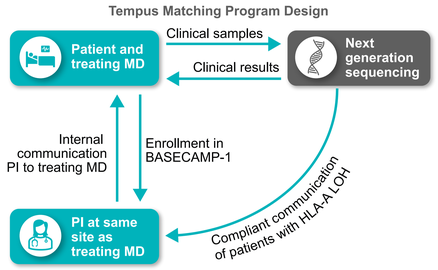
CAR T, chimeric antigen receptor T cell; CEA, carcinoembryonic antigen 5; D, day; HLA, human leukocyte antigen; LOH, loss of heterozygosity; MSLN, mesothelin.

- Key inclusion criteria for BASECAMP-1 include adults with germline HLA-A*02 heterozygosity and unresectable advanced or metastatic solid tumors and tumor-associated HLA-A*02 LOH
- Participants in BASECAMP-1 undergo leukapheresis so their CAR T treatment can be prepared without delay when they begin the interventional clinical trials

EFFICIENTLY IDENTIFYING PARTICIPANTS FOR BASECAMP-1 USING A CLINICAL NGS WORKFLOW

- Initially, we identified participants for BASECAMP-1 by having investigators screen all potentially eligible patients for HLA haplotypes; then HLA-A*02:01 heterozygous patients were screened for HLA-A*02 LOH using NGS
- We later worked with our partner Tempus to identify patients with tumors that had HLA-A*02 LOH identified during routine clinical diagnostics. With the patient-matching program, when a patient with HLA-A*02 LOH is identified at a BASECAMP-1 study site, Tempus communicates with the site investigators that one of their patients might be eligible for BASECAMP-1 (**Figure 2**)

Figure 2: Tempus Patient-Matching Program Identifies Eligible Patients for BASECAMP-1

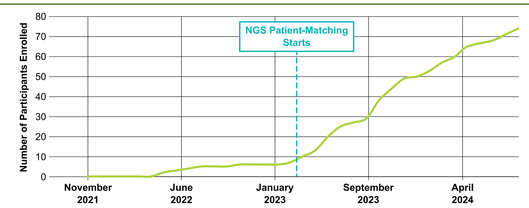


HLA, human leukocyte antigen; LOH, loss of heterozygosity; PI, principal investigator.

EFFICIENTLY IDENTIFYING PARTICIPANTS FOR BASECAMP-1 USING A CLINICAL NGS WORKFLOW

- As of September 1, 2024, 74 participants have been enrolled in BASECAMP-1 (**Figure 3**): 32 participants through individual screening methods and 42 through the Tempus patient-matching program

Figure 3: BASECAMP-1 Enrollment Since 2021



NGS, next-generation sequencing.

- Through individual screening methods, 1538 patients were screened (**Table 1**)
- During 22 months of using the Tempus patient-matching program at 11 study sites, 247 patients with tumor HLA-A*02 LOH were identified
- The Tempus patient-matching program was approximately 8-fold more efficient in identifying participants than the individual screening method

Table 1: BASECAMP-1 Screening and Enrollment Statistics

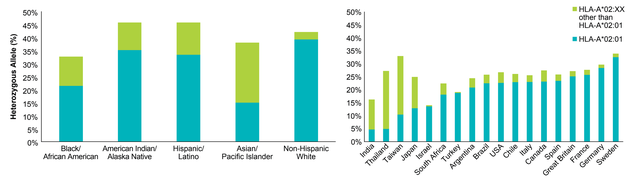
	Individual patient screening methods by study investigators	Tempus patient-matching program
Length of enrollment period, months	35	22
Sites with participant enrolled, n	13	11[a]
Patients consented, n	1538	54[b]
Patients with germline heterozygous HLA-A*02, n	636	247[b]
Participants with tumor HLA-A*02 LOH who enrolled, n	32	42
Average participants enrolled per month, n	1	2
Participants enrolled:patients screened or identified	1:48	1:6

[a] Of the 11 sites, 7 have enrolled participants via the Tempus matching program.
[b] Tempus identified 247 patients in its database who were germline heterozygous HLA-A*02. Of these, 54 patients consented to be screened for BASECAMP-1.

EXPANDING HLA-A*02 ELIGIBILITY CRITERIA TO ALLELE SUBTYPES MORE PREVALENT IN NON-WHITES

- When BASECAMP-1 enrollment began in 2021, eligibility was restricted to patients with germline HLA-A*02:01, based on nonclinical data
- However, HLA-A*02 allele subtypes vary by ethnicity and race (**Figure 4**)

Figure 4: Frequencies of HLA-A*02 Alleles in Global Population [5, 6]



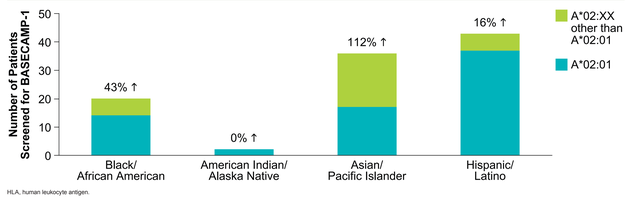
HLA, human leukocyte antigen; LOH, loss of heterozygosity; US, United States.

- Therefore, limiting HLA-A*02 allele subtypes to HLA-A*02:01 may lead to a participant population that is enriched for non-Hispanic Whites

EXPANDING HLA-A*02 ELIGIBILITY CRITERIA TO ALLELE SUBTYPES MORE PREVALENT IN NON-WHITES

- Additional nonclinical analyses were performed and revealed the Tmod construct had activity across HLA-A*02 subtypes [7]
  - In examining the selectivity of the Tmod inhibitory receptor and by solving the crystal structure of the antibody complex, the HLA-A*02–directed blocker was shown to recognize conserved epitopes across the HLA-A*02 alleles
- Based on these data, eligibility criteria were amended to allow for patients with germline HLA-A*02:XX heterozygosity to be enrolled
  - As of July 1, 2024, this amendment led to identification of 16% more Hispanic/Latino, 43% more Black/African American, and 112% more Asian/Pacific Islander patients, improving the racial and ethnic diversity of the BASECAMP-1 study population (**Figure 5**)

Figure 5: Patients Screened for BASECAMP-1 by Ethnicity, Race, and Heterozygous HLA-A*02 Subtype

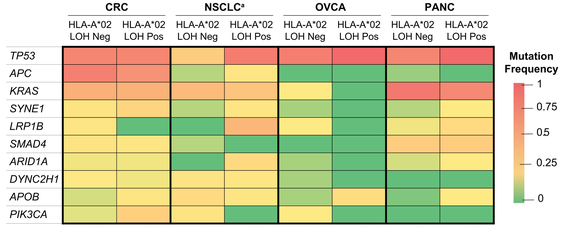


HLA, human leukocyte antigen.

PROVIDING A LARGE DATASET AVAILABLE FOR TRANSLATIONAL STUDIES

- Correlative data from xT were available for 318 patients with germline HLA-A*02
- Tumor purity was lower in pancreatic cancer (PANC) and higher in ovarian cancer (OVCA) specimens vs colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), providing insight into projected screening success rates based on LOH assay sensitivity thresholds
- Mutation distribution was as expected with mutations in *TP53* being most prevalent and mutations in *APC* restricted to CRC. Trends in greater prevalence of *TP53* and *LRPB1* mutations in NSCLC patients with LOH than without were noted, although absolute numbers are small (**Figure 6**)
  - LOH status was not associated with tumor-specific differences
- *CEACAM5* was expressed higher in CRC and *MSLN* in PANC and OVCA as measured by RNA sequencing (RNA-Seq)
- RNA-Seq–imputed immune cell infiltrates were higher in NSCLC
- Microbiome RNA-Seq–based analysis identified *Acinetobacter* specifically in CRC, as expected, and *Mesorhizobium*, *Paeniclostridium*, *Delftia*, and *Afipia* in PANC

Figure 6: Tumor Mutation Distribution by Cancer Type Among Participants With HLA-A*02 LOH in BASECAMP-1



[a] *TP53* and *LRPB1* were more common in participants with NSCLC with HLA-A*02 LOH than without (chi-squared =0.05).
This heat map includes participants enrolled in BASECAMP-1 with germline HLA-A*02 LOH status and correlative data available. Data as of June 1, 2024.
CRC, colorectal cancer; HLA, human leukocyte antigen; LOH, loss of heterozygosity; Neg, negative; NSCLC, non-small cell lung cancer; OVCA, ovarian cancer; PANC, pancreatic cancer; Pos, positive.

CONCLUSIONS

- BASECAMP-1 demonstrates that pre-screening observational studies that leverage pre-existing clinical workflows can address many challenges associated with precision medicine clinical trials
  - We have implemented a patient-matching program that has accelerated identification and enrollment of participants with tumors with HLA-A*02 LOH
  - Through careful evaluation of the Tmod blocker, we recognized that it functioned as well against additional HLA-A*02 variants as HLA-A*02:01; this enabled enrollment of additional participants with broader ethnic and racial diversity
  - Concurrent xT analysis demonstrated expected results in tumor purity, mutation distribution, target expression, and microbiome. The large volume of data provides opportunities to augment analyses from therapeutic trials, including robust propensity-matched comparisons, response correlation studies, and other translational discovery
  - Information from microbiome mining captured in the BASECAMP-1 study provides a large dataset for correlative analysis to further characterize tumors with and without HLA-A*02 LOH

NEXT STEPS

- To further improve access to the BASECAMP-1 study, we are developing additional strategies including the following:
  - Increased geographic location of study sites
  - Leveraging NGS use across the United States, including academic and community sites
  - Creating patient-facing materials to help patients understand complex clinical trials

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