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Improving ethnic and racial diversity in biomarker-driven clinical trials: a proof of concept with the BASECAMP-1 master prescreening study of patients with high-risk solid tumors with human leukocyte antigen-A*02 (HLA-A*02) loss of heterozygosity (LOH)

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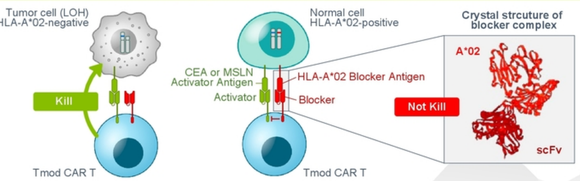
OVERALL SUMMARY

- BASECAMP-1 is a prescreening, precision medicine study that identifies patients with unresectable advanced or metastatic solid tumors and tumor-associated HLA-A*02 LOH for the Tmod™ chimeric antigen receptor T-cell (CAR T) clinical trials EVEREST-1 and EVEREST-2.
- When BASECAMP-1 enrollment began, we screened for patients with the HLA-A*02:01 allele only. After additional nonclinical testing, we determined that Tmod could work with other HLA-A*02:XX alleles, so we expanded enrollment to any HLA-A*02 allele subtype. Because HLA-A*02:01 is the most prevalent allele in Whites and HLA-A*02:XX subtypes are more prevalent in non-Whites, this change improved the racial and ethnic diversity of the BASECAMP-1 study population.
- Initially, we identified patients for BASECAMP-1 by having investigators screen all potential patients for HLA haplotypes; then HLA-A*02:01 heterozygous patients were screened for HLA-A*02 LOH using next-generation sequencing (NGS). We later partnered with Tempus, a third-party NGS provider, to identify patients with tumors that had HLA-A*02 LOH. This has been a much more efficient method of finding patients for our clinical trials.

STUDY RATIONALE: FINDING PATIENTS FOR PRECISION MEDICINE CLINICAL TRIALS

- Identifying patients for clinical trials with molecular enrollment requirements can be time-consuming and financially burdensome.
- We are screening patients for 2 active precision medicine clinical trials of autologous logic-gated Tmod CAR T therapies **(EVEREST-1 and EVEREST-2, ASCO Posters 162b and 163a)**. Tmod cells are logic-gated: the blocker component prevents CAR-mediated killing of normal cells; whereas, in tumor cells with HLA-A*02 LOH, the blocker is no longer engaged, allowing the CAR to activate tumor cell killing (**Figure 1**).

Figure 1: Tmod CAR Ts Discriminate Normal and Tumor Cells With HLA-A*02 LOH

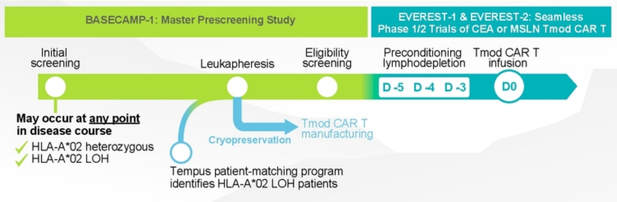


CAR T, chimeric antigen receptor T cell; CEA, carcinoembryonic antigen 5; HLA, human leukocyte antigen; LOH, loss of heterozygosity; MSLN, mesothelin; scFv, single-chain variable fragment.

THE BASECAMP-1 STUDY DESIGN

- BASECAMP-1 (NCT04981119) is a master prescreening, observational study to identify patients for the Tmod clinical trials (**Figure 2**). The main eligibility criteria for BASECAMP-1 are germline HLA-A*02 heterozygous adults with unresectable advanced or metastatic solid tumors and tumor-associated HLA-A*02 LOH.
- Patients in BASECAMP-1 undergo leukapheresis so their CAR T treatment can be prepared without delay when they begin the clinical trials.

Figure 2: BASECAMP-1 Study Schema

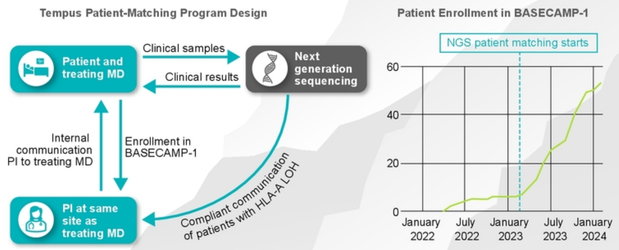


CAR T, chimeric antigen receptor T cell; CEA, carcinoembryonic antigen 5; D, day; HLA, human leukocyte antigen; LOH, loss of heterozygosity; MSLN, mesothelin

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

- Initially, we identified patients for BASECAMP-1 by having investigators screen all potential patients for HLA haplotypes; then HLA-A*02:01 heterozygous patients were screened for HLA-A*02 LOH using NGS.
- We later partnered with Tempus, a third-party NGS provider, to identify patients with tumors that had HLA-A*02:01 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 3**).
- During the first 19 months of the BASECAMP-1 study, 1281 patients consented and were screened, 508 patients were identified as HLA-A*02 heterozygous, and 23 patients were identified with HLA-A*02 LOH in tumor tissue and enrolled on BASECAMP-1.
- During 10 months of using the patient-matching program, 169 patients with LOH of HLA-A*02 in tumor tissue were identified, and 30 patients enrolled on BASECAMP-1. Thus, the NGS algorithm was dramatically more efficient at identifying patients.

Figure 3: Tempus Patient-Matching Program Identifies Eligible Patients for BASECAMP-1

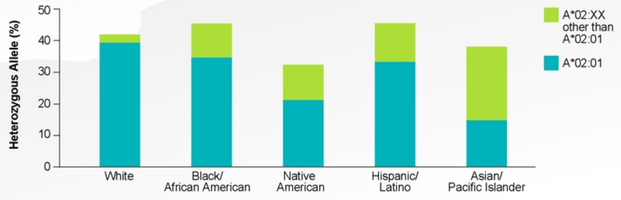


HLA, human leukocyte antigen; LOH, loss of heterozygosity; PI, principal investigator.

EXPANDING HLA-A*02 PATIENT MATCHING 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**)
  - The frequency of HLA-A*02:01 is 96% in non-Hispanic Whites, but ranges from 53% to 73% in other ethnicities and races [1,2].
  - The frequency of all other HLA-A*02 allele subtypes (HLA-A*02:XX) is <5% in non-Hispanic Whites but up to 66% in other ethnicities and races.
- Therefore, limiting HLA-A*02 allele subtypes to HLA-A*02:01 may lead to a patient population that is enriched for non-Hispanic Whites.

Figure 4. Frequencies of HLA-A*02 Alleles in US Populations [1]

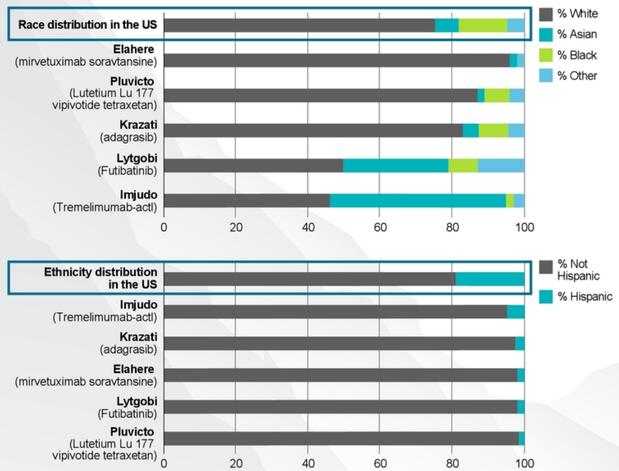


HLA, human leukocyte antigen; US, United States.

EXPANDING HLA-A*02 PATIENT MATCHING TO ALLELE SUBTYPES MORE PREVALENT IN NON-WHITES

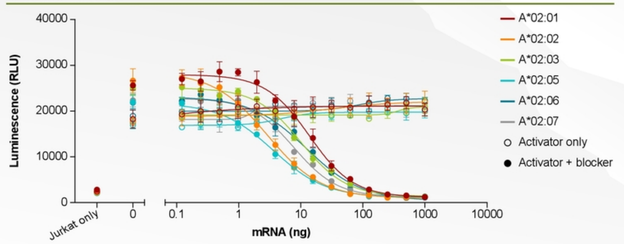
- Diversity in clinical studies is essential to address health disparities, but racial and ethnic minorities are often underrepresented in clinical studies, especially in precision medicine studies using genetic data (**Figure 5**) [3].

Figure 5. Distribution of Race and Ethnicity in the US and Clinical Trial Populations for Recently-Approved Anti-Cancer Products for Solid Tumors [4,5]



- Additional nonclinical analysis revealed the Tmod construct had activity across HLA-A*02 subtypes (**Figures 1 and 6**). 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.
- Binding to a wider set of allele subtypes allows for inclusion of patients beyond HLA-A*02:01, which may improve overall diversity of patients enrolled onto BASECAMP-1 [6].

Figure 6. The LIR-1–Based Inhibitory Receptor (Blocker) Recognized Additional HLA-A*02 Alleles

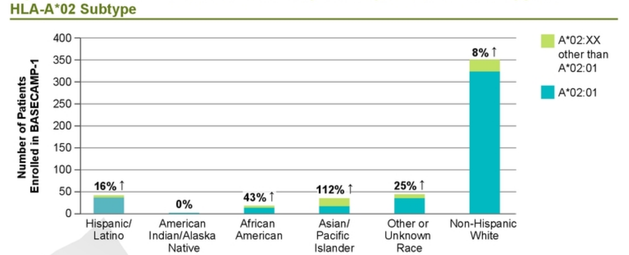


Jurkat-NFAT luciferase functional assay to measure huPA2.1–derived A*02 blocker activity against HLA-A*02 alleles. huPA2.1 blocker was paired with MSLN CAR.
CAR, chimeric antigen receptor; HLA, human leukocyte antigen; LIR, leukocyte immunoglobulin-like receptor; mRNA, messenger RNA; MSLN, mesothelin; RLU, relative luminescence unit.

RESULTS

- Expanding eligibility for BASECAMP-1 to all HLA-A*02 allele subtypes resulted in enrollment of a more racially and ethnically diverse patient population (**Figure 7**).
  - A total of 1124 patients were screened for germline HLA-A*02 typing before January 16, 2024; 431 patients were HLA-A*02:01 heterozygous, of whom 37 (9%) were Hispanic, 14 (3%) African American, 2 (<1%) American Indian or Alaska Native, 17 (4%) Asian or Pacific Islander, and 324 (75%) non-Hispanic White.
  - The eligibility expansion identified 62 additional patients with HLA-A*02:XX heterozygosity, of whom 6 (10%) were Hispanic, 6 (10%) African American, 19 (31%) Asian or Pacific Islander, and 25 (40%) non-Hispanic White.
- By expanding enrollment to include HLA-A*02:XX, 16% more Hispanic, 43% more African-American, and 112% more Asian or Pacific Islander patients were identified.

Figure 7. BASECAMP-1 Patients Screened by Ethnicity, Race, and Heterozygous HLA-A*02 Subtype



HLA, human leukocyte antigen.

SUMMARY AND FUTURE STRATEGIES TO INCREASE ENROLLMENT AND MAXIMIZE DIVERSITY

- By carefully evaluating our blocker (**Figure 1**), we recognized that additional HLA-A*02 variants functioned as well as HLA-A*02:01 (**Figure 6**). This enabled enrollment of additional subjects with broader ethnic and racial diversity (**Figure 7**).
- We have implemented a patient matching service to identify patients with tumors that had HLA-A*02 LOH identified during routine clinical diagnostics (**Figure 3**), which has dramatically increased our enrollment.
- We are developing additional strategies to increase patient access and improve both the size and the diversity of the BASECAMP-1 study population. These strategies include:
  - Increased geographic location of study sites.
  - Leveraging NGS use across the US, including academic and community hospitals.
  - Creating patient-facing materials to help patients understand complex clinical trials.

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  - Agnes E. Hamburger, PhD, Chief Operating Officer
  - Jee-Young Mock, PhD, Senior Scientist Discovery Research
  - Aaron Winters, MS, Principal Scientist Discovery Research
  - Claudia Jette, PhD, Scientist Discovery Research
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