AACR2022 Highlights

Tumor-Infiltrating Lymphocytes and Neoantigen-Targeted Peripheral Blood T Cells:

Improving utility, specificity, and memory

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TILs Making Early Progress into Solid Tumors

Tumor-infiltrating lymphocyte (TIL) therapies offer unique advantages over other adoptive cell therapies in treating solid tumors, driven by polyclonal T-cell populations that target multiple diverse antigens arising from genetic mutations, superior tumor-homing ability, and low off-target toxicity. The first TIL therapy could be available for Melanoma with Iovance expected to complete BLA submission for Lifileucel in August 2022. The company will also design its registrational strategy for Lifileucel in Cervical Cancer following a BLA discussion with the FDA; it already has a breakthrough therapy designation for advanced Cervical Cancer.[1] Another TIL therapy, ITIL-168 (Instil Bio) was also granted orphan drug designation for Stage IIB-IV Melanoma in 2021.[2]

At the recently concluded AACR 2022 annual meeting updated eligibility criteria for Lifiluecel was presented for the IOV-LUN-202 study which not only broadens enrollment to include NSCLC patients with additional prior therapies, but also allows patient enrollment for TIL generation prior to disease progression. This provides an option, to patients with residual disease after either concurrent or sequential ICI and platinum therapy, to minimize the time between confirmed disease progression and initiation of TIL therapy.[3]

Despite the above-mentioned advances with unmodified TILs, there is considerable room for further improvement and a broader application of this therapeutic approach. For instance, altering of genes in TILs might circumvent exhaustion and provide durable clinical responses. Iovance also reported superior anti-tumor activity of PD-1 knockout (KO) TIL, suggesting that endogenous PD-1 inhibition may confer a functional advantage to TILs. In addition, this obviates the need for combining with an anti-PD-1 antibody and its associated drawbacks. The FDA has allowed the IND for IOV-4001, an autologous PD-1 KO TIL therapy, to proceed for the treatment of unresectable or metastatic Melanoma and Stage III or IV NSCLC.[4,5]

Neoantigen-targeted Peripheral Blood T-cells (NPTs), an Alternative when TILs are Hard to Procure

Like TILs, T-cells expanded from the peripheral blood of cancer patients also utilize a diverse TCR repertoire and could provide an alternative source of tumor-reactive autologous polyclonal T-cell populations when TILs are hard to procure due to lack of fresh accessible tumor tissue. However, effectively enriching, or isolating neoantigen-specific T cells from TILs or peripheral blood is still a challenge. GEN-011 is a neoantigen-targeted peripherally derived T cell therapy (NPT) comprised of autologous CD4+ and CD8+ T cells that are specific for up to 30 neoantigens to limit tumor escape. This was tested in the TiTAN clinical trial and also featured at AACR 2022.[6,7] GEN-011 uses a technology that not only identifies and selects immunogenic neoantigens, but also Inhibigens™, antigens for suppressive T cells, for exclusion.[6] These NPTs are consistently 80-90% CD8+ and 10-20% CD4+ T cells, of which 97% (64.9–99.8%) are effector memory and 1% (0.1--32.3%) central memory cells.[7] Preliminary data reported administrable doses were successfully manufactured for 100% of patients to date.[6] In 5 evaluable patients (3 SCCHN and 2 NSCLC), early best response with the more intense regimen (n=2) was stable disease with reduction in tumor and resolution of pain and neuropathy, extending for 2 months.[6,7]

Multiplex Genome Engineering for Personalized Adoptive Cell Therapies with Neoantigen-specific TCRs

While both unmodified TILs and NPTs obtained from peripheral blood are steps towards precision targeting, there is room for further improvement. This will require engineering such personalized T-cell therapies with specific tumor-reactive TCRs. To accomplish this, it is critical to identify clinically relevant antigens in patients and isolate their cognate TCRs. PACT Pharma uses its imPACT Isolation Technology® platform, to selectively capture specific CD8 T cells from the blood of cancer patients to isolate such TCRs.

PACT Pharma presented several studies describing various aspects of their technology.[8-12] One study presented a landscape analysis of neoantigen-specific TCRs from patients with Melanoma, Bladder, Endometrial, Ovarian, Colorectal, Head and Neck, Urothelial, Renal, Stomach, or Breast Cancer which revealed that most of these T cells express TCRs that are specific for private mutations in each cancer and only low frequencies of TCRs against driver mutations[9]. Two other posters described precision genome engineering of these T cells using a single-step multiplex non-viral platform called the PACT^NV™ platform which accomplished the simultaneous targeted knockout of endogenous TCR genes, knock-in of neoTCR (alpha and beta chains) into the endogenous TRAC locus, co-expression of a target payload (CD8coR), and knockout of TGFBR2.[8,11]

PACT Pharma also described a method called PACT-ESCAPE to enable detection of immune resistance from HLA LOH and other alterations in antigen presentation genes. The study reported that HLA LOH was found in 19.6% of PACT's clinical cohort and varied extensively among tumor types and spanned all three HLA-A, B and C loci.[12]

The AACR 2022 annual meeting featured a number of innovations in cell therapies which were focused on finding solutions to factors leading to resistance such as antigen heterogeneity/loss, immune editing, exhausted immune responses, or naturally occurring immune suppressive T-cell responses. While these innovations are expected to address some of the technological challenges with adoptive cell therapies, challenges around logistics, referral pathways, cost, market access and geographic footprint need to be simultaneously addressed to drive broader adoption and approval.

References

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