Target antigen levels in NSCLC samples define a clinically relevant activation threshold for NY-ESO-1 TCR T-cell therapy

Background

Adaptive T-cell therapy is a promising treatment for recurrent or metastatic solid and hematologic malignancies with encouraging activity demonstrated in patients with synovial sarcoma, melanoma, myeloid cell leukemia, and multiple myeloma.1,2

Unlike chimeric antigen receptor T cells (CAR T) that primarily target cell surface proteins, engineered T-cell receptor T cells (TCR T) recognize intracellular antigens presented in the context of human leukocyte antigen (HLA).3

NY-ESO-1 and LAGE-1a are intracellular cancer-testis antigens that generate a shared SLLM971GQC peptide bound to HLA-A:2 and are expressed across multiple malignancies, including non-small cell lung cancer (NSCLC).4

Expression of HLA-A:2 in NY-ESO-1 TCR T cells are autologous, polyclonal, terminally LV-transduced T cells engineered to express an affinity-enhanced TCR recognizing the SLLM971GQC-HLA-A:2/01,02:05 and 02:06 peptide complex.5

GSK is currently running a Phase 1b/2a, null-arm, open-label pilot study (NCT03793910) of GSK3377794 as a monotherapy or in combination with pembrolizumab in HLA-A:2+ positive patient's whose tumours express NY-ESO-1 and/or LAGE-1a (Figure 1).

Aims

Systematically assess the prevalence and expression levels of NY-ESO-1 and LAGE-1a in NSCLC and melanoma cell lines and primary patient samples

Determine the product-specific threshold of target antigen required to induce a specific GSK3377794 response to inform the ongoing clinical trials in NSCLC and melanoma

Methods

A NSCLC tumour biobank consisting of (1) primary patient tumour (adenocarcinoma and squamous cell carcinoma) samples, (2) patient derived xenograft (PDX) models and (3) tumour cell lines was established.

Expression of HLA-A:2 was characterized by flow cytometry and levels of NY-ESO-1 and LAGE-1a antigens were measured via RT-qPCR.

Tumour samples were ordered by total antigen expression (Total antigen-δCq).

GSK3377794 and ND T (non-transduced T) cell response against NY-ESO-1/LAGE-1a expressing tumour samples was measured via Masayo Scale Diagnostics for interferon (IFN)-γ, interleukin (IL)-17 and tumour necrosis factor (TNF)-α secretion (24 hour co-culture at 1:1 ratio).

Results

Figure 3. GSK3377794 activation by tumour cell lines correlates with target antigen expression levels

Figure 4. IFN-γ responses by GSK3377794 in NSCLC PDX tumour samples depends on level of target antigen expression

Figure 5. Functional readouts identify an antigen expression threshold for preclinical and clinical relevant NY-ESO-1 response

Figure 6. Understanding of the expected GSK3377794 response towards primary patient NSCLC tumour samples based on threshold defined from PDX models

Figure 7. Translating target antigen expression threshold for GSK3377794 activation to the potential patient population with NSCLC in HLA-A:2 positive samples

Conclusions

We performed a systematic analysis that correlates target antigen expression in NSCLC with functional responses of GSK3377794 using a set of clinically relevant samples. The functional readouts identify a product-specific antigen expression threshold for GSK3377794 in NSCLC, which could translate to a potential NSCLC patient population that may benefit from cell therapy with GSK3377794.

Ongoing work and future steps

Ongoing GSK clinical trials in NSCLC (NCT03793910) will help us understand the relevance of these preclinical findings.

Identification of antigen expression threshold for GSK3377794 in other key indications of solid cancer.

Evaluate predictively the potential for epigenetic modulators to upregulate NY-ESO-1/LAGE-1a expression to enhance targeting by GSK3377794 in NSCLC and move to an exploratory medicine style study in key indications.

Disclosures

All authors made a substantial contribution to the work and will take public responsibility for the content of this manuscript. All authors have no conflict of interest to declare.

References


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