Cellular and genomic disease signature of peripheral blood mononuclear cells in patients with malignant pleural mesothelioma

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Abstract

Background: Recent data on the incidence malignant pleural mesothelioma (MPM) and the continued large-scale use of asbestos throughout the developing world portends an epidemic of asbestos-related disease. MPM patients were enrolled in a Phase 1b study utilizing CRS-207, an established Listeria monocytogenes strain engineered to express the tumor-associated antigen, mesothelin. Four different multiple flow cytometry panels were used to provide resolution on major immune cell populations of T cells, NK cells, B cells, dendritic cells, monocytes, and neutrophils, whether these panels provided disease resolution on 39 distinct subpopulations of major immune cell subsets. RNA from these cells was used to perform multiple gene expression analysis on 770 genes using the NanoString nSolver Pathway Panel.

Materials and Methods: Here we present pre-treatment cellular and genomic biomarker data on a cohort of chemotherapy-naïve MPM patients, and the continued large-scale use of asbestos throughout the developing world portends an epidemic of asbestos-related disease. MPM patients were enrolled in a Phase 1b study utilizing CRS-207, an established Listeria monocytogenes strain engineered to express the tumor-associated antigen, mesothelin. Four different multiple flow cytometry panels were used to provide resolution on major immune cell populations of T cells, NK cells, B cells, dendritic cells, monocytes, and neutrophils, whether these panels provided disease resolution on 39 distinct subpopulations of major immune cell subsets. RNA from these cells was used to perform multiple gene expression analysis on 770 genes using the NanoString nSolver Pathway Panel.

Methods

- Chemotherapy-naive patients with MPM (N=34) from both cohorts of Aduro’s Phase 1b trials that were selected for analysis, with healthy donors (HDs) (N=10) matched by median age, sex and ethnicity.
- Four different multiple flow cytometry panels were used to analyze cryopreserved peripheral blood mononuclear cells (PBMCs) in order to provide a comprehensive immune phenotype.
- PBMCs were stained with panels to phenotype T cells, B cells, NK cells, dendritic cells (DC) and monocytes. (Table 2).
- FACs data were analyzed using Cytabank. (Nishida N et al. Curr Protoc Cytom. 2014) Four different multiple flow cytometry panels were used to provide resolution on 39 distinct subpopulations of major immune cell subsets. RNA from these cells was used to perform multiple gene expression analysis on 770 genes using the NanoString nSolver Pathway Panel.
- The abundance of some immune subsets were identified using the nSolver software (nSolver). A total immune signature was generated by performing unsupervised hierarchical clustering of all samples and genes in the PanImmune Profiling Panel using Euclidean distance and average linkage, and Treeview software suites.

Results

- Aduro Biotech Inc. has developed CRS-207, an immunotherapy platform composed of a live, attenuated, double-deleted Listeria monocytogenes (LAD2) strain, engineered to express human mesothelin.
- LADD has broad applications in the development of immunotherapies to treat both cancer and infectious diseases.
- An ongoing Phase 1b study enrolled chemotherapy-naive patients with unsuitable MPM. All enrolled patients were diagnosed with either epithelial or biphasic histological diagnosis.
- First-line treatment with combination of CRS-207 and pembrolizumab (or cetuximab in case CRS-207 was not tolerated) resulted in a 90% disease control rate (SDR, PR, and CR) and a 56% objective response rate (ORR).
- Aduro Biotech’s currently enrolling Phase 2 study of CRS-207 with pembrolizumab will assess safety and efficacy of this combination immunotherapy, and use biomarker approaches to characterize the immune response.

Discussion

- Patients with MPM exhibit lower frequencies of T and B cells, and higher frequencies of monocytes as compared to demographically matched HDs.
- Here we present the first cellular and genomic immune signature of MPM using a non-invasive approach to accurately define the overall immune response, with resolution on 39 distinct immune cell populations and 770 genes.
- All patients with MPM in this study participated in the ongoing Phase 2 immune oncology trial, testing Aduro Biotech’s CRS-207 immunotherapy.
- Biomarker distribution was observed for some immune cell populations including T cells and patient subgroups were identified by hierarchical clustering of genomic data. This variability amongst patient immune signatures warrants further investigation of how these patient subpopulations correlate with treatment outcome.
- Deep immune profiling techniques, such as those utilized in this study, may inform patient selection in clinical trials amidst the complex and broadening immunotherapeutic landscape.

References


Acknowledgements

Funding: Aduro Biotech, Inc.

Special thanks to the referring physicians and all of the patients and their families.