275 TRANSLATIONAL ENDPOINTS ASSOCIATED WITH STK11 MUTATIONS IN PATIENTS WITH NON-SQUAMOUS NSCLC

Song Wu, Nathan Standifer, Melissa de los Reyes, Micheal Oberst, Rajv Raja, Carl Barrett, Maria Ascierto*. *Astrazeneca, Gaithersburg, MD, USA*

Background Emerging data suggest poor outcome to anti- PD (L)1 blocking agents in patients with STK11mut tumors1. In the current study, we undertook in-depth translational evaluations of three Ph1/Ph2 independent studies of Durvalumab ± Tremelimumab to elucidate the biology associated with STK11 mutations leading to reduced clinical response in patients with non-squamous NSCLC.

Methods Mutational status was evaluated by ctDNA or Foundation One CDx as previously described1. RNA sequencing was conducted on baseline frozen biopsies (N=70). Selected proteins (N=66) were measured by Myriad RBM multiplexed immunoassays on baseline serum (n=91). Screening and longitudinal whole blood was assessed for circulating quantities of T, B or NK cells and activated or memory T cell subsets using bioanalytically-validated, flow cytometry-based immunophenotyping assays. Exploratory analyses of translational endpoints according to STK11 mutational status were conducted by Wilcoxon rank-sum test.

Results In the periphery, a reduced number (> 2-fold decreased in median quantities) of NK cells, CD4+ effector memory, CD4+ HLA-DR+, CD8+ effector memory and CD8 + HLA-DR+ T cells was observed at baseline and following treatments in patients with STK11mut vs. STK11wt tumors. At baseline, increased levels of IL6 (p=0.002) and the neutrophil-attracting cytokine IL8 (p=0.02) were found in serum of patients with STK11mut tumors. In the tumor microenvironment, significantly increased expression (p< 0.05; fold change > 2) of markers associated with neutrophils, (i.e. CXCL2, IL6, CSF3), Th17 contexture (i.e. IL17A) and immune checkpoints (i.e. KIRs, PD-L1) was found in STK11mut vs. STK11wt tumors.

Conclusions The poor outcomes to immunotherapy observed in NSCLC patients with STK11mut tumors might be determined by a compromised peripheral and intra-tumoral immune phenotype. These results might help the development of novel therapeutic interventions able to unleash response to immune checkpoints in NSCLC patients harboring STK11 mutations.

Trial Registration NCT01693562, NCT02087423, NCT02000947

REFERENCE

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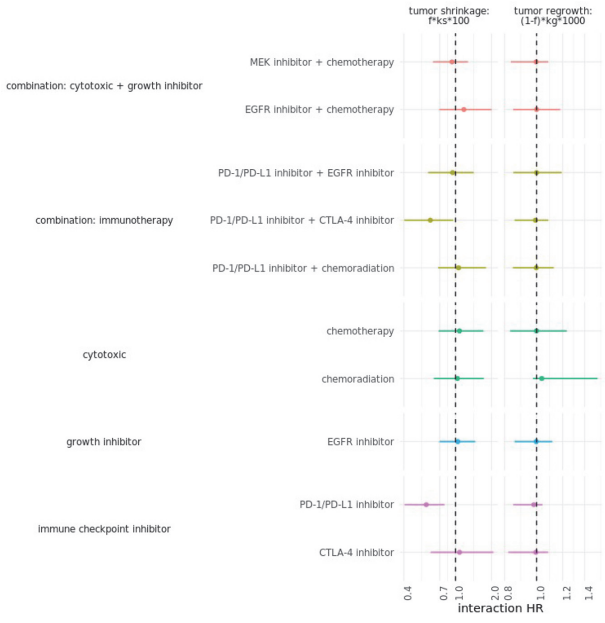
276 PROGNOSTIC VALUE OF TUMOR SIZE VARIES BY TREATMENT IN A META-ANALYSIS OF 15 RANDOMIZED CLINICAL TRIALS IN ADVANCED NON-SMALL CELL LUNG CANCER ACROSS IMMUNOTHERAPY, TKI, AND CHEMOTHERAPY REGIMENS

[1]Jacqueline Buros*, [1]Krzysztof Sakrejda, [1]Daniel Lee, [1]Eric Novik, [2]Philip Jewsbury. [1]*Generable, Inc., Brooklyn, NY, USA*; [2]*AstraZeneca, Cambridge, UK*

Background RECIST[1] is commonly used to characterize intermediate outcomes for clinical trials in the context of solid tumors, and it is largely based on a standardized measure of tumor size known as the sum of longest diameters (SLD). In recent years, the FDA has granted accelerated approvals for several new compounds based on improvements in RECIST-based surrogate outcomes like overall response rate and progression-free survival.[2] However, there are concerns regarding the robustness of these surrogate endpoints relative to overall survival (OS),[3 4] and it is not known whether their prognostic value is similar across TKI, chemotherapy, and immunotherapy regimens.

Methods We have developed a Bayesian meta-analytic joint model for longitudinal SLD and OS in order to predict Phase III outcomes from early Phase II data. We validated this model in extensive simulation studies. The model utilizes a generalized Stein-Fojo equation[5] to characterize SLD over time in terms of 3 parameters: f (proportion of tumor that is treatment-susceptible), ks (the decay rate among susceptible cells), and kg (the growth rate among resistant cells). Two quantities [tumor shrinkage (f * ks) and tumor regrowth ((1-f) * kg)] are then associated with survival in the context of a proportional-hazards survival model. We estimated this model using Stan[6] on a dataset of >6,000 subjects in 15 randomized clinical trials in advanced non-small cell lung cancer.

Results Both tumor shrinkage and tumor regrowth were found to be associated with OS (HR for tumor shrinkage: median 0.51, 90% CrI 0.42 - 0.61; HR for tumor regrowth: median 1.24, 90% CrI 1.18 - 1.32). There is a stronger association between tumor shrinkage and OS among patients randomized to a PD-1/PD-L1 inhibitor, either as a monotherapy or in combination with a CTLA-4 inhibitor, than among patients in other trial arms (figure 1). By contrast, there were negligible



Abstract 276 Figure 1
Hazard associated with SLD submodel parameters varies according to the class of treatment in a joint model for SLD and overall survival with varying association by assigned treatment regimen. The points represent posterior median values per treatment, with lines representing 90% posterior credible intervals (CrI). Two treatment classes demonstrated posterior probability greater than 90% of a non-zero treatment-specific effect for the response term: the combination PD-1/PD-L1 inhibitor + CTLA-4 inhibitor [interaction HR = 0.64 (90% CrI 0.39 - 1.00; posterior probability of HR<1: 95.2%)] and the PD-1/PD-L1 inhibitor alone [interaction HR = 0.62 (90% CrI 0.42 - 0.89; posterior probability of HR<1: 99.2%)].