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

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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

1. Jure Kunkel M *et al*, JCO.2018.36.15_suppl.3028.

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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

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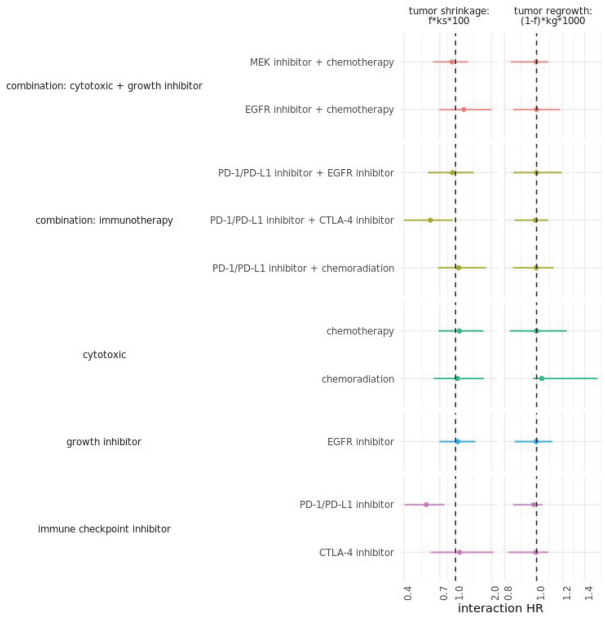
Background RECIST[1] is commonly used to characterize intermediate outcomes for clinical trials in the context of solid tumors, and it is largely based on a standardized measure of tumor size known as the sum of longest diameters (SLD). In recent years, the FDA has granted accelerated approvals for several 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%)].

differences across treatment classes in the association between tumor regrowth and OS.

Conclusions Our results suggest that not all reductions in tumor size are equal. A patient with a certain degree of tumor shrinkage on the PD-1/PD-L1 inhibitor will have lower mortality risk than a patient with a similar degree of shrinkage on the other regimens evaluated. More research is needed to determine whether the result is unique to this particular PD-1/PD-L1 inhibitor, to determine what mechanisms of action mediate these treatment-specific effects, and to develop improved surrogate measures of treatment efficacy.

REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, *et al*: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**:228–247.
2. Of Health USD, Services H, *Others*: Clinical trial endpoints for the approval of non-small cell lung cancer drugs and biologics: guidance for Industry, 2015
3. Mandrekar SJ, An M-W, Meyers J, *et al*: Evaluation of Alternate Categorical Tumor Metrics and Cut Points for Response Categorization Using the RECIST 1.1 Data Warehouse. *J Clin Orthod* **32**:841–850, 2014
4. Blumenthal GM, Karuri SW, Zhang H, *et al*: Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. *J Clin Oncol* **33**:1008–1014, 2015
5. Stein WD, Figg WD, Dahut W, *et al*: Tumor growth rates derived from data for patients in a clinical trial correlate strongly with patient survival: a novel strategy for evaluation of clinical trial data. *Oncologist* **13**:1046–1054, 2008
6. Carpenter B, Gelman A, Hoffman MD, *et al*: Stan: A probabilistic programming language [Internet]. J Stat Softw 2017;76, Available from: http://www.stat.columbia.edu/~gelman/research/published/Stan-paper-aug-2015.pdf

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277 COMBINED NEOADJUVANT CHEMO-IMMUNOTHERAPY THERAPY ACHIEVES SUPERIOR DOWNSTAGING OF RESECTABLE NON-SMALL CELL LUNG CANCER AS COMPARED TO CHEMOTHERAPY, MONO OR DUAL IMMUNOTHERAPY

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Background Tumor and nodal downstaging following neoadjuvant therapy in resectable non-small cell lung cancer (NSCLC) are important markers of therapeutic response associated with favorable prognosis. We studied the impact of four different systemic neoadjuvant therapies on tumor, nodal and overall pathological downstaging of surgically resectable I-IIIA NSCLC (AJCC 7th edition).

Methods Our study cohorts consisted of NSCLC patients treated with three cycles of neoadjuvant platinum doublet chemotherapy from 2001–2012 (N=302, 84%), and patients treated on the NEOSTAR study (NCT03158129) who received neoadjuvant nivolumab (N=21,6%), nivolumab plus ipilimumab (N=16, 4%), or platinum doublet chemotherapy plus nivolumab (N=22, 6%). Clinical and pathological (yp) T and N staging were evaluated for downstaging and upstaging; differences were assessed using Fisher's exact test.

Results Following neoadjuvant platinum doublet chemotherapy, nivolumab, nivolumab plus ipilimumab and platinum doublet chemotherapy plus nivolumab, the rates of clinical-to-pathological ypT downstaging were 26% (N=79), 29% (N=6), 38% (N=6) and 59% (N=13), respectively, p =0.012 (table 1). The rates of clinical-to-pathological ypN downstaging in patients with clinical N1 or N2 disease with each therapy were 55% (N=96), 50% (N=3), 50% (N=2), and 42% (N=5) respectively, p =0.862. Overall clinical-to-pathological (ypT and/or ypN) downstaging rates were 38% (N=114), 38% (N=8), 38% (N=6), and 68% (N=15) respectively, p=0.048. The proportions of patients being overall upstaged following each therapy were 28% (N=85), 38% (N=8), 38% (N=6) and 14% (N=3), respectively, p=0.251. These results suggest superior downstaging effect and clinically meaningful lower upstaging probability of combined platinum doublet chemotherapy plus nivolumab as compared to other neoadjuvant regimens.

Abstract 277 Table 1 Response to Chemotherapy, Immunotherapy, and Combination Therapy

TABLE: Response to Chemotherapy, Immunotherapy, and Combination Therapy

	Chemotherapy N=302	Single-agent ICI N=21	Dual-agent ICI N=16	Chemotherapy+ ICI N=22	p
ypT downstaged vs. stable/upstaged	26% (79)	29% (6)	38% (6)	59% (13)	0.012
ypN downstaged vs. stable/upstaged*	55% (96)	50% (3)	50% (2)	42% (5)	0.862
Overall yp downstaged vs. stable/upstaged	38% (114)	38% (8)	38% (6)	68% (15)	0.048

*Among those with cN1 disease

ICI: immune checkpoint inhibitor

Conclusions The combination of neoadjuvant platinum doublet chemotherapy with nivolumab achieves the most robust tumor and overall pathological downstaging and decreases the probability of upstaging at surgery. Whether the overall downstaging effect results in improved survival will be determined with longer follow-up, in conjunction with results from ongoing phase III neoadjuvant chemo-immunotherapy trials.

Trial Registration NCT03158129

Ethics Approval This study was approved by the University of Texas MD Anderson Institutional Review Board with a waiver of informed consent, protocol 2020-0337.

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278 PHASE I CLINICAL TRIAL EVALUATING THE SAFETY OF ADP-A2M10 SPEAR T-CELLS IN PATIENTS WITH MAGE-A10$^+$ ADVANCED NON-SMALL CELL LUNG CANCER

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Background ADP-A2M10 SPEAR T-cells are genetically engineered autologous T-cells that express a high affinity MAGE-A10-specific T-cell receptor targeting MAGE-A10$^+$tumors in the context of HLA-A*02. This trial is now complete (NCT02592577).

Methods This first-in-human dose escalation trial utilized a modified 3+3 design to evaluate safety and antitumor activity. Eligible patients (pts) were HLA-A*02$^+$ with advanced non-small cell lung cancer (NSCLC) expressing MAGE-A10. Pts underwent apheresis; T-cells were isolated, transduced with a lentiviral vector containing the TCR targeting MAGE-A10, and expanded. Pts underwent lymphodepletion (LD) with varying doses/schedules of fludarabine (Flu) and cyclophosphamide (Cy) prior to receiving ADP-A2M10. ADP-A2M10 was