33 BLOOD-BASED TUMOR MUTATION BURDEN (BTMB) PREDICTS RESPONSE TO IMMUNE CHECKPOINT BLOCKADE-BASED COMBINATION THERAPY (ICBC) IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): A REAL-WORLD (RW) ANALYSIS

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Background Studies have shown that high TMB (≥10mut/MB on tissue) across solid tumors is associated with improved overall survival (OS) in patients (pts) treated with ICBC. For a subset of pts, including those with insufficient tissue, blood-based TMB analysis may be more feasible. Here, we report RW outcomes of bTMB-low (bTMB-L) and -high (bTMB-H) advanced NSCLC pts treated with ICBC therapies.

Methods Outcomes were assessed using the Guardant INFORM database. Previously untreated (1L) pts with NSCLC tested with G360 from Sept 2018-Sept 2022 receiving ICBC (often combined with chemo) within 90 days after G360 testing were identified. ICBC-treated pts were compared to those treated with chemo alone. Cox-proportional hazard (CPH) estimates were used to examine time to next treatment (TTNT) and OS. Gender, age, and comorbidities were included in the CPH model, and maximum somatic variant allele fraction (MSAF) was used as a stratifying factor. bTMB-H was defined according to the 80th percentile of G360 NSCLC bTMB as ≥20mut/MB and bTMB-L as <20mut/MB.

Results 1,059 pts with advanced NSCLC received 1L ICBC, and 82% (n=873) were evaluable for bTMB. Among evaluable pts that received ICBC, bTMB-H (n=243) status was associated with significantly longer TTNT (13.3 vs 9.9 mo; HR=0.53, p=0.005) and OS (HR=0.58; p=0.02) compared to bTMB-L. For pts treated with chemotherapy alone, bTMB-H status was not associated with significantly longer OS (HR=0.96, p=0.92, bTMB-L as reference group) nor TTNT (HR=1.23, p=0.31). Within the ICBC group, bTMB-H pts without mutations in (*EGFR, ERBB2, KIT, STK11, or KEAP1* had longer OS (HR=0.34, p=0.009) and TTNT (15.7 vs 9.9 mo; HR=0.36, p=0.007) as compared to pts with bTMB-L. Similarly, for pts treated with chemotherapy alone, bTMB-H pts without mutations did not have longer OS (HR=0.96, p=0.94) nor TTNT (HR=1.44, p=0.14) compared to bTMB-L pts. Pts with bTMB non-evaluable (n=186), with low levels of ctDNA (median non-evaluable MSAF of 0.4 vs MSAF of 3.4 for evaluable), had significantly longer TTNT (11.6 vs 9.9 mo; HR=0.67, p=0.02) and OS (HR=0.58, p=0.008) than bTMB-L (n= 630) pts, but did not have significantly longer TTNT (HR=0.87, p=0.50) or OS (HR=0.74, p=0.20) than bTMB-H (table 1).

Conclusions These data provide evidence that bTMB effectively identifies pts who are more likely to benefit from ICBC, particularly when combined with broad genomic profiling for variants associated with lack of benefit. Moreover, these findings demonstrate the ability of a combined RW clinicogenomics database to validate existing biomarkers as well as discover and validate new candidates.

Ethics Approval This study used a deidentified database in accordance with US patient confidentiality requirements set forth in Sections 164.514 (a)–(b)1ii of the Health Insurance Portability and Accountability Act (HIPAA) regarding the determination and documentation of statistically deidentified data.

Abstract 33 Table 1 Outcomes for patients receiving 1L ICB + chemo by biomarker status

Biomarker	Outcome variable	CPH HR (95% CI)	CPH HR, p-value	Median TTNT [months]	Reference group
bTMB-H	OS	0.58 [0.36-0.93]	0.02	NR	bTMB-L
bTMB-L	OS	1.73 [1.08-2.79]	0.02	NR	bTMB-H
bTMB-H, variant -ve*	OS	0.36 [0.15-0.76]	< 0.01	NR	bTMB-L
bTMB-H variant +ve*	OS	0.65 [0.38-1.10]	0.11	NR	bTMB-L
bTMB non-evaluable[§]	OS	0.58 [0.39-0.87]	< 0.01	NR	bTMB-L
bTMB-H	TTNT	0.53 [0.35-0.82]	< 0.01	13.3	bTMB-L
bTMB-L	TTNT	1.87 [1.22-2.88]	< 0.01	9.9	bTMB-H
bTMB-H, variant -ve*	TTNT	0.36 [0.17-0.75]	< 0.01	15.7	bTMB-L
bTMB-H variant +ve*	TTNT	0.84 [0.48-1.4]	0.55	10.3	bTMB-L
bTMB non-evaluable[§]	TTNT	0.67 [0.48-0.94]	0.02	11.6	bTMB-L

* Negative for likely oncogenic variants in EGFR, ERBB2, KIT, KRAS/STK11 double mutant, KRAS/KEAP1 double mutant.
* Positive for likely oncogenic variants in EGFR, ERBB2, KIT, KRAS/STK11 double mutant, KRAS/KEAP1 double mutant.
[§]No stratification by MSAF due to overlapping signal with bTMB non-evaluable category.
NR=not reached

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