Abstract 3130: Nivolumab plus Ipilimumab in patients with solid tumors with high tumor mutational burden: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

ASCO TAPUR
Targeted Agent and Profiling Utilization Registry Study

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Background:

- TAPUR is a phase II basket study that evaluates antitumor activity of commercially available targeted agents in patients (pts) with advanced cancers with specific genomic alterations.
- **Results of a cohort of pts with various solid tumors with high tumor mutational burden (HTMB) treated with nivolumab plus ipilimumab (N+I) are reported.**

Methods:

Study Design:

- **Eligible pts:** Advanced solid tumors, ECOG performance status (PS) 0-2, adequate organ function, measurable disease, and no standard treatment (tx) options. Tx was assigned according to prespecified matching rules based on genomic tests performed in CLIA-certified, CAP-accredited laboratories selected by sites. PD-L1 expression testing was not required. HTMB was defined *a priori* as ≥9 mutations per megabase (Muts/Mb) via a qualifying test for TAPUR or approved by the Molecular Tumor Board.
- Pts received N at 1 mg/kg IV every 3 weeks (wks) for 4 doses in combination with I at 3 mg/kg every 3 wks for 4 doses. N was then continued at 240 mg every 2 wks or 480 mg every 4 wks until disease progression, unacceptable toxicity or pt or physician choice to discontinue.
- **Primary endpoint:** Disease control (DC) defined by investigator assessment of objective response (OR) or stable disease (SD) of at least 16 wks duration (SD16+) per RECIST v1.1. Radiographic confirmation of response was not required.
- **Secondary endpoints:** OR, progression-free survival (PFS), overall survival (OS), duration of response (DOR), duration of SD, Grade 3-5 adverse events (AEs) or serious adverse events (SAEs) per CTCAE v4.0 at least possibly related to tx are reported. DOR is defined as time from pt's first documented OR to progressive disease (PD). Duration of SD is defined as time from tx start to PD.
- Low accruing histology-specific cohorts with HTMB were collapsed into one histology-pooled cohort for this analysis per protocol defined collapsing rules.

Statistical Methods:

- Inferences are based on a one-sided exact binomial test with a null hypothesis of DC rate ≤15%; power and alpha were 86% and 0.10, respectively. Two-sided 95% CIs are used for other efficacy endpoint estimates.

Results:

- 26 pts were enrolled from December 2017 to July 2020. Tumor mutational burden (TMB) ranged from 8-374 Muts/Mb (median TMB = 16 Muts/Mb). Microsatellite (MS) status was stable for 21 pts, high for 2 pts, indeterminate for 1 pt, and not tested for 2 pts. PD-L1 status was not tested for 13 pts, positive for 1 pt and negative for 12 pts.
- **Demographics:** Median age 63 (range, 37-86); 54% female; 65% self-identified as White, 15% as Asian/Asian American, 12% as Black/African American, 4% as other, 4% as prefer not to answer; 89% as not Hispanic or Latino, 8% as Hispanic or Latino, and 4% preferred not to answer.
- **Clinical Characteristics**: 96% PS 0-1, 4% PS 2; 35% received ≥3 prior systemic regimens. Primary tumor origin (# pts): unspecified site (4), pancreas (4), uterus (3), basal cell carcinoma (2), small intestine (2), biliary tract (2), ovary (2), duodenum (1), liver (1), CNS (1), peritoneum (1), soft tissue sarcoma (1), skin squamous cell carcinoma (1), and vagina (1).
- **Outcomes**: CR 1, PR 7, and SD16+ 1 for a DC rate of 35% (1-sided 90% CI, 22 to 100) and OR rate of 31% (95% CI, 14 to 52). (**Tables 1 and 2**). The null DC rate of ≤15% was rejected (p=0.011). Median TMB of pts with DC was 26 Muts/Mb; median TMB of others was 13 Muts/Mb.
- Duration of CR was 36 wks; duration of SD was 26 wks. Median duration of PR was 20 wks (range, 5-231). Pt with uterine cancer and best response of PR is still on treatment at 231 wks.
- **Safety:** 10 pts (38%) had ≥1 SAE or grade 3 AE at least possibly related to tx including ALT/AST/ALP increase, autoimmune hepatitis, colitis, fever, hyponatremia, pneumonitis, and maculo-papular rash.

Conclusion: Nivolumab plus ipilimumab demonstrated clinical activity in patients with various solid tumors with HTMB.

Future Direction: Additional study is warranted to confirm the utility of HTMB to identify patients who might benefit from nivolumab plus ipilimumab treatment.

Table 1. Tumor Origin and Alterations of Pts Meeting Response Criteria (n=9)

Pt[a]	Response	Primary Tumor Origin	MS/PD-L1[b] Status	Muts/Mb	Co-alterations[c]
A	CR	Duodenum	MS High	48	*ARID1A* N2220S *RB1* E533G *KRAS* G12V
B	PR	Unspecified site	MS Stable	11	--
C	PR	Unspecified site	MS Stable, PD-L1 Positive	17	*ATM* M1T
D	PR	Unspecified site	MS Stable, PD-L1 Negative	51	--
E	PR	Uterus	MS Stable	374	*ATM* R250*, R2598Q *BRCA1* E1725* *BRCA2* R2842C *CDK12* E1145* *CTNNA1* R451* *FANCC* R555Q *FANCL* E147* *MSH2* E749*, K82T, R621Q *MTOR* S2215F *PIK3R1* R348*, R386* *POLE* V411L *PPP2R1A* R183W *PTEN* R130Q, R173H *RAD50* splice site 214-1G>T *STAG2* R146*, E510D, T624A *TOP2A* K1237N
F	PR	Vagina	MS Stable, PD-L1 Negative	9	*PIK3CA* E545K
G	PR	Biliary tract	MS Stable, PD-L1 Negative	17	*ATR* G1738C
H	PR	Soft tissue sarcoma	MS Stable	58	*ERBB4* G565C *EZH2* P193S *MAGI2* G213E *PPP2R1A* D176N, S187F *RAF1* S257L *TERT* splice site *TOP2A* R162* *RAD51B* L87F
I	SD16+	Pancreas	MS Stable	26	*ARID1A* Q909* *KRAS* G12D

[a] Pt letter corresponds to letter/bar in Figure 2.
[b] Unless otherwise noted, PD-L1 expression was not tested.
[c] Of the following genes examined: *ARID1A, ATRX, ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CDC73, CDK12, CHEK1, CHEK2, CTNNA1, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, EZH2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL, JAK2, KEAP1, KRAS, MAGI2, MAP2K1, MAP2K4, MLH1, MRE11, MSH2, MTOR, NBN, NFE2L2, PARP1, PARP2, PARP3, PIK3CA, PIK3R1, PMS2, POLD1, POLE, POLQ, PPP2R1, PPP2R1A, PPP2R2A, PTEN, PTPN11, RAD50, RAD51, RAD51D, RAD52, RAF1, RASA1, RB1, RUNX1, SMAD2, STAG2, TERT, TOP2A, XPO1, XRCC1, XRCC3.* Variants of unknown significance are not included in this reporting.

Table 2: Efficacy Outcomes (n=26)

DC rate, % (1-sided 90% CI) (p-value)	35 (22, 100) (p=0.011)
OR rate, % (95% CI)	31 (14, 52)
Median PFS, wks (95% CI)	9 (8, 18)
Median OS, wks (95% CI)	48 (18, 108)
Duration of CR, wks (n=1)	36
Median duration of PR (range), wks (n=8)	20 (5, 231)
Duration of SD in pt with SD16+, wks (n=1)	26

Figure 1: Best Percent Change from Baseline in Target Lesion Size (n=26)

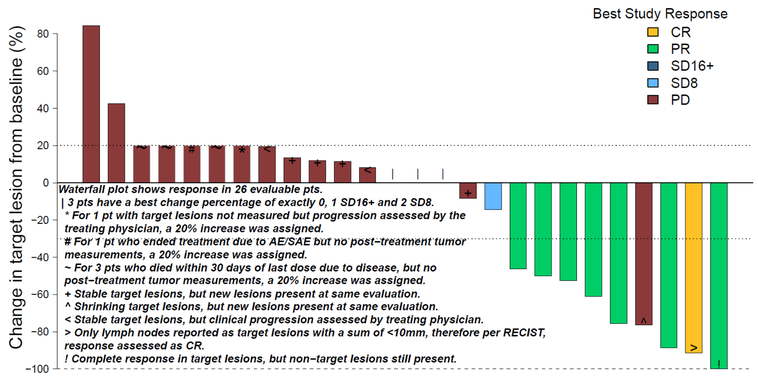
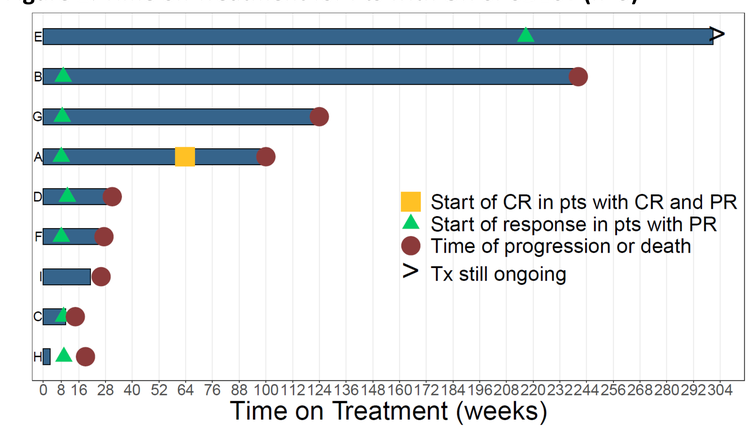


Figure 2: Time on Treatment for Pts with OR or SD16+ (n=9)



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