Abstract 107: Nivolumab + Ipilimumab in patients with colorectal cancer with high tumor mutational burden (hTMB): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

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Background:

- TAPUR is a phase II basket study that evaluates anti-tumor activity of commercially available targeted agents in patients (pts) with advanced cancers with specific genomic alterations.
- **Results of a cohort of pts with colorectal cancer (CRC) with high tumor mutational burden (hTMB), defined as ≥9 mutations/Megabase (Mut/Mb), treated with nivolumab plus ipilimumab (N+I) are reported.**

Methods:

Study Design:

- **Eligible pts:** Advanced CRC, no standard treatment (tx) options, ECOG PS 0-2, adequate organ function, measurable disease. Tx assigned according to pre-specified matching rules based on genomic tests selected by sites.
- Pts received N at 1 mg/kg IV every 3 weeks for 4 doses in combination with I at 3 mg/kg every 3 weeks for 4 doses. N was then continued at 240 mg every 2 weeks or 480 mg every 4 weeks until disease progression.
- **Primary endpoint:** Disease control (DC) defined as objective response (OR) or stable disease (SD) at 16+ wks per RECIST v1.1. **Secondary endpoints:** Progression-free survival (PFS), overall survival (OS), and toxicity per CTCAE. Grade 3-5 adverse events (AEs) or serious adverse events (SAEs) at least possibly related to N+I are reported.

Statistical Methods:

- Simon's optimal two-stage design used to test null hypothesis of 15% DC rate vs. alternative of 35%. Power = 85%; 1-sided α = 10%.
- At least 7 of 28 pts must achieve DC to reject null hypothesis and consider N+I worthy of further study.

Nivolumab plus ipilimumab does not show anti-tumor activity in this cohort of patients with microsatellite stable, hTMB colorectal cancer.

Other treatment options should be considered for these patients, including treatments offered in clinical trials.

Results:

- 12 pts enrolled February 2018 to May 2020. 2 pts were not evaluable and excluded from efficacy analysis. Of the 10 evaluable pts, 1 pt had only a baseline visit followed by an SAE due to clinical progression and was not included in Fig 1. TMB ranged from 9-233 Mut/Mb (median 13); for 1 pt Mut/Mb were not specified. Tumor microsatellite (MS) status was stable for 11 pts; indeterminate for 1 pt. PD-L1 status was not tested for 8 pts and negative for 4 pts.
- **Demographics**: Median age 58 y (range 43,69); 75% male.
- **Clinical characteristics:** 33% PS 0, 67% PS 1; 83% received ≥3 prior systemic regimens; 17% received 2 prior regimens.
- **Outcomes**: 1 PR (10%) and 0 pts SD16+ (Table 1 and Figure 1). OS and PFS are shown in Table 1 and Figure 2.
- **Safety:** 4 pts (33%) had ≥1 SAE or Grade 3-4 AE at least possibly related to N+I, including myasthenia gravis, diarrhea, glucose intolerance, hyperglycemia, and small intestinal obstruction.

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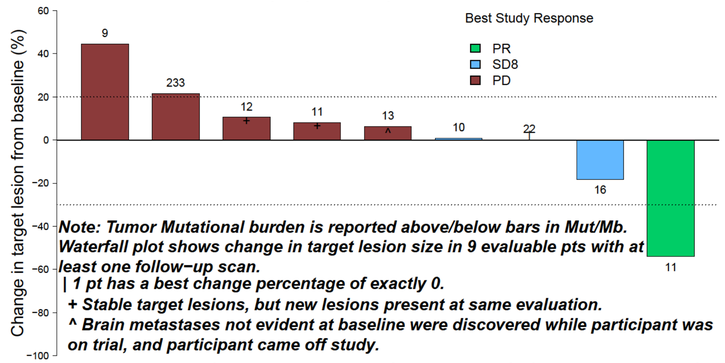
Table 1: Efficacy Outcomes (N=10)	
DC rate, % (95% CI)	10 (0, 45)
OR rate, % (95% CI)	10 (0, 45)
Median PFS, wks (95% CI)	8.9 (5.1, 16.1)
Median OS, wks (95% CI)	42.9 (13.0, 57.4)

Figure 1: Best Percent Change from Baseline in Target Lesion Size (N=9) [PR, partial response; SD8*, SD at 8 wk follow-up visit; PD, progressive disease]

*Pts with SD<16 wks do not meet the study endpoint for response but SD8 is shown here for reference



Note: Tumor Mutational burden is reported above/below bars in Mut/Mb. Waterfall plot shows change in target lesion size in 9 evaluable pts with at least one follow−up scan.
| 1 pt has a best change percentage of exactly 0.
+ Stable target lesions, but new lesions present at same evaluation.
^ Brain metastases not evident at baseline were discovered while participant was on trial, and participant came off study.

Figure 2: OS and PFS in pts with CRC with hTMB treated with N+I (N=10)