The differential response to immune checkpoint inhibitors (ICIs) according to mismatch repair alterations in gastrointestinal (GI) non-colorectal cancers (non-CRCs) and the impact of dual vs. monotherapy ICIs on survival in GI (CRC and non-CRC) cancers

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Introduction

- In patients with mismatch repair deficient (dMMR) colorectal cancers (CRCs), we previously reported that loss of expression of MSH2 and MSH6 (MutS co-loss) was associated with better response to ICIs and longer median overall survival (mOS) compared to loss of expression of MLH1 and PMS2 (MutL co-loss).
- Here, we expanded our analysis and included gastrointestinal (GI) non-CRCs and explored the impact of dual vs. monotherapy ICIs on mOS in GI (CRC and non-CRC) cancers.

Material and Methods

- Specimens were profiled by next-generation sequencing (592, NextSeq; WES, WTS NovaSeq) (Caris Life Sciences, Phoenix, AZ).
- MMR/microsatellite instability (MSI) status was determined by immunohistochemistry (IHC) of MMR protein.
- Real world OS was extracted from insurance claims and calculated using Kaplan-Meier estimates for molecularly defined cohorts from first treatment with ICIs (Nivolumab, Nivo; Ipilumumab, Ipi; or Pembrolizumab, Pembro) to last contact.
- Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q < 0.05$).

Results

- The GI non-CRC cohort (N= 19,767) included cancers of the esophagus, stomach, gastroesophageal junction, pancreas, bile duct and small bowel with 97 (0.49%) patients having MutS co-loss, and 494 (4.03%) patients having MutL co-loss.
- MutS co-loss was associated with increased *KRAS* (45.4% vs 25.2%, q<0.01), *CDKN2A* (29.2% vs 9.0%), *GNAS* (27.8% vs 7.8%) and *SMAD4* (17.5% vs 5.9%) mutations compared to MutL co-loss.
- Independent of treatment, MutS co-loss (N=74) had improved mOS compared to MutL co-loss (N=332) (40.4 m vs. 26.2 m, HR = 0.66; (95% CI: 0.46-0.95), P=0.024).
- In patients treated with ICIs, the mOS in MutS co-loss (N=21) was better compared to MutL co-loss (N=76) (not reached (NR) vs. 25.4 m, HR= 0.23 (95% CI: 0.07-0.75), p=0.008).
- At 3 years, more than 80% of the patients with MutS co-loss were alive.
- Of particular importance, when looking at all GI (CRC and non-CRC) patients, the mOS of MutL co-loss treated with ipi/nivo (N=18) trended for better mOS compared to MutL co-loss treated with pembro (N=215) (NR vs. 28.2m (HR=0.39; (95% CI:0.14-1.07), p=0.057), while the mOS of MutS co-loss treated with ipi/nivo (N=6) was not different compared to MutS co-loss treated with pembro (N=44) (NR vs. NR, HR=0.75 (95% CI: 0.094-5.92), p=0.78).

Results

Figure 1: Prevalence of MutS and MutL in non-CRC GI cancers

All Non-CRC GI		MLH1							
		pos				*neg*			
PMS2	*pos*	MSH2				MSH2			
		pos		*neg*		*pos*		*neg*	
		MSH6		MSH6		MSH6		MSH6	
		pos	*neg*	*pos*	*neg*	*pos*	*neg*	*pos*	*neg*
		19057	37	3	97	0	0	0	0
	neg	MSH2				MSH2			
		pos		*neg*		*pos*		*neg*	
		MSH6		MSH6		MSH6		MSH6	
		pos	*neg*	*pos*	*neg*	*pos*	*neg*	*pos*	*neg*
		69	2	0	0	494	6	0	2

Figure 2: Molecular features in MutS and MutL non-CRC cancers

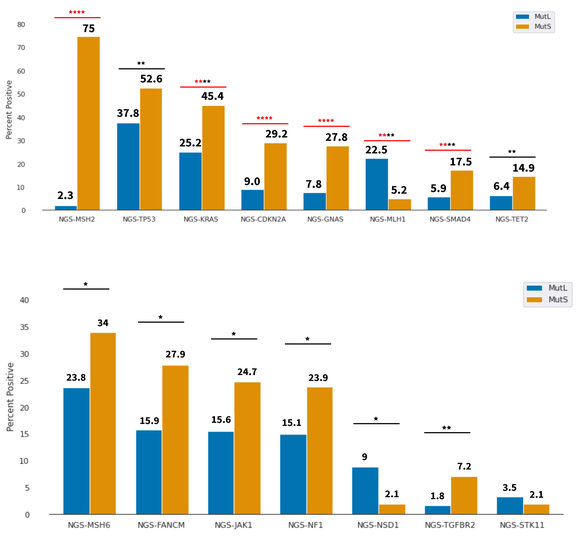


Figure 3: Median Overall survival (collection to last contact)

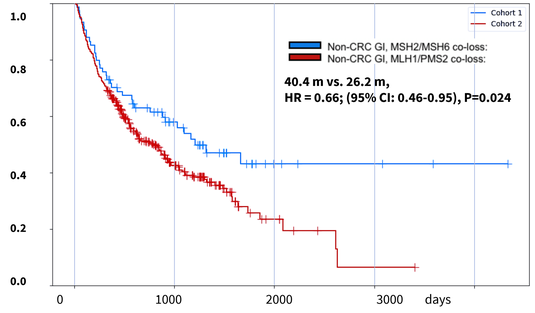


Figure 4: Median Overall survival (ICIs treatment to last contact)

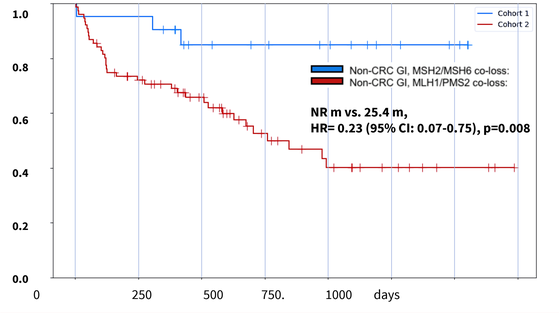


Figure 5: mOS in GI (CRC and non-CRC) MutL (Ipi/Nivo vs Pembro)

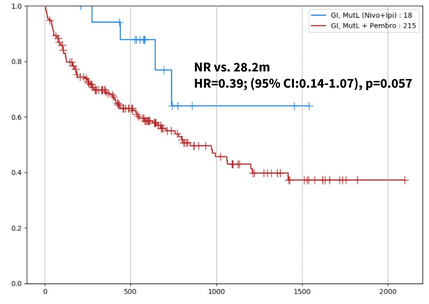
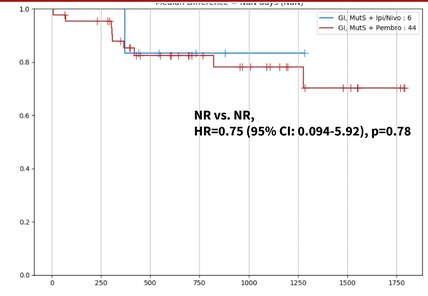


Figure 6: mOS in GI (CRC and non-CRC) MutS (Ipi/Nivo vs Pembro)



Conclusion

- In ICI-treated GI non-CRCs, the mOS was longer in MutS co-loss compared to MutL co-loss.
- In ICI-treated GI (CRC and non-CRC) patients with MutL co-loss, there was a trend for better survival with ipi/nivo compared to pembro.
- Our data suggest that the MutS vs. MutL status may guide the choice of ICIs regimen (Dual vs. Monotherapy) but more data are needed.

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