355: Tumor mutational burden (TMB), microsatellite instability (MSI) status and mutational frequency of 30 DDR genes in Chinese patients with gastric or gastroesophageal junction (GEJ) cancers with different levels of PD-L1 expression

Xiancheng Zeng[1] , Xinyi Liu[2], Mengli Huang[2]; [1]Guangdong Second Provincial General Hospital, Guangzhou 510317, Guangdong, China, [2]Department of Medical, 3D Medicines Inc., Shanghai, China

Background

- Gastric or GEJ cancer with positive PD-L1 expression have been proved a subgroup who can benefit from first-line and second-line therapy of PD-1 inhibitors. Positive PD-L1 expression promises to be the most effective biomarker in gastric/GEJ cancer patients. The results of CheckMate-649 further revealed that patients with PD-L1 CPS≥5 were more favorable to PD-1 inhibitors. On the other hand, high level of tumor mutational burden, MSI-H and mutations in DDR genes had also been identified as biomarkers in setting of immune checkpoint inhibitors in cancers. The difference of genomic features in subgroups with PD-L1 expression level in gastric/GEJ cancers is a question of interest.

Methods

- 613 cases of Chinese gastric/GEJ cancer patients were included in our analysis. Immunohistochemistry and 381-gene panel next-generation sequencing (NGS) testing had been performed in their tumor tissue specimen. PD-L1 expression level was evaluated by the combined positive score (CPS). Tumor mutational burden (TMB) and MSI status were evaluated via NGS testing. Somatic and germline mutations in 30 DDR genes had also been analyzed.

Results

- 493 out of 613 patients were CPS<1, 54 cases were CPS<5, 64 cases were CPS<49, 16 cases were CPS≥50. The median TMB score of four subgroups were 5.59, 7.26, 7.26 and 8.06 respectively (Figure 1).
- The proportion of MSI-H patients in four subgroups were 2.91%, 9.26%, 12.7%, and 12.5% respectively (Figure 2).

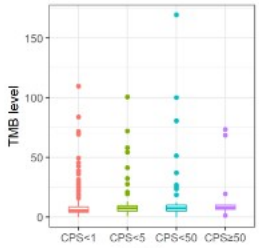

Figure 1

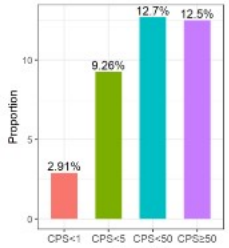

Figure 2

Figure 1. TMB levels in different PD-L1 expression subgroups.

Figure 2. Proportion o MSI-H patients in different PD-L1 expression subgroups.

Results

- ARID1A and ARTX genes only were detected somatic mutated. There was a negative correlation trend in germline mutational proportion and PD-L1 expression level in some genes, such as MSH2, POLE, POLD1, and PTEN. However, the somatic mutational proportion of MSH6, PMS2, POLE genes had a positive correlation trend with PD-L1 expression level (Table).

	gene	CPS<1	CPS<5	CPS<50	CPS≥50
Germline	ATM	60.83	50	30.16	31.25
	BLM	80.83	72.22	44.44	43.75
	BRCA1	51.46	44.44	23.81	43.75
	BRCA2	6.88	3.7	3.17	6.25
	BRIP1	75.42	68.52	42.86	43.75
	CHEK2	56.67	48.15	25.4	37.5
	ERCC1	77.08	66.67	42.86	50
	FANCD2	10.62	11.11	7.94	6.25
	MSH2	81.46	70.37	44.44	50
	MSH6	4.17	1.85	4.76	6.25
	POLD1	79.17	70.37	44.44	50
	POLE	23.75	12.96	11.11	12.5
	PRKDC	80.21	70.37	44.44	50
	PTEN	26.04	24.07	12.7	6.25
	SMARCA4	1.88	5.56	1.59	6.25
	TP53	82.08	72.22	42.86	50
Somatic	ARID1A	14.79	14.81	9.52	18.75
	ATRX	3.75	3.7	9.52	12.5
	MSH6	1.46	5.56	4.76	6.25
	PMS2	2.08	1.85	1.59	6.25
	POLE	0.83	1.85	3.17	6.25
	TP53	55.42	53.7	31.75	37.5

Table. Germline and somatic mutional percentage in different PD-L1 expression subgroups.

Conclusion

- In Chinese gastric/GEJ cancer population, the TMB level of CPS≥1 subgroup was significantly higher than CPS<1 subgroup. MSI-H patients were enriched in CPS>5 subgroup. In addition, DDR genes had distinct mutational frequency in subgroups with different levels of PD-L1 expression, indicating they impact the immunogenicity of gastric/GEJ cancer through different mechanisms.