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Immunotherapy in Advanced Solid Tumour

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Abstract

With the evolving understanding of the interaction between tumor and the immune system, novel therapies with sophisticated mechanisms of action are establishing themselves as the standards of care. In human cancer, the immune system plays a double edged sword with both protecting against tumor development as well as promoting tumor growth. In recent times innumerable practice-changing clinical studies have being reported on immunotherapy. In this review article, we highlight the recently approved immunotherapy and chemotherapy combination in adjuvant and 1st line metastatic setting in various solid tumors except renal cell carcinoma and melanoma.

Keywords: Gastroesophageal; Chemoradiotherapy; Pembrolizumab; Nivolumab

Introduction

Immunotherapy in unrespectable and metastatic oesophageal cancer

Keynote 590 trial compared pembrolizumab plus chemotherapy versus chemotherapy alone as first-line treatment in advanced oesophageal cancer and Sievert type 1 gastro-esophageal junction cancer with PD-L1 CPS of 10 or more in terms of both overall and progression-free survival. Pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy with overall survival (median 13.9 months *vs.* 8.8 months; hazard ratio 0.57 (95% CI 0.43–0.75; p<0.0001. Also in term of progression-free survival Pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy (7.5 months *vs.* 5.5 months; 0.51 (0.41–0.65; p<0.0001 [1-4].

Literature Review

Immunotherapy in metastatic/unrespectable head and neck cancer (excluding Nasophaynx)

In Keynote 048 trial Pembrolizumab alone improved overall survival versus Cetuximab with chemotherapy in the CPS of 20 or more population (median 14.9 months *vs.* 10.7 months, Hazard Ratio (HR) 0.61 (95% CI 0.45–0.83), p=0.0007) and CPS of 1 or more population (12.3 *vs.* 10.3,0.78 (0.64–0.96), p=0.0086) and was non-inferior in the total population (11.6 *vs.* 10.7,0.85 (0.71−1.03)). Pembrolizumab with chemotherapy had better overall survival compared with Cetuximab and chemotherapy in the total population (13.0 months *vs.* 10.7 months, HR 0.77 (95% CI 0.63–0.93), p=0.0034) at the second interim analysis and in the CPS of 20 or more population (14.7 *vs.* 11.0,0.60 (0.45–0.82), p=0.0004) and CPS of 1 or more population (13.6 *vs.* 10.4,0.65 (0.53-0.80), p<0.0001) at final analysis. However neither pembrolizumab alone nor pembrolizumab with chemotherapy improved progression free survival at the second interim analysis. Based on result of Keynote 048 trial Pembrolizumab with chemotherapy is first line treatment in recurrent, unrespectable or metastatic head and neck tumor. Pembrolizumab also improved overall survival compared to chemotherapy in patients having CPS>1 [5]. NCCN recommends Single agent pembrolizumab (category 1) for CPS>20. Consolidation Immunotherapy in Stage III Non-small cell carcinoma lung

Regardless of PDL-1 expression, consolidation Durvalumab after concurrent chemo radiotherapy (the 'PACIFIC regimen') is the standard of care in patients with unrespectable Stage III NSCLC whose disease had not progressed after platinum based cCRT. Updated Median OS and PFS in Durvalumab *vs*. placebo arm was 47.5 *vs.* 29.1 months (stratified HR 0.72, 95% CI 0.59–0.89) and 16.9 *vs.* 5.6 months (stratified HR 0.55, 95% CI 0.45–0.68) respectively. The 60-month OS rates were 42.9% and 33.4% and 60 months PFS rates were 33.1% and 19.0% with Durvalumab and placebo, respectively. These updated survival analyses, showed continue sustained OS and PFS benefit with the PACIFIC regimen [6].

Non driver mutation advanced NSCLC

By phase III KEYNOTE-024 study, Pembrolizumab alone significantly improved progression-free survival and Overall Survival (OS) compared with platinum-based chemotherapy in patients with previously untreated advanced non–small-cell carcinoma PDL 1>50%. Median OS was 30.0 months (95% CI, 18.3 months to not reached) with Pembrolizumab and 14.2 months (95% CI, 9.8 to 19.0 months) with chemotherapy (hazard ratio, 0.63; 95% CI, 0.47 to 0.86). Pembrolizumab had less Grade 3 to 5 adverse events compared with chemotherapy (31.2% *vs.* 53.3%, respectively) [7]. After keynote 189 and keynote 407 trial Pembrolizumab with chemotherapy combination became standard of treatment in non-driver mutation NSCLC regardless of PDL 1 expression.

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Discussion

Extensive stage small lung cancer

Immunotherapy has also demonstrated clinical activity in Extensive-Stage SCLC (ES-SCLC) wherein most patients with Small-Cell Lung Cancer (SCLC) fall at presentation, and for whom the prognosis remains poor.

In IMpower 133 trial, Atezolizumab was combined with chemotherapy. At a median follow-up of 13.9 months, the median overall survival was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (hazard ratio for death, 0.70; 95% Confidence Interval (CI), 0.54 to 0.91; P=0.007). The median progression-free survival was 5.2 months and 4.3 months, respectively (hazard ratio for disease progression or death, 0.77; 95% CI, 0.62 to 0.96; P=0.02). The addition of atezolizumab to chemotherapy in the first-line treatment of extensive stage small cell lung cancer led to significantly longer overall survival and progression free survival than chemotherapy alone [8].

The CASPIAN trial assessed Durvalumab, with or without Tremelimumab, in combination with platinum topside in treatment naive patients with ES-SCLC. Durvalumab plus platinum topside was associated with a significant improvement in overall survival, with a hazard ratio of 0.73 (95% CI 0.59–0.91; p=0.0047); median overall survival of 13.0 months (95% CI 11.5–14.8) in the Durvalumab plus platinum topside group versus 10.3 months (9.3–11.2) in the platinum topside group.

First-line Durvalumab plus platinum topside significantly improved overall survival in patients with ES-SCLC [9].

Triple negative early carcinoma breast

At the first interim analysis of keynote 522 trial, the percentage of patients with a pathological complete response was 64.8% (95% Confidence Interval (CI), 59.9 to 69.5) in the Pembrolizumab chemotherapy group and 51.2% (95% CI, 44.1 to 58.3) in the placebo-chemotherapy group (estimated treatment difference, 13.6 percentage points; 95% CI, 5.4 to 21.8; P<0.001). After a median follow-up of 15.5 months, disease progression that precluded definitive surgery, had local or distant recurrence or a second primary tumor, or died from any cause was observed in 58 of 784 patients (7.4%) in the Pembrolizumab chemotherapy group and 46 of 390 patients (11.8%) in the placebo chemotherapy group had (hazard ratio, 0.63; 95% CI, 0.43 to 0.93). Among patients with early triple-negative breast cancer, Pembrolizumab plus neoadjuvant chemotherapy receiving patients had significantly higher percentage with a pathological complete response than those who received placebo plus neo-adjuvant chemotherapy [10].

Metastatic triple negative carcinoma breast

Atezolizumab received approval in March 2019 based on data from the phase 3 IM passion130 trial which demonstrated a statistically significant benefit to progression-free survival with the exploratory regimen *vs.* placebo/chemotherapy (HR, 0.60; 95% CI, 0.48-0.77; P<. 0001), however, results published in 2021 indicated that the trial failed to meet the primary end point of PFS superiority in the frontline treatment of patients with PD-L1 positivity (HR, 0.82; 95% CI, 0.60-1.12; P=.20). Also, there was observed no difference in survival advantage in the PD-L1–positive (HR 1.11, 95% CI 0.76-1.64) nor the intention to treat population [11]. After this the indication for Atezolizumab in combination with nab-paclitaxel chemotherapy as treatment for patients with Triple-Negative Breast Cancer (TNBC) with tumors expressing PD-L1 was withdrawn by FDA in 2021. Role of immunotherapy is limited to recurrent, unrespectable or metastatic in carcinoma breast patients having MSI high or tumor mutation burden >10 mutt/mob [12].

Hepatocellular carcinoma

IMbrave150 trial included patients with unrespectable hepatocellular carcinoma who had not previously received systemic treatment. The hazard ratio for death with Atezolizumab–Bevacizumab as compared with Sorafenib was 0.58 (95% Confidence Interval (CI), 0.42 to 0.79; P<0.001). Overall survival at 12 months was 67.2% (95% CI, 61.3 to 73.1) with Atezolizumab–Bevacizumab and 54.6% (95% CI, 45.2 to 64.0) with Sorafenib. Median progression free survival was 6.8 months (95% CI, 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6) in the respective groups (hazard ratio for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001). In patients with unresectable hepatocellular carcinoma, Atezolizumab combined with Bevacizumab resulted in better overall and progression free survival outcomes than Sorafenib (Table 1).

Table 1 : Justify about clinical trial and its outcomes.

Clinical trial		Main Objective	DFS/PFS	OS	outcome
Esophagus, GE junction and Gastric cancer					
CheckMate 649	Adjuvant Nivolumab *vs.*		22.4 months	-	Adjuvant Nivolumab became part of treatment
(stage II& III)	Placebo		11 months		
			7.7 months	14.4 months	
CheckMate 649	Nivolumab+ chemotherapy *vs.* Chemotherapy		6.0 months	11.1 months	Nivolumab + chemotherapy approved in 1st line treatment in advanced gastric and GE junction tumour oesophageal adenocarcinoma CPS >5
Keynote 590	Pembrolizumab+ chemotherapy *vs.* Chemotherapy		7.5 months	5.5 months	
			13.9 months	8.8 months	Pembrolizumab+ chemotherapy approved in 1st line treatment in

					unresected and metastatic esophageal cancer CPS>10
Head and Neck					
Keynote 048		Pembrolizumab *vs.* Cetuximab +chemotherapy	HR 0·99 95% CI 0.75−1.29 (p=0.4562)	14·9 months (CPS >20) 10.7 months	pembrolizumab +chemotherapy became *vs.* 1st choice Recurrent, unresectable or metastatic head and neck tumour. pembrolizumab alone in patient with CPS >20
		Pembrolizumab +chemotherapy *vs.* Cetuximab+ chemotherapy	HR 0·73 95% CI 0.55−0.97 p=0.0162	14·7 months (CPS >20) 11.0 months	
Lung (NSCLC)					
PACIFIC trial		Durvalumab *vs.* Placebo	10.3 months	47.5 months	consolidation durvalumab became standard of treatment in stage III NSCLC whose disease had not progressed after cCRT
			6 months	29.1 months	
Lung (advanced NSCLC)					
Keynote 024 trial		Pembrolizumab *vs.* chemotherapy	16.9 months	30 months (PDL-1 >50%)	Pembrolizumab improved OS and PFS in advanced untreated NSCLC PDL1>50% without driver mutation
			5.6 months	14.2 months	
Extensive stage small cell carcinoma lung					
Impower 133 trial		atezolizumab + chemotherapy *vs.* chemotherapy	5.2 months 4.3 months 10.3 months	12.3 months	atezolizumab added with chemotherapy improved OS and PFS in 1st line extensive stage small cell lung cancer regardless of PDL1 expression
CASPIAN trial		durvalumab+ chemotherapy *vs.* chemotherapy	- -	13 months 10.3 months	durvalumab added with chemotherapy improved OS in 1st line extensive stage small cell lung cancer
Hepatocellular carcinoma					
Imbrave 150 trial		atezolizumab+Bev *vs.* sorafenib	6.8 months 4.3 months	67.2% at 12 months 54.6% at 12 months	atezolizumab with bevacizumab improved OS and PFS in hepatocellular carcinoma regardless of PDL1 expression

Conclusion

Immunotherapies have revolutionized the treatment standards in solid tumours. They have provided meaningful survival improvements in patients with poor-prognosis cancers and for certain cancer types in which therapeutic options were limited. Many aspects of their use, including optimal combinations, sequencing, duration, and clinical setting, remain to be clarified. On-going clinical trials will serve to further increase their role, but careful consideration must be given to finding the safest, most individualized, and most cost-effective way to integrate them into the core of cancer care.

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