Emerging role of immunotherapies in early stage solid tumors

Immunotherapies are expected to become a part of the standard preoperative and adjuvant treatment settings in various solid cancers. In the early stages, the immune microenvironment is robust and healthy, with a broader response to immunotherapies and more patients could be drawn into long-term remission or downstaging of the tumors. This has been supported by the recent approval of immunotherapies such as pembrolizumab in non-muscle invasive bladder cancer (NMIBC) and high-risk triple-negative breast cancer (TNBC), and durvalumab in Stage III unresectable non-small cell lung cancer (NSCLC). We saw continued momentum with new data presented at ESMO 2021 demonstrating the benefits of immunotherapy in early stage disease.

The KEYNOTE-716[1] trial demonstrated that pembrolizumab as adjuvant immunotherapy prolonged recurrence-free survival (RFS) and decreased the risk of death in resected high-risk Stage IIb and IIc melanoma patients.

- KEYNOTE-716, a Phase III double-blind trial, evaluated pembrolizumab (pembro) vs. placebo in patients with complete resection of cutaneous IIB or IIC melanoma with negative sentinel lymph node biopsy.
- 976 patients (64% Stage IIB; 34.8% Stage IIC) were randomized (pembro: placebo) and followed up for a median of 14.4 months.
  - Adjuvant pembrolizumab for resected Stage IIB and IIC melanoma decreased the risk of disease recurrence or death by 35% compared with placebo and was associated with significantly prolonged RFS; 12-month RFS rate was 90.5% vs. 83.1%.
  - Grade ≥3 drug-related adverse events (pembro vs. placebo group) occurred in 16.1% vs. 4.3% patients and 15.3% vs. 2.5% discontinued due to a drug-related AE. No deaths were reported due to any-cause AE or drug-related AEs in the pembro arm.

Atezolizumab demonstrated improvement in disease-free survival (DFS) in the adjuvant NSCLC setting, after complete resection and platinum-based chemotherapy[2].

- IMpower010, a randomized Phase III study, showed significant DFS improvement with adjuvant cancer immunotherapy (CIT) after adjuvant chemotherapy in patients with early stage resected NSCLC.
  - 1,269 patients received adjuvant chemotherapy; 1,005 patients were randomized to atezolizumab (n=507) or best supportive care (BSC; n=498); 495 in each group received treatment.
  - Atezolizumab, following surgery and chemotherapy, reduced the risk of disease recurrence or death (DFS) by 34% (hazard ratio [HR] = 0.66, 95% CI: 0.50–0.88) in Stage II-IIIA NSCLC patients whose tumors express PD-L1 ≥ 1%, compared with BSC.
  - An extended analysis of PD-L1 subgroups in the Stage II-IIIA population showed a higher magnitude of benefit from adjuvant atezolizumab, in patients with PD-L1 expression ≥50%, compared with 1–49% PD-L1 expression.
  - Atezolizumab-related Grade 3 and 4 AEs occurred in 53 (11%) of 495 patients and Grade 5 events in 4 patients (1%).

Interim results from the AURA Phase II trial demonstrated a high pCR rate with neoadjuvant avelumab in combination with cisplatin-based NAC regimen in MIBC[3].

- AURA is a prospective, non-comparative, multicenter, randomized, Phase II trial for patients with MIBC irrespective of their platinum sensitivity.
- Cisplatin-eligible patients receive cisplatin-gemcitabine (CG) plus avelumab or dose-dense MVAC (dd-MVAC) plus avelumab (1:1). Whereas cisplatin-ineligible patients receive paclitaxel- gemcitabine (PG) plus avelumab or avelumab alone (1:1).
  - 56 cisplatin-eligible patients were evaluated at interim analysis data cut-off. High pCR rates were observed for dd-MVAC + avelumab: 64% and CG + avelumab: 57%.
  - Manageable AEs that did not compromise on surgery were observed. The most common Grade 3/4 AEs were thrombocytopenia (29%), acute kidney injury (18%), neutropenia (14%), and anemia (13%); no treatment-related deaths were reported.

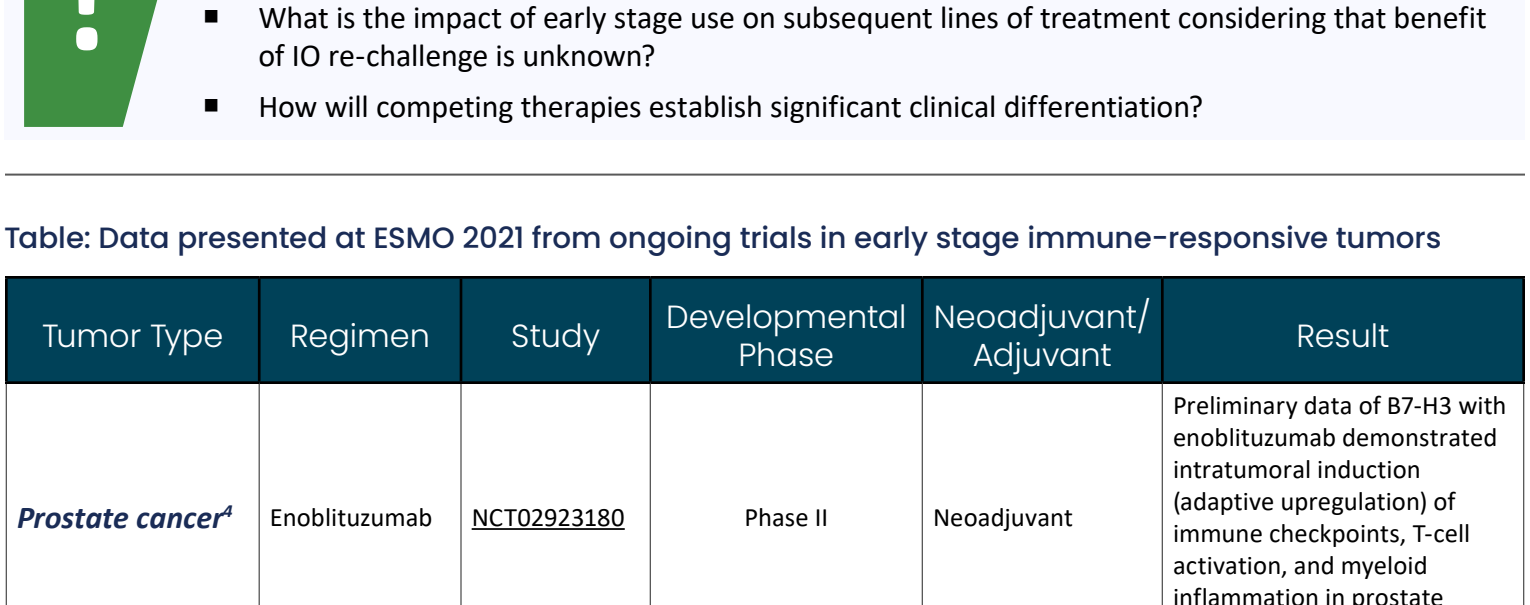
Additional clinical outcomes reported with I/O therapies in early stage cancer are summarized in Table and Figure below. New data readouts from ongoing I/O clinical trials will help address some key questions in early stage tumors:

- Will monotherapy approaches succeed or will combinations be required?
- Who are the appropriate patients for treatment in the adjuvant setting?
- What is the optimum duration of therapy?
- What is the impact of early stage use on subsequent lines of treatment considering that benefit of IO re-challenge is unknown?
- How will competing therapies establish significant clinical differentiation?

Table: Data presented at ESMO 2021 from ongoing trials in early stage immune-responsive tumors

Tumor Type	Regimen	Study	Developmental Phase	Neoadjuvant/ Adjuvant	Result
Prostate cancer[4]	Enoblituzumab	NCT02923180	Phase II	Neoadjuvant	Preliminary data of B7-H3 with enoblituzumab demonstrated intratumoral induction (adaptive upregulation) of immune checkpoints, T-cell activation, and myeloid inflammation in prostate cancer patients
Non-small cell lung cancer (NSCLC)[5]	Toripalimab + Carboplatin	ChiCTR19000-24014	Phase II	Neoadjuvant	Interim data of neoadjuvant toripalimab + chemotherapy reported PR of 57.5% and CR of 17.5% in patients with Stage II and III EGFR/ALK wild-type NSCLC
Hepatocellular carcinoma (HCC)[6]	Camrelizumab + apatinib	NCT03722875	Phase II	Adjuvant	Camrelizumab + apatinib showed promising efficacy with mRFS of 11.7 months, OS @ 2-year was 75.7%; RFS @ 2-year was 41.0%
Triple-negative breast cancer (TNBC)[7]	Atezolizumab + Paclitaxel ± Ipatasertib	BARBICAN	Phase II	Neoadjuvant	Ipatasertib (IPAT) + neoadjuvant chemotherapy + atezolizumab did not improve pCR rates (49.3% vs. 48.5%, without IPAT)

Figure: Recently initiated trials in early stage solid tumors



References

1. J. J. Luke, P. Rutkowski, P. Queirolo. Pembrolizumab versus placebo after complete resection of high-risk Stage II melanoma: Efficacy and safety results from the Keynote 716 double-blinded Phase III trial (KEYNOTE-716). [Abs#LBA3].
2. E. Felip, E. Vallieres, C. Zhou, et al. Sites of relapse and subsequent therapy from a Phase III study of atezolizumab vs best supportive care after adjuvant chemotherapy in Stage IB-IIIA NSCLC (IMpower010). Abs# LBA9.
3. M. Chanza, A. Carnot, P. Barthelemy, et al. Avelumab (A) as the basis of neoadjuvant chemotherapy (NAC) regimen in platinum eligible and ineligible patients (pts) with non-metastatic muscle invasive bladder cancer (AURA). Abs#659MO.
4. E. Shenderov, A. De Marzo, T. Lotan, et al. Phase II neoadjuvant trial of the anti–B7-H3 antibody, enoblituzumab, in men with localized prostate cancer: Safety, efficacy and immune correlates. [Abs#627P].
5. X. Zhu, L. Sun, N. Song, et al. Neoadjuvant PD-1 inhibitor (toripalimab) plus chemotherapy in patients with potentially resectable NSCLC: An open-label, single-arm, Phase II trial. [Abs#1176P].
6. X. Yang, H. Sun, B. Hu, et al. Adjuvant camrelizumab combined with apatinib treatment after resection of hepatocellular carcinoma in CNLC II and III stage: A single-center prospective Phase II trial. [Abs#944P].
7. P. Schmid, F. J. Salvador Bofill, B. Bermejo, et al. BARBICAN: A randomized, Phase II study to determine the contribution of ipatasertib (AKTi) to neoadjuvant chemotherapy plus atezolizumab in women with TNBC. [Abs#123MO].
8. G. Bregni, C. Senti, E. Acedo Reina, et al. REGINA: A Phase II trial of neoadjuvant regorafenib (rego) in combination with nivolumab (nivo) and short-course radiotherapy (SCRT) in intermediate-risk, Stage II-III rectal cancer (RC). [Abs#505TiP].
9. X. Kang, J. Xu, R. Zhang, et al. Adjuvant immunotherapy for resected esophageal squamous cell carcinoma with high risk of recurrence (AIRES): A multicenter, open-label, randomized, controlled Phase III Trial. [Abs# 1435TiP].
10. C. Wang, M. Wang, B. Yu, et al. Penpulimab (PD1i)-based combination neoadjuvant/adjuvant therapy for patients with resectable locally advanced NSCLC: A phase II clinical study (ALTER-L043). [Abs# 1169TiP].

SmartAnalyst is helping clients interpret the data presented at ESMO 2021 focusing on key developments in cancer research. Contact us to learn more

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