Industry corner: perspectives and controversies

New realities of phase I clinical trials in the era of immuno-oncology: the durvalumab experience

The rapid emergence of cancer immunotherapy has been driven by unique development strategies including novel study designs, resulting in new therapeutics being brought to the market with unprecedented speed. For example, development of durvalumab, a human immunoglobulin G1 (IgG1) anti-programmed death-ligand 1 (PD-L1) monoclonal antibody, was initiated by AstraZeneca in 2012 with a multicenter, open-label, first-time-in-human phase I study, later expanded into a phase I/II study in 2014 (Study 1108; NCT01693562; Figure 1). The expansion phase of this study included tumor types selected based on unmet medical need, tumoral PD-L1 expression, and underlying biology. Tolerable safety profiles and durable clinical activity have been observed in patients with various solid tumor types (supplementary Figure S1 and Table S1, available at *Annals of Oncology* online). While early-phase registrational studies were uncommon in the pre-immuno-oncology (IO) era, there have been several notable examples of phase I studies leading to approval of checkpoint inhibitors, including Study 1108; results from the urothelial cancer (UC) cohort led to accelerated approval in the United States for postplatinum locally advanced or metastatic UC in 2017. Such rapid development is associated with unique challenges, including evolving study parameters and treatment paradigms as well as emerging biomarker research.

Antibodies targeting the PD-1/PD-L1 pathway are associated with predominantly immune-related toxicity, which may not be strictly dose-related and therefore presents a challenge when investigating the maximum tolerable dose. Dose selection criteria for durvalumab were based on pharmacokinetics (PK; linearity, exposure-response and exposure-safety profiles), pharmacodynamics (including low rate of antidrug antibodies), and clinical activity [1], leading to the selection of a 10 mg/kg Q2W dose and schedule. Subsequently, population PK analyses using data from Study 1108 and ATLANTIC [a phase II, open-label, single-arm study of durvalumab monotherapy in non-small-cell lung cancer (NSCLC)] demonstrated similar median steady state PK concentrations for weight-based and fixed-dose regimens [2], which resulted in a more convenient, less frequent dosing schedule, and adoption of a 1500 mg Q4W durvalumab dose (equivalent to 20 mg/kg Q4W; average body weight of 75 kg) in the majority of durvalumab studies moving forward.

For combination regimens, including 'IO-IO' and 'IO-targeted therapy' [e.g. tyrosine kinase inhibitors (TKIs)], determination of the appropriate dose of two agents previously evaluated as monotherapies must balance the anticipated clinical benefit and likely increased toxicity resulting from the combination. Existing toxicity management guidelines for single-agent immunotherapies may need to be modified due to the increased frequency and severity of adverse events (AEs) with combination regimens. There is an additional challenge in providing adequate management guidance for combination treatment-emergent toxicities with an as yet unknown etiology, such as the increased occurrence of interstitial lung disease observed with durvalumab in combination with the epidermal growth factor receptor TKI osimertinib, which led to a hold on study recruitment [3]. This led to adverse event management guidelines based on data from AstraZeneca studies being continuously updated in response to emerging internal and external data; these are available to trial investigators online for rapid dissemination.

Appropriate oversight of patient safety in the context of a rapidly expanding and increasingly complex study, which might eventually serve as the basis for early approval, is another critical aspect. To ensure appropriate oversight, Study 1108 had a study-specific dose-escalation committee, which regularly reviewed safety, including all AEs, laboratory parameters, and PK and pharmacodynamic data. This committee also made dose-escalation decisions and recommendations regarding further study conduct. An internal pharmacovigilance team, independent of study teams, also continuously assessed safety across multiple durvalumab studies including Study 1108.

Training and validation of the VENTANA SP263 Assay (Ventana Medical Systems, Inc., Tucson, Arizona, USA) was carried out using NSCLC and head and neck squamous cell carcinoma data from Study 1108 to define a cutoff of 25% PD-L1 expression on tumor cells (TCs) [4]. For UC, while preliminary data suggested that PD-L1 expression might be higher on tumor-infiltrating immune cells (ICs), a 25% cutoff based on TC or IC staining was chosen as both seemed to contribute to the stratification of response [5]; the VENTANA SP263 Assay has since been approved as a complementary diagnostic test for use with durvalumab for patients with UC.

The development of a diagnostic assay while other PD-L1 assays were simultaneously under development presented several challenges. Evaluation, use, and comparison of assays are complicated by the various cutoffs, cell types, and algorithms used to assess PD-L1 and there are limitations to their interchangeability [6]. Even where concordance might be considered acceptable between PD-L1 antibodies, variability in pathologist scoring can be another source of discrepancies, particularly when evaluating low levels of PD-L1 expression [7]. Novel phenomic methodologies have been developed to automate image analysis of tissue samples to assess CD8 and PD-L1 expression, which could provide more accurate stratification of patient populations into responders and non-responders to anti-PD-1/PD-L1 antibodies [8] and minimize discordance across different assay platforms and between pathologists.

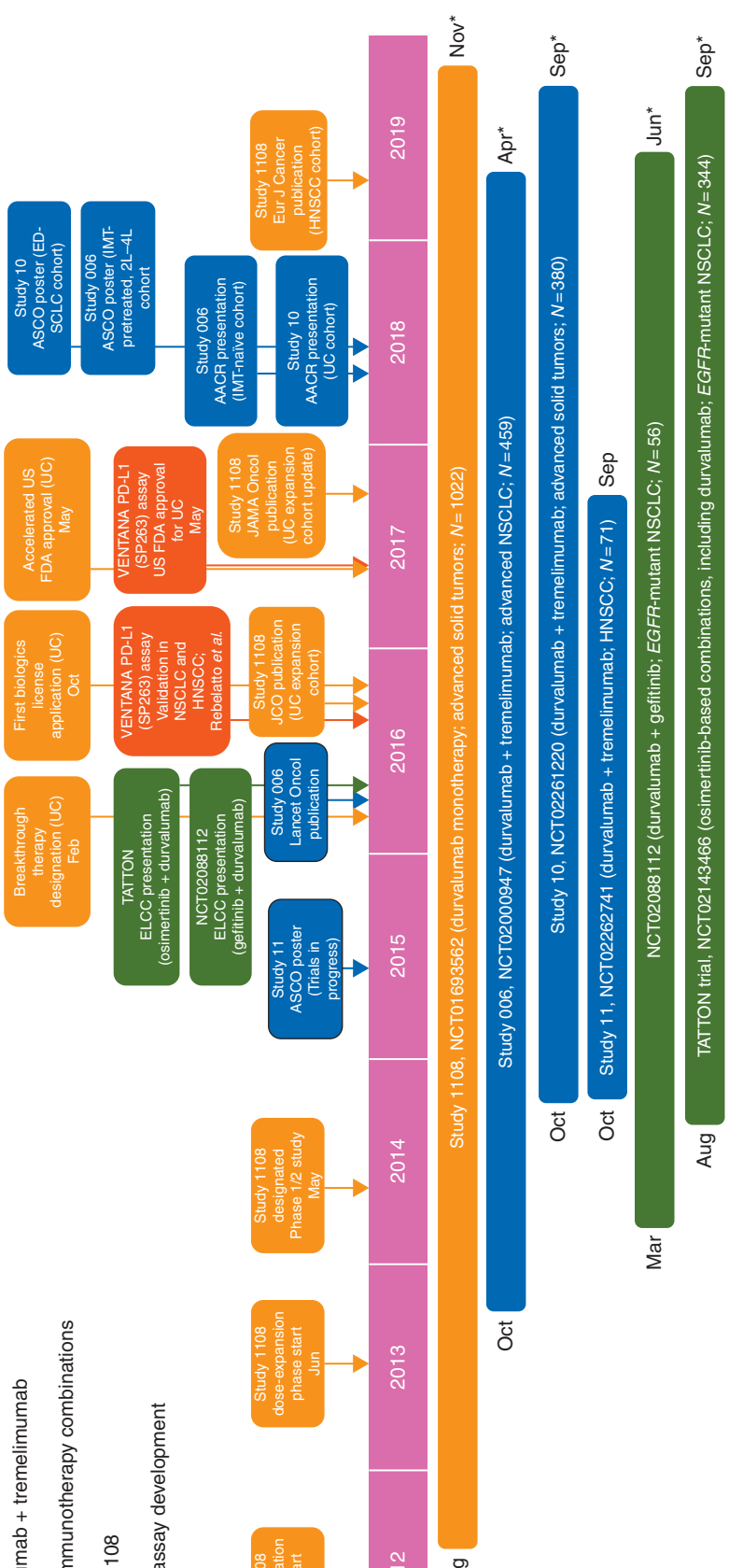

Figure 1. Timeline of key events in the development of Study 1108, the VENTANA SP263 Assay, and the start and completion dates for key Phase 1 combination studies. *All expected primary outcome measure completion dates correct at the time of publication. ELCC; VENTANA, PD-L1, programmed death-ligand 1; FDA, Food and Drug Administration; UC, urothelial carcinoma; ASCO; ED-SCLC, extensive-disease small-cell lung cancer, 2L/4L, second-line and fourth-line treatment; IMT, immunotherapy; ASCO, American Society of Clinical Oncology; AACR, American Association for Cancer Research; HNSCC, head and neck squamous cell carcinoma; *EGFR*, epidermal growth factor receptor; ELCC, European Lung Cancer Congress; NSCLC, non-small-cell lung cancer.

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The relatively large dataset from Study 1108 (pooled when possible with data from other early phase monotherapy and combination studies) and incorporation of biomarker analyses into protocol amendments based on evolving research have enabled identification of potential prognostic and predictive biomarkers associated with response to durvalumab. These results have informed subsequent durvalumab trial designs in later phases and in studies of new indications, as exploratory efficacy end points or for patient selection to enrich populations. While distinguishing between prognostic and predictive factors can be challenging when early phase studies lack comparator arms, population-based tumor kinetic modeling was used in UC patients receiving durvalumab to identify liver metastasis as a significant prognostic factor impacting tumor growth rate, and baseline tumor size and IC PD-L1 expression as predictive factors for tumor killing after durvalumab treatment; this modeling also identified multiple significant covariates for overall survival [9]. Noninvasive biomarkers, such as somatic mutations in circulating tumor DNA, permit longitudinal monitoring of tumor burden [10]. Subgroup analyses of ORR data from Study 1108 indicated that patients with tumoral PD-L1 expression $\geq$90% were more likely to respond to durvalumab, and this cutoff has been investigated in patients with NSCLC in ATLANTIC [11]. Finally, novel patterns of antitumor response to immunotherapy, such as baseline lesion shrinkage with new lesions, durable stable disease followed by a slow decrease in tumor burden, and response after an initial increase in total tumor burden, can be captured using modified immune-related RECIST criteria [12], which has been incorporated as an exploratory end point in later studies investigating durvalumab.

Patterns of response and resistance to immunotherapy in phase I trials will continue to inform the design of future studies to identify rational combinations to overcome each of the specific resistance mechanisms underlying both primary and acquired forms of IO resistance by combining PD-1/PD-L1 antagonists with chemotherapy, radiotherapy, and other novel molecules (including IO agents). HUDSON (NCT03334617), a platform phase II study in patients with IO-pretreated metastatic NSCLC, uses a modular design to systematically understand mechanisms of resistance, and evaluate efficacy, safety, and tolerability of multiple treatment arms based on a durvalumab backbone. Other early-phase IO studies are planned or continue to enroll IO-pretreated patients, such as cohort C of the phase 1/2 durvalumab + tremelimumab study in NSCLC (Study 006; NCT02000947), with the aim of better characterizing immune dysfunction and the heterogeneity of the tumor microenvironment, and ultimately improving outcomes with new combinations in this emerging population. Biomarker-based tumor-agnostic study designs enable enrichment without a restriction to specific tumor types and may help separate general resistance mechanisms from differential effects due to tumor location. Lastly, another approach to overcome IO resistance is to move the use of IO agents into earlier stages of disease, which is strongly supported by the promising results from PACIFIC (NCT02125461) [13] and other neoadjuvant trials of PD-1 and PD-L1 agents in NSCLC.

These experiences in early-phase IO research are now enabling a more informed and efficient approach to future clinical development paradigms. This includes adaptive platform studies to assess multiple treatment combinations within one study, use of biomarkers to prescreen or screen patients for enrollment or therapy allocation, use of predictive factors to identify patients who are more likely to benefit from immunotherapy, and incorporation of novel end points [14]. Implementation of these approaches will continue to offer promise and help to more accurately identify the right treatment of the right patient.

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