1072P Beyond classical surrogate endpoints in trials of PD1/PD-L1 immune checkpoint inhibitors (ICI) plus chemotherapy (CT)

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Background: Several studies showed the inaccuracy of classical surrogate endpoints, such as progression-free survival (PFS) and objective response rate (ORR), in predicting overall survival (OS) in trials of ICI. Patients that respond to immunotherapy have longer median duration of response (mDR) than those that achieve an ORR with standard CT. We aimed to explore the validity of new surrogate endpoints that take into account ORR and mDR in the context of combination ICI trials.

Methods: Systematic review of randomized controlled trials (RCT) investigating anti-PD1/PD-L1 drugs plus CT versus CT alone (published until May 2020). We performed both (i) arm-level analysis to evaluate median overall survival (mOS) predictors; and (ii) comparison-level analysis for OS hazard ratio (HR). Linear regression models weighted by trial size were fitted and adjusted R^2 was used to quantify OS prediction.

Results: A total of 11 RCT involving 6,675 patients met the inclusion criteria (5 non-small cell lung, 2 small-cell lung, and one bladder, breast, gastric and head & neck cancer each). All RCT were conducted in first-line setting, 55% with anti-PD-L1 and 45% with anti-PD1 combinations. mOS ranged from 10 to 25 months across trials and HR for OS ranged from 0.49 to 0.85. In the arm-level analysis, the best mOS prediction was obtained with a new endpoint that combines ORR and mDR (mDORR = ORR*mDR), with an adjusted $R^2 = 0.71$ (Table). In the comparison-level analysis, the best predictor for OS HR was again mDORR ratio (ORR odds ratio * mDR ratio) with an adjusted $R^2 = 0.55$. The classical PFS HR showed a weaker association with OS HR (adjusted $R^2 = 0.38$).

Table: 1072P

Median OS (arm-level analysis)	*Adjusted R^2*
Surrogates	
ORR * mDR	0.71
1-year PFS	0.66
mDR	0.58
ORR	0.19
OS HR (comparison-level analysis)	
ORR odds-ratio * mDR ratio	0.55
ORR odds-ratio	0.54
PFS HR	0.38
mDR ratio	0.01

Conclusions: The new surrogate endpoint ORR*mDR is a promising predictor of mOS in trials of anti-PD1/PD-L1 plus CT. There is moderate association with OS HR, but the new surrogate is still more accurate than PFS for this purpose. mDORR may be used for estimating the potential efficacy of ICI combinations in early trials and making a decision to proceed to larger RCT.

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1073TiP A phase I, first-in-human, multicenter, open-label, dose-escalation study of IPH5201 as monotherapy or in combination with durvalumab ± oleclumab in advanced solid tumours

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Background: CD39, an extracellular enzyme, is overexpressed in the tumor microenvironment, on both tumor infiltrating cells and stromal cells in several cancer types. CD39 promotes immunosuppression by degrading adenosine triphosphate (ATP) into adenosine monophosphate (AMP), that is then further degraded into adenosine by CD73. IPH5201, an anti-CD39 blocking monoclonal antibody, has the potential to promote accumulation of immune-stimulatory ATP and reduce the formation of immunosuppressive adenosine, thereby leading to increased antitumor immunity for multiple tumor types. Preclinical studies demonstrated that IPH5201, in combination with PD-L1 checkpoint inhibitors, increased antitumor efficacy versus a PD-L1 inhibitor alone. This is a phase I, first-in-human, multicenter, open-label, dose-escalation study of IPH5201 as monotherapy or in combination with durvalumab (anti—PD-L1) ± oleclumab (anti-CD73) in patients with advanced solid tumors.

Trial design: Eligible subjects are aged ≥18 years, with advanced solid tumors, and an ECOG PS of ≤1, no conventional or investigational anticancer therapy (eg, anti—CTLA-4, anti—PD-1, anti—PD-L1 antibodies) within 21 days prior to the first dose and no prior agents targeting CD73, CD39, or adenosine receptors. The study will consist of 3 distinct dose-escalation parts given every 3 weeks: IPH5201 monotherapy (part 1), IPH5201 + durvalumab (anti—PD-L1; part 2), and IPH5201 + durvalumab + oleclumab (anti-CD73; part 3). Dose escalation will be based on an m-TPI-2 algorithm of 3 to 12 subjects per cohort. For parts 1 and 2, additional pharmacodynamic cohorts will enroll 6 to 12 subjects at a specific dose with mandatory paired biopsies. The primary endpoint will evaluate safety and tolerability and determine the MTD of IPH5201 in monotherapy and in combination with durvalumab +/- oleclumab. Secondary endpoints will evaluate preliminary antitumor activity and characterize pharmacokinetics and immunogenicity. Up to 204 subjects will be enrolled in the United States, France, Spain, and Switzerland.

Clinical trial identification: NCT04261075.

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1074TiP SGNTGT-001: A phase I study of SGN-TGT, an effector-function enhanced monoclonal antibody (mAb), in advanced malignancies

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Background: T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is an inhibitory immune checkpoint receptor expressed on subsets of T cells and NK cells. SGN-TGT is an effector-function enhanced human mAb that targets TIGIT with pico-molar affinity and blocks TIGIT's interaction with CD155 and CD112. SGN-TGT was developed to have amplified binding to and engagement of Fcγ receptors. Enhanced effector function increases TIGIT+ T-regulatory cell depletion, enhances innate immune cell activation, and augments naïve and memory CD8+ T-cell responses. Preclinically, SGN-TGT elicits superior anti-tumor immune responses compared to other TIGIT mAbs without effector-enhanced backbones, with curative anti-tumor activity as monotherapy and in combination with other immune-modulators.

Trial design: This phase I, open-label, multicenter, dose-escalation study [NCT04254107] is assessing the safety and tolerability of SGN-TGT monotherapy in ~85 adults (≥18 years) with histologically or cytologically confirmed relapsed, refractory, or progressive metastatic solid tumors (non-small cell lung or gastric carcinomas) or lymphomas (classical Hodgkin lymphoma, diffuse large B-cell lymphoma, or peripheral T-cell lymphoma, not otherwise specified). SGN-TGT will be infused on Day 1 of 21-day cycles. In Part A, the safety and tolerability of SGN-TGT will be assessed in ~25 subjects to identify the maximum tolerated dose and recommended phase II dose (RP2D). In Part B, the safety and antitumor activity of the RP2D will be assessed in ~60 subjects in disease-specific expansion cohorts. Primary endpoints are adverse events, laboratory abnormalities, dose-limiting toxicities, and dose-level safety and activity. Secondary endpoints are objective response (OR) rates, best response rates, duration of OR, complete response, progression-free survival, and overall survival, PK, and antidrug antibodies. Exploratory biomarkers of SGN-TGT-mediated PD effects, PK-PD correlations, and correlative analyses of PD measurements and response, toxicity, and resistance will be explored. The study was opened April 2020 and is enrolling.

Clinical trial identification: NCT04254107.

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