415 TORIPALIMAB PLUS NAB-PACLITAXEL AND CARBOPLATIN AS NEOADJUVANT THERAPY FOR PATIENTS WITH ESOPHAGEAL SQUAMOUS CELL CARCINOMA AT CLINICAL STAGE T2-T4/N0-N2/M0: A SINGLE-ARM, SINGLE-CENTER CLINICAL STUDY

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Background Several immune checkpoint inhibitors (ICIs), represented by programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) antibodies, have been approved for treatment of various malignant tumors (including advanced esophageal cancer) worldwide, and previous studies confirmed that they can significantly improve overall survival.[1] However, there has been limited research on the use of ICIs as neoadjuvant therapy for patients with esophageal cancer. Toripalimab is a humanized IgG4 monoclonal antibody that targets PD-1. The objective of this study is to evaluate the efficacy and safety of toripalimab plus chemotherapy as a neoadjuvant therapy regimen for treatment of patients with locally advanced esophageal squamous cell carcinoma (ESCC).

Methods This single-arm, single-center study enrolled patients with ESCC at clinical stage T2-T4/N0-N2/M0, who were eligible for radical resection and regional lymph node dissection. The patients received 2–3 cycles of toripalimab (240 mg d1, Q3W) in combination with nab-paclitaxel (260 mg/m^2 d1, Q3W) and carboplatin (AUC=5 d1, Q3W) before surgery. Preoperative evaluation was performed within 4 weeks after the last administration of chemotherapy. The primary endpoints were pathologic complete response (PCR) and major pathologic response (MPR), and the secondary endpoints were safety and feasibility of the neoadjuvant immunotherapy.

Results Seventeen patients diagnosed with ESCC at a pre-treatment clinical stage of T2-T4/N0-N2/M0 were included. After neoadjuvant therapy, 15 of 17 patients (88.2%) experienced downstaging and met the surgical criteria. Twelve patients (80.0%) underwent surgery without delay and 3 patients (20.0%) refused surgery. The tumors were completely removed in all 12 patients (R0 resection rate: 100%). Seven patients (58.3%) achieved MPR and 2 (16.7%) achieved PCR. The median post-surgical follow-up time was 4.5 months, and there were no recurrences. Treatment-related adverse events (TRAEs) of the neoadjuvant therapy were tolerable. Grade 3 or higher TRAEs occurred in 2 patients (11.8%), but these did not delay surgery.

Conclusions Toripalimab in combination with chemotherapy as neoadjuvant therapy showed promising anti-tumor activity with acceptable tolerance for locally advanced ESCC, as demonstrated by reducing the tumor burden, improving the R0 resection rate, reducing the postoperative recurrence rate, and no delays in surgery.

Acknowledgements N/A

Ethics Approval This study was approved by the Ethics Board of the Army Medical center of the PLA, approval number 142(2018).

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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416 SQ3370–001 IS A MULTI-CENTER OPEN-LABEL PHASE I DOSE-ESCALATION STUDY TO TEST A NOVEL INTRATUMORAL AND SYSTEMIC APPROACH TO TREAT ADVANCED SOLID TUMORS

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Background Cancer immunotherapies have been very successful in recent times; however, they benefit only a subset of patients and have varying response rates across tumor types. Conversely, conventional chemotherapies are effective in a large group of patients, but have limited dosing capabilities, lack specificity, and often result in systemic adverse events. Here, we present SQ3370, a novel approach that activates doxorubicin (Dox) at the tumor site while avoiding systemic toxicities commonly associated with the therapy, and also potentially activates an immune response against tumors. SQ3370 is based on a local intratumoral injection of a prodrug-capturing biomaterial (SQL70) followed by 5 daily systemic infusions of an attenuated form of Dox (SQP33). Mutually-reactive click chemistry groups in the 2 components allow the capture and release of active Dox at the tumor site. While conventional Dox is known to induce immune activation[1] and enhance tumor responsiveness to checkpoint inhibitors,[2] its benefit is limited by cumulative dose cardiotoxicity. We safely administered SQ3370 in dogs at 8.95-times the veterinary clinical dose of Dox with minimal side effects including cardiotoxicity and immunosuppression. In syngeneic mouse models, SQ3370 improved overall survival and induced a robust anti-tumor response against the biomaterial-injected lesion compared to conventional Dox. Surprisingly, SQ3370 also induced regression of the non-injected tumor and enhanced T-cell infiltration in both injected and noninjected tumors. We hypothesize that activating Dox at a local site with SQ3370 promotes activation of the native immune system against the tumor. Thus, SQ3370 represents a new therapeutic modality to treat solid tumors by using a drug with known efficacy, Dox, and expanding its therapeutic window. SQ3370 could potentially also benefit patients with widely disseminated or micro-metastatic lesions.

Methods SQ3370-001 (NCT04106492), the first-in-human Phase 1 study, is currently open in the United States and Australia to treat patients with advanced solid tumors. SQ3370-001 is enrolling patients $\geq$ 18 years of age with an injectable local or metastatic lesion, for which published data indicates responsiveness to anthracyclines. Patients must be relapsed or refractory following standard of care therapy and must not have received more than 225 mg/m^2 of Dox (or equivalent anthracycline). Each cycle will be for 21 days with no limit on total cycles. Primary objectives include determining the safety, tolerability, and recommended Phase 2 dose. Additional

objectives include assessment of the pharmacokinetic profile, preliminary efficacy per RECIST 1.1, and immune response.

Results N/A

Conclusions N/A

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Ethics Approval This study was approved by:1. The Institutional Review Board (IRB) of Stanford University; eProtocol Number: 54928.2. The IRB of The University of Texas MD Anderson Cancer Center; IRB ID Number: 2020-0185_MOD001.3. Western IRB, on behalf of The Angeles Clinic and Research Institute and Henry Ford Health System IRB Office; IRB Tracking Number: 20200758.4. Bellberry Limited Human Research Ethics Committee, on behalf of Royal North Shore Hospital and Chris O'Brien Lifehouse; Application Number: 2019-10-848.

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417 DESIGN AND RATIONALE OF A PHASE 1 STUDY EVALUATING AMG 256, A NOVEL, TARGETED, IL-21 RECEPTOR AGONIST AND ANTI-PD-1 ANTIBODY, IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Checkpoint inhibitors are a promising therapy for patients with solid tumors; however, many patients require additional therapies to maximize clinical benefit or overcome resistance.[1] The type-1 cytokine interleukin-21 (IL-21) is a promising candidate for combination and has shown clinical activity in melanoma and renal cell cancer.[2] IL-21 has also shown improved efficacy when combined with anti-programmed death (PD)-1 antibodies in preclinical models.[3 4] AMG 256 is a mutated IL-21 cytokine fused to an anti-PD-1 antibody to combine IL-21 pathway stimulation with checkpoint inhibition—a strategy that is designed to prime and extend the activity of cytotoxic and memory T cells and induce anti-tumor immunity. This first-in-human (FIH) study will assess safety, tolerability, and estimated dosing of AMG 256 monotherapy in patients with advanced solid tumors.

Methods This is a FIH, multicenter, non-randomized, open-label, phase 1 study (NCT04362748) of AMG 256 in patients with advanced solid tumors. The planned sample size is approximately 100 patients in two parts: part 1 will evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and determine the maximum tolerated dose (MTD), part 2 will evaluate the MTD determined in part 1 to further characterize the safety profile and preliminary tumor response. AMG 256 will be delivered by intravenous (IV) infusion. Enrollment criteria include adults with life expectancy of > 3 months, ECOG performance status ≤ 2, histologically or cytologically confirmed metastatic or locally advanced solid tumors not amenable to curative treatment with surgery or radiation, and at least one measurable lesion ≥ 10 mm that has not undergone biopsy within 3 months of screening scan. Exclusion criteria include primary brain tumor, untreated or symptomatic brain metastases, currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or drug study, history of solid organ transplantation or major surgery within 28 days of study day 1, live vaccine therapy within 4 weeks prior to study day 1, and active infection requiring oral or IV therapy. The primary endpoints are incidence of dose-limiting toxicities and adverse events, MTD, and recommended phase 2 dose. Secondary objectives will evaluate PK parameters, preliminary antitumor activity (objective response, duration of response, progression-free survival, disease control rate, duration of stable disease, overall survival), and immunogenicity of AMG 256 via incidence of anti-AMG 256 antibodies.

Results N/A

Conclusions N/A

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Trial Registration NCT04362748

Ethics Approval The study was approved by all institutional ethics boards.

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418 A PHASE 1, DOSE ESCALATION AND DOSE EXPANSION STUDY OF SQZ PBMC HPV AS MONOTHERAPY AND IN COMBINATION WITH ATEZOLIZUMAB IN HLA-A*02+ PATIENTS WITH HPV16+ RECURRENT, OR METASTATIC SOLID TUMORS

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Background SQZ-PBMC-HPV is a therapeutic cancer vaccine created with Cell Squeeze®, a proprietary cell-engineering system. SQZ-PBMC-HPV is a novel cancer vaccine generated from peripheral blood mononuclear cells (PBMC) squeezed with HPV16 E6 and E7 antigens, resulting in delivery into the cytosol. The resulting antigen presenting cells (APCs) provide enhanced antigen presentation on MHC-I to potentially