291 PHASE IB STUDY OF SELICRELUMAB (CD40 AGONIST) IN COMBINATION WITH ATEZOLIZUMAB (ANTI-PD-L1) IN PATIENTS WITH ADVANCED SOLID TUMORS

[1]Fabrice Barlesi*, [2]Martijn Lolkema, [3]Kristoffer Staal Rohrberg, [4]Cinta Hierro, [5]Aurelien Marabelle, [6]Albiruni Abdul Razak, [7]Luis Teixeira, [8]Valentina Boni, [9]Wilson H Miller, [10]Charu Aggarwal, [11]Martin Stern, [12]Olivera Cirovic, [12]Olivera Cirovic, [12]Barbara Romagnoli, [12]Randolph Christen, [13]Raksha Dodia, [13]Kevin Smart, [12]Bernhard Reis, [11]Nicolas Staedler, [14]Carl Watson, [15]Neeltje Steeghs. *[1]Gustave Roussy Cancer Campus, Villejuif, France; [2]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [3]Rigshospitalet, Copenhagen, Denmark; [4]Vall d'Hebron University Hospital, Barcelona, Spain; [5]Gustave Roussy, Université Paris Saclay, Villejuif, France; [6]Princess Margaret Cancer Centre, Toronto, Canada; [7]Saint-Louis Hospital, APHP, Paris, France; [8]START Madrid, Madrid, Spain; [9]Jewish General Hospital, Montreal, Canada; [10]University of Pennsylvania, Philadelphia, USA; [11]Roche Innovation Center Zurich, Schlieren, Switzerland; [12]Roche Innovation Center Basel, Basel, Switzerland; [13]Roche Innovation Center Welwyn, Welwyn Garden City, UK; [14]A4P Consulting Ltd, Sandwich, UK; [15]Netherlands Cancer Institute, Amsterdam, Netherlands*

Background Selicrelumab is a human IgG2 agonistic anti-CD40 monoclonal antibody. Binding of the antibody to CD40 expressed on antigen-presenting cells results in T- cell priming and T-cell dependent anti-tumor activity. In response to T-cell activation, tumor cells express programmed-death ligand 1 (PD-L1) that can suppress effector T-cells. Atezolizumab interrupts this feedback loop by blocking PD-L1, thereby supporting the combination with selicrelumab.

Methods This phase Ib open-label, multicenter, dose escalation (DE)/expansion clinical study (NCT02304393) investigated safety, pharmacokinetic (PK), pharmacodynamics (PD) and efficacy of selicrelumab in combination with atezolizumab in unselected patients with advanced/metastatic solid tumors, not amenable to standard therapy. In DE cohorts, a single dose of selicrelumab was given, either by intravenous (IV) infusion at a 16 mg fixed dose or subcutaneously (SC) at a range from 1 to 64 mg/dose. In dose-expansion cohorts (small bowel and colorectal cancer, head and neck squamous cell carcinoma [HNSCC] and non-small cell lung carcinoma), patients received multiple doses of selicrelumab SC at a dose of 16 mg. In all treatment cohorts, patients received atezolizumab at a fixed dose of 1200 mg IV Q3W.

Results In this study, 140 patients were treated. This included 95 patients in DE cohorts (6 patients in the IV cohort, 89 patients in the SC cohorts) and 45 patients in dose-expansion cohorts. In the IV cohort, infusion related reaction was the most frequent treatment-related adverse event (TRAE; 50%), while Grade $\geq$ 3 TRAE occurred in 1 patient (16.7%). In this cohort one dose-limiting toxicity (DLT) was reported (Grade 3 pancytopenia). In the SC cohorts, the most frequent TRAE was injection site reaction (ISR; 92%). Four DLTs were reported in four patients: three Grade 3 ISR and one Grade 3 transaminase increase. Grade $\geq$ 3 TRAE were reported in 22 patients (16.4%). Anti-tumor activity was observed across cohorts receiving SC selicrelumab (dose range 1 to 36 mg). Eight of 80 evaluable patients in DE cohorts experienced objective responses (9% ORR). In the dose-expansion HNSCC cohort, three of 16 evaluable patients responded (15.8% ORR). There were no objective responses in the IV cohort. Treatment with selicrelumab resulted in significant peripheral B-cell depletion and activation and CD8+ T cell proliferation.

Conclusions Treatment with selicrelumab in combination with atezolizumab was well tolerated in patients with advanced solid tumors. Signals of clinical and PD activity were observed. However, efficacy of the combination in this unselected population was limited, when compared to monotherapy efficacy of atezolizumab.

Trial Registration NCT02304393

Ethics Approval This study was approved by the local IRB at each participating study site.

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292 IMMUNE CHECKPOINT INHIBITOR INDUCED OVERLAPPING CARDIAC AND NEUROMUSCULAR TOXICITIES: HIGHLIGHT OF EARLY DIAGNOSIS, EARLY INITIATION OF IMMUNOSUPPRESSIVE THERAPY AND MULTIDISCIPLINARY MANAGEMENT

[1]Ho Wai Siu*, [2]Robert O'Neill, [2]Matthew Tong, [1]JunHee Hong, [3]Carole A Harris, [4]Morteza Aghmesheh, [5]Hussein Soudy. *[1]St George Hospital, Sydney, Australia; [2]The Sutherland Hospital, Sydney, Australia; [3]1. St George Hospital, 2. University of New South Wales, Sydney, Australia; [4]1. The Wollongong Hospital 2. University of Wollongong, Wollongong, Australia; [5]1. St George Hospital 2. University of New South Wales, Sydney, Australia*

Background The use of immune checkpoint inhibitors (ICIs) against programmed cell death protein -1 (PD-1), its ligand (PD-L1) and cytotoxic T- lymphocyte associated protein 4 (CTLA4) have been increasing. Immune induced myocarditis, myositis and myasthenia gravis are rare but potentially severe complications from these agents. Here we report 3 cases of ICI induced myocarditis, myositis, myasthenia gravis and transaminitis as a cluster, and highlights early diagnosis, prompt initiation of steroid sparing immunosuppressive therapy and multidisciplinary management.

Methods Three patients received anti-PD-1 ICIs developed cardiac, neuromuscular complications and transaminitis within 4 weeks after initiation. Clinical data were retrospectively reviewed from medical records.

Results All patients had elevated cardiac enzymes, developed complete heart block and underwent coronary catheterisation and pacemaker insertion. All patients developed myositis and myasthenia gravis (table 1) and were managed by multi-disciplinary team involving oncology, cardiology and neurology. Single-fibre electromyography was performed to confirm presence of myositis. One of three patients had positive acetylcholinesterase antibody, anti- muscle specific kinase antibody was negative in all cases. All patients developed grade 2–3 transaminitis with normal bilirubin. All patients received high-dose steroids. Steroid sparing therapy including intravenous immunoglobulin and mycophenolate mofetil were used early in 2 cases and was associated with rapid recovery of toxicities.

Abstract 292 Table 1 Patient characteristics, management and outcome of ir-AEs

Age, gender and primary malignancy	ICI agent and time of onset	Signs and Symptoms	Treatment of toxicity	Outcome of ICI related toxicities
81, M, advanced melanoma	Pembrolizumab, 4 weeks	Exertional dyspnoea Fatigue Diplopia	Prednisone 50mg daily IVIG	Ongoing deterioration
74, M, resected melanoma	Nivolumab, 3 weeks	Dysphonia, dyspnoea, muscle weakness	Methylprednisolone 1g IVIG Mycophenolate mofetil	Recovered and discharged after 32 days
63, M, advanced renal carcinoma	Pembrolizumab, 3 weeks	Chest pain, dyspnoea and lethargy	Methylprednisolone 1g IVIG Mycophenolate mofetil	Recovered and discharged after 20 days

Conclusions ICI induced myocarditis can be associated with myositis, myasthenia gravis and transaminitis. A high index of suspicion, comprehensive investigations and early involvement of multi-disciplinary teams are key to early accurate diagnosis.

In steroid refractory cases, we propose early initiation of steroid sparing immunosuppressive therapy after 3 days.

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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293 RESULTSOF THE FIRST-IN-HUMAN CLINICAL TRIAL WITH PERSONALIZED MULTI-TARGET ADOPTIVE CELL THERAPY (ACTOLOG IMA101)

[1]Apostolia Tsimberidou*, [2]Kerstin Guenther, [3]Amir Alpert, [4]Borje Andersson, [3]Zoe Coughlin, [2]Jens Fritsche, [2]Norbert Hilf, [4]Patrick Hwu, [3]Mamta Kalra, [3]Sabrina Kuttruff-Coqui, [2]Dominik Maurer, [2]Regina Mendrzyk, [3]Ali Mohamed, [4]Becky Norris, [2]Anna Nowak, [4]Rita Ort, [2]Carsten Reinhardt, [2]Fabian Richter, [3]Arun Satelli, [2]Oliver Schoor, [3]Kerry Sieger, [2]Harpreet Singh, [4]David Vining, [2]Claudia Wagner, [2]Toni Weinschenk, [4]Cassian Yee, [3]Steffen Walter. *[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Immatics Biotechnologies GmbH, Tuebingen, Germany; [3]Immatics US, Inc, Houston, TX, USA; [4]UT – MD Anderson Cancer Center, Houston, TX, USA*

Background ACTolog (IMA101) is a personalized multi-target adoptive cell therapy (ACT) approach in which autologous T-cell products are redirected against multiple novel defined peptide-HLA (pHLA) cancer targets identified by the target discovery platform XPRESIDENT®. The primary endpoint was to assess the safety of ACTolog. Secondary endpoints were to assess the in vivo persistence of transferred T-cells and antitumor activity (www.clinicaltrials.gov NCT02876510).

Methods HLA-A*02:01 positive patients with relapsed/refractory solid tumors whose tumor expressed ≥1 cancer target underwent leukapheresis and endogenous T-cells specific for up to 4 targets were primed and expanded in vitro. Patients received lymphodepletion (fludarabine 40 mg/m² and cyclophosphamide 500 mg/m² on days -6 to -3) followed by up to 4×10^{10} cells (day 0), and IL-2 (1×10^6 IU/m² SC twice daily, 14 days) (Cohort 1). In addition, cohort 2 received atezolizumab (1200 mg IV) every 21 days upon hematologic recovery. Infused T-cells were tracked in patients' blood via flow cytometry-based immunomonitoring as well as TCRβ sequencing. TCRs from target specific T-cells were identified from patients' T-cell products and characterized.

Results From 07/2017–03/2020, 214 patients were screened, and 14 heavily pre-treated patients with various tumor types were infused with 1–3 T-cell products each (table 1). The treatment was generally well tolerated. The most common adverse events observed to date were expected cytopenias, mostly attributed to the lymphodepleting regimen, and Grade 1–2 cytokine release syndrome. Prolonged disease stabilization was noted in three patients for 12 months, 12+ months, and 7 months. High frequencies of target-specific T-cells up to 78.7% of CD8+ cells were detected in the blood of treated patients, persisted for >1 year and were detected in post-treatment tumor biopsies. Characterization of individual TCRs contained in T-cell products showed a broad variation of TCR avidities with the majority of TCRs being of low avidity. High-avidity TCRs were identified from products of some patients, including a patient with 26% decrease in tumor measurements 6 weeks post-treatment. Tracking the respective T-cell clonotypes in patients' blood and tumor provides insights into the mechanism of tumor control. Six-month data will be presented at the conference.

Abstract 293 Table 1 Patient pre-treatment characteristics and response assessment

Disposition	No. of patients (%)
Screened	214 (100)
HLA-A*02:01 positive	100 (46.7)
Screening tumor biopsy	60 (28.0)
≥1 Target positive	55 (25.7)
Leukapheresis	43 (20.1)
Cohort 1: ACTolog	6 (2.8)
Cohort 2: ACTolog + Atezolizumab	8 (3.7)
Treated total	14 (6.5)
Number of T-cell products received (N=14)	**No. of patients (%)**
1	7 (50.0)
2	3 (21.4)
3	4 (28.6)
Pretreatment characteristics (N=14)	**median (range)**
No. of prior systemic therapies	7 (3-14)
Results (N=14)	**No. of patients (%)**
Response (RECIST 1.1)	
Stable disease	
At 6 weeks post T-cell infusion	11 (78.6)
At 12 weeks post T-cell infusion	6 (42.9)

Conclusions This is the first reported trial demonstrating the feasibility and tolerability of a personalized ACT approach using multiple defined T-cell products directed to multiple precisely defined pHLA cancer targets. These results support further exploration of a multi-target ACT approach, particularly in the context of T-cells expressing high-avidity TCRs to such defined pHLA targets.

Trial Registration https://clinicaltrials.gov/ct2/show/NCT02876510

Ethics Approval The study was approved by WCG WIRB, IRB tracking number 20162235. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All the study participants provided written informed consent before enrollment.

Consent Patient consent for publication is not required. Patients consented to participate in the study.

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294 CD8 PET IMAGING OF TUMOR INFILTRATING T CELLS IN ADVANCED SOLID TUMORS: A PHASE I FIRST-IN-HUMAN STUDY OF 89ZR-IAB22M2C, A RADIOLABELED ANTI-CD8 MINIBODY

[1]Michael Farwell*, [1]Raymond Gamache, [2]Neeta Pandit-Taskar, [2]Mike Postow, [3]Michael Gordon, [4]Ian Wilson, [4]Alessandro Mascioni, [5]Anna Wu, [4]William Le, [4]Avital Weiss, [4]Ronald Korn. *[1]University of Pennsylvania, Philadelphia, PA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]HonorHealth Research Institute, Scottsdale, AZ, USA; [4]ImaginAb, Ingelwood, CA, USA; [5]City of Hope, Duarte, CA, USA*

Background Tumor infiltration by CD8 T cells is associated with favorable outcomes to immunotherapy (IOT). However, biopsies to assess T cell infiltration are invasive and prone to sampling error. CD8 PET imaging could provide an effective non-invasive method of visualizing T cell trafficking and tumor infiltration and predicting early response to IOT.

Methods A phase 1 first-in-human PET imaging study using an anti-CD8 radiolabeled Minibody, 89Zr-IAB22M2C (CD8-tracer), to detect whole body and tumor CD8 distribution in patients with metastatic solid tumors was completed. Patients received 3 mCi 89Zr-IAB22M2C followed by serial PET scans over a 5–7-day period. A two-stage design included protein dose escalation phase[1] (n=6, 0.2 mg to 10 mg API) to