

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

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**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.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0291>

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

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**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.