Background The presence of CD1c (BDCA-1)-/CD141 (BDCA-3)+ conventional dendritic cells (cDC1) and CD1c (BDCA-1)/CD141 (BDCA-3)+ conventional dendritic cells (cDC2) in the tumor microenvironment (TME) is a necessary prerequisite to induce an effector CD8+ T cell response and for response to immune checkpoint blockade (ICB).1-4 AS01b is an adjuvant component of a commercialized prophylactic shingles vaccine which induces adaptive immunity through recruitment and activation of cDC1 and cDC2.5-6 Previously, intratumoral (IT) administration of ipilimumab and autologous myDC has shown promising antitumoral activity.7

Methods In this phase Ib clinical trial, patients with metastatic melanoma refractory to ICB and BRAF/MEK inhibitors (in case of BRAF V600-mutant melanoma) were recruited. Patients underwent a leukapheresis followed by immunomagnetic bead isolation of CD1c (BDCA-1)/CD141 (BDCA-3)+ myDC. Patients received an intravenous (IV) administration of low dose nivolumab (10mg d1 and q2w) plus an IT administration of ipilimumab 10 mg (d1 and q2w). The isolated myDC were injected (palpation or ultrasound-guided) as a single injection into a metastatic lesion on day 2; together with AS01b0.5 ml (d2 and q2w). Response assessment was performed by PET/CT q12w. Blood and tissue samples were collected each treatment cycle. Translational research including gene expression profiling, TCR analysis and multiplex immunohistochemistry is ongoing. (figure 1)

Results Between July 2021 and May 2022, 8 patients were recruited (all female) with a median age of 63 years (range 33-83). All patients had been treated with ICB as well as BRAF/MEK inhibitors when applicable. Median number and range of treatment administrations was 4 (range 1-7) for IT and 4.5 (range 1-15) for IV. Three patients remained on treatment at data cutoff date. Median PFS was 10.1 weeks (95% CI 5.193-15.007), median OS has not been reached. One patient obtained a complete remission on PET/CT 6 months after the start of study treatment. One patient obtained a pathological complete response 4 weeks after start of study treatment. One patient obtained a complete remission of injected lesions but progressed in non-injected lesions. Three patients died due to progressive disease. Treatment was well tolerated. There were no unexpected adverse events. One patient had G3 pyrexia, leading to prolongation of hospital stay with 1 day.

Conclusions In this clinical trial, IT injection of CD1c (BDCA-1)/CD141 (BDCA-3)+ myDC in combination with repeated IT administration of ipilimumab and AS01b and systemic low dose nivolumab has shown promising early results and no unexpected safety signals, deserving further clinical investigation. Translational investigations are ongoing.

Trial Registration Clinicaltrials.gov: NCT03707808

REFERENCES