Background The tumor microenvironment (TME) contains immunosuppressive myeloid cells that contribute to checkpoint inhibitor (CPI) resistance. One approach as part of Pionyr Immunotherapeutics’ Myeloid Tuning™ strategy is to reprogram immunosuppressive myeloid cells to acquire an immunostimulatory anti-tumor phenotype. Macrophage Receptor with a Collagenous Structure (MARCO) is an attractive target for myeloid reprogramming, considering its immunomodulatory function and expression on tumor-associated macrophages (TAMs) and monocytic myeloid derived suppressor cells (mMDSCs) in the TME. Pionyr has developed a humanized IgG1 k anti-MARCO monoclonal antibody, PY265, to investigate the potential of MARCO modulation as an anti-cancer immunotherapeutic strategy.

Methods MARCO expression on TAMs and mMDSCs from multiple solid tumor indications was determined by single-cell RNA sequencing and by using immunohistochemistry (IHC). PY265 activity on human monocyte derived macrophages (hMDMs) in vitro was evaluated by transcriptional profiling, phosphoprotein array, flow cytometry, and cytokine/chemokine measurements. In vivo efficacy and pharmacodynamic studies using a surrogate anti-mouse MARCO antibody, PY265m, as single agent or in combination with anti-PD-1, were evaluated using syngeneic mouse tumor models.

Results MARCO is specifically enriched in a cluster of TAMs and mMDSCs that correlates with immunosuppressive signatures in multiple solid tumor types. Moreover, IHC profiling shows that MARCO is commonly expressed in the TME of these tumors, and maintain expression in metastatic lesions, as well as in chemo- and CPI-treated tumors. PY265 induces reprogramming in hMDMs in vitro through induction of rapid phosphorylation events, transcriptional activation of pro-inflammatory pathways, production of cytokines and chemokines, and upregulation of cell surface activation receptors. PY265m demonstrates significant anti-tumor activity in syngeneic mouse models as single agent in CPI-sensitive models and in combination with anti-PD-1 in CPI-resistant models. Pharmacodynamic studies suggest that PY265m induces immune activation by reprogramming pro-tumorigenic, M2-like TAMs and mMDSCs to pro-inflammatory anti-tumor M1-like macrophages and monocytes, leading to an increase in infiltration of effector cells in the tumor, spleen, and tumor draining lymph nodes. In a non-human primate toxicokinetic study, PY265 was generally well tolerated at all dose levels tested.

Conclusions Our study demonstrates that targeting MARCO reprograms myeloid cells and remodels the TME to unleash anti-tumor immunity and convert CPI-resistant tumors into treatment responsive tumors. Collectively, these preclinical data support PY265 immunotherapy, alone or in combination with a CPI, in cancer patients resistant or refractory to CPI therapies, to potentially improve both the overall response rate as well as durability of response. First-in-human testing of PY265 will be initiated in 2023.