UI-101, A TLR7/8 AGONIST ENCAPSULATED IN CHOLESTERYL PULLULAN NANOPARTICLE TARGETING TUMOR-ASSOCIATED MACROPHAGES VIA BINDING TO DC-SIGN, ELICITS POTENT anti-TUMOR IMMUNITY WITHOUT SEVERE SIDE EFFECT

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**Background** Tumor-associated macrophages (TAMs), including immune-suppressive M2-like subsets, have attracted great interest as an immunotherapy target because they are considered one of the key mechanisms contributing tumor immune resistance. Various therapeutic approaches aimed at depleting or inhibiting TAMs have been tested in clinical settings; however, none have been approved yet due to limited efficacy and safety concerns associated with the lack of TAM specificity.

**Methods** We generated UI-101 by encapsulating a TLR7/8 agonist within cholesteryl pullulan nanoparticles, a polysaccharide-based drug delivery system capable of specifically delivering various cargos to M2-like TAMs through binding to C-type lectin, DC-SIGN (CD209). The pharmacological activity of UI-101 was examined in human PBMC-derived macrophages in vitro and in syngeneic mouse tumor models by intravenous administration. Side effects were also assessed in mice.

**Results** UI-101 converted human M2-like macrophages into immune-stimulatory M1 phenotype, as assessed by phagocytosis in vitro. Compared to a naked form of the TLR7/8 agonist, UI-101 demonstrated a better pharmacokinetic profile, enhanced tumor accumulation, and reduced side effect such as cytokine storm in mice. In syngeneic mouse tumor models, UI-101 increased M1/M2 TAM ratio within the tumors and significantly inhibited tumor growth. Combination of UI-101 and anti-PD-1 antibody resulted in significant enhancement of tumor growth inhibition compared to each monotherapy.

**Conclusions** These results indicate that UI-101 improves the tumor immune microenvironment by promoting the conversion of M2 to M1 macrophages among TAMs, leading to a potent anti-tumor effect without severe side effects. We anticipate that UI-101 offers a new therapeutic option to the majority of solid tumor patients who are refractory to standard therapies. A first-in-human clinical trial is planned for early 2025.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1147-E