## 721 PIXATIMOD (P) IN COMBINATION WITH NIVOLUMAB (N) +/- LOW-DOSE CYCLOPHOSPHAMIDE (CY) IN ADVANCED CANCERS: A PHASE IIA BASKET TRIAL

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**Background** Immune checkpoint inhibitors (ICI) directed against PD-(L)1 are associated with improved response rates in melanoma (MEL), and squamous/non-squamous non-small cell lung cancer (NSCLC).[1-4] Conversely, anti-PD(L)1 blockade is minimally efficacious in microsatellite stable (MSS) colorectal carcinoma (CRC). Pixatimod (P) is a heparan sulfate (HS) mimetic that is a cholestanol-sulfotetrasaccharide conjugated small molecule compound with unique NK- and T cell-dependent immunomodulatory properties. P does not possess CpG ODN motifs and hence does not activate TLR9 directly. Rather, P increases CpG ODN accumulation in lysosomal compartment of DCs, leading to enhanced production of IL-12 and NK cell activation.[5] Preclinically, in combination with anti-PD-1, P led to increased infiltration of both central and effector memory CD4 and CD8 T cells in a IL-12 and TLR9 dependent fashion in multiple tumor modes.[5-9] Low dose Cy has immunostimulatory and antiangiogenic properties and has synergy with CpG,[10, 11] and PD-1 ICI.[12] In MSS mCRC, P/N demonstrated objective response rate (ORR) 12% in a Phase Ib study.[13]

We hypothesized that P and nivolumab (N) combination may overcome resistance in PD-1 relapsed/refractory (R/R) tumors; and that the addition of Cy may facilitate P+N activity in MSS CRC.

**Methods** This is a nonrandomized, open-label, multichort, phase IIA study (NCT05061017) evaluating several pixatimod combinations in 3 cohorts (figure 1). The recommended phase 2 dose (RP2D) of P is 25mg IV Q1W and N is dosed at 480mg IV Q4W. Immunomodulatory dose of Cy is 50 mg twice daily, 1-week-on, 1-week-off.

P+N+low-dose Cy will be evaluated in PD-1 naïve MSS CRC (cohort 1). P+N will be evaluated in PD-1 R/R melanoma (cohort 2) and NSCLC (cohort 3). In 1st stage of each cohort, 9-13 patients will be enrolled. If ≥1 response(s) are seen, 8-14 additional patients will be enrolled in the 2nd stage.

The primary endpoint in this Simon two-stage trial is objective response rate (ORR) using RECIST v1.1. Key secondary endpoints include ORR by iRECIST, median and landmark survival (PFS, OS) and safety. Exploratory endpoints will characterize pharmacokinetics, immune contexture, immunophenotypic analyses and gut microbiome pre- and post- treatment blood, tumor and stool samples.

**Acknowledgements** We would like to thank all the participating patients, and their families.

We would like to thank the research staff of the Hillman Cancer Center's (HCC) Immunotherapy and Drug Development Center (IDDC).

**Trial Registration** Clinical trial information: NCT05061017.

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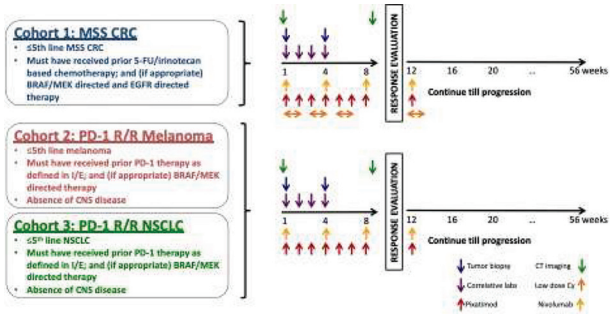
**Ethics Approval** The study was approved by University of Pittsburgh's Institutional Review Board, approval number MOD21060203-002.

**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.




**Abstract 721 Figure 1** Clinical Trial Schema for Phase IIA Study Evaluating Pixatimod and Nivolumab +/- Low-dose Cy in MSS CRC, PD-1 R/R Melanoma and PD-1 R/R NSCLC

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0721