Women with MLH1PHM tumors are considered at low risk for Lynch Syndrome and forgo referral to cancer genetic clinics. Regardless of MLH1PHM status, MLH1-d IHC helps to classify EC according to TCGA-based molecular classification and for consideration of immunotherapy. This study sought to examine the proportion of MLH1PHM in MLH1-d cases.

Methods Retrospective audit of pathology reports (2018–2021) in a major community laboratory in Ontario, Canada (Life Labs) identified EC samplings that were evaluated by IHC for MMR proteins (MLH1, MSH2, MSH6, and PMS2) followed by MLH1PHM test, when appropriate.

Results Among 1229 consecutive EC samples tested by MMR-IHC, 14 could not be classified due to insufficient tumor cells or ambiguous staining. The remaining 1215 ECs were classified into MMR-d (n=324, 26.7%) or proficient (n=891, 73.3%). Among MMR-d cases, 274 showed loss of MLH1 and 206 had available MLH1 methylation testing data. MLH1PHM was detected in 201/206 (97.6%), designated as most likely sporadic whereas 5/206 cases (2.4%) were not hypermethylated raising the possibility for Lynch syndrome.

Conclusions Our audit confirms the feasibility of testing endometrial samplings for MMR-IHC and promoter hypermethylation testing. MLH1PHM accounts for vast majority of MLH1/PMS2-deficient cancers in a universally screened EC population. The very high proportion of MLH1PHM challenges the practice algorithm and raises the need to explore practice revision.
Objective Dostarlimab is an approved programmed death 1 (PD-1) inhibitor. PD-1 therapy can lead to immune-related adverse events (irAEs). Here we report on the management of irAEs across multiple tumor types evaluated in GARNET.

Methods GARNET is a multicenter, open-label, single-arm phase 1 study with dose expansion in multiple tumor types: dMMR solid tumors, mismatch repair proficient EC, non-small cell lung cancer, and platinum-resistant ovarian cancer. Patients received 500 mg of dostarlimab intravenously Q3W for 4 cycles, then 1000 mg Q6W until disease progression, discontinuation, or withdrawal.

Results At this third interim analysis of GARNET, the safety population included 605 patients. irAEs were experienced by 32.2%, with 10.1% of patients experiencing grade ≥3 irAEs (table 1). Few, 5.5%, discontinued treatment because of an irAE. No irAEs led to death. Of patients experiencing irAEs, 64.6% were treated with immune modulatory medications (IMMs; referring to steroids, immune suppressant, and/or thyroid therapy); 58.7% of these patients experienced resolution. Average time to resolution was 69 days. For the 35.4% of patients not treated with IMMs, 56.5% experienced resolution. Average time to resolution was 67 days. The most common irAEs were hypothyroidism (7.6%; 45 of 46 [97.8%] patients treated with thyroid therapy) and arthralgia (5.6%; 8 of 34 [23.5%] patients treated with steroids).

Conclusions Across all tumor types evaluated in GARNET, 32.2% of patients experienced irAEs, 68.7% of whom experienced grade 2 events. 58.7% of patients experienced resolution of irAEs upon treatment with an IMM. Overall discontinuation due to irAEs was low.

Poster rounds with the professors: Group C1

Abstract 7/#178 Figure 1 (A) Tumor burden was decreased after MEM-288 treatment as measured by ascites volume, (B) number of metastatic sites, and (C) decreased tumor weights compared to saline-treated mice. (D) Enzyme-linked immunospot (ELISPOT) assay demonstrated higher number of tumor-reactive splenocytes for saline, Adv-GFP, and MEM-288 treated mice. Number of spots per well represents number of splenocytes secreting IFN-γ in after exposure to irradiated STOSE-luc target cells.

Results MEM-288-treated mice demonstrated improved tumor control compared to Adv-GFP and saline across multiple parameters (mean ± SD), including ascites volume (0.02 ± 0.04 mL vs. 1.1 ± 1.5 mL vs. 1.6 ± 0.95 mL; p = 0.01); metastatic sites (3.1 ± 0.8 vs. 4.4 ± 2.2 vs. 5.4 ± 1.4; p = 0.03); and tumor weight (0.41 ± 0.21 g vs. 0.91 ± 1.1 g vs. 1.1 ± 0.66 g; p = 0.20). These anti-tumor effects directly correlated with T cell-associated immune responses in the tumor microenvironment through expansion of tumor-infiltrating CD8+ T-cells (p = 0.0005). MEM-288 induced a systemic immune response with increased number of tumor-reactive T-cells in splenocytes via IFN-γ ELISPOT assay (p = 0.004) compared to other groups. CD8+ T-cell inhibitory markers CTLA4+/PD1- (p = 0.002) and CTLA4+/PD1+ (p = 0.01) were decreased with MEM-288 treatment.

Conclusions MEM-288 has potent anti-tumor activity in an immune competent ovarian cancer mouse model, likely through recruitment of cytotoxic T-cells and promotion of a systemic anti-tumor T-cell response.