Abstract #: 2651

A Phase 1b/2 Open-Label Study of the Efficacy and Safety of Etigilimab (anti-TIGIT antibody MPH313) Administered in Combination with Nivolumab (anti-PD-1 antibody) to Subjects with Locally Advanced or Metastatic Solid Tumors (ACTIVATE)^

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Background

- TIGIT (T cell immunoreceptor with Ig and ITIM domains) is a novel inhibitory immune checkpoint on activated T and NK cells in multiple cancers.[1]
- Etigilimab (etig), a humanized IgG1 monoclonal antibody with an intact Fc region, blocks TIGIT interaction with its ligand PVR and is expected to restore anti-tumor activity.
- Etig+/- nivolumab (nivo) showed acceptable safety and preliminary activity in a FIH Phase 1a/b study in solid tumors.[2]
- ACTIVATE, an open-label Phase 1b/2 basket study is evaluating further efficacy, safety, tolerability, and PK/PD of etig+nivo in select advanced/metastatic solid tumors.
- This is a preliminary efficacy and safety analysis from ACTIVATE actively enrolling 6 cohorts (NCT04761198).

Key Study Elements

Inclusion	Exclusion
No available curative/SOC therapies Confirmed path diagnosis Baseline archival or fresh tissue Adequate hematologic and end organ status ECOG 0-1 Baseline measurable disease by RECIST 1.1	CNS tumors Concurrent active malignancy Prior treatment with CD137 agonists, anti-CTLA-4 and anti-TIGIT antibodies

Cohort A: Endometrial Cancer, checkpoint inhibitor-naïve (CPI-n)
Cohort C: Cervical Cancer (CC), CPI-n, CPS>1%
Cohort E: TMB-H+MSS, CPI-n & post-CPI
Cohort F: Rare Tumors (CPI-n):
Soft tissue sarcomas (Dediff LPS, UPS, other)
Uveal melanoma
Germ cell tumor (testicular)
Cohort G: Endometrial Cancer, post-CPI
Cohort H: Ovarian (HGSOC), post front-line platinum

Tumor scans: Q8 weeks
Primary endpoint: Investigator-assessed ORR (RECIST 1.1)
Secondary endpoints: Safety, DOR, DCR
Exploratory endpoints: include PFS and OS.

Table 1. Baseline characteristics (Safety analysis set; n=50)

Variable	n, %
Median age (years; range)	61 (28-83)
Gender: Female/Male	31(62); 19(38)
Race: Asian/African-American/White/Other	0; 1(2); 47(94); 2(4)
ECOG 0/1	22(44); 28(56)
Locally advanced/Metastatic	14(28); 42(84)
Brain mets/Liver mets	2(4); 16(32)
Tumor type by cohort	
Cervical	6(12) ^
Endometrial CPI-naïve	3(6)
Ovarian	10(20)
Uveal melanoma	6(12)
Sarcoma	14(28)
Dediff LPS/UPS/Other	6(12); 4(8); 4(8)
GCT (testicular)	4(8)
TMB-H/MSS	6(12)
Head and Neck	1 (2)
1-2 prior lines of therapy*	23(46)
≥ 3 prior lines of therapy*	21(42)

* Incomplete data in clinical database ^ Includes 1 TMB-H cervical subject with CPS >1% by central lab.

Conclusions

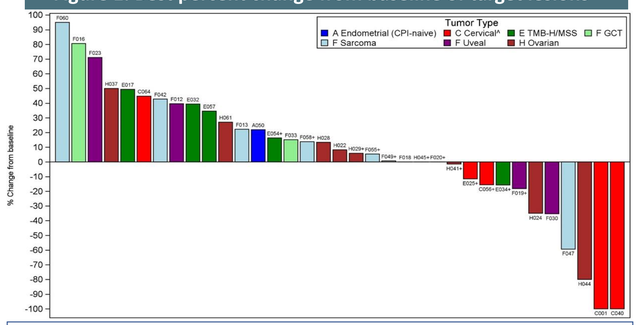
Encouraging preliminary efficacy noted across multiple tumor types (2 CRs, 4 PRs; 42% DCR) in heavily pre-treated, CPI-naïve subjects
7 subjects with clinical benefit remained on study treatment for ≥ 18 weeks
Etig+nivo is safe and well tolerated; no new safety signals noted for the combination
Robust target engagement extending Phase 1 study findings
Data supports continued evaluation of etig+nivo.

Table 2. Response summary (efficacy analysis set; n=38)*

ORR by RECIST 1.1	A Endometrial cancer CPI-n (n=1)	C Cervical Cancer (n=5)^	E TMB-H /MSS (n=6)	F (Rare) Uveal (n=6)	F (Rare) Sarcoma (n=7)	F (Rare) GCT (T) (n=4)	H Ovarian (HGSOC) (n=9)	Total (n=38)
CR (n)	0	2[1]	0	0	0	0	0	2
PR (n)	0	0	0	1[2]	1[3]	0	2	4
SD (n)	0	2	1	2	3	0	2	10
PD (n)	1	1	5	3	3	4	5	22
ORR (%)	15.8							
DCR (%)	42.1							

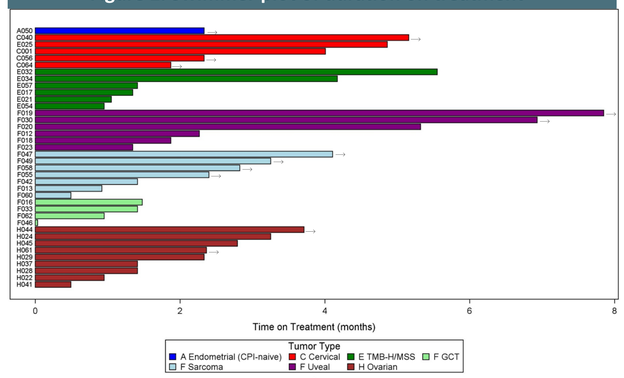
*Efficacy analysis set: Response evaluable subjects by investigator-assessed response per RECIST 1.1/clinical progression
Excludes 5 non-prioritized histology subjects enrolled prior to amended, current version of protocol (V3.0).
^ Includes 1 TMB-H cervical subject E025 with CPS >1% by central lab.
[1]1 CR and [2]1 PR confirmed respectively after data cutoff date; [3]Dedifferentiated liposarcoma histology, [4] Post-CPI, NSCLC, CPS<1%

Figure 1. Best percent change from baseline of target lesions*



*Efficacy analysis set n=35: E021, F062 and F046 had clinical progression before 1st scan.
+ = Overall RECIST response of Stable Disease [E054 and H041 had progression clinical, non-target lesion respectively; with BOR of PD at the time of SD on scan].

Figure 2. Swimmer plot of duration on treatment*

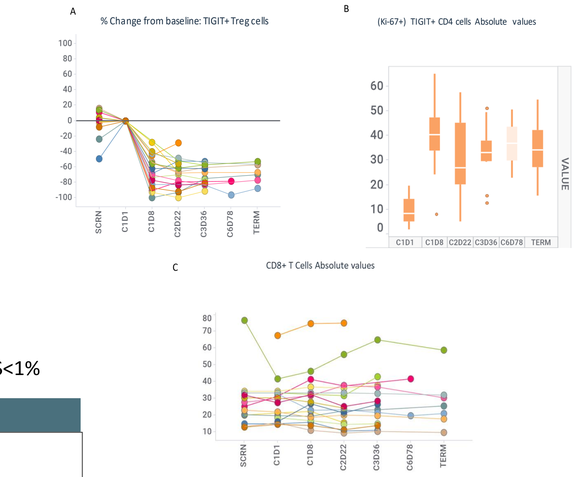


*Duration represents time from start to end of treatment/cutoff date if on treatment; efficacy analysis set n=38.
E032: TMB-H/MSS CRC subject with prolonged iUPD

Key Safety Results

- Rate of treatment-related adverse events (TRAEs) was 24%
- Most common TRAEs were G1-2 skin rashes: (24%), nausea (14%), diarrhea (10%), fatigue (12%).
- Four G3 TRAEs (immune-related diabetes mellitus, maculopapular rash, abdominal pain, and diarrhea) were reported.
  - Gr 3 diarrhea and abdominal pain downgraded to Gr 1 post data cutoff date, treated symptomatically, no steroid given.
- No treatment-related SAEs, discontinuations, or deaths.

Figure 3. Etigilimab shows robust target engagement



At the indicated timepoints (x-axis):
(A) TIGIT+ Tregs (CD4+ TIGIT+ Foxp3+) showed significant reduction.
(B) Proliferating (Ki-67+) TIGIT+ CD4 T-cells showed significant increases post treatment demonstrating robust target engagement. Increases in proliferation also seen in other populations including CD4 EM (Ki-67+ CD45RA- CCR7- CD4+) cells (data not shown).
(C) Levels of circulating CD8+ T-cells remained unchanged during monitoring.
18 subjects included at baseline. Absolute values = frequencies of cell populations by Flow.

References
1. Manieri et al. Trends Immunol. 38:20-28 2017.
2. Mettu et al. Clin Cancer Res. 28:882-892, 2022.
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^Data cutoff date 4/20/2022.

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