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ENVASARC: A Pivotal Trial Of Envafolimab, And Envafolimab In Combination With Ipilimumab, In Patients With Advanced Or Metastatic Undifferentiated Pleomorphic Sarcoma Or Myxofibrosarcoma Who Have Progressed On Prior Chemotherapy

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INTRODUCTION

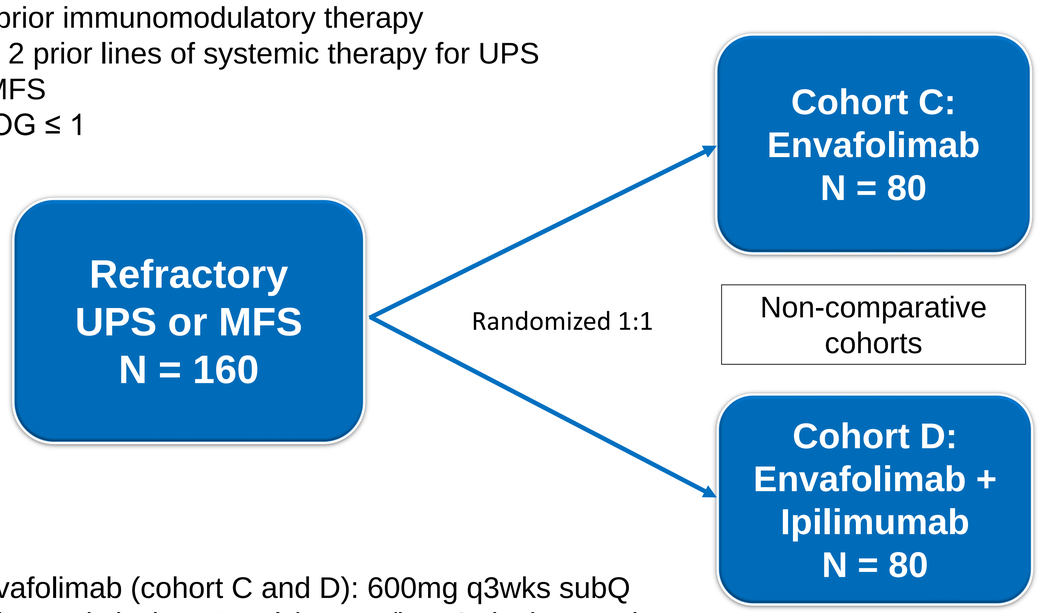
- Undifferentiated Pleomorphic Sarcoma (UPS) and the genetically related myxofibrosarcoma (MFS) are soft tissue sarcoma (STS) subtypes with poor prognoses, typically treated with doxorubicin or gemcitabine/docetaxel in the first line setting [1]. Pazopanib is the only approved treatment for refractory UPS and MFS in the United States, with an objective response rate (ORR) of 4% [2].
- Pembrolizumab, a PD-1 immune checkpoint inhibitor (ICI) was studied in refractory UPS in the SARC028 Phase 2 trial and demonstrated a 23% ORR by Response Evaluation Criteria in Solid Tumours (RECIST), with the majority of responses durable beyond 6 months [3].
- Nivolumab was studied as a single agent and with ipilimumab in patients with refractory UPS in the ALLIANCE trial. ORR to nivolumab and nivolumab combined with ipilimumab was 8% and 29%, respectively [4].
- Envafolimab is a single domain antibody to PD-L1 that is given by rapid low volume subcutaneous (subQ) injection in ~30 seconds [5].
- Envafolimab has no infusion reactions and available data suggest a lower risk of pneumonitis and colitis compared to approved PD-(L)1 ICIs [6].
- In the pivotal Phase 2 MSI-H/dMMR advanced solid tumor trial, the confirmed ORR by blinded independent central review (BICR) in MSI-H/dMMR colorectal cancer (CRC) patients treated with envafolimab with disease progression on a fluoropyrimidine, oxaliplatin and irinotecan was 32%. As indicated in Table 1, envafolimab demonstrated similar efficacy to other similar ICIs in MSI-H/dMMR CRC who failed a prior fluoropyrimidine, oxaliplatin and irinotecan [6-8].

Table 1: Comparison of ICIs in MSI-H/dMMR Colorectal Cancer

	Envafolimab	Nivolumab (CHECKMATE-142)	Pembrolizumab (KEYNOTE-164)
Indication	MSI-H/dMMR colorectal cancer that progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan		
Sample Size	41	53	61
ORR by independent radiographic review	32%	28%	33%
Duration of Response ≥ 12 months	75%	40%	NA

ENVASARC PIVOTAL STUDY DESIGN

- Advanced or metastatic UPS or MFS
- Age ≥ 12 years
- Measurable disease by RECIST 1.1
- No prior immunomodulatory therapy
- 1 or 2 prior lines of systemic therapy for UPS or MFS
- ECOG ≤ 1



- Envafolimab (cohort C and D): 600mg q3wks subQ
- Ipilimumab (cohort D only): 1 mg/kg q3wks i.v. x 4 doses

Note: ENVASARC initially enrolled patients in cohort A at an envafolimab dose of 300 mg q3wks or cohort B at an envafolimab dose of 300 mg q3wks with ipilimumab. Following the IDMC recommendation of December 2021, the trial was amended to increase the envafolimab dose by enrolling patients in Cohorts C (600 mg envafolimab) and D (600 mg envafolimab + ipilimumab).

STUDY OBJECTIVES

Primary

- ORR by BICR of envafolimab (cohort C) and of envafolimab combined with ipilimumab (cohort D), in separate cohorts of patients with locally advanced, unresectable or metastatic UPS or MFS, without a formal statistical comparison between the two cohorts.

Secondary

- Duration of response by RECIST 1.1 by BICR
- Disease control rate by RECIST 1.1 by BICR
- Progression free survival (PFS) by RECIST 1.1 by BICR
- Overall survival
- Safety and tolerability
- PK profile of envafolimab as a single agent and in combination with ipilimumab
- PK profile of ipilimumab when given with envafolimab
- ORR and PFS by RECIST 1.1 by Investigator assessment
- Immunogenicity of envafolimab and ipilimumab

Exploratory

- Correlate efficacy endpoints with PD-L1 expression on FFPE tumor samples
- Correlate efficacy endpoints with tumor mutational burden on FFPE tumor samples
- Correlate efficacy endpoints with sarcoma immune classification on FFPE tumor samples

STUDY RATIONALE

- Refractory UPS and MFS represent a high unmet need patient population, with a single approved treatment with a < 5% ORR.
- PD-(L)1 antibodies have demonstrated activity in refractory UPS and MFS as single agents and when combined with ipilimumab.
- Envafolimab appears to be as efficacious as nivolumab and pembrolizumab in trials of comparable patients, with a differentiated safety profile and the convenience of rapid low volume subQ dosing.

Table 2: Comparison of ORRs that were the Basis for Accelerated Approvals of ICIs

	PD-L1+ Gastric (pembrolizumab)	Urothelial (atezolizumab)	Small Cell Lung (nivolumab)	PD-L1+ Cervical (pembrolizumab)
ORR	**13%**	**15%**	**12%**	**14%**
CDX in label	**Yes**	**No**	**No**	**Yes**

Note: CDX is a Companion Diagnostic

- PD-(L)1 antibodies have been approved as single agents and in combination with ipilimumab based on single arm trials with a primary endpoint of ORR in high unmet need indications.
- Despite demonstrated activity of ICIs in STS, the ENVASARC Phase 2 trial (NCT04480502) is the first pivotal trial conducted in STS using a PD-(L)1 ICI.

PRIMARY ENDPOINT AND STATISTICS

- Confirmed ORR by RECIST 1.1 by BICR; 9/80 responses in either cohort (11.25% ORR) will produce a lower bound of the 95% confidence interval that excludes the documented pazopanib ORR of < 5%.

SUMMARY

- The pivotal ENVASARC trial is enrolling at 30 sites in the U.S. and U.K.
- The primary endpoint in each of two parallel cohorts (cohort C of single agent envafolimab and cohort D of envafolimab combined with ipilimumab) is ORR confirmed by BICR with 9/80 objective responses needed to exclude the known < 5% ORR of pazopanib, the only agent approved for patients with refractory UPS or MFS.
- ENVASARC trial design details are available at https://clinicaltrials.gov/show/NCT04480502

REFERENCES

1. Seddon B et al, Lancet Oncology 2017
2. Pazopanib package insert
3. Burgess MA et al, ASCO 2019
4. Chen JL et al, ASCO 2020
5. Zheng F et al, Cancer Discovery 2017
6. Shen L et al, ASCO 2020 and CSCO 2020
7. Nivolumab package insert
8. Le DT et al, J Clin Onc 2020