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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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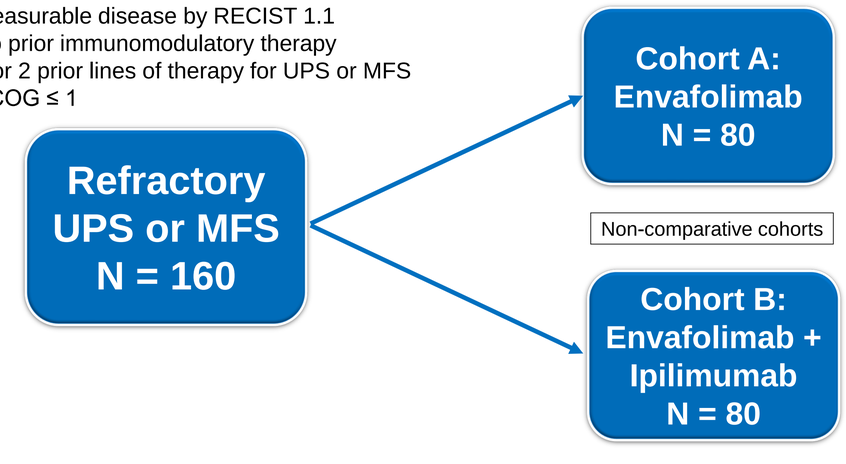
INTRODUCTION

- 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, with an objective response rate (ORR) of 4% [2].
- Pembrolizumab was studied in refractory UPS in the SARC028 Phase 2 trial and demonstrated a 23% ORR by 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 and ipilimumab was 8% and 29%, respectively [4].
- Envafolimab is a single domain antibody to PD-L1 that is given by rapid low volume subcutaneous injection in ~30 seconds [5].
- Envafolimab has no infusion reactions and available data suggests a lower risks of pneumonitis and colitis compared to approved PD-(L)1 checkpoint inhibitors.
- 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 who failed a fluoropyrimidine, oxaliplatin and irinotecan was 32%. As indicated in table below, envafolimab demonstrated similar efficacy to other similar checkpoint inhibitors in MSI-H/dMMR CRC who failed a prior fluoropyrimidine, oxaliplatin and irinotecan [6-8].

	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
- Measurable disease by RECIST 1.1
- No prior immunomodulatory therapy
- 1 or 2 prior lines of therapy for UPS or MFS
- ECOG ≤ 1



- Envafolimab (cohort A and B): 300mg q3wks subQ
- Ipilimumab (cohort B only): 1 mg/kg q3wks i.v. x 4 doses

STUDY RATIONALE

- PD-(L)1 inhibitors have demonstrated robust 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.
- PD-(L)1 inhibitors 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.

	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**

- Refractory UPS and MFS represent a high unmet need patient population, with a single approved treatment with a < 5% ORR.
- Despite the activity of checkpoint inhibitors in STS, the ENVASARC Phase 2 trial (NCT04480502) is the first pivotal trial conducted in STS using a PD-(L)1 checkpoint inhibitor.

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%.

STUDY OBJECTIVES

Primary

- ORR by BICR of envafolimab (cohort A) and of envafolimab combined with ipilimumab (cohort B), 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
- Pharmacokinetic (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 formalin fixed paraffin embedded (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

SUMMARY

- The pivotal ENVASARC trial is enrolling at approximately 20 sites in the U.S
- The primary endpoint in each of two parallel cohorts (cohort A of single agent envafolimab and cohort B of envafolimab with ipilimumab) is confirmed ORR 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

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