A PHASE 2 STUDY OF ACR-368 IN PATIENTS WITH ENDOMETRIAL CARCINOMA AND PROSPECTIVE VALIDATION OF ONCOSIGNATURE PATIENT SELECTION (NCT05548296)

Acrivon Therapeutics

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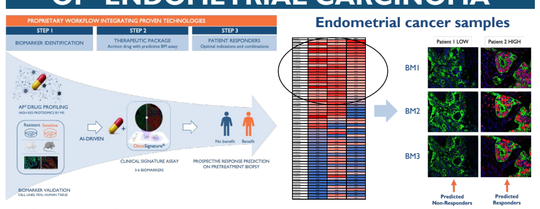
BACKGROUND

ACR-368 (prexasertib), a potent, selective CHK1/2 inhibitor, has shown durable single-agent activity at RP2D in patients with ovarian carcinoma. ACR-368-OncoSignature (BM) is a predictive biomarker test derived from Acrivon Predictive Precision Proteomics (AP3) designed to predict benefit from ACR-368. It has been evaluated in 2 prospectively designed, blinded studies on pretreatment tumor biopsies from past trials demonstrating significant responder enrichment. Importantly, based on preclinical screening of human cancer tissues ("AP3 Indication Finding"), it identified endometrial carcinoma as a new tumor type predicted to be particularly sensitive to ACR-368 (Murshid et al, AACR-EORTC-NCI 2023). This is now being studied in a prospective Phase 2 trial treating subjects with high grade, advanced stage (III, IV) endometrial cancer based on BM status, irrespective of MMR or other molecular alterations.

ONCOSIGNATURE IDENTIFICATION OF ENDOMETRIAL CARCINOMA



AP3 Indication Finding

Heatmap for the 3 OncoSignature biomarkers (BM1, BM2, BM3) across tumor samples. Tumor samples elevated for all 3 biomarkers (red; ~30%) predict sensitivity to ACR-368. The right graphic illustrates imaging of tumor samples from a predicted responder and predicted non-responder (biomarkers in red, tumor epithelium in green).

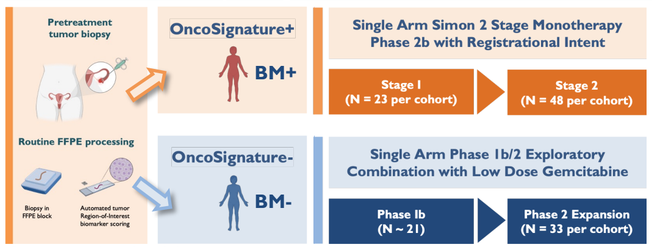
DEMOGRAPHICS AND DISPOSITION OF ALL ENROLLED SUBJECTS (N=35)

Subject Demographics	BM+ N = 12	BM- N = 23
Median Age (range)	66 (60-76)	68 (42-78)
Race (%)		
White	8 (67)	16 (70)
Black/African American	3 (25)	3 (13)
Asian	0 (0)	3 (13)
Other	0 (0)	1 (4)
Unknown	1 (8)	0 (0)
Current Stage (%)		
III	3 (25)	12 (52)
IV	9 (75)	10 (43)
unk	0 (0)	1 (4)
Histology (%)		
Serous	8 (67)	7 (30)
Endometrioid	3 (25)	7 (30)
Carcinosarcoma	1 (8)	3 (13)
Clear Cell Carcinoma	0 (0)	2 (9)
Other	0 (0)	4 (17)
ECOG Status at Baseline (%)		
0	5 (42)	10 (43)
1	7 (58)	13 (57)

Subject Disposition	BM+ N = 12	BM- N = 23
Median Prior Lines (range)	2 (1-4)	3 (1-4)
Prior PD-1/PD-L1 Therapy (%)		
Yes	12 (100)	22 (96)
No	0 (0)	1 (4)*
Discontinued Study Drug (%)	3 (25)	13 (57)
Reason for Discontinuing Study Drug (%)		
PD	2 (17)	10 (43)
PI Decision	1 (8)	0 (0)
Unacceptable Tox	0 (0)	1 (4)
Subject Decision	0 (0)	1 (4)
Subject Withdrawal of Consent	0 (0)	1 (4)
Survival Status (%)		
Alive^	10 (83)	14 (61)
Deceased	2 (17)	7 (30)
Unknown	0 (0)	2 (9)

*Subject deemed ineligible for immune checkpoint inhibitor (ICI) therapy.
^1 BM+ and 4 BM- subjects are still on study for follow-up, but no longer receiving study drug.
Data current as of 25July2024 and includes all subjects enrolled with registrational intent after OncoSignature threshold lock.
BM- includes all subjects treated with ACR-368 + low dose gemcitabine (LDG) at RP2D (105 mg/m^2 and 10 mg/m^2, respectively).

ACR-368-201 STUDY DESIGN AND CLINICAL ACTIVITY IN THE RECIST-EVALUABLE SUBJECTS (SUBJECTS WITH AT LEAST ONE ON-TREATMENT SCAN; N = 23)



Prospective clinical trial design

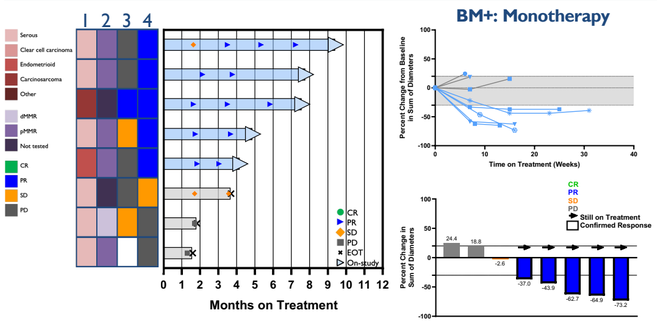
BM+ subjects are treated with single-agent ACR-368 as part of a potentially registrational Phase 2 Simon 2 stage design. BM- subjects are treated with ACR-368 + LDG based on AP3-predicted sensitization to ACR-368 in an exploratory Phase 1b/2 trial

Overall Response	BM+	BM-
	N = 8	N = 15
	N (%)	N (%)
CR	0 (0)	1 (7)
cPR	5 (63)	0 (0)
uPR	0 (0)	1 (7)
SD	1 (13)	6 (40)
PD	2 (25)	7 (47)
cORR (95% CI)	62.5% (30.4, 86.5)	6.7% (0.84, 31.8)
OncoSignature BM+ vs BM- Segregation P = 0.009		

- Confirmed ORR in BM+ subjects = **62.5%** [N=8; 95% C.I. (30.4, 86.5)]
- OncoSignature segregation of BM+ vs BM- (N = 23; **P = 0.009**)

Data current as of 25July2024, includes efficacy-evaluable subjects (at least one on-treatment scan) enrolled after OncoSignature threshold lock (BM+ and BM-) at RP2D for LDG (BM-); cPR = confirmed partial response, uPR = unconfirmed partial response, cORR = confirmed overall response rate; Nonparametric bootstrap method for calculating OncoSignature BM+ vs BM- segregation; Agresti-Coull method for calculating 95% confidence interval (CI).

CONFIRMED RECIST RESPONSES IN BM+ pMMR SUBJECTS WHO HAVE ALL PROGRESSED ON PRIOR IMMUNE CHECKPOINT INHIBITOR THERAPY



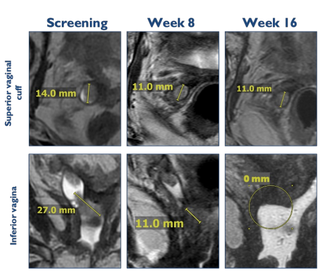
Data current as of 25July2024, includes all BM+ subjects enrolled after OncoSignature threshold lock.
1 – Histology; 2 – MMR; 3 – BOR on most recent prior line; 4 – BOR on ACR-368

BM+ Summary of Prior Therapies

Endometrial subtype	MMR Status	Number of Prior Lines	Last Prior Therapy	BOR on Last Prior Therapy	BOR on ACR-368
Serous	pMMR	3	Pembrolizumab/Lenvatinib	PD	cPR
Serous	pMMR	2	Pembrolizumab/Lenvatinib	PD	cPR
Carcinosarcoma	*NT*	2	Pembrolizumab/Lenvatinib	PR	cPR
Serous	pMMR	1	Pembrolizumab	SD	cPR
Endometrioid	pMMR	4	Cisplatin	PD	cPR
Serous	dMMR	3	Pembrolizumab/Lenvatinib	*UNK*	PD
Serous	*NT*	4	Liposomal doxorubicin	PD	SD
Serous	pMMR	3	Pembrolizumab/Lenvatinib	*NA*	PD

- mDOR not yet reached (5.7+ months at time of data cut-off); all responding patients still on therapy
- BOR in last prior line predominantly PD in confirmed ACR-368 responders
- Confirmed responses in pMMR subjects failed to respond to immune checkpoint inhibitor (ICI) in last prior line of therapy
- Additional 4 subjects enrolled awaiting first on-treatment scan

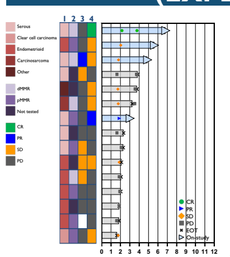
BOR = Best Overall Response, UNK = unknown, NA = not applicable
Data shown current as of 25Jul2024 and includes all efficacy-evaluable (at least one scan on-treatment) BM+ subjects enrolled after OncoSignature threshold lock

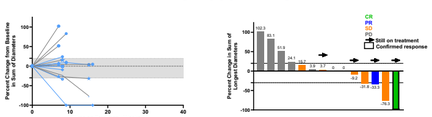


BM+ Monotherapy Subject

- 72-yo female with Stage III serous endometrial carcinoma (pMMR)
- PD on last prior line (pembrolizumab/lenvatinib)
- Confirmed PR at Week 16
- 73% overall decrease in sum of target lesions from baseline

CLINICAL ACTIVITY IN BM- SUBJECTS (EXPLORATORY PHASE 1B/2)





- Notable clinical activity (1 cCR, 1 uPR, and 6 SD) in a proportion of BM- subjects

Data current as of 25July2024, includes all BM- subjects enrolled after OncoSignature threshold lock at RP2D for LDG (10 mg/m^2). 1– Histology; 2 – MMR; 3 – BOR on most recent prior line; 4 – BOR on ACR-368 + LDG

SAFETY

Treatment-Related Adverse Events of Note	ACR-368 (BM+) N = 12 All (%)	ACR-368 (BM+) N = 12 Gr 3/4 (%)	ACR-368 + LDG (BM-) N = 23 All (%)	ACR-368 + LDG (BM-) N = 23 Gr 3/4 (%)
Thrombocytopenia	6 (50)	2 (17)	12 (52)	8 (35)
Anemia	4 (33)	3 (25)	12 (52)	9 (39)
Neutropenia	3 (25)	3 (25)	7 (30)	7 (30)
Febrile Neutropenia	0 (0)	0 (0)	3 (13)	3 (13)
Fatigue	3 (25)	0 (0)	7 (30)	0 (0)
Vomiting	3 (25)	0 (0)	2 (9)	0 (0)
Diarrhea	2 (17)	0 (0)	2 (9)	0 (0)
Infusion Reaction	0 (0)	0 (0)	1 (4)	0 (0)
Palmar-plantar erythrodysesthesia	0 (0)	0 (0)	0 (0)	0 (0)
Hypertension	0 (0)	0 (0)	1 (4)	1 (4)
Hypothyroidism	0 (0)	0 (0)	0 (0)	0 (0)
Peripheral Sensory Neuropathy	0 (0)	0 (0)	0 (0)	0 (0)
Liver Toxicity*	0 (0)	0 (0)	0 (0)	0 (0)
Dyspnea	0 (0)	0 (0)	2 (9)	0 (0)
Pulmonary Disorders (Pneumonitis)	0 (0)	0 (0)	0 (0)	0 (0)
Left Ventricular Dysfunction	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac Failure	0 (0)	0 (0)	0 (0)	0 (0)
LVEF	0 (0)	0 (0)	0 (0)	0 (0)
Death (Drug-related)	0 (0)	0 (0)	0 (0)	0 (0)

- Encouraging safety profile with limited, predominantly transient, reversible, mechanism-based hematological AEs, typically occurring during the first 1-2 cycles of therapy
- Notable absence of long-lasting myelosuppression or the typical more severe non-hematological AEs commonly seen with ADCs and chemotherapy

ACR-368 data current as of 25July2024 and includes the safety population of endometrial carcinoma subjects (any subject who has received at least one dose of ACR-368) enrolled post-threshold lock (BM+ and BM-) and at the RP2D for LDG (BM-).
Prophylactic G-CSF encouraged in BM+ and mandated in BM- subjects (compatible with q14d dosing regimen).
*This category includes the preferred terms aminotransferase levels increased, aspartate aminotransferase increased, alanine aminotransferase increased, γ-glutamyltransferase increased, liver function test abnormal, and hepatic function abnormal.

CONCLUSIONS

- Endometrial carcinoma was identified as a new tumor type predicted to be particularly sensitive to ACR-368 based on preclinical AP3 Indication Finding
- Confirmed ORR = 62.5% [95% CI (30.4, 86.5%)] in high grade, advanced stage BM+ subjects (irrespective of subtype) who all have progressed on ICI therapy
- Confirmed responses in pMMR subjects failing to respond to last prior line, including ICI therapy
- mDOR not yet reached (5.7+ months at data cut) with all responders still on therapy
- Further validation of ACR-368 OncoSignature showing segregation of responders between BM+ and BM- subjects with p=0.009
- Encouraging safety profile with predominantly mechanism-based, transient, and reversible hematological AEs with notable absence of non-hematological AEs
- Accelerating development towards potential registrational opportunity in second line setting of high grade, advanced stage endometrial carcinoma

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