Vudalimab Monotherapy in Patients with mCRPC

Study XmAb717-05

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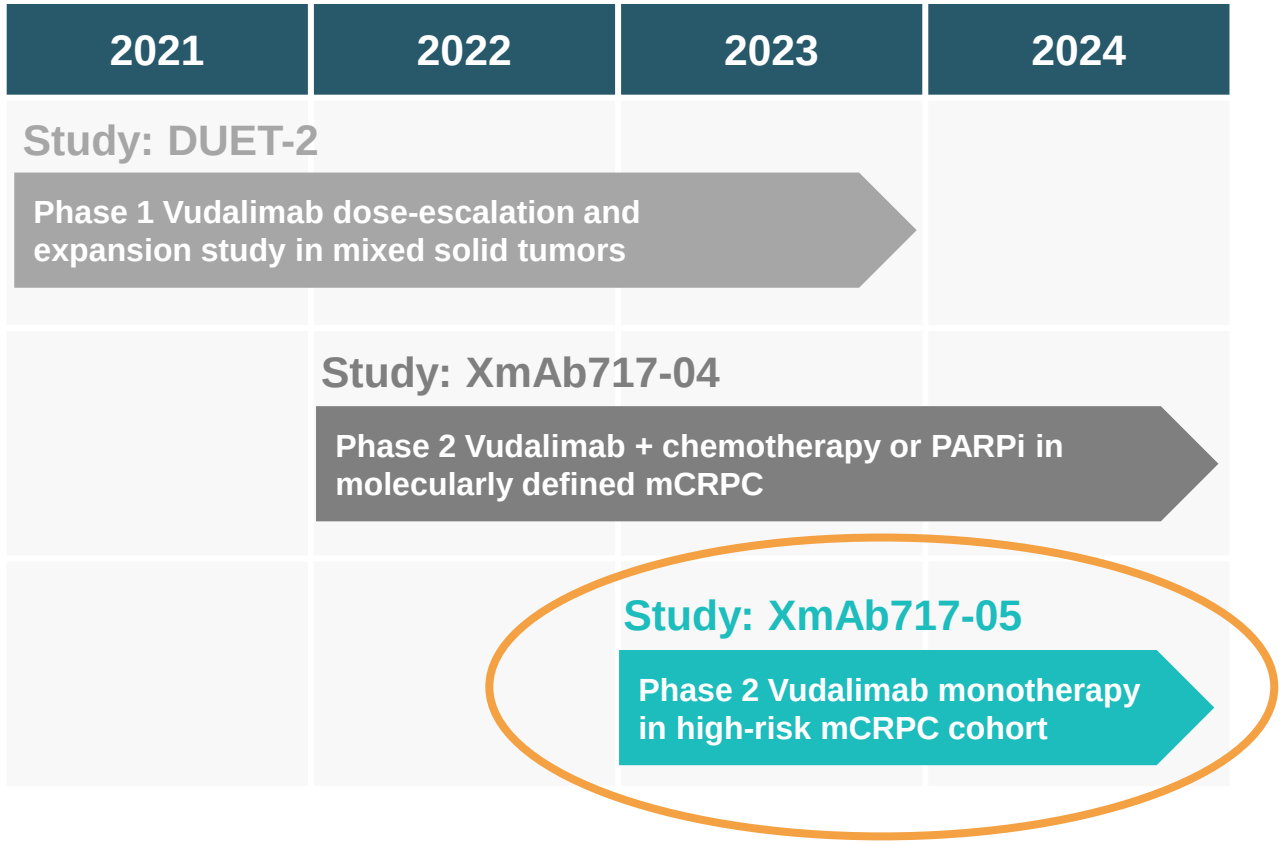
Evolution of Vudalimab Development Program for mCRPC



mCRPC Cohort in Study XmAb717-05

- Visceral, soft tissue, or lymph node metastases (“high-risk” mCRPC)
- Measurable disease by RECIST 1.1
- Progressed after all approved, medically appropriate therapies
- < 2 prior chemotherapy regimens
- No prior treatment with anti-CTLA-4 or PD-1

Study status

- 14/30 mCRPC patients enrolled

Vudalimab Q3W flat dose schedule: 1000 (< 80 kg) or 1200 mg (≥ 80 kg) IV

Summary of Preliminary Data

Vudalimab monotherapy has been associated with clinical response in 5 out of 12 evaluable mCRPC patients with visceral or lymph node metastases

- Findings consistent with observations of durable responses (41 and 27 weeks) in Phase 1 mCRPC cohort in 2 patients with visceral and lymph node (extrapelvic and/or intrapelvic) metastases

Vudalimab monotherapy safety profile has been consistent with other checkpoint inhibitor therapies

- Low rate of discontinuation of treatment due to adverse events

Additional data will inform future development efforts in monotherapy, and/or contribution of monotherapy to combination treatment

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Demographics and Baseline Characteristics and Prior Treatment

Characteristic	mCRPC (n = 14)
Age, median (range)	72 (58-89)
Liver or Lung metastases at baseline, (%)	6 (42.9)
PSA (ng/ml) at baseline, median (range)	152.9 (35-1873)
ECOG 1, n (%)	12 (85.7)
Metastatic disease at diagnosis, n (%)	11 (78.6)

Prior Treatment	mCRPC (n = 14)
Median (range) lines of prior therapy	4 (2-8)
Chemotherapy, n (%)	13 (92.8)
Lines of chemotherapy, median (range)	1 (1-2)
Prior AR Therapy	14 (100.0)
Abiraterone, n (%)	11 (78.6)
Enzalutamide, n (%)	8 (57.1)
Lu-177 PSMA, n (%)	4 (28.6)
Prior radiation, n (%)	9 (64.3)

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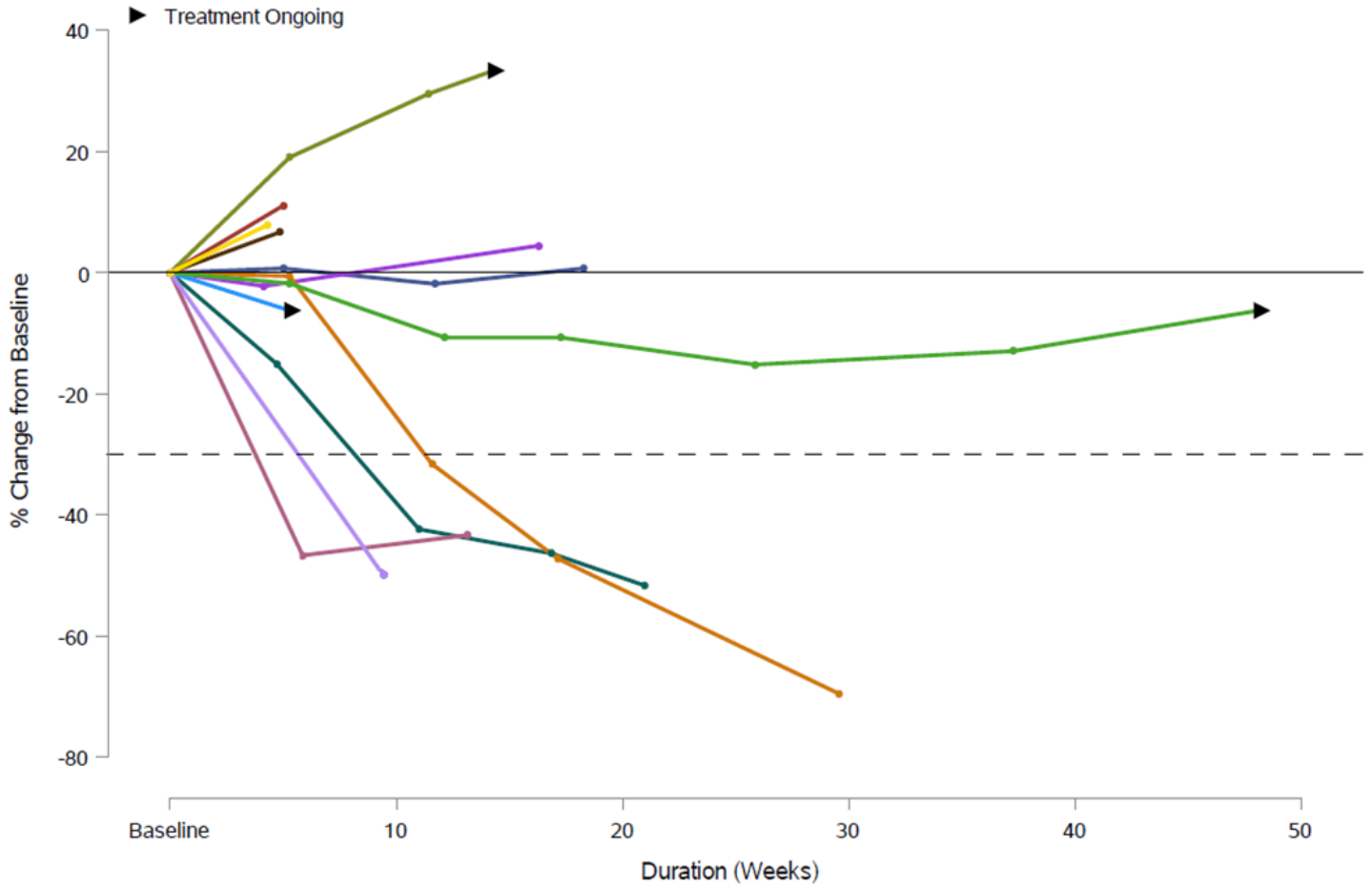
Response to Treatment and Percent Change in Target Lesions

RECIST 1.1 (PCWG3), n (%)	mCRPC (n = 12*)
Objective response rate	4 (33)
Best overall response	
Complete response	0
Partial response	4 (33)
Confirmed	3 (25)
Unconfirmed	1 (8)
Stable disease	2 (17)
Progressive disease	3 (25)
Not evaluable	3 (25)
Disease control rate	6 (50)

*Subjects who have baseline and at least one post-baseline RECIST assessment.



Duration of response for confirmed responders: 18, 10 and 7 weeks

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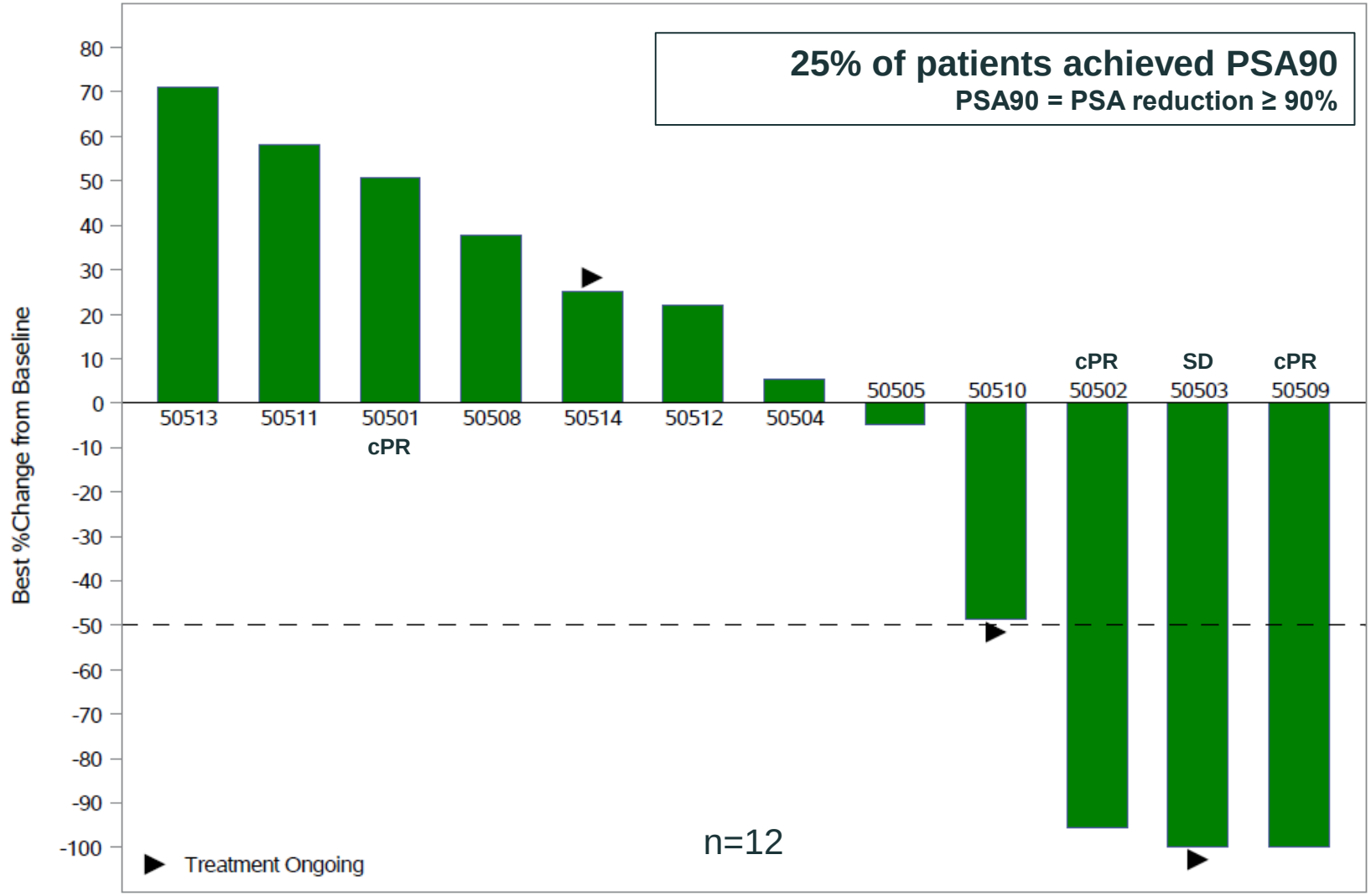
Best Percent Change in PSA From Baseline



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Characteristics of Patients with Clinical Response

Patient	Age/ Race	Prior Systemic Therapies	Prior Radiation	Metastases at Baseline	PSA (ng/mL)	BOR/ Duration of Response	EOT reason
50509	66/AA	Docetaxel Enzalutamide Abiraterone	None	Bone Extrapelvic LN Pelvic LN (SoD = 45.1 mm)	Baseline: 165 Nadir: <0.02 Last: <0.02	cPR 10 weeks	AE: Immune mediated hepatitis
50506	69/W	Carboplatin Bicalutamide Leuprolide + abiraterone	Unspecified RT: Non-castrate clinically localized disease	Retroperitoneal LN (SoD = 34.5 mm)	Baseline: 111 Nadir: Not available Last: Not available	uPR	Lost to follow up
50503	79/AA	Bicalutamide Leuprolide	None	1 liver lesion Bone (SoD = 44.8 mm)	Baseline: 1873 Nadir: 4 Last: 12	SD (PSA90)	Still on study >48 weeks
50502	89/AA	Bicalutamide Leuprolide + abiraterone Enzalutamide Docetaxel Cabazitaxel Olaparib	External beam IMRT (thoracic spine)	3 liver lesions Bone (SoD = 118.5 mm)	Baseline: 180 Nadir: 8 Last: 47	cPR 18 weeks	PD
50501	60/W	Leuprolide + enzalutamide Docetaxel	None	Bone Retroperitoneal LN (SoD = 30 mm)	Baseline: 140 Nadir:211 Last: 549	cPR 7 weeks	PD

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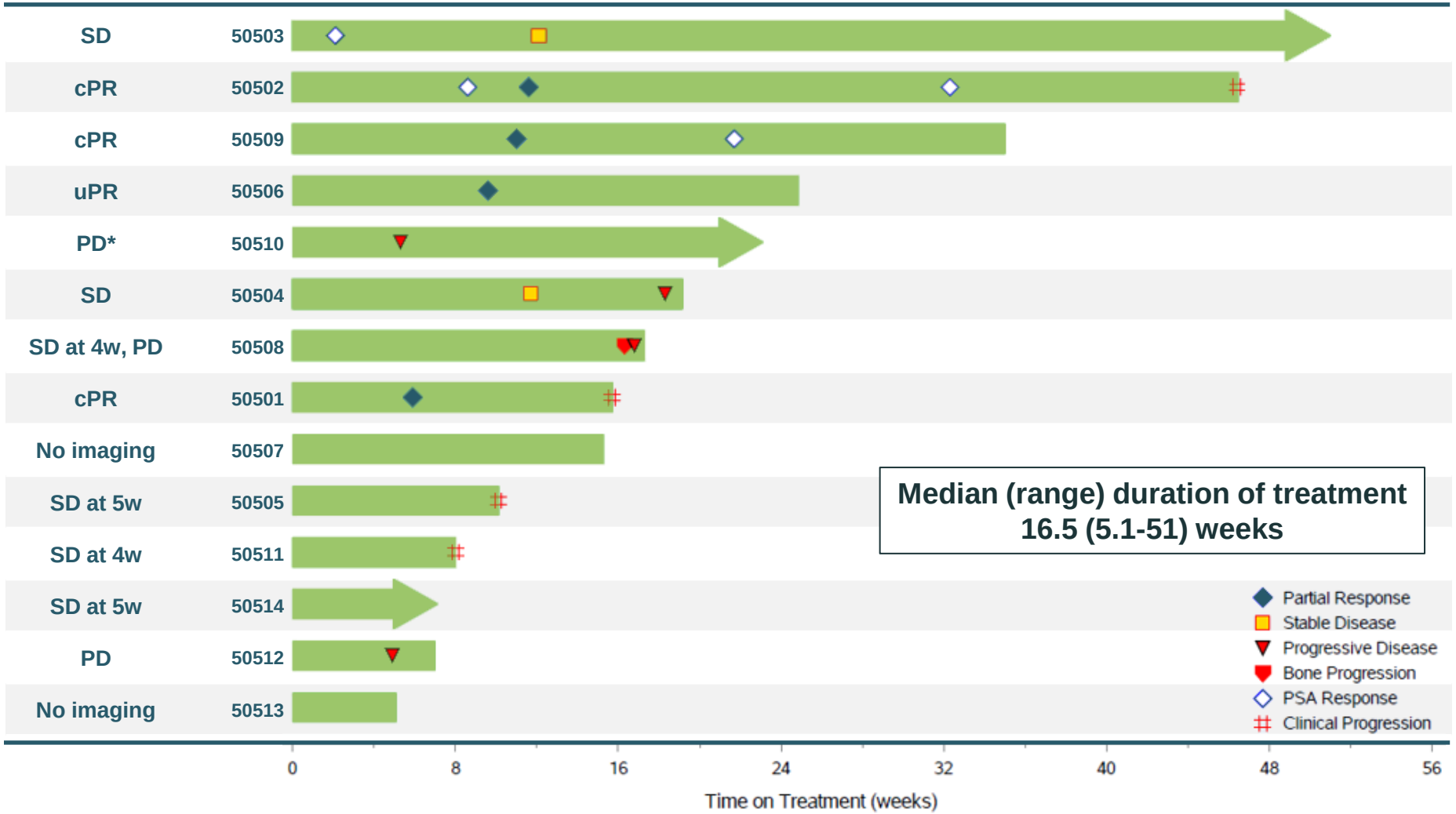
AE: adverse event; BOR: best overall response; cPR: confirmed partial response; SD: stable disease; PD: progressive disease; uPR: unconfirmed partial response

Time on Treatment (n=14)



RECIST 1.1: end of Cycle 2 then Q6W through Cycle 8, Q9W thereafter. Bone scans: end of cycle 2, Q9W through cycle 12, Q12W, thereafter. PSA: end of Cycle 1, Q6W thereafter. * Patient is seeing clinical benefit and is being treated beyond progression.

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Summary of Treatment-Emergent Adverse Events

Event, n (%)	mCRPC (n = 14)
Any	13 (92.9)
Grade ≥ 3	9 (64.3)
Treatment related	9 (64.3)
Serious adverse event	7 (50.0)
Related serious adverse event	4 (28.6)
Leading to dose modification*	8 (57.1)
Leading to treatment discontinuation	2 (14.3)
Leading to death	1 (7.1)

* Dose modification includes dose reduced and/or held.

One Grade 5 adverse event of autoimmune hepatitis was deemed treatment related; there have been no known additional cases of Grade 5 autoimmune hepatitis among three clinical studies of vudalimab with more than 240 patients treated.

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irAEs of Any Grade in ≥ 2 Patients and Grade ≥ 3 in Any Patients

Any Grade, n (%)	mCRPC (n = 14)
Number of subjects with ≥ 1 event	8 (57.1)
Rash maculo-papular	4 (28.6)
ALT increased	3 (21.4)
Amylase increased	2 (14.3)
AST increased	2 (14.3)
Blood bilirubin increased	2 (14.3)
Hyperthyroidism	2 (14.3)

Grade ≥ 3, n (%)	mCRPC (n = 14)
Number of subjects with ≥ 1 event	3 (21.4)
ALT increased	1 (7.1)
AST increased	1 (7.1)
Blood AP increased	1 (7.1)
Blood bilirubin increased	1 (7.1)
Diabetic ketoacidosis	1 (7.1)
Hyperkalaemia	1 (7.1)
Immune-mediated hepatitis	1 (7.1)
Lipase increased	1 (7.1)

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Benchmark Rates of Immune-Mediated Hepatitis

Drug (Target)	**Vudalimab** (PD-1 x CTLA-4)	**Ipilimumab** (CTLA-4)	**Ipilimumab** (CTLA-4)	**Ipilimumab** (CTLA-4) **+ Nivolumab** (PD-1)	**Ipilimumab** (CTLA-4) **+ Nivolumab** (PD-1)
Dosage	N=218*, includes 10 mg/kg Q2W & 1000 mg/1200mg Q3W	3 mg/kg	10 mg/kg	1 mg/kg ipilimumab + 3 mg/kg nivolumab for RCC or mCRC	3 mg/kg ipilimumab + 1 mg/kg nivolumab for melanoma or HCC
Immune-Mediated Hepatitis†, All Grade	7.3%	4.1%	15.0%	7.0%	15.0%
Immune-Mediated Hepatitis†, Grade 3 - 5	5.0%	1.6%	10.8%	6.1%	13.4%

† Immune-Mediated Hepatitis defined as:

For vudalimab: Treatment-related adverse event (TRAE) immune-mediated hepatitis, hepatitis, autoimmune hepatitis, hepatic cirrhosis, hepatic failure, hepatitis acute, hyperbilirubinemia, immune-mediate cholangitis, or liver injury.

For ipilimumab: U.S. FDA label, Yervoy® (ipilimumab) injection, for intravenous use, as revised 2/2023. Yervoy is a registered trademark of Bristol-Myers Squibb Company.

* Excludes 27 patients treated at vudalimab doses less than 10 mg/kg.

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Novel Therapeutic Development Landscape for mCRPC

Drug	Vudalimab[1]	Xaluritamig[2]	Pluvicto + SoC[3]	Lorigerlimab[4]	MK-5684 (ODM-208)[5]	ARX517[6]	Vobramitamab Duocarmazine[7]
Study	**Phase 2**	FIH / Dose Escalation	Phase 3 (VISION)	Phase 1 Expansion Cohort	Phase 2	Phase 1b Dose Expansion	Phase 1 Expansion Cohort
MoA	**PD1xCTLA4**	STEAP1xCD3	177Lu-PSMA-617	PD1xCTLA4	CYP11A1 Inhibitor	PSMA ADC	B7xH3 ADC
Selected Population	**No**	No	PSMA+	No	AR-LBD mut	No	No
Xencor Interest	**Wholly Owned**	**Mid- to High-Single Digit Royalty**	-	-	-	-	-
Dosing	**1000 or 1200 mg IV Q3W**	1.5 mg IV QW (3-step, D1/8/15/22: 0.1/0.3/1.0/1.5 mg)	7.4 GBq IV Q6W for 4-6 cycles + SoC	6 mg/kg IV Q3W	5 mg BID with dexamethasone 1 mg/fludrocortisone 0.1 mg	Tested up to 2.88 mg/kg Q3W, putative therapeutic doses ≥2.0 mg/kg	3 mg/kg IV Q3W
Enrolled (N)	**14**	97	385	42	66	32 (≥2.0 mg/kg)	40
ECOG PS 0 / 1	**85.7% ECOG 1**	46% / 54%	91.4% (ECOG 0 or 1)	28.6% / 71.4%	24.2% / 74.2%	37% / 59%	42.5% / 57.5%
Measurable Disease	**100%**	69%	48%	83%	59%	15.5% (C4 - C8)	40%
Prior Lines Median (Range)	**4 (2 - 8)**	4 (1, 9)	~4*	2 (1, 9)	~3 - 4*	4 (1, 13)	3 (2 - 7)
Prior Taxane	**93%**	85%	98%	98%	98.5%*	66%	100%
PSA50	**25%**	40% Low Dose (N=43)/ 59% High Dose (N=44)	46%	28.6% (N=42)	56%	52% (2.0 - 2.88 mg/kg) (N=23)	54% (N=39)
PSA90	**25% (N=12)**	19% Low Dose (N=43)/ 36% High Dose (N=44)	33% PSA80	21.4% (N=42)	24%*	26% (2.0 - 2.88 mg/kg) (N=23)	~10% (est.) (N=39)
PR (RECIST v1.1)	**25% cPR, 33% uPR (N=12)**	3% cPR Low Dose (N=30)/ 41% cPR High Dose (N=37)	51%	25.7% cPR (N=35)	21%	22% cPR (Dose Levels 1.4 - 2.88 mg/kg) (N=9)	12.5% cPR, 25% uPR (N=16)
Grade 3+ TEAE	**64%**	76%	53%	62%	48%	12.5% (TRAE)	56%
TRAE Disc.	**14%**	19%	11.9% (Lu-PSMA-617)	25%	3% hospitalization rate for adrenal insufficiency	3%	7%

Novel Therapeutic Development Landscape for mCRPC - Sources

* Xencor Estimate

[1] Xencor.

[2] Interim Results From a Phase 1 Study of Xaluritamig (AMG 509), a STEAP1 x CD3 XmAb® 2+1 Immune Therapy, in Patients With Metastatic Castration Resistant Prostate Cancer (mCRPC), Kelly and Appleman et al.; Amgen, ESMO 2023.

[3] Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer, de Bono and Krause et al.; NEJM, Sept 2021.

[4] Lorigerlimab, a Bispecific PD-1 ×CTLA-4 DART® Molecule in Patients With Metastatic Castration-Resistant Prostate Cancer: A Phase 1 Expansion Cohort, Luke and Cybulska-Stopa et al.; MacroGenics, ASCO GU 2023.

[5] MK-5684 (ODM-208), a CYP11A1 inhibitor, in metastatic castration-resistant prostate cancer (mCRPC) patients with and without AR-LBD mutations: CYPIDES Phase 2 results; Fizazi and Antonarakis et al.; Merck, ASCO GU 2024.

[6] ARX517, an Anti-Prostate-Specific Membrane Antigen (PSMA) Antibody-Drug Conjugate (ADC), Demonstrates Promising Safety and Efficacy in Heavily Pre-Treated Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC); Shen and Tagawa et al.; Ambrx Biopharma, ESMO 2023.

[7] MGC018, an Anti-B7-H3 Antibody-Drug Conjugate (ADC), in Patients With Advanced Solid Tumors: Preliminary Results of Phase 1 Cohort Expansion; Shenderov and Lugowska et al.; MacroGenics ESMO 2021.

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