ARV-766: Phase 1 and interim Phase 2 data

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ARV-766 is showing promising efficacy signals in late-line mCRPC and is well-tolerated, supporting its potential as an earlier-line treatment

ARV-766 is showing promising efficacy signals in a heavily pretreated patients, including in patients with androgen receptor (AR) L702H mutations

- 42% of patients with AR ligand binding domain (LBD) mutations achieved PSA_{50}
  - 3 of 3 patients with co-occurring AR T878/H875/L702H mutations achieved PSA_{50}
- RECIST partial responses were observed:
  - Two of four RECIST-evaluable patients with AR LBD mutations achieved partial responses (1 confirmed, 1 unconfirmed)

ARV-766 has been well tolerated to date

- Majority of treatment related adverse events (TRAEs) are Grade 1 or 2, with no Grade ≥4 TRAEs
- Low rates of discontinuation or dose reduction

The emerging efficacy signals and tolerability profile of ARV-766 support continued development in mCRPC and CSPC, and Arvinas will initiate a trial in pre-NHA patients in 2H 2023

mCRPC, metastatic castrate-resistant prostate cancer; CSPC, castrate-sensitive prostate cancer; LBD, ligand binding domain; RECIST, Response Evaluation Criteria in Solid Tumors

ARV-766: A novel AR degrader designed to address multiple resistance mechanisms, including AR L702H point mutations

- Tumor resistance mechanisms are increasing with earlier use of novel hormonal agents (abiraterone/enzalutamide), leaving limited treatment options in the post-NHA space
- The prevalence of AR LBD mutations is increasing, especially L702H

The prevalence of AR LBD mutations, especially L702H, has increased over time

AR LBD mutation	2016[1]	2020[2]	2023[3]
L702H	**~2%**	**~9%**	**~11%**
T878X*	~6%	~6%	~8%
H875Y	~4%	~4%	~5%

- In total, the prevalence of AR LBD mutations in mCRPC is 20-25%[4,5,6]
- **ARV-766 was designed to target L702H and all other clinically relevant AR mutations**, including T878X*, H875Y, and less frequent mutations

*878X = T878A or T878S; mCRPC, metastatic castrate-resistant prostate cancer; LBD, ligand binding domain

1 Coutinho et al 2016 DOI: 10.1530/ERC-16-0422. 2 Ledet et al 2020 DOI: 10.1634/theoncologist.2019-0115. 3 Antonarakis et al, Abstract 395182, ASCO/GU 2023. 4 Beltran H. Eur Urol. 2013;63(5):920-926. 5 Wyatt AW. JAMA Oncol.2016;2(12):1598-1606. 6 Bernard-Tessier et al, Abstract 39698, ASCO/GU 2023

The Phase 1/2 trial of ARV-766 is enrolling a post-NHA, all-comers, heavily pretreated patient population

Parameters	Phase 1 (n=34)	Phase 2 (interim data)* (n=13)
Median age (range), years	70 (59–86)	67 (60–76)
ECOG performance status, n (%)		
0	20 (59)	9 (69)
1	14 (41)	4 (31)
Visceral disease†, n (%)	23 (68)	7 (54)
Measurable disease at baseline, n (%)	15 (44)	3 (23)
Median duration of treatment (weeks)	10.8 (3.9 – 38.1)	8.0 (2.3 – 15.9)
Median no. of prior systemic anti-cancer regimens (all setting)	4	5
Prior radiotherapy, n (%)	19 (61)	12 (92)
Type of prior therapy, n (%)		
Novel hormonal agent	34 (100)	13 (100)**
Abi alone	8 (24)	4 (31)
Enza/Daro/Apa alone	8 (23)	6 (46)
Combination NHA	18 (53)	2 (15)
Chemotherapy	24 (71)	4 (31)

ECOG, Eastern Cooperative Oncology Group; NHA, novel hormonal agent
*Phase 2 enrollment ongoing (April 2023 data cutoff date); **Prior NHA data on one subject was entered into the database after the data cutoff
†Soft tissue disease other than lymph node, including liver or lung

AR LBD Mutations Were Present in 28% (13 of 47) of Patients' Tumors in the Phase 1/2 Trial

Parameters	Phase 1 (n=34)	Phase 2 (interim data)† (n=13)
AR LBD Mutation Status, n (%)		
LBD Mutant	10 (29)	3 (23)
H875Y/T878X†† without L702H	4 (12)	3 (23)
H875Y/T878X†† with L702H	3 (9)	0 (0)
L702H alone	2 (6)	0 (0)
Other LBD missense mutations	1 (3)	0 (0)
Non-LBD Mutant†††	23 (68)	9 (69)
Unknown/Missing	1 (3)	1 (8)

† Enrollment ongoing (April 2023 data cutoff date). ††T878X = T878A or T878S. †††Includes wild type, amplified, and other non-LBD mutations

ARV-766 has been well tolerated, with no grade ≥4 TRAEs and low rates of dose reduction and discontinuation

Phase 1

TRAE >5%, n (%)	Total (n=34)			
	Gr 1	Gr 2	Gr 3	Total
Any TRAE	9 (27)	7 (21)	2 (6)	18 (53)
Fatigue	3 (9)	3 (9)	1 (3)	7 (21)
Nausea	2 (6)	2 (6)	0 (0)	4 (12)
Diarrhea	3 (9)	1 (3)	0 (0)	4 (12)
Vomiting	2 (6)	0 (0)	0 (0)	2 (6)
Dry Mouth	2 (6)	0 (0)	0 (0)	2 (6)
AST increased	2 (6)	0 (0)	1 (3)	3 (9)
Cr increased	2 (6)	1 (3)	0 (0)	3 (9)
Hypophosphataemia	3 (9)	0 (0)	0 (0)	3 (9)
Subjects with any TRAE leading to tx discontinuation				0 (0)
Subjects with any TRAE leading to dose interruption				1 (3)
Subjects with any TRAE leading to dose reduction				2 (6)

TRAE, treatment related adverse event; AST, aspartate aminotransferase; Cr, creatinine; tx, treatment
Gr 1 decreased appetite (2), Gr 2 alopecia (2), Gr 1 dry skin (2), Gr 1 & 2 rash maculopapular (2), Gr 1 headache (2) not included in the Table

Phase 2 (ongoing)

TRAE >5%, n (%)	100 mg (n = 6)			300 mg (n = 7)		
	Gr 1	Gr 2	Gr 3	Gr 1	Gr 2	Gr 3
Any TRAE	2 (33)	0 (0)	0 (0)	1 (14)	3 (43)	1 (14)
Abdominal pain	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)	1 (14)
Nausea	0 (0)	0 (0)	0 (0)	2 (29)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)
Dyspepsia	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dry Mouth	0 (0)	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)
Dysgeusia	1 (17)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)
Fatigue	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)
Anemia	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)
Subjects with any TRAE leading to tx discontinuation						1 (14)
Subjects with any TRAE leading to dose interruption				1 (14)	1 (14)	1 (14)
No dose reductions						

100 mg: Gr 1 Alk Phos increased (1) not included in the Table
300 mg: Gr 1 neutrophil decreased (1), Gr 1 WBC decreased (1), Gr 1 alopecia (2), Gr 1 dry skin (1), Gr 1 onychoclasis (1), Gr 1 pruritus (1), Gr 2 dehydration (1), Gr 2 hypertension (1) not included in the Table

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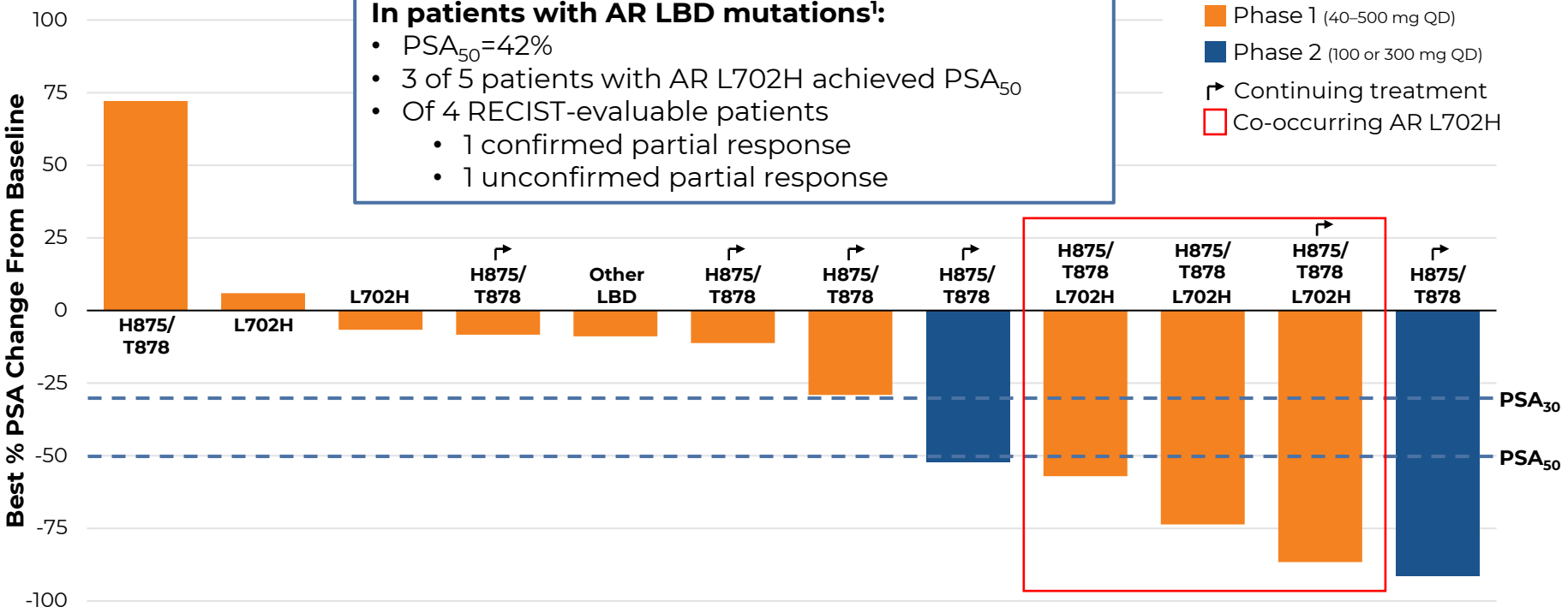
3 of 3 patients with co-occurring AR H875/T878/L702H mutations achieved best PSA reductions ≥50%[1]

In patients with AR LBD mutations[1]:
- PSA_{50}=42%
- 3 of 5 patients with AR L702H achieved PSA_{50}
- Of 4 RECIST-evaluable patients
  - 1 confirmed partial response
  - 1 unconfirmed partial response



1 Analysis includes biomarker-evaluable, AR LBD-positive patients with ≥4 weeks of PSA follow-up.

LBD, ligand-binding domain; PSA, prostate-specific antigen; PSA_{30}, best PSA declines ≥30%; PSA_{50}, best PSA declines ≥50%; H875, H875Y; T878, T878A or T878S; RECIST, Response Evaluation Criteria in Solid Tumors

Arvinas' AR franchise is on track for development across the treatment landscape in mCRPC and CSPC

ARV-766: Promising data in mCRPC, and moving into pre-NHA patients in 2H23

- Phase 1/2 data showing promising efficacy signals and a good tolerability profile, including in patients with AR L702H mutations, supporting further development in mCRPC
- Profile also supports an additional, broader opportunity to advance ARV-766 in earlier treatment settings

Next milestone: Pre-NHA combo of ARV-766 + abiraterone to initiate in 2H23

Bavdegalutamide: Phase 3 trial in mCRPC to initiate in 2H23

- Precision medicine opportunity in a growing population with few treatment options
  - In the U.S. alone: Addressable population of 8,000-11,000 patients with AR LBD+ mutations[1]
  - Addresses an unmet need for durable and tolerable treatments in late-line settings

Next milestone: Updated data from the Phase 1/2 trial, including radiographic progression-free survival (rPFS), at a medical congress in 2H23

mCRPC, metastatic castrate resistant prostate cancer; CSPC, castrate sensitive prostate cancer; LBD, ligand-binding domain; NHA, novel hormonal agent

1 Excludes patients with AR L702H alone