BMS at ASCO GU 2024
AR LDD Phase 1 Highlights

January 25th, 2024

Bristol Myers Squibb™

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BMS at ASCO GU 2024 – AR LDD Phase 1 Data Highlights

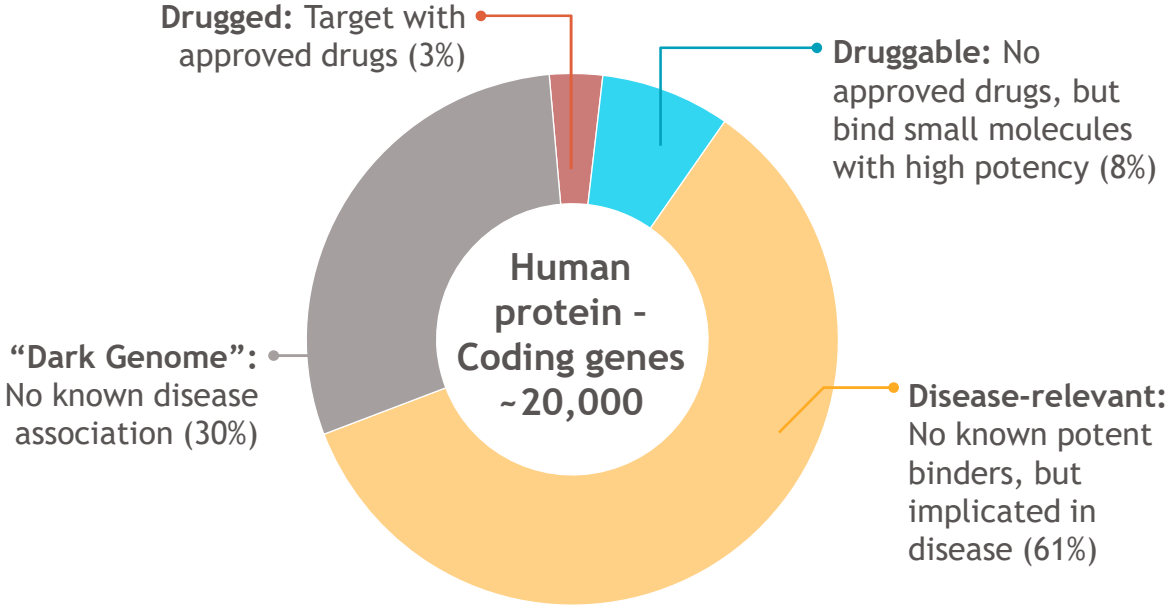
- Potential **best-in-class** oral androgen receptor (AR) ligand-directed degrader in mCRPC
- **Promising efficacy & durability** across AR status (e.g., wildtype, amplified, & mutant) in heavily pre-treated patients
- **Well-tolerated** with a **manageable** safety profile
- Dose optimization ongoing to **enable registrational program**

Continues to validate potential of the targeted protein degradation platform in solid tumors

AR LDD is the first example in solid tumors with our targeted protein degradation platform

Expanded universe of targets

(e.g., scaffolding proteins, transcription factors)



Opportunity in Targeted Protein Degradation

10 assets in clinical development with **4 assets** in/entering **registrational** stage

Industry leading IND-engine positioned to deliver **4** INDs annually

Potential to **expand across all of our TAs**

iberdomide	golcadomide	Immunology
mezigdomide	AR LDD	Neuroscience

Targeted protein degradation offers the promise of novel targets and clinical differentiation for existing targets

Legend: Oncology | Hematology | Immunology | Neuroscience

Effective & tolerable treatment options needed in Metastatic Castration Resistant Prostate Cancer (mCRPC)

High unmet need remains in prostate cancer:

- Expected U.S. mortality is ~35K[1] men in 2023
- 5-year OS[2] decreases from >97% to ~32.5% in the localized vs. metastatic setting

Current SOC - ARPI[2]

- AR is a key driver of prostate cancer and AR-targeted therapies remain current SoC
- Traditional AR antagonists (e.g., enzalutamide) inhibit AR in a reversible manner
- AR inhibition by current SoC is overcome by upregulation of WT or mutation of AR in cancer cells, leading to resistance:
  - AR WT + amplification (~75-80%)[3]
  - AR mutations (~20-25%)[3]
- Post-ARPI progression, limited options for patients (e.g., chemo)

AR LDD

- AR LDD induces irreversible AR degradation in a catalytic manner leading to deeper, more potent AR inhibition with best-in-class potential
- Potentially paradigm-shifting MoA with encouraging clinical activity to overcome resistance mechanisms to ARPI across AR status (WT, amplification & mutations)
- Potential to improve treatment outcomes in the post-ARPI setting

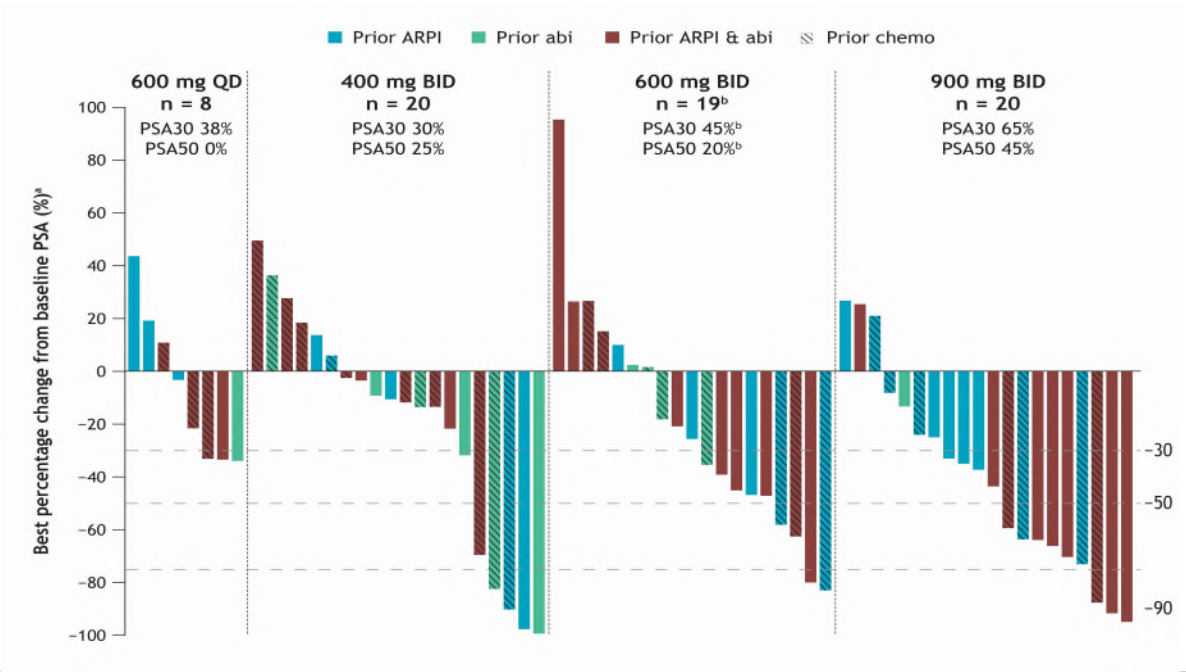
1. Source: Decision Resources Group; BMS Internal Analysis 2. Source: SEER 2023; 3. Source: Robinson et al., 2015, Cell 161:1215; Abida et al., 2019, PNAS 116:11428
AR: androgen receptor; AR LDD: Androgen receptor ligand-directed degrader; mPC: metastatic prostate cancer; ARPi: Androgen Receptor Pathway inhibitor

AR LDD has shown promising PSA reduction in heavily pre-treated patients with mCRPC

Prostate Specific Antigen (PSA) change from baseline by prior treatment

Dose-dependent increase in PSA30 response from 400 to 900 mg BID

PSA reduction **across different pre-treatment regimens** including prior ARPi & chemotherapy



PSA reduction is associated with improved clinical outcomes (e.g., OS) in mCRPC

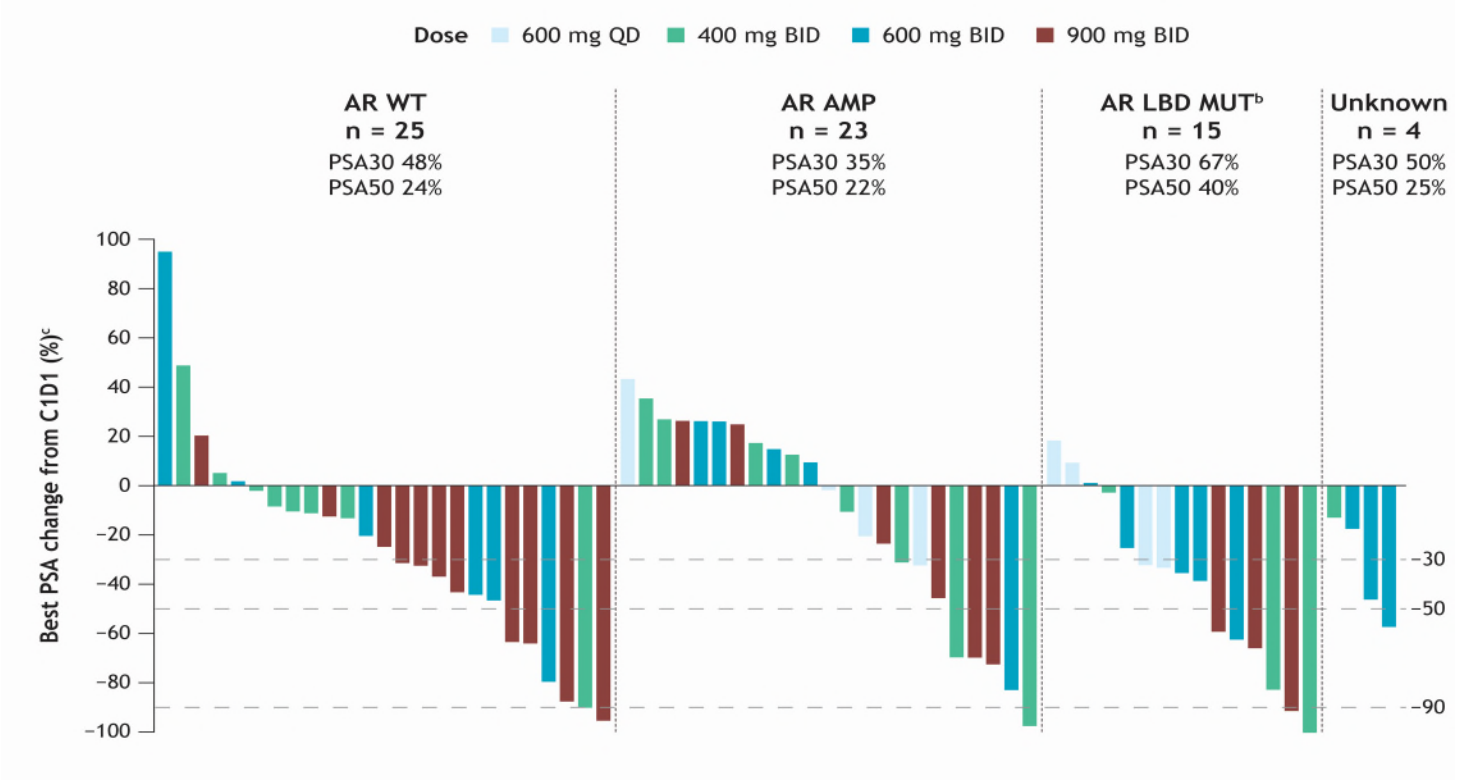
Data cutoff: August 21, 2023; [a]Confirmed PSA by dose include: 600 mg QD, none; 400 mg BID, cPSA30 = 30%, cPSA50 = 25%; 600 mg BID, cPSA30 = 30%, cPSA50 = 10%; 900 mg BID, cPSA30 = 55%, cPSA50 = 35%
[b]One patient excluded, no postdose PSA collections were taken due to worsening disease. Percentages based on all treated patients (n = 20)
Data are taken from local PSA assessments. abi, abiraterone; ARi, androgen receptor inhibitor (enzalutamide, darolutamide, or apalutamide); cPSA, confirmed PSA; PSA30/50, PSA decline of ≥ 30/50% from baseline.

AR LDD displayed efficacy across AR wildtype, amplification & mutant settings

PSA change from baseline by AR status and dose (Part B)[a]

Potentially paradigm-shifting MoA

Promising clinical activity & ability to overcome resistance to ARPi, with best-in-class potential across AR status



Data cutoff: November 16, 2023; [a]Out of the 67 patients who were assessable, genomic data of cell-free DNA was analyzed for 64 patients ("Unknown": two patients failed the quality control, and two patients did not have their baseline plasma collected). [b]AR LBD mutations consisted of the following: L702H; T878A; H875Y; W742C; L702H + T878A; L702H + H875Y; W742C + T878A; and L702H + W742C + T878A. [c]Confirmed PSA by AR status include AR WT, cPSA30 = 44%, cPSA50 = 24%; AR AMP, cPSA30 = 26%, cPSA50 = 22%; AR LBD MUT, cPSA30 = 33%, cPSA50 = 20%.

Abbreviations: AR WT (AR wild Type; AR AMP (AR Amplification); AR LBD MUT (AR Ligand Binding Mutation)

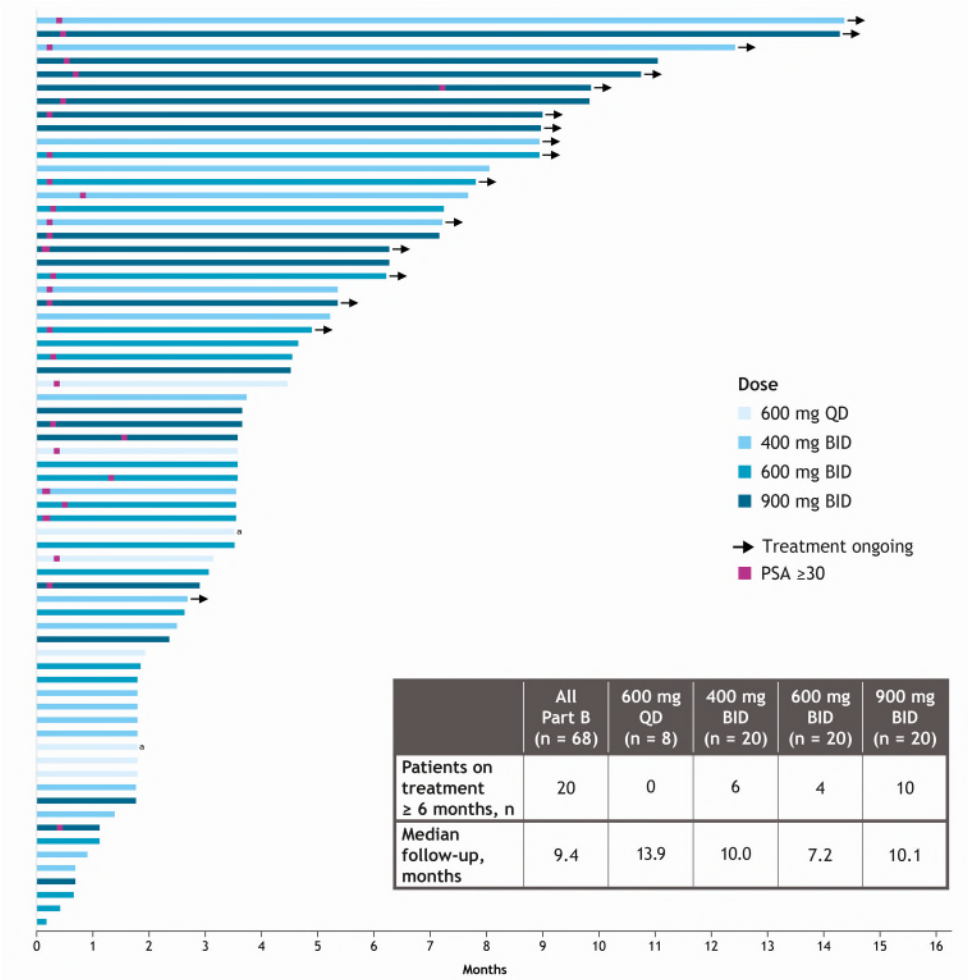
AR LDD has shown signs of durable clinical benefit

Durable clinical benefit was observed for a substantial proportion of patients

~50% of patients in the 900mg BID group still on treatment after 6 months

Median follow up for all patients in dose expansion (Part B) was ~9.4 months

Figure 5. Treatment duration for individual patients in Part B



	All Part B (n = 68)	600 mg QD (n = 8)	400 mg BID (n = 20)	600 mg BID (n = 20)	900 mg BID (n = 20)
Patients on treatment ≥ 6 months, n	20	0	6	4	10
Median follow-up, months	9.4	13.9	10.0	7.2	10.1

Data cutoff: August 21st, 2023

[a]Patients were intrapatient dose escalated after the decision was made to close enrollment in the 600 mg QD cohort for lack of durable efficacy

Phase 1 data supports a well tolerated & manageable safety profile

Safety Profile*

- No Grade 4 treatment-related adverse events (TRAEs) & no discontinuations or death due to TRAEs
- Most common TRAEs were asymptomatic QTc prolongation, fatigue, & bradycardia
- Grade 3 QTc prolongation resolved with dose interruption/ modification; highest incidence at 900mg BID

Treatment-Emergent Adverse Events (TEAE)

	Part A, Dose escalation (n = 27)		Part B, Dose expansion (n = 68)		All patients (N = 95)	
TEAE, n (%)[a]	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with ≥ 1 TEAE	26 (96)	8 (30)	65 (96)	24 (35)	91 (96)	32 (34)
QTc prolongation	7 (26)	2 (7)	32 (47)	6 (9)	39 (41)	8 (8)
Fatigue	7 (26)	0	24 (35)	3 (4)	31 (33)	3 (3)
Bradycardia[b]	5 (19)	0	23 (34)	0	28 (30)	0
Nausea	12 (44)	0	11 (16)	1 (1)	23 (24)	1 (1)
Anemia	6 (22)	3 (11)	12 (18)	5 (7)	18 (19)	8 (8)
Hypertension	2 (7)	0	14 (21)	5 (7)	16 (17)	5 (5)
Vomiting	7 (26)	0	7 (10)	1 (1)	14 (15)	1 (1)
Diarrhea	2 (7)	0	9 (13)	0	11 (12)	0
ALT increased	3 (11)	0	7 (10)	0	10 (11)	0
Back pain	1 (4)	0	9 (13)	1 (2)	10 (11)	1 (1)

*Both (TEAE) and (TRAE) adverse events data were collected; Table shows TEAE as summarized in the ASCO GU poster

Data cutoff: August 21, 2023; [a]Table includes TEAEs that occurred in ≥ 10% of all patients. [b]Combined data from preferred terms bradycardia + sinus bradycardia
ALT, alanine transaminase; DLT, dose limiting toxicity; MTD, maximum tolerated dose; QTc, heart-rate corrected QT interval

AR LDD: Clinical development plan

Current Status

Ph 1 data across AR subgroups presented at ASCO GU January 2024

Discussion of **pivotal study** options with health authorities is ongoing

Next Steps

Continue dose optimization to enable registrational program

Consider expanding into earlier lines (e.g., **hormone sensitive**) & explore synergistic combinations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Source & References

Poster

Rathkopf et.al. **First-in-human phase 1 study of CC-94676, a first-in-class androgen receptor (AR) ligand-directed degrader (LDD), in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).// Abstract:** 134, ASCO GU 2024

References

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