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

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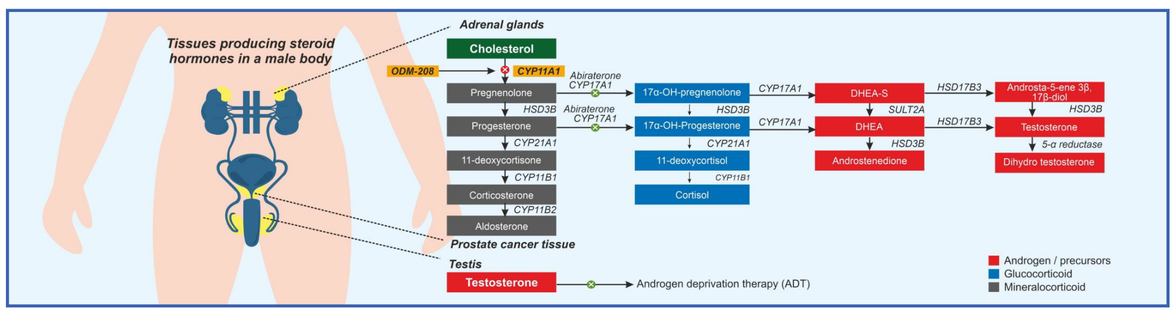
Background/Methods

- MK-5684 (formerly ODM-208) inhibits the production of all adrenal steroid hormones and precursors
- Initial phase 1 and 2 results [*NEJM Evid* 2024;3(1)] demonstrated frequent PSA responses in heavily pretreated mCRPC patients, especially in the presence of activating ligand-binding domain (*AR*-LBD) mutations
- Activating *AR*-LBD mutations occur in 20%-25% of patients previously treated with novel hormonal agents and are associated with resistance to such treatment
- Here we present initial results of a new phase 2 cohort of patients in CYPIDES, mostly *AR*-LBD wild-type, consolidated with the prior phase 2 expansion patients (datacut 17 July 2023)

ODM-208 inhibits prostate cancer progression by shutting down the entire steroid biosynthesis



Patients

- Progressing mCRPC treated with ≥1 NHA and ≥1 taxane
- *AR*-LBD mutation expansion: 45 pts (all *AR*-LBD mutated), enrolled in 2021-22 (median follow-up 7.1 months)
- Mainly *AR*-LBD wild-type extension: 89 pts, enrolled in 2023 (median follow-up 2.6 months)
- *AR*-LBD status determined by Guardant360 ctDNA assay*

Treatment

- Open label, non-randomized trial
- MK-5684 5 mg BID + adrenal hormone replacement (dexamethasone 1-1.5 mg and fludrocortisone 0.1 mg) + ADT until disease progression
- Clinical sites in France, Finland, USA, and UK

*Guardant360 liquid biopsy included the following AR-LBD activating mutations: L702H, V716M, W742C, W742L, H875Y, F877L, T878A, T878S, M896T, and M896V.

Results

Patient demographic characteristics

Variable		*AR*-LBD mut (n=66)	*AR*-LBD wt (n=68)
Baseline characteristics			
Age	Median	69.5	67.5
ECOG performance status	0 1	16 (24.2%) 49 (74.2%)	22 (36.1%) 38 (62.3%)
PSA (µg/L)	Median	277.6	47.3
Testosterone (ng/dL)	Median	3.1	4.2
Prior treatments			
Abiraterone		58 (87.9%)	41 (60.3%)
Enzalutamide		42 (63.6%)	45 (66.2%)
Both Abi and Enza		35 (53.0%)	23 (33.8%)
Docetaxel		65 (98.5%)	68 (100%)
Cabazitaxel		42 (63.6%)	38 (55.9%)
Both Doce and Caba		42(63.6%)	38 (55.9%)

- Patients without *AR*-LBD mutations appear less likely to have received abiraterone and had lower median PSA values at baseline. Differences could reflect patient enrolment during different time periods

Conclusions

Following MK-5684 treatment in men with extensively treated mCRPC

- PSA responses occurred in men without *AR*-LBD mutations, but were more frequent in those with such mutations
- The AEs of MK-5684 reported were clinically manageable. The rate of serious adrenal insufficiency was low on hormone replacement therapy
- Phase 3 studies of MK-5684 in mCRPC are under way

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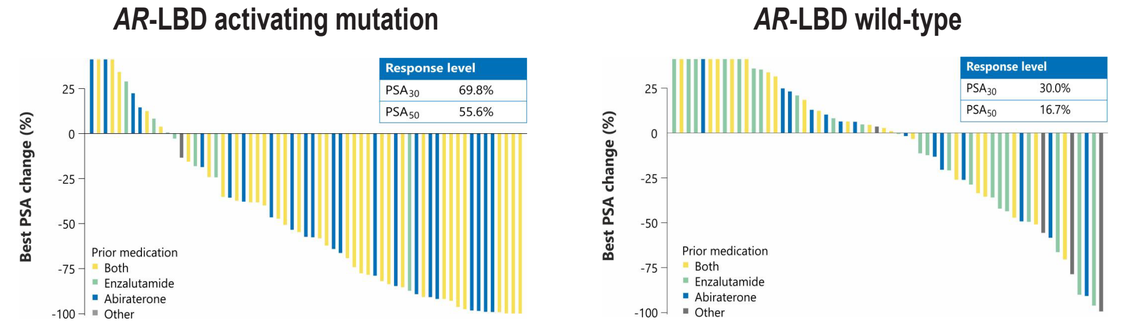
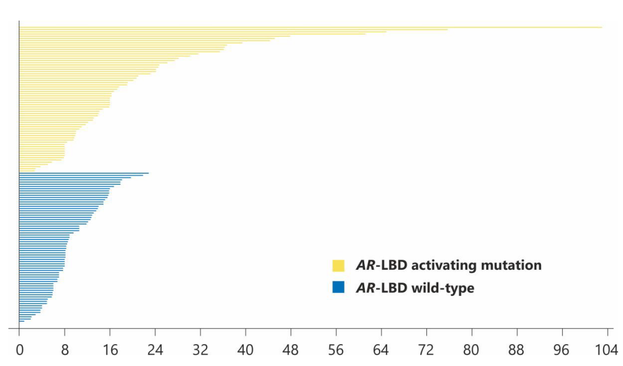
Results

Best PSA change (unconfirmed)

- Although more common in mCRPC patients with an activating *AR*-LBD mutation, PSA responses also occurred in patients without an *AR*-LBD mutation

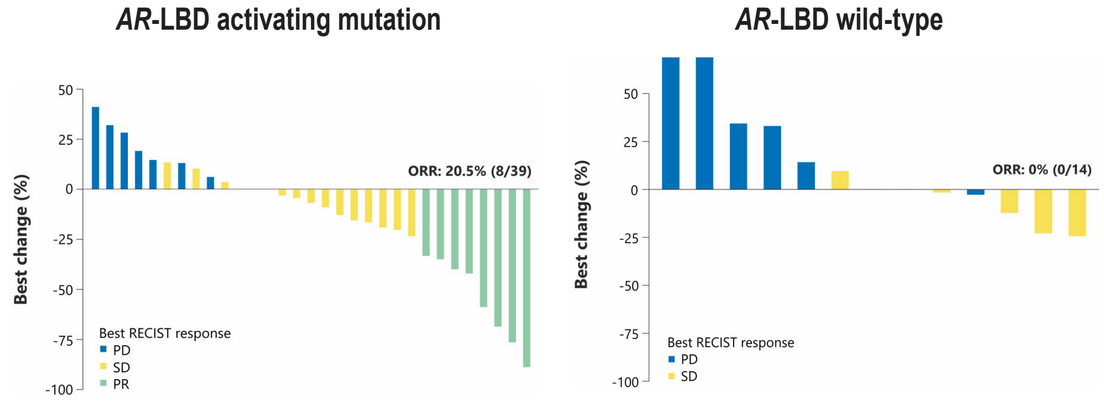


- At time of analysis, 17 *AR*-LBD mutated patients and 52 *AR*-LBD wild-type patients were ongoing on treatment
- Data are too immature for comparison of treatment duration between groups
- Durable responses have occurred in patients with and without *AR*-LBD mutation



Best objective response (%) in RECIST evaluable patients

- Although more common in mCRPC patients with an activating *AR*-LBD mutation, PSA responses also occurred in patients without an *AR*-LBD mutation



ORR = Overall response rate

Safety

- Almost all patients have reported an adverse event during study treatment with 943/1098 (85.9%) grade 1 or 2 severity
- Minor signs/symptoms of inadequate adrenal hormone replacement (eg, electrolyte disturbances) were common but adrenal insufficiency requiring hospital admission was infrequent in phase 2
- 26 deaths had been recorded at the time of datacut, none related to study treatment

Adverse events in CYPIDES Phase 2 (N=134)			
	n (%)		
Patients reporting an adverse event (all)	113 (84.3%)		
Grade ≥3 AEs	64 (47.8%)		
Most commonly reported SERIOUS adverse events (>1 event total)			
Preferred Term	**n (%)**	**Preferred Term**	**n (%)**
Adrenal insufficiency	4 (3.0)	General physical health deterioration	2 (1.5)
Sepsis	4 (3.0)	Hyperkalaemia	2 (1.5)
Dyspnoea	3 (2.2)	Oxygen saturation decreased	2 (1.5)
Prostate cancer	3 (2.2)	Pain	2 (1.5)
Pulmonary embolism	3 (2.2)	Pleural effusion	2 (1.5)
Asthenia	2 (1.5)	Pneumonia	2 (1.5)
Confusional state	2 (1.5)	Renal failure	2 (1.5)
Fall	2 (1.5)	Urosepsis	2 (1.5)

Many patients are still on treatment and hence further events may be reported.

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