Innovative Medicines Research & Development

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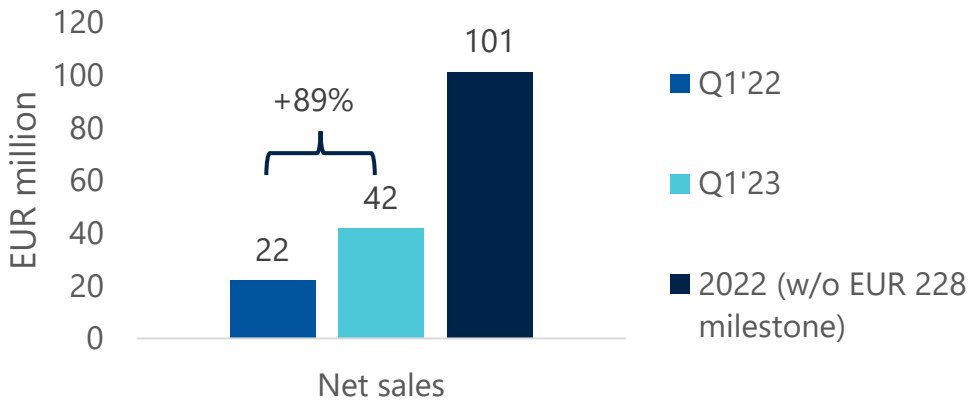
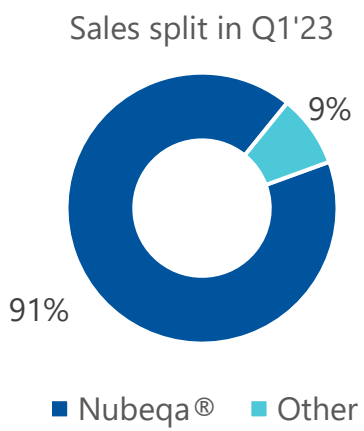
Innovative Medicines

Overview of Innovative Medicines





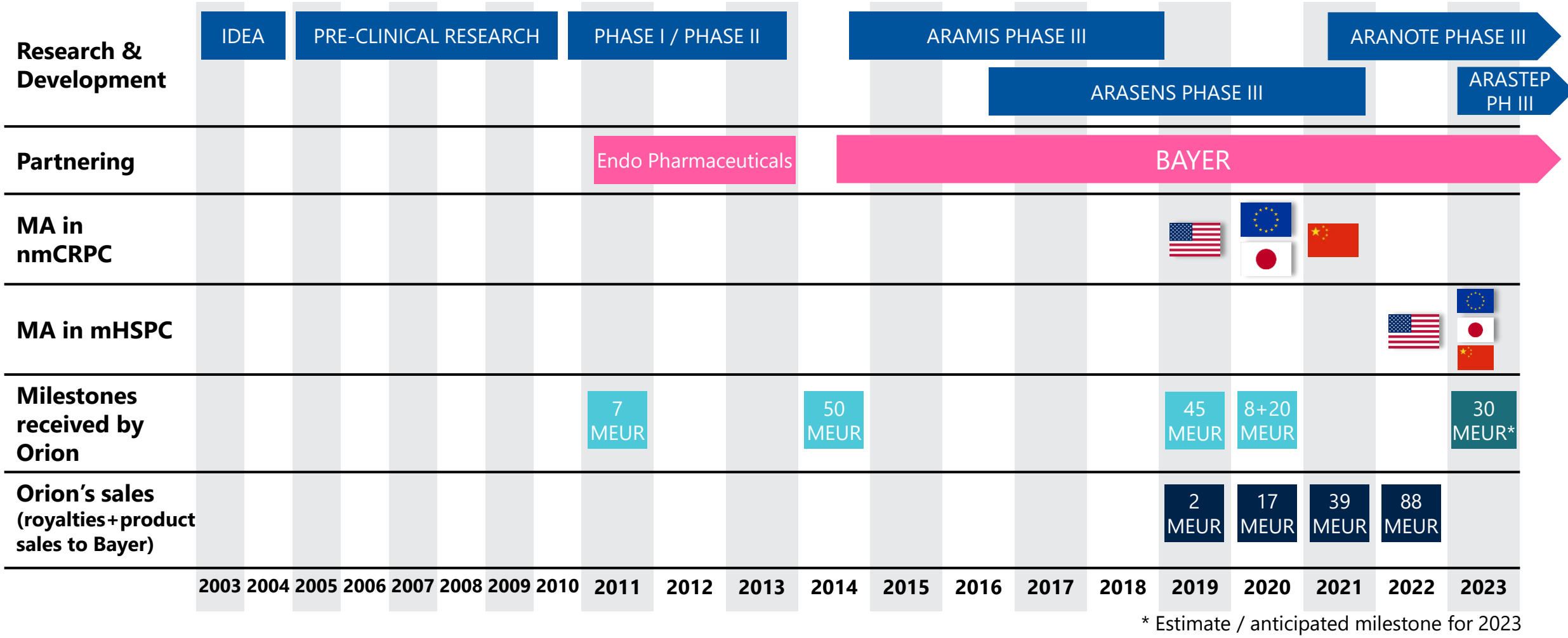
Other = milestone payments or other income related to the products or research and development projects of the business division

Innovative Medicines launch and business model is very different from that of branded generics or generics

R&D of Innovative Medicines requires different approach than development of generic medicines

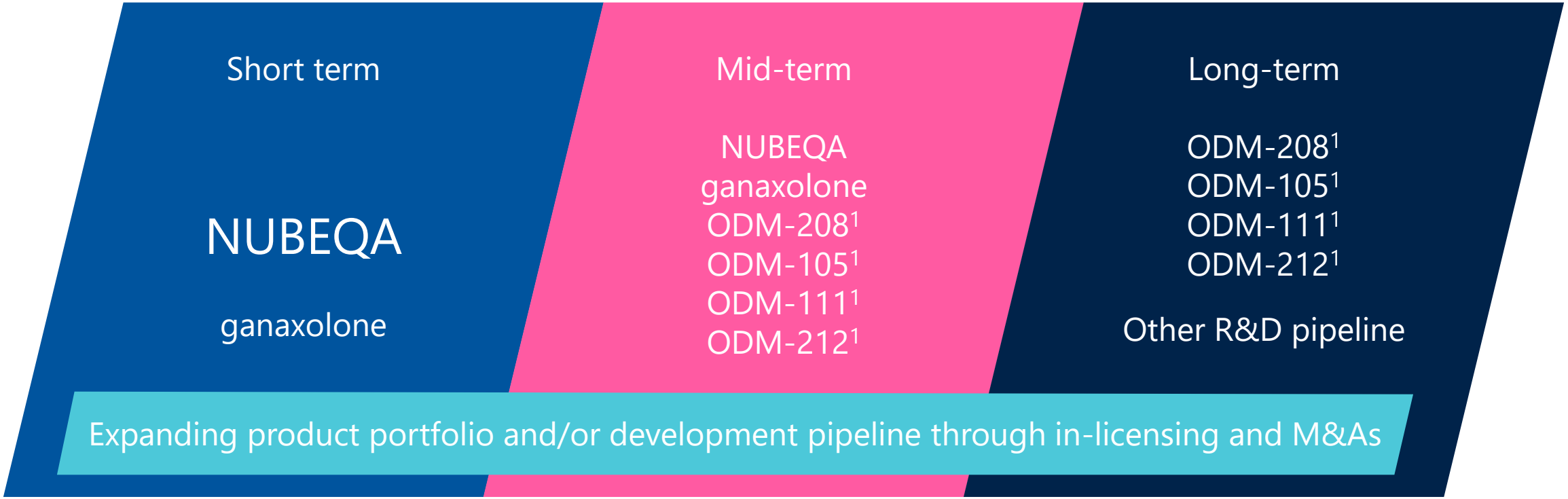
R&D and business of Innovative Medicines can achieve more for the patients when work tightly together

Darolutamide (Nubeqa®) – lifecycle so far



* Estimate / anticipated milestone for 2023

Building blocks for growth – Innovative Medicines



Nubeqa has peak sales potential of more than EUR 3 billion = EUR ~750 million (-COGS) potential for Orion [2]

[1] Development phase molecule – requires success in clinical development and regulatory approval
[2] Nubeqa's in-market peak sales potential is provided by Bayer. Orion's share is annually tiered royalty. If annual in-market sales is EUR 3 billion, Orion's average annual royalty rate would be slightly above 25%. Orion manufactures Nubeqa and carries the cost of goods sold.

Research & Development

Overview of Orion's Research & Development

Number of R&D personnel ~400

R&D expenses in 2022: EUR 133 million
- ~10% of Group net sales
- ~40% of Innovative Medicine's net sales

FOCUS AREAS	
PAIN	ONCOLOGY

RE-FOCUSING OF R&D IN 2022
Why pain and oncology?

- Orion R&D has a proven track record of success on discovery and development of innovative medicines for cancer patients, i.e. darolutamide and ODM-208
- Focusing on pain provides the best opportunities for ODM-111 program to take its potential as a game-changer of non-opioid pain treatment
- Deep scientific understanding of disease drivers in pain and oncology requires resourcing, which can be delivered only via focusing

Oncology	Neurological disorders	Respiratory
No change	More narrow focus	
Oncology	**Pain**	**discontinued**

Research aims to deliver new projects to clinical phase

ONGOING **8** RESEARCH PROJECTS

ONCOLOGY

Research areas

- Immuno-oncology
  - FiCAR T-cell therapy
  - 2nd generation immune-checkpoint inhibitors
- Cancer genomics and cell signalling
- Antibody drug conjugates

Key partnerships

ALLIGATOR bioscience
Finnish Red Cross Blood Service
AURIGENE Accelerating Discovery
Schrödinger
PROTEROS REACH RIGHT FASTER
Sai
JUBILANT BIOSYS
ABZENA
iOR

PAIN

Research areas

- Ion channels
- Neuro-immune interaction

Key partnerships

AnaBios Early Human Insights
OFFSPRING BIOSCIENCES senior partners in cell and tissue imaging
Jemincare
University of Nottingham UK | CHINA | MALAYSIA
UNIVERSITY OF LEICESTER

Key clinical development pipeline

Project/compound	Indication	PHASE I	PHASE II	PHASE III	REGISTRATION
ARASENS / darolutamide [1]	Prostate cancer (mHSPC)				
ARANOTE / darolutamide [1]	Prostate cancer (mHSPC)				
ARASTEP / darolutamide [1]	Prostate cancer (BCR)				
ODM-208 [2]	Prostate cancer (mCRPC)				
ODM-105 / tasipimidine	Psychiatric disorders				
ODM-111 (NaV 1.8 blocker)	Pain				

Oncology | Pain / neurology

Phase completed | Phase ongoing

[1] In collaboration with Bayer
[2] In collaboration with MSD

Darolutamide (Nubeqa®)

Clinical trial and treatment	Indication	Primary endpoint and results	Key secondary endpoints
ARAMIS darolutamide + ADT	nmCRPC	**Metastasis free survival** prolongation by 22.0 months, 59% risk reduction (HR=0.41, p<0.001)	**Overall survival** 31% risk reduction (HR=0.69, p=0.003)
ARASENS darolutamide + ADT + docetaxel	mHSPC	**Overall survival** 32.5% risk reduction (HR=0.675, p<0.001)	**Time to castration resistant PC** 64% risk reduction (HR=0.36, p<0,001)
ARANOTE darolutamide + ADT	mHSPC	**Radiological progression-free survival** (study ongoing)	**Overall survival** (study ongoing)
ARASTEP darolutamide + ADT	BCR	**Radiological progression-free survival** (study ongoing)	**Metastasis free survival** **Time to castration resistant PC** **Overall survival**
Overall incidence of treatment-emergent adverse events was similar between treatment arms (darolutamide group vs. placebo group) both in ARAMIS and ARASENS trials			

ADT = androgen deprivation therapy
nmCRPC = non-metastatic castration-resistant prostate cancer
mHSPC = metastatic hormone-sensitive prostate cancer
BCR = biochemical relapse
Orion develops darolutamide in collaboration with Bayer.

ODM-208

- ODM-208 is a CYP11A inhibitor blocking synthesis of steroids and thus ligands for androgen receptor activation
- Partnering with Merck / MSD in 2022
- CYPIDES Ph II trial is on-going
- Plan to proceed to Ph III studies by the end of 2023

Preliminary Phase II results – published at ESMO 2022

- ODM-208 5mg BID (with dexamethasone and fludrocortisone) was evaluated in an open-label expansion cohort in patients with progressing mCRPC who had previously received ≥1 line of 2nd generation AR pathway inhibitor and ≥1 line of taxane-based chemotherapy.
- All patients had a pre-specified activating AR LBD mutation
- Of 45 (43 at data cut-off 17 March 2022) patients, 51% had previously received both abiraterone and enzalutamide, and 65% both docetaxel and cabazitaxel.
- Based on the emerging data ODM-208 profoundly suppressed androgen synthesis resulting in >50% best PSA reduction in more than 50% patients and at least 4 RECIST partial responses in 17 evaluable patients (data immature).
- ODM-208 has been well-tolerated with a much lower rate of hospitalisation for adrenal insufficiency than in phase 1 with typically higher doses (2.3% vs. 33% to date). Efficacy and safety data will be presented for the complete cohort with at least 5 months follow-up for all patients.

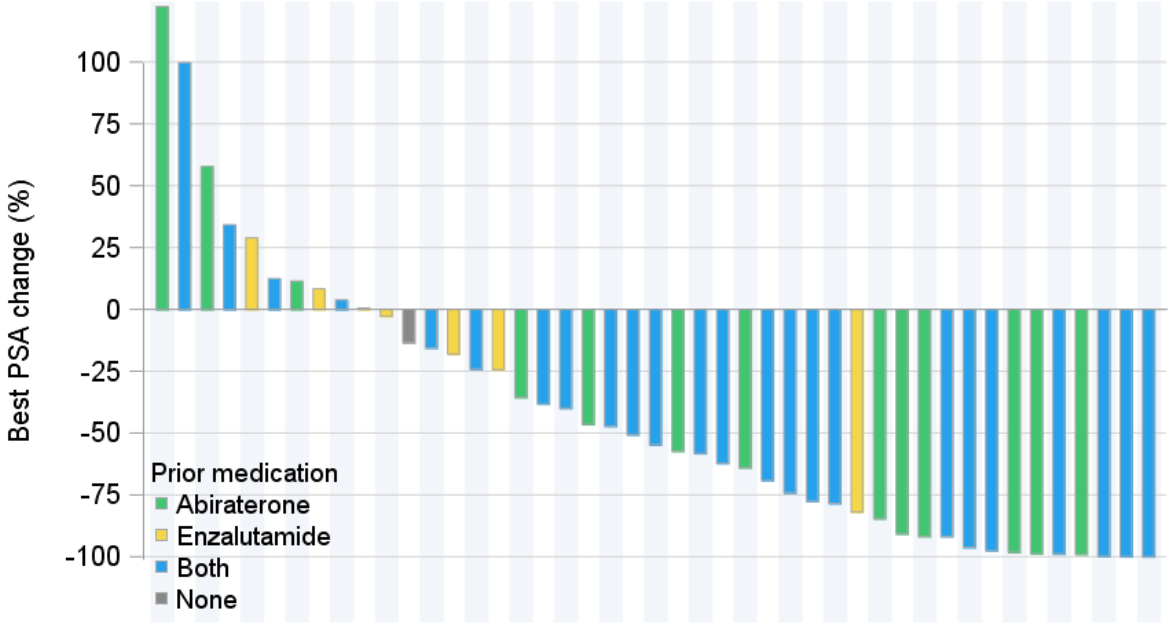
→ Administration of ODM-208 to heavily pre-treated mCRPC patients with AR LBD mutation was highly effective in blocking the production of steroid hormones and showed promising antitumor activity.

https://oncologypro.esmo.org/meeting-resources/esmo-congress/preliminary-phase-ii-results-of-the-cypides-study-of-odm-208-in-metastatic-castration-resistant-prostate-mcrpc-cancer-patients

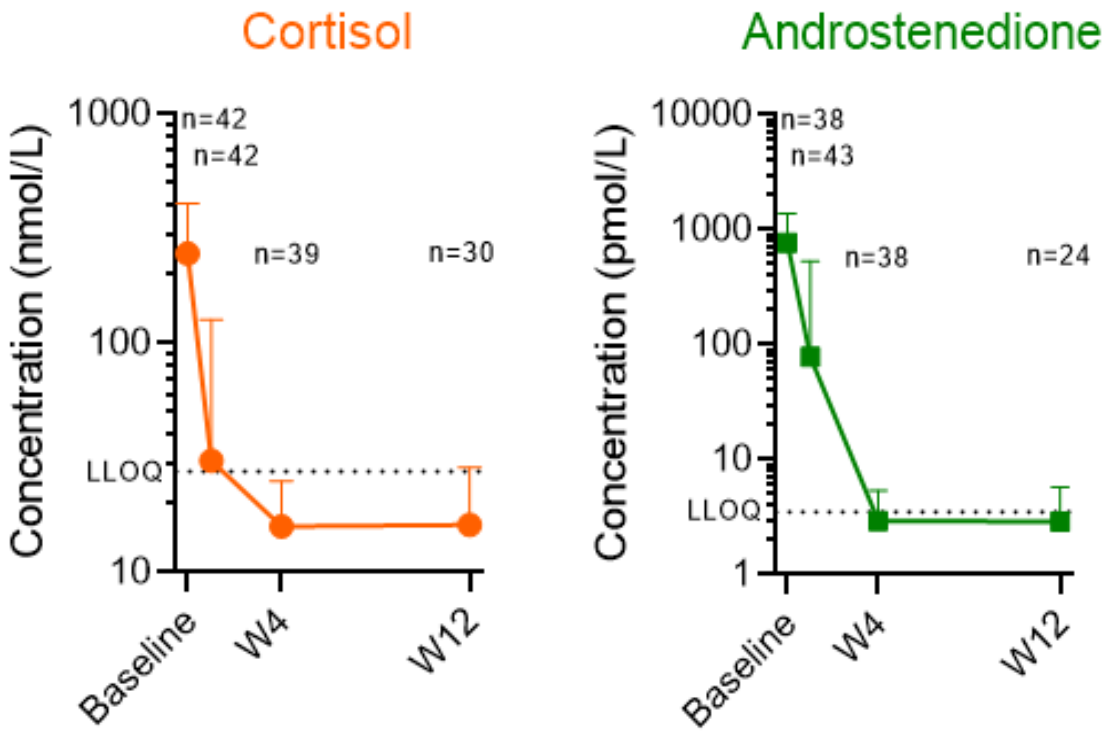
ODM-208 suppressed steroid hormone biosynthesis and led to frequent PSA declines in men with extensively pre-treated mCRPC with AR-LBD mutations

53% (24/45) of patients achieved a serum PSA reduction of at least 50% from the baseline concentration

Best PSA change from baseline, all patients AR-LBD mutation positive

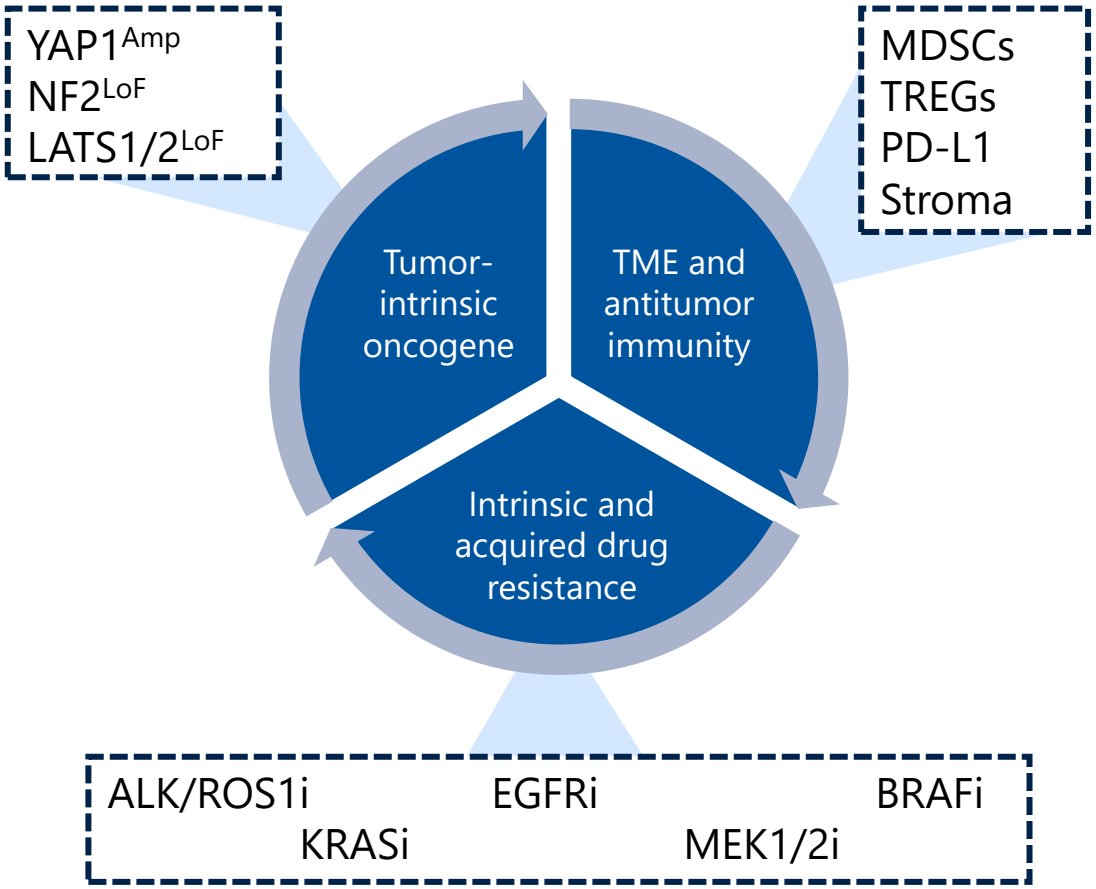


Unmeasurable steroid hormone levels were achieved in almost all patients



ODM-212 – about to enter the clinical phase

Role of YAP/TEAD activation in cancer



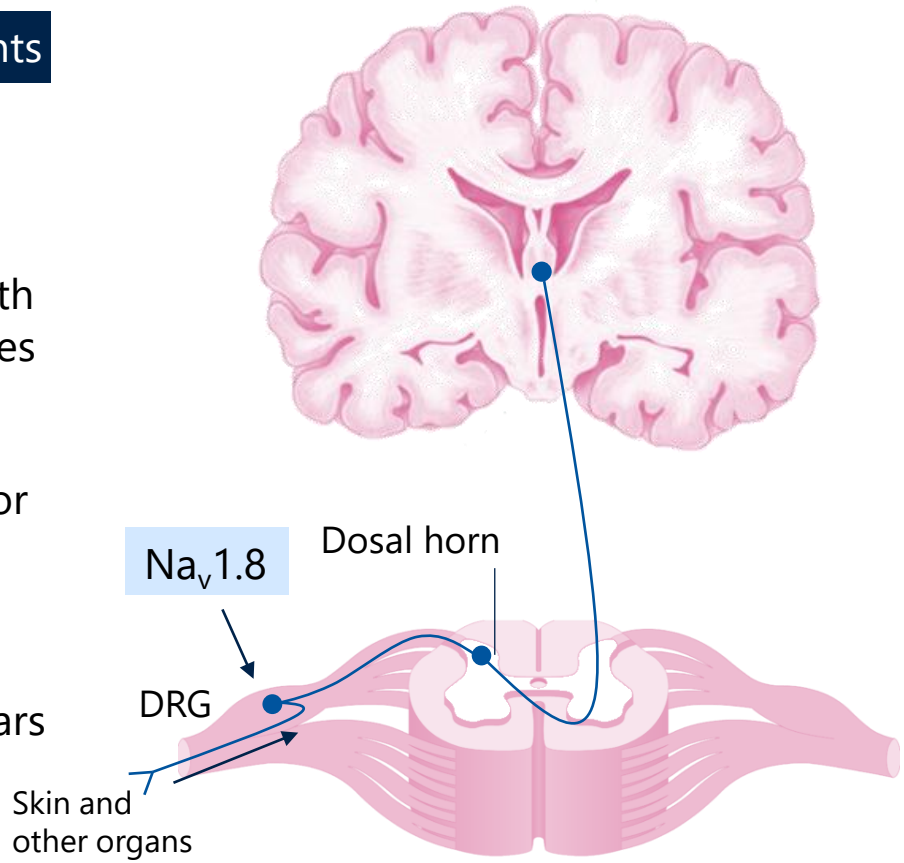
- ODM-212 is an oral small molecule blocking TEAD activity
- Targeted indication(s): solid tumors with YAP/TEAD activation
- Ph I start in H2 2023

YAP1 = Yes-associated protein 1
TEAD = TEA domain family member, transcriptional enhancer factor
EGFR = Epidermal growth factor receptor

ODM-111

Unmet clinical need for pain treatments

- Almost one fifth of the adult population suffer from pain
- Novel, non-addictive analgesics with improved efficacy and safety profiles are needed to address the shortcomings of the presently available treatment options both for chronic and acute pain
- Scientific knowledge about the mechanisms related to pain has increased significantly in recent years



Orion's solution

- ODM-111 is a non-opioid oral small molecule blocking $Na_v1.8$ ion channel that mediates pain signalling
- Ph1 study is on-going in multiple ascending dose cohorts
- Ph2 studies in acute and chronic pain are planned to start in 2024
- Currently there are several new molecules in Orion's research pipeline that differentiate based on their mechanism of action targeting various drivers of pain phenotypes

Key takeaways

1. Nubeqa® is the growth driver in short & mid-term
2. Research focus in oncology and pain
3. Orion's development pipeline more robust than earlier with ODM-212 entering clinical phase I and ODM-208, ODM-105, and ODM-111 proceeding to next phases


ORION
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