PROSTATE CANCER: POSTER DISCUSSION

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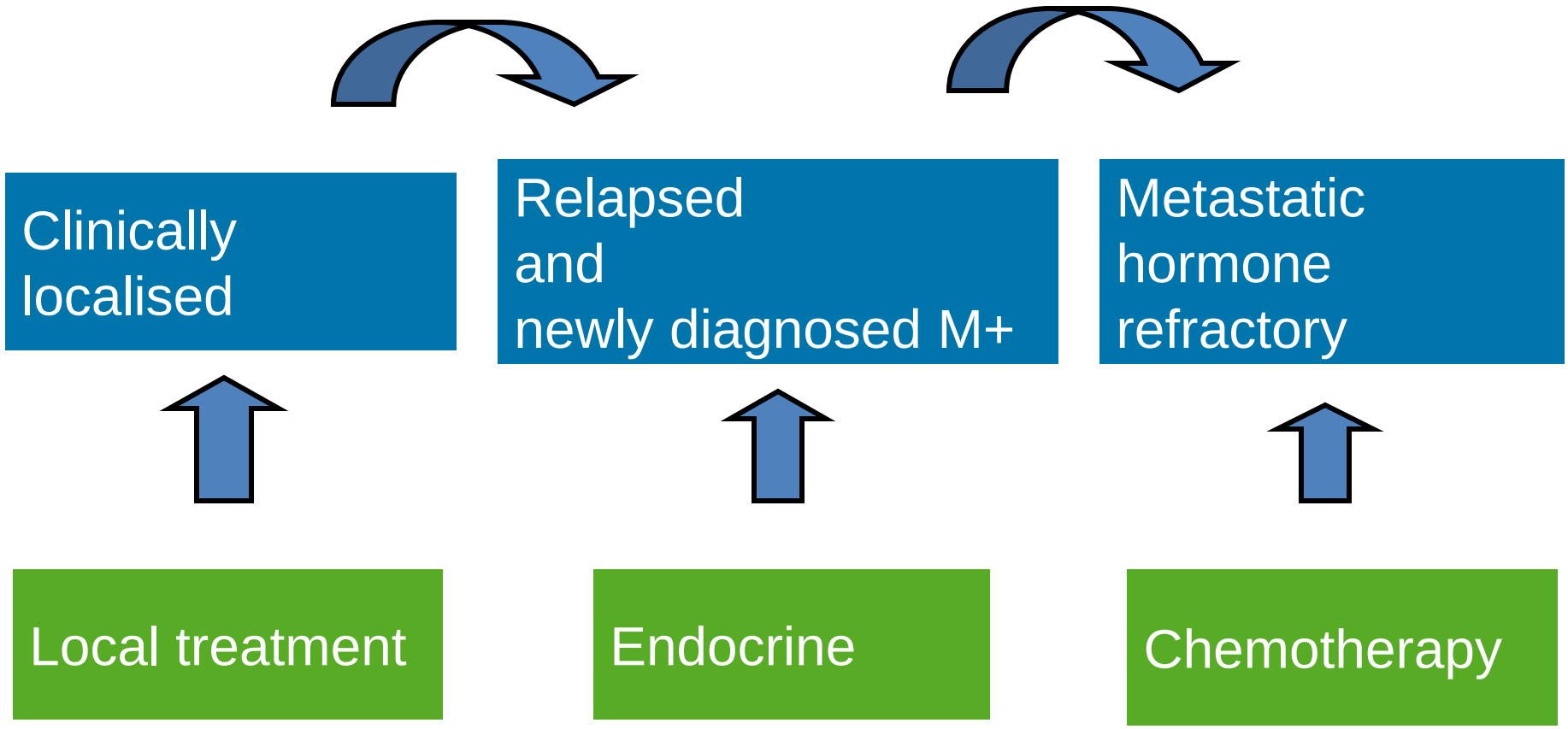
DISCLOSURE SLIDE

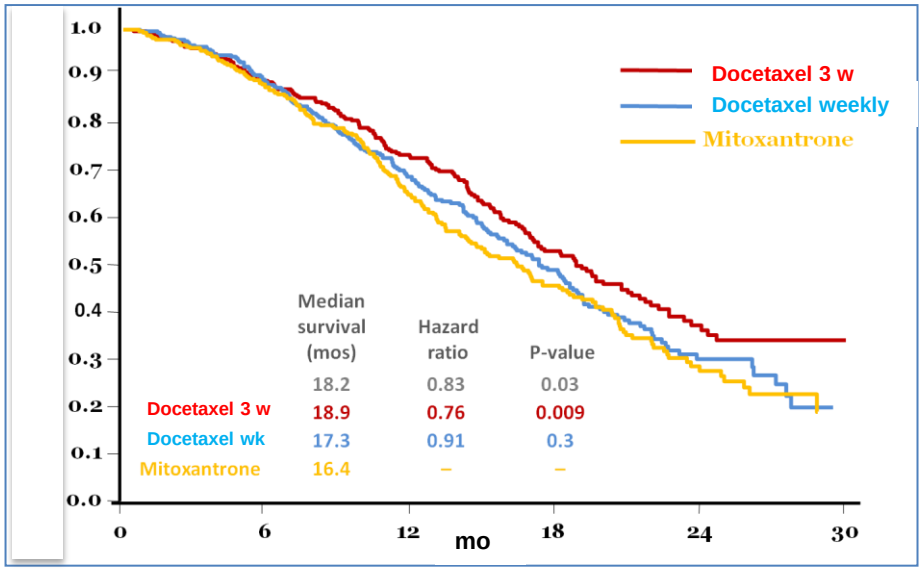
- Participation to advisory boards / speaker for:
  - Amgen
  - Astellas
  - Bayer
  - BMS
  - GSK
  - Janssen / J&J
  - Novartis
  - Pfizer
  - Sanofi - Aventis
  - Teva / Oncogenex

PROSTATE CANCER: TREATMENT PARADIGMS

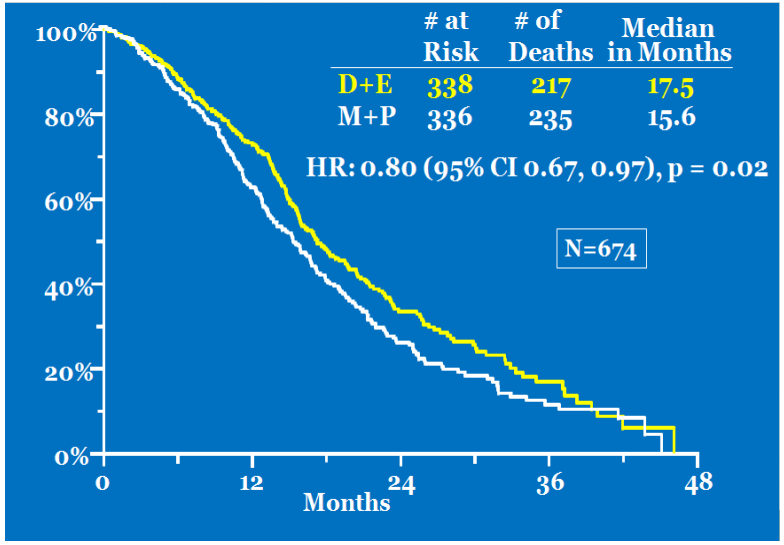


DOCETAXEL IS THE STANDARD TREATMENT IN FIRST-LINE CPRC

Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer



Docetaxel and Estramustine Compared with Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer



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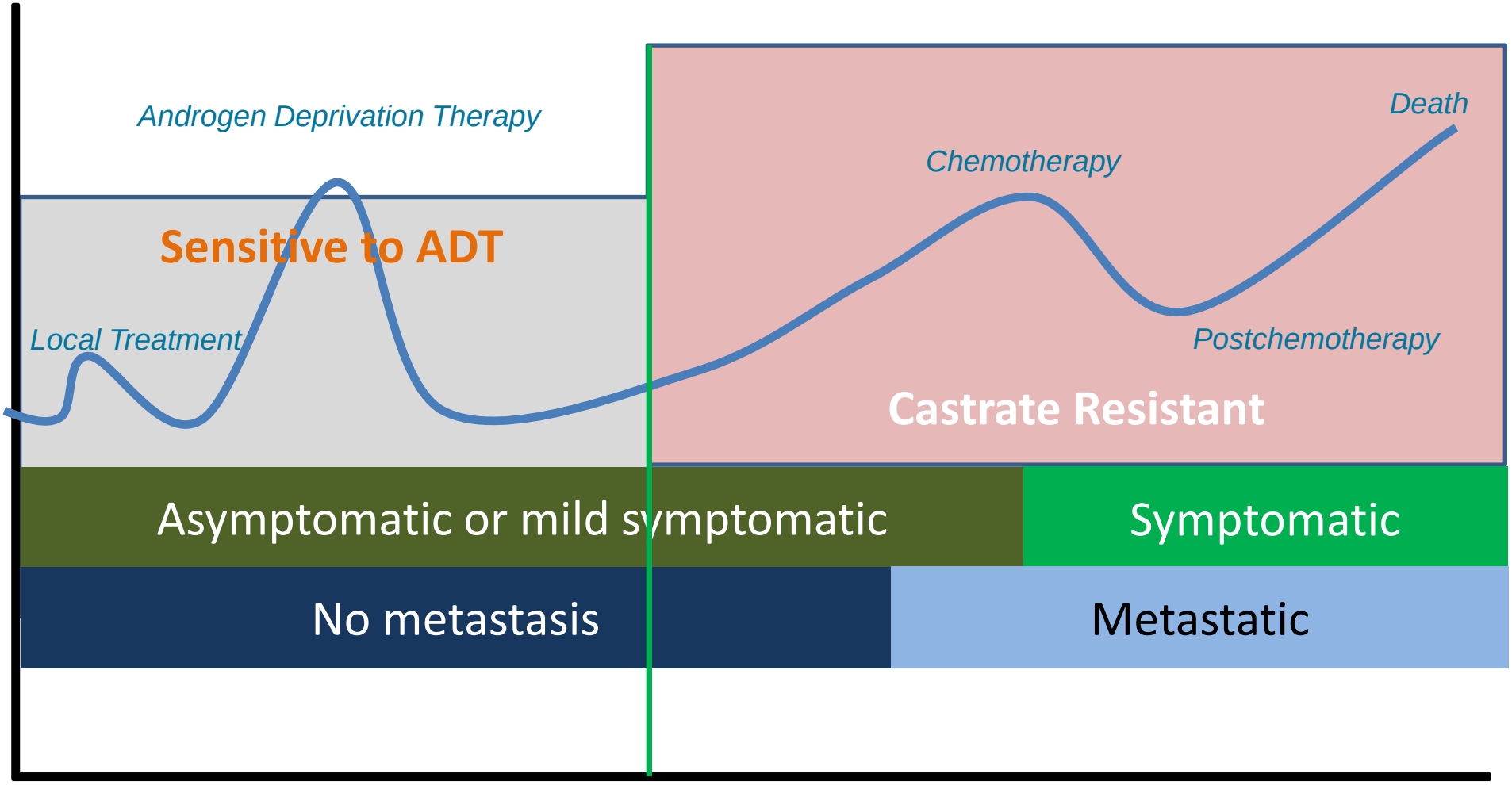
www.esmo2012.org

Tannock et al, NEJM 2004; 351(15):1502-12

Petrylak et al, NEJM 2004; 351(15): 1513-20.

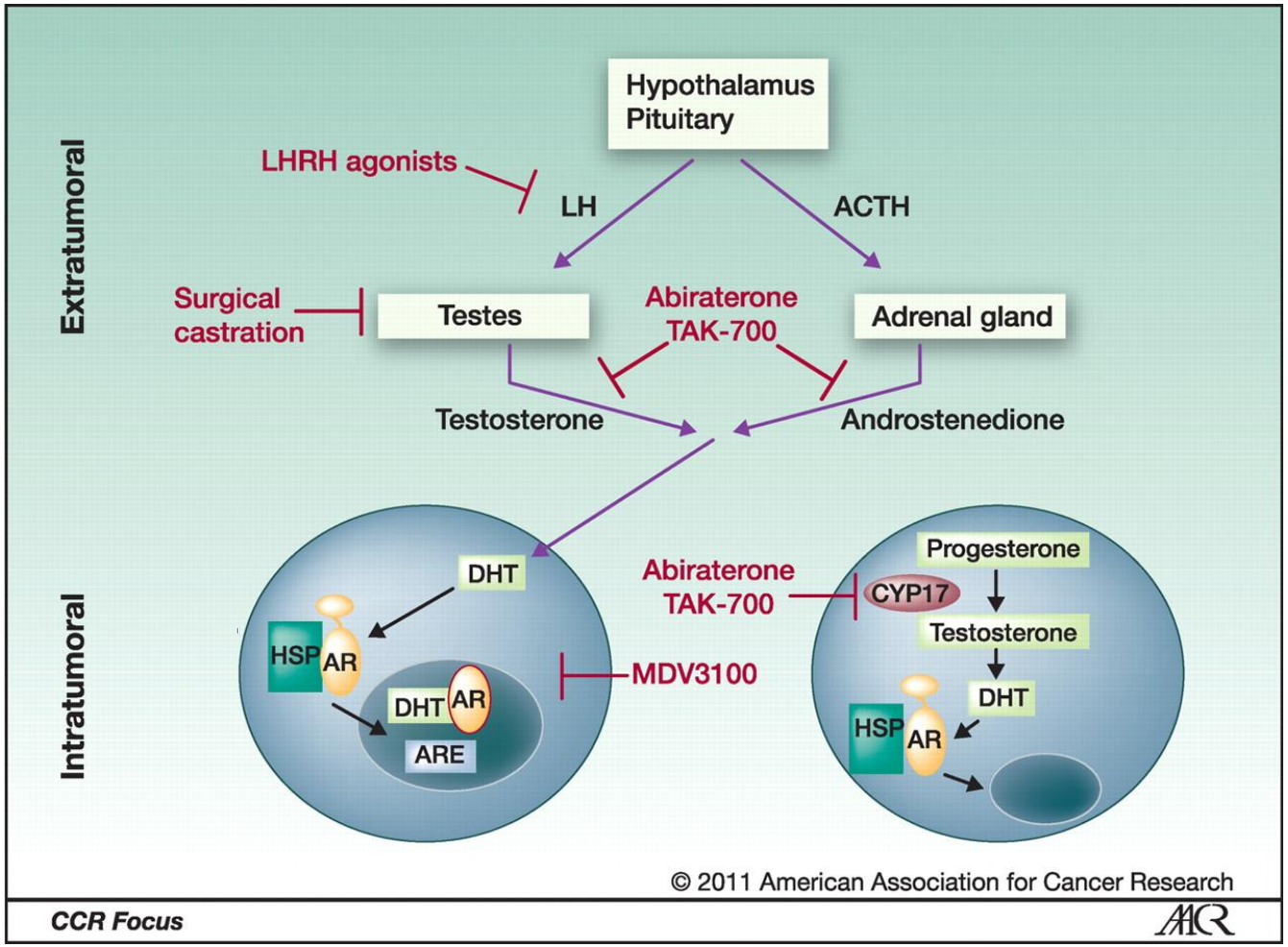
NATURAL EVOLUTION FOR PATIENTS WITH PROSTATE CANCER



Since 2010 a plethora of new trials have shown benefit in CRPC

Trial/ Agent Approved	Disease state	Comparator	Hazard Ratio	*P* value
IMPACT (Provenge vaccine) 2010	Chemo-naïve CRPC	Placebo	0.775	0.032
COU-AA-302 (Abiraterone acetate) 2012	Chemo-naïve CRPC	Placebo Prednisone	UK	UK
TAX327 (Docetaxel) 2004	Chemo-naïve CRPC	Mitoxantrone Prednisone	0.76	0.009
TROPIC (Cabazitaxel) 2010	Post-Docetaxel CRPC	Mitoxantrone Prednisone	0.70	<0.0001
COU-AA-301 (Abiraterone acetate) 2010	Post-Docetaxel CRPC	Placebo Prednisone	0.646	<0.0001
ALSYMCA (Radium 223) 2011	Post-Docetaxel CRPC	BSC	0.695	<0.00046
AFFIRM (MDV3100)	Post-Docetaxel CRPC	BSC	0.631	<0.0001

AR signaling pathway.



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Massard C , Fizazi K Clin Cancer Res 2011;17:3876-3883

NEW HORMONAL TREATMENTS

- CYP 17 modulators:
  - TAK 700
- Drugs against androgen production and antiandrogens:
  - HE 3235
  - TOK-001
- Second Generation antiandrogens:
  - ARN - 509
  - ODM -201
  - BMS 641988
- Androgen Receptor Co-factors modulators:
  - EPI - 001
- Chaperon inhibitors:
  - OGX-427
  - OGX-011

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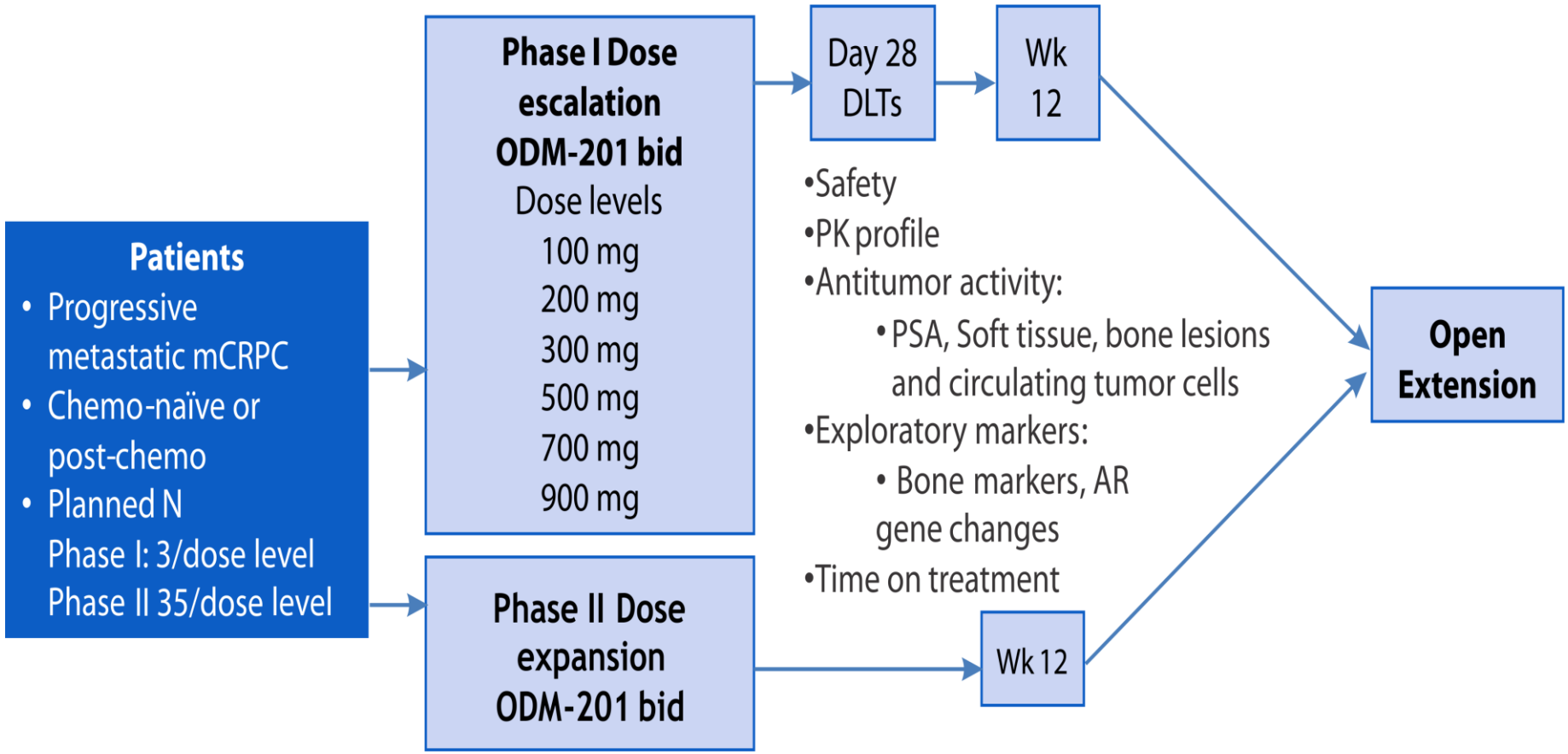
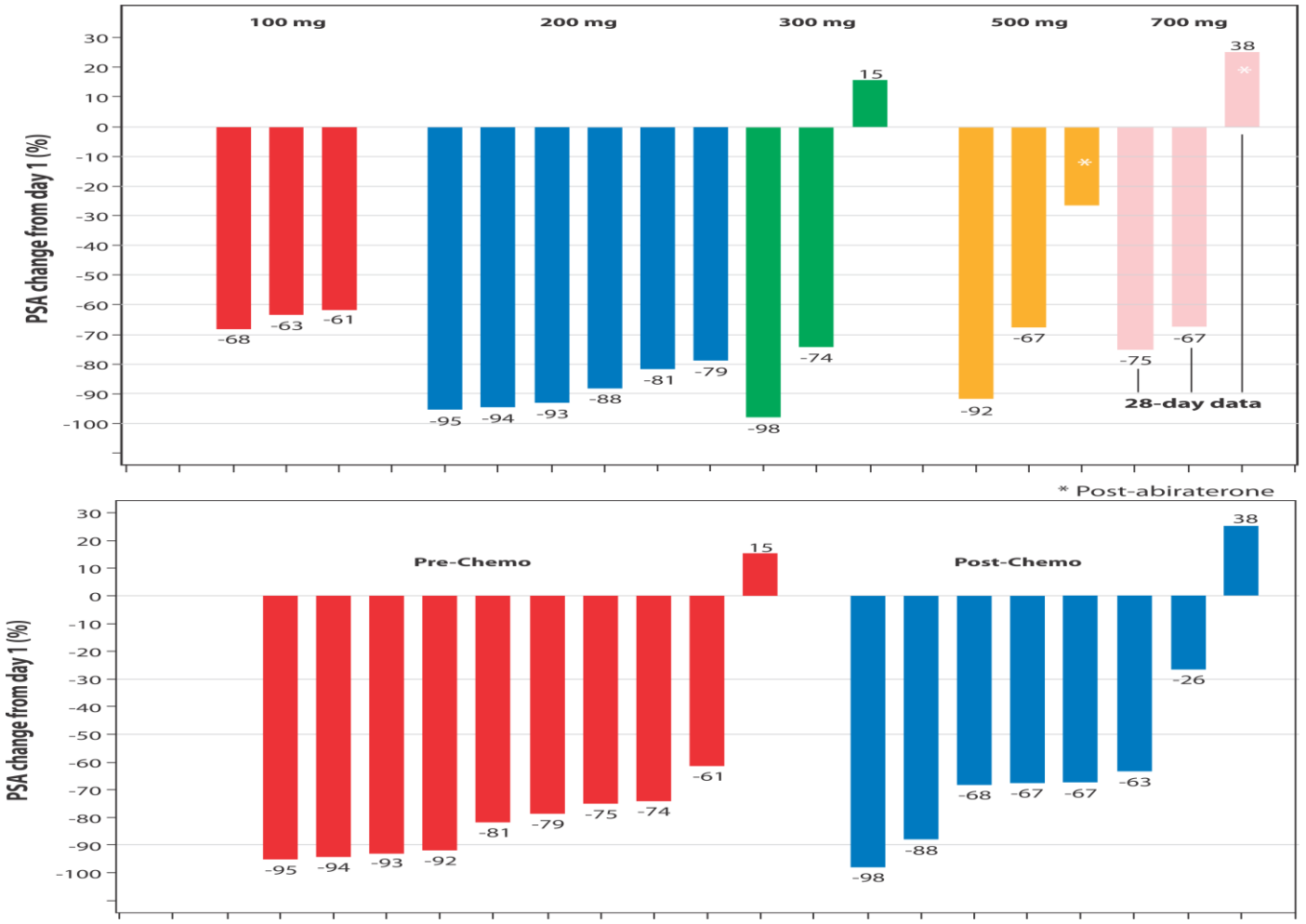
2450 LBA.- C. Massard, N. James, S. Culine, R. Jones, A. Vuorela, M. Mustonen, K. Fizazi

ARADES trial: A first-in-man, open-label, phase I/II safety, pharmacokinetic, and proof-of-concept study of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer



Open, non-randomised, uncontrolled multicenter multiple dose escalation study with a randomised phase II expansion component

ODM-201 - PSA waterflows (by dose and previous chemo-therapy)



ODM-201 ACTIVITY

	MDV 3100 PHASE I/II [1]		ODM - 201 PHASE I	
	Chemo Naive (n: 65)	**Post Chemo (n:75)**	**Chemo Naive (n: 10)**	**Post Chemo (n:8)**
PSA response	62%	51%	90%	75%
Soft Tissue disease (No PD)	80 %	65 %	90 %	90 %
Bone Disease (w 12) No PD	63 %	51 %	90 %	90 %

Scher HI. Lancet 2010. 375:1437-1446

ODM-201 - safety

Table 2. Most common AEs by dose (subject count) and median duration of treatment (days)

System Organ Class	Total N=21	100 mg bid N=4	200 mg bid N=7	300 mg bid N=3	500 mg bid N=4	700 mg bid N=3
Median Treatment Duration (d)	168	146	248	224	113	26
Gastrointestinal disorders						
Constipation	3	1	2			
Diarrhoea	4	3	1			
Nausea	4	1	2		1	
General disorders and administration site conditions						
Asthenia	6	3	3			
Oedema peripheral	2	2				
Musculosketal and connective tissue disorders						
Arthralgia	2	2	1			
Back pain	3		3			
Bone pain	2	1			1	
Myalgia	2	2				
Nervous system disorders						
Headache	3		1		1	1
Somnolence	2	1	1			
Sciatica	2		2		2	

MDV3100: PHASE I/II

	30 mg per day (n=3)	60 mg per day (n=27)	150 mg per day (n=28)	240 mg per day (n=29)	360 mg per day (n=28)	480 mg per day (n=22)	600 mg per day (n=3)	Total (n=140)
Grade 3–4 adverse events occurring in more than two patients								
Fatigue	0	0	0	5 (17%)	6 (21%)	5 (23%)	0	16 (11%)
Anaemia	0	2 (7%)	1 (4%)	0	1 (4%)	0	0	4 (3%)
Arthralgia	0	2 (7%)	0	0	0	1 (5%)	0	3 (2%)
Asthenia	0	0	0	0	2 (7%)	1 (5%)	0	3 (2%)
Seizure	0	0	0	0	1 (4%)	1 (5%)	1 (33%)	3 (2%)
Adverse events leading to discontinuation of treatment								
Seizure	0	0	0	0	1 (4%)	1 (5%)	1 (33%)	3 (2%)
Rash	0	0	0	0	0	1 (5%)	1 (33%)	2 (1%)
Nausea/vomiting	0	0	0	0	0	1 (5%)	0	1 (1%)
Fatigue	0	0	0	1 (3%)	0	0	0	1 (1%)
Myocardial infarction	0	0	0	0	1 (4%)	0	0	1 (1%)

Data are number (%) of patients.

Table 5: Grade 3–4 adverse events and patients who discontinued treatment because of an adverse event, by dose

N Engl J Med 2012.DOI: 10.1056/NEJMoa1207506

ODM - 201

- **Strengths:**
  - High efficacy
  - Well tolerated
  - Linear pharmacokinetics
- **Weakness:**
  - Few patients

Recommended dose for Phase 2/3 trials?

900PD.- K. Chi, E.Y. Yu, S. Ellard, S.J. Hotte, J.R. Gingerich, A.M. Joshua, M.E. Gleave

A RANDOMIZED PHASE II STUDY OF OGX-427 PLUS PREDNISONE (P) VS. P ALONE IN PATIENTS (PTS) WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER (CRPC)

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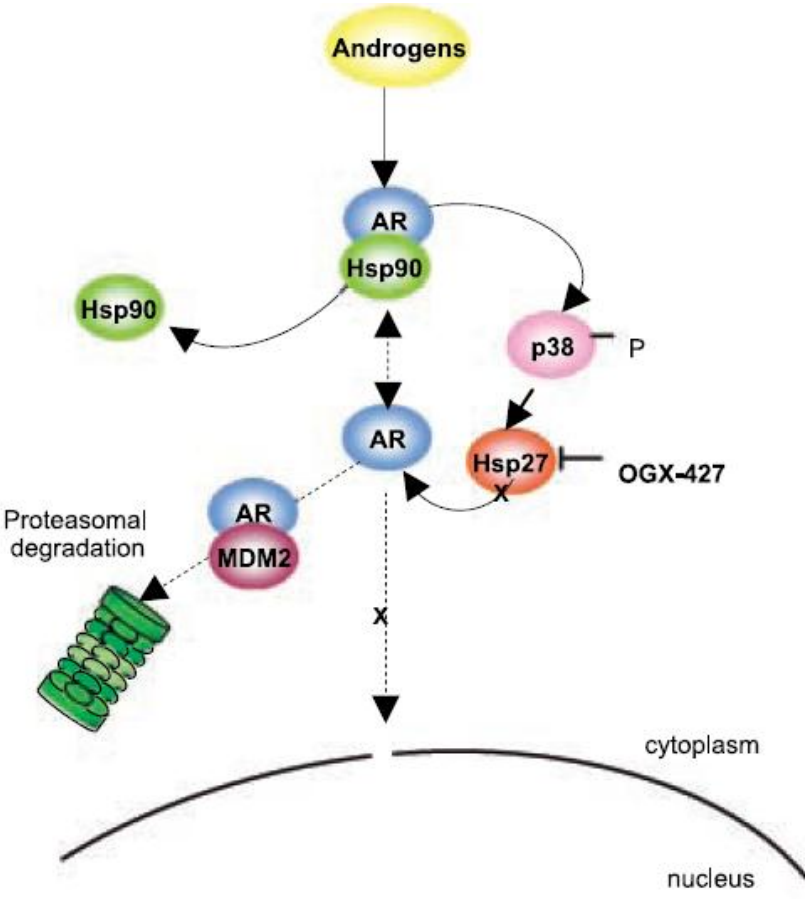
Targeting Chaperone Proteins in CRPC

- **Targets**: Heat Shock Proteins
  - Clusterin (HSP 24)
  - HSP 27
- **Objective**: Promote cell survival
- **The agents**: Antisense oligonucleotides:
  - OGX - 011
  - OGX - 427

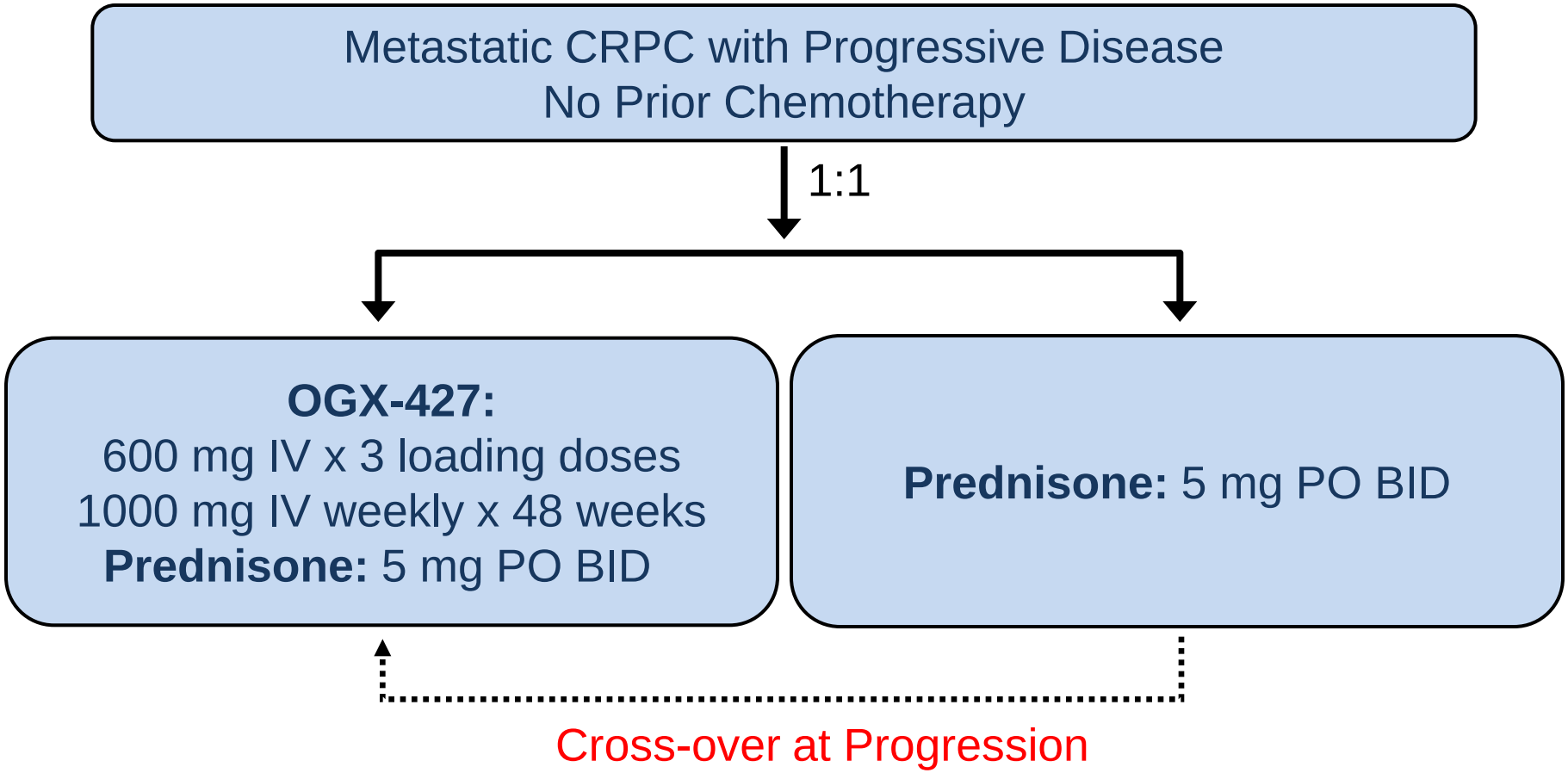
HSP inhibitor OGX-427



- HSP 27 is a stress activated chaperone highly expressed in CRPC that inhibits therapy-induced apoptosis
- HSP 27 is induced by anti-AR and chemotherapy
- OGX-427 (HSP 27 inhibitor) delays progression and enhances activity of chemotherapy in CRPC
- Phase II studies in CRPC and metastatic bladder cancer are ongoing

Zoubeidi A et al. Cancer Res 2007;67:10455-10465
Kumano M et al. Mol Cancer Ther 2012 (epub ahead of print)
Clinicaltrials.gov identifyer: NCT01120470

Study Design



OGX 427 RANDOMIZED PHASE II STUDY

- **Two stage design:**
  - Stage 1 presented at ASCO 2012
  - Stage 2 presented today
- **Primary end point:**
  - To improve 12 weeks PFR from 5% to 20% in CRPC patients
- **Secondary end points**:
  - % of patients with PSA decline
  - Measurable disease RR
  - Estimated PFS and TTP
  - Evaluation of CTC's
  - Safety and tolerability

Baseline Characteristics

Parameter	OGX-427 + Prednisone (N=32)	Prednisone (N=33)
Median Age, years (range)	66 (53-86)	73 (31-89)
Median PSA, ug/L (range)	57 (<1-638)	50 (<1-606)
Median Hemoglobin, g/L (range)	132 (98-157)	130 (104-167)
ECOG PS 0 : 1	22 (69%) : 10 (31%)	20 (61%) : 13 (39%)
Disease Sites		
Bone	23 (72%)	24 (73%)
Liver	1 (3%)	2 (6%)
Lung	3 (9%)	3 (9%)
Lymph Node	16 (50%)	21 (64%)
Gleason Score		
≤7	16 (50%)	14 (42%)
>7	14 (44%)	17 (52%)
Missing	2 (6%)	2 (6%)
Lactate Dehydrogenase >ULN	11 (34%)	6 (18%)
Alkaline Phosphatase >ULN	8 (25%)	4 (12%)
Prior Prednisone Therapy	6 (19%)	3 (9%)
CTC/7.5 ml		
Median (Range)	13 (1-72)	15 (3-273)
≥5	26 (81%)	29 (88%)

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Primary Endpoint: Progression Free Rate at 12 Weeks

	ASCO 2012 Stage 1		ESMO 2012 Stage 2	
	OGX-427 + Prednisone (N=22)	Prednisone (N=20)	OGX-427 + Prednisone (N=32)	Prednisone (N=33)
Non-evaluable	5 (13%)	5 (12%)	4 (13%)	4 (12%)
Evaluable	17	15	28	29
No Disease Progression	12 (71%) (95%CI: 0.440, 0.897)	6 (40%) (95% CI: 0.163, 0.677)	20 (71%) (95%CI: 0.513, 0.868)	14 (48%) (95% CI: 0.295, 0.675)
Disease Progression	5 (29%)	9 (60%)	8 (29%)	15 (52%)

Secondary Endpoints

	ASCO 2012 Stage 1		ESMO 2012 Stage 2	
	OGX-427 + Prednisone (N=22)	Prednisone (N=20)	OGX-427 + Prednisone (N=32)	Prednisone (N=33)
% of patients PSA response	50%	20%	47%	21%
Measurable Disease RR	44%	0%	25%	12%
CTC evaluation > 5 to < 5	55%	41%	52%	41%

Adverse Events

Incidence of Non-Lab Treatment Related AE*	OGX-427 + Prednisone (N=32)***	
Grade	*1-2*	*3-4*
Chills**	18 (56%)	1 (3%)
Diarrhea**	11 (34%)	
Fatigue**	10 (31%)	1 (3%)
Nausea**	10 (31%)	
Flushing**	6 (19%)	
Pyrexia**	5 (16%)	
Vomiting **	5 (16%)	
Dizziness	3 (9%)	1 (3%)
Hot flashes	4 (13%)	
Muscular Weakness	2 (6%)	1 (3%)
Hypertension	1 (3%)	2 (6%)
Presyncope		1 (3%)
Tachycardia		1 (3%)
Hemolytic Uremic Syndrome		1 (3%)
Hypoxia		1 (3%)
Pulmonary embolism		1 (3%)
Vasculitis Purpura (worsening)		1 (3%)

*All Grade 3-4 events and any AE occurring in >3 patients
**Mainly related to OGX-427 infusion reactions
***93% were Grade 1-2

CONCLUSION

- Androgen Receptor remains the cornerstone in the treatment of prostate cancer
- Two new agents with promising activity in CRPC:
  - ODM - 201
  - OGX - 427
- Both agents target the Androgen Receptor at different level and with different mechanisms of action
- My concerns for the next years:
  - How to choose the best treatment option?
  - How to optimize combination with other emerging novel therapies?