When is prostate cancer truly androgen independent?

Gerhardt Attard MD MRCP PhD

Cancer Research UK Clinician Scientist and Honorary Consultant

The Institute of Cancer Research and

the Royal Marsden NHS Foundation Trust

CANCER RESEARCH UK

ICR The Institute of Cancer Research

THE ROYAL MARSDEN

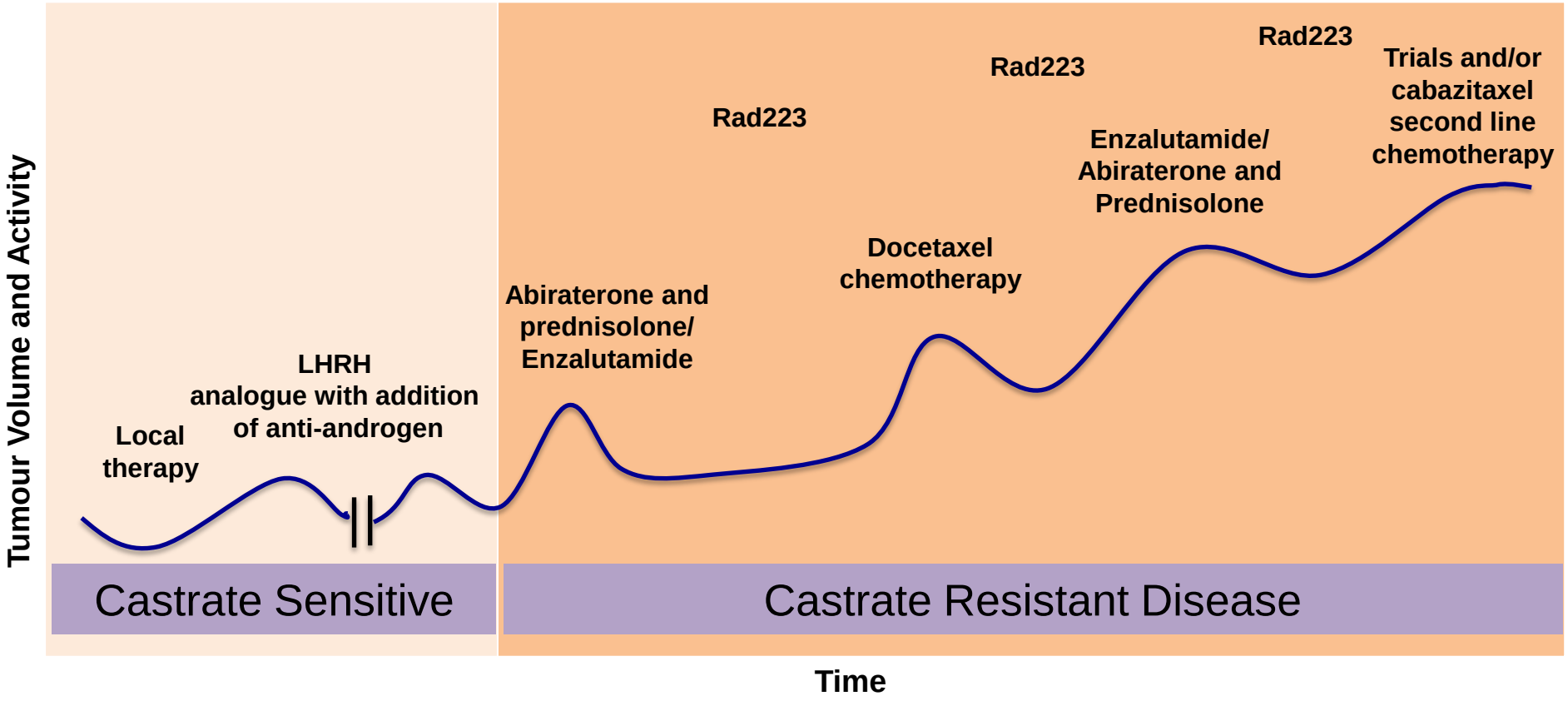
Disclosure slide

- Employee of the Institute of Cancer Research (ICR); abiraterone acetate was developed at the ICR, which therefore has a commercial interest in the development of this agent.

- Received:-
  - Consulting fees and travel support from Janssen-Cilag, Veridex, Roche/Ventana, Astellas, Medivation, Novartis, Millennium Pharmaceuticals and Abbott Laboratories.
  - Speaker's fees from Janssen, Ipsen, Takeda and Sanofi-Aventis.
  - Grant support from Janssen and AstraZeneca.

- On The ICR rewards to inventors list of abiraterone acetate.

Management of CRPC v2014

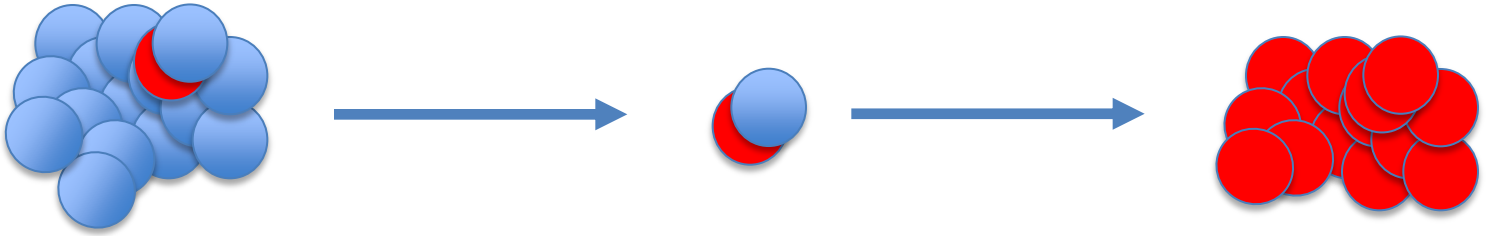


- **Hypothesis**: A subset of patients with advanced CRPC may eventually evolve into an AR–independent phenotype, associated with rapidly progressive disease involving visceral sites and hormone refractoriness, often in the setting of a low PSA

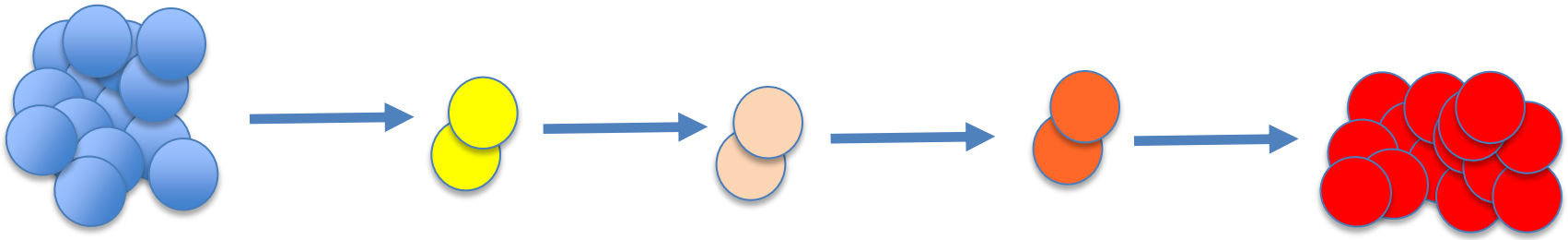
Beltran et al, Clin Cancer Res. 2014

Progression to the AR-negative phenotype

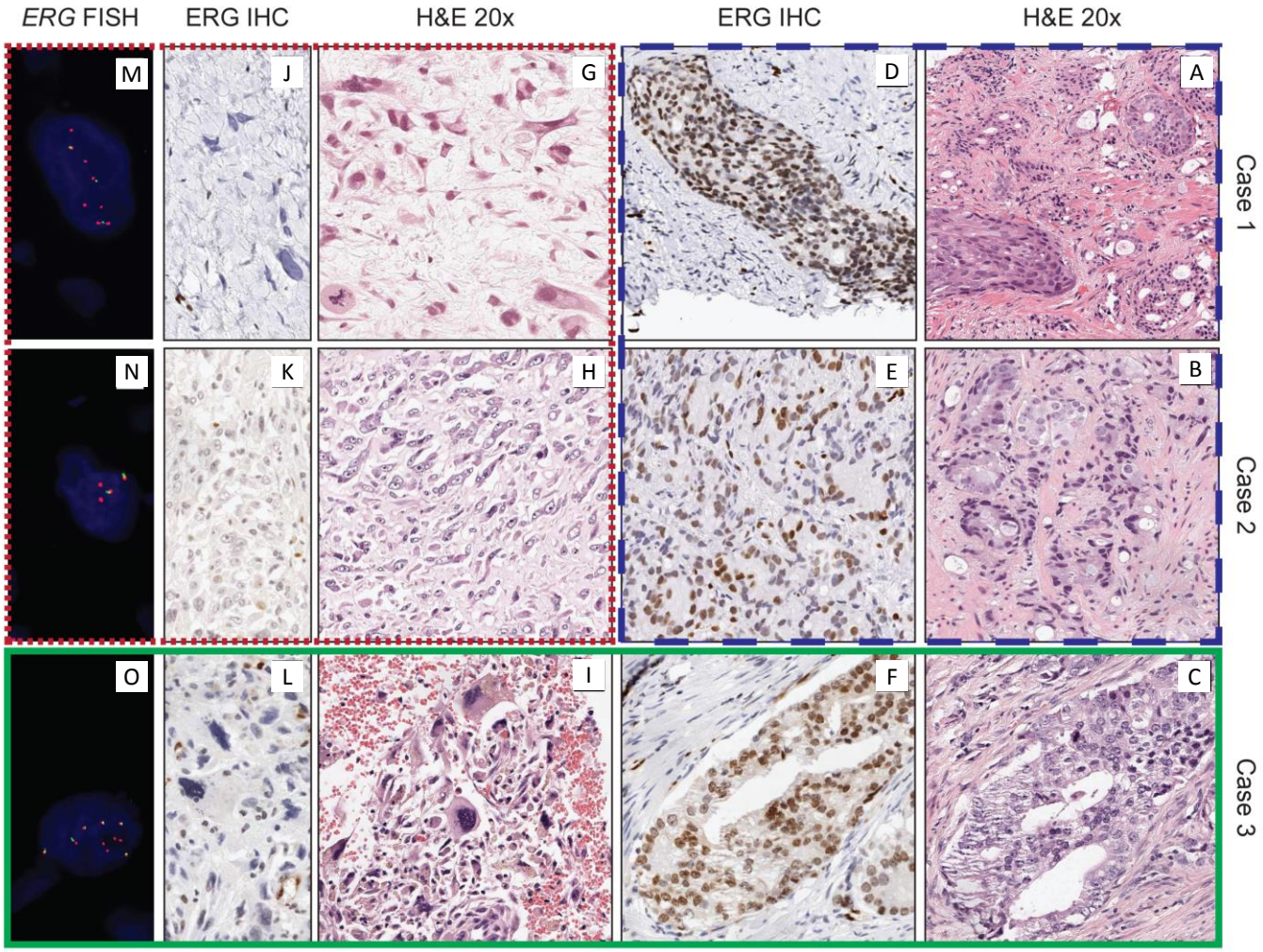
Treatment selects a rare AR-negative clone



Treatment selects for genomic aberrations that accumulate, leading to the AR-negative phenotype



Sarcomatoid differentiation occurring early on with castration

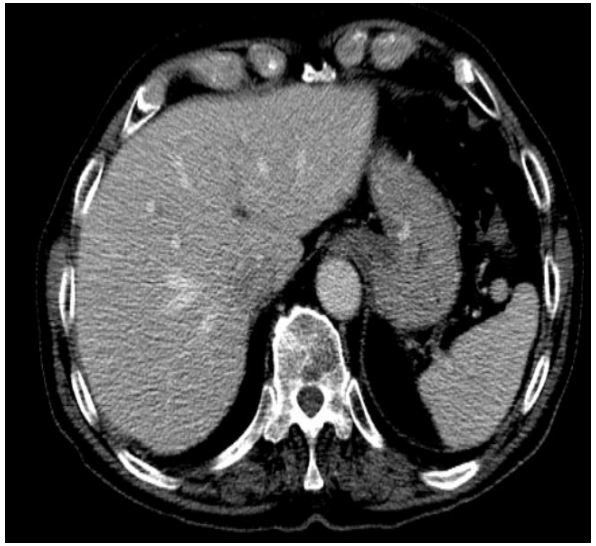


Rodrigues DN et al, Histopathology 2014

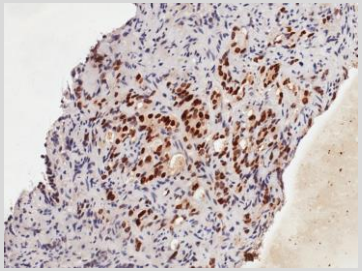
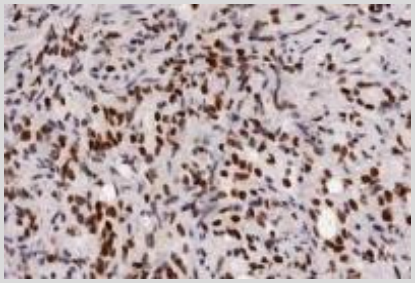
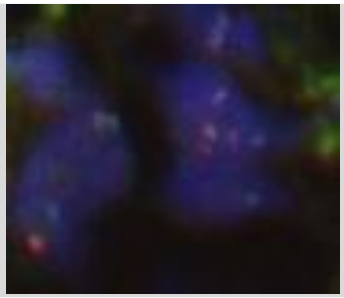
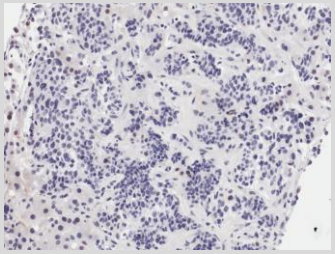
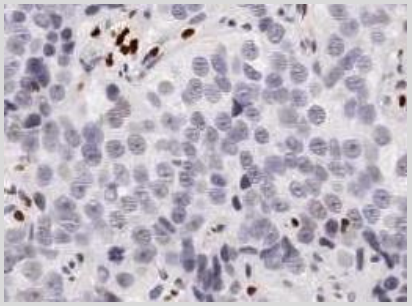
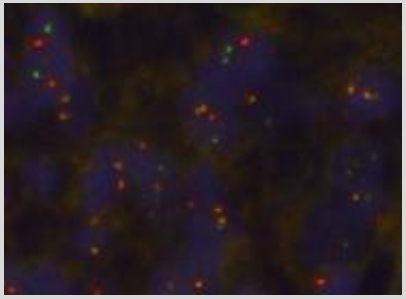
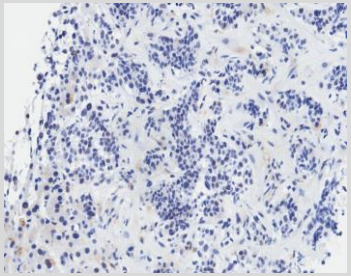
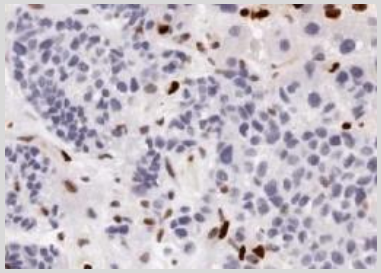
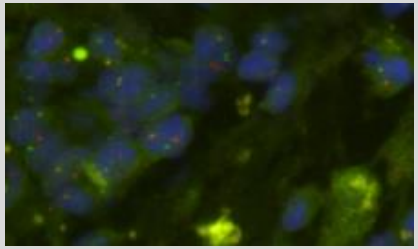
AR-negative disease progression

- 75 year old previously progressed on castration, bicalutamide, dexamethasone
  - Started abiraterone and prednisone in Jan 2010
  - Baseline PSA 50ng/dl
  - Good PSA response (nadir: 6.7, July 2010)

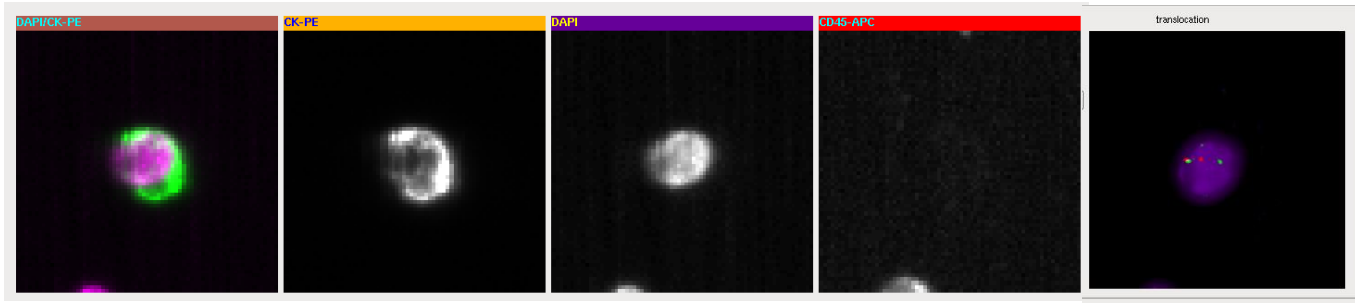
March 2011	June	1 Sep	15 Nov	8 Dec
10	11	18	18	11



Biopsied x2

	AR IHC	ERG IHC	*ERG* FISH
Pre-treatment biopsy			
Tumor biopsy whilst responding to treatment			
New liver metastasis			

Circulating tumor cells N=36



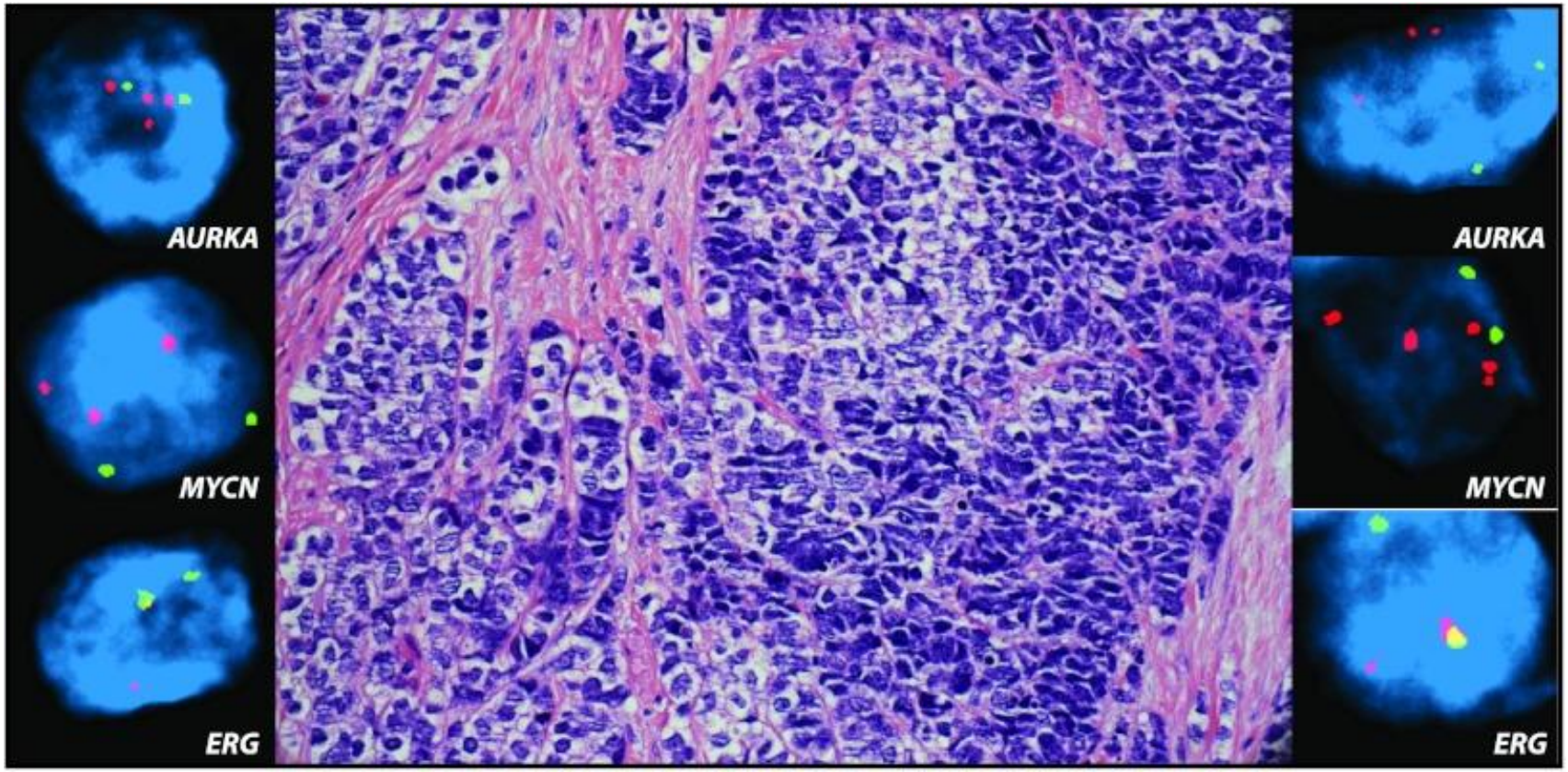
Pezaro et al, Eur Urol 2014

Pathologic classification of neuroendocrine differentiation in prostate carcinoma

Usual prostate adenocarcinoma
Adenocarcinoma with paneth cell neuroendocrine differentiation
Carcinoid tumor
Small cell carcinoma
Large cell neuroendocrine carcinoma
Mixed (small and large cell) neuroendocrine carcinoma—acinar adenocarcinoma

Beltran et al, Clin Cancer Res. 2014

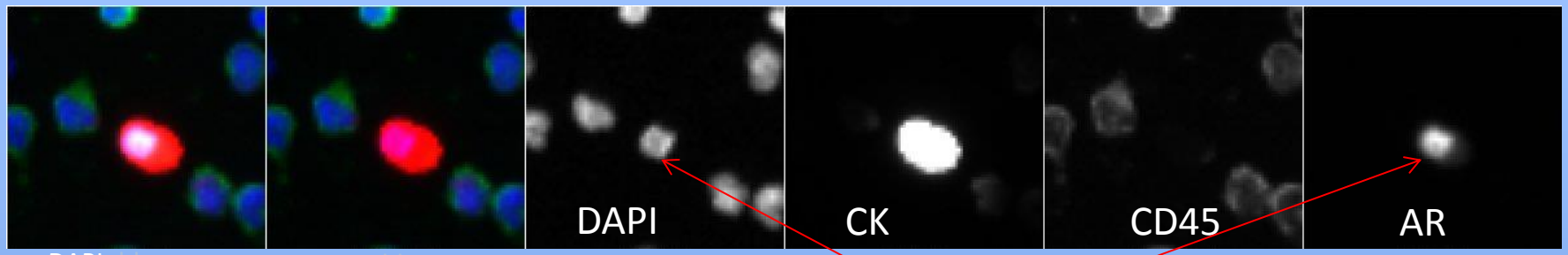
Genomic aberrations associating with "neuro-endocrine" phenotype



Mosquera et al, Neoplasia, 2013

Using CTC to identify AR-negative phenotypes

Baseline - CTCs exhibit nuclear expression & localization of AR

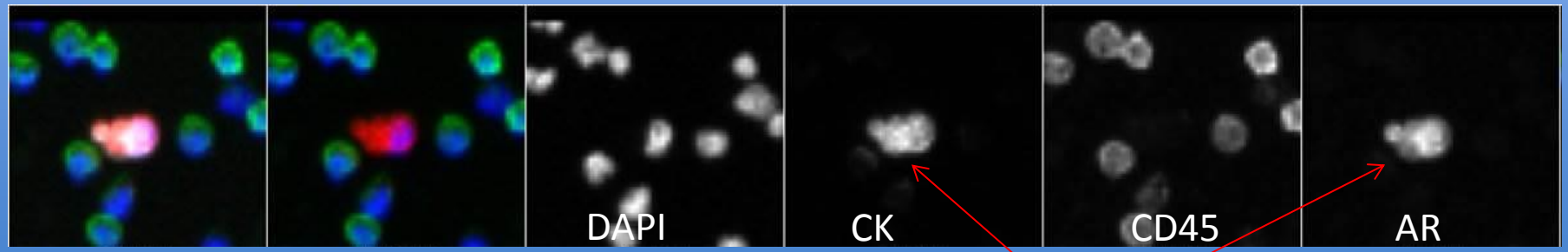


DAPI- blue
CK- red
CD45- green
AR- white

DAPI- blue
CK- red
CD45- green

AR signal similar to the nucleus (DAPI)

Enzalutamide-Res - CTCs continue to exhibit cytoplasmic expression & localization of AR



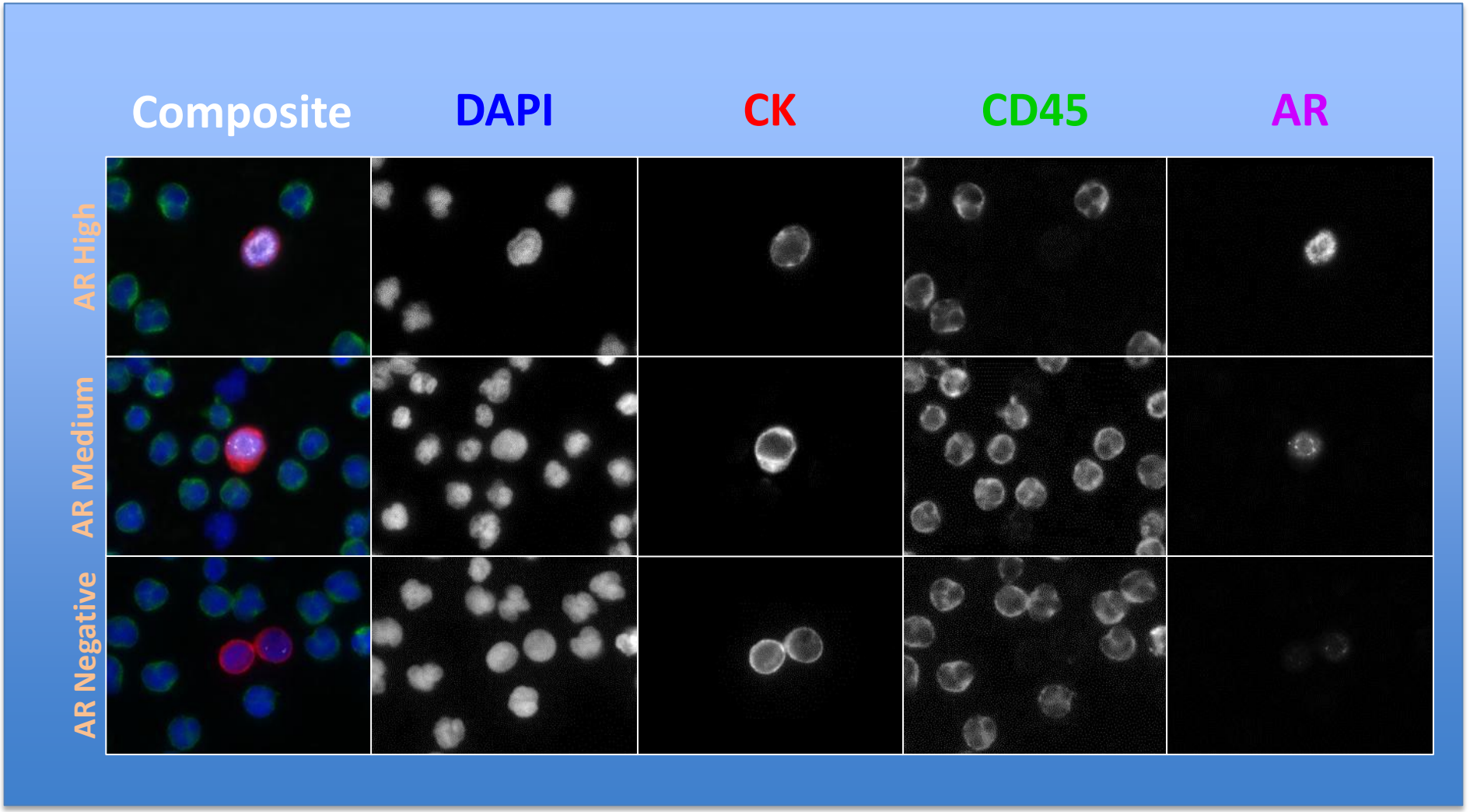
DAPI- blue
CK- red
CD45- green
AR- white

DAPI- blue
CK- red
CD45- green

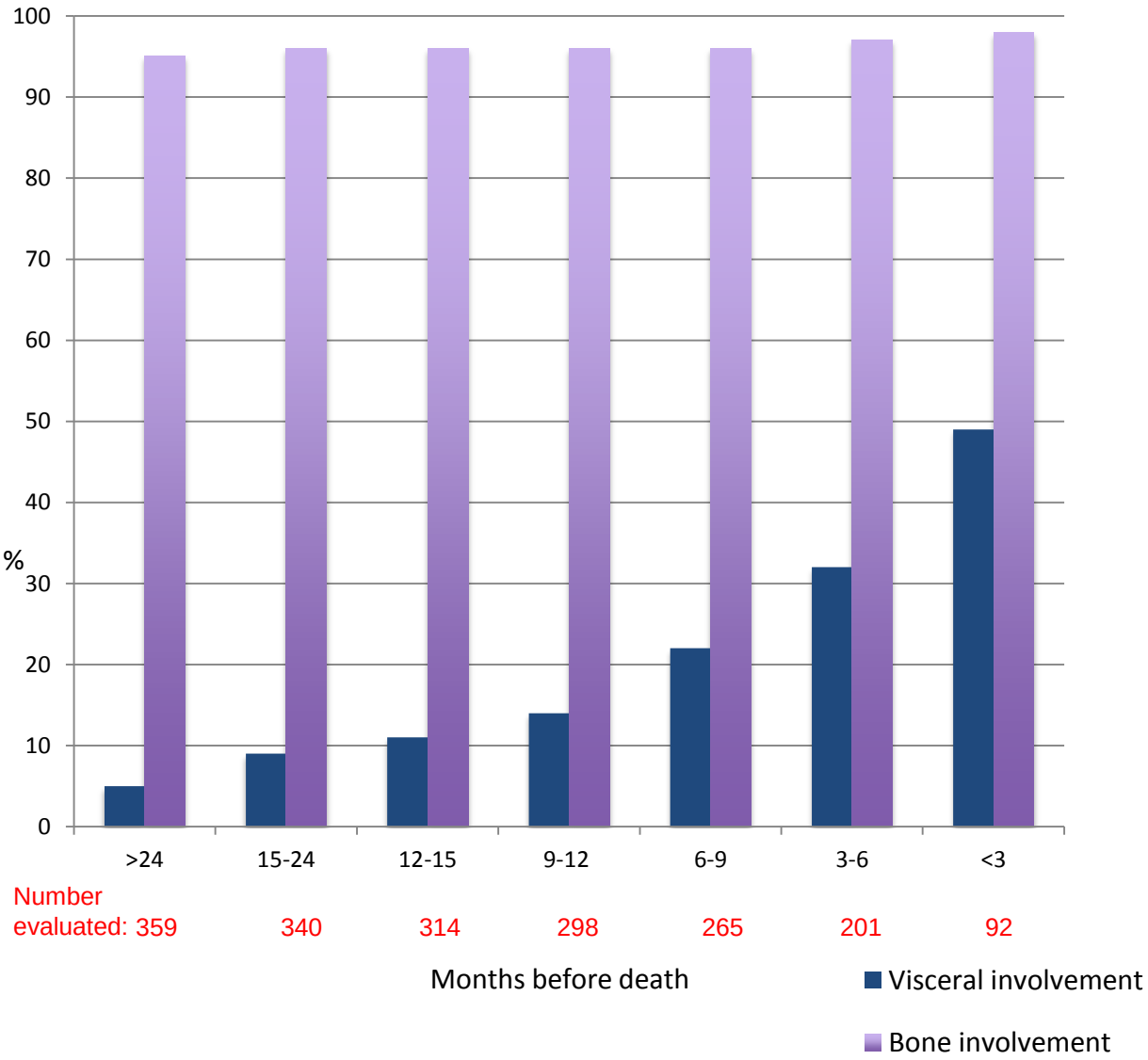
AR signal similar to the cytoplasm (CK)

In collaboration with Epic Biosciences

Heterogeneity of intra-patient CTC AR expression

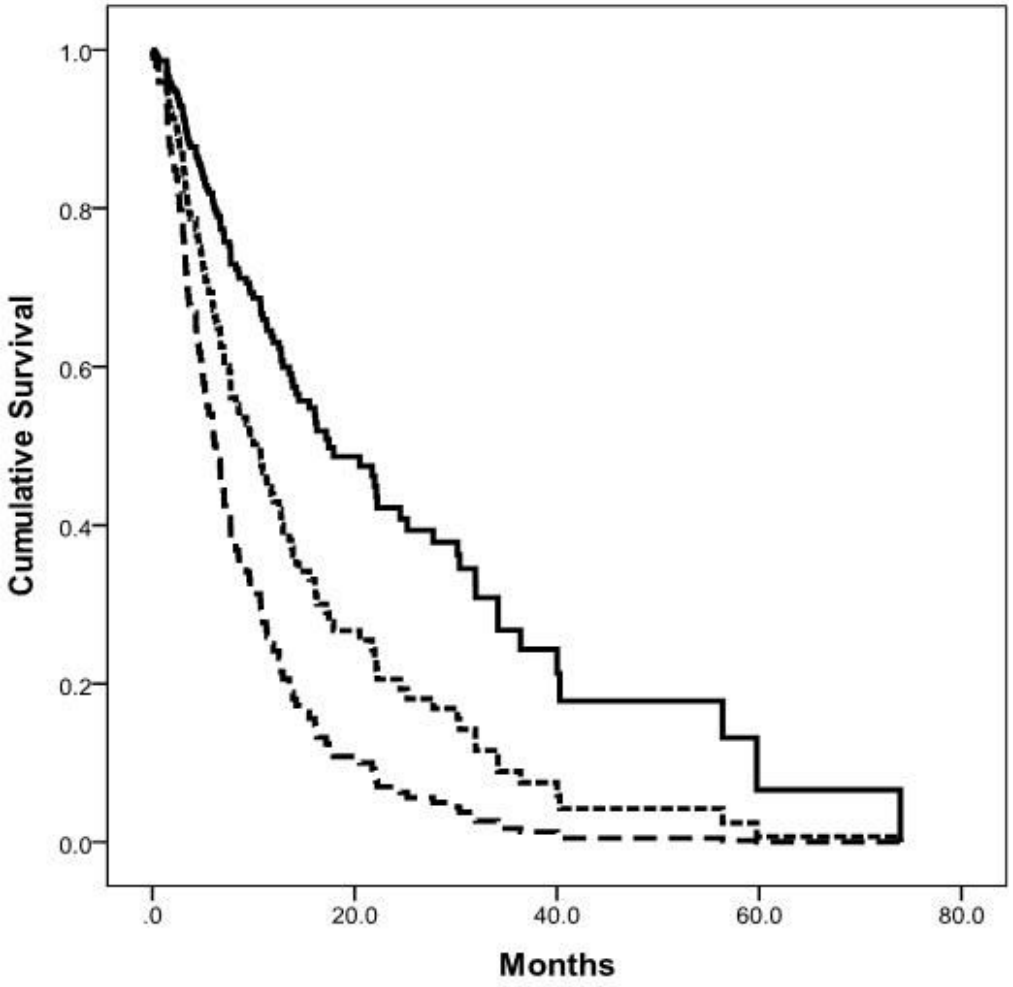


CRPC disease distribution has changed



Pezaro et al, Eur Urol, 2014

Visceral disease alone is not associated with worse survival



Visceral mets only, 18.2m
<6 bone mets, 8.1m
≥6 bone mets, 6.1m
***

Pezaro et al, Eur Urol, 2014

Conclusions – androgen-independent prostate cancer

- AR-negative phenotype may include several different morphological appearances
- Commonly recognised due to no rise in PSA in presence of disease progression
- Commonly involves visceral disease but not all visceral disease is AR-independent
- May become more common due to more effective AR targeting
- Requires novel treatment strategies, that may include platinum chemotherapy