Discussion of oral presentations Abstracts 8930 and LBA3523

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Disclosures

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Abstract 8930

Survival analysis of a randomized phase III trial comparing androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in hormone-sensitive metastatic prostate cancer (GETUG-AFU 15/0403).

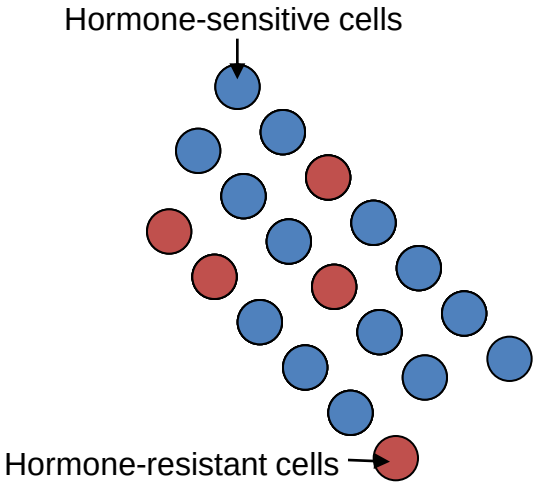
G. Gravis, K. Fizazi, F. Joly Lobbedez, S. Oudard, F. Priou, I. Latorzeff, R. Delva, B. Esterni, M. Habibian, M. Soulie

Hormone-sensitive advanced/metastatic prostate cancer

- Androgen deprivation therapy (ADT) by LH-RH analogues or orchidectomy is a gold standard for hormone-sensitive advanced/metastatic prostate cancer.
  - ↘ prostate cancer-related symptoms and complications, ↗ increases survival
- However resistances develop within 14 to 20 months
- There may be additive effect of ADT combined with radiation in patients with localized prostate cancer

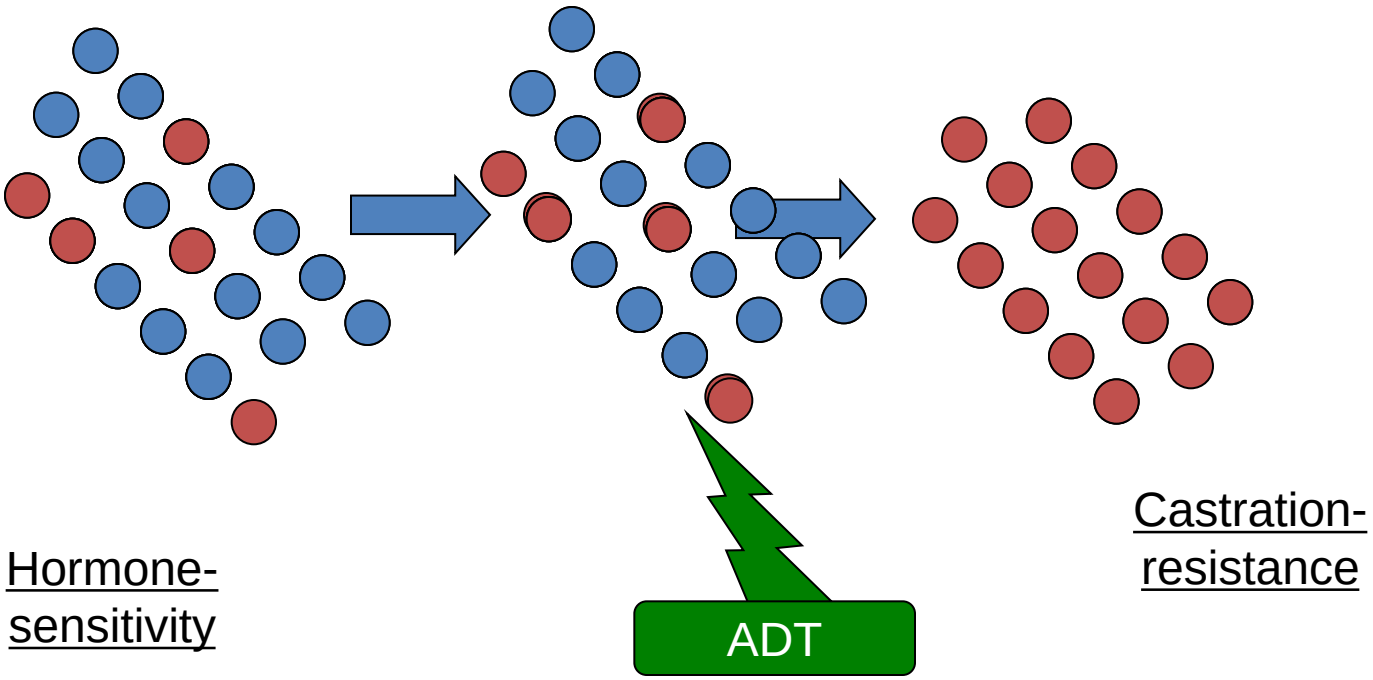
Huggins et al, Cancer Res 1941;1:293. Sharifi et al, JAMA 2005; 294:238. Pagliarulo et al, Eur Urol 2012; 61:11

What about the combination of chemotherapy with ADT in hormone-sensitive metastatic patients ?



Hormone-sensitivity

What about the combination of chemotherapy with ADT in hormone-sensitive metastatic patients ?



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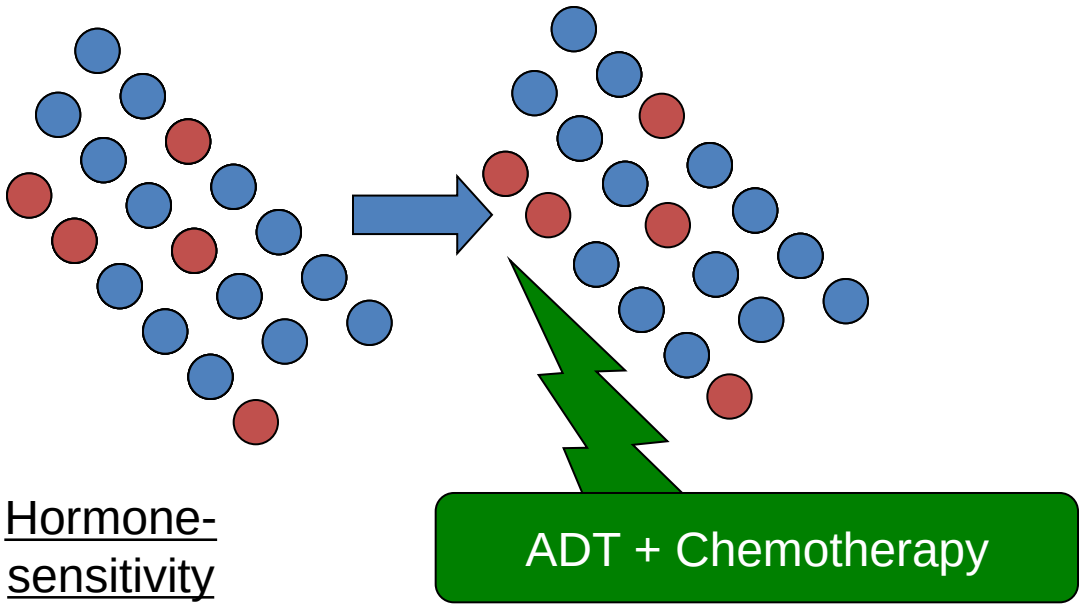


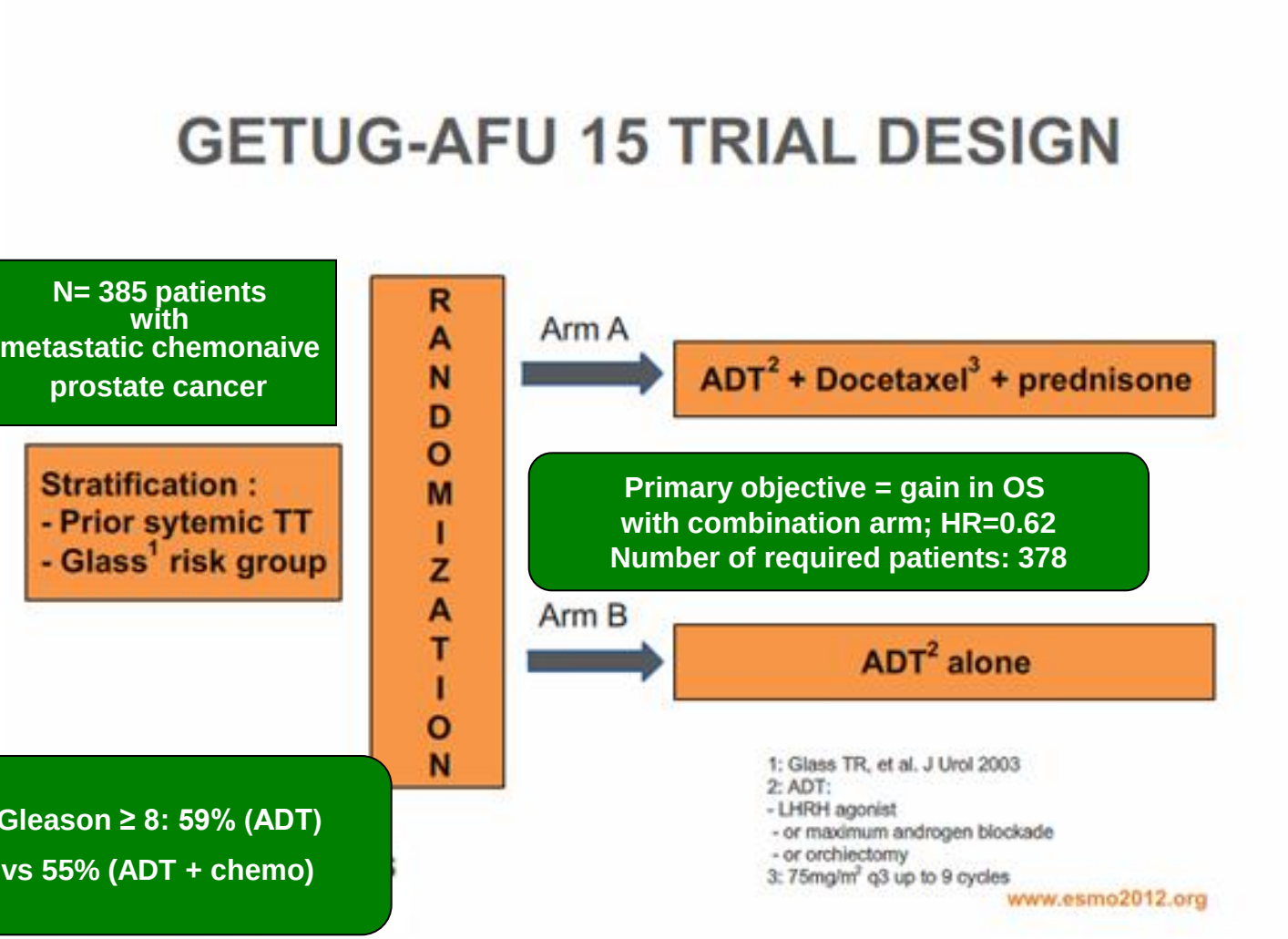
The literature data…

First Author and Year	No pts	Therapy	Median TTP	Median OS
Murphy, 1983	246	A: DES, orch; B: DES, cyclophosphamide C: Estramustine, **cyclophosphamide**	Not reported	21 months in all arms
Murphy, 1986	296	A: DES or orch B cyclophosphamide /**5-FU**/DES C :Estramustine	15 months in all arms	33 months in all arms
Osborne, 1990	137	A:DES, orch B: DES or orch + cyclophosphamide /**doxorubicin**	A: 15 months B: 18 months (p = 0.8)	A: 26 months B: 22 months (p = 0.55)
Pummer, 1997	114	A: orch/flutamide B: orch/flutamide+ **epirubicin**	A: 12 months B: 22 months **(p = 0.02)**	A: 18 months B: 30 months (p = 0.12)
Janknegt, 1997	385	A: orch B: orch + **estramustine**	A: 17 months B: 24 months (p = 0.3)	A: 24 months; B: 27 months (NS)
Fontana, 1998	55	A: LHRH agonist B: LHRH + **mytomycin**	A: 19 months B: 25 months (NS)	A: 32 months B: 29 months (NS)
Boel, 1999	148	A:orch B: orch + **mitomycin**	A: 29 months B:26 months (NS)	31 months in all arms
de Reijke, 1999				**(p = .04)**
Kuriyama, 2001				= 0.13)
Noguchi, 2004		B: LHRH + **estramustine**	B: 25.4 months **(p = 0.03)**	
Millikan, 2008	286	A: LHRH superagonist or orch B: LHRH superagonist or orch + **ketoconazole /doxorubicin alternating with vinblastine/estramustine**	A: 24 months B: 35 months (p = 0.39)	A: 6.4 years B: 6.1 years (NS)

No data about addition of a modern chemotherapy to ADT

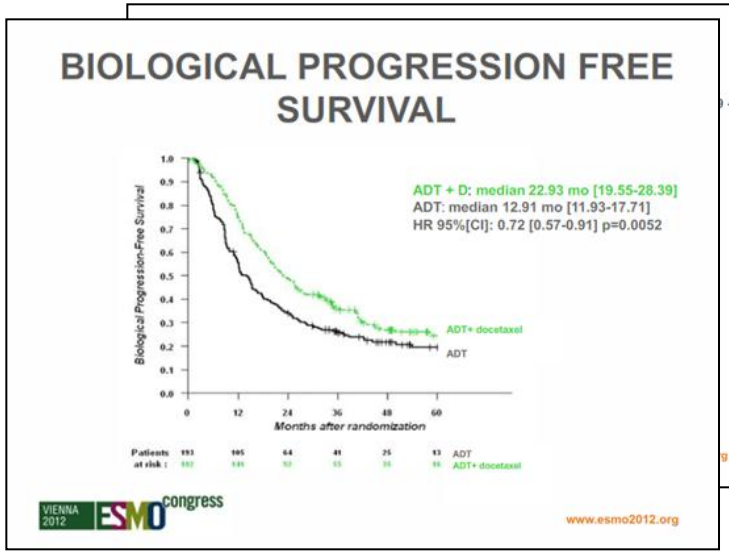
Adapted from Millikan et al. JCO 2008; 26:5936

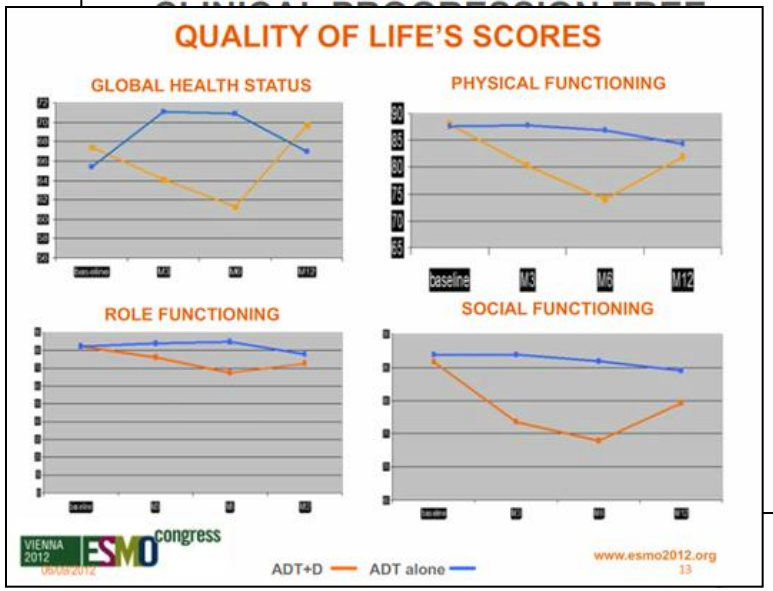
GETUG-AFU 15/0403 study



GETUG-AFU 15/0403 study

- Primary endpoint: OS
  - No benefit
- Secondary endpoints
  - Significant gain in:
    - biological PFS
    - clinical PFS
    - PSA response: 94% vs 85%, p=0.0096
  - More grade 3-4 neutropenia: 32% vs 0%
  - Quality of life: reduced during treatment with docetaxel





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GETUG-AFU 15/0403 study

- The question is relevant and this trial gives some answers:
  - ↳ Docetaxel added to ADT increases biochemical and clinical PFS but not OS
- Issues
  - Patient population
    - Median ECOG PS = 0
    - 55% to 59% patients Gleason ≥ 8
    - 53% lymph node involvement

The patient population is not really representative of our routine activity

The poor surrogacy of PSA response based on percentage decrease

- PSA response: 94% vs 85%, p=0.009, Δ =7%
- The best method to analyse PSA kinetics has not been defined yet
  - Since 1999, ↘ of PSA ≥ 50% with 2 measurements ≥ 3-4 weeks apart = official definition of a biochemical PSA response by PSA working group [1]
  - SWOG-9916 and TAX-327: ↘ of PSA ≥ 30% was a better predictor of survival [2]
  - Definition of PSA progression is still discussed [1]
  - PSA variations explain 17% in overall survival changes [3]
  - The role of mathematical modeling of PSA kinetics has to be defined
- In phase III trials of metastatic prostate cancers, overall survival is the gold standard [4]
- PSA kinetic parameters and clinical PFS are not good surrogate markers of overall survival [4]

1. Scher et al. JCO 2008; 26: 1148. 2. Fitzpatrick BJU Intern 2009; 103-578. 3. Verbel et al. Clin Cancer Res 2002;8:2576
4. Buyse et al Cancer J. 2009;15:421-5, Bull Cancer 2012 Epud ahead of print.

Is there a survival benefit to administer doce

TAX-327: Castration resistant patients (n=1

Docetaxel

Mitoxantrone

MS = 18.9 vs 16.5, Δ = 2.4 month

HR = 0.83, [0.70 - 0.99], P=0.0

SWOG-9916: Castration resistant patients (

Estramustine + docetaxel

Mitoxantrone

MS = 17.5 vs 15.6, Δ = 1.9 months

HR = 0.80 [0.67 to 0.97], P = 0.02

HR is close to 1 in GETUG-15 study

Hypotheses:

-Number of patients was lower

-The major job in terms of survival was done by hormone treatment

-No synergestic effects between ADT and chemotherapy

➔Confirms some preclinical data

Fizazi et al. Anticancer Res 2004;24:2897

GETUG-15: Hormone sensitive patients (n=385)

Hormone sensitive breast cancer

No benefit in overall survival by addition of chemotherapy to hormone treatment in metastatic breast cancer patients

Sledge et al. JCO 2000; 18:262

Δ = 4.7 months

1 [0.7-1.3], NS

2 years

5 years

Key message

- The primary objective of the trial was not met
- Gain in biochemical and clinical PFS did not translate in overall survival benefit
- Hematology toxicity was higher & QOL lower
- Of note, 62% patients in ADT arm received docetaxel at castration resistance
  - Why so few patients ? What happened with the remaining patients ?
  - The sequential strategy implies successive treatments can be administered
- Chemotherapy remains indicated in castration resistant patients only

Is there a population of patients with aggressive metastatic disease who may benefit from treatment combination ?

Aggressive treatment for aggressive disease?

- GETUG-15 study
  - Stratification based on risk groups defined by Glass et al.
    - median OS (months) =
      - GOOD: 69.1 [95%CI: 60.9-NR]
      - INTERMEDIATE: 46.5 [95%CI: 37.7-NR]
      - POOR: 36.6 [95%CI9: 28.5-58.9]

No difference between ADT vs ADT + docetaxel arms

New predictive biomarkers are needed …

Glass et al. J Urol 2003; 169:164

Abstract LBA3523

Derivation and validation of blood mRNA expression signatures to stratify castration resistant prostate cancer patients and predict poor outcome

D. Olmos Hidalgo, D. Brewer, G. Attard, D. Danila, J. Clark, C. Parker, E. Castro, M. Fleischer, A.H.M. Reid, S. Sandhu, R.J. Jones, C.S. Cooper, H.I. Scher, J.S. De Bono

Identifying the aggressive prostate cancers

- 1 men out 6 will be diagnosed with prostate cancer in his life
- 80% men ≥ 80 years old have cancer cells in prostate
- The challenge is to identify the aggressive prostate cancers
  - Among all prostate carcinomas

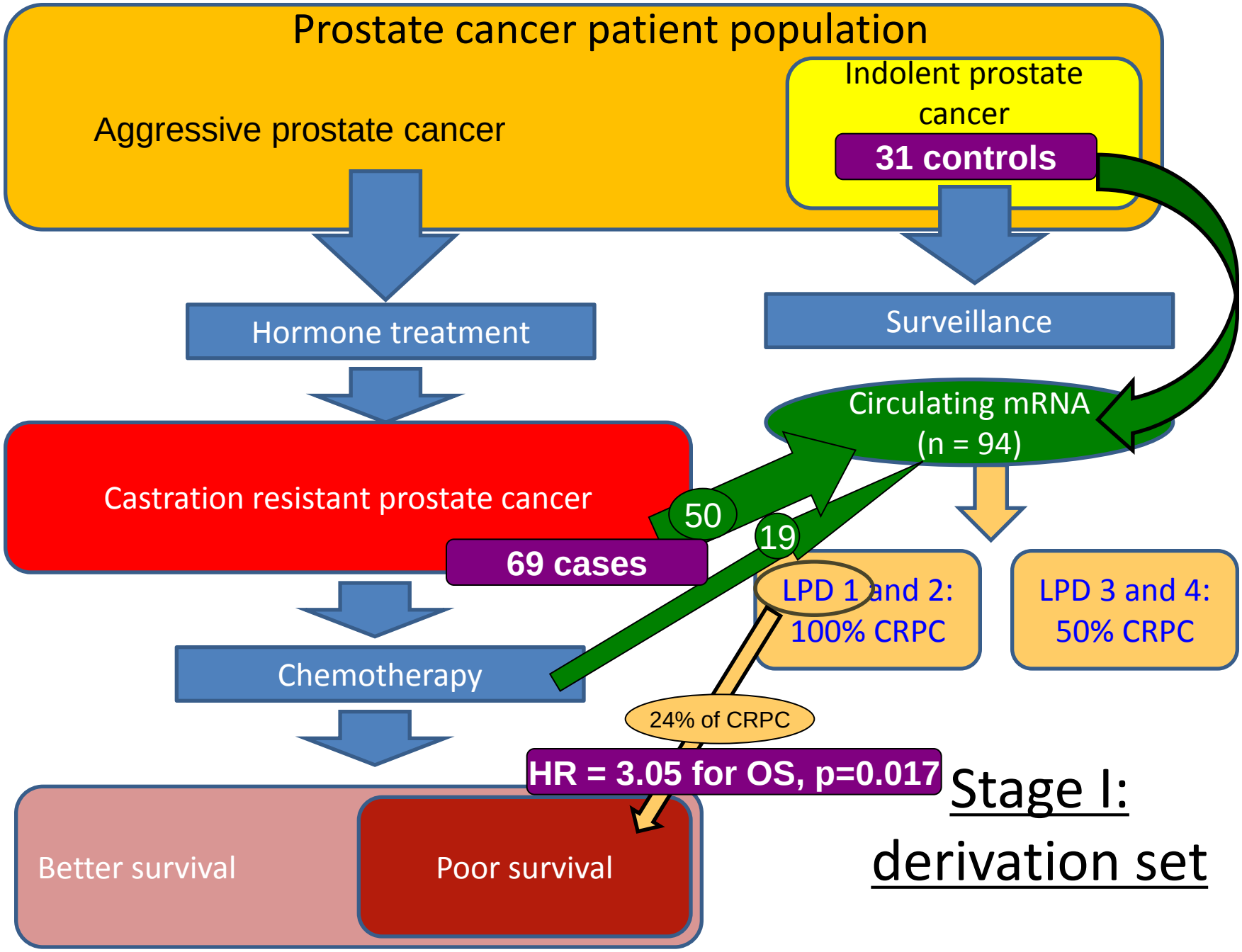
    ↳ Treatment or not treatment ?
  - Among the 10-20% patients who develop castration resistant prostate cancers patients

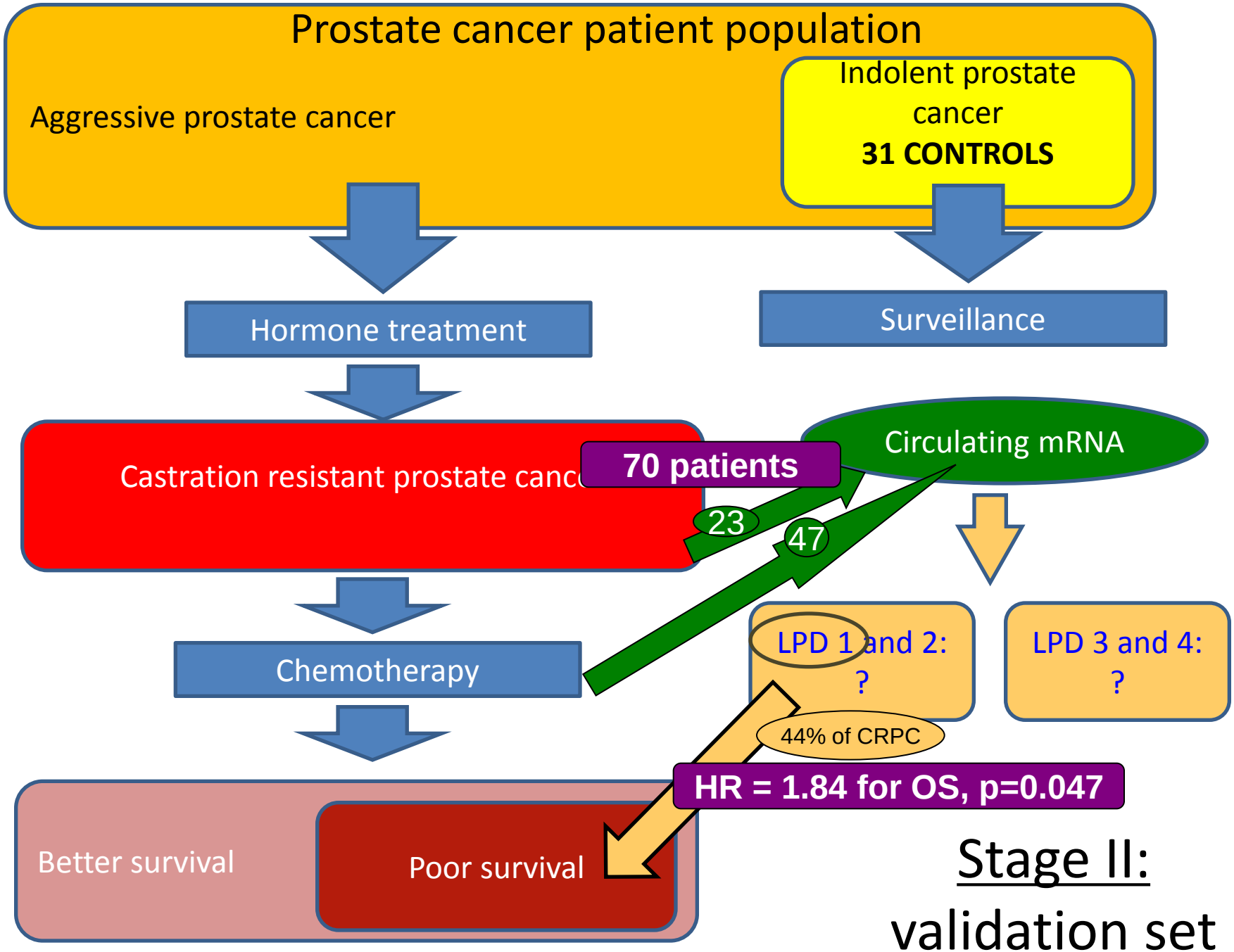
    ↳Response to chemotherapy ?

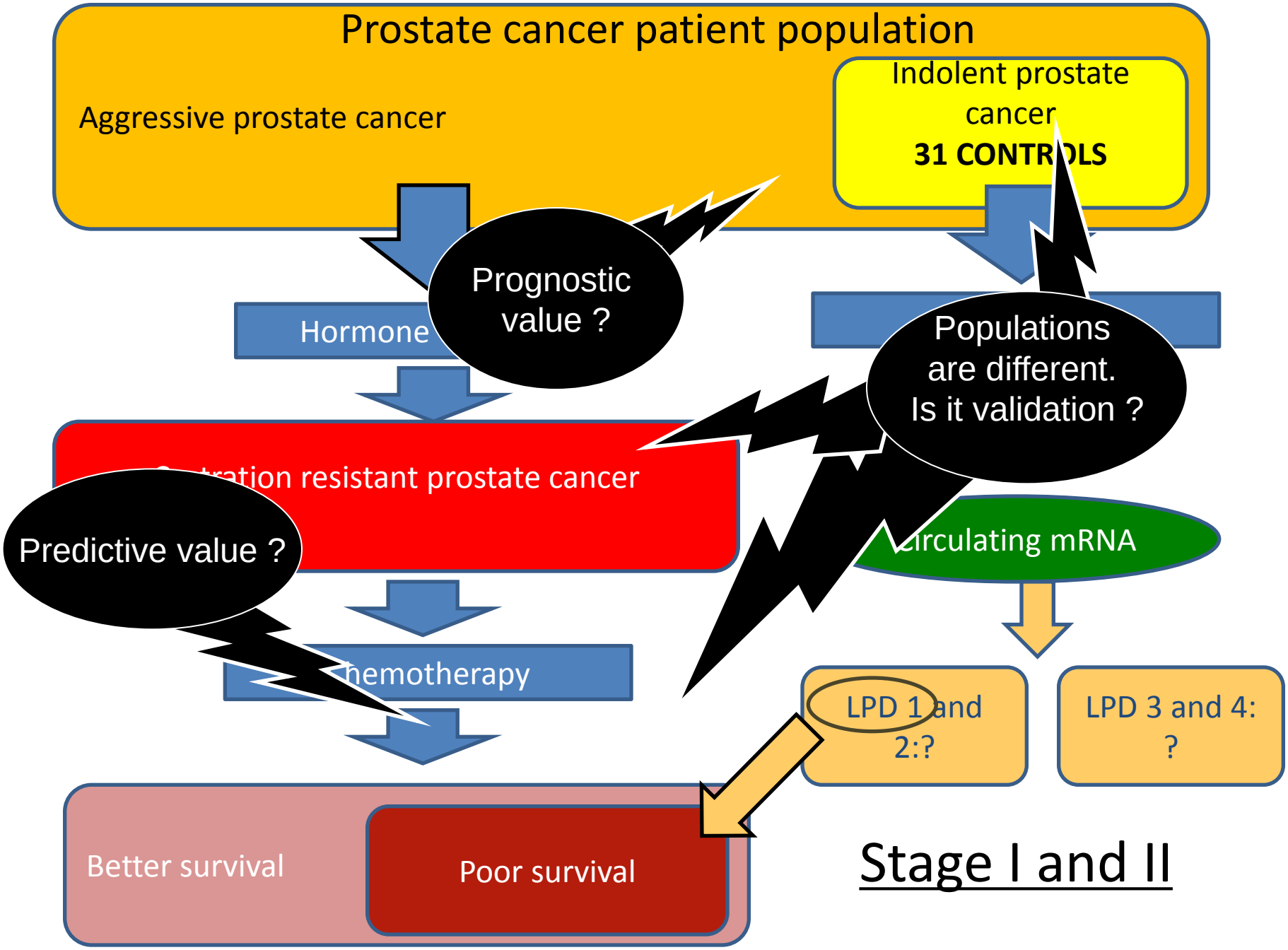
Ferlay et al. Eur J Cancer 2010; 46: 765 –781. http://prostate.icr.ac.uk/ActiveSurveillance.htm.
Kirby Int J Clin Pract 2011, 65, 11, 1180–1192

Circulating gene-expression signatures as prognostic factors in prostate cancer patients

- Primary objective: to elucidate whole blood gene expression profiles associated with aggressive CRPC
- mRNA extraction from whole blood from prostate cancer patients
- Among 16000-20000 gene transcripts, Latent Process Decomposition (LPD), an unsupervised approach, used to classifying samples into 4 groups : LPD1 to 4
- Random forest algorithm showed the expressions of 9 genes are discriminative for classification into LPD groups
- Multivariate tests showed the prognostic value of LPD1 group vs the LPD2-4 groups regarding overall survival in 2 independent datasets


Prostate cancer patient population
Aggressive prostate cancer
Indolent prostate cancer
31 controls
Hormone treatment
Surveillance
Circulating mRNA (n = 94)
Castration resistant prostate cancer
50
19
69 cases
LPD 1 and 2: 100% CRPC
LPD 3 and 4: 50% CRPC
Chemotherapy
24% of CRPC
HR = 3.05 for OS, p=0.017
Better survival
Poor survival
Stage I: derivation set


Prostate cancer patient population
Aggressive prostate cancer
Indolent prostate cancer
31 CONTROLS
Hormone treatment
Surveillance
Castration resistant prostate canc
70 patients
Circulating mRNA
23
47
Chemotherapy
LPD 1 and 2:
?
LPD 3 and 4:
?
44% of CRPC
HR = 1.84 for OS, p=0.047
Better survival
Poor survival
Stage II:
validation set


Prostate cancer patient population
Aggressive prostate cancer
Indolent prostate cancer
31 CONTROLS
Prognostic value ?
Hormone
Populations are different. Is it validation ?
ration resistant prostate cancer
Predictive value ?
irculating mRNA
hemotherapy
LPD 1 and 2:?
LPD 3 and 4: ?
Better survival
Poor survival
Stage I and II

Circulating prognostic gene signature

- Issues
  - Methodology
    - Populations are different between stage I and II tests: *different settings*, *different treatments* but *the same signatures*
      - Do we assume that gene signatures are constant or differ as prostate cancers go through phenotypes: diagnosis, castration-resistance, chemotherapy outcomes? What is the best time to assess them ?
      - Does it explain the difference in HRs (**3.05**, 95% CI = 1.22-7.64, p=0.017 vs **1.84**, 95% CI = 1.01 – 3.35, p=0.047) ?
    - Do the authors think that qRT-PCR is confirmative of the of the measurements or of the models, given the studied sample is the same ?

Circulating prognostic gene signature

- What do we predict using the 9-gene signature ?
  - Expressions of the 9 discriminative genes associated with functions of early erythroid cells, lymphocytes-T and B.
    - How do the authors explain these genes are not related to proliferation and cell cycle regulation, as they are in prognostic/predictive breast cancer signatures (Sotiriou, et al, N Engl J Med 2009;360:790-800) ?
  - A poor prognosis ? Stage I, prediction of CRPC: sensitivity 24%, specificity=100%, PPV=100%, NPC=37%
  - Prediction of poor chemotherapy efficacy ? If yes, to what treatment?

- In the future: what will the clinicians do with such signatures ?
  - When should they test them ?
    - Before start of hormone treatment ?
    - Before start of chemotherapy ?
  - Should the treatment be adjusted on basis on these signatures?

Despite these issues

- There is a need for identifying the patients with aggressive prostate cancers who may benefit from
  - Treatment at diagnosis (prognosis)
  - Treatment densification and chemotherapy at castration resistance (prediction)

- This very interesting study highlights the promising role of a circulating prognostic/predictive gene signature

- Further studies are warranted to confirm what this test actually predicts.

Acknowledgements

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- The authors who shared their data to prepare this discussion
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- Prof Pascal Roy (Department of statistics, Lyon, France)