Are we generating abstracts or answers in TCC?

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What are the questions?

NMIBC

- Will it recur?
- How to monitor non-invasively?
- Risk of progression?
- Better local therapy?

MIBC

- Choice of therapy for organ-confined?
- Prediction of risk of metastasis?
- Prediction of chemoresistance?
- Personalised therapy?

NMIBC

Many molecular features defined –> great abstracts!

Low risk tumours

- Oncogenic mutations – FGFR3, PIK3CA
- Copy number changes
- MicroRNA expression profiles
- mRNA expression profiles
- Genome-wide methylation profiles

"signatures"

- Differentiation markers

High risk tumours

- Tumour suppressor mutations – TP53, RB1…
- Copy number changes
- mRNA expression signatures

Good repertoire of common events for urine-based assays

NMIBC prognosis

Recurrence:

Clinico-pathologic factors

- Multiplicity, size, CIS, prior recurrence rate

Sylvester *et al. Eur Urol 2006;49:466 –77.*

http://www.eortc.be/tools/bladdercalculator.

- Multiplicity most important

Molecular biomarkers – None in clinical use

- Many linked to grade and stage but **not to recurrence**
- Suggested but not confirmed – p53, MDM2, survivin, FGFR3 mutation, chr 9 LOH…etc ..
- Gene signatures e.g. 26 gene signature not validated (Dyrskjøt et al. Clin Cancer Res 2007;13:3545–51)

Are biomarkers of recurrence a realistic/useful goal??

NMIBC prognosis

Progression

Clinico-pathologic factors

- CIS, grade 3, stage T1, micropapillary, lymphovascular invasion

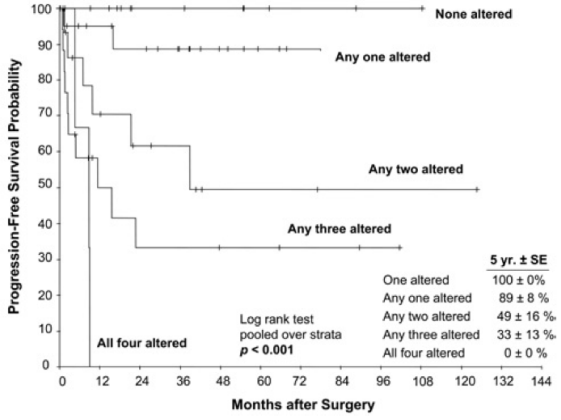
Sylvester *et al. Eur Urol 2006;49:466 –77.*

http://www.eortc.be/tools/bladdercalculator.

Molecular biomarkers – None in clinical use

- Several single markers associated with reduced progression-free survival

- Multiple markers – immunohistochemistry
  p53, p21, p27, RB (Shariat et al, J Urol 177, 481-487, 2007)



RNA expression signature

Clin Can Res 11: 4029-36, 2005

A Molecular Signature in Superficial Bladder Carcinoma Predicts Clinical Outcome

Lars Dyrskjøt,[1] Karsten Zieger,[1,2] Mogens Kruhøffer,[1,5] Thomas Thykjaer,[1,5] Jens L. Jensen,[4] Hanne Primdahl,[1] Natasha Aziz,[6] Niels Marcussen,[3] Klaus Møller,[2] and Torben F. Ørntoft[1]

Imaging, Diagnosis, Prognosis

Clin Can Res 13: 3535-51, 2007

Gene Expression Signatures Predict Outcome in Non–Muscle-Invasive Bladder Carcinoma: A Multicenter Validation Study

Lars Dyrskjøt,[1] Karsten Zieger,[1,2] Francisco X. Real,[4] Núria Malats,[5] Alfredo Carrato,[6] Carolyn Hurst,[7] Sanjeev Kotwal,[8] Margaret Knowles,[7] Per-Uno Malmström,[9] Manuel de la Torre,[10] Kenneth Wester,[10] Yves Allory,[11] Dimitri Vordos,[11] Aurélie Caillault,[12] François Radvanyi,[12] Anne-Mette K. Hein,[1] Jens L. Jensen,[3] Klaus M.E. Jensen,[2] Niels Marcussen,[13] and Torben F. Ørntoft[1]

British Journal of Cancer (2012), 1–7

www.bjcancer.com

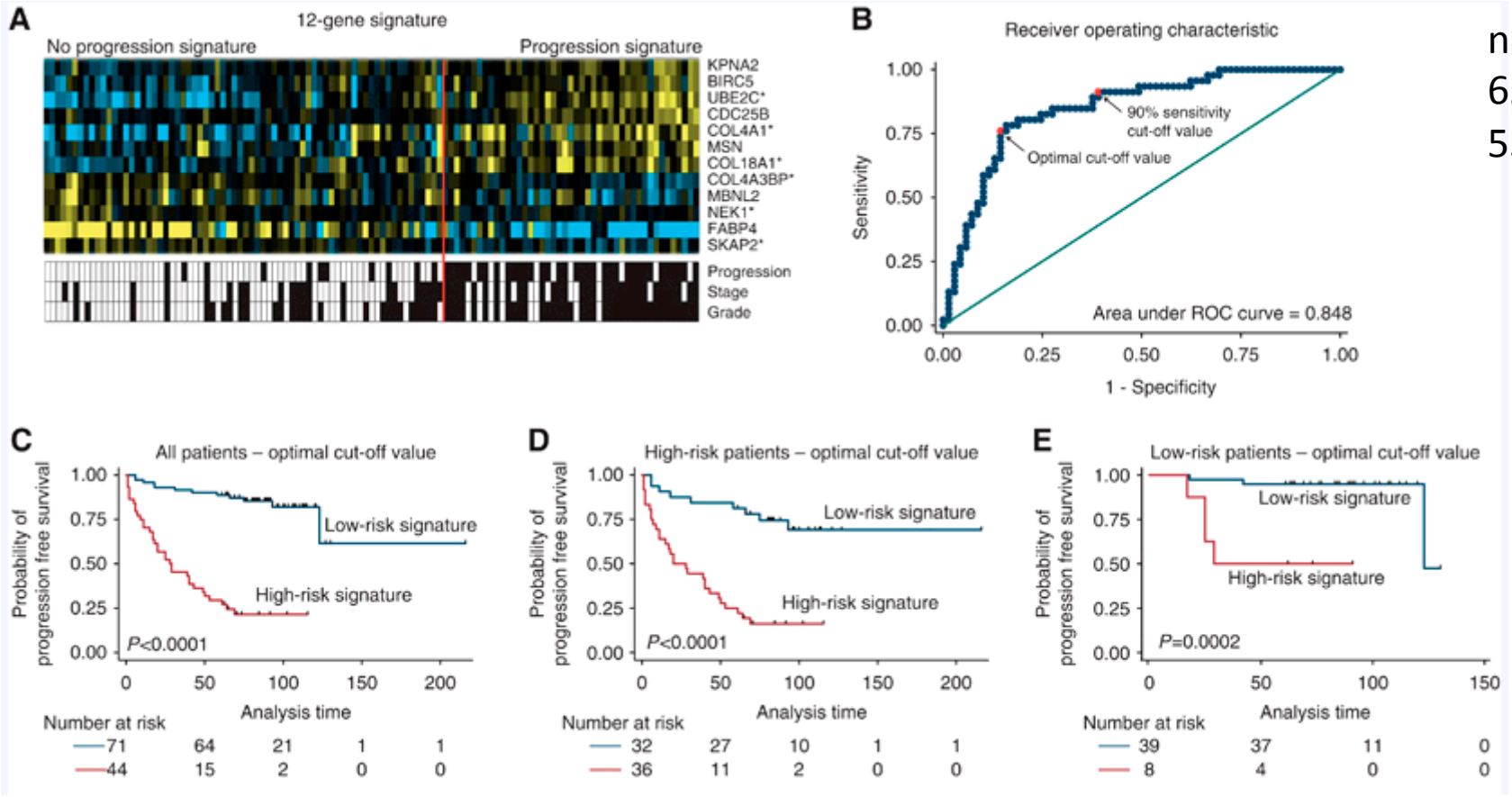
Full Paper

Analysis of molecular intra-patient variation and delineation of a prognostic 12-gene signature in non-muscle invasive bladder cancer; technology transfer from microarrays to PCR

L Dyrskjøt*[,1], T Reinert[1], A Novoradovsky[2], TCM Zuiverloon[3], W Beukers[4], E Zwarthoff[4], N Malats[5], FX Real[5], U Segersten[6], P-U Malmström[6], M Knowles[7], C Hurst[7], J Sorge[2], M Borre[8] and TF Ørntoft[1]

[1]Department of Molecular Medicine, Aarhus University Hospital, Brendstrupgaardsvej 100, Skejby, Aarhus N, 8200 Aarhus, Denmark; [2]Decisive Diagnostics, Jackson, WY 83002, USA; [3]Department of Urology, Erasmus Medical Center, Rotterdam 3000 DR, The Netherlands; [4]Department of Pathology, Erasmus Medical Center, Rotterdam 3000 DR, The Netherlands; [5]Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid 28029, Spain; [6]Department of Surgical Sciences, Urology, Academic Hospital, Uppsala 75185, Sweden; [7]Cancer Research UK Clinical Centre, St James's University Hospital, Leeds LS9 7TF, UK; [8]Department of Urology, Aarhus University Hospital, Brendstrupgaardsvej 100, Skejby, Aarhus N, 8200 Aarhus, Denmark

12-gene PCR-based progression signature



n= 115
62 Ta
53 T1

All

T1/CIS

Ta

Predictive accuracy
73% - Clinical variables
75% - 12 gene signature
83% -both included in model

But…RNA-based

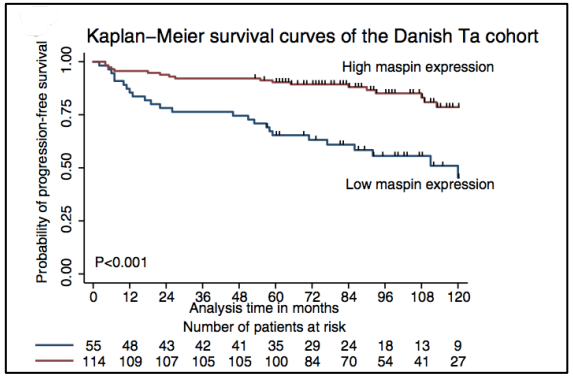
Validation at protein level?

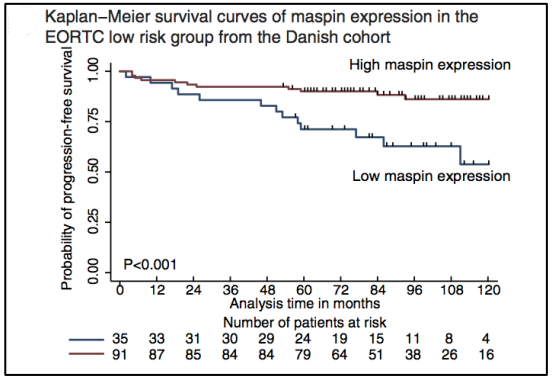
Fristrup et al Am J Path 180: 1824-34, 2012

Most differentially expressed RNAs: maspin, survivin, polo-like kinase and survivin

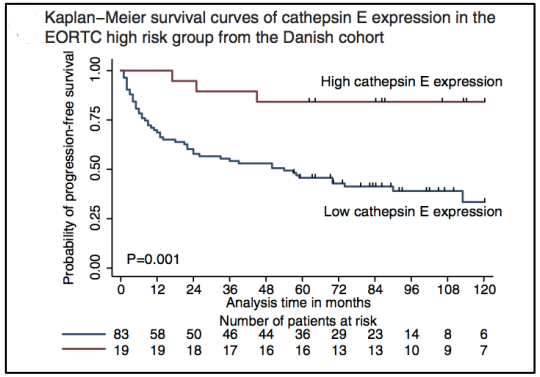
Variable	Ta/T1 cohort	Ta cohort	T1 cohort
Progression prediction accuracy* without molecular markers	73.5%	67.3%	68.7%
Prediction accuracy including 4 molecular markers	78.6%	77.7%	74.5%

*Harrell's concordance index





Very low risk – 4.5%



Highest risk – 47%

Potential to add to EORTC risk Table?

CANCER RESEARCH UK

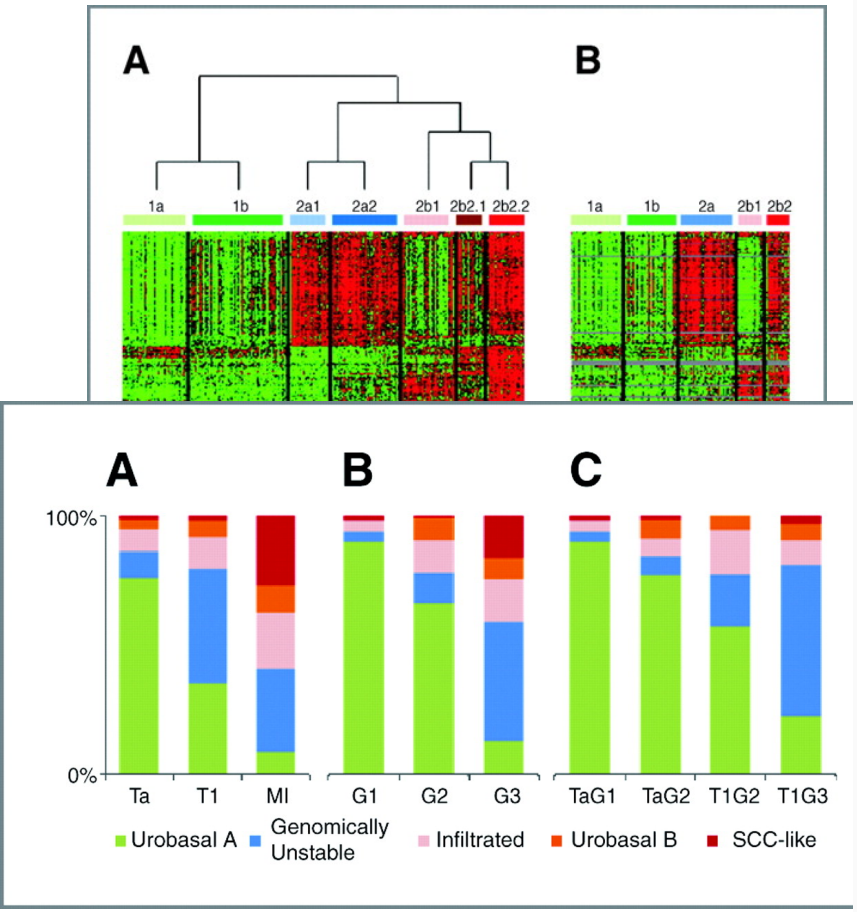
Leeds Institute of Molecular Medicine

yorkshire cancer research

Barriers to translation?

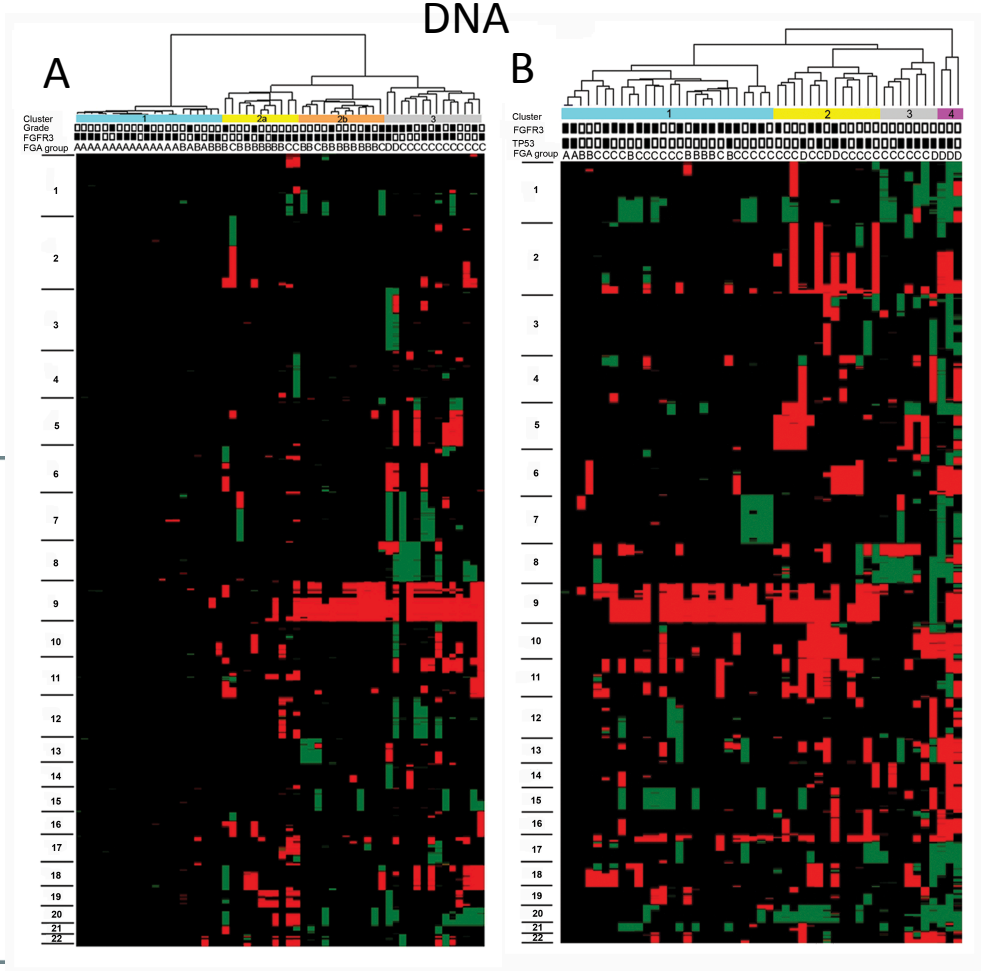
More heterogeneity in NMI disease than previously suspected

mRNA



Sjödahl G et al. Clin Cancer Res 2012;18:3377-3386

DNA



Hurst C et al. Clin Cancer Res 2012;Epub 29th August

Barriers to translation in NMI-BC?

1. Definition of "actionable" molecular features

What level of evidence is needed

to reduce number of cystoscopies?

to make decision for cystectomy in T1?

etc…

2. Well-designed biomarker studies –following REMARK guidelines

Validation of molecular subtypes in larger independent series

Relationship to clinical features?

Assay development - suitable for clinical application

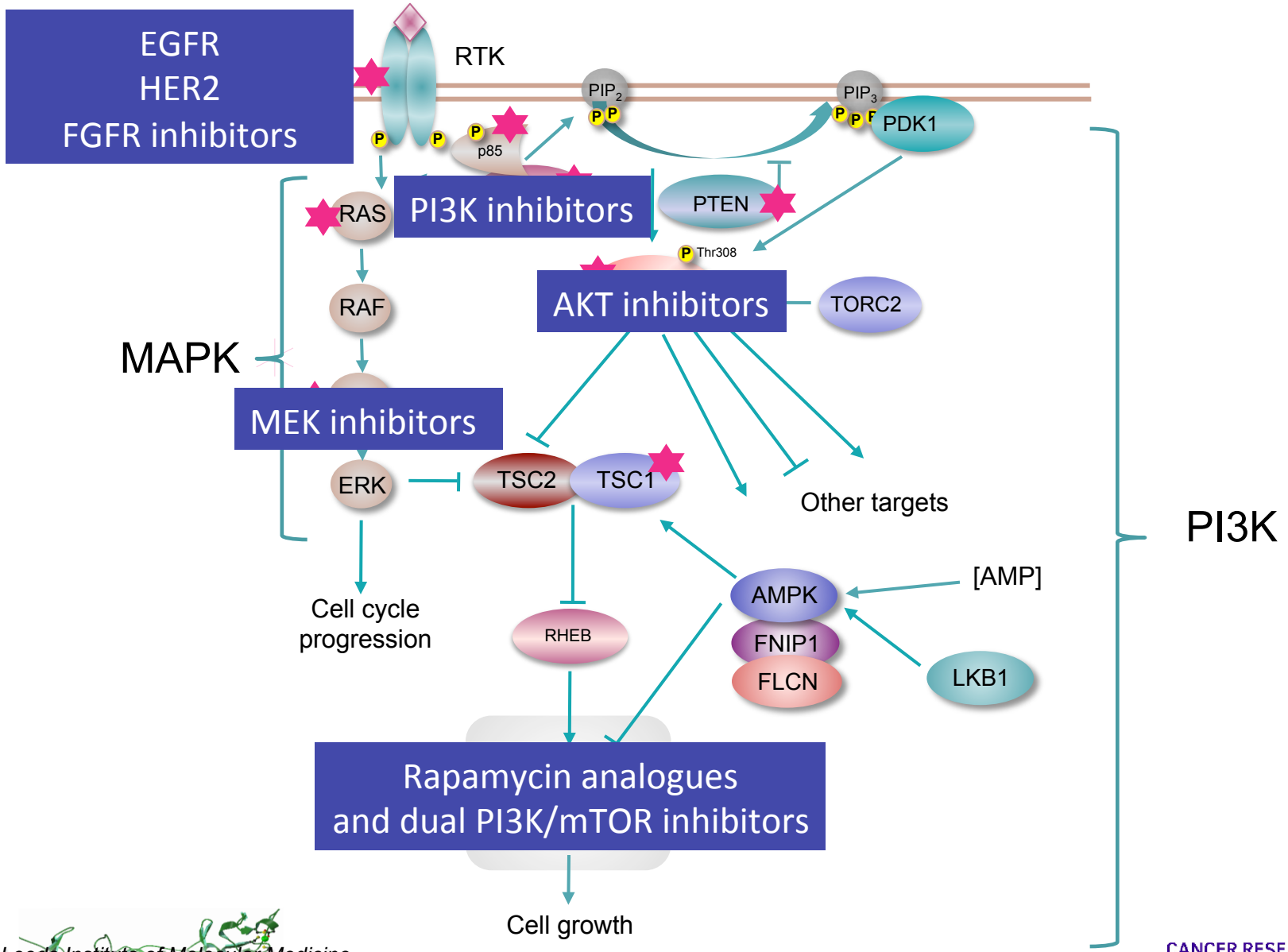
Therapy for MIBC

In other cancers molecular subtyping is in routine clinical practise
Multiple targeted agents with associated predictive biomarkers are approved

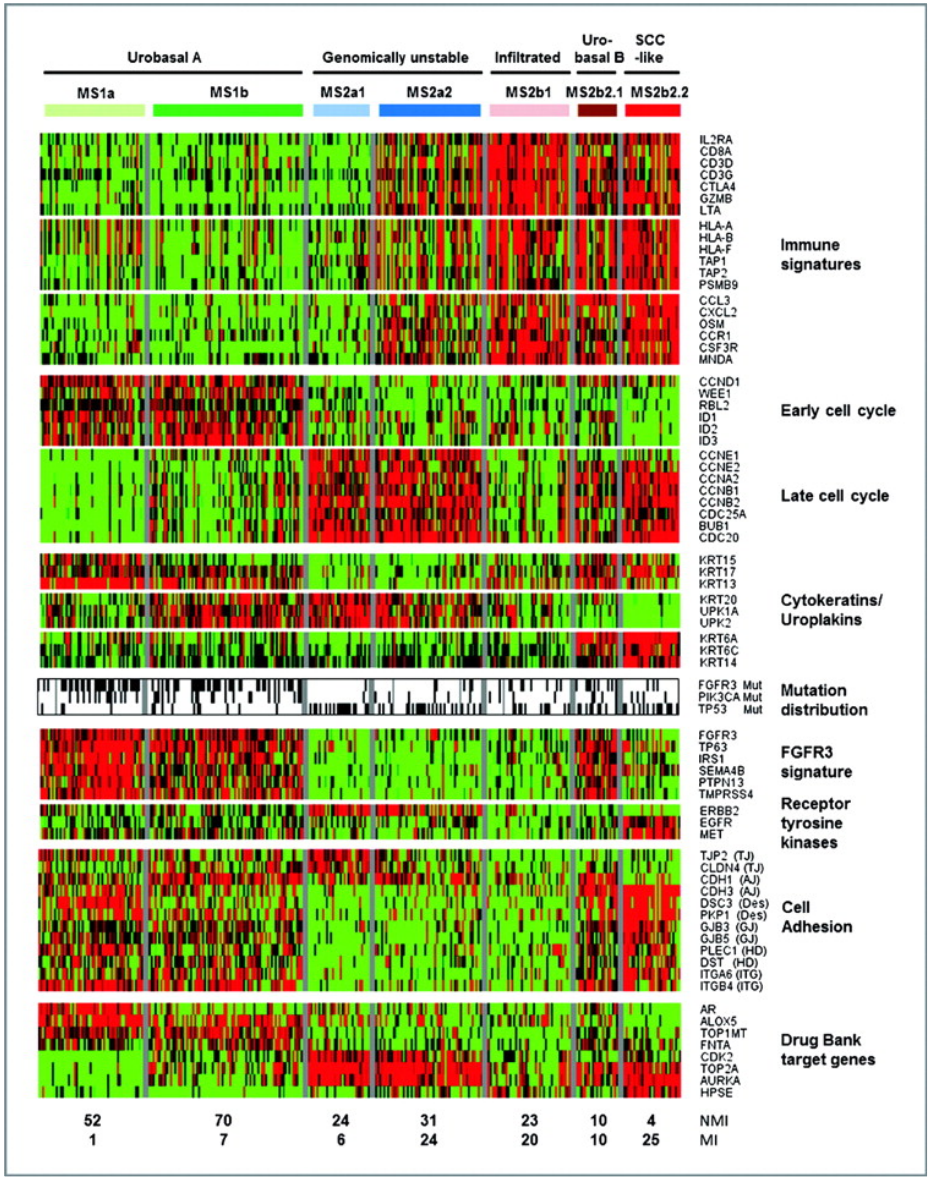
- Haematological -> widespread use of molecular features to select therapy
- Breast – HER2 (Herceptin)
- Lung – EML4-ALK fusion (Crizotinib); EGFR mutation (Erlotinib)
- Colorectal – KRAS/BRAF (contraindication of EGFR inhibitors)
- Melanoma – BRAF (Vemurafenib)

No targeted agents in regular use in bladder cancer despite identification of potential targets

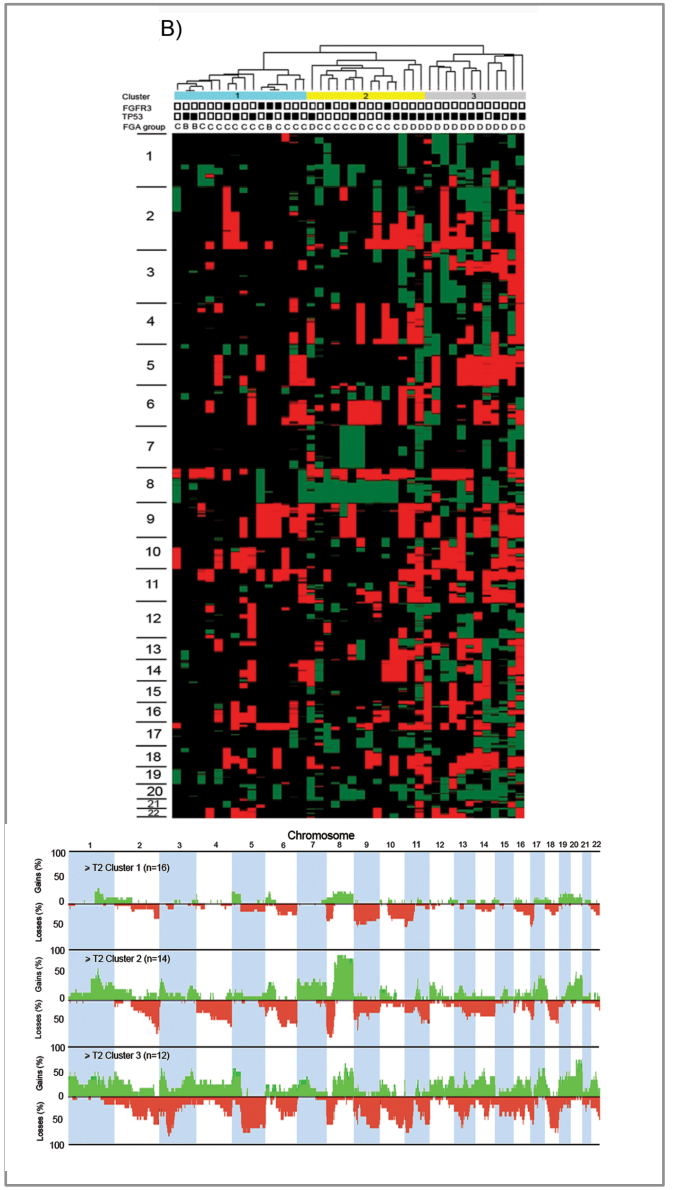
RAS- MAPK and PI3K pathway alterations



Barriers? Inter-tumour heterogeneity



Sjödahl G et al. Clin Cancer Res 2012;18:3377-3386

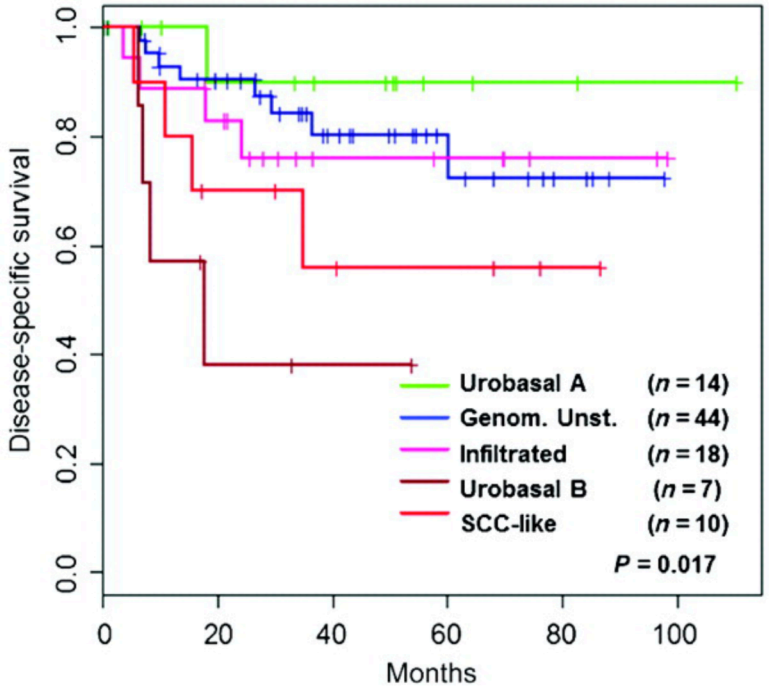


≥T2

Hurst C et al. Clin Cancer Res 2012;Epub 29th August

Molecular subtypes are clinically relevant

All grade 3 tumours

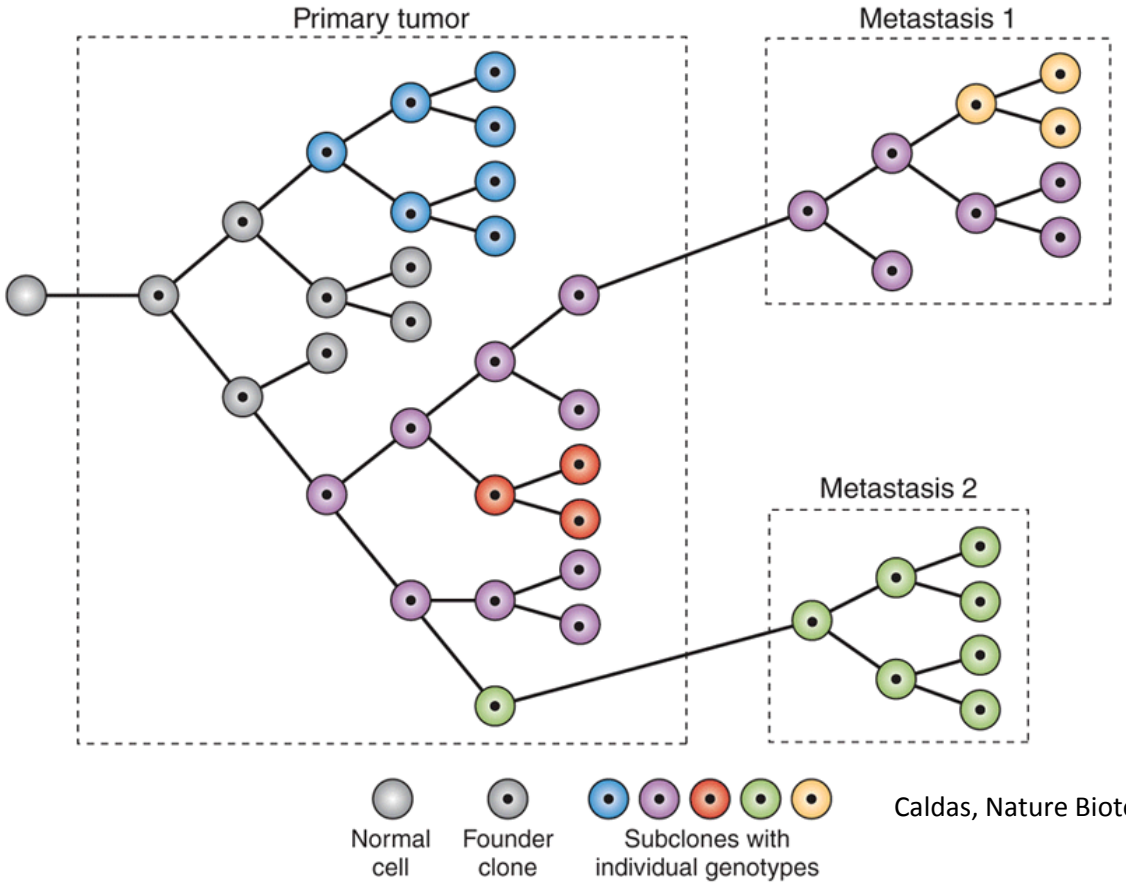


Sjödahl G et al. Clin Cancer Res 2012;18:3377-3386

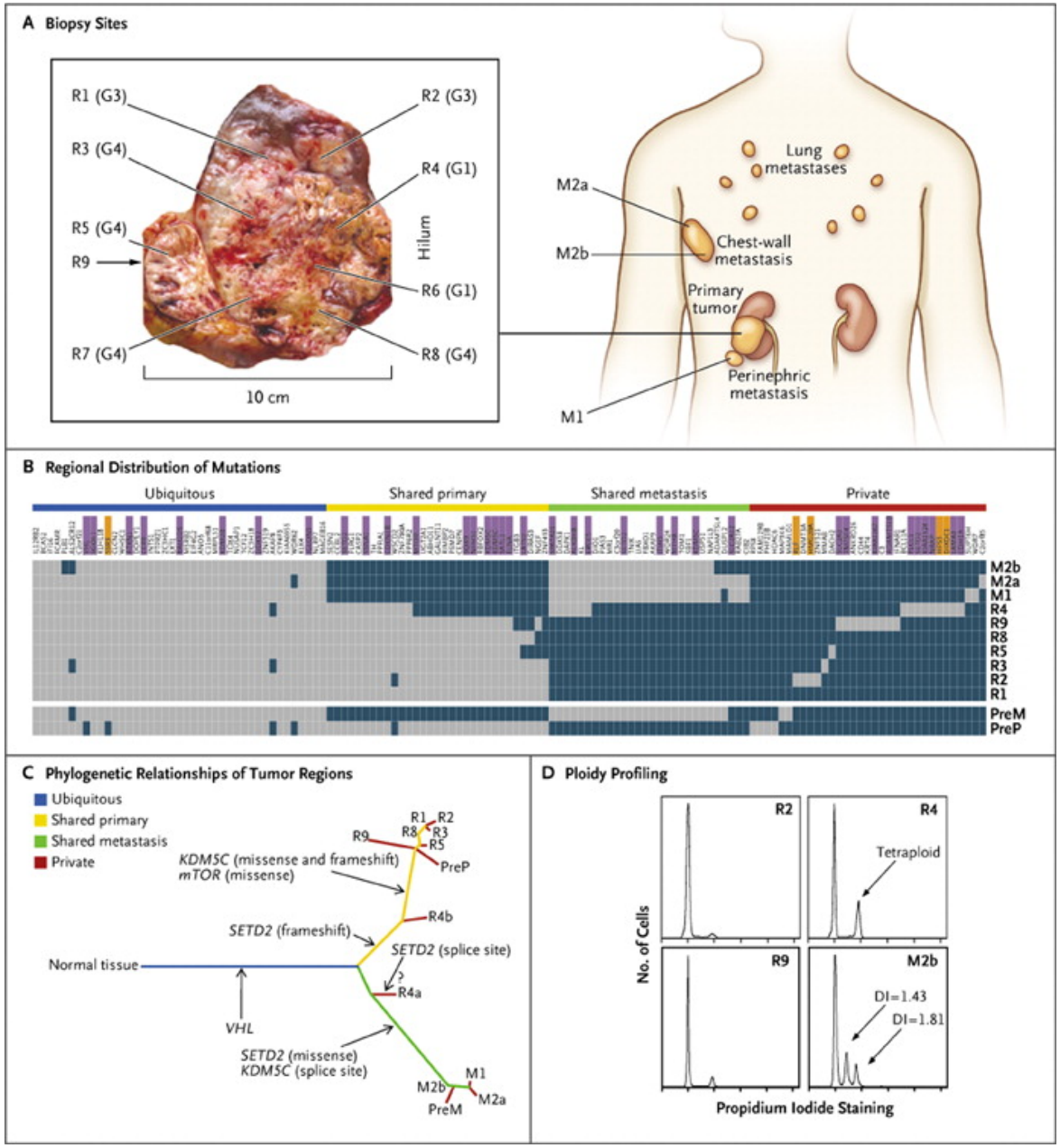
What are the "actionable" targets in the bad subgroups?

Barriers? Intra-tumour heterogeneity

Branching clonal architecture



Caldas, Nature Biotechnology 30, 408–410 (2012)



Gerlinger M et al. N Engl J Med 2012;366:883-892.

Future studies?

1. Definition of "actionable" molecular features

In the worst prognosis molecular subgroups

In rare tumour subclones

2. Well-designed biomarker studies –following REMARK guidelines

- Validation of molecular subtypes in larger independent series
- Relationship to clinical features?
- Assay development - suitable for clinical application

3. Clinical trials

- Testing novel agents in neoadjuvant setting?

Are we generating abstracts or answers in TCC?

A fair amount of both?

With more care to define relevant questions -> will do better?

More funding -> more abstracts -> more answers !