Predicting Response to Immunotherapy in Bladder Cancer

Ashish M. Kamat, MD, MBBS, FACS

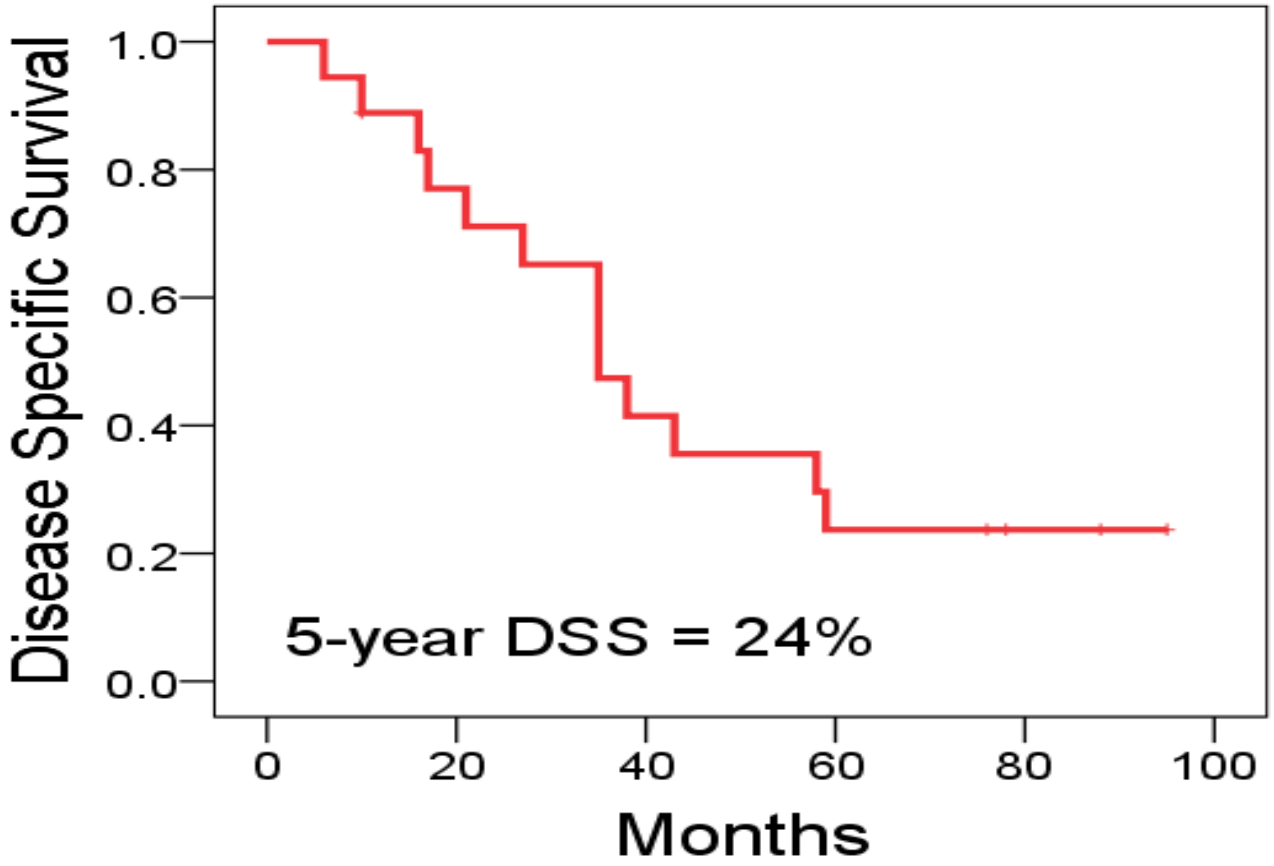
Professor of Urologic Oncology
Wayne B. Duddlesten Professor of Cancer Research
President, International Bladder Cancer Group (IBCG)
Associate Cancer Center Director, RFHNH, Mumbai

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Immunotherapy: The story of BCG

- BCG most effective therapy for NMIBC
  - Reduces recurrence, progression; prevents deaths
- However, ~30% patients fail BCG therapy
  - In non-responders, disease often progresses before curative cystectomy - decreased survival
- If we can identify non responders early, offer alternate therapy at earlier time point

Progression after BCG = Decreased Survival



- Micropapillary Bladder Cancer
- Median time to progression: 8 mo.
- Median survival: 35 mo.
- 5 yr DSS = 24%
  - 56% radical cystectomy
  - 50% primary chemotherapy

Willis, … Kamat et al, J Urol, 2015

Predicting Response to BCG

Available Now (March 2018)

1. Gender, Grade and Stage of Tumor, +/- CIS
2. Depth of Lamina Propria Invasion (T1 ab, T1 me)
3. Variant Histology
4. reTUR data
5. Prior Intravesical Therapy
6. FISH patterns

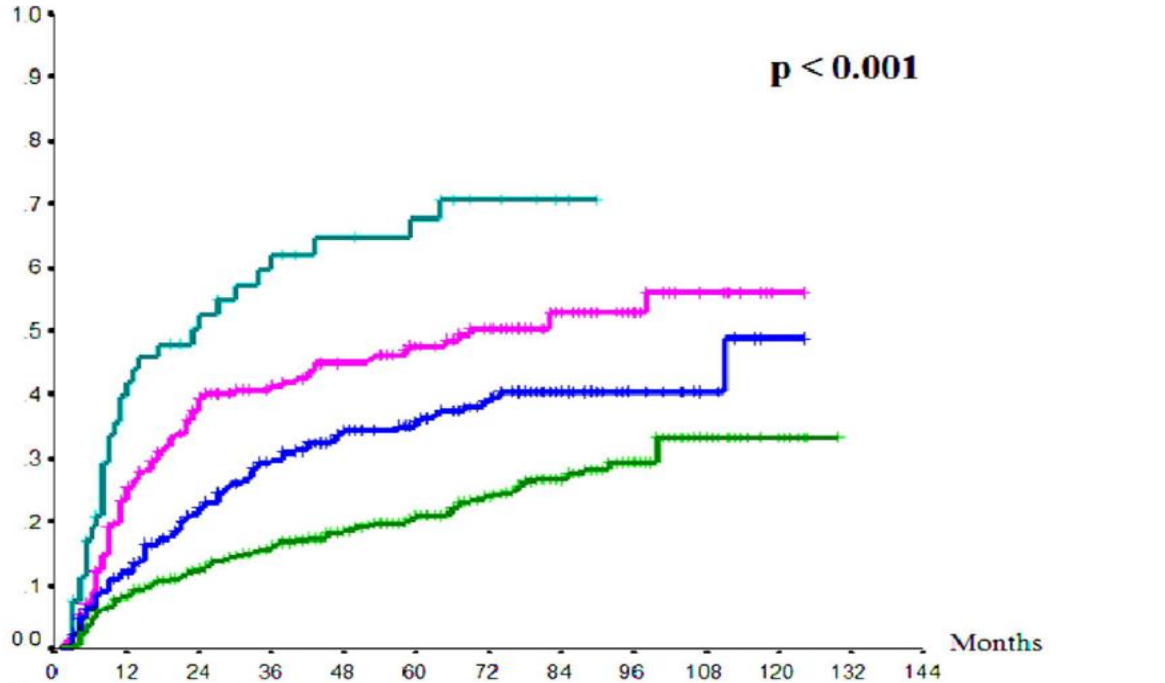
CUETO Score

BCG Response Prediction

1062 patients treated with BCG in four CUETO trials

Recurrence: gender, age, grade, tumor status, multiplicity, Tis.

Progression: age, grade, tumor status, T category, multiplicity , Tis.

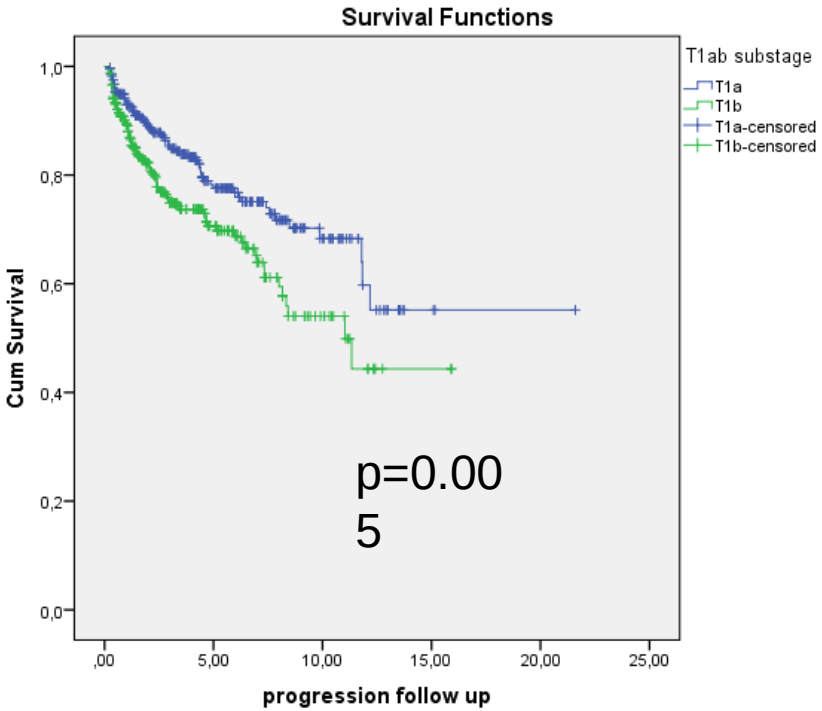


O	N
124	541
87	246
102	221
33	54

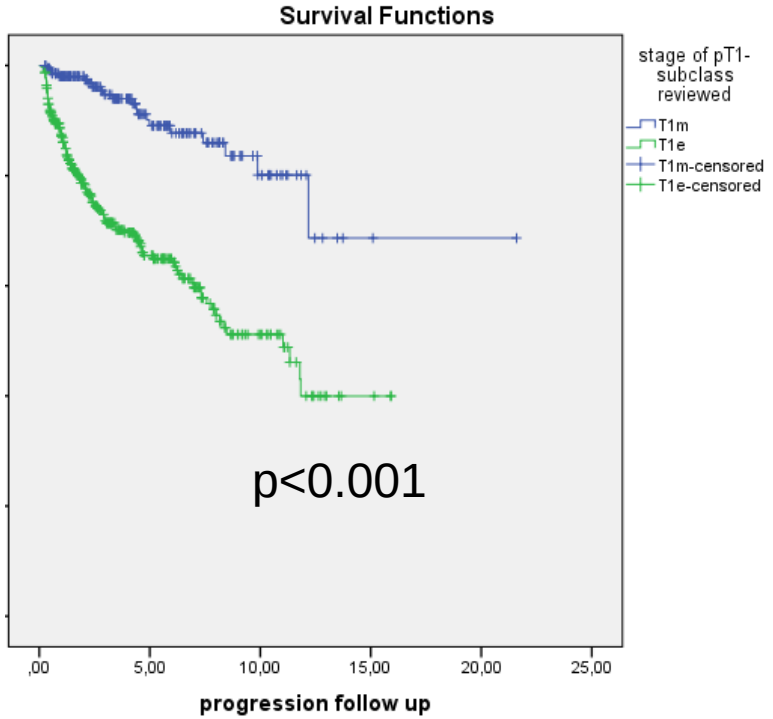
Fernandez-Gomez J, et al J. Urol, 2009

T1 HG disease: Sub-stage & Progression

T1 a/b



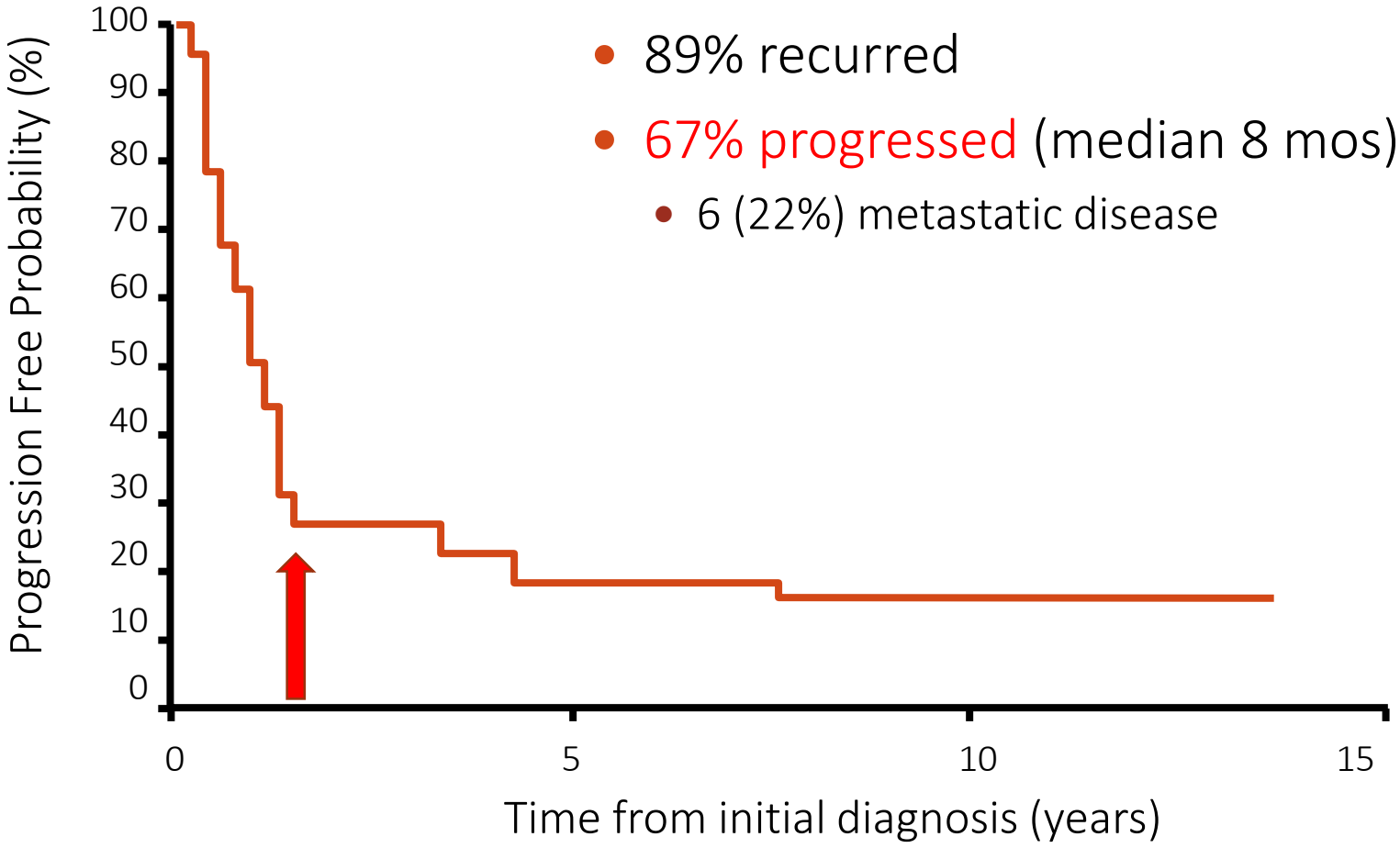
T1 m/e



Slide: Bas Van Rhijn

Variant Histology

Micropapillary T1HG Progresses with Intravesical BCG

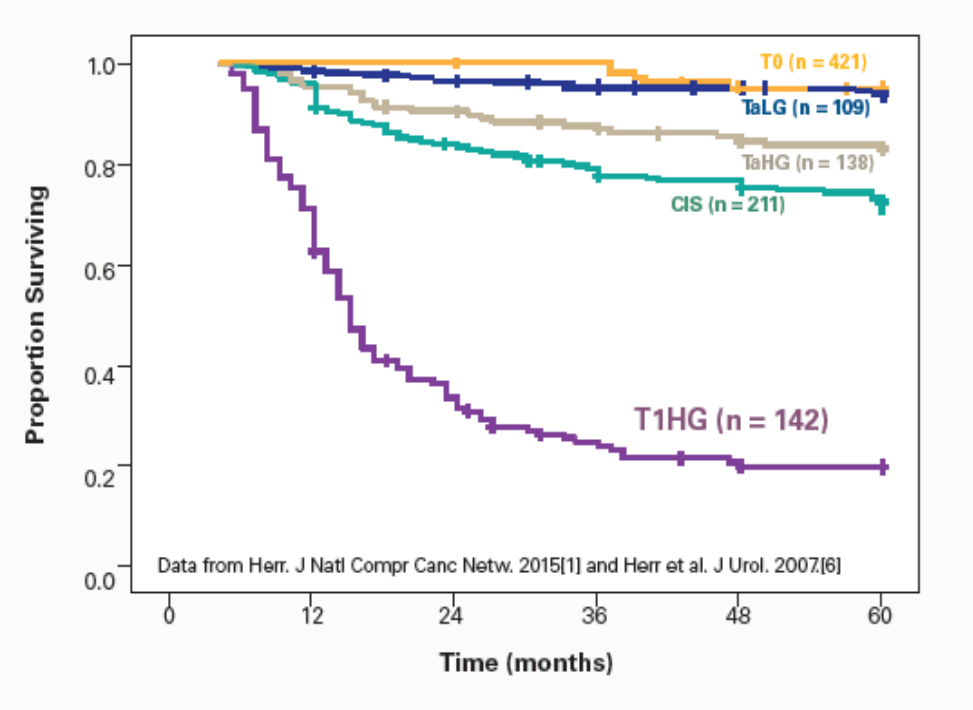


- 89% recurred
- 67% progressed (median 8 mos)
  - 6 (22%) metastatic disease

Kamat et al, J Urol, 2006; Kamat et al Cancer, 2007; updated Willis et al, 2015

T1 on reTUR predicts response to BCG

- T1 HG patients
- 5 yr progression
  - =T1 on re-TUR: **82%**
  - <T1 on re-TUR: 19%

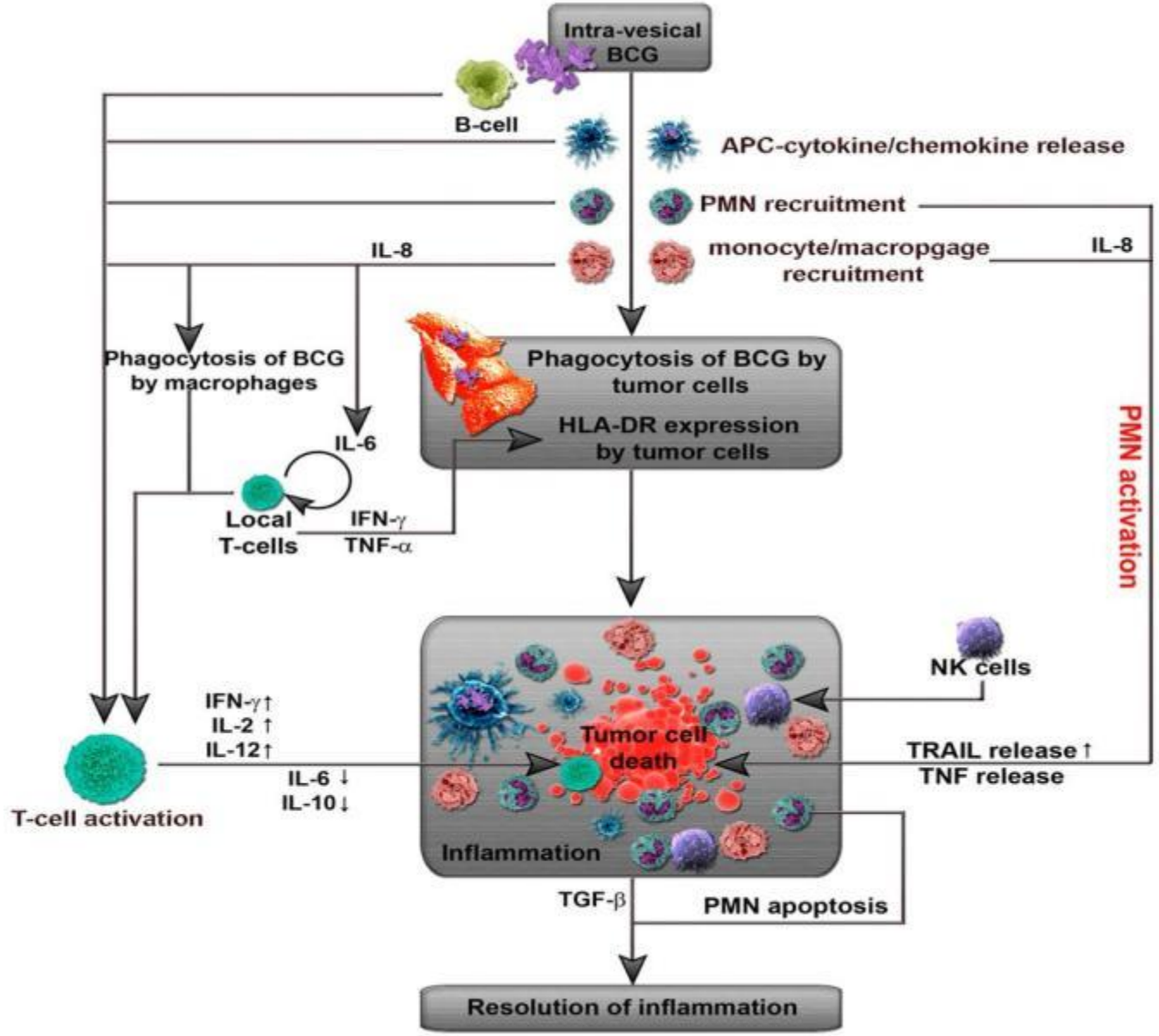


Herr et al, JNCCN, 2015
Herr J Urol, 2007

Tumor Biomarkers

- Tumor P53
  - Correlated: Saint, 2004; Lopez-Beltran, 2004; Palou, 2009
  - Not correlated: Lebret , 1998; Zlotta, 1999; Peyromaure , 2002; Esuvaranathan, 2007

- Same problem with Ki-67, Rb ….



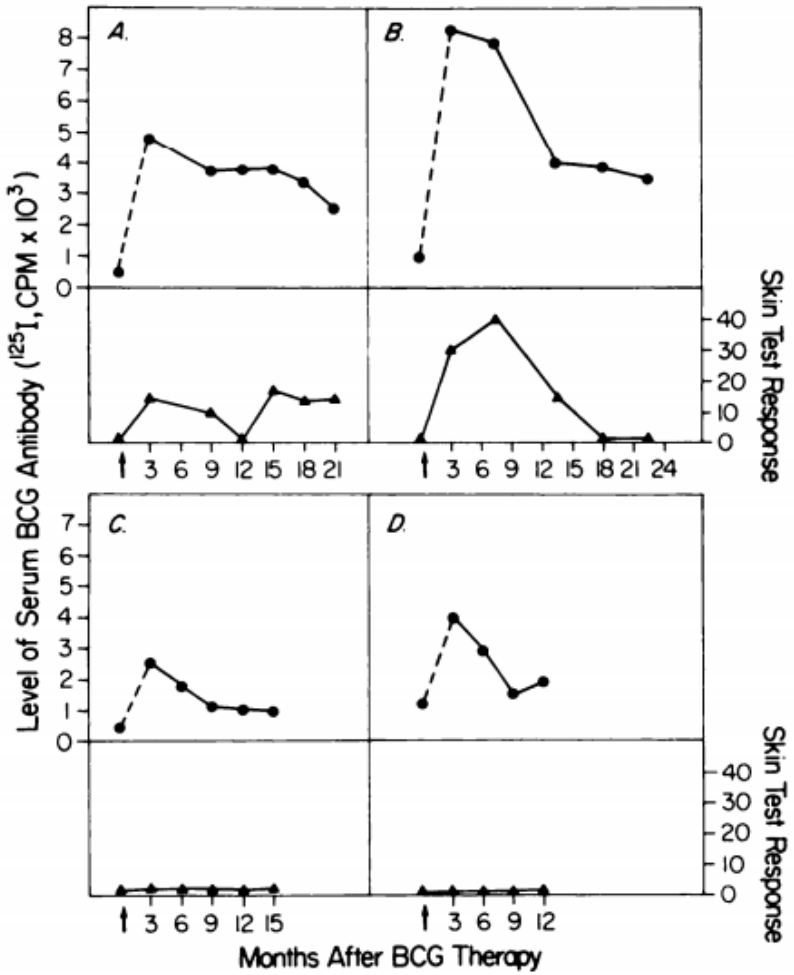
Jinesh G & Kamat A, Oncoimmunology, 2012

[CANCER RESEARCH 41, 2672–2676, July 1981]
0008-5472/81/0041-0000$02.00

Antibody Responses to *Bacillus Calmette-Guérin* during Immunotherapy in Bladder Cancer Patients[1]

Wendell D. Winters[2] and Donald L. Lamm

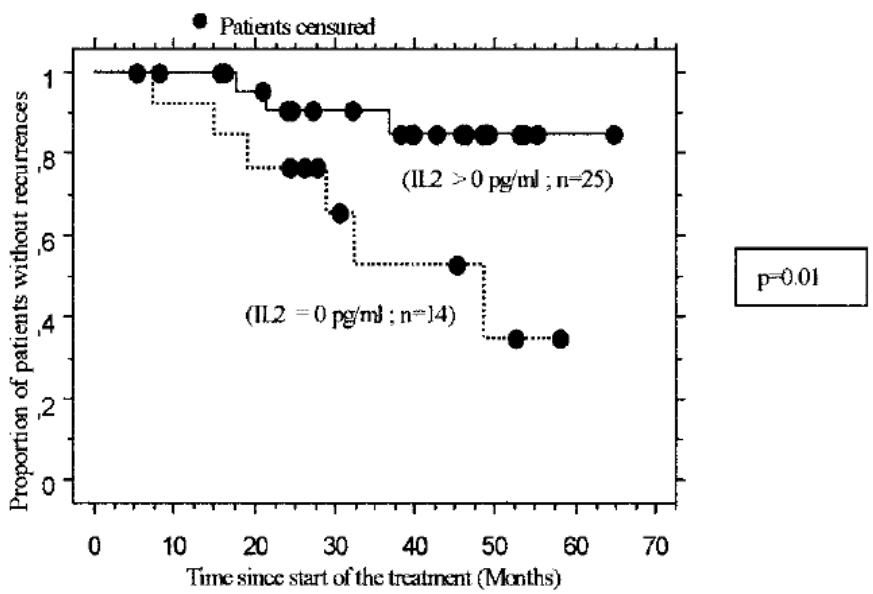
Departments of Microbiology [W.D.W.] and Urology [D.L.L.], University of Texas Health Science Center, San Antonio, Texas 78284



Published in 1981

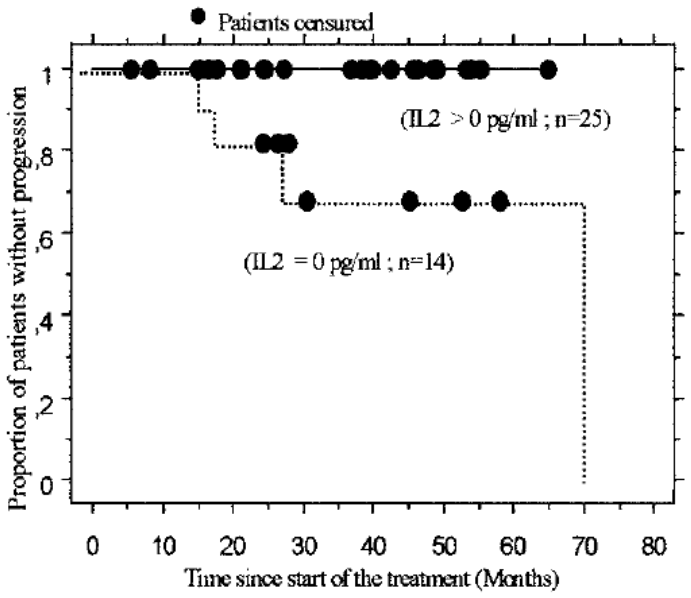
Cytokines (eg IL-2) and BCG response

Recurrence after 6+3



p=0.01

Progression after 6+3



p=0.01

Saint et al, Int J Cancer 107:434, 2003

Prospective Trial: Markers of Response to Intravesical BCG

Hypotheses

- Comprehensive Panel of Cytokine response to BCG will differentiate responders from non-responders
- Innate intricacies of the immune response

- Cytogenetically abnormal cells: patterns will predict clinical tumor recurrence

PI: Kamat; NCT01007058

Cytokines and BCG Response

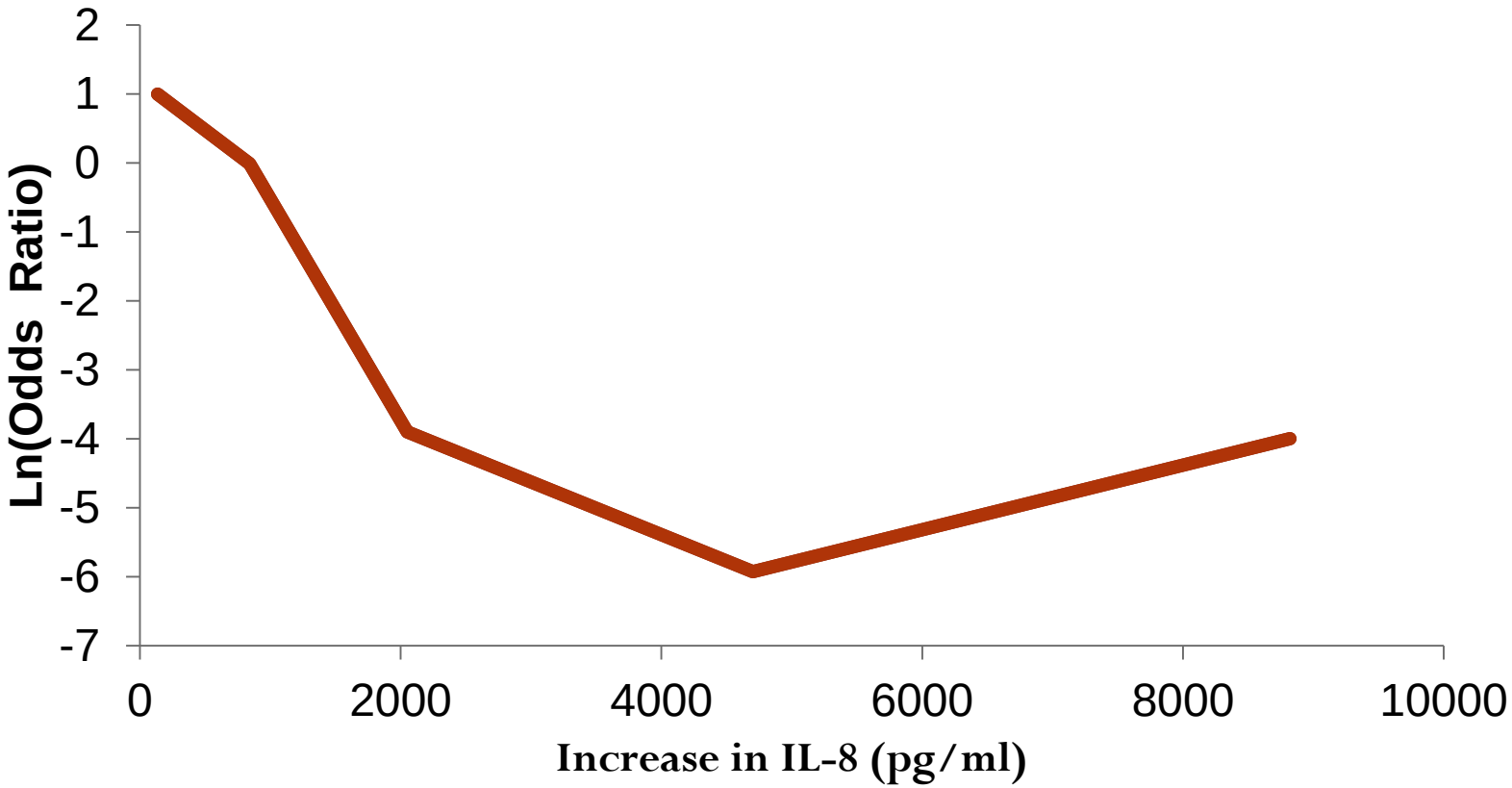
- Cytokine response to BCG does differentiate responders from non-responders
  - Responders have higher levels of BCG induced cytokines at BCG #6
  - Magnitude of induction of cytokines correlates with recurrence rate and time to recurrence
  - Complex interplay of cytokines

Proportional Hazards Model to Predict Time to Recurrence

Cytokine*	Coefficient	Hazard Ratio	P-Value	95% Confidence Interval
$I(\Delta_{IL\text{-}2} \geq 200)$	-1.90	0.15	0.0574	0.02 - 1.06
$I(\Delta_{IL\text{-}6} \geq 425)$	-2.39	0.09	0.0102	0.02 - 0.57
$I(\Delta_{IL\text{-}8} \geq 1500)$	-0.78	0.46	0.0805	0.19 - 1.10
$I(\Delta_{IL\text{-}18} \geq 40)$	-3.20	0.04	0.0030	0.01 - 0.34
IL-1r	0.0025	1.003	0.0005	1.001 - 1.004
TRAIL	0.0021	1.002	0.0055	1.001 - 1.004
IFN-γ	-0.0009	0.999	0.0384	0.998 – 1.000
IL-12(p70)	0.24	1.27	0.0003	1.12 - 1.45
TNF-α	0.006	1.01	0.0011	1.002 - 1.01

* Change from before to just after 6th instillation of BCG

Risk function for ΔIL-8 with 6th BCG



Risk Assessment Calculator to Predict Recurrence

- $\eta = 0.2267 - 2.8594 * I(\Delta IL\text{-}2 \geq 200) - 4.6366 * I(\Delta IL\text{-}6 \geq 425) - 1.0933 * I(\Delta IL\text{-}8 \geq 1500) - 5.4155 * I(\Delta IL\text{-}18 \geq 40) + 0.00428 * \Delta IL\text{-}1r + 0.00459 * \Delta TRAIL - 0.00235 * \Delta INF\text{-}\gamma + 0.4328 * \Delta IL\text{-}12(p70) + 0.0123 * \Delta TNF\text{-}\alpha$

- Cutpoint: Predict recurrence if $\eta \geq -0.1527$

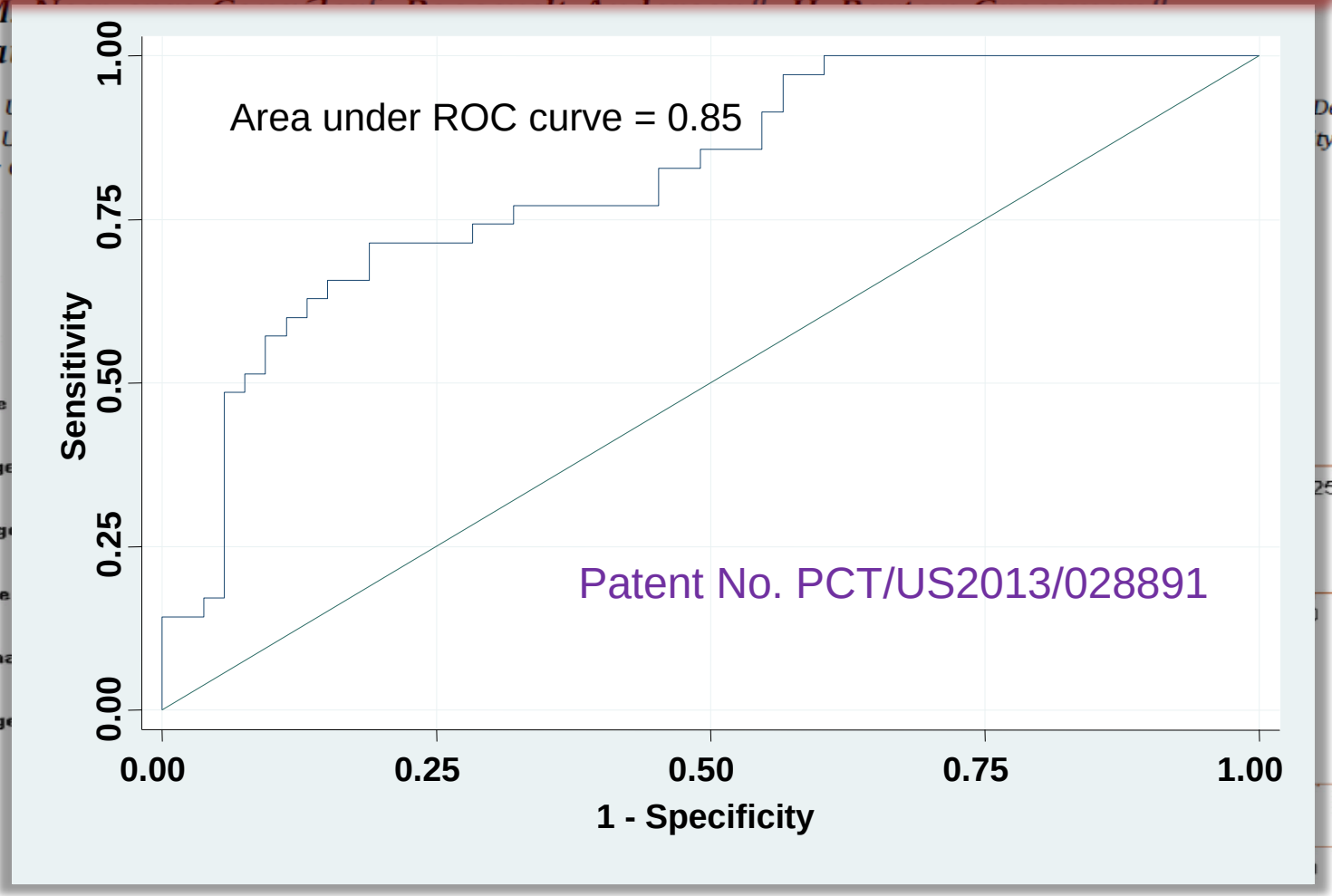
Cytokine Panel for Response to Intravesical Therapy (CyPRIT): Nomogram of Changes in Urinary Cytokine Levels Predicts Patient Respon

Ashish M.
Graciela M
Ferran Pra

[a]*Department of*
Biostatistics, The U
Anderson Cancer

Department of
ty of Texas MD

CyPRIT Assay



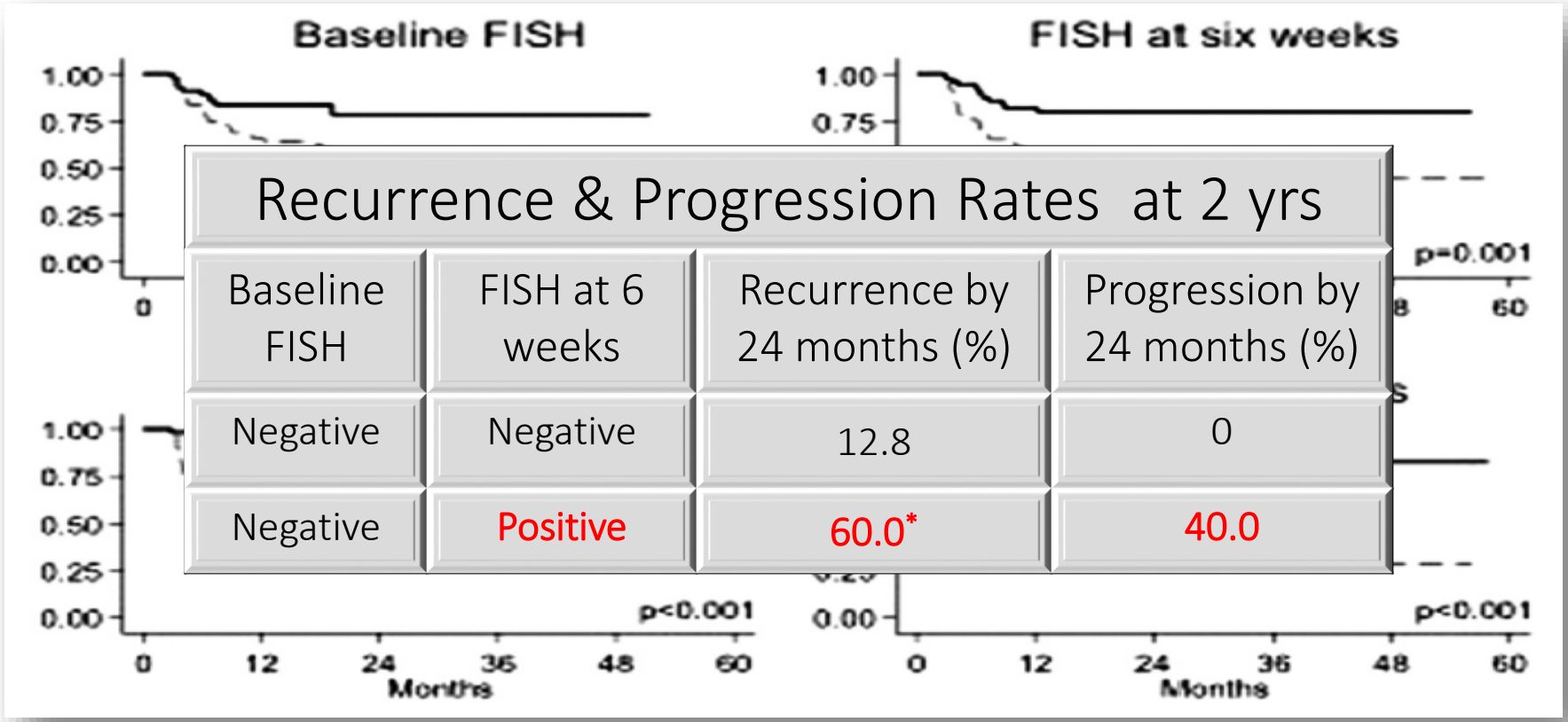
IL-2 pg/ml Change
IL-6 pg/ml Change
IL-8 pg/ml Change
IL-18 pg/ml Change
IL-1ra pg/ml Change
TRAIL pg/ml Change
IFN-γ pg/ml Change
IL-12(p70) pg/ml Cha
TNF-a pg/ml Change
Total points
Linear predictor
Probability of recurrence

2500 3000
-1000
220 240
2 4 6
0.01 0.1 0.5 0.95

Kamat et al, Eur Urol, 2015

Use of Fluorescence In Situ Hybridization to Predict Response to Bacillus Calmette-Guérin Therapy for Bladder Cancer: Results of a Prospective Trial

Ashish M. Kamat,*,† Rian J. Dickstein,‡ Fabrizio Messetti,‡ Roosevelt Anderson,‡ Shanna M. Pretzsch,‡ Graciela Noguera Gonzalez,‡ Ruth L. Katz,§ Abha Khanna,‡ Tanweer Zaidi,‡ Xifeng Wu,‡ H. Barton Grossman‖ and Colin P. Dinney¶



Recurrence & Progression Rates at 2 yrs

Baseline FISH	FISH at 6 weeks	Recurrence by 24 months (%)	Progression by 24 months (%)
Negative	Negative	12.8	0
Negative	Positive	60.0*	40.0

0022-5347/12/1873-0862/0
THE JOURNAL OF UROLOGY®

Vol. 187, 862-867, March 2012
Printed in U.S.A.
DOI:10.1016/j.juro.2011.10.144

CNN Health » Diet + Fitness | Living Well | Parenting + Family Live TV

Can your own immune system kill cancer?

REUTERS U.S. FDA approves Roche's immunotherapy for bladder cancer

HEALTH NEWS | Wed May 18, 2016 | 4:53pm EDT

U.S. FDA approves Roche's immunotherapy for bladder cancer

Business Markets World Politics

HEALTH NEWS | Thu Feb 2, 2017 | 8:18pm EST

Nivolumab Gets FDA Appr
Carcinoma

FDA Grants Atezolizumab Accelerated Approval as Initial Treatment for Some Advanced Bladder Cancers

By The ASCO Post
Posted: 4/18/2017 2:12:
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On April 17, the U.S.
(Tecentriq) for the t
not eligible for cispl

REUTERS AstraZeneca immunotherapy wins first approval in bladder cancer

HEALTH NEWS | Tue May 2, 2017 | 9:56am EDT

AstraZeneca immunotherapy wins first approval in bladder cancer

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HEALTH NEWS | Tue May 9, 2017 | 5:10pm EDT

Pfizer immuno-oncology drug wins U.S. approval for bladder cancer

REUTERS Roche's star cancer drug stumbles in study, raising doubts about future

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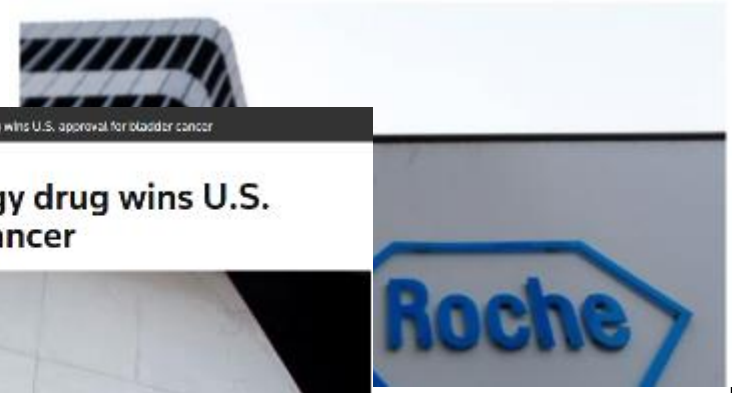
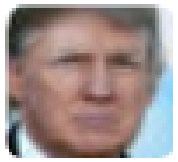
Roche's star cancer drug stumbles in study, raising doubts about future





Donald J. Trump

@realDonaldTrump

Checkpoint blockade is YUGE; urologists use immunotherapy in bladder cancer for 1st time EVER. #AUA17

RETWEETS	LIKES
3,264	10,726

12:31 PM - 06 May 2017

353 3K 11K

FAKE NEWS!

Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

- PD-L1 Status
- Molecular Subtyping (TCGA, MDACC, etc.)
- Tumor Mutational Burden
- Immune Gene Expression Profiling

Aggen DH, Drake, CG. *J Immunother Cancer. 2017.*

Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

- PD-L1 Status
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- Immune Gene Expression Profiling

PD-L1 as a Resistance Mechanism to BCG Therapy in NMIBC

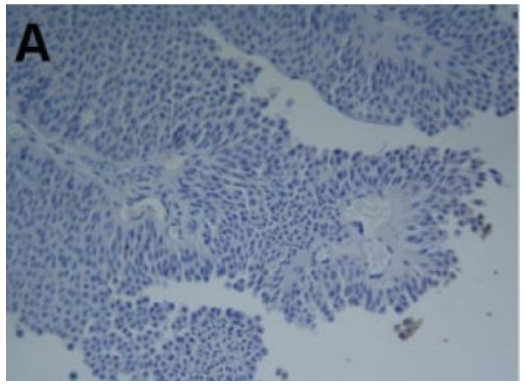


Figure A: PD-L1(-) NMIBC

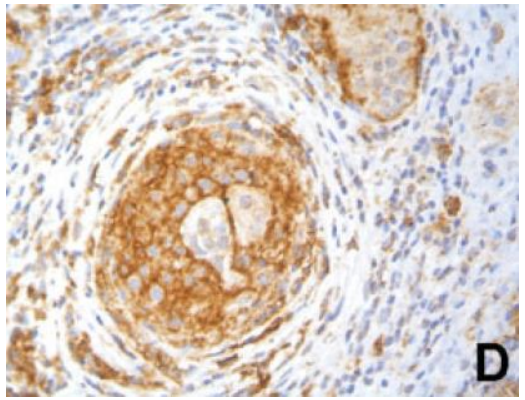
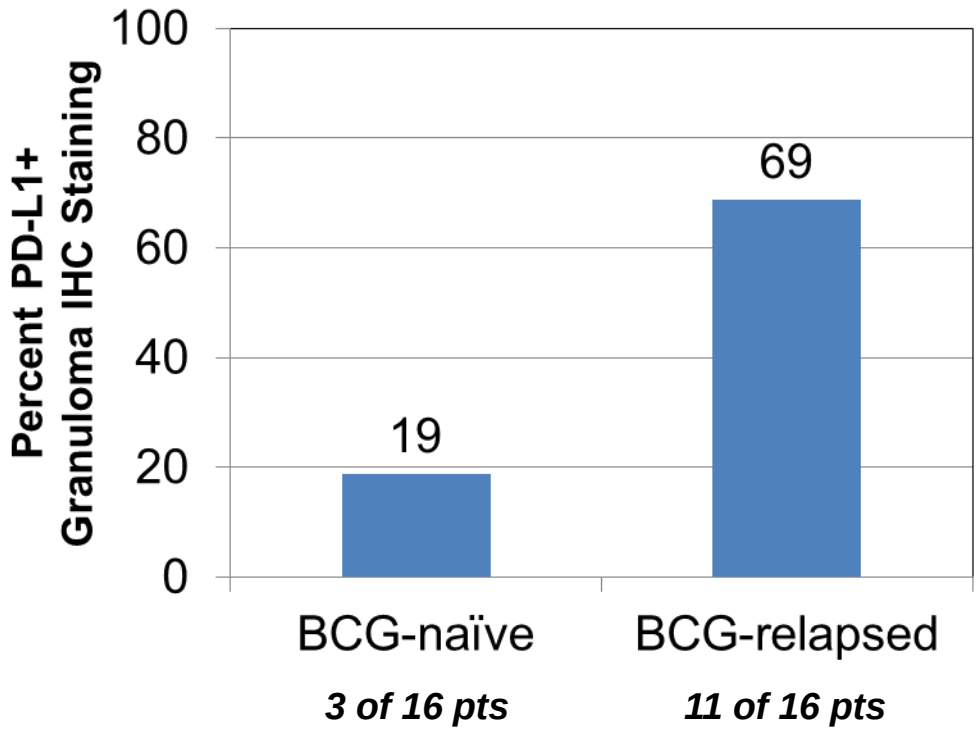
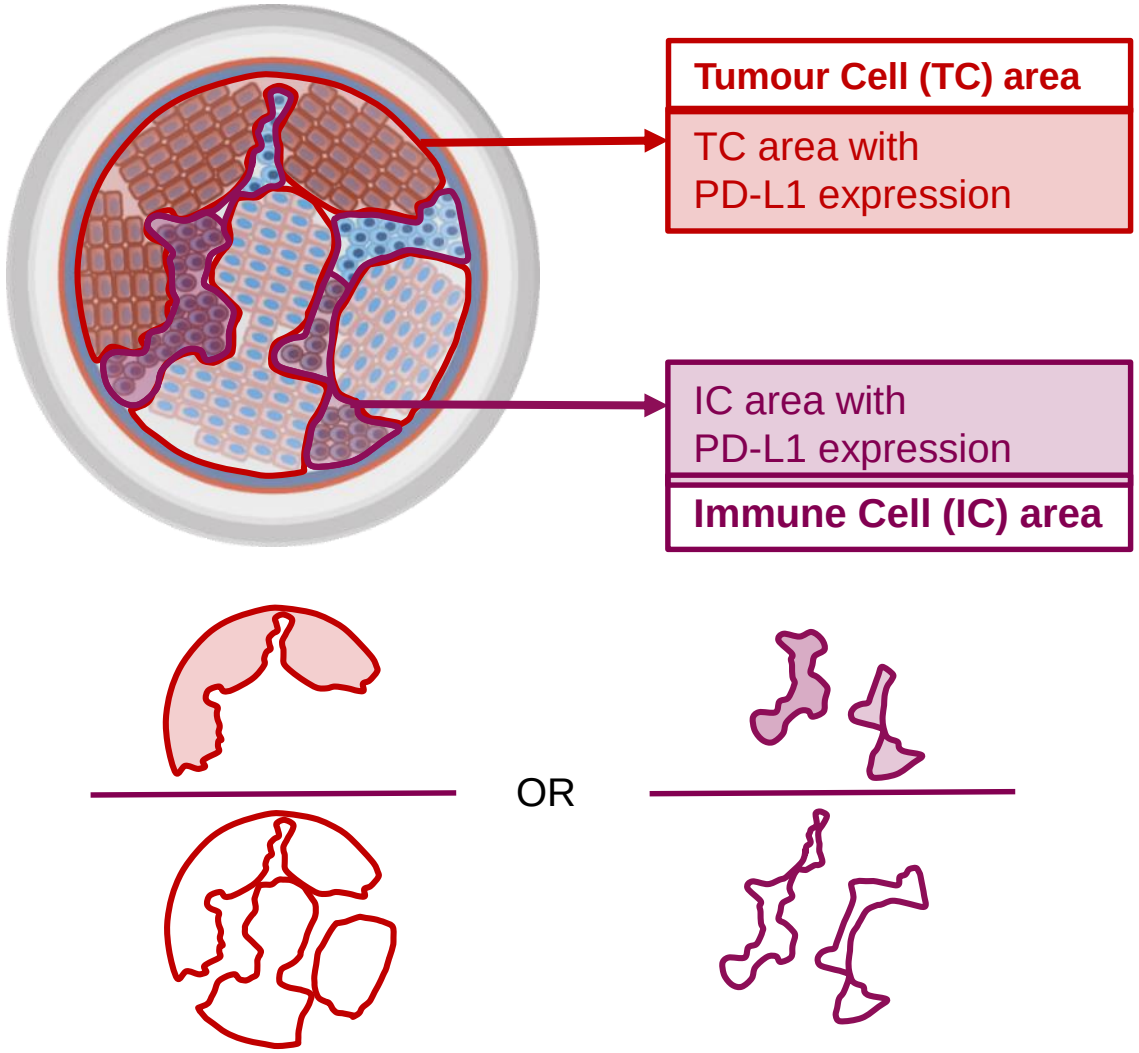


Figure B: PD-L1(+) NMIBC Post-BCG Treatment Granuloma



Inman et al, Cancer 2007

UC: SP263 uses tumour and immune cell scores

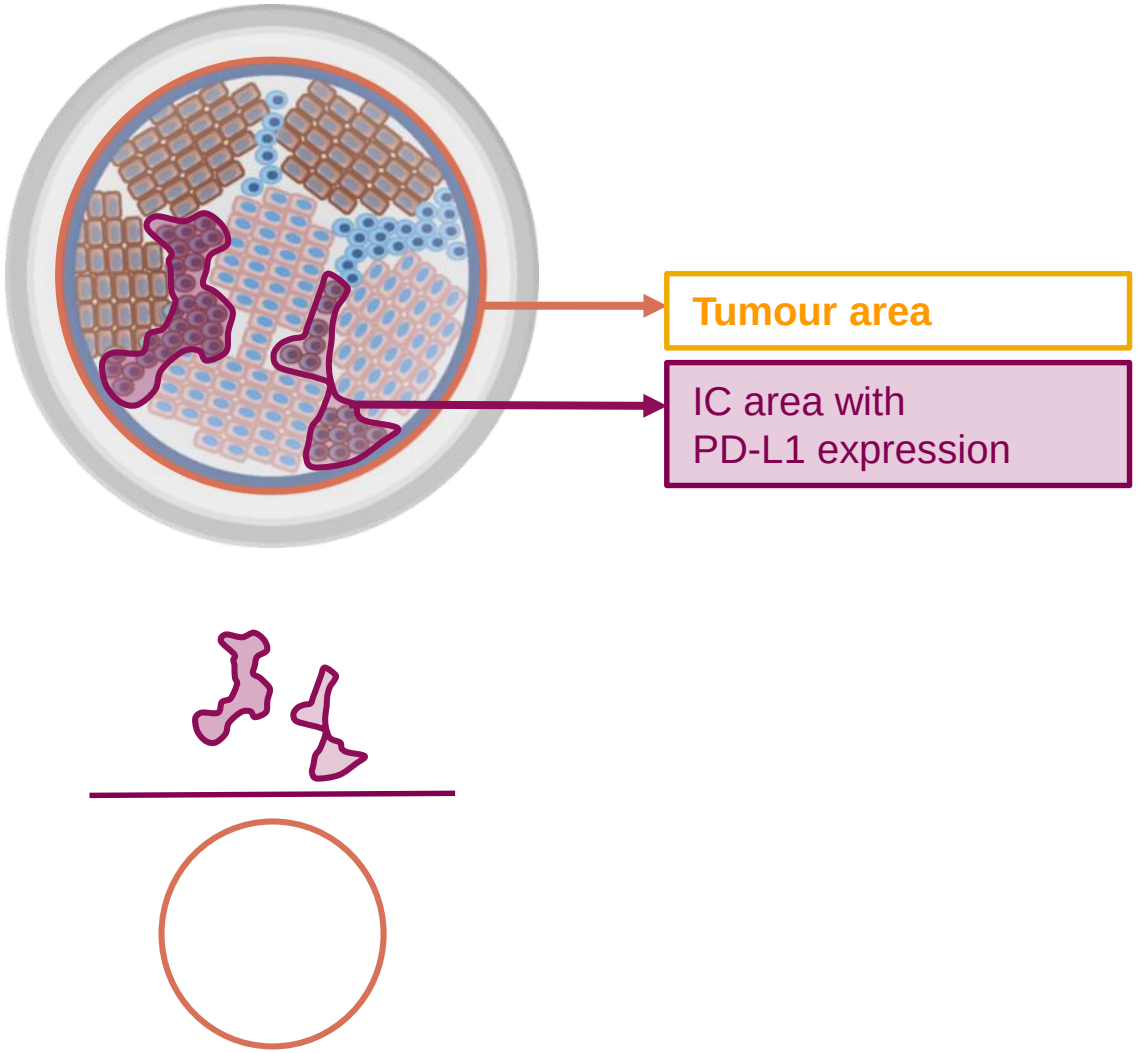


Definition
Tumour Cell: Proportion of tumour cells with membrane staining for PD-L1 at any intensity above background staining **Immune Cell:** Proportion of tumour associated immune cells with staining for PD-L1 at any intensity above background staining

Assay	Cut offs for PD-L1 High
SP263	TC ≥25% or IC ≥25%

Slide: Bellumunt, 2017

UC: SP142 uses immune cell score



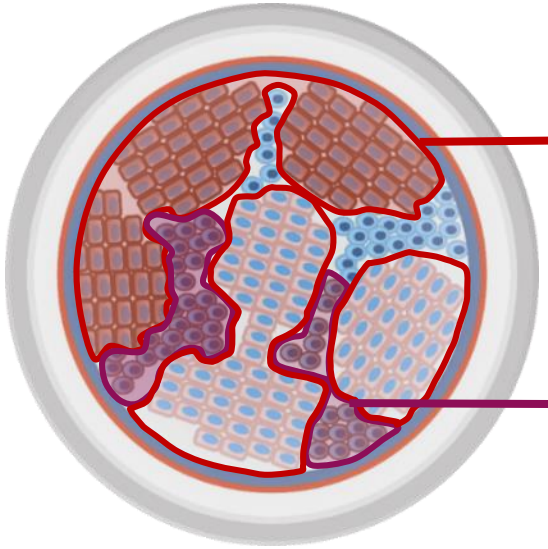
Definition

The proportion of tumour area occupied by PD-L1 expressing tumour-infiltrating immune cells of any intensity

Assay	Cut offs for PD-L1 High
SP142	≥5%

Slide: Bellumunt, 2017

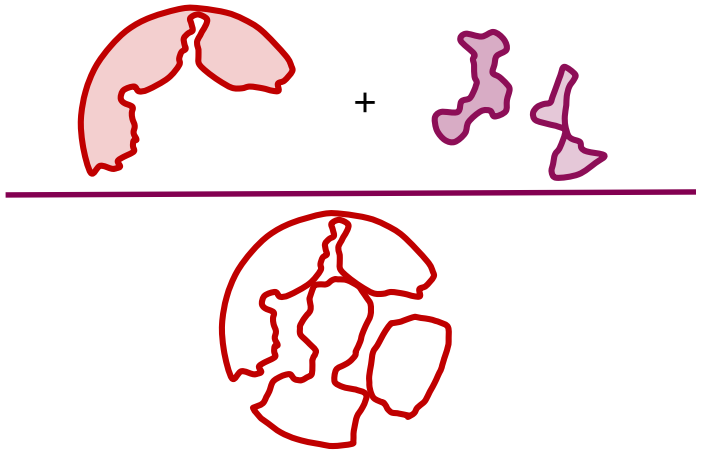
UC: 22C3 uses Combined Proportion Score (CPS)



tumour Cell (TC) area

TC area with
PD-L1 expression

IC area with
PD-L1 expression



Definition
The percentage of PD-L1 expressing tumour and infiltrating immune cells relative to the total number of immune cells.

Assay	Cut offs for PD-L1 High
22C3	≥10%

Slide: Bellumunt, 2017

PD-L1 Expression as a Predictor of Checkpoint Blockade Sensitivity in UC

Study	Agent	Companion IHC Antibody	Threshold for Positivity	Target Cells	Assay Associated with Response?
Powles T, et al. *Nature*. 2014.	Atezolizumab	"Proprietary"	5%	TILs	Yes
Rosenberg JE, et al. *Lancet*. 2016.	Atezolizumab	SP142	5%	TILs	Yes
Balar AV, et al. *Lancet*. 2017. (platinum ineligible)	Atezolizumab	SP142	5%	TILs	No
Massard C, et al. *J Clin Oncol*. 2016.	Durvalumab	SP263	25%	TILs & TCs	Yes
Sharma P, et al. *Lancet Oncol*. 2016.	Nivolumab	Dako 28-8	1%	TCs	No
Sharma P, et al. *Lancet Oncol*. 2017.	Nivolumab	Dako 28-8	1%	TCs	Yes
Plimack ER, et al. *Lancet Oncol*. 2017.	Pembrolizumab	22C3	1%	TILs & TCs	TILs only

Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

- PD-L1 Status
- Molecular Subtyping (TCGA, MDACC, etc.)
- Tumor Mutational Burden
- Immune Gene Expression Profiling

THE LANCET

Bladder cancer

Seminar

Ashish M Kamat, Noah M Hahn, Jason A Efstathiou, Seth P Lerner, Per-Uno Malmström, Woonyoung Choi, Charles C Guo, Yair Lotan, Wassim Kassouf

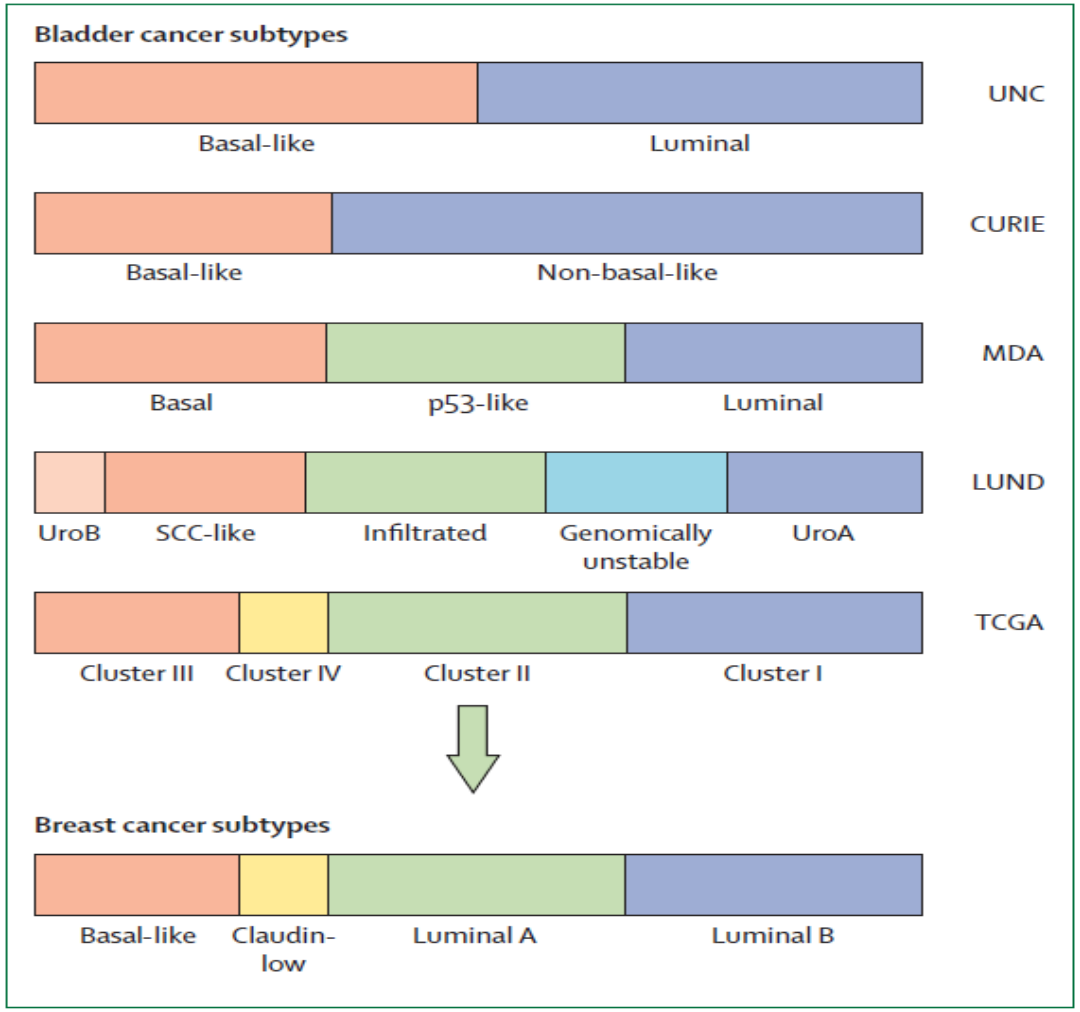
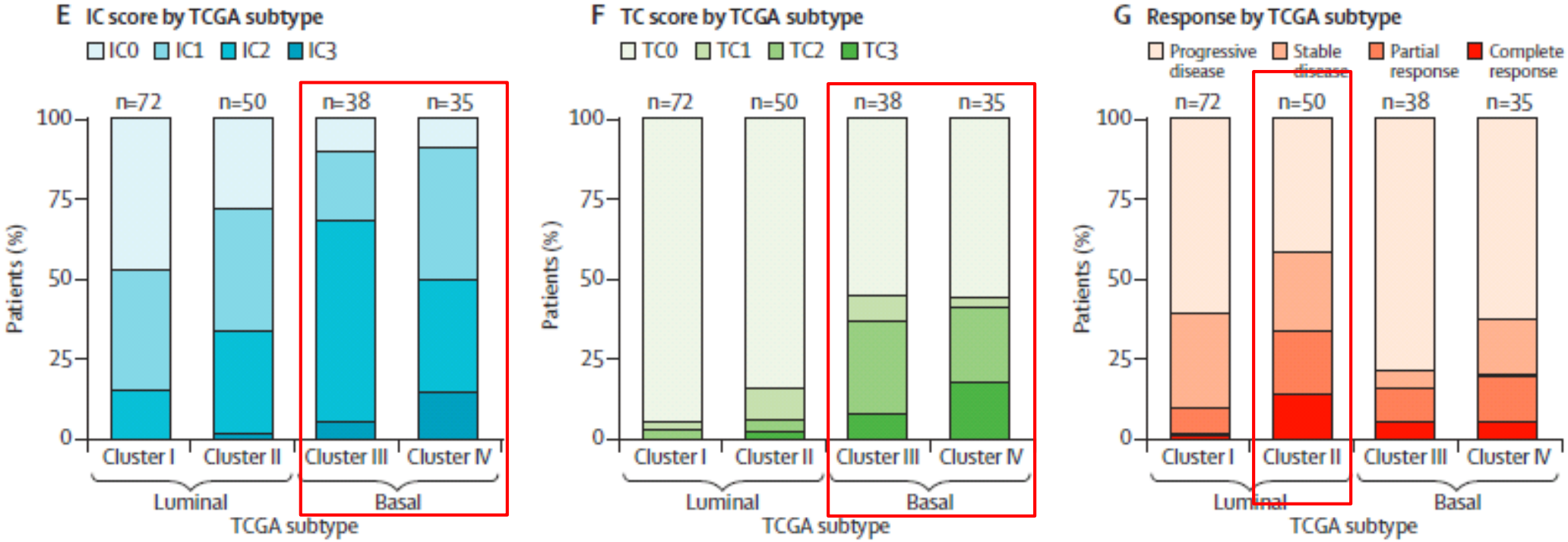


Figure 3: **Molecular subtype classification of bladder cancer and breast cancer**

Kamat et al, Lancet, June 2016

IMvigor 210 Trial: *Atezolizumab*

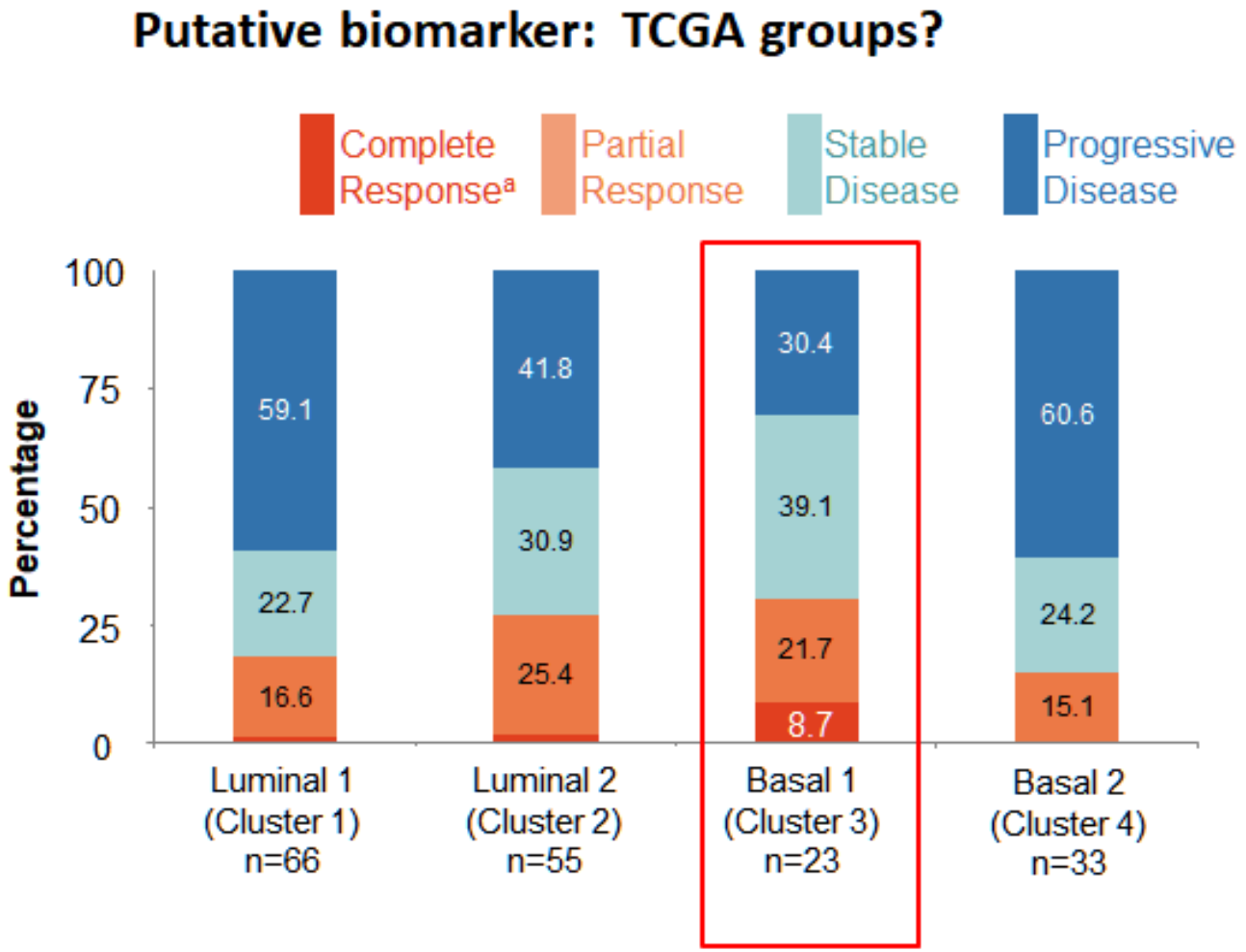


- Basal Clusters had highest prevalence of IC 2/3 PD-L1 (60% vs 23%) and TC 2/3 (39% vs 8%)
- Highest response in luminal cluster II subtype (ORR=34%, *P*=0.0017)
  - luminal cluster I, basal cluster I, and basal cluster II : ORR 10%, 16%, and 20%

Rosenberg JE, et al. *Lancet.* 2016

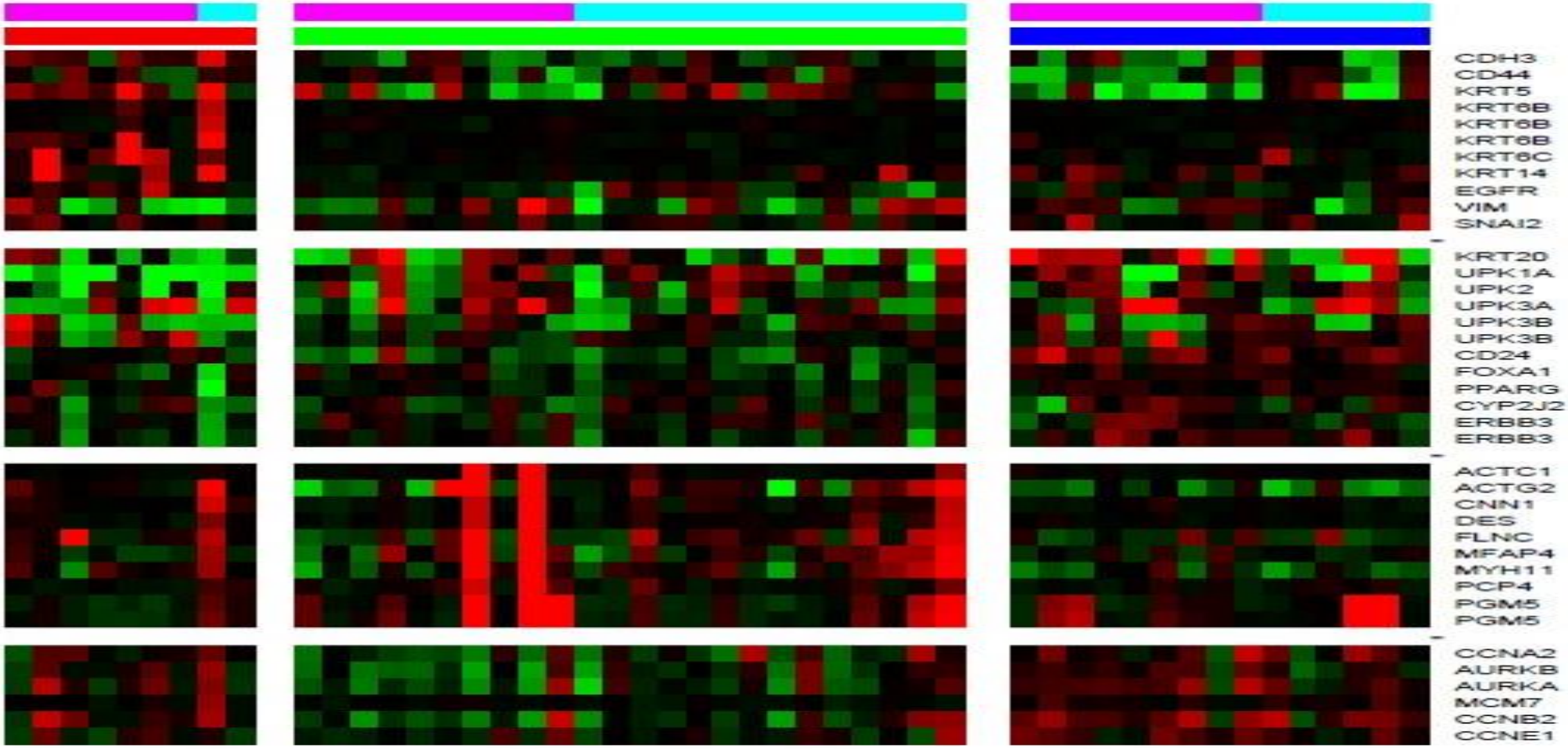
However…

- Phase II CheckMate 275 (nivolumab)
  - TCGA basal I subtype showed highest proportion of responders (7/23, ORR 30%).
  - Luminal cluster II tumors ORR: ~25%.
  - Interferon-γ genes enriched in responders vs those with progressive disease (*P*<0.01)



Slide: Courtesy of L Albiges; Sharma P, et al. *Lancet Oncol.* 2017.

Correlation of MDACC Subtypes with Response to BCG



MDACC Analysis of Chungbuk (Korean) cohort, Choi et al

Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

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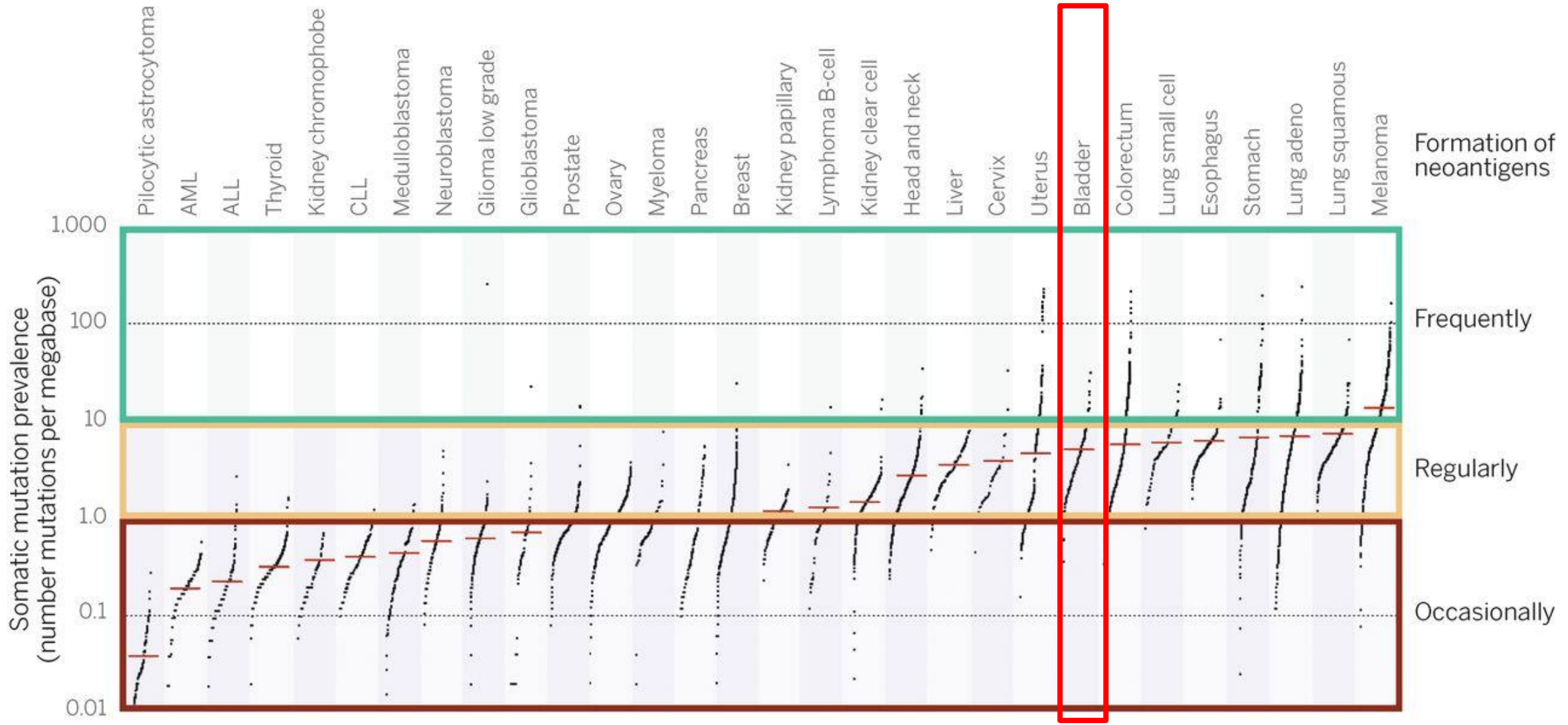
- Tumor Mutational Burden
- Immune Gene Expression Profiling

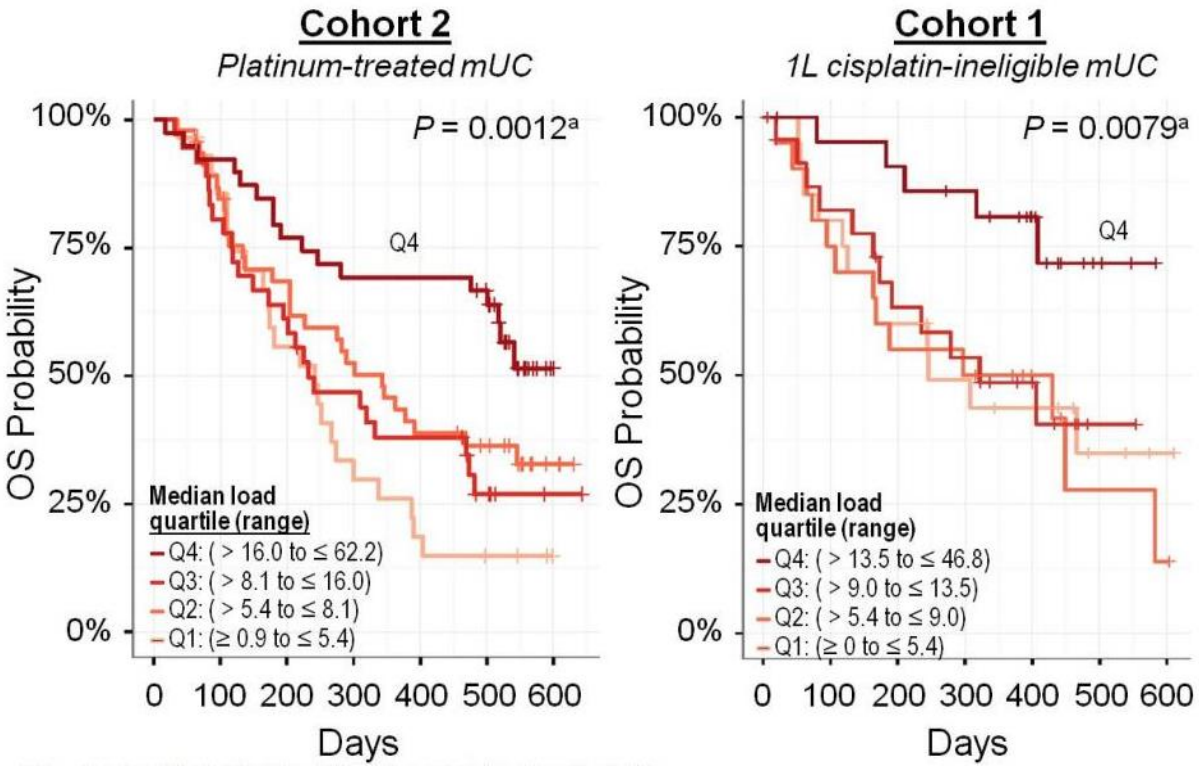
Tumor Mutational Burden/Neoantigen Burden



Schumacher TN, Schreiber RD. *Science.* 2015.

Tumor Mutational Burden/Neoantigen Burden

- IMvigor 210 Cohort II; 315 genes
  - Higher mutation load in responding vs non-responding patients (12.4 vs 6.4 per megabase, *p* <0.0001)
  - Smoking status and TCGA subtype did not correlate with mutational burden
- Cohort I of IMvigor 210
  - Improved OS in highest quartile of TMB (>16 to <62.2 mutations per MB) vs quartiles 1–3
  - Estimated survival probability 75% at 1 year



Improvement in OS independent of TCGA subtype; responses noted in all four subgroups

Patients in the lowest 3 quartiles similar; Top quartile with increased response rate and overall survival benefit; ? threshold effect

MB, mutational burden; TMB, tumor mutational burden.

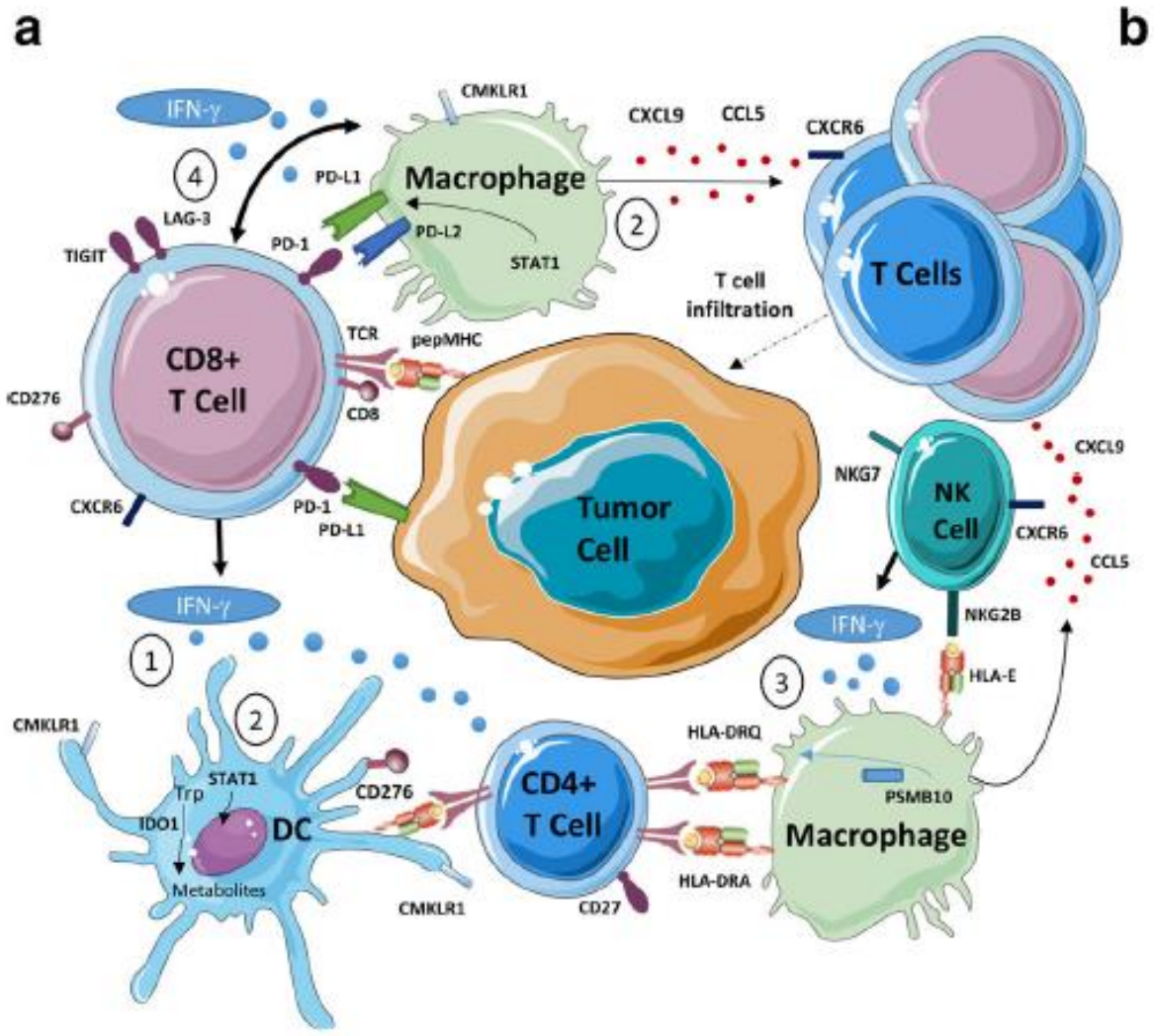
Balar AV, et al. *Lancet*. 2017.

Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

- PD-L1 Status
- Molecular Subtyping (TCGA, MDACC, etc.)
- Tumor Mutational Burden
- Immune Gene Expression Profiling

Multiparameter Immune Gene Expression Profiling

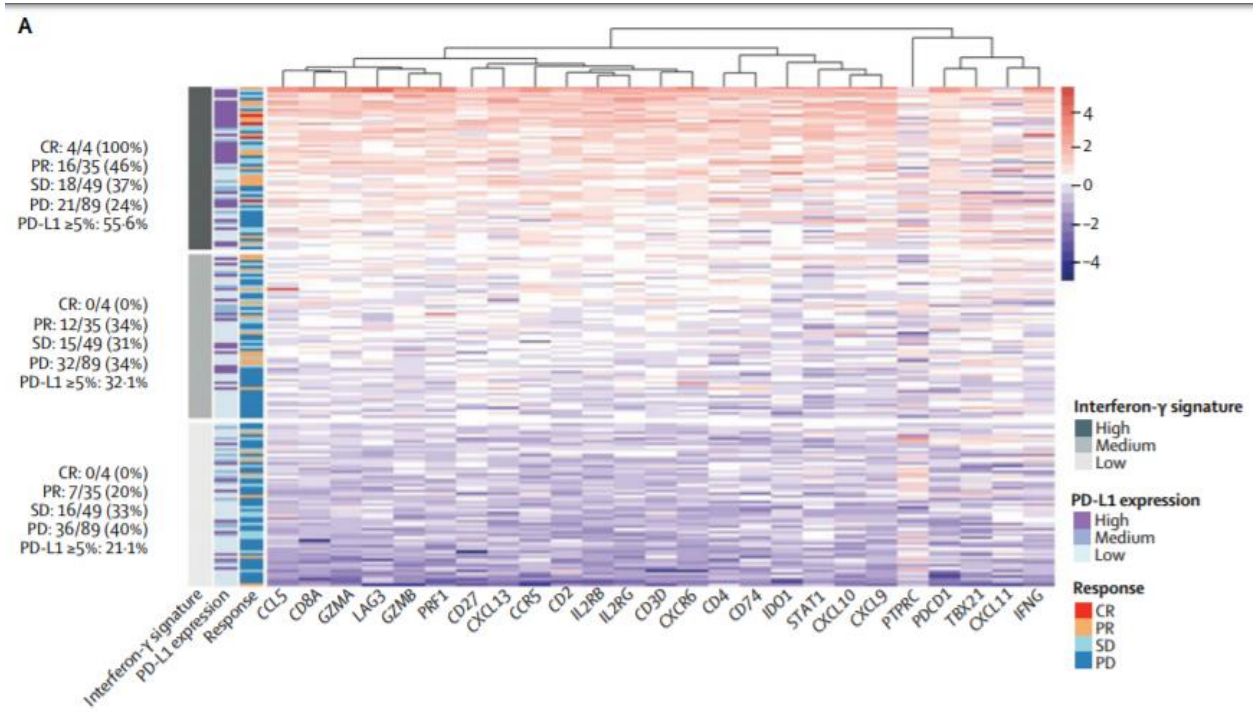
- RNA can be quantified from multiple cell types within a specimen
  - More fully representative of the tumor microenvironment
  - Accurately determine the inflammatory status of a tumor (“hot” tumors)



Aggen DH, Drake, CG. *J Immunother Cancer. 2017.*

Multiparameter Immune Gene Expression Profiling

- CheckMate 275: nivolumab in mUC
- 25-gene IFN-γ signature in 177 pretreatment samples
- IFN-γ gene signature correlated with response to nivolumab
  - High IFN-γ signature: CR or PR in 20/59 patients
  - Medium or low IFN-γ signature: CR or PR in 19/118 patients, p=0.0003



NPV problematic as some responses noted in non-inflamed cytokine signature

Sharma P et al, Lancet Oncology, 2017.

Proposed Prognostic Model for Advanced UC

405 pts receiving post-platinum atezolizumab in locally advanced or metastatic UC as frontline therapy or following progression occurring >12 mo after neo/adj chemo

6 prognostic factors:

- ECOG performance status (HR, 1.64; *P*=.002)
- Liver metastasis (HR, 1.45; *P*=.014)
- ↑ platelet count (HR, 1.73; *P*=.010)
- ↑ neutrophil-lymphocyte ratio (HR, 1.84; *P*<.001)
- ↑ lactate dehydrogenase level (HR, 1.54; *P*≤.001)
- Anemia (HR, 1.60; *P*=.004)

Not significant:

- PD-L1 status
- Site of primary/metastases
- Stage at diagnosis
- Smoking
- Number of prior therapies

Overall Survival	
0-1 factors	19.4-10.6 mo
2-3 factors	5.9-7.2 mo
4+ factors	2.6-2.8 mo

Pond GR, Niegisch G, Rosenberg JE, e bst 413).

Predicting Response to Intravesical Bacillus Calmette-Guérin Immunotherapy: Are We There Yet? A Systematic Review

Ashish M. Kamat [a,*], *Roger Li* [a], *Michael A. O'Donnell* [b], *Peter C. Black* [c], *Morgan Roupret* [d], *James W. Catto* [e], *Eva Comperat* [f], *Molly A. Ingersoll* [g], *Wim P. Witjes* [h], *David J. McConkey* [i], *J. Alfred Witjes* [j]

Table 1 Consensus classification of factors as 'Definitely useful' and 'Probably useful' in predicting response. Evidence not robust enough to be classified is listed as 'Emerging strategies'.

DEFINITELY USEFUL	
Before treatment	
Clinicopathologic features (Level of evidence)	
Grade	(+++)
Stage	(+++)
Recurrent tumors	(++)
Multiplicity	(++)
CIS	(+)
Female gender	(+)
Age	(+)
During and after treatment	
FISH pattern on cytologic examination	

Kamat et al, Eur Urol, 2017

The Richard Peto Effect

"Aspirin didn't seem to work as treatment for heart attack if you're born under Libra or Gemini, but it produced halving of risk if you were born under Capricorn.

It's just complete junk.

And, actually, a lot of subgroup analyses are junk".

-Professor Sir Richard Peto

ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet.* 1988 Aug

Thank You

Ashish M. Kamat, MD, MBBS, FACS

akamat@mdanderson.org

@UroDocAsh

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