Individualized management of urogenital tumors
The impact of ACCC

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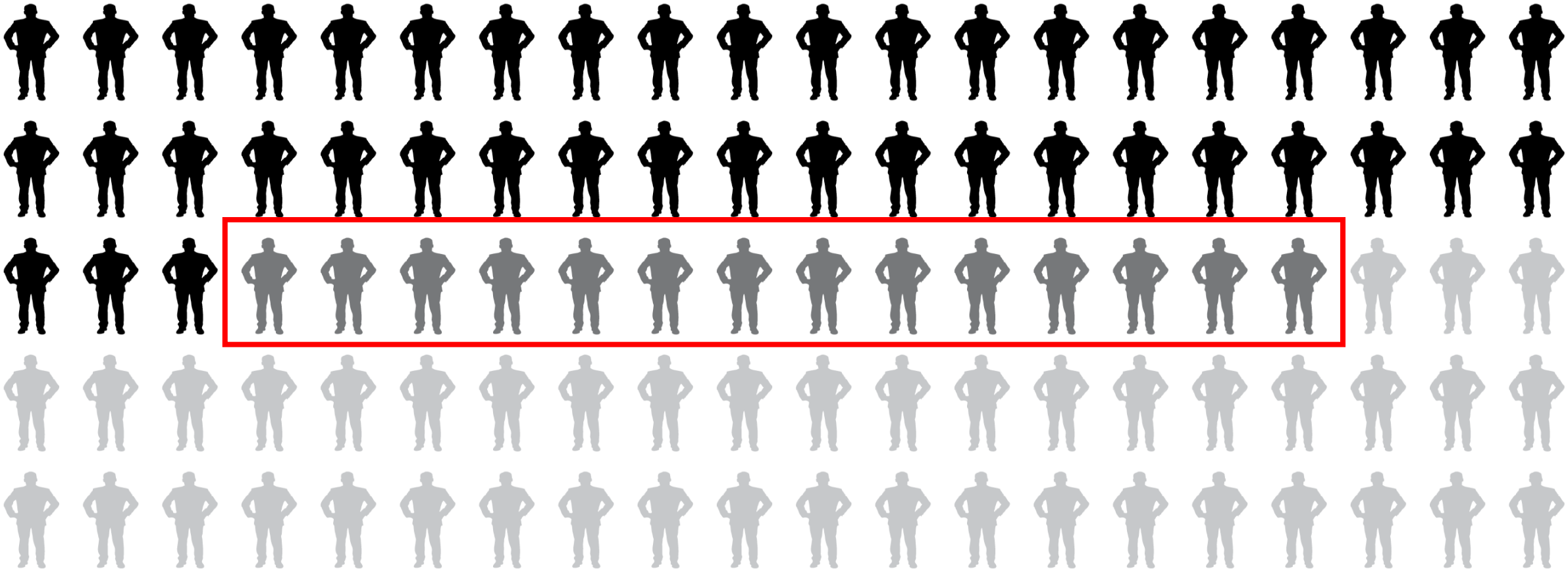
Individualized anti-cancer therapy

- One treatment FITS all
- Solid tumors = Polyclonal populations
- One treatment DOES NOT FIT all

Outcomes at 5 years after neoadjuvant chemotherapy and/or cystectomy in patients with muscle invasive bladder cancer*



data are derived from the Southwest Oncology Group (SWOG) trial 8710

Griffiths G, Hall R, Sylvester R, et al. J Clin Oncol. 2011;29:2171-2177
Galsky MD, Domingo-Domenech J. Clin Adv Hematol Oncol 2013;11:86-92

Advantages of individualized anti-cancer therapy

- Increased efficacy
- Increased tolerance
- Avoidance of unnecessary toxicity
- Favorable pharmacoeconomics

Targeted therapies in urogenital cancer

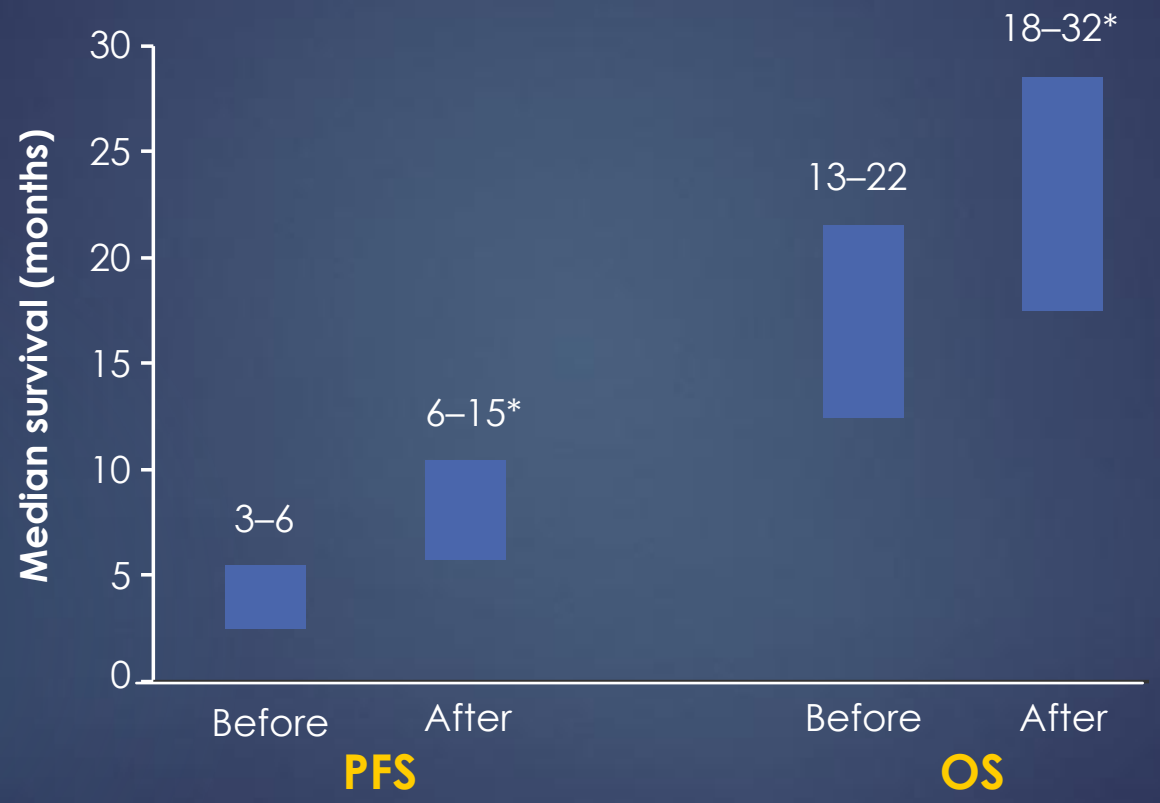
VEGF/VEGFR targeting	mTOR inhibitors	Checkpoint inhibitors
• Sorafenib • Sunitinib • Bevacizumab • Pazopanib • Axitinib • Cabozantinib • Lenvatinib	• Everolimus • Temsirolimus	• Nivolumab • Pembrolizumab • Atezolizumab • Avelumab • Durvalumab

mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

1. Sanchez-Gastaldo A, et al. Cancer Treat Rev. 2017;60:77-89.

Evolution in the first-line treatment of mRCC

Median survival before and after the introduction of targeted agents (TKIs)[1–11]



*With targeted agents as first-line mRCC therapy primarily in favourable/intermediate risk patients

1. Coppin *et al. Cochrane Database Syst Rev* 2005; 2. Gore *et al. Lancet* 2010; 3. Motzer *et al. N Engl J Med* 2007; 4. Escudier *et al. Lancet* 2007; 5. Rini *et al. J Clin Oncol* 2008; 6. Motzer *et al. N Engl J Med* 2013; 7. Motzer *et al. J Clin Oncol* 2009; 8. Escudier *et al. J Clin Oncol* 2010; 9. Rini *et al. J Clin Oncol* 2010; 10. Michel *et al.* ASCO GU 2014; 11. Motzer *et al.* ASCO 2013.

Immunotherapy for RCC: targeting the PD-1/PD-L1 Pathway

PD-1 receptor
(T lymphocytes)

+

PD-L1 ligand
(tumor cells)

↓

Blocking PD-1/PD-L1 signaling can enhance the immune response

Suppression of immune response to tumor

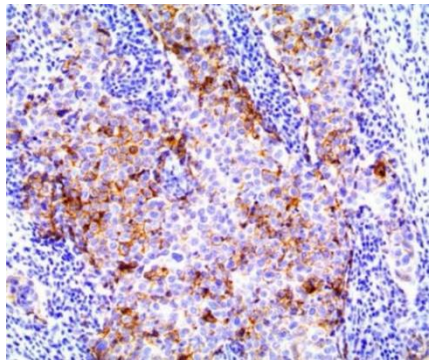
PD-1, programmed cell-death protein 1; PD-L1, programmed death-ligand 1;PD-L2, programmed death-ligand 2.

Ortega RMM, Drabkin HA. Exp Opin Biol Ther. 2015;15:1049-60.

PD-L1 Is Expressed in a Range of Tumor Types

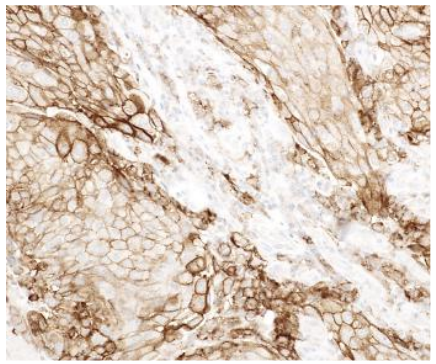
Examples of Tumor Types with Strong PD-L1 Staining (≥10% of cells):

Breast[1]

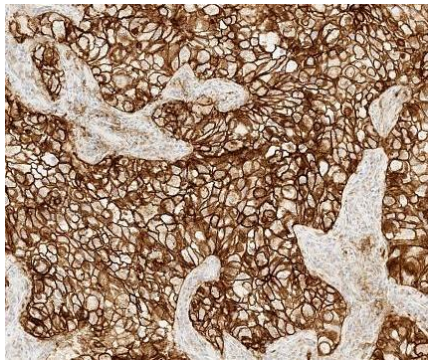


Reprinted from *J Transl Med.* 14:173. Sun WY, Lee KY, Koo JS, Expression of PD-L1 in triple-negative breast cancer based on different immunohistochemical antibodies, © Sun WY, Lee KY, Koo JS 2016.

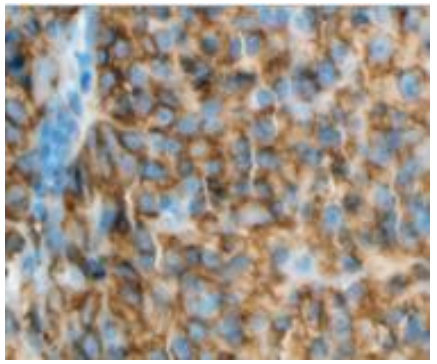
Bladder[2]



Lung Cancer[3]

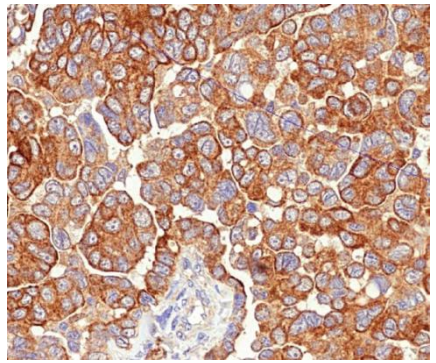


Melanoma[4]

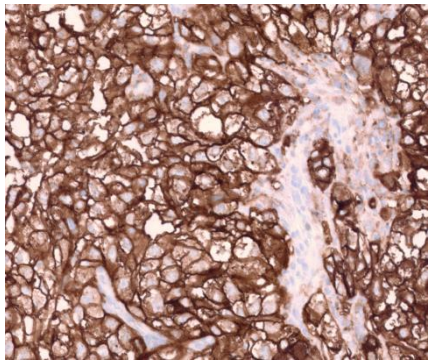


Adapted by permission from Macmillan Publishers Ltd: *Nature Rev Cancer* Topalian SL, et al. *Nat Rev Cancer.* 2016; 16:275-287, copyright 2016.

Ovarian[5]



SCCHN[3]



Adapted from *Oncotarget* 7(2) Darb-Esfahani S, et al. Prognostic impact of programmed cell death-1 (PD-1) PD-ligand 1 (PD-L1) expression in cancer cells and tumor-infiltrating lymphocytes in ovarian high grade serous carcinoma, Pages 1486-1499, Copyright @ 2016 Impact Journals, LLC.

1. Sun WY, et al. *J Transl Med.* 2016;14:173. 2. Massard C, et al. *J Clin* Oncol. 2016;34(suppl): Abstract 4502. 3. Rebelatto MC, et al. *J Clin* Oncol. 2016;34(suppl): Abstract 8033. 4. Topalian SL, et al. *Nat Rev Cancer.* 2016; 16:275-287. 5.Darb-Esfahani S, et al. *Oncotarget.* 2015;7:1486-1499.

CheckMate 214: Study Design

- **Co-primary endpoints**: ORR, PFS, and OS in patients with IMDC-defined poor-/intermediate--risk RCC
- **Co-secondary endpoints**: ORR, PFS, and OS in ITT patients; AE incidence rate

ITT, intention-to-treat; i.v., intravenous; KPS, Karnofsky performance status; ORR, overall response rate; p.o., orally; q2w, every 2 weeks; q3w, every 3 weeks.

Escudier B, et al. *Ann Oncol*. 2017;28(Suppl 5): Abstract LBA5.

CheckMate 214: Exploratory Endpoint Antitumor Activity by Tumor PD-L1 Expression Level

	IMDC-defined poor/intermediate risk				ITT			
	PD-L1 < 1%		**PD-L1 ≥ 1%**		**PD-L1 < 1%**		**PD-L1 ≥ 1%**	
Outcome	NIVO + IPI n = 284	SUN n = 278	NIVO + IPI n = 100	SUN n = 114	NIVO + IPI n = 386	SUN n = 376	NIVO + IPI n = 113	SUN n = 127
ORR								
ORR,[a] % (95% CI)	37 (32–43)	28 (23–34)	58 (48–68)	22 (15–31)	36 (31–41)	35 (31–40)	53 (44–63)	22 (15–30)
	p = 0.0252		p < 0.0001		p = 0.8799		p < 0.0001	
BOR								
BOR,[a] % CR	7	1	16	1	9	2	14	1

PFS IMDC-defined poor/intermediate risk

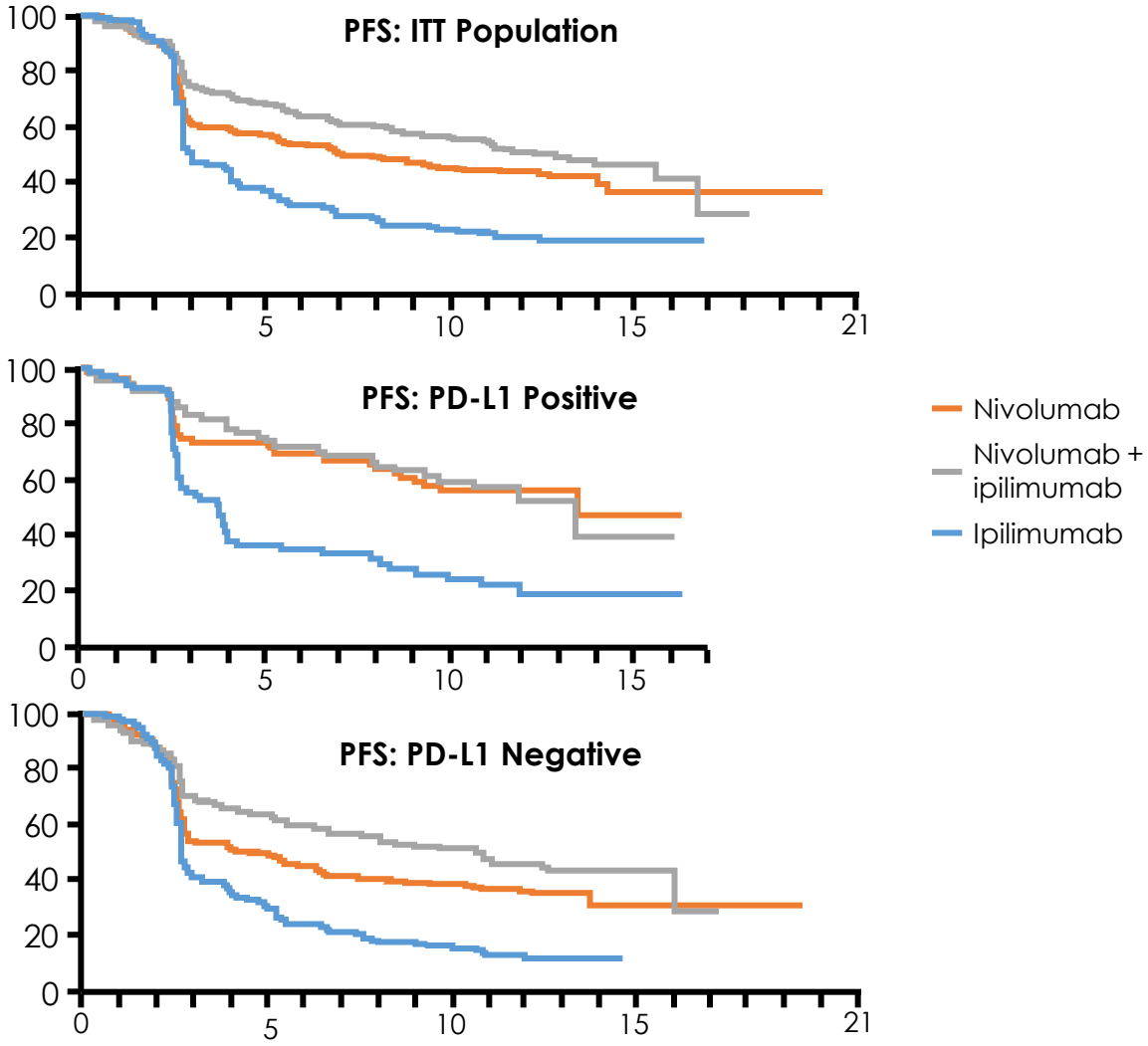
	PD-L1 < 1% (n = 562)	PD-L1 ≥ 1% (n = 214)
	Median PFS, months (95% CI)	
NIVO + IPI	11.0 (8.1–14.9)	22.8 (9.4–NE)
SUN	10.4 (7.5–13.8)	5.9 (4.4–7.1)
	HR (95% CI) 1.00 (0.74–1.36) p = 0.9670	HR (95% CI) 0.48 (0.28–0.82) p = 0.0003

[a] IRRC assessed.

Escudier B, et al. *Ann Oncol*. 2017;28(Suppl 5): Abstract LBA5.

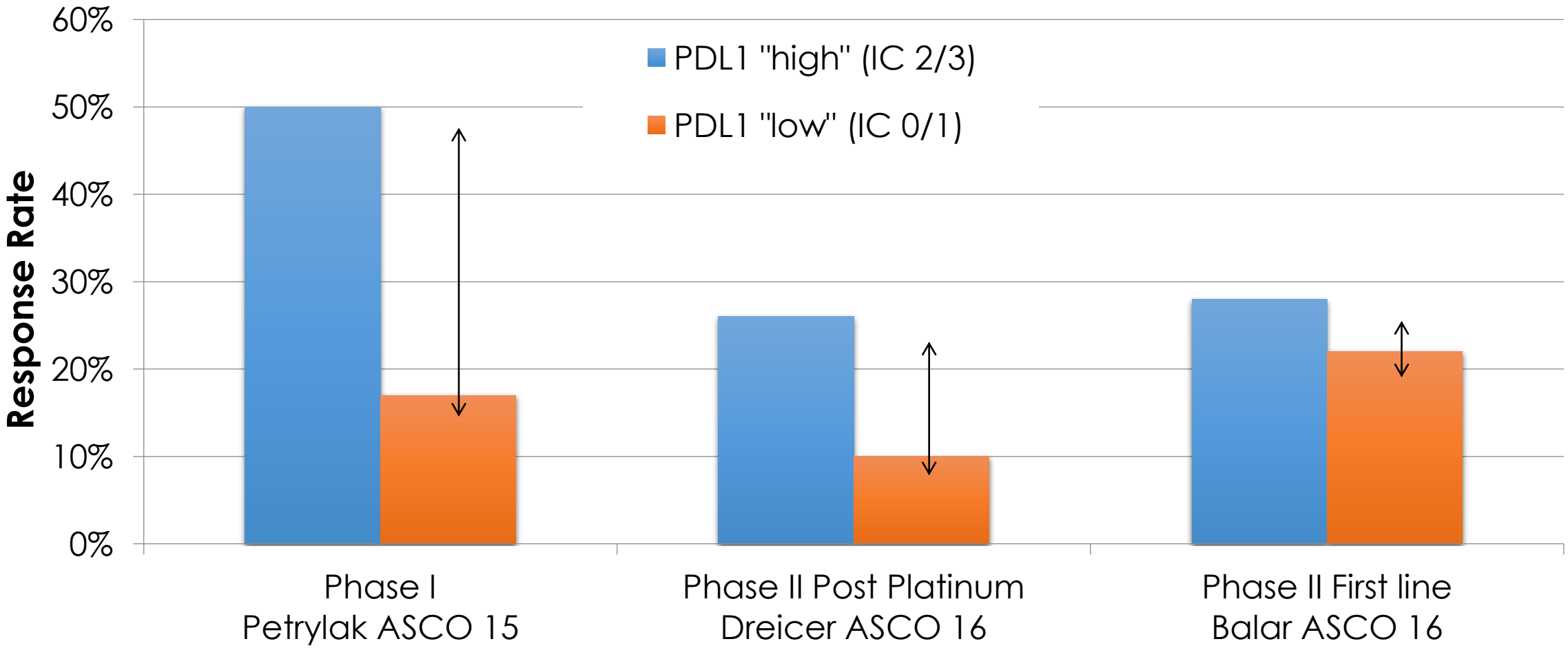
Combinations May Only Be Needed in PD-L1 Negative Tumors

- **Addition of CTLA-4 inhibition may only lead to toxicity in pts with PD-L1–high tumors**
- **No data yet in bladder cancer**



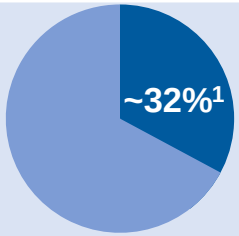
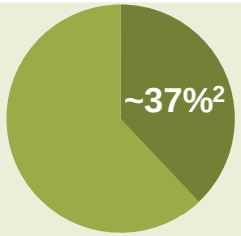
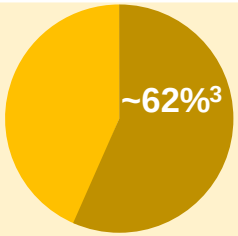
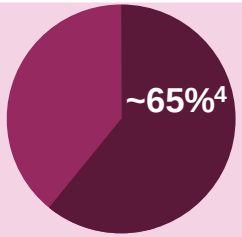
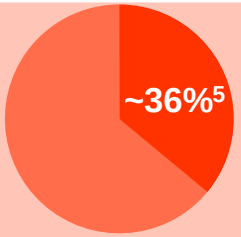
Larkin J, et al. *N Engl J Med.* 2015;373(1):23-34.

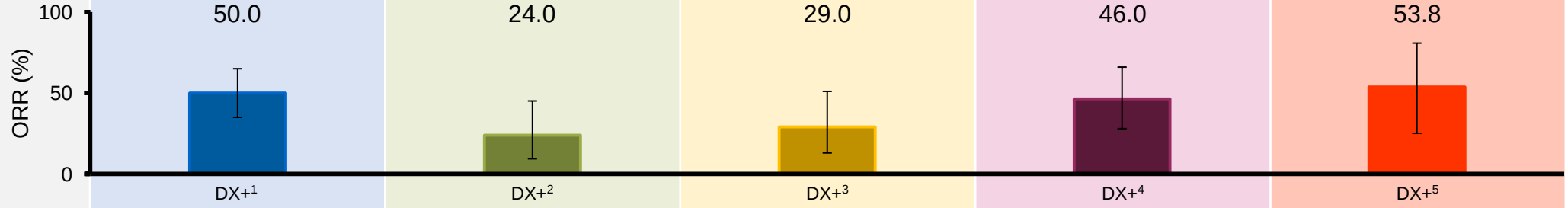
PDL1 Testing (IC 2/3 vs 1/2) Loses Ability to Enrich for Response Across Atezolizumab Studies



Plimack E. ASCO 2016

Phase I Data: Assays for Measurement of PD-L1 Expression in Advanced Urothelial Cancer

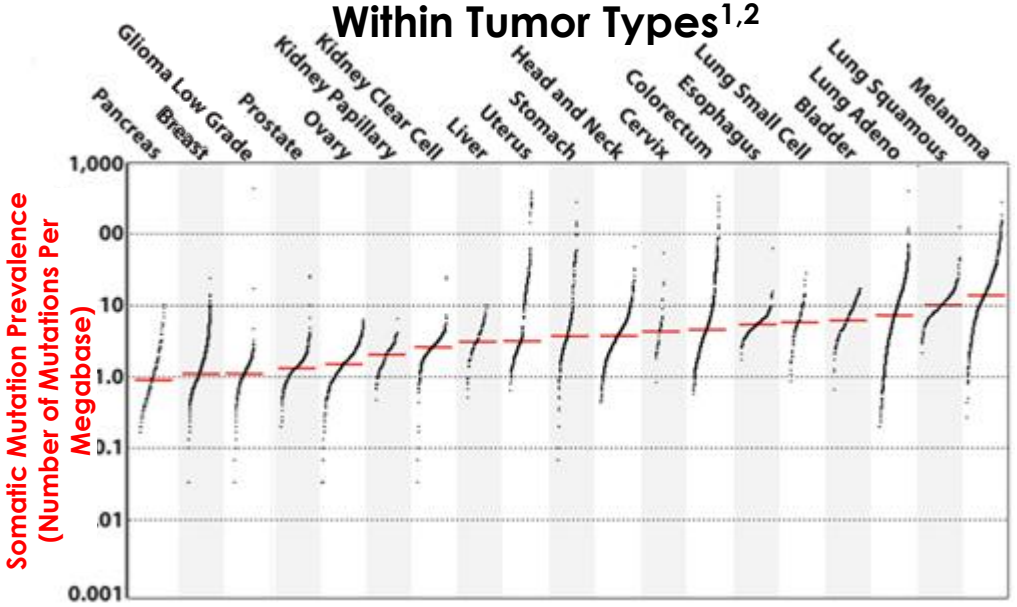
	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Durvalumab[4]	Avelumab[5]
Detection antibody	SP142	28-8	22C3	SP263	73-10
IHC platform	Ventana	Dako	Dako	Ventana	Dako
Cell types scored for urothelial cancer	IC	TC	TC	IC and TC	IC and TC
Cut-off definitions for urothelial cancer	PD-L1+ (IHC 2/3) as ≥5% of ICs PD-L1+	PD-L1+ ≥1% TC expression	PD-L1+ ≥1% TC staining	PD-L1+ as ≥25% of ICs and TCs with membrane PD-L1 staining	PD-L1+ as ≥5% TC staining or ≥10% IC staining
Estimated PD-L1 prevalence in urothelial cancer trials					
PD-L1+ ORR (phase I trials)	50.0	24.0	29.0	46.0	53.8



1. Petrylak DP, et al. *J Clin Oncol.* 2015;33(suppl): Abstract 4501. 2. Sharma P, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 4501. 3. Plimack ER, et al. *J Clin Oncol.* 2015;33(suppl): Abstract 4502. 4. Massard C, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 4502. 5. Apolo AB, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 4514.

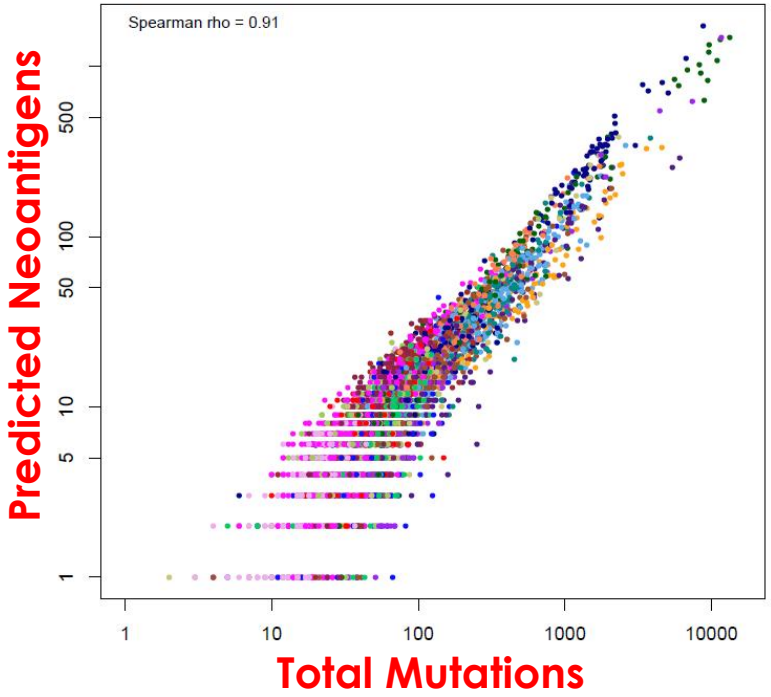
Antigenicity Is a Major Component of Tumor Immunogenicity

Tumor Mutational Load Varies Across and Within Tumor Types[1,2]



Adapted by permission from Macmillan Publishers Ltd: *Nature* Alexandrov LB, et al. *Nature*. 2013;500:415-421, copyright 2013.

Neoantigens Per Tumor Correlates With Mutation Burden[2,3]

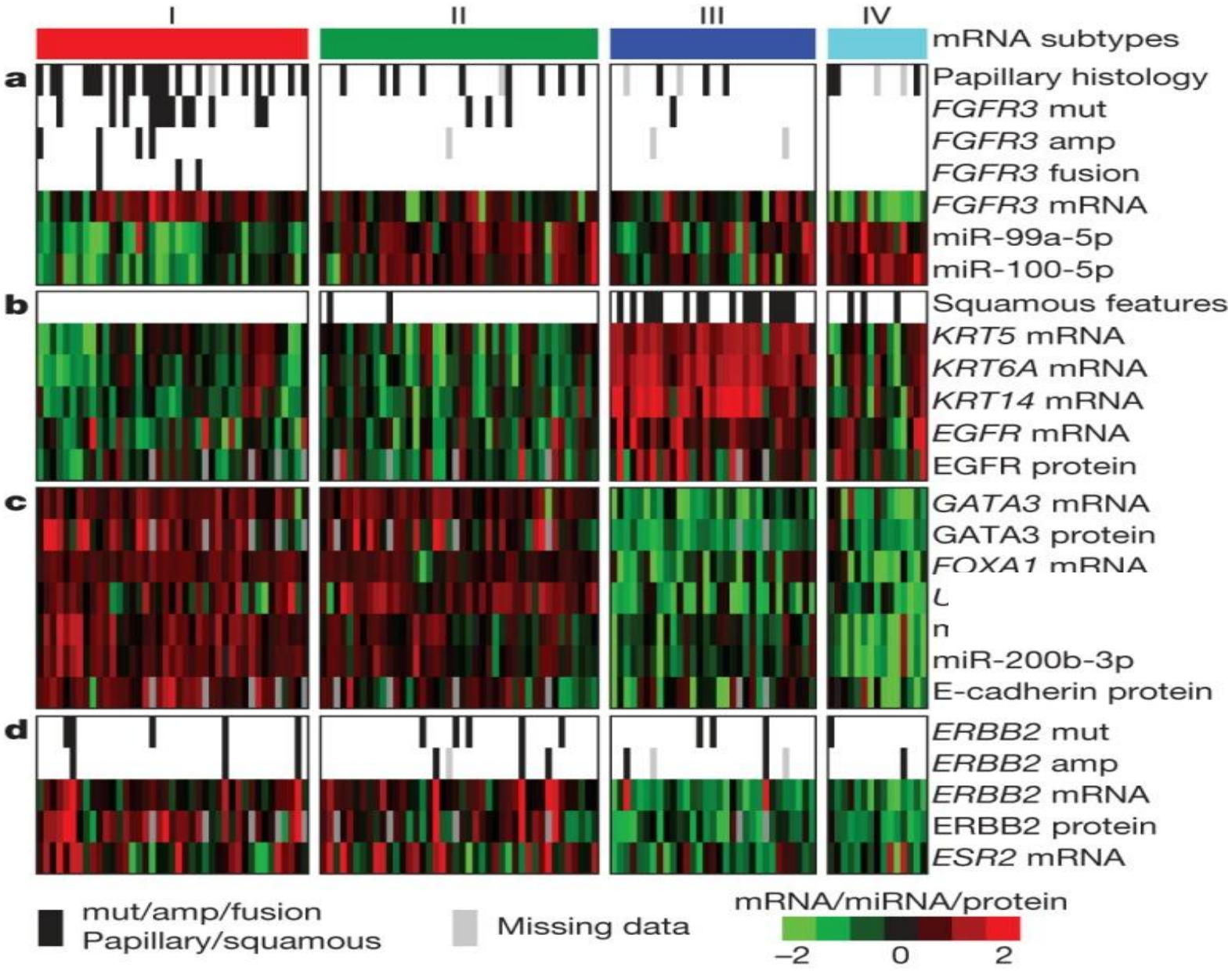


Reprinted from *Cell*, Vol. 160(1-2), Rooney MS, Shukla SA, We CJ, et al. Molecular and genetic properties of tumors associated with local immune cytolytic activity, Pages 48-61, Copyright 2015, with permission from Elsevier.

Downregulation and disruption of antigen-presenting machinery reduces immunogenicity[4]

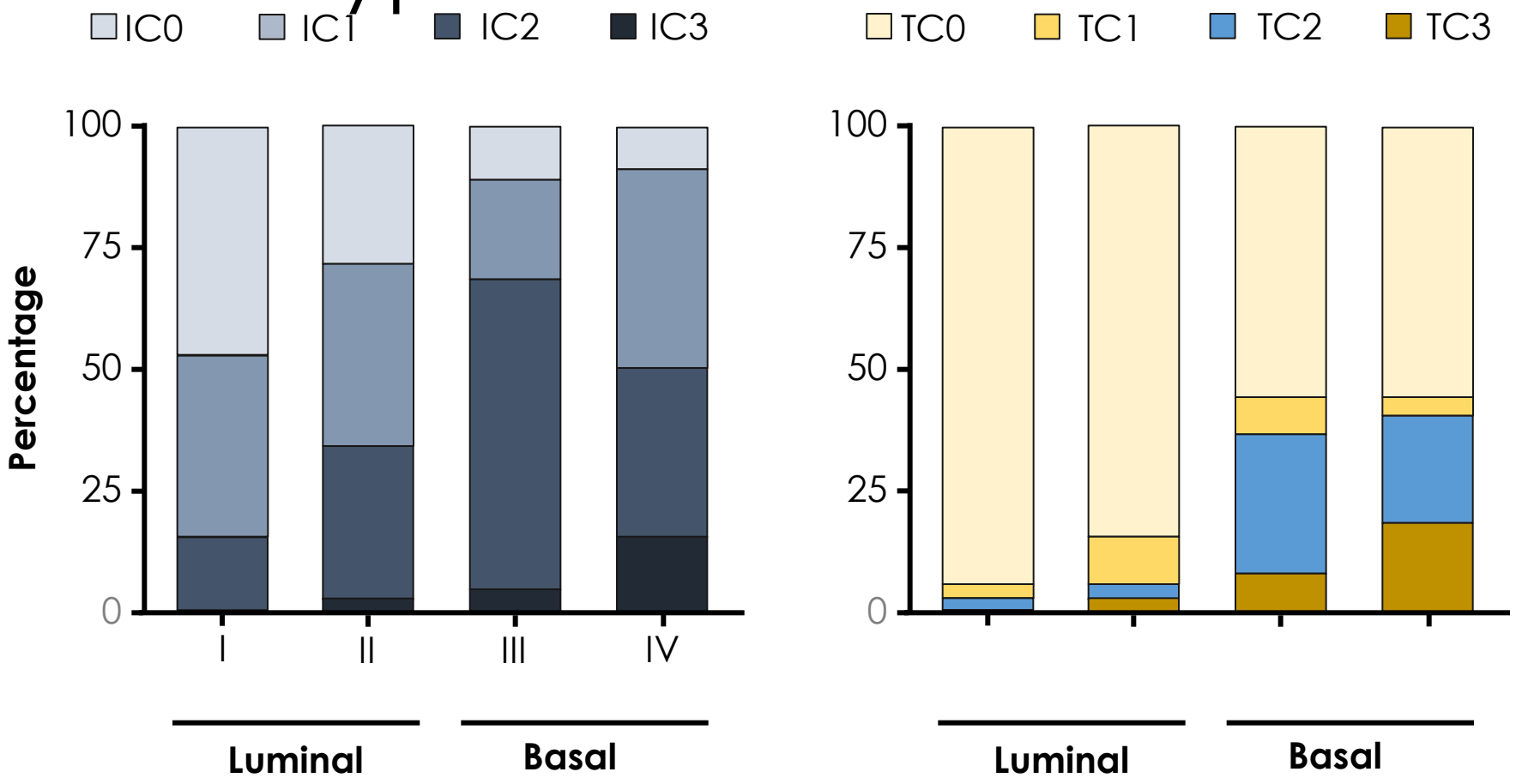
1. Alexandrov LB, et al. *Nature.* 2013;500:415-421. 2. Rizvi NA, et al. *Science.* 2015;348:124-128. 3. Rooney MS, et al. *Cell.* 2015;160:48-61.
4. Beatty GL, et al. *Clin Cancer Res.* 2015:21:687-692.

Molecular characterization of urothelial cancer



The Cancer Genome Atlas Research Network. Nature 2014; 507: 315-322

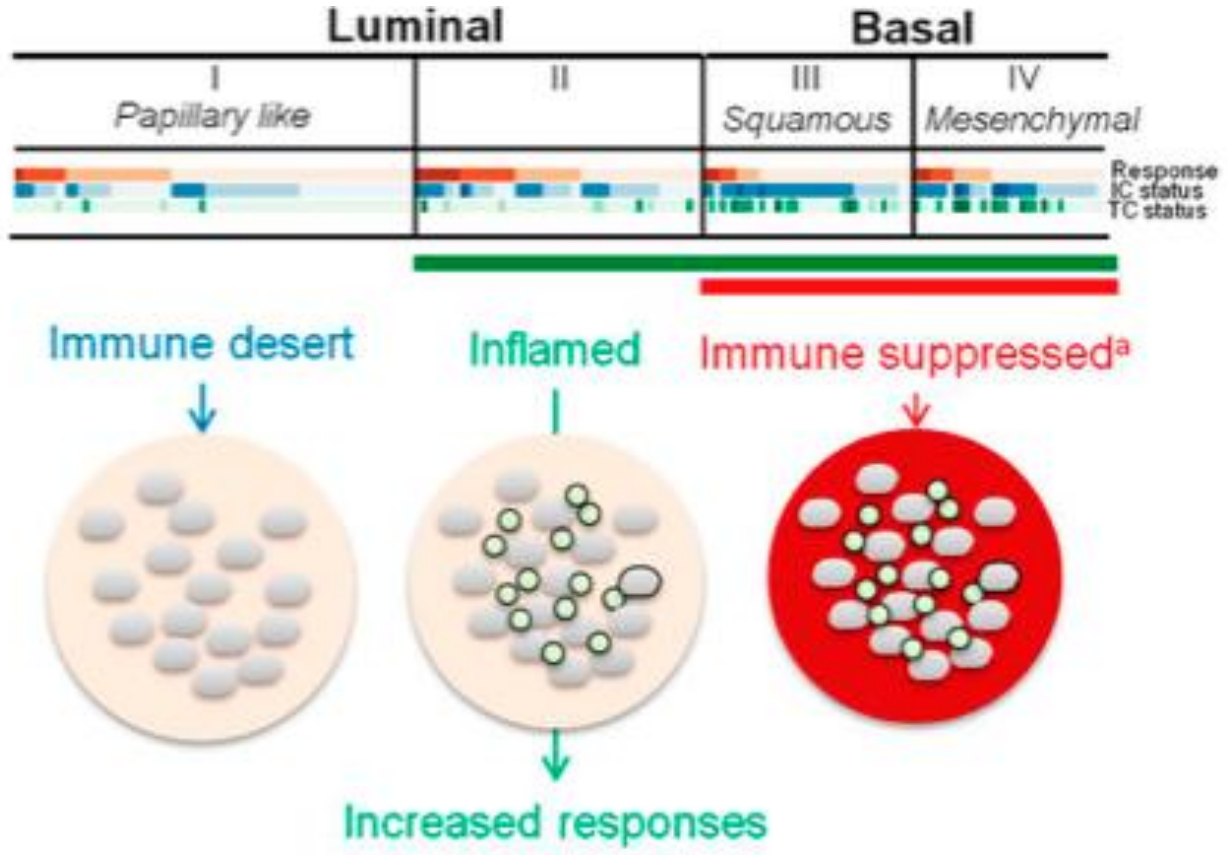
IMvigor210: PD-L1 IC and TC Scores Associated With Basal Phenotype



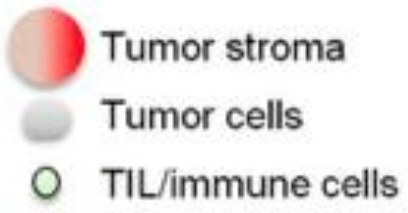
Rosenberg JE, et al. *Lancet*. 2016;387(10031):1909-1920.

Gene Signatures in the Tumor Microenvironment

IMvigor210: TCGA Subtype in metastatic urothelial cancer



- **IMvigor 210 subtypes have distict tumor-immune landscapes that reflect responsiveness to atezolizumab**

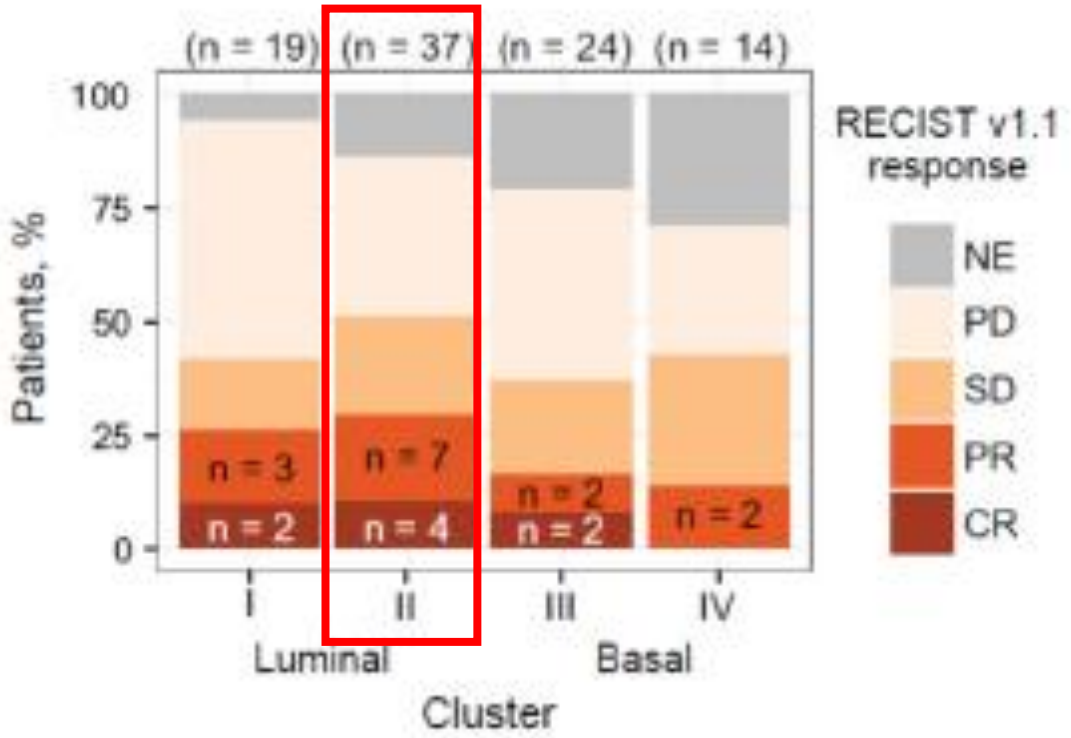


TIL, tumor-infiltrating lymphocyte. [a]High myeloid, inflammatory, activated stromal/fibroblast markers

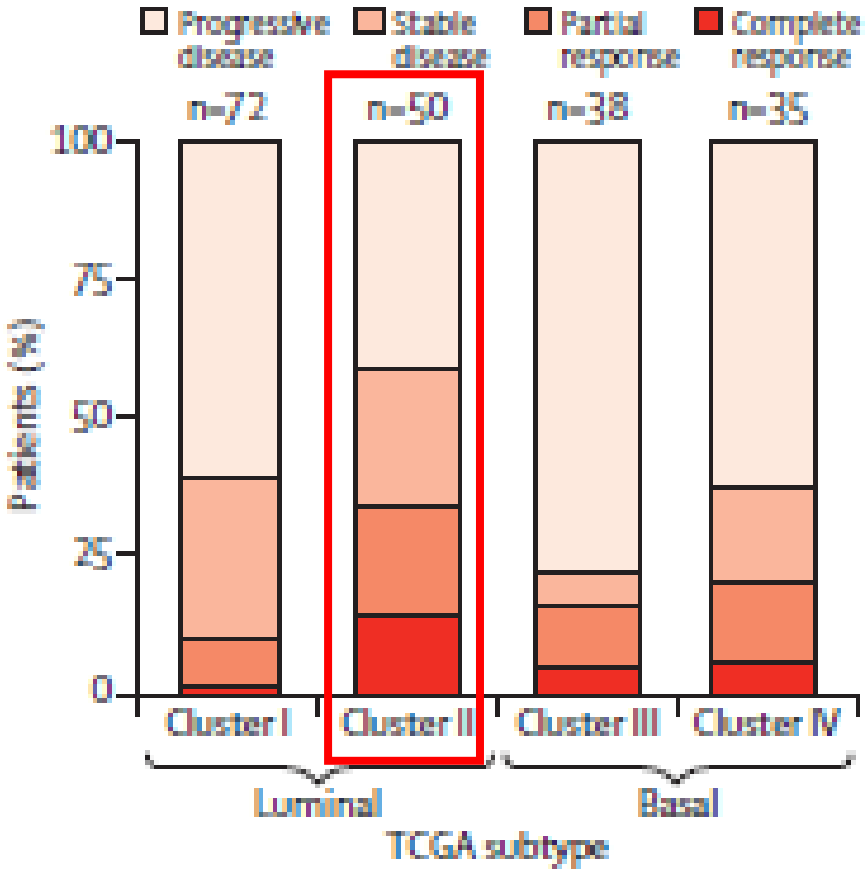
Rosenberg JE, et al. *Lancet*. 2016;387(10031):1909-1920.

Response by TCGA Molecular Subtype

Atezolizumab 1st-line[1]



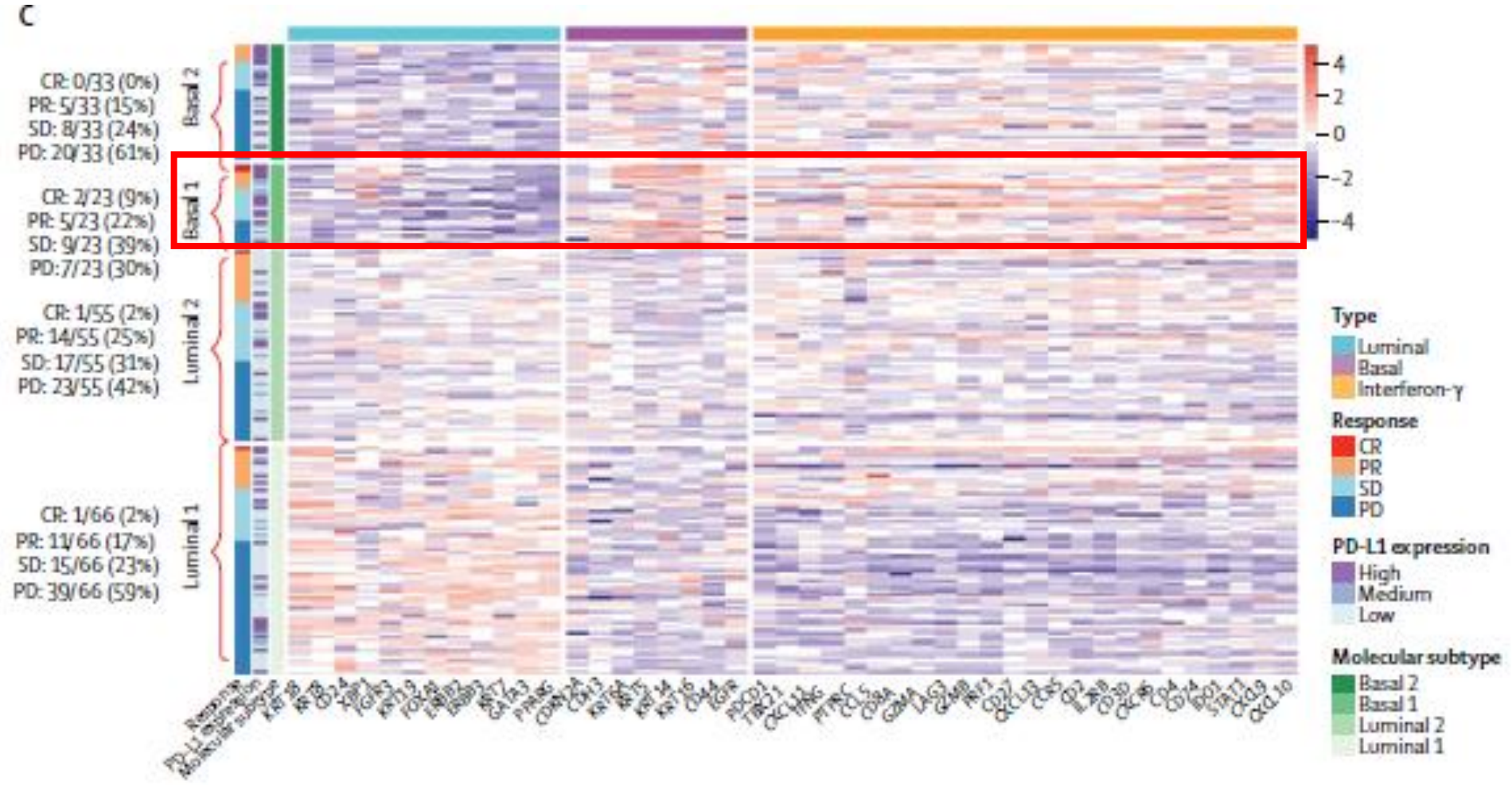
Atezolizumab 2nd-line[2]



1. Balar AV et al. Lancet 2017; 389:67-76. 2. Rosenberg JE, et al. *Lancet*. 2016;387(10031):1909-1920.

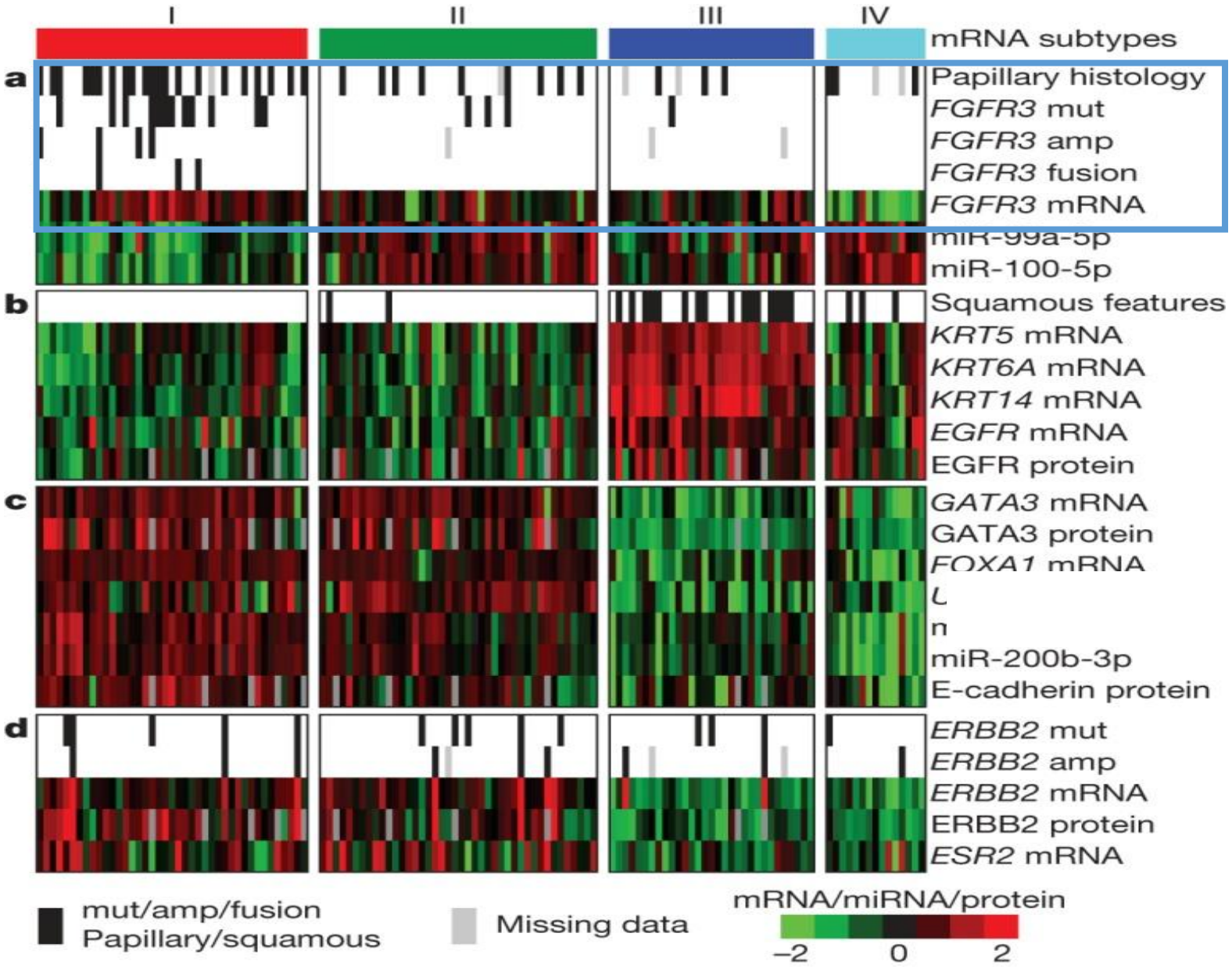
Response by TCGA Molecular Subtype

Nivolumab 2nd-line[1]



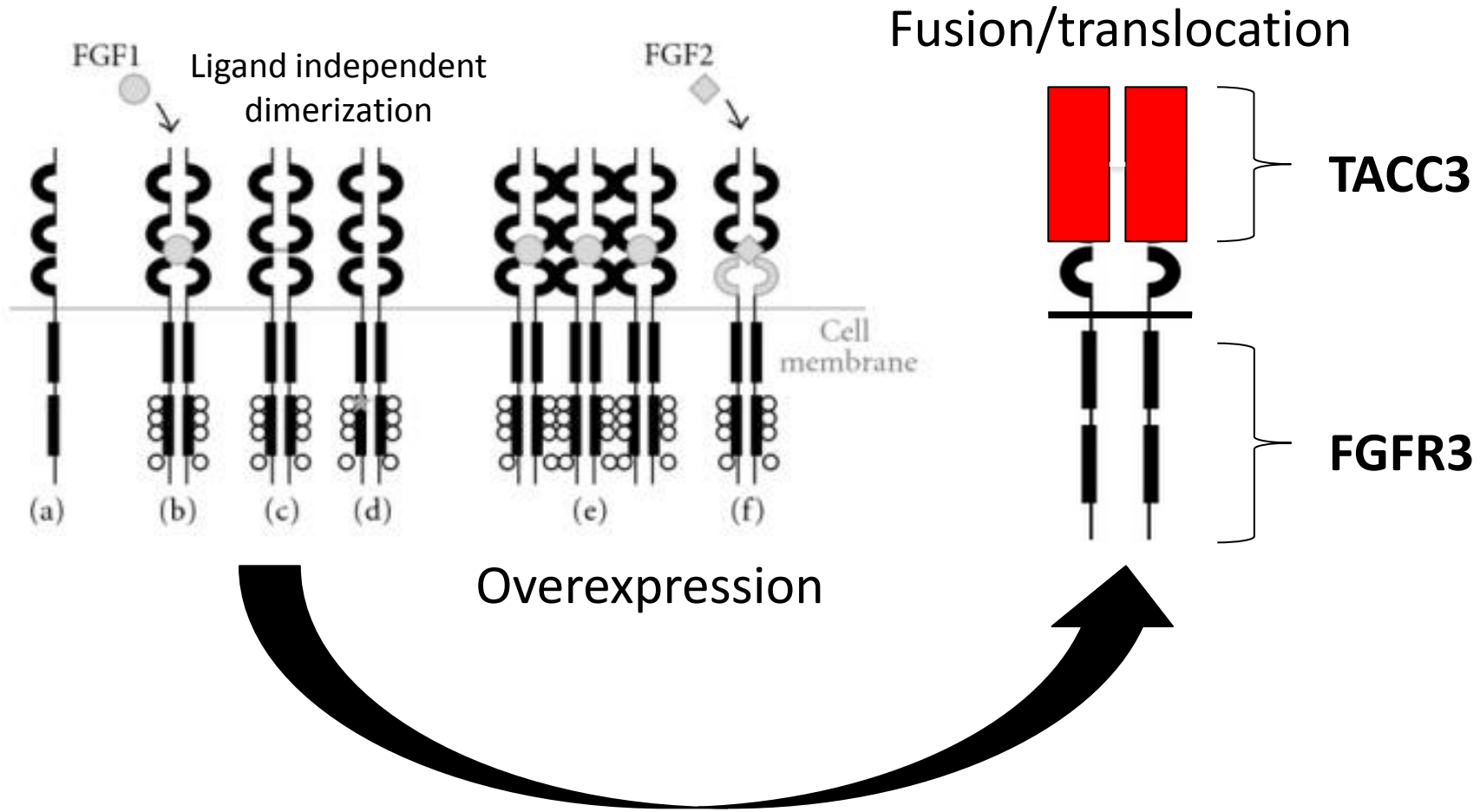
1.Sharma P, et al. Lancet Oncol. 2017;18(3):312-322.

Molecular characterization of urothelial cancer



The Cancer Genome Atlas Research Network. Nature 2014; 507: 315-322

FGFR3 activation can occur by mutation, overexpression or gene fusion



di Martino et al. Advances in Urology 2012

FGFR

- FGF signaling promotes oncogenesis, tumor neoangiogenesis and drug resistance[1]

- FGF signaling alterations, particularly those involved in FGFR3 and FGFR1 pathway, are implicated in bladder tumors[2]

- Important molecular alteration in bladder cancer[3]

Significance in resistance to chemotherapy

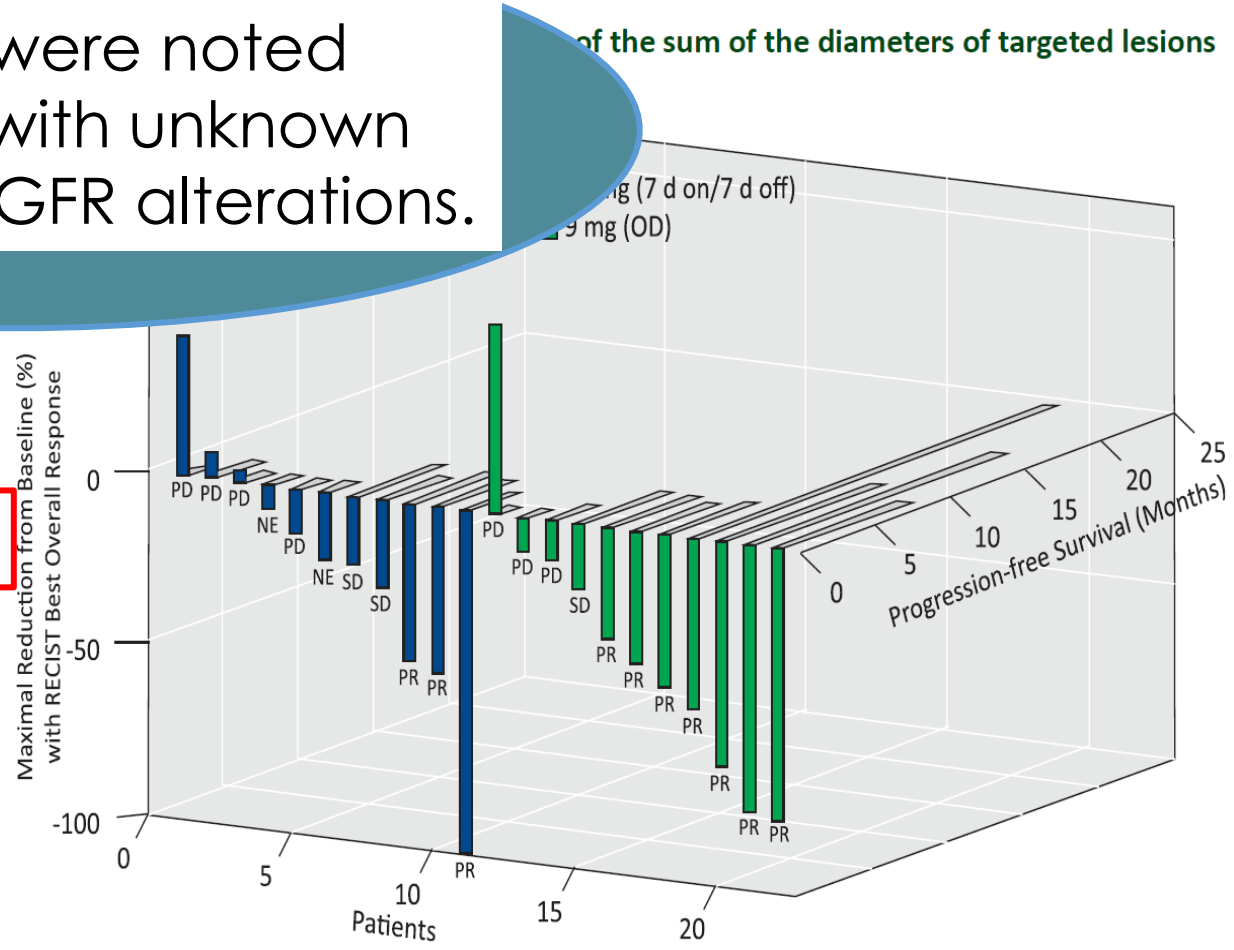
1. Dieci et al., 2013; 2. di Martino et al., 2012 ; 3. http://dx.doi.org/10.1038/nature12965.

Soria et al: Safety and Activity of the Pan–Fibroblast Growth Factor Receptor (FGFR) Inhibitor Erdafitinib in Phase 1 Study Patients with Advanced Urothelial Carcinoma (UC)

Antitumor Efficacy

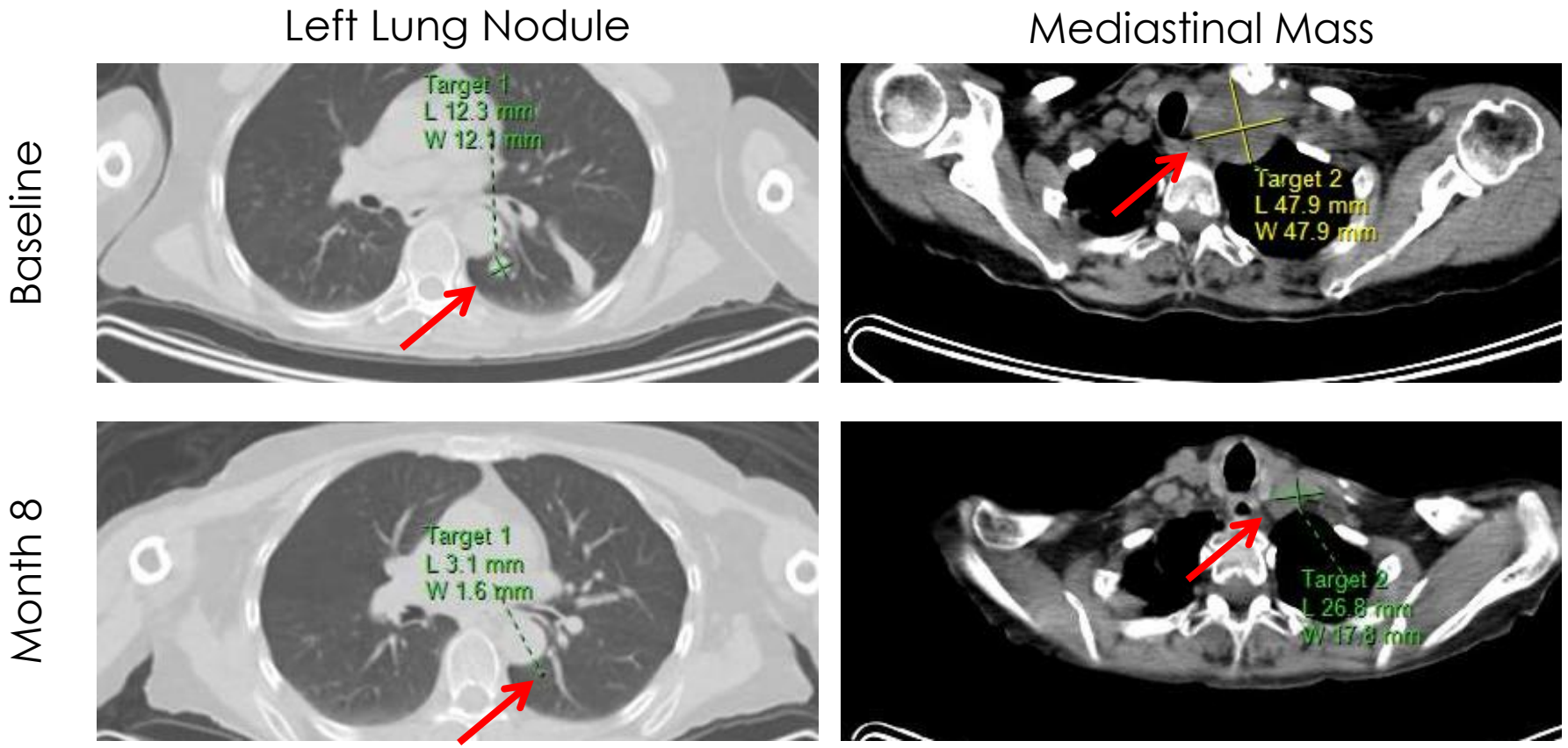
- Responses were obs
  and 10 mg intermitte
  2016)
  - 11 PR out of 24 FGFR+ pts, ORR of 45.8% (95% CI 25.6%, 67.2%)
    - 9 mg QD: 7 PR of 11 pts, ORR of 63.6%
    - 10 mg intermittent: 4 PR of 13 pts, ORR of 30.8%
- Median duration of response: 7.2 mo (1.6+ to 15.3 mo), (95% CI 3.3 to 15.3 mo)
- Median PFS: 5.1 mo (95% CI 2.8 to 5.9 mo)
  - 6-mo PFS of 24% and 12-mo PFS of 12%

No responses were noted in 36 patients with unknown or no known FGFR alterations.



Metastatic urothelial cell carcinoma case study

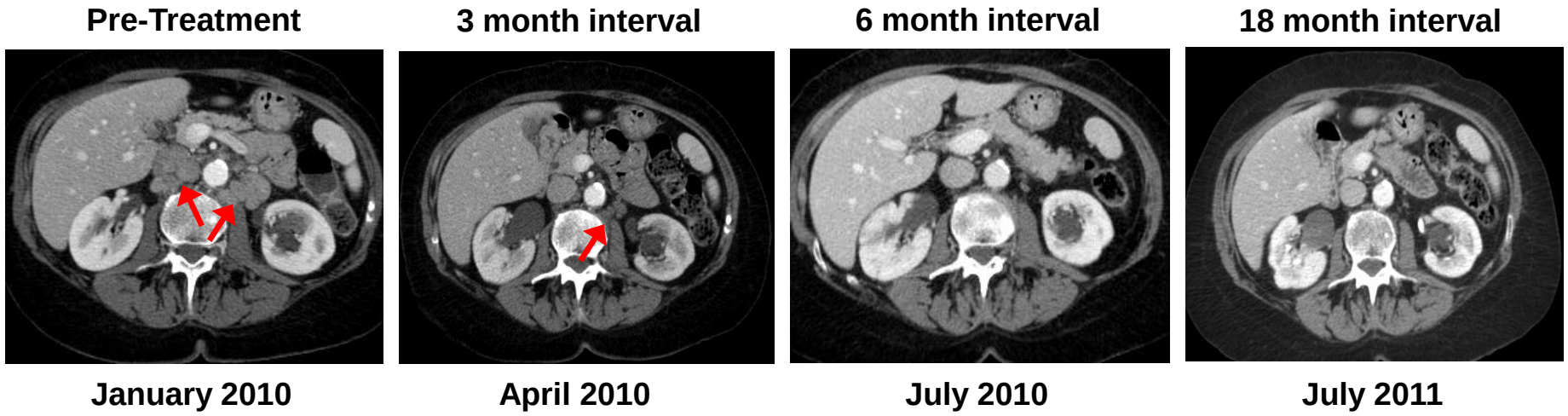
- **Patient ongoing (9+ cycles) with PR (45% tumor reduction)**



Images courtesy of Jason Luke, MD, and Geoff Shapiro, MD, Dana-Farber Cancer Institute

Response to everolimus on MSKCC IRB protocol 08-123.

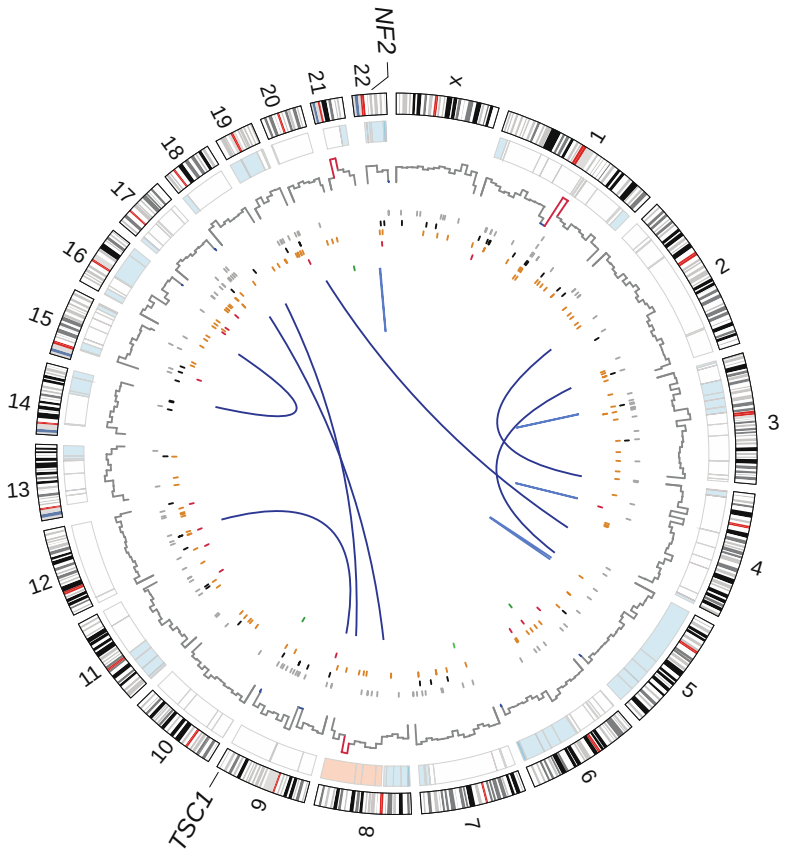
- 73 year old women with metastatic bladder cancer with progression after platinum-based treatment.
- Achieved a complete response to everolimus (mTORC1 inhibitor) on MSKCC protocol 08-123.
- The patient remains on drug with no evidence of disease > 48 months after starting treatment.
- This patient was one of only 2 of 45 patients who responded to drug.

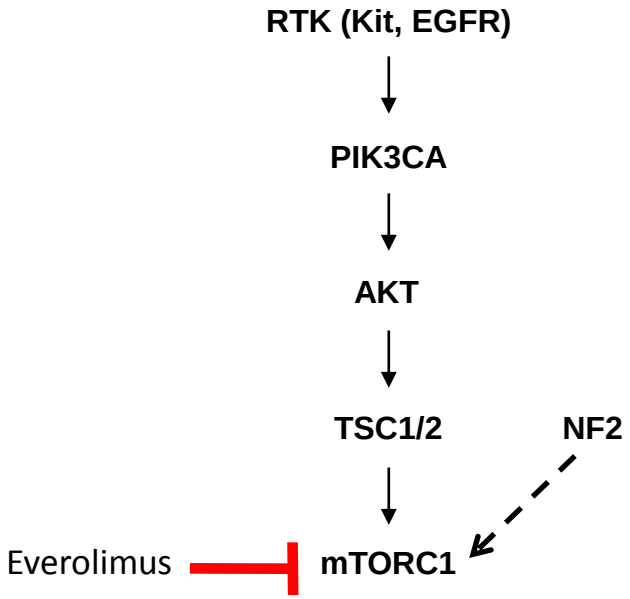


Why did this patient respond so dramatically to mTORC1 inhibition?

First Cancer Genome at MSKCC

- 17,000+ somatic mutations
- 140 NS coding mutations





Iyer et al., Science, 2012

Moving to personalized medicine

- Cancers emerge from genomic errors
- Sequencing technology is now at the bedside

- Clinical computational biology:
  - Computational algorithms to analyze and interpret genomic data from patient samples are available

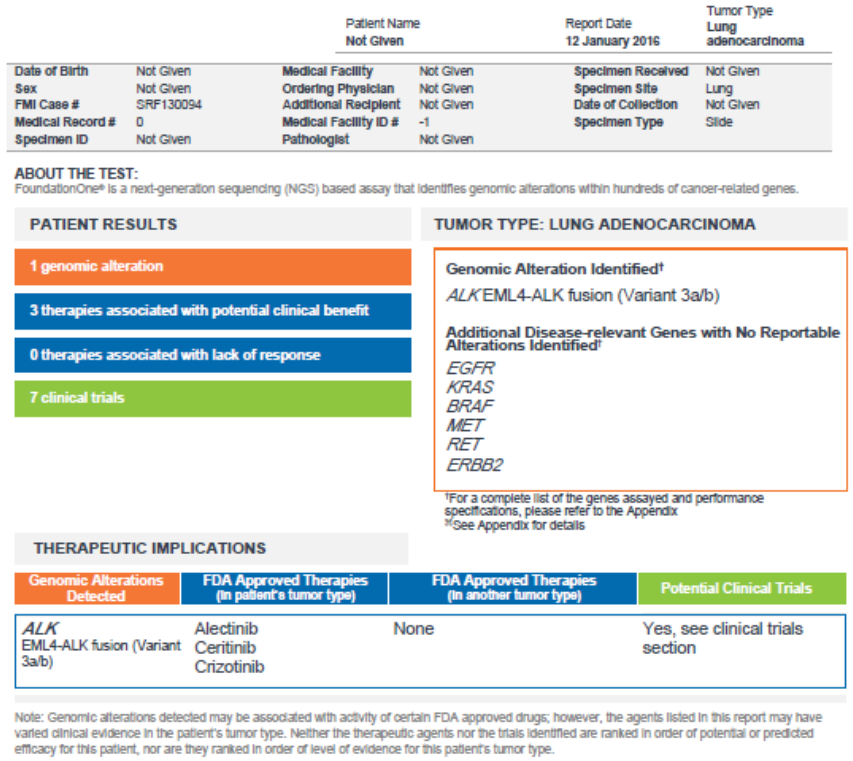
How this translates to daily clinical practice ?

An opportunity for genomic “media”

- *Can we visually represent an exome to enable clinical interpretation?*
- *Can we make complex genomic data approachable for busy clinicians (and patients)?*
- *Can we place these data in a useful portion of the medical record?*
- *Do we need to include expression analysis, mutational burden, nanostring when deciding for Immunotherapy ?*

Contents of a Report

Summary of genomic alterations and therapeutic implications



Patient Name	Report Date	Tumor Type
Not Given	12 January 2016	Lung adenocarcinoma

Date of Birth	Not Given	Medical Facility	Not Given	Specimen Received	Not Given
Sex	Not Given	Ordering Physician	Not Given	Specimen Site	Lung
FMI Case #	SRF130094	Additional Recipient	Not Given	Date of Collection	Not Given
Medical Record #	0	Medical Facility ID #	-1	Specimen Type	Slide
Specimen ID	Not Given	Pathologist	Not Given		

ABOUT THE TEST:
FoundationOne® is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

- 1 genomic alteration
- 3 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 7 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alteration Identified†
ALK EML4-ALK fusion (Variant 3a/b)

Additional Disease-relevant Genes with No Reportable Alterations Identified†
EGFR
KRAS
BRAF
MET
RET
ERBB2

†For a complete list of the genes assayed and performance specifications, please refer to the Appendix
‡See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
ALK EML4-ALK fusion (Variant 3a/b)	Alectinib Ceritinib Crizotinib	None	Yes, see clinical trials section

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

Patient and ordering physician information

Summary of results and genomic alterations identified

Targeted therapies and clinical trials that may be relevant based on genomic alterations identified

Analysis
Pipeline

Informatics
Review

QC control/Lab
Director Approval

Content
Creation

NCBI

PubMed

OMIM
Online Mendelian Inheritance in Man

COSMIC
Catalogue of somatic mutations in cancer

The Cancer Genome Atlas

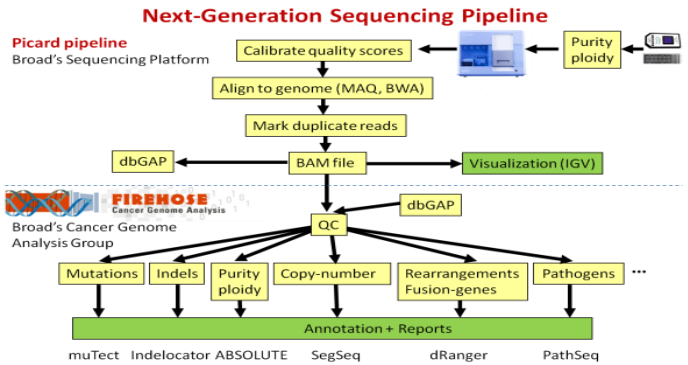
ClinicalTrials.gov

Online Databases

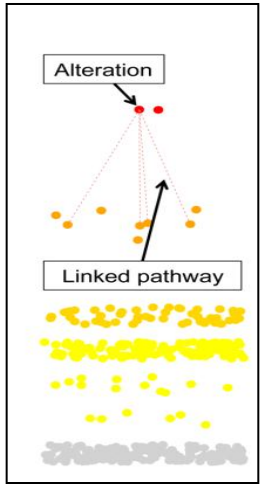
COPENHAGEN 2016 ESMO congress

Clinical Interpretation Needs

Clinical Sequencing Pipeline Development



Clinical Genomics Data Interpretation



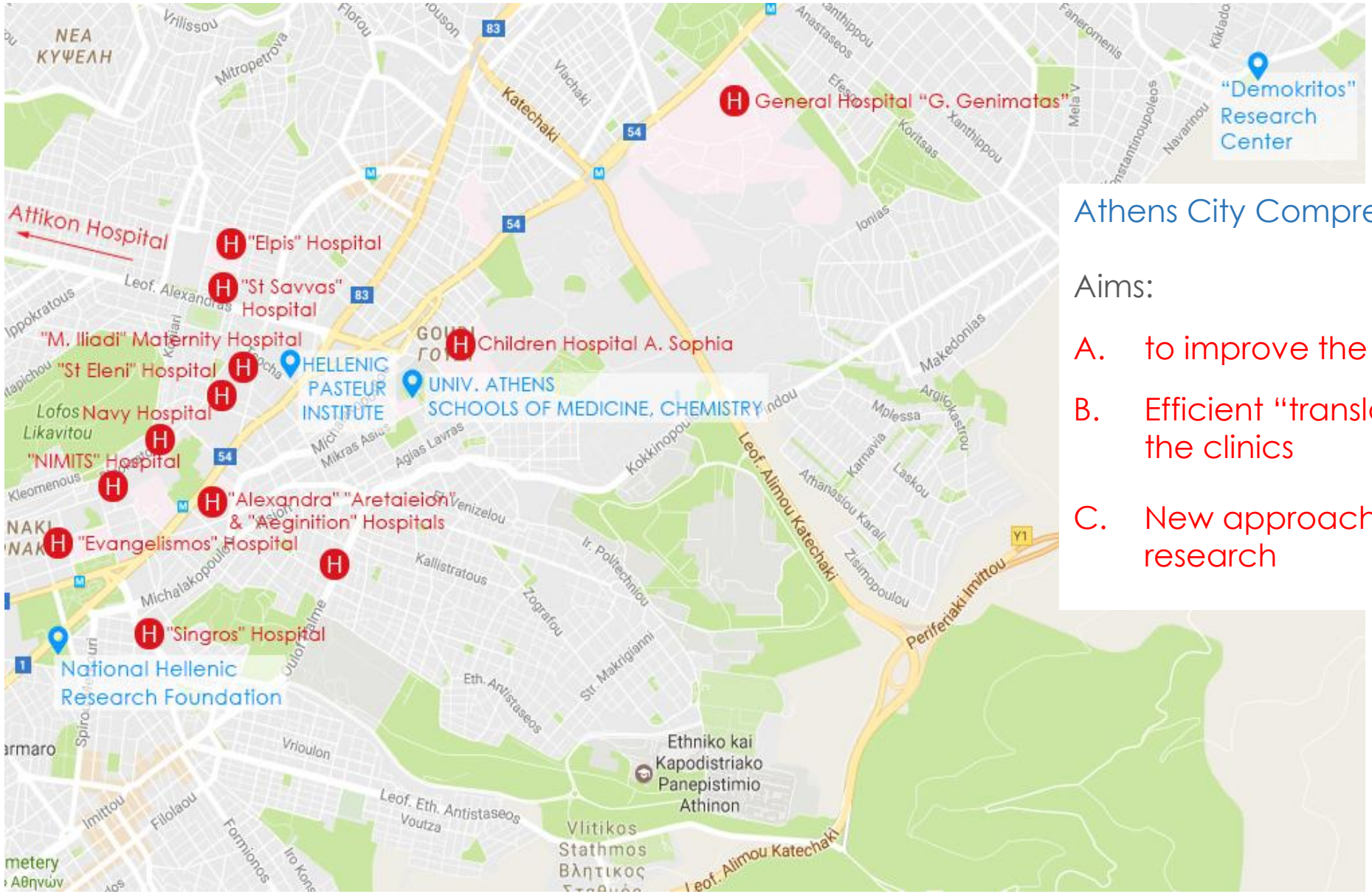
Data Representation for Clinicians

Van Allen, et al ASCO oral abstract (2012)

Genomic media in clinical cancer medicine

- A field in its infancy
- Needs standardization
- Needs best practices
- Needs prospective testing in the clinic
- Needs regulatory evaluation

Impact of Athens Comprehensive Cancer Center (ACCC)



Athens City Comprehensive Cancer Center

Aims:

A. to improve the health of Athens citizens

B. Efficient "translation" of research results into the clinics

C. New approaches derived from recent cancer research

Athens Comprehensive Cancer Center (ACCC)

Participating Organization	Responsible Scientist
1. National Hellenic Research Foundation (preclinical drug studies, bioinformatics)	Dr Alex Pintzas
2. Alexandra Hospital (University Clinics)(urogenital, leukaemias, gynaecological)	Prof. Aristotelis Bamias
3. Aghios Savas Hospital (Oncology Clinic) (breast, colorectal, lung, melanoma)	Dr George Koumakis
4. Pediatric Hospital Aghia Sofia (University Clinic) (pediatric cancers)	Assoc. Prof. Antonis Kattamis
5. Attikon Hospital (University Clinic) (head and neck cancer)	Ass. Prof. Amanda Psyrri
6. General Hospital of Athens G. Genimmatas (colorectal, thyroid, adrenal gland)	Dr George Zografos
7. National Center of Scientific Research Demokritos (hereditary cancer genetics)	Dr Drakoulis Yannoukakos
8. University of Athens -School of Chemistry (liquid biopsy, CTCs, ctDNA)	Prof Evi Lianidou

Professors/Researchers from International Partner Organisations for ACCC networking:

DKFZ (Heidelberg, Germany)

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

JP No.	Joint Project Title	Start Month	End Month
1	Data Integration	1	30
2	Biobanking and Omics Technology	1	36
3	Multiple Myeloma (MM)	1	36
4	Paediatric Cancers	1	36
5	Colorectal Cancer (CRC)	1	36
6	Gynaecological (breast and ovarian) cancer	1	36
7	Head and neck cancer (HNSCC)	1	36