Molekulare Subtypen und prädiktive Marker des Urothelkarzinoms

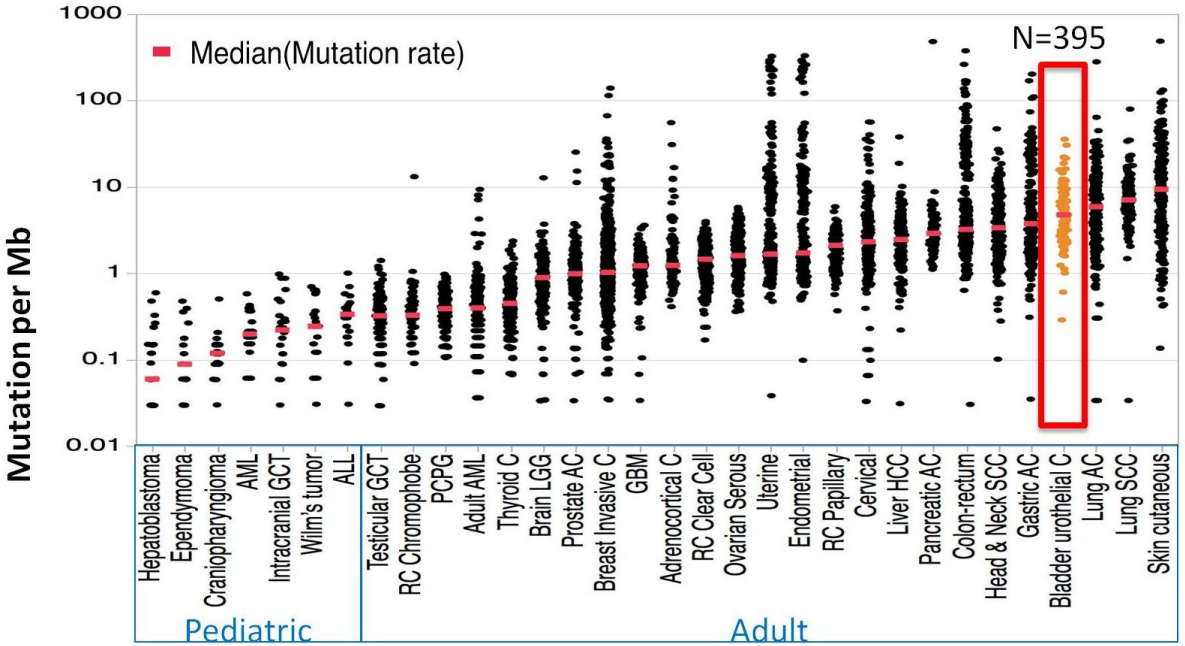
Thomas Bauernhofer

DGHO Tagung, Stuttgart 01.10.2017

„The greatest single advance in our understanding of bladder cancer in the past 5 years has been the description of molecular subtypes“

Peter C. Black Editorial Eur Urol 2017; 72: 366-367

MIBC- Somatic Mutation Rate

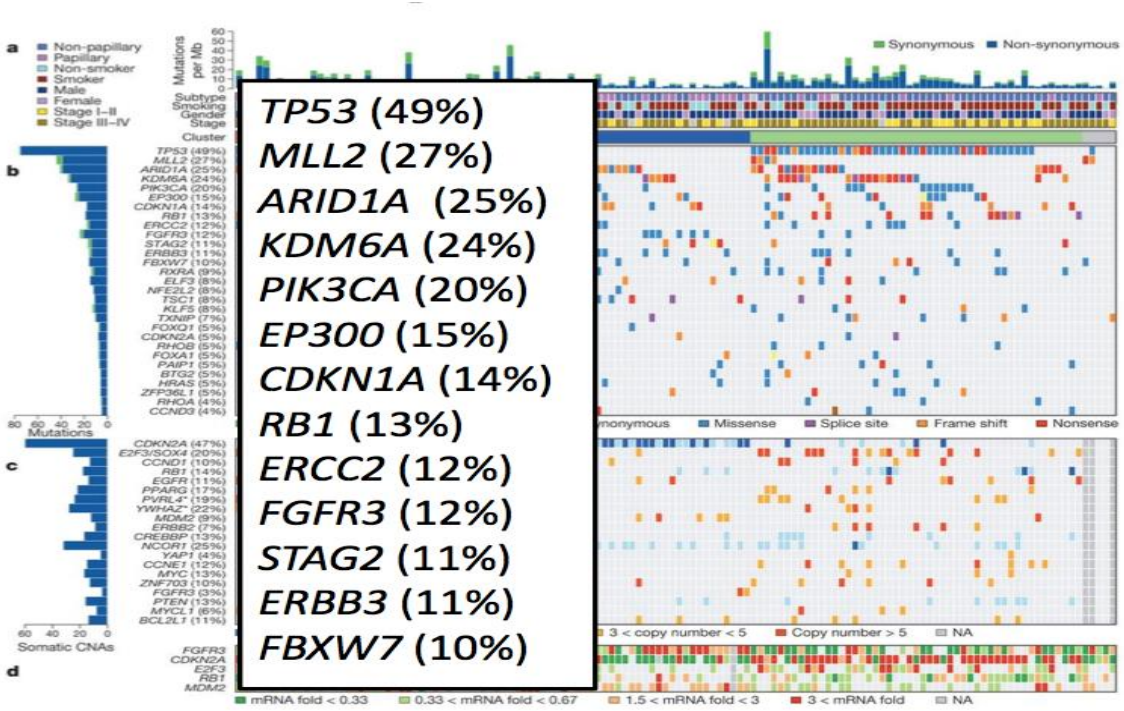


Mean somatic mutation rate 8.2/Mb (Median 5.8)

Linghua Wang, BCM 4/16

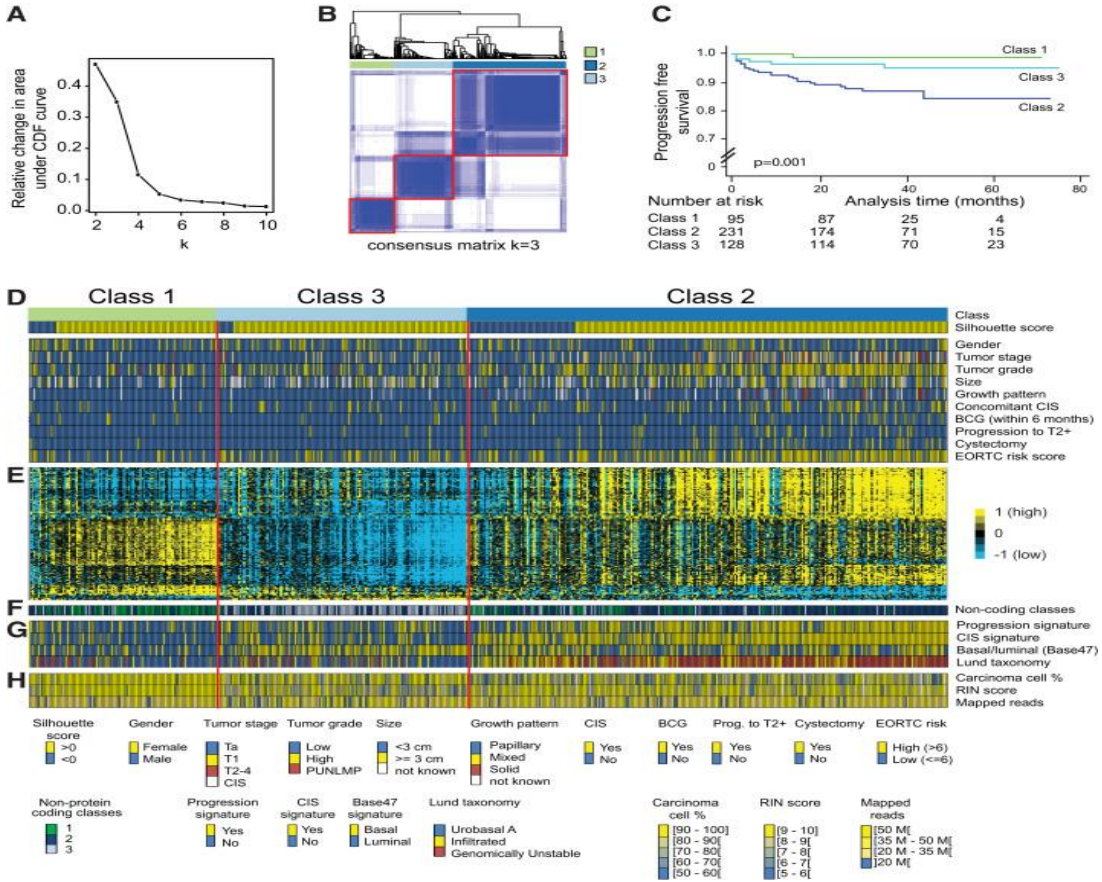
Presented By Seth Lerner at 2017 ASCO Annual Meeting

Molekulare Heterogenität des MIBC



TCGA, *Nature*, 2014

Molekulare Heterogenität - NMIBC



Hedegaard J. et al Cancer Cell 2016; 30:27-42

Blasenkarzinomsubtypen

Papillary

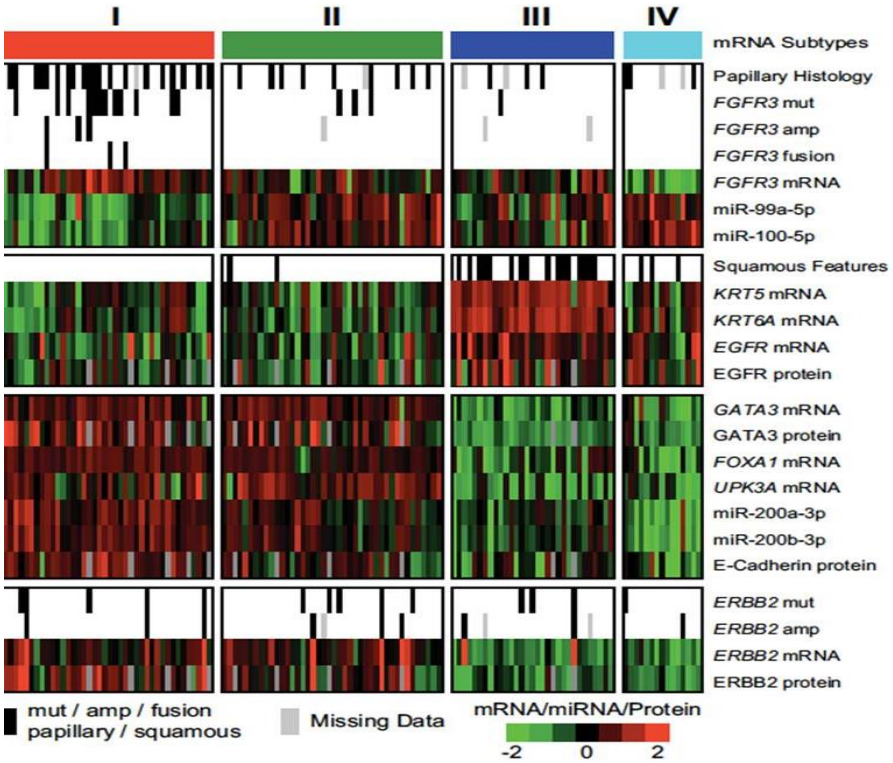
- Most NMIBCs
- Activating FGFR3 mutation, RAS activation
- TP53 wild type
- Genomically stable

Non-Papillary

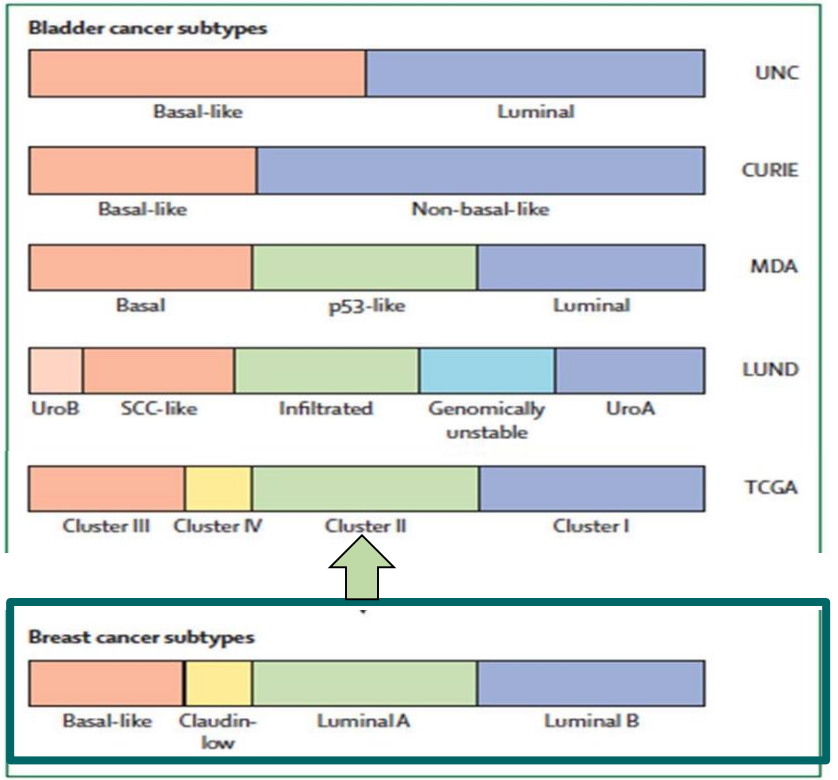
- Most MIBCs
- Loss of function mutations and CNAs including TP53 and RB1
- Genomically unstable

Choi W. et al., Eur Urol 2017; 72: 354-365

Molekulare Subtypen des MIBC

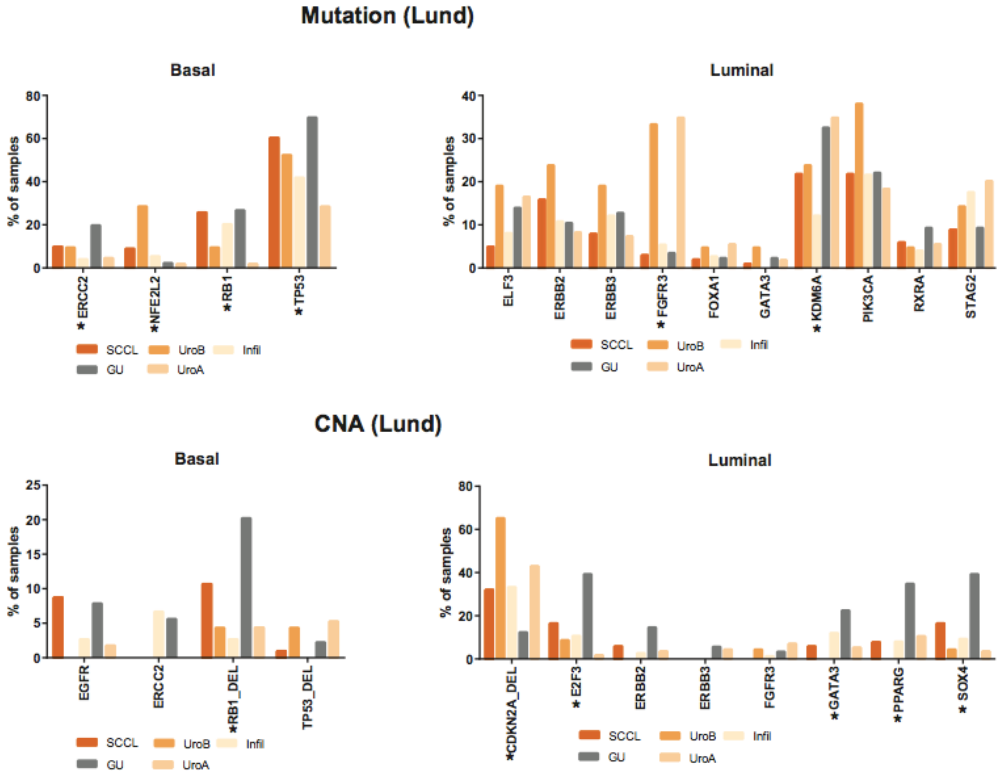


TCGA, Nature 2014



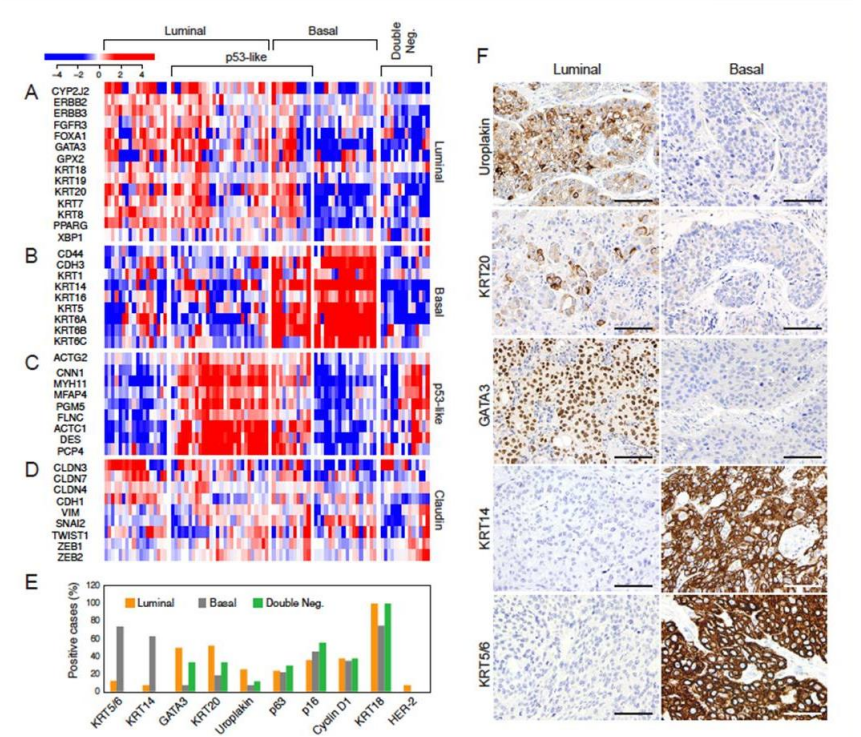
Lancet 388:2796, 2016

Enrichment of significantly mutated genes in the Lund Molecular Subtypes

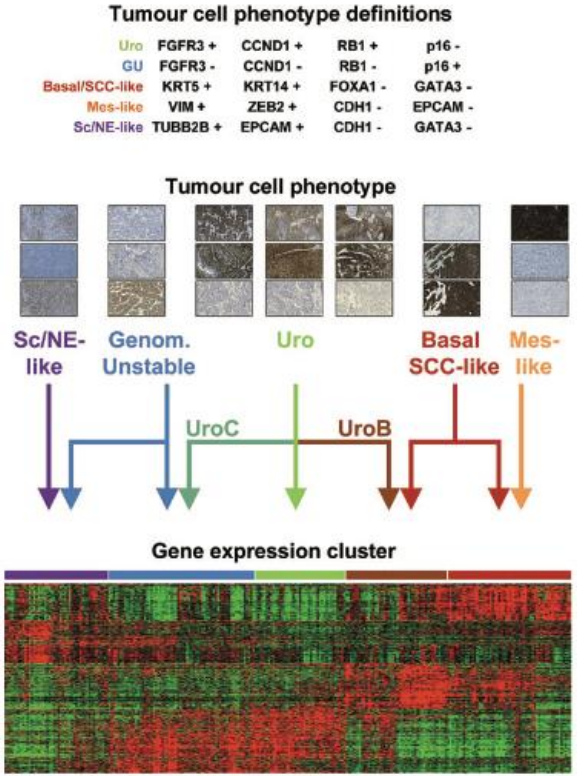


Choi W. et al.,Eur Urol 2017; 72: 354-365

Molecular Subtypes might be distinguished by IHC



Czerniak, eBiomedicine, 2017



Sjödal G et al., J Pathol, 2017; 242:113-125

Zusammenfassung - Molekulare Subtypen des MIBC

- Ähnlich dem Mammakarzinom können Urothelkarzinome in luminale und basal-like Subtypen unterteilt werden
  - Luminal: kann je nach Classifier weiter in p53-like, UroA, infiltrated, genetic unstable, bzw Cluster I und Cluster II unterteilt werden
  - Basal: kann je nach Classifier weiter in SCCL, UroB, Claudin low, bzw in Cluster III und IV

Zusammenfassung - Molekulare Subtypen des MIBC

- Mit IHC lassen sich luminale von basal-like Tumoren unterscheiden, wie auch die weiteren molekularen Subtypen identifizieren
- Die verschieden molekularen Subtypen weisen eine differentielle Anreicherung von signifikant mutierten Genen auf, die für die Identifizierung von drugable targets bedeutsam sind, bzw. prädiktiv für Therapieansprechen sein können

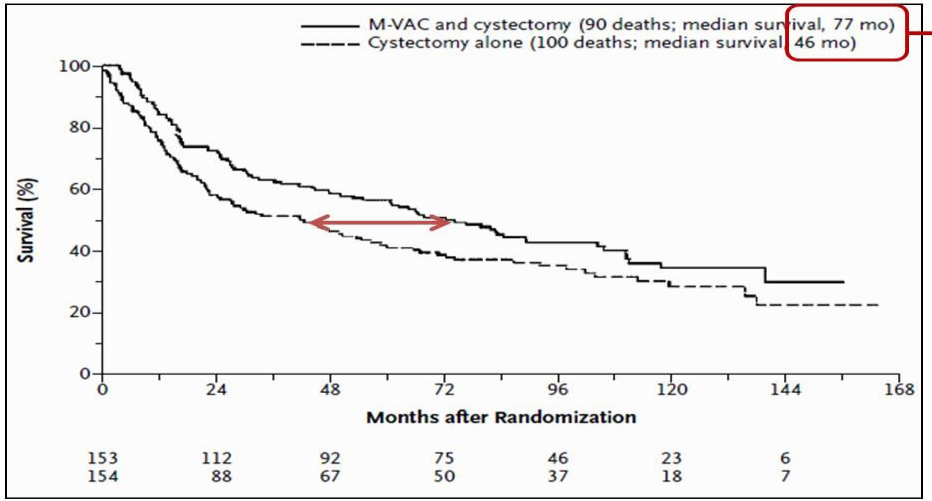
Biomarker für Response

NEOADJUVANTE CHEMOTHERAPIE

Neoadjuvante Chemotherapie ist Standard of Care für MIBC

SWOG-8710

3 cycles standard MVAC → Cystectomy
Vs.
Cystectomy alone

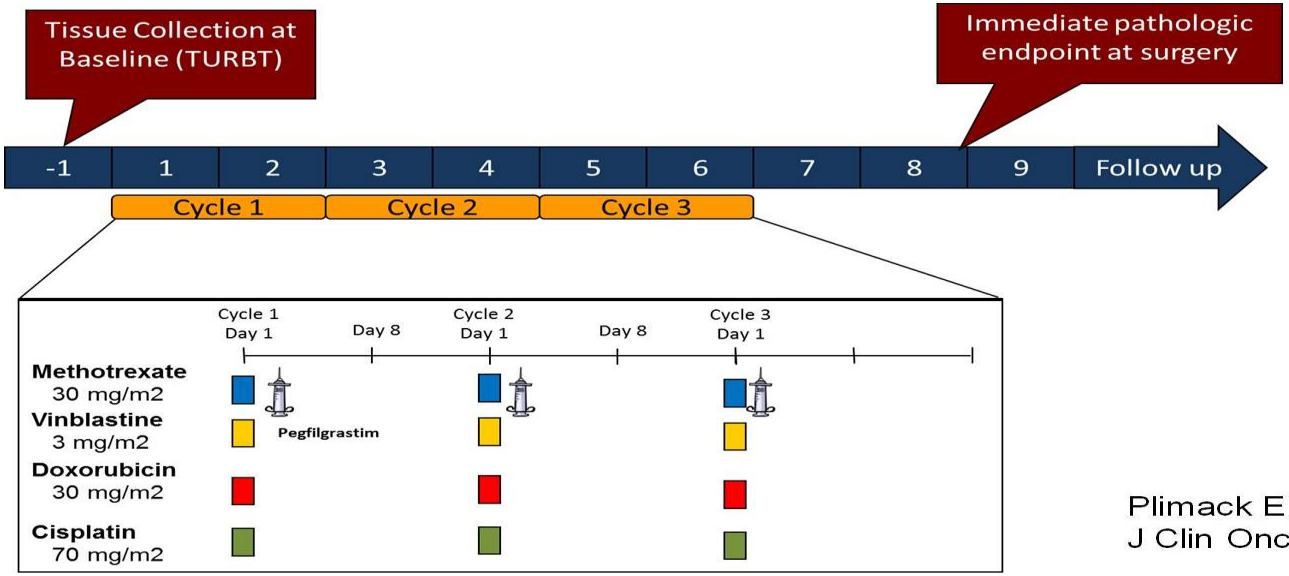


2.6 year median overall survival benefit

Grossman et al, NEJM, 2003

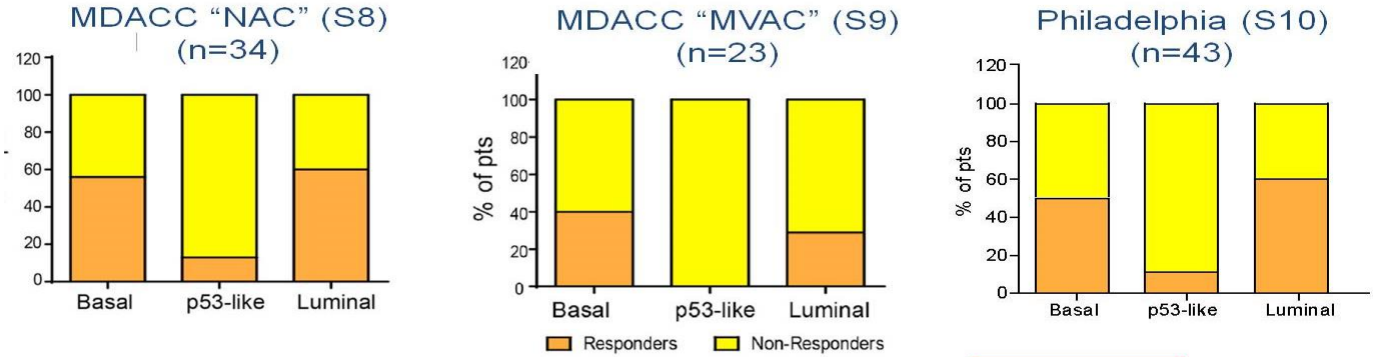
Grouman et al., NEJM, 2003

Neoadjuvantes Setting ist optimal für prädiktive Biomarker Forschung



Plimack ER, Hoffman-Censits JH, et al
J Clin Oncol. 2014

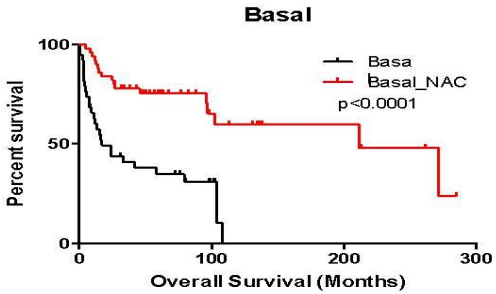
p53-like signature at baseline TUR predicts chemo-resistance (≥T2)

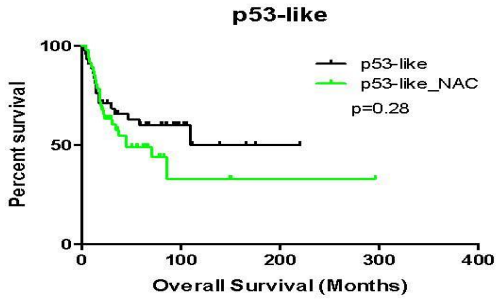


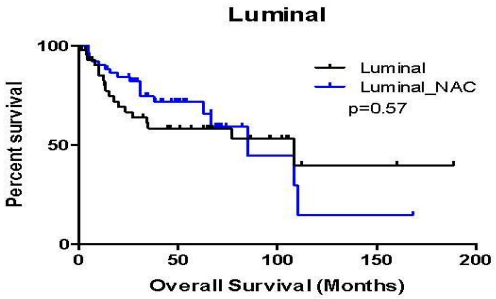
P53-like Subset	n	Sensitivity for resistance	Specificity for resistance	PPV for resistance	NPV for resistance
Discovery: MDACC S8 retro	34	62%	85%	87%	58%
Validation: MDACC S9 pre/post	23	35%	100%	100%	35%
Validation: S10 Philadelphia (DDGC + AMVAC)	43	40%	96%	89%	65%

Choi et al, Cancer Cell 2014

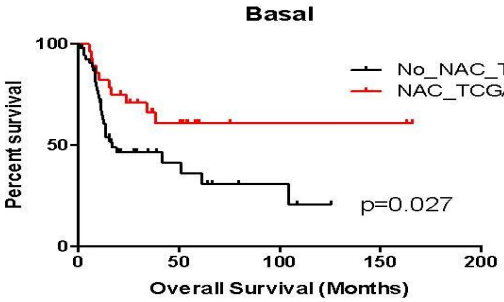
MDA/FoxChase data

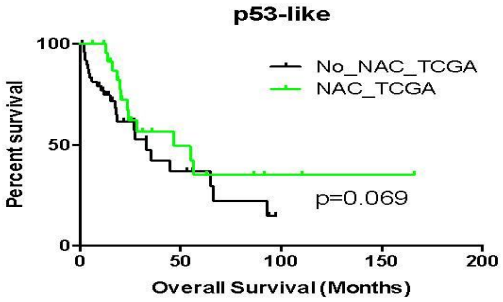


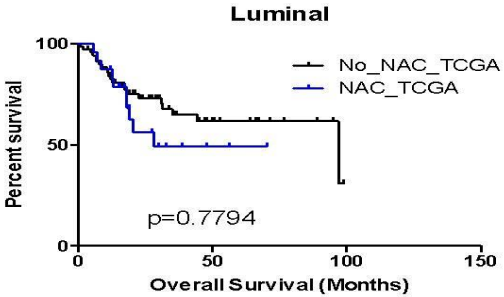




TCGA data

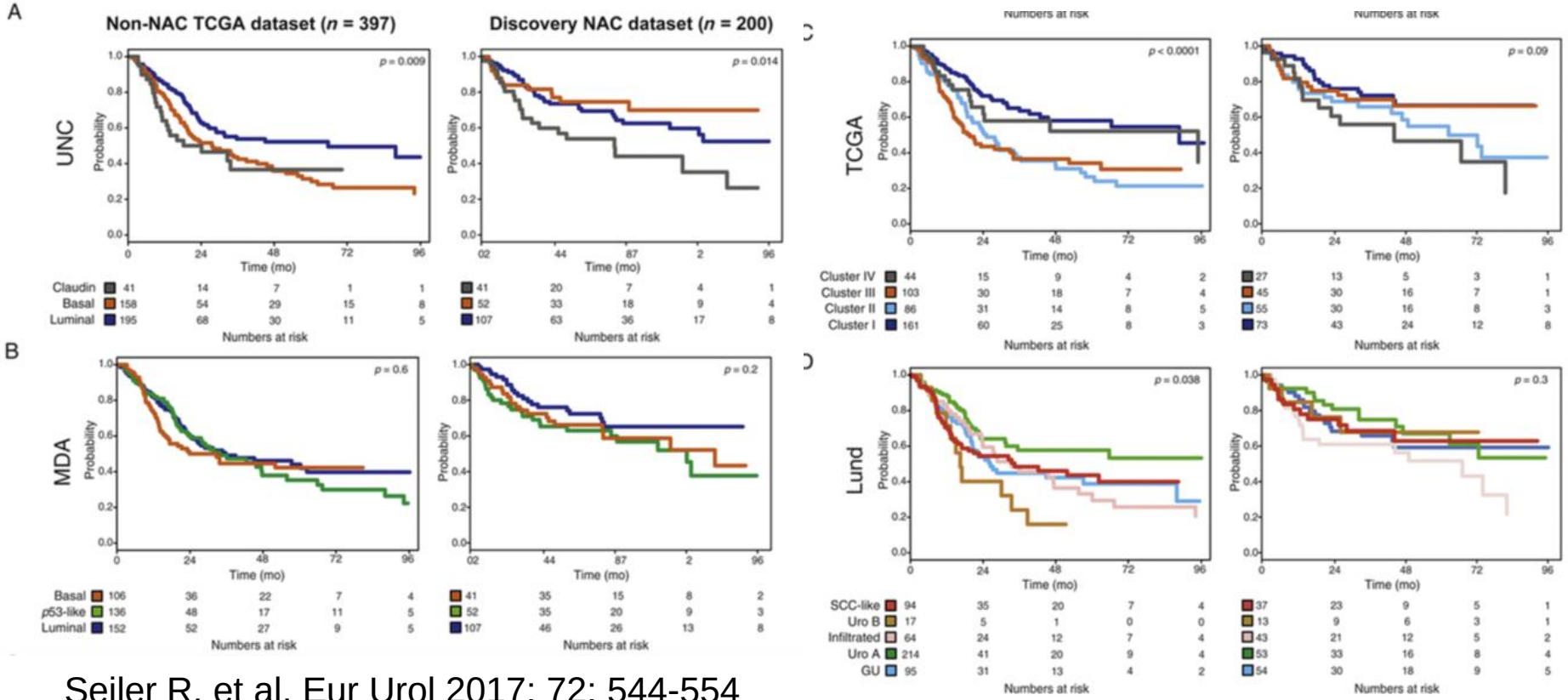






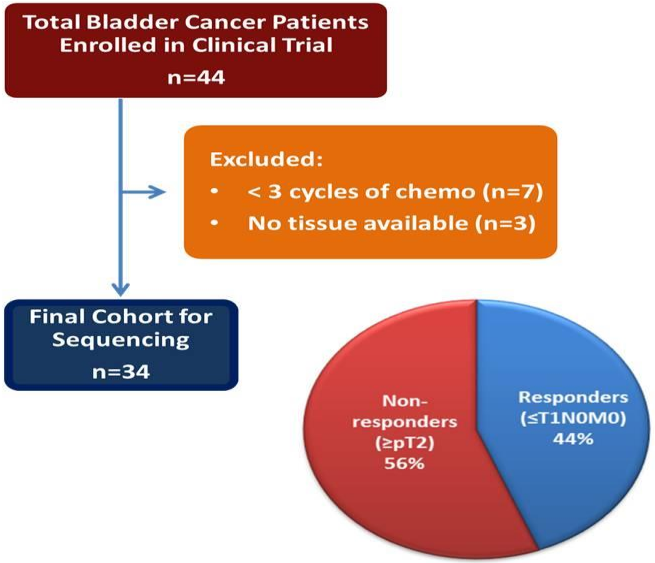
Presented By David McConkey at 2017 Genitourinary Cancers Symposium

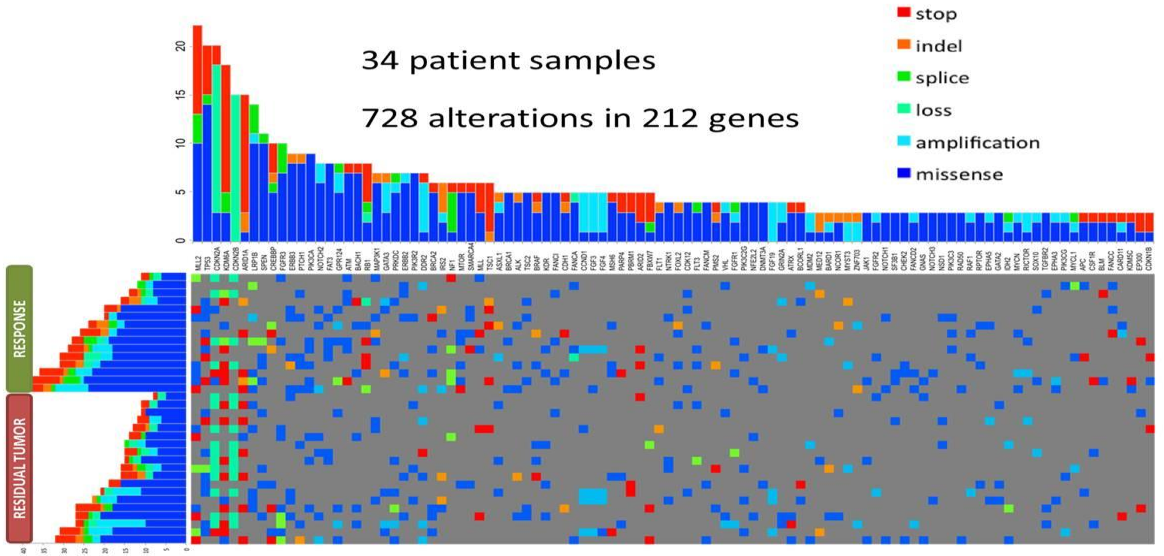
OS assoziiert zu molekular Subtyp in den non-NAC (li) und NAC (re) Discovery Datasets (n=269)



Seiler R. et al. Eur Urol 2017; 72: 544-554

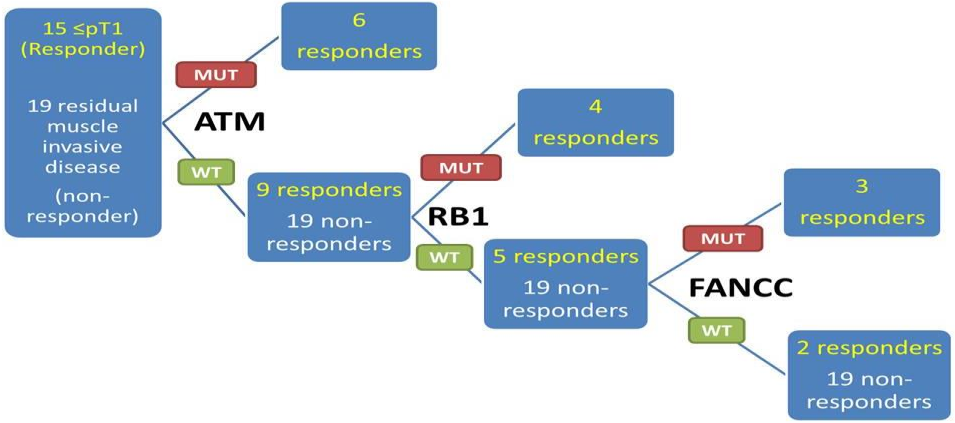
Genomische Analyse von prä-therapeutischen MIBC Samples (FoundationOne)

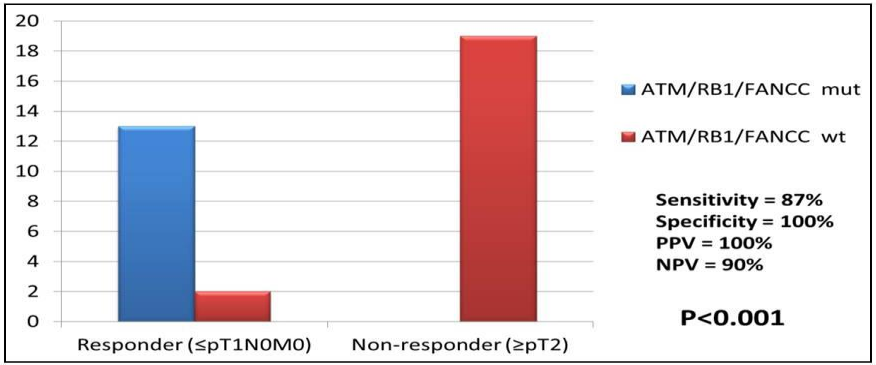




Plimack et al, European Urology, 2015

3-Gensignature: Alterationen in ATM, RB1 oder FANCC sig. assoziiert mit pathologischer Response

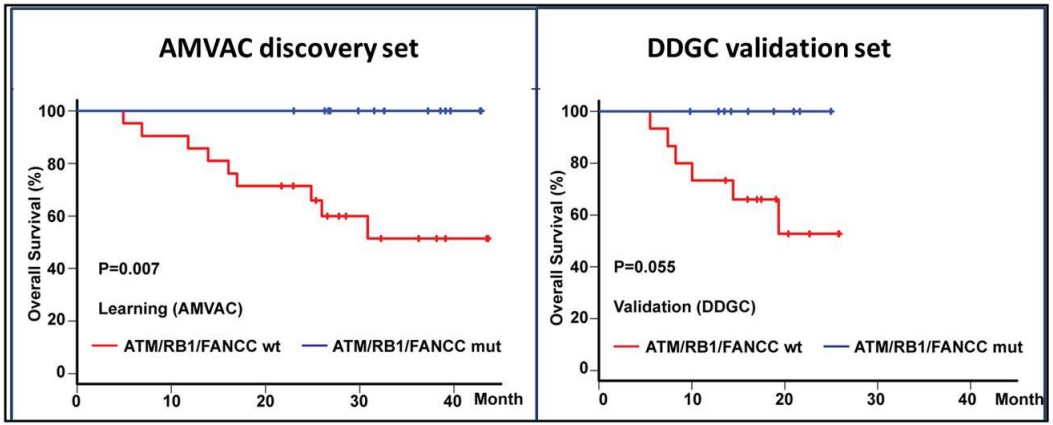




Plimack et al, European Urology, 2015

Presented By Elizabeth Plimack at 2017 Genitourinary Cancers Symposium

ATM/RB1/FANCC Mutationen korrelieren mit verbessertem Response und Survival

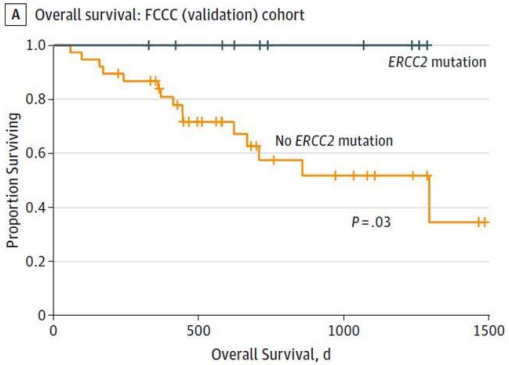


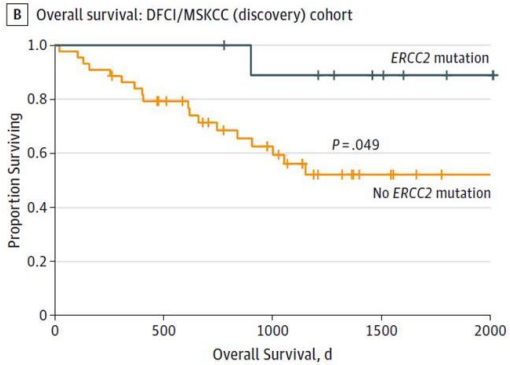
ATM, RB1, FANCC	n	Sensitivity for response	Specificity for response	PPV for response	NPV for response
Discovery: Philadelphia AMVAC	34	87%	100%	100%	90%
Validation: Philadelphia DDGC	24	64%	85%	78%	73%

Plimack et al, European Urology, 2015

ERCC2 Alterationen korrelieren mit verbesserter RR und OS in Discovery und Validation Sets

Philadelphia Validation Cohort





MSK/DFCI Discovery Cohort

No. at risk by time

No *ERCC2* mutation	38	20	8	0	44	32	20	7	3
ERCC2 mutation	10	8	4	0	10	10	8	5	2

ERCC2	n	Sensitivity for response	Specificity for response	PPV for response	NPV for response
Discovery: MSKCC DFCI	50	36%	100%	100%	61%
Validation: Philadelphia (DDGC+AMVAC)	48	80%	93%	80%	93%

Liu, et al. JAMA Onc 2016

Liu et al., JAMA Oncol, 2016

Hypothese: Defekte in DNA Reparaturgenen bewirken Sensitivität für platin-hältige Chemotherapie

- ATM, RB1, FANCC, and ERCC2 mutations cause defects in DNA damage repair that confer sensitivity to cisplatin-based chemotherapy
- The accumulation of alterations seen among patients with pathologic complete response reflects this phenotype.
  (p=0.024 FCCC AMVAC discovery, p= 0.018 FCCC DDGC validation, p= 0.0003 in MSKCC/DFCI cohort)

Gene	Gene Dysfunction Results in Impaired DNA repair
ATM	Dysfunctional ATM impedes DNA repair induced by cisplatin. Accumulation of damaged, unrepaired DNA triggers apoptosis.
Rb1	Dysfunctional Rb1 results in increased double-strand breaks. Accumulation of cisplatin-damage triggers apoptosis by a mechanism other than Rb1 checkpoint tumor suppression.
FANCC	Dysfunctional FANCC impedes DNA repair induced by cisplatin. Accumulation of damaged, unrepaired DNA triggers apoptosis.
ERCC2	Dysfunctional ERCC2 leads to inability for nucleotide excision repair after cisplatin-induced DNA damage. Accumulation of damaged, unrepaired DNA triggers apoptosis.

Zusammenfassung NAC bei MIBC

- Basale Subtypen des UC profitieren von Platin-hältiger NAC
- p-53 like Subtypen bzw. Claudin low Subtypen und luminal(infiltrated) Subtypen profitieren eher nicht von NAC
- Luminale Tumoren (non-infiltrated) haben die beste Prognose profitieren nicht/ brauchen keine NAC

Zusammenfassung NAC bei MIBC

- Genetische Alterationen in ATM, RB1, FANCC sowie ERCC2 Mutationen haben möglicherweise einen prädiktiven Wert für Responsevorhersage auf NAC bei MIBC,
- Wilde type Tumoren in den oben gelisteten Genen zeigen praktische keine Response
- Caveat: Alle Daten sind retrospektiv zum Teil in nur kleinen Kohorten gezeigt –Prospektive Validierung noch ausständig

Biomarker für Response

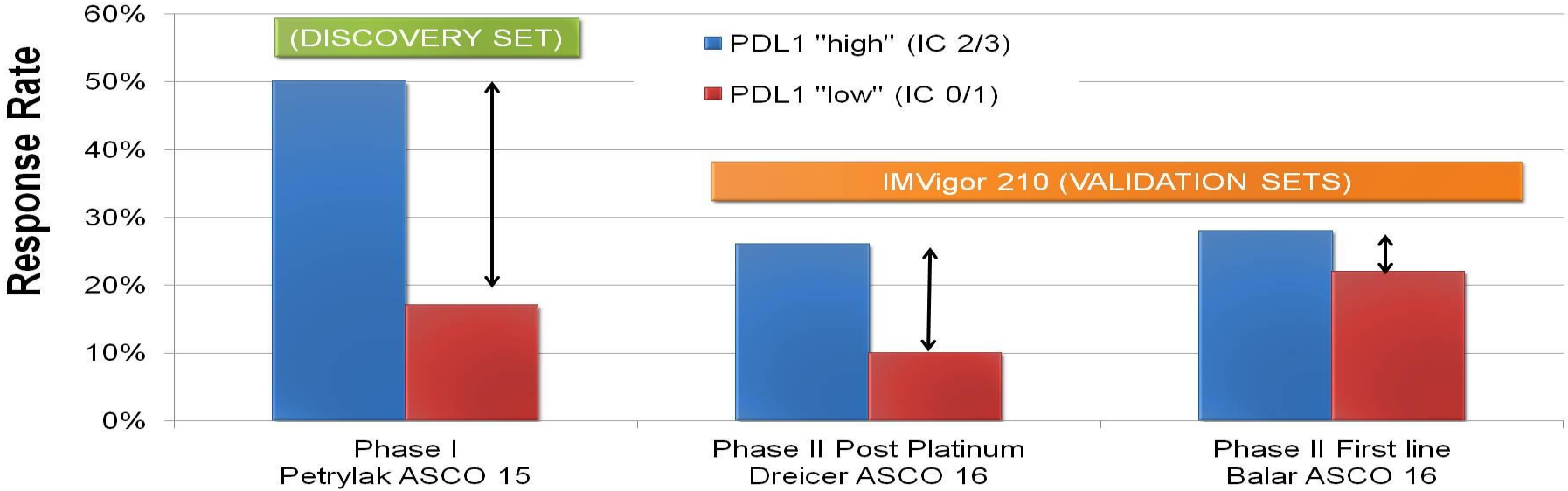
IMMUNCHECKPOINT INHIBITOR THERAPIE

Rolle der PD-L1 IHC

- PD-L1 is expressed both on tumor and immune cells in urothelial cancer
- Higher level of staining leads to higher response rates with some agents, and may be linked to overall survival
- Multiple PD-L1 assays exist and are being evaluated in bladder cancer
- Interpretation of assays depends on the antibody

Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920.
Sharma P, et al. *Lancet Oncol*. 2017;18:312-322.
Bellmunt J, et al. *N Engl J Med*. 2017;376:1015-1026.

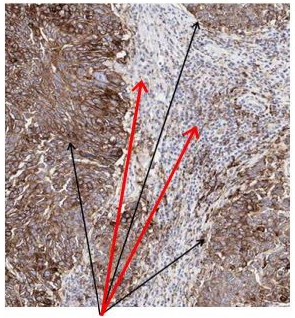
PD-L1 Testing (IC 2/3 vs. 1/2 IHC) Fehlender Nachweis Responder in den Atezolizumab mUC Studien zu identifizieren



Presented By Elizabeth Plimack at 2017 Genitourinary Cancers Symposium

PDL1 Testing (CPS ≥ 10%) Fehlender Nachweis Responder in den Pembrolizumab mUC Studien zu identifizieren

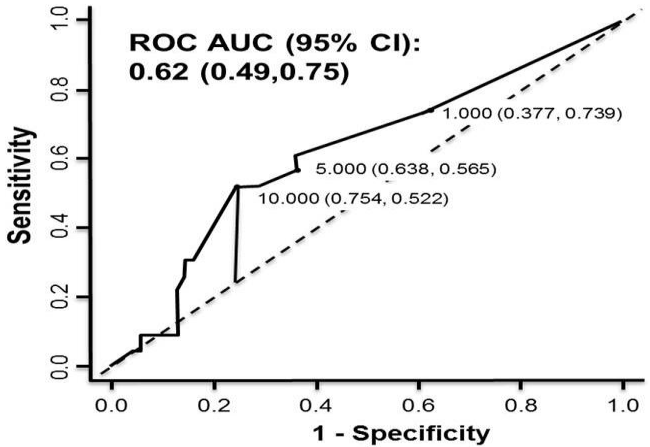
Combined positive score (CPS) is determined by IHC using the PD-L1 22C3 pharmDx assay



PD-L1 positive cells (Tumor, inflammatory cells)

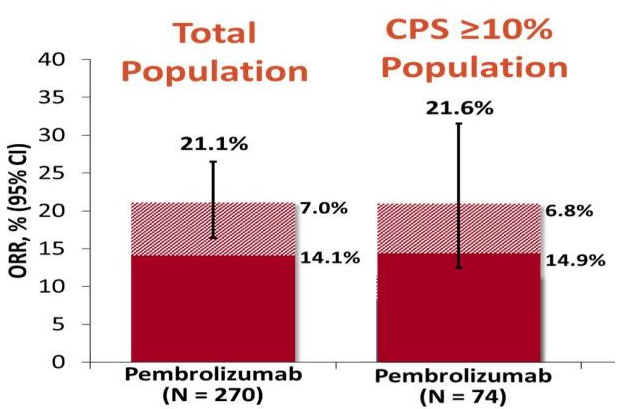
Balar et al. ESMO 2016.

KEYNOTE 52 (DISCOVERY SET)



Confirmed and Unconfirmed Best Overall Response

KEYNOTE 45 (VALIDATION SET)

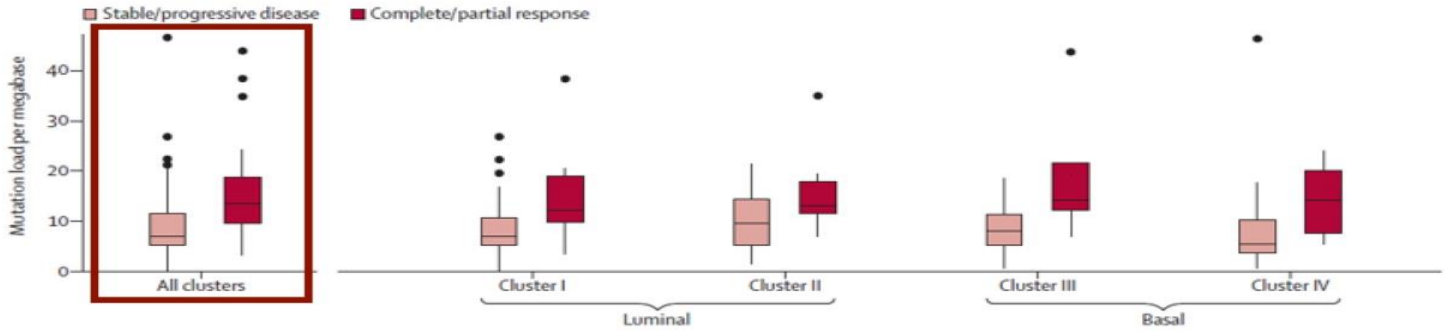


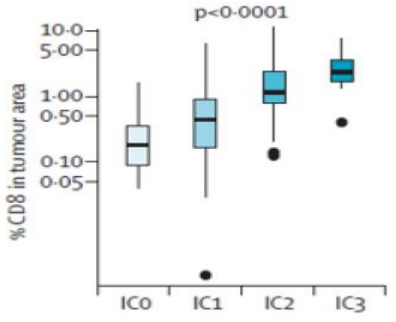
Bellmunt et al. SITC 2016.

Presented By Elizabeth Plimack at 2017 Genitourinary Cancers Symposium

Biomarker beyond PD-L1 Mutational Load und RR

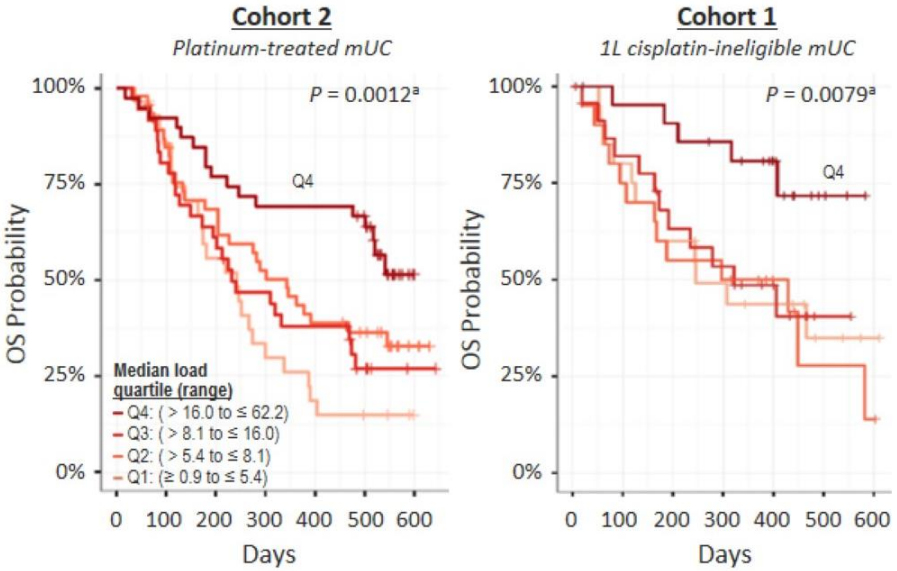
- Atezolizumab in platinum-pretreated patients
- Estimated using a targeted panel
- Focuses on non-hotspot alterations
- Extrapolates from 3% of genome covered in assay
- Mutation load associated with higher objective responses





Reprinted from Lancet, 387, Rosenberg JE, et al., Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a singlearm, multicentre, phase 2 trial, 1909-1920., Copyright 2016, with permission from Elsevier.

Biomarker beyond PD-L1 Mutational Load und OS

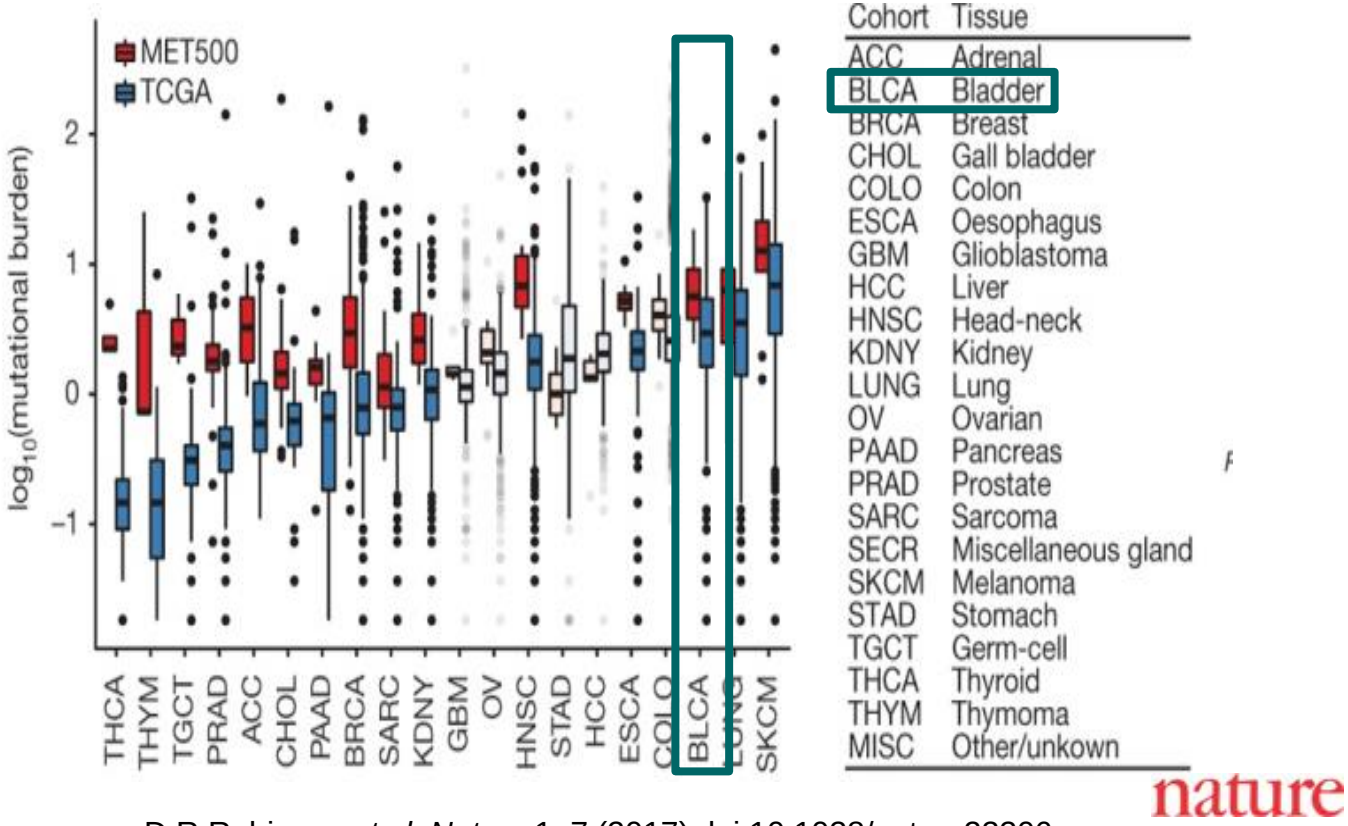


Rosenberg JE, et al. ASCO 2016. Abstract 104. Reprinted with permission.

- Patients treated with atezolizumab
- Mutation load associated with ORR
- Quartile-split mutation load was associated with OS in platinum-treated patients (cohort 2)
- Similar results were seen for 1L cisplatin-ineligible patients (cohort 1)
- In both cohorts, patients with the highest median mutation load (Q4) had significantly longer OS vs those in Q1-Q3

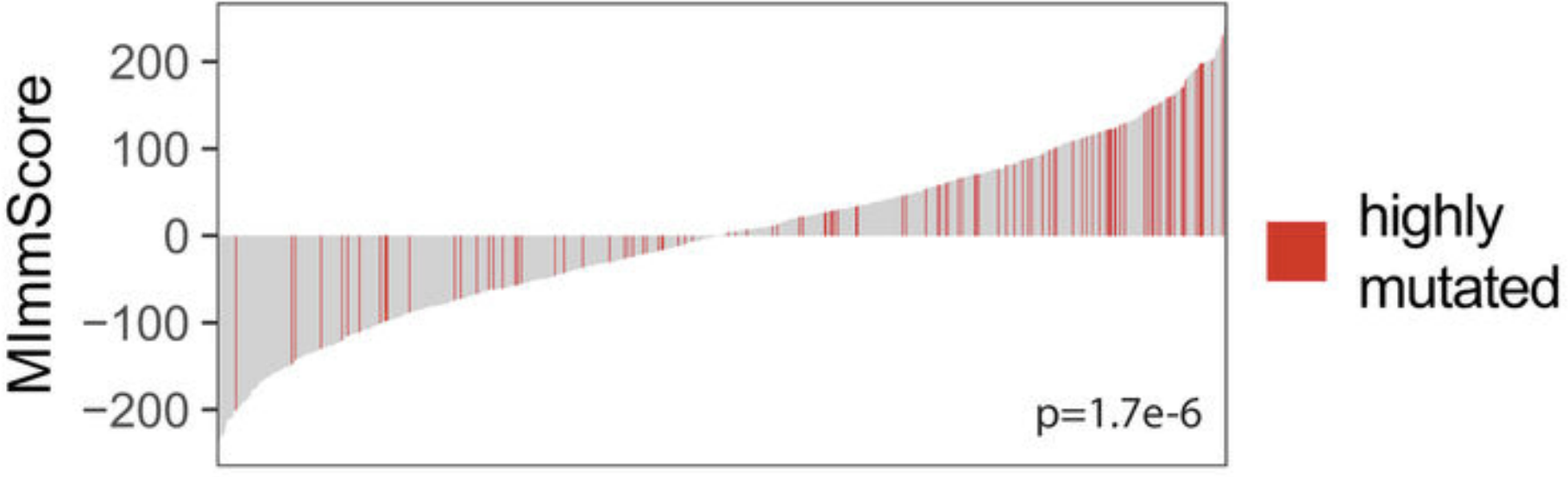
Rosenberg JE, et al. *J Clin Oncol.* 2016;34(suppl). Abstract 104.
Balar AV, et al. *Lancet*. 2017;389:67-76.

Molekulare Heterogenität bei metastasierten Tumoren



D R Robinson *et al. Nature* 1–7 (2017) doi:10.1038/nature23306

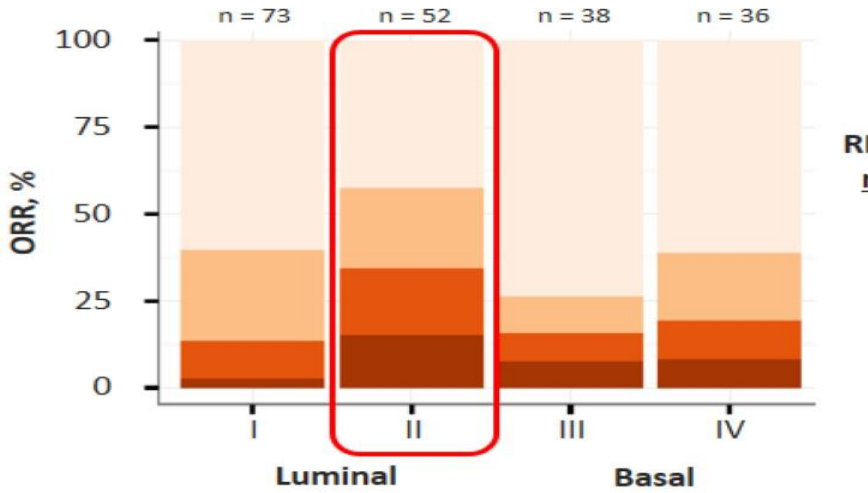
Zusammenhang Mutational Load und Immunzellinfiltrat



D R Robinson *et al. Nature* 1–7 (2017) doi:10.1038/nature23306

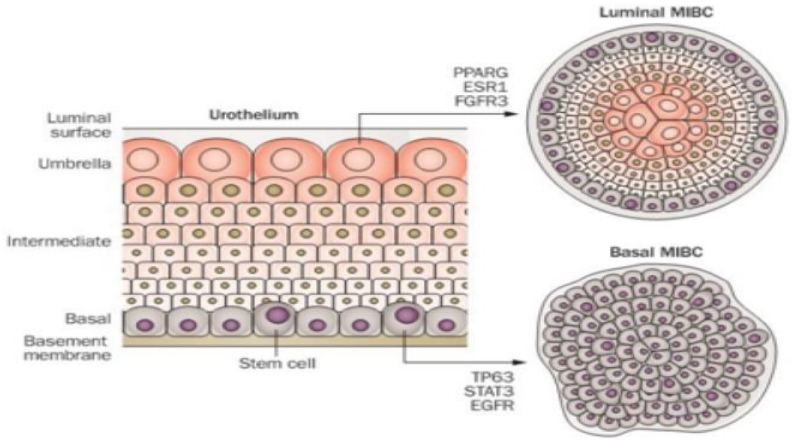
nature

Biomarkers Beyond PD-L1: Expression Subtype



Rosenberg JE, et al. ASCO 2016. Abstract 104. Reprinted with permission. © 2016 American Society of Clinical Oncology. All rights reserved.

- Gene expression data used to classify IMvigor210 tumor samples recapitulated TCGA subtypes
- Responses occurred in all subtypes, but ORR was significantly higher in luminal 2 vs other subtypes ($P = .0072$)

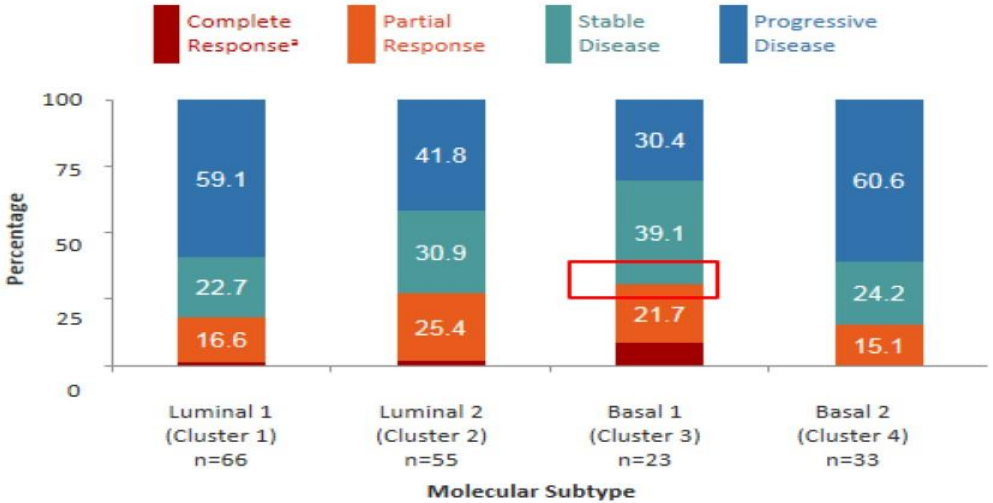


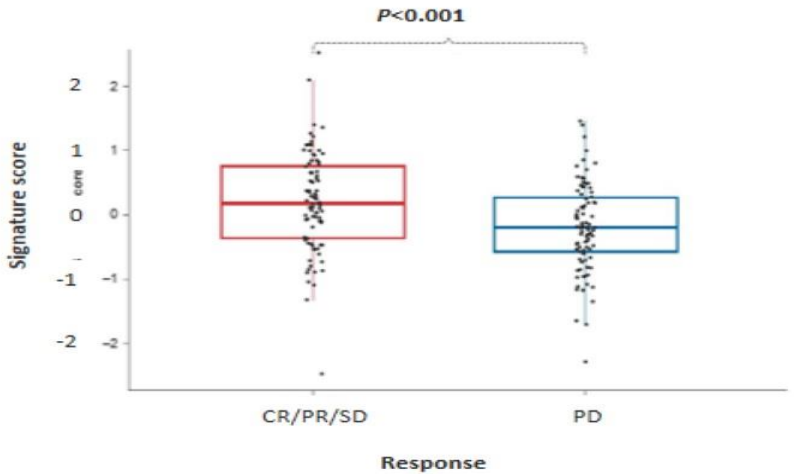
Reprinted by permission from Macmillan Publishers Ltd: Choi W, et al. Nat Rev Urol. 2014;11:400-410.

Rosenberg JE, et al. *J Clin Oncol.* 2016;34(suppl). Abstract 104.
Choi W, et al. *Nat Rev Urol*. 2014;11:400-410.

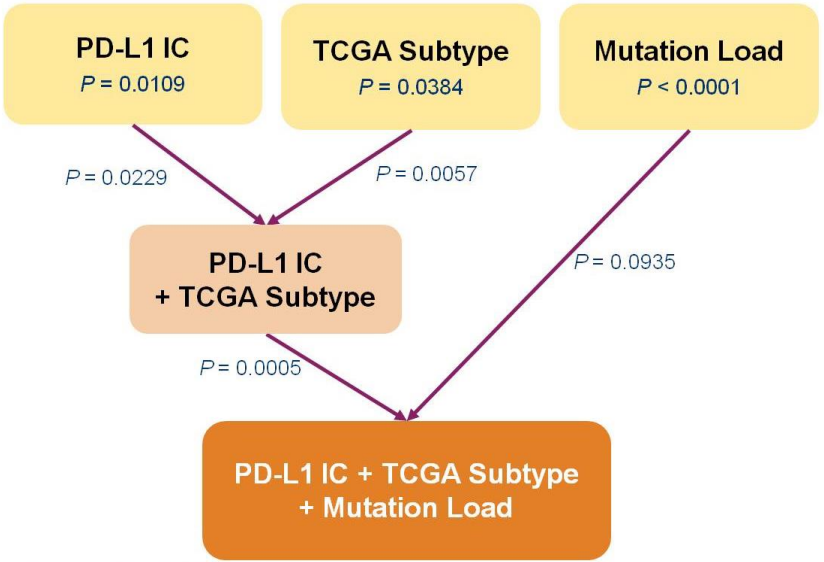
Molecular Subtype, 25-Gene Interferon-γ Signature, and Response to Nivolumab

- Basal 1 and luminal 2 have higher response rates vs the other 2 subtypes
- Interferon-γ genes are enriched in responders vs those with progressive disease (P <0.01)





Predictors of Response to Atezolizumab



- PD-L1 IHC, TCGA subtype and mutation load were significant independent predictors of response
- PD-L1 IC + subtype combination significantly improved on PD-L1 IC alone or subtype alone
- 3-biomarker combination significantly improved on PD-L1 IC + subtype combination
- These data highlight the importance of the interaction between the tumor and its microenvironment in understanding response to atezolizumab

Based on data cutoff: March 14, 2016.

Presented By Jonathan Rosenberg at 2016 ASCO Annual Meeting

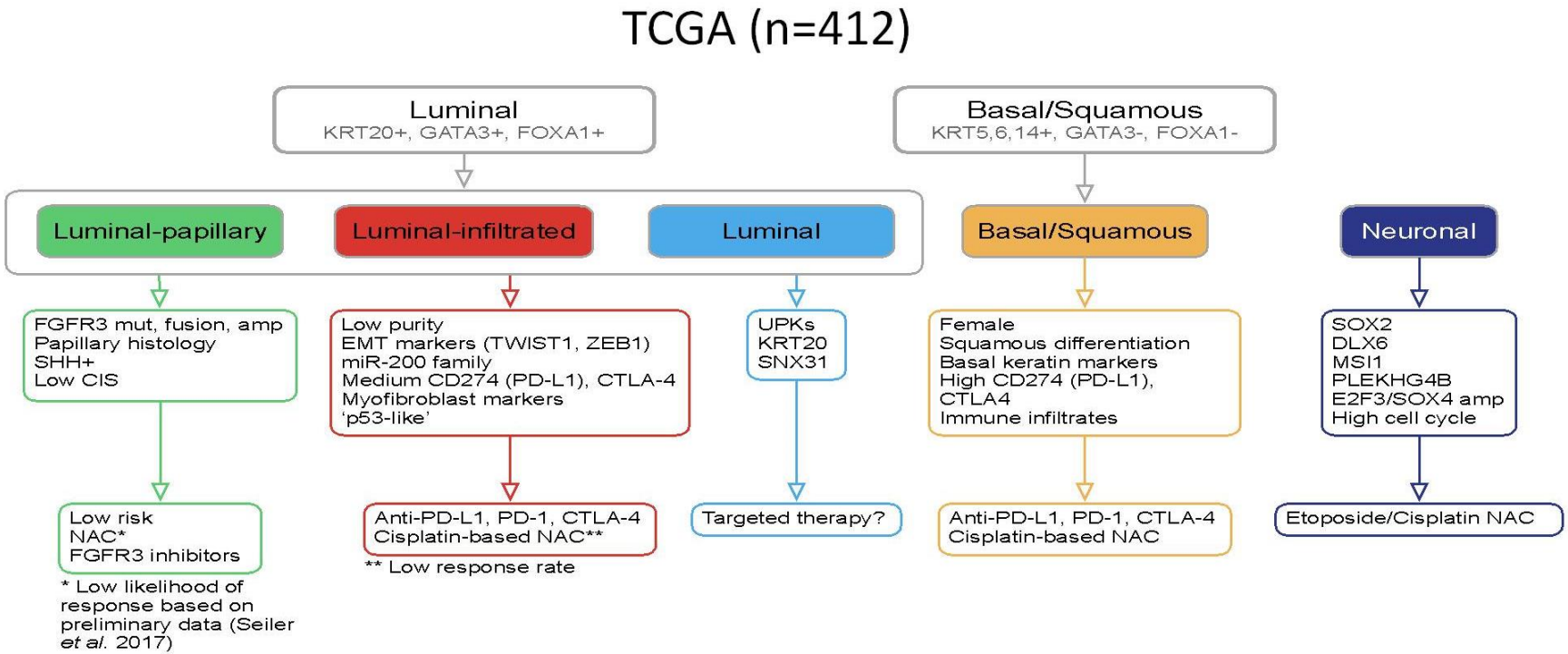
Zusammenfassung für IO

- PD-L1 hoch-exprimierende Tumoren (CS >10 bzw. IC2/3) zeigen möglicherweise eine bessere Response auf PD-1/PD-L1 zielgerichtete Therapien voraus
- Höherer Mutational Load ist mit höherer objektiver Response-Rate assoziiert
- Luminal 2 (Cluster 2 infiltrated) und Basal 1 (Cluster 3) molekulare Subtypen zeigen einen signifikant höhere Responsrate, Cluster IV zeigt hohes Immunzell-infiltrat aber schlechtes Ansprechen auf I-O

Zusammenfassung für IO

- Caveat: Die Methodik der molekulare Subtypisierung in gezeigten beiden Studien wurde nicht veröffentlicht
- Zusammenhang Qualität des Immunzellinfiltrat (Effektoren vs, Suppressoren) und Mutational load nicht ausreichend gut charakterisiert
- Weitere prospektive Studien mit möglichst standardisierter molekularer Subtypisierung notwendig

Zukünftiger Behandlungsalgoritmus für MIBC ?



Presented By Seth Lerner at 2017 ASCO Annual Meeting

Cell, submitted

„Releasing the Brake“