Highlights in GU 2015

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SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Monday , 21 December 2015 – 14:30-16:00 - Hall Summit

Conflict of Interest Disclosure

- **Advisor**
  - **OncoGenex, Pierre Fabre, Astellas, Genentech, Merck**

- **Non-paid Advisor and/or Research Support**
  - **Sanofi, Novartis, Janssen, ImClone, Genentech, Merck, BMS**

Outline Bladder

- Chemotherapy for Metastatic Disease
  - First line Cisplatin Fit
  - Maintenance after 1st line
  - Second Line chemotherapy
- New Approaches
    - Predictive genomics
    - Targeted therapies
    - Immunotherapy

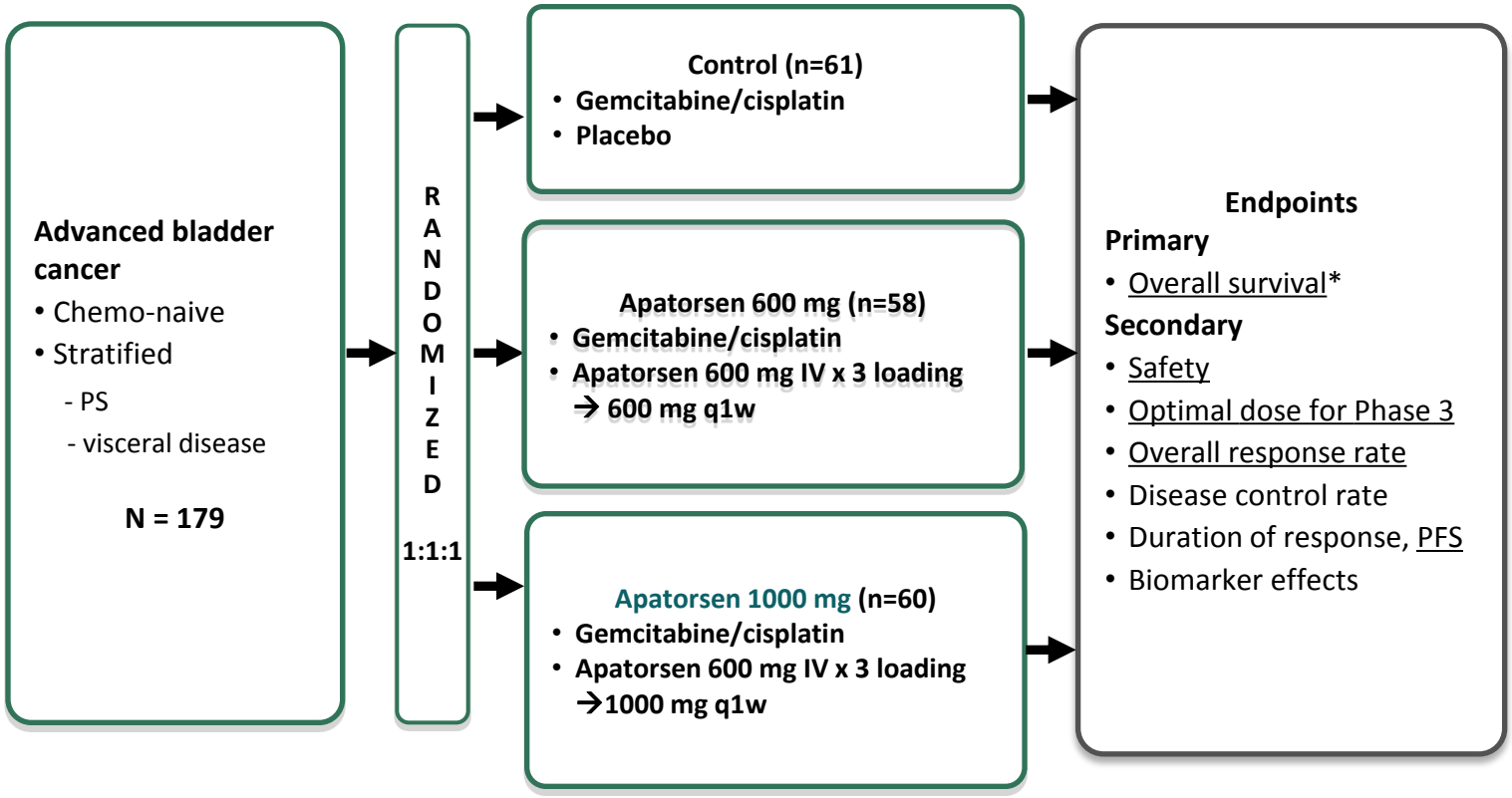
First-Line Randomized Phase 2 Study of Gemcitabine/Cisplatin plus Apatorsen or Placebo in Patients with Advanced Bladder Cancer: The International Borealis-1 Trial

Joaquim Bellmunt, Bernhard Eigl, Elżbieta Senkus, Yohann Loriot, Przemyslaw Twardowski, Daniel Castellano, Normand Blais, Srikala S. Sridhar, Cora N. Sternberg, Margitta Retz, Brent Blumenstein, Cindy Jacobs, Patricia S. Stewart, Daniel Petrylak

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

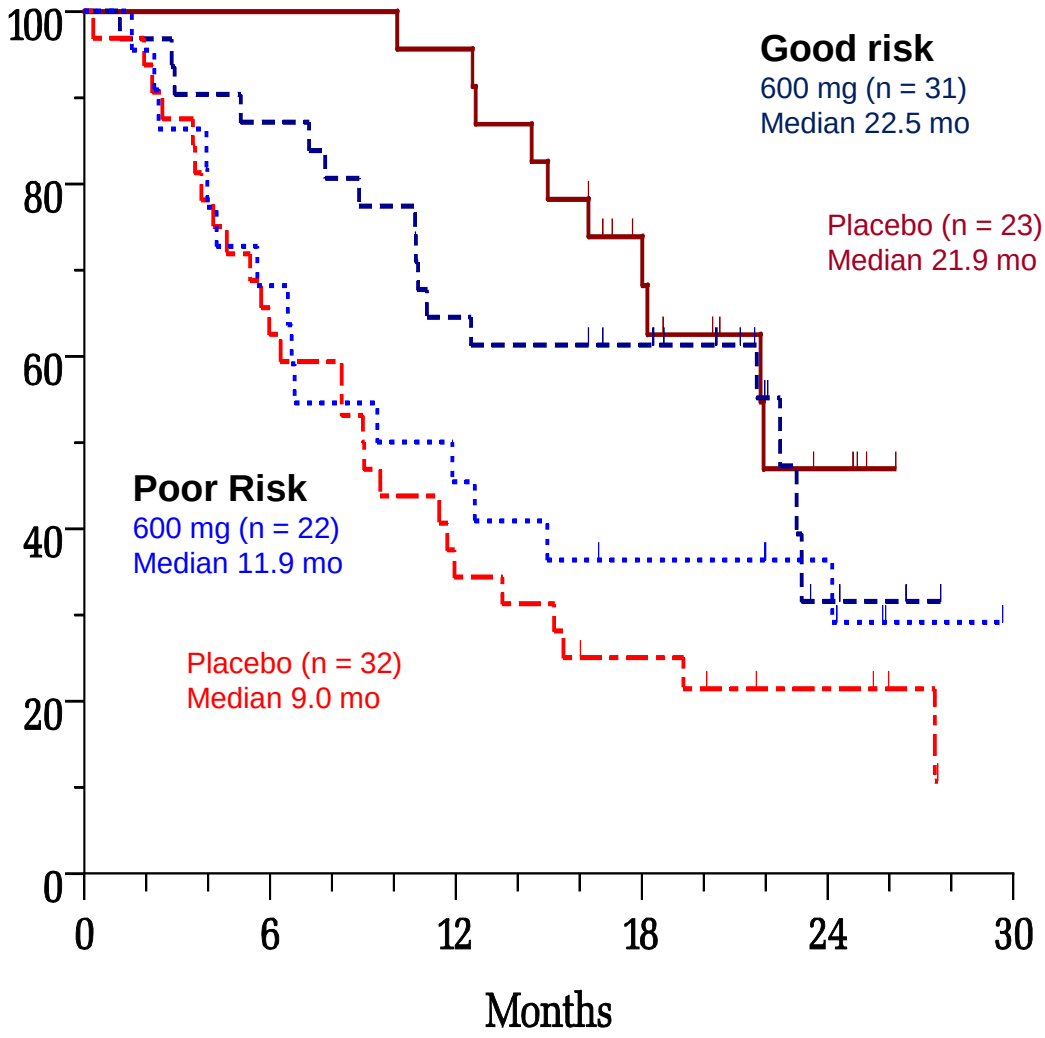
Study Design

Randomized, first-line, placebo-controlled, multinational phase 2 study in urothelial cancer conducted in 50 centers in 7 countries



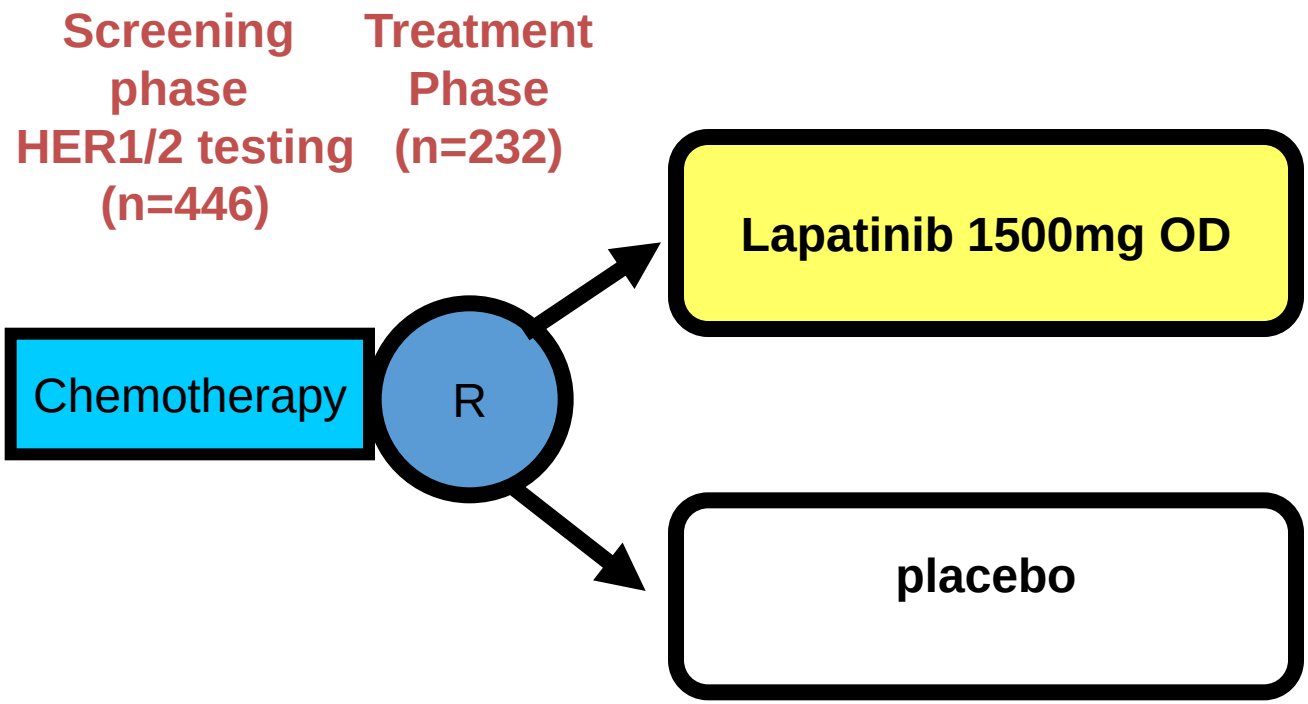
*Patients were to continue to receive weekly Study Drug maintenance until disease progression or the patient fulfills other reasons for withdrawal (tox, others)

Survival in 600 mg Apatorsen vs Control Arms by Risk



Good risk: HR = 1.44
Poor risk: HR = 0.72

Overview of study design



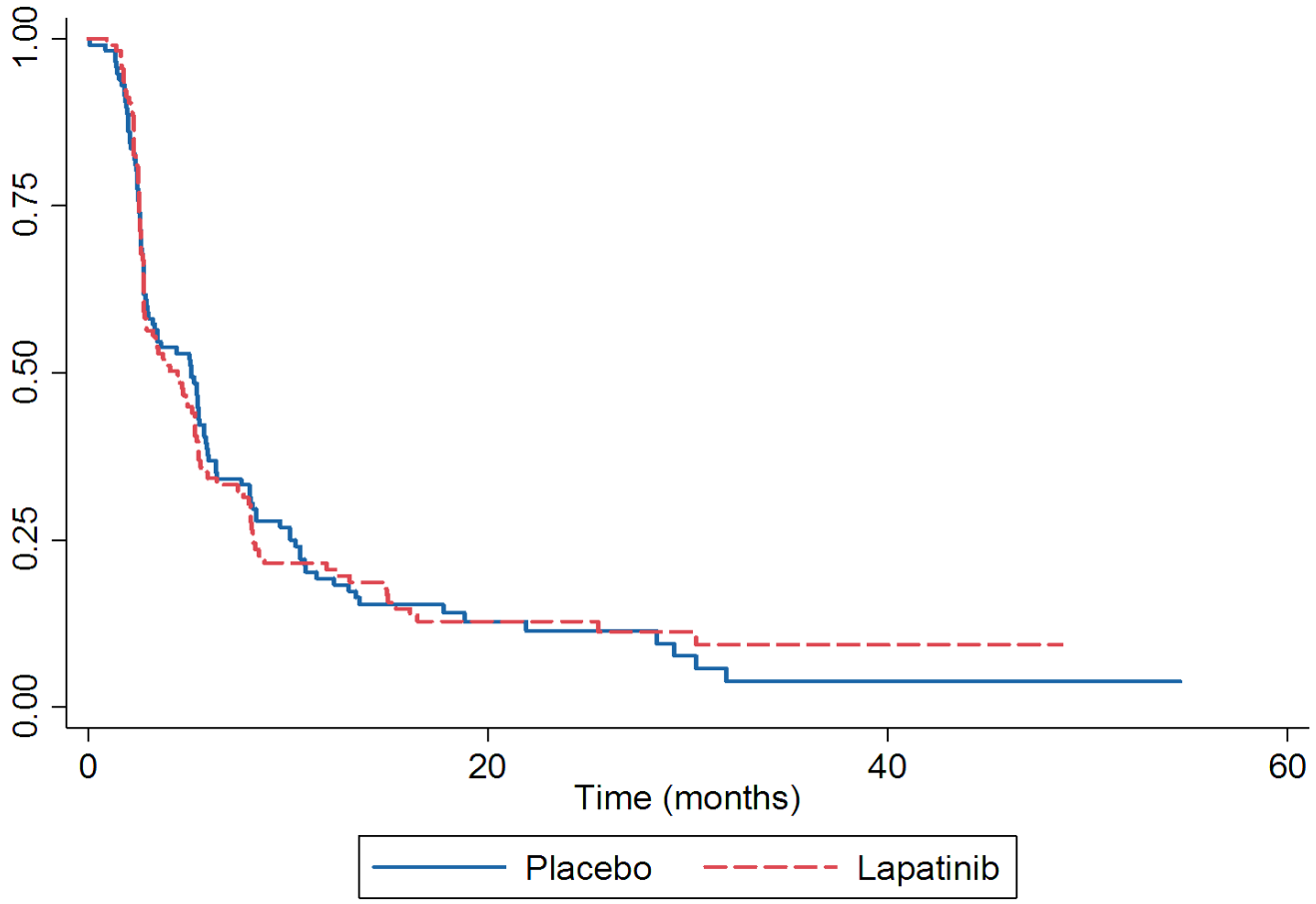
Eligibility criteria for randomisation

1. Metastatic or advanced UBC
2. HER1 or 2 positive transitional cell histology
3. Clinical benefit with first line chemotherapy
4. Normal ejection fraction

Endpoints

Primary: Progression free survival (PFS)
Secondary: Overall survival (OS) /adverse events.
Exploratory: subset analysis
Stratification: Chemotherapy response & PS

Randomised population:
PFS for lapatinib vs. placebo (primary endpoint)

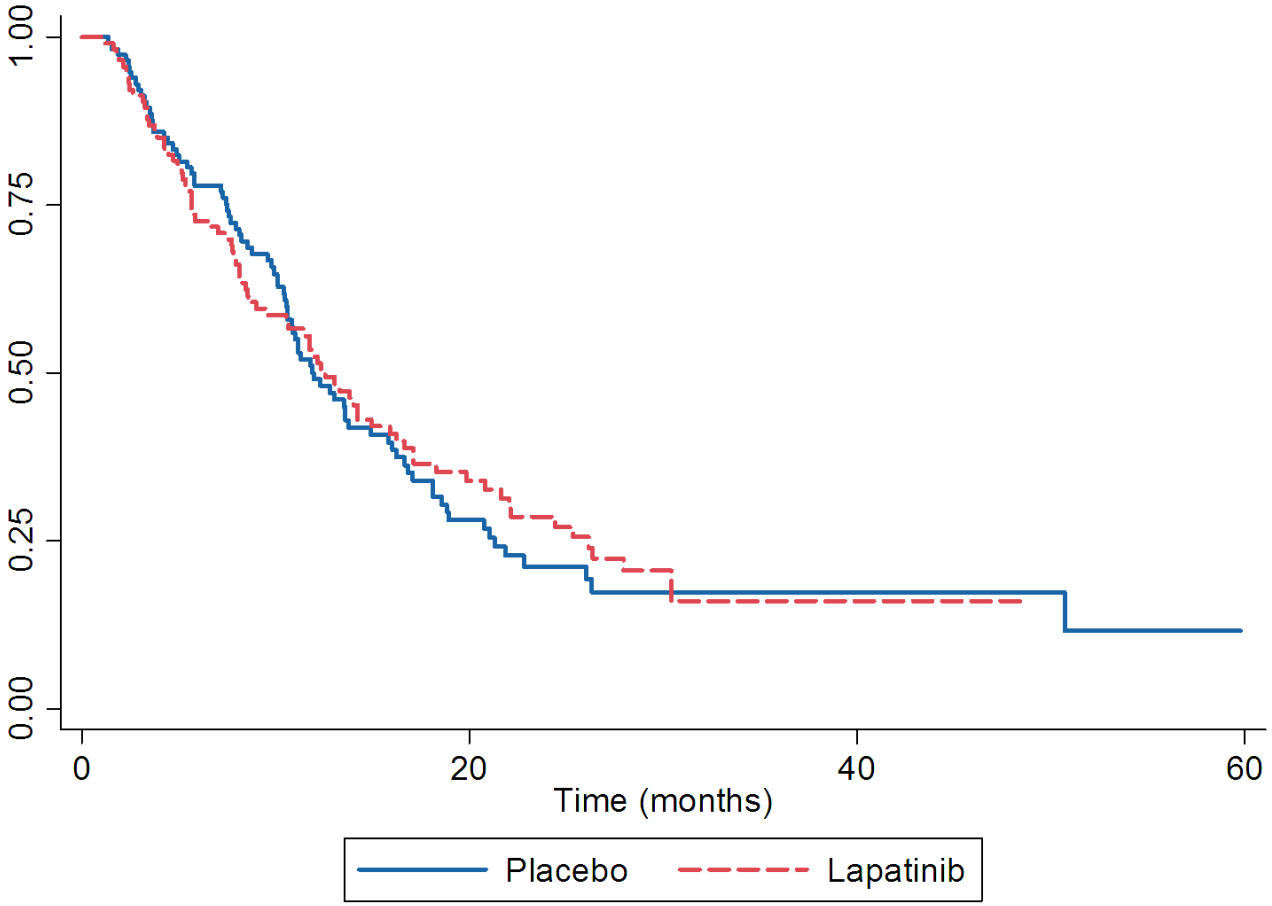


HR 1.1
(95%CI: 0.8-1.4)
P=0.62

Median PFS
lapatinib
4.6 months
(95%CI: 2.8-5.4)
Placebo
5.1 months
(95%CI: 3.0-5.8)

Response rate
lapatinib=14%
Placebo=8%
P=0.14

Randomised population: OS for lapatinib vs. placebo



HR 0.96
(95%CI: 0.7-1.3)
P=0.79

Median PFS
lapatinib
12.6 months
(95%CI: 9-16.2)

Placebo
12.0 months
(95%CI:10.6-15.8)

Further Therapy: Lapatinib = 58 (50%), Placebo = 64 (55%)

MAINTENANCE THERAPY IN BLADDER (after 1st line)

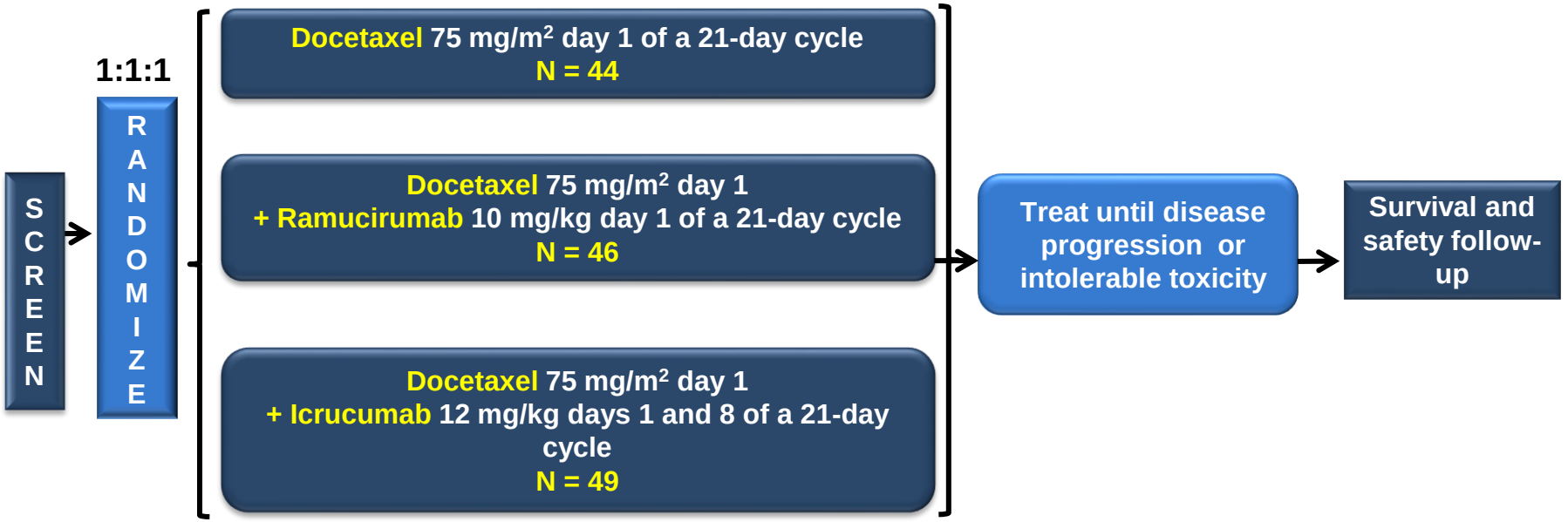
- No role of maintenance therapy

- Ongoing Studies (vs observation)
  - JASIMA, MAJA: Vinflunine
  - MRC: Lapatinib in her1/2 +

Study Design

PD within 1 year of perioperative platinum chemotherapy OR after no more than 1 line of platinum chemotherapy for metastatic disease

Prior paclitaxel allowed



Primary Endpoint:

- Progression-free survival (PFS)

Secondary Endpoints:

- Overall survival, objective response rate, duration of response, safety, PK/PD and immunogenicity profile

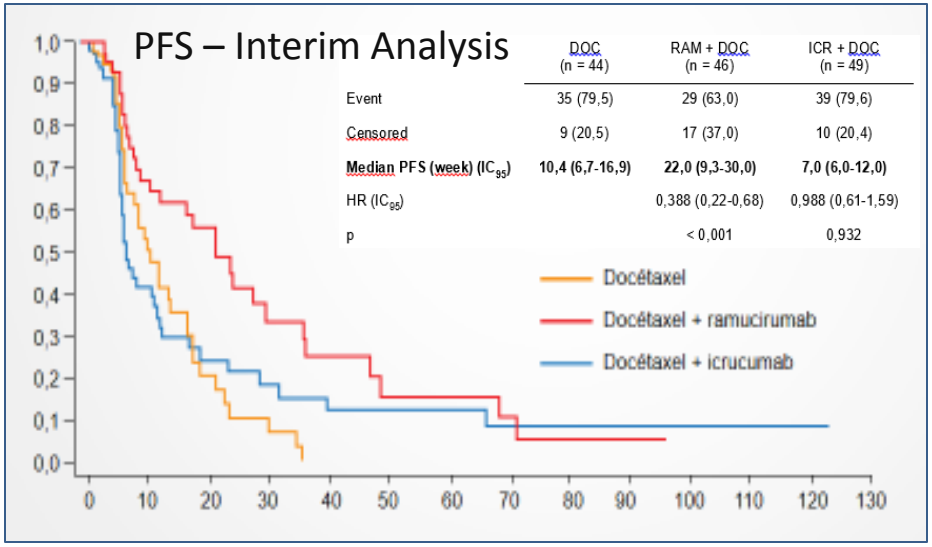
Stratification factors:

- Visceral metastasis (yes vs. no)
- Prior anti-angiogenic therapy (yes vs. no)

Ramucirumab + docetaxel in pretreated patients

D.P. Petrylak, Abs 295 ASCO-GU 2015

- Anti-VEGF-2 (ramucirumab) or anti-VEGF-1 (icrucumab) in combination with docetaxel
- In a 3 arm randomized phase II, pts PS 0-1 having progressed ≤ 12 months
  - Docetaxel 75 mg/m^2 on day 1 of a 21-day cycle
  - Docetaxel plus ramucirumab (10 mg/kg on day 1 of a 21-day cycle)
  - Docetaxel plus icrucumab (12 mg/kg on days 1 and 8 of a 21-day cycle)

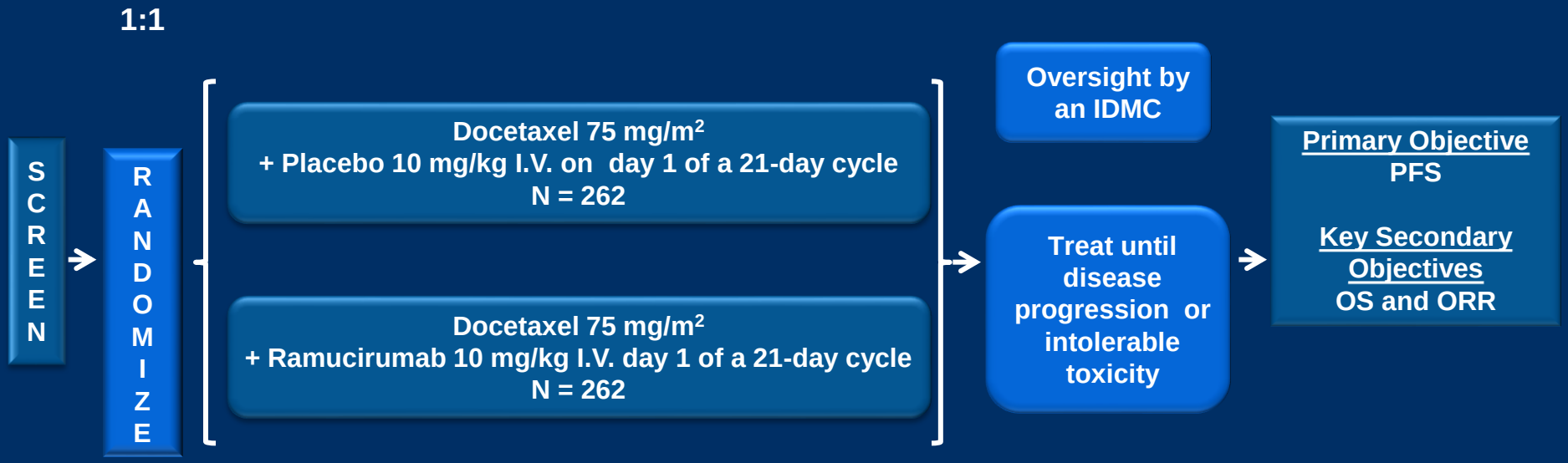


Interim analysis	N	OR (%)	DCR (%)	OS (mo)
DCT	44	5 p = 0.050	43 p = 0.033	7,7*
DCT + RAM	46	20	67	11,3*
DCT + ICR	49	10	31	6,4*

* OS is not mature

Ramucirumab enter in phase III (DCT + RAM vs DCT + plac), 524 pts ; end point is PFS

RANGE (trial I4T-MC-JVDC): Study Design



Important Inclusion Criteria:

- Locally advanced or unresectable or metastatic UC and ECOG PS 0 or 1
- Progression on or after first-line platinum-based chemotherapy (≤ 14 months; or ≤ 24 months if prior treatment with one immune checkpoint inhibitor)

Key Exclusion Criteria:

- Hemoglobin < 9 g/dL
- Uncontrolled bleeding or thrombotic disorder
- Known untreated brain metastasis

Pazopanib + paclitaxel in pretreated patients

S. Srinivas Abs 294 ASCO-GU 2015

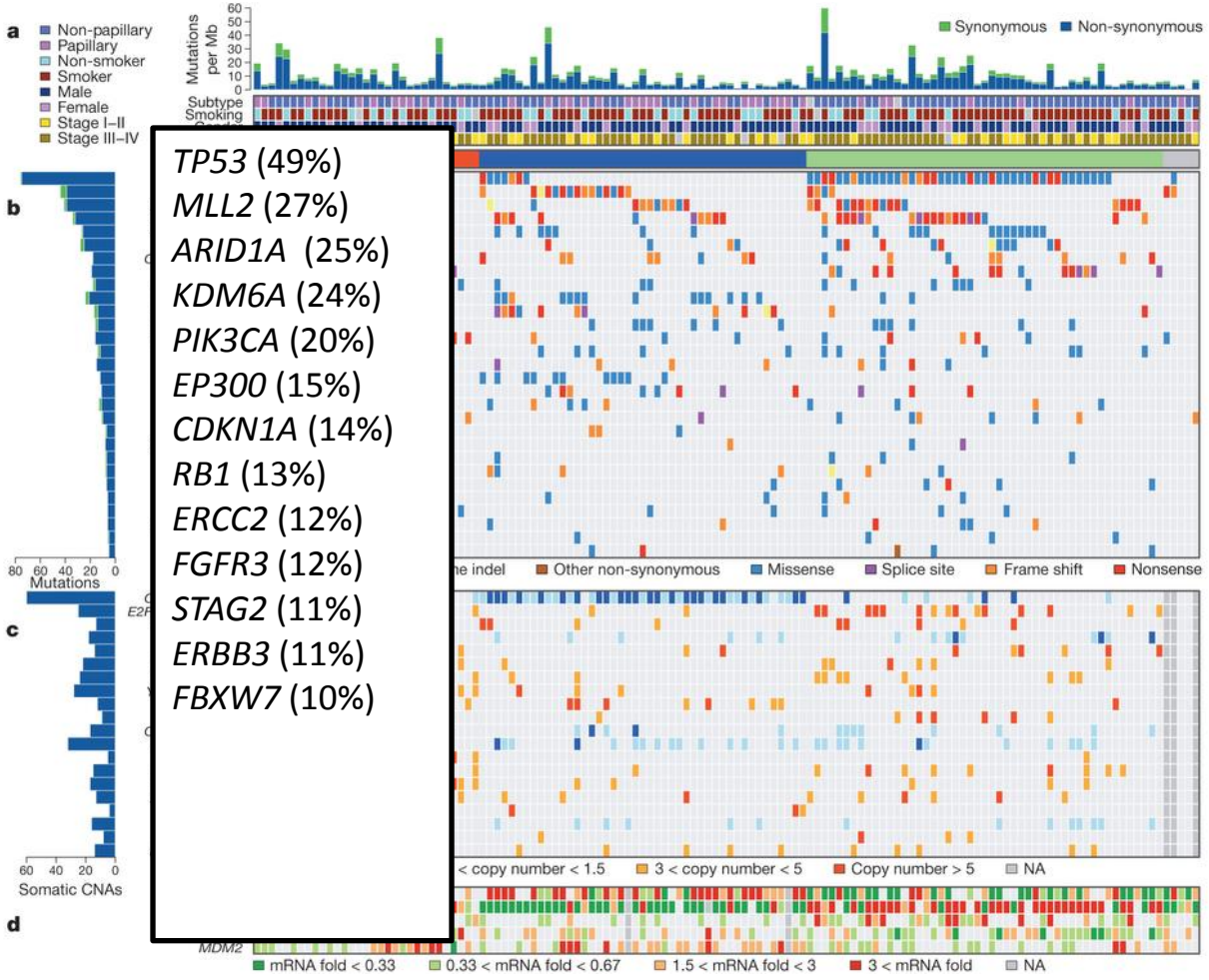
- Single arm phase II study in patients PS 0-1 having progressed after ≤ 2 prior CT regimen
  - Paclitaxel 80 mg/m^2 on day 1, 8 & 15 of a 28-day cycle
  - Pazopanib 800 mg/day of a 28-day cycle)
- Primary endpoint: ORR

Response	OR (%)	PFS (mo)	OS (mo)
N= 32 (28 ev.)	50	6	8

- 59% received 2 prior regimen
- 12,5% node only, 2 patients PS 2
- 75% of patients required dose reduction
- 44% of patients received growth factors

Impressive ORR but OS is similar to many other trials, myelosuppression is significant
Sponsor cancelled the planned phase III study

Bladder Cancer is a molecularly heterogeneous disease



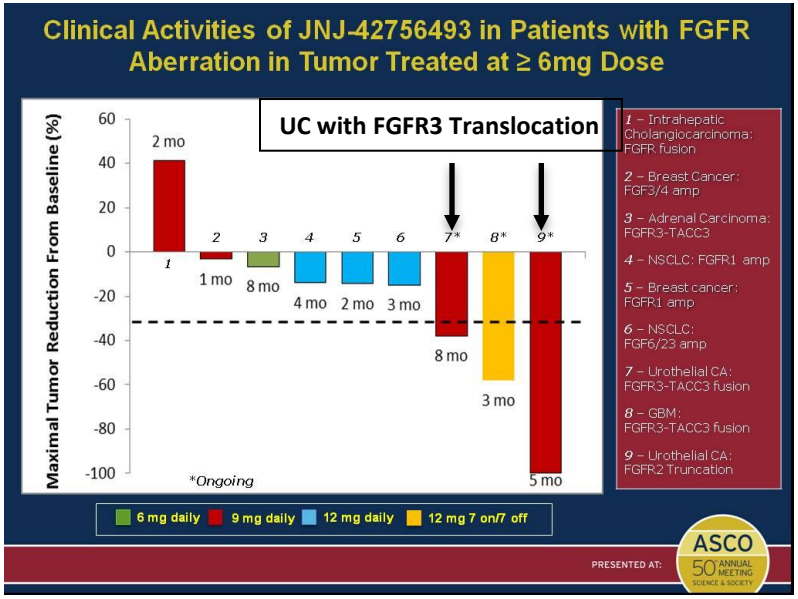
TP53 (49%)
MLL2 (27%)
ARID1A (25%)
KDM6A (24%)
PIK3CA (20%)
EP300 (15%)
CDKN1A (14%)
RB1 (13%)
ERCC2 (12%)
FGFR3 (12%)
STAG2 (11%)
ERBB3 (11%)
FBXW7 (10%)

Proof of Concept Established for Targeting FGFR3 in FGFR3-Mutant Metastatic Urothelial Cancer

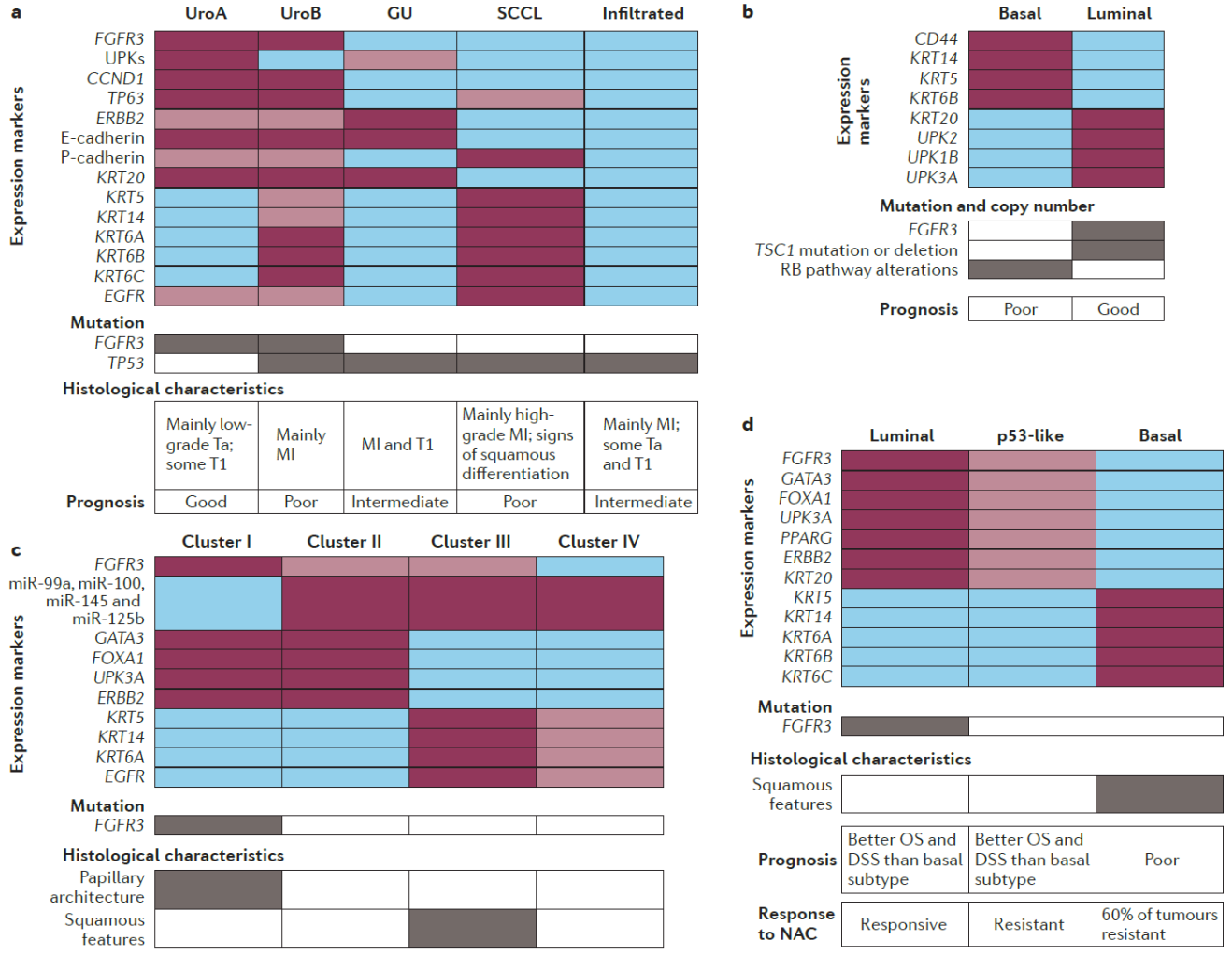
BGJ398 has clinical activity in patients with *FGFR3*-mutated urothelial carcinoma

Age/Sex	Tumor	Schedule (125 mg/day)	Best Overall Response (% tumor change)	Duration on Study
86 ♀	*FGFR3*-mutated	Continuous	PR (–48%)	5 cycles
62 ♀	*FGFR3*-mutated	3 weeks on/ 1 week off	PR (–45%)	9+ cycles
53 ♂	*FGFR3*-mutated	3 weeks on/ 1 week off	SD (–28%)	4 cycles
77 ♂	*FGFR3*-mutated	Continuous	SD (–27%)	4 cycles
52 ♂	*FGFR3*-mutated	Continuous	SD (+11.4%)	3 cycles
80 ♀	*FGFR1*-amplified	3 weeks on/ 1 week off	PD	< 2 weeks

In *FGFR3*-mutated urothelial carcinoma: Overall response rate 40% (2/5); Disease control rate 100% (5/5)



Sequist, AACR, 2014
Bahleda, ASCO, 2014



Molecular subtypes of bladder cancer. mRNA expression profiling studies.

a | Sjödahl *et al five major subtypes urobasal A (UroA), UroB, genomically unstable (GU), squamous cell carcinoma-like (SCCL) and 'infiltrated'.*

b | Damrauer et al. classified bladder cancer into basal and luminal subtypes.

c | The Cancer Genome Atlas (TCGA) study defined four expression clusters (I–IV).

d | Choi et al.defined a 'p53-like' luminal subtype

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European Association of Urology

Platinum Priority – Bladder Cancer

Editorial by XXX on pp. x–y of this issue

A Prognostic Gene Expression Signature in the Molecular Classification of Chemotherapy-naïve Urothelial Cancer is Predictive of Clinical Outcomes from Neoadjuvant Chemotherapy: A Phase 2 Trial of Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin with Bevacizumab in Urothelial Cancer

David J. McConkey [a,b,†], Woonyoung Choi [a,†], Yu Shen [c], I.-Ling Lee [a], Sima Porten [a], Surena F. Matin [a], Ashish M. Kamat [a], Paul Corn [d], Randall E. Millikan [e], Colin Dinney [a], Bogdan Czerniak [f], Arlene O. Siefker-Radtke [d,]*

doi:10.1016/j.eururo.2015.08.034

Paradigm Shift in Urothelial Cancer

- Urothelial cancer is no longer just 1 disease:

"Basal"

- Chemo-sensitive
- Immune signature
- Angiogenesis

Therapies:

- GC/DDMVAC
- CTLA4/PD1/PDL-1?
- VEGF inhibitors?

"p53-like"

- Chemo-resistance
- Stromal enrichment
- Bone mets

Therapies:

- Met inhibitors?
- Initial surgery?

"Luminal"

- Still some chemo-sensitivity
- "FGFR" signature

Therapies:

- GC/DDMVAC
- FGFR inhibitors?

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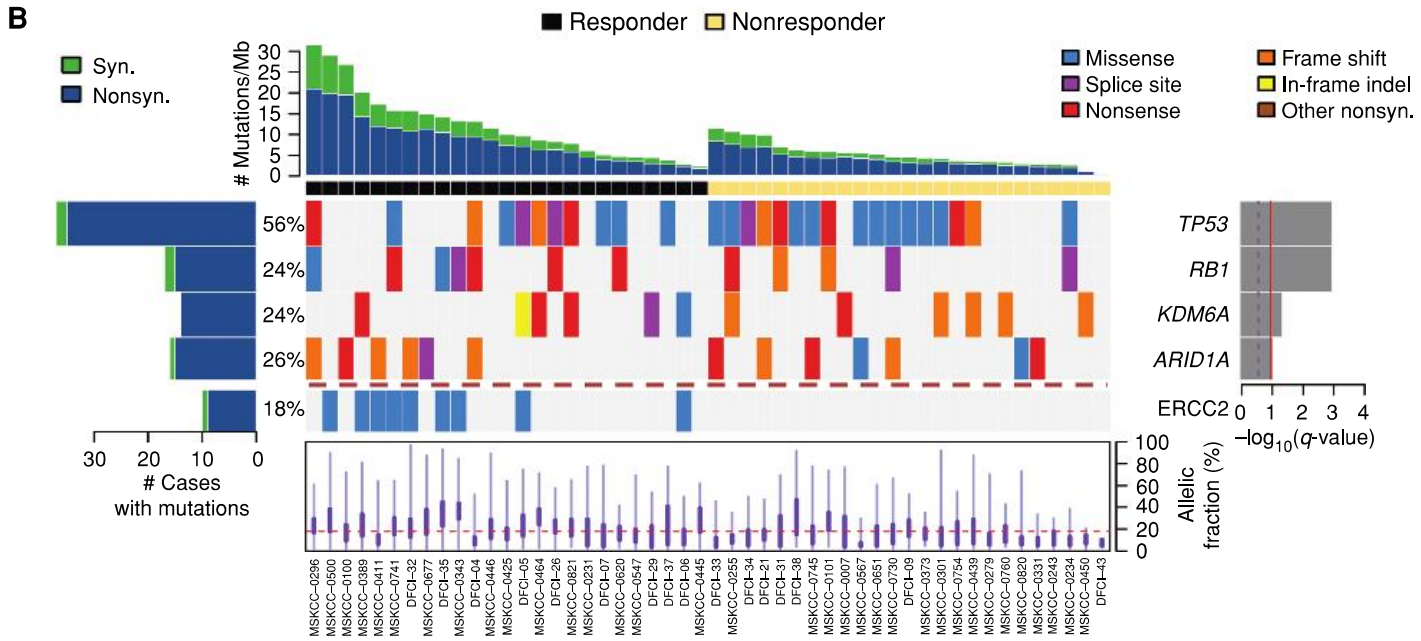
Published OnlineFirst August 5, 2014; DOI: 10.1158/2159-8290.CD-14-0623

RESEARCH ARTICLE

Somatic *ERCC2* Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma

Eliezer M. Van Allen[1,2], Kent W. Mouw[3,4], Philip Kim[5], Gopa Iyer[6,7], Nikhil Wagle[1,2], Hikmat Al-Ahmadie[6,8], Cong Zhu[2], Irina Ostrovnaya[9], Gregory V. Kryukov[2], Kevin W. O'Connor[3], John Sfakianos[5], Ilana Garcia-Grossman[7], Jaegil Kim[2], Elizabeth A. Guancial[10], Richard Bambury[7], Samira Bahl[2], Namrata Gupta[2], Deborah Farlow[2], Angela Qu[1], Sabina Signoretti[11], Justine A. Barletta[11], Victor Reuter[6,8], Jesse Boehm[2], Michael Lawrence[2], Gad Getz[2,12], Philip Kantoff[1], Bernard H. Bochner[5,6], Toni K. Choueiri[1], Dean F. Bajorin[6,7], David B. Solit[6,7,13], Stacey Gabriel[1], Alan D'Andrea[3,4], Levi A. Garraway[1,2], and Jonathan E. Rosenberg[6,7]



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Platinum Priority – Bladder Cancer
Editorial by XXX on pp. x–y of this issue

Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy in Muscle-invasive Bladder Cancer

Elizabeth R. Plimack[a,], Roland L. Dunbrack[a], Timothy A. Brennan[b], Mark D. Andrake[a], Yan Zhou[a], Ilya G. Serebriiskii[a], Michael Slifker[a], Katherine Alpaugh[a], Essel Dulaimi[a], Norma Palma[b], Jean Hoffman-Censits[c], Marijo Bilusic[a], Yu-Ning Wong[a], Alexander Kutikov[a], Rosalia Viterbo[a], Richard E. Greenberg[a], David Y.T. Chen[a], Costas D. Lallas[c], Edouard J. Trabulsi[c], Roman Yelensky[b], David J. McConkey[d], Vincent A. Miller[b], Erica A. Golemis[a], Eric A. Ross[a]*

[a] *Fox Chase Cancer Center, Philadelphia, PA, USA;* [b] *Foundation Medicine Inc., Cambridge, MA, USA;* [c] *Thomas Jefferson University Hospital, Philadelphia, PA, USA;* [d] *MD Anderson Cancer Center, Houston, TX, USA*

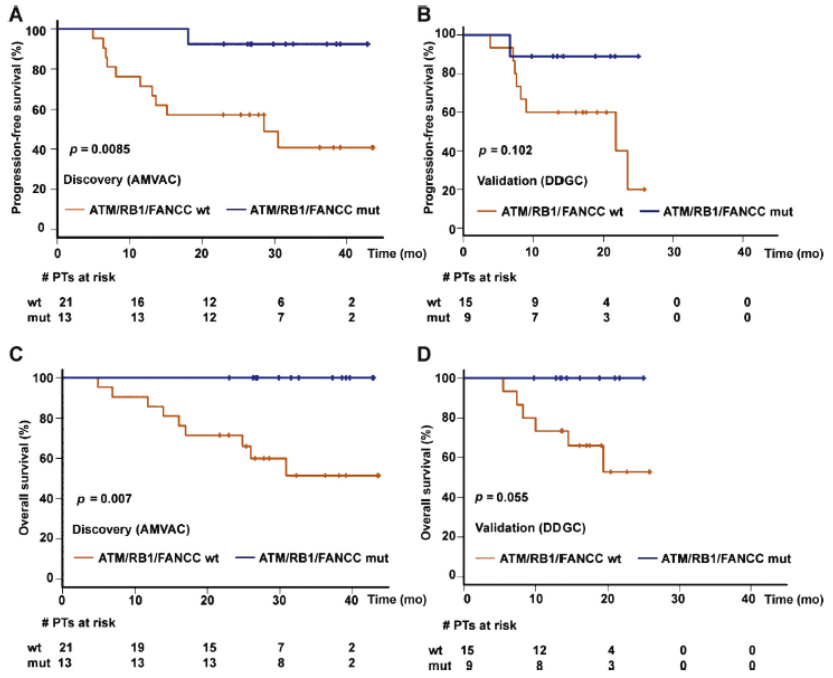


Fig. 2 – Progression-free survival (PFS) and overall survival (OS) by *ATM/RB1/FANCC* mutation status for the AMVAC discovery and DDGC validation sets. Alteration in any one of *ATM/RB1/FANCC* predicts better PFS ($p = 0.0085$) and OS ($p = 0.007$) in the AMVAC discovery set, with a trend towards significance for OS ($p = 0.0545$) in the DDGC validation set. wt = wild type; mut = mutation; PTs = patients.

Results and limitations: Patients with a pathologic complete response had more alterations than those with residual tumor in both the discovery ($p = 0.024$) and validation ($p = 0.018$) sets. In the discovery set, alteration in one or more of the three DNA repair genes *ATM*, *RB1*, and *FANCC* predicted pathologic response ($p < 0.001$; 87% sensitivity, 100% specificity) and better overall survival ($p = 0.007$). This test remained predictive for pathologic response in the validation set ($p = 0.033$), with a trend towards better overall survival ($p = 0.055$). These results require further validation in additional sample sets.

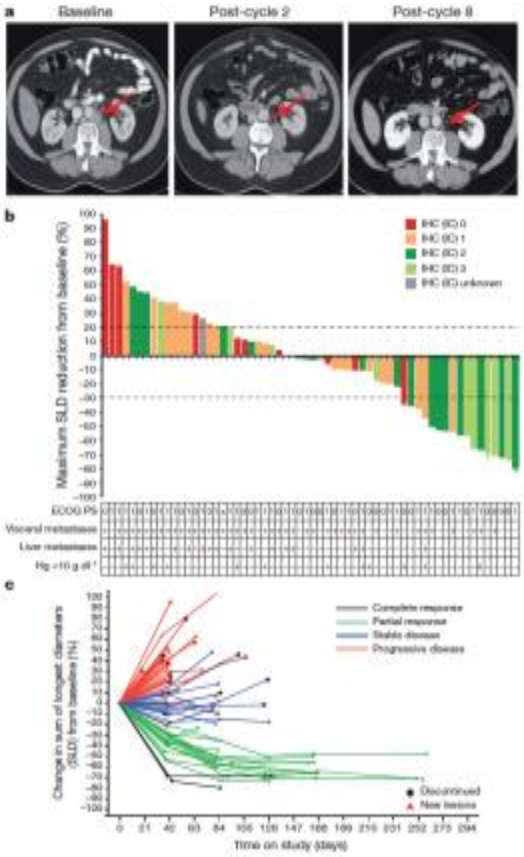
Conclusions: Genomic alterations in the DNA repair-associated genes *ATM*, *RB1*, and *FANCC* predict response and clinical benefit after cisplatin-based chemotherapy for MIBC. The results suggest that defective DNA repair renders tumors sensitive to cisplatin.

LETTER

doi:10.1038/nature13904

MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

Thomas Powles[1], Joseph Paul Eder[2], Gregg D. Fine[3], Fadi S. Braiteh[4], Yohann Loriot[5], Cristina Cruz[6], Joaquim Bellmunt[7], Howard A. Burris[8], Daniel P. Petrylak[2], Siew-leng Teng[1], Xiaodong Shen[3], Zachary Boyd[3], Priti S. Hegde[3], Daniel S. Chen[3] & Nicholas J. Vogelzang[9]



A Phase Ia Study of Atezolizumab (MPDL3280A/Anti-PDL1): Updated Response and Survival Data in Urothelial Bladder Cancer (UBC)

Daniel P. Petrylak,[1] Thomas Powles,[2] Joaquim Bellmunt,[3] Fadi Braiteh,[4] Yohann Loriot,[5] Cristina Cruz,[6] Howard A. Burris III,[7] Joseph W. Kim,[1] Howard M. Mackey,[8] Zachary S. Boyd,[8] Priti S. Hegde,[8] Oyewale Abidoye,[8] Nicholas J. Vogelzang[9]

[1]Yale Cancer Center, New Haven, CT; [2]Barts Cancer Institute, Queen Mary University of London, London, UK; [3]Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA; [4]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [5]Gustave Roussy, Villejuif, France; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]Sarah Cannon Research Institute, Nashville, TN; [8]Genentech, Inc., South San Francisco, CA; [9]University of Nevada School of Medicine, Las Vegas, NV, and US Oncology/Comprehensive Cancer Centers of Nevada, Las Vegas, NV

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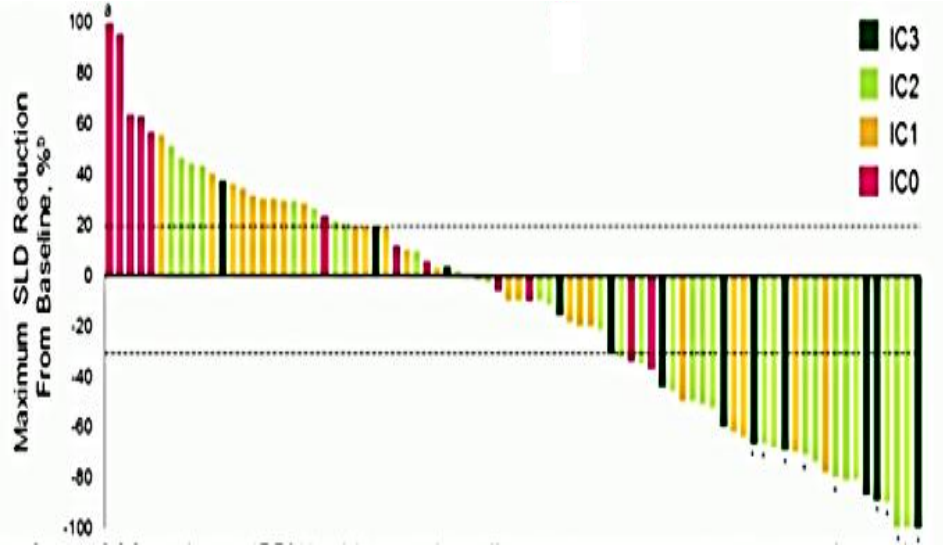
Pembrolizumab (MK-3475) for Advanced Urothelial Cancer: Updated Results and Biomarker Analysis from KEYNOTE-012

Elizabeth R. Plimack,[1] Joaquim Bellmunt,[2] Shilpa Gupta,[3] Raanan Berger,[4] Bruce Montgomery,[5] Karl Heath,[6] Jonathan Juco,[6] Kenneth Emancipator, [6] Kumudu Pathiraja, [6] Jared Lunceford, [6] Rodolfo Perini, [6] Peter H. O'Donnell[7]

[1]Fox Chase Cancer Center, Philadelphia, PA, USA, [2]Dana-Farber Cancer Institute, Boston, MA, USA
[3]H.Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA, [4]Sheba Medical Center, Tel hashomer, Israel
[5]University of Washington, Seattle, WA, USA, [6]Merck & Co, Inc., Kenilworth, NJ, USA,
[7]University of Chicago, Chicago, IL, USA

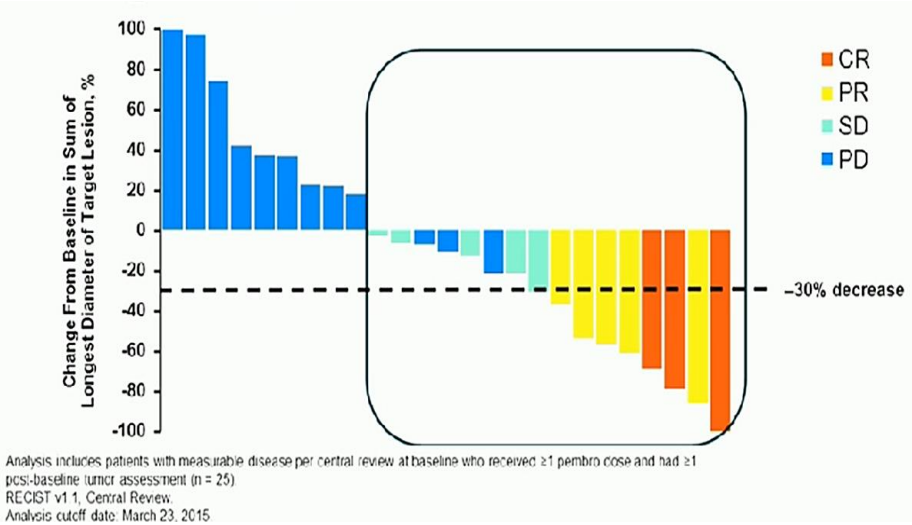
Anti-PD-1/PD-L1 in Heavily Pretreated Metastatic Urothelial Cancers Including Bladder Carcinoma

Atezolizumab (MPDL3280A)[1]



- ORR:
  - IC2/3: 50%; IC0/1: 17%
- Median PFS:
  - IC2/3: 6 months; IC0/1: 1 month
- Median OS:
  - IC2/3: Not reached; IC0/1: 8 months

Pembrolizumab[2]



- ORR: 28%
- Median PFS: 2 months
- Median OS: 12.7 months

1. Petrylak DP et al. J Clin Oncol 33, 2015 (suppl; abstractl 4501)
2. Plimack ER et al. J Clin Oncol 33, 2015 (suppl;abstr 4502)

Atezo and Pembro Fast Facts

	[1]Atezolizumab	[2]Pembrolizumab	History
Target	PD-L1	PD-1	Cytotoxics and TKIs
Schedule	q3wk	q2wk	Variable
Grade 3-4 Toxicity	8%	15%	~40-50%
ORR	35%	28%	12%
Median OS	10-14 months	13 months	7 months

[1]ASCO 2015;abst 4501 / [2]ASCO2015;abst 4502.

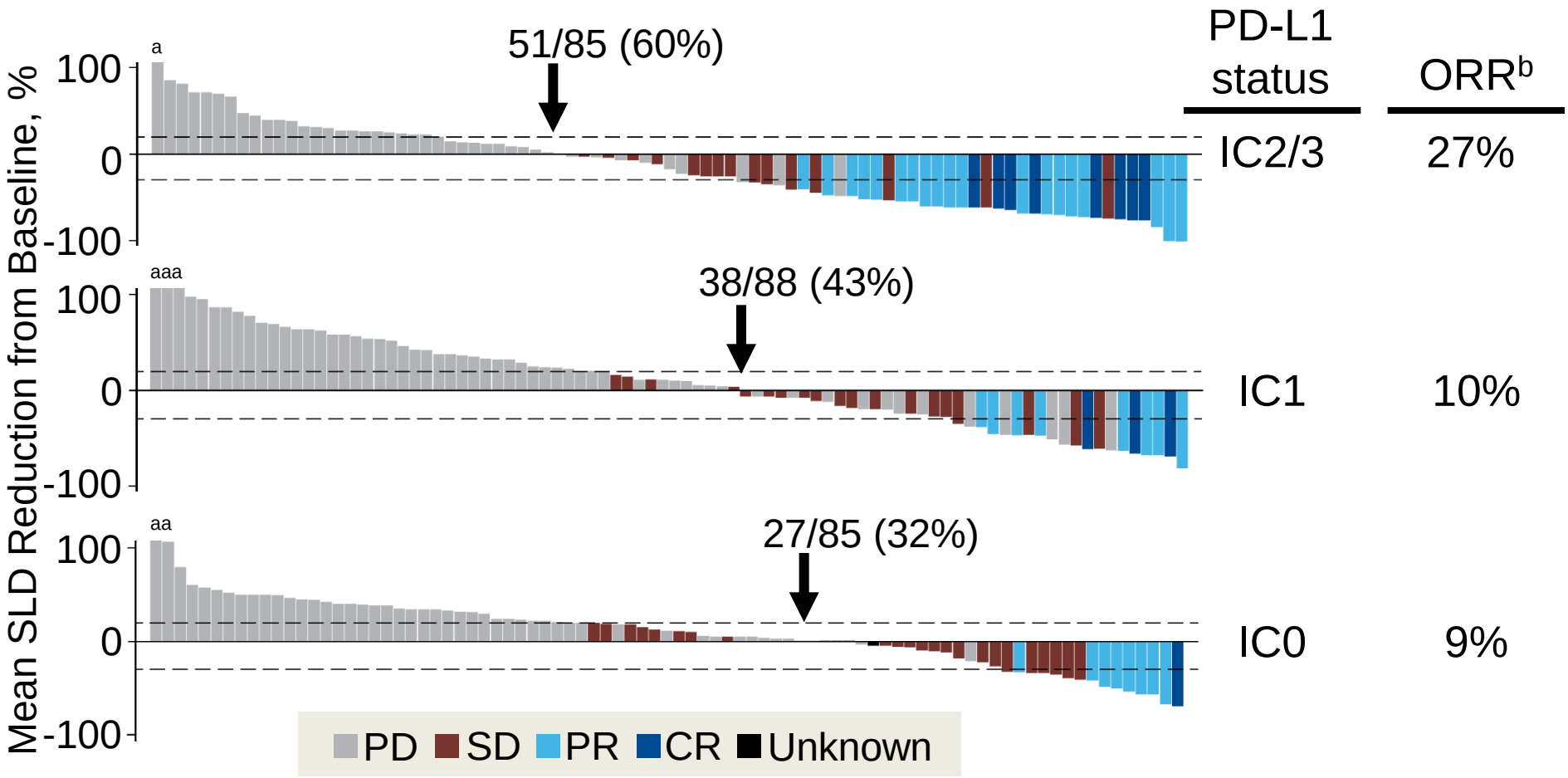
Atezolizumab in Patients with Locally-Advanced or Metastatic Urothelial Carcinoma (mUC): Results from a Pivotal Multicenter Phase II Study (IMvigor 210)

Jonathan E. Rosenberg,[1] Daniel P. Petrylak,[2] Oyewale Abidoye,[3] Michiel S. van der Heijden,[4] Jean Hoffman-Censits,[5] Andrea Necchi,[6] Peter H. O'Donnell,[7] Ani Balmanoukian,[8] Yohann Loriot,[9] Margitta Retz,[10] Jose Luis Perez-Gracia,[11] Nancy A. Dawson,[12] Arjun V. Balar,[13] Matthew D. Galsky,[14] Mark T. Fleming,[15] Thomas Powles,[16] Na Cui,[3] Sanjeev Mariathasan,[3] Gregg D. Fine,[3] Robert Dreicer[17]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Yale Cancer Center, New Haven, CT, USA; [3]Genentech, Inc., South San Francisco, CA, USA; [4]Netherlands Cancer Institute, Amsterdam, the Netherlands; [5]Thomas Jefferson University Hospital, Philadelphia, PA, USA; [6]Istituto Nazionale dei Tumori, Milan, Italy; [7]University of Chicago, Chicago, IL USA; [8]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [9]Gustave Roussy, Villejuif, France; [10]Urologische Klinik und Poliklinik, Technische Universität München, Munich, Germany; [11]Clinica Universidad de Navarra, Pamplona, Spain; [12]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; [13]Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA; [14]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [15]Virginia Oncology Associates, Norfolk, VA, USA; [16]Barts Cancer Institute, Queen Mary University of London, London, UK; [17]Division of Hematology/Oncology, University of Virginia, Charlottesville VA USA

IMvigor 210: Efficacy

Changes in Target Lesions by PD-L1 Subgroup



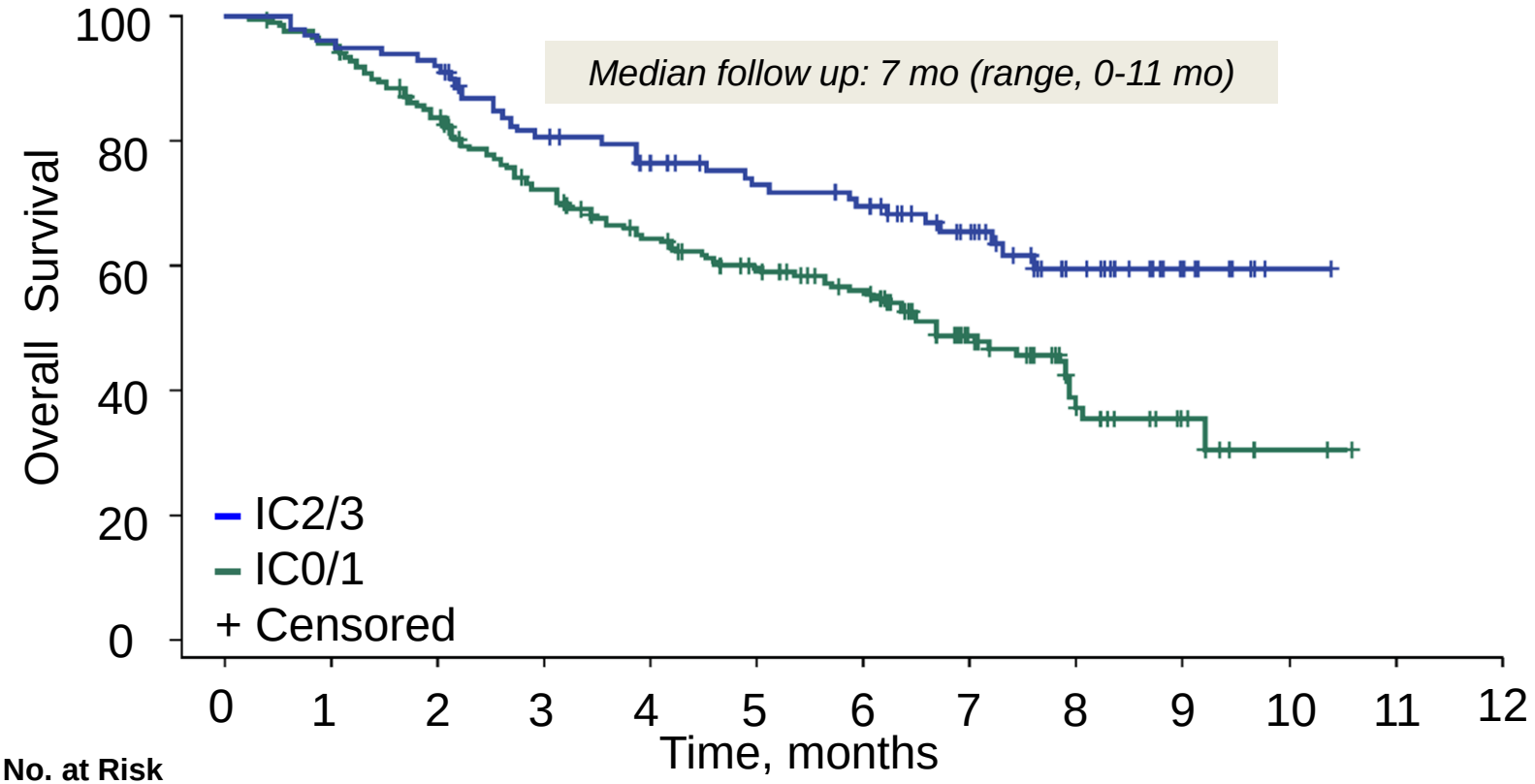
111/258 (43%) patients with tumor assessments had SLD reduction

SLD, sum of longest diameters. [a]> 100% increase. [b]Per confirmed RECIST v1.1 (independent review).
Data cutoff May 5, 2015. Follow up ≥ 24 weeks. Patients without post-baseline tumor assessments not included.
Several patients with CR had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

IMvigor 210: Efficacy

Preliminary Analyses of Overall Survival

Survival	IC2/3 n = 100	IC0/1 n = 211	All N = 311
Median OS, mo (95% CI)	NR (7.6, NE)	6.7 (5.7, 8.0)	7.9 (6.7, NE)



No. at Risk

IC2/3:	100	96	92	78	71	64	60	41	22	11	1
IC0/1:	211	201	173	143	123	107	90	50	23	10	2

NR, not reached; NE, not estimable. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Outline Kidney

- Adjuvant TKI (Assure)
- First line:
  - Failure of peptide vaccines IMA901
  - Non Clear Cell histology (ASPEN)
- Second Line: Nivo and Cabo

Dose analysis of ASSURE (E2805): Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma, an ECOG-ACRIN-led, NCTN Phase 3 Trial

Naomi B. Haas[1] MD

- Co-authors: **J Manola[2], K Flaherty[3], R Uzzo[4], C Wood[5], C Kane[6], M Jewett[7], J Dutcher[8], M Atkins[9], M Pins[10], G Wilding[11], D Cella[12], L Wagner[12], S Matin[5], T Kuzel[12], W Sexton[13], Y Wong[3], T Choueiri[14], R Pili[15], R Puzanov[16], M Koli[17], W Stadler[18], B Coomes[19], R DiPaola[20]**

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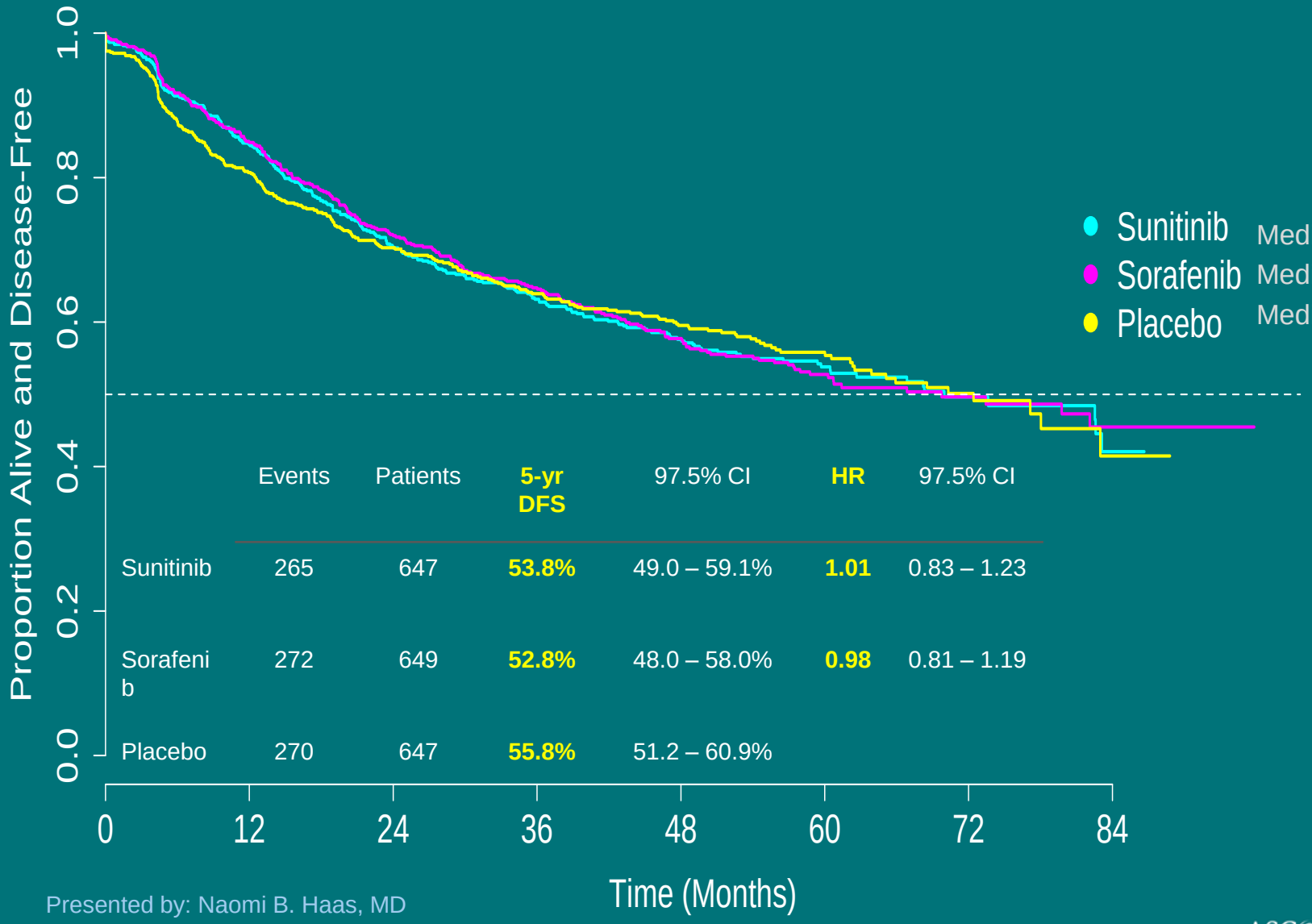
PRESENTED AT: ASCO Annual '15 Meeting

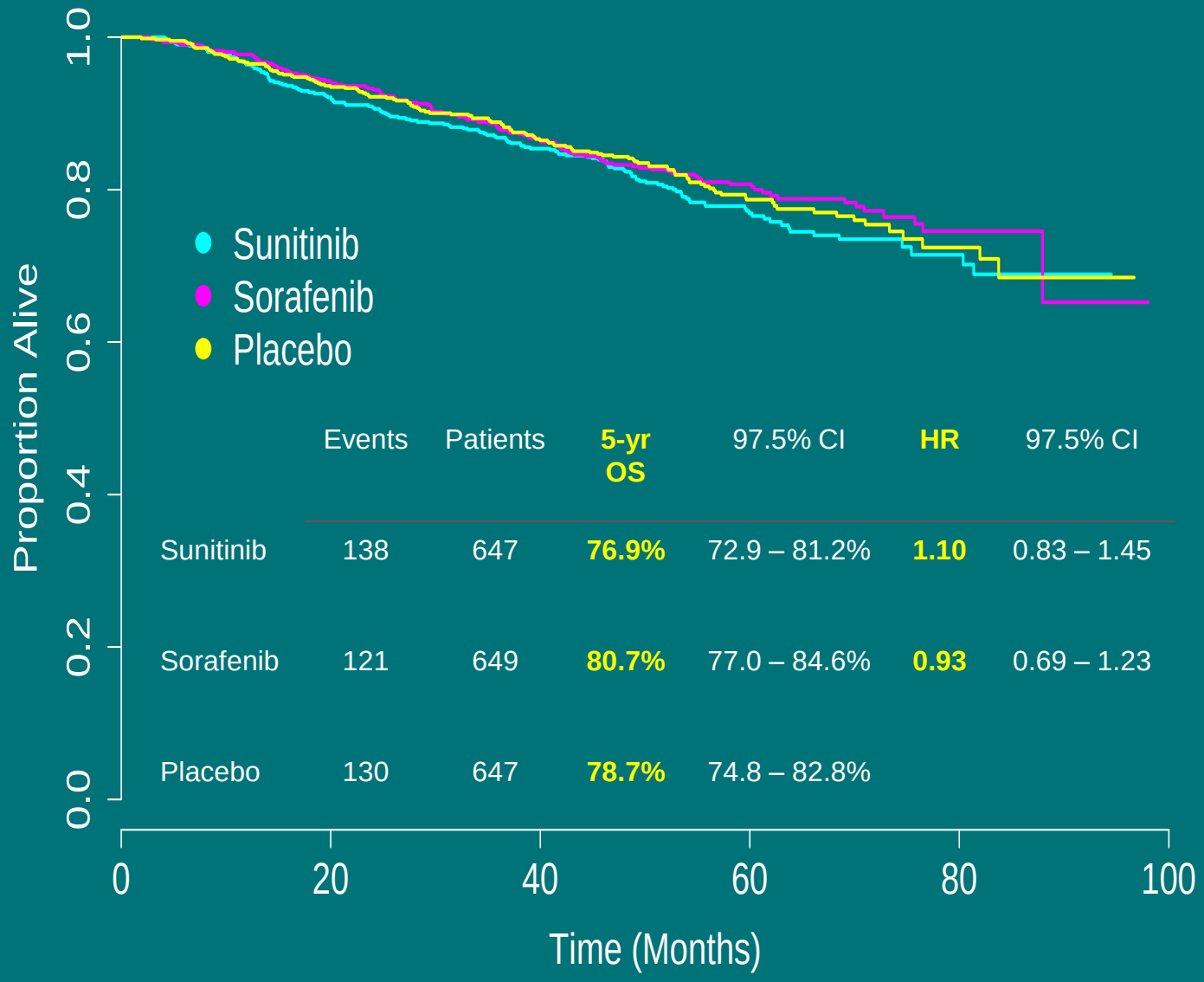
Disease-Free Survival



	Events	Patients	5-yr DFS	97.5% CI	HR	97.5% CI
Sunitinib	265	647	**53.8%**	49.0 – 59.1%	**1.01**	0.83 – 1.23
Sorafenib	272	649	**52.8%**	48.0 – 58.0%	**0.98**	0.81 – 1.19
Placebo	270	647	**55.8%**	51.2 – 60.9%		

Presented by: Naomi B. Haas, MD

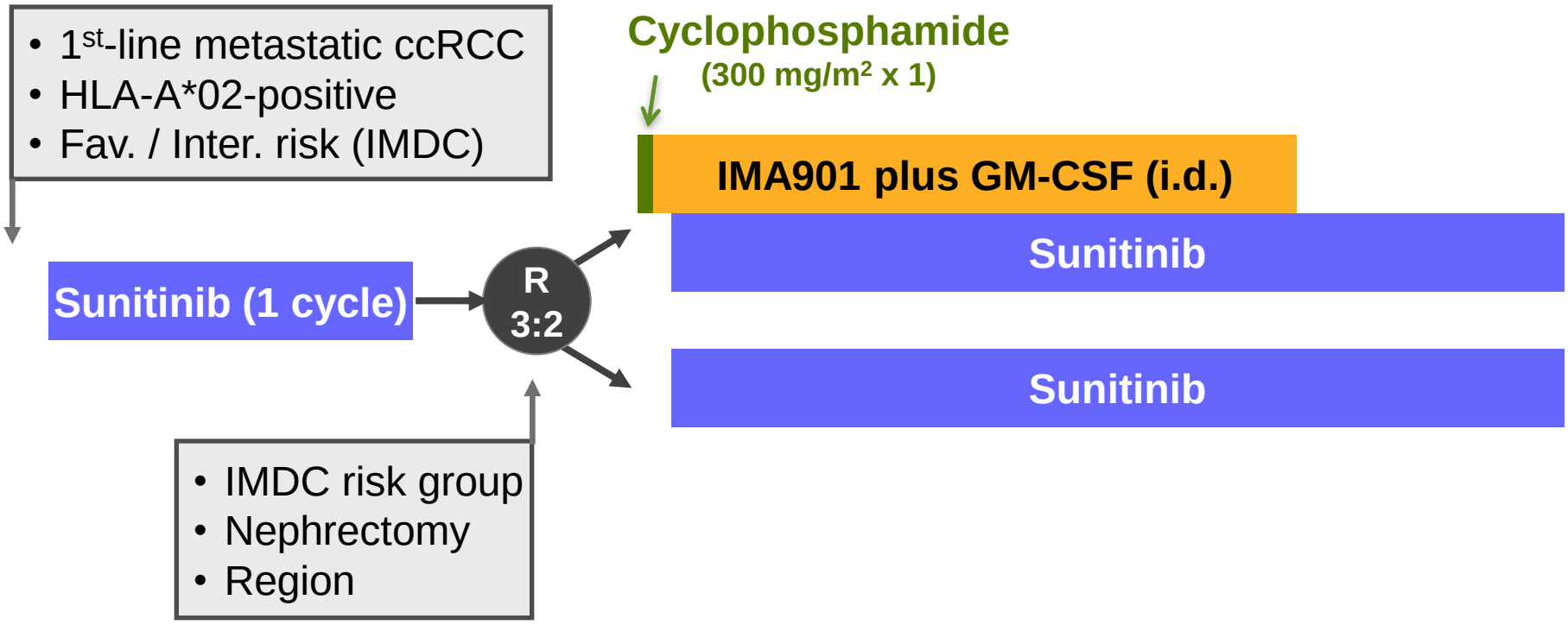
Overall Survival



	Events	Patients	5-yr OS	97.5% CI	HR	97.5% CI
Sunitinib	138	647	**76.9%**	72.9 – 81.2%	**1.10**	0.83 – 1.45
Sorafenib	121	649	**80.7%**	77.0 – 84.6%	**0.93**	0.69 – 1.23
Placebo	130	647	**78.7%**	74.8 – 82.8%		

Presented by: Naomi B. Haas, MD

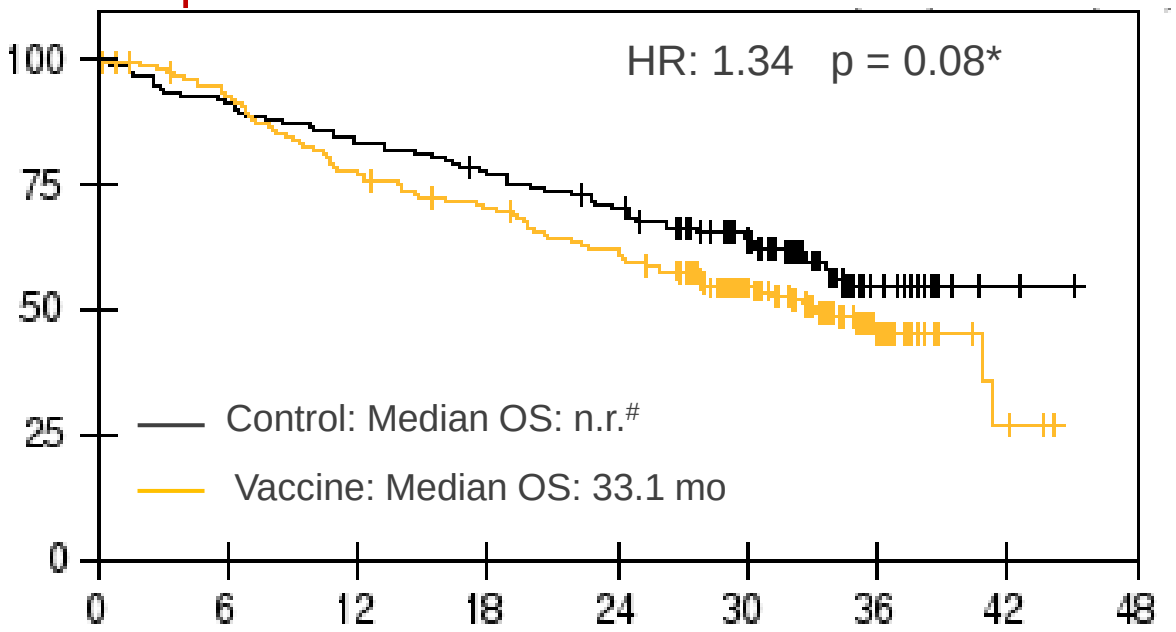
Study Design



- 1,171 pts screened → 366 started 1st sunitinib cycle (HLA-A2-negativity main exclusion) → 339 pts randomized
- Study was not blinded (HLA match peptide based vaccine)

Overall Survival

All patients



n.r. = not reached

* logRank statified on risk group

** unstratified logRank

ASPEN Trial Schema

NCT01108445 **Andrew J. Armstrong**

18 global sites: 10 USA, 5 UK, 3 in Canada

Metastatic RCC

- Non-clear cell pathology: papillary, chromophobe, unclassified
- No prior therapy
- Measurable disease

Stratified by Histology, MSKCC Risk Group

n=108

RANDOMIZE

Everolimus 10 mg orally once daily
Days 1-42
Cycle = 6 weeks

Sunitinib 50 mg orally
Days 1-28
Cycle = 6 weeks

Radiographic PFS Primary Endpoint

No planned crossover

Duke Cancer Institute was coordinating center and central biorepository for this multinational randomized open label trial, monitoring by inVentiv Health clinical

Summary and Conclusions

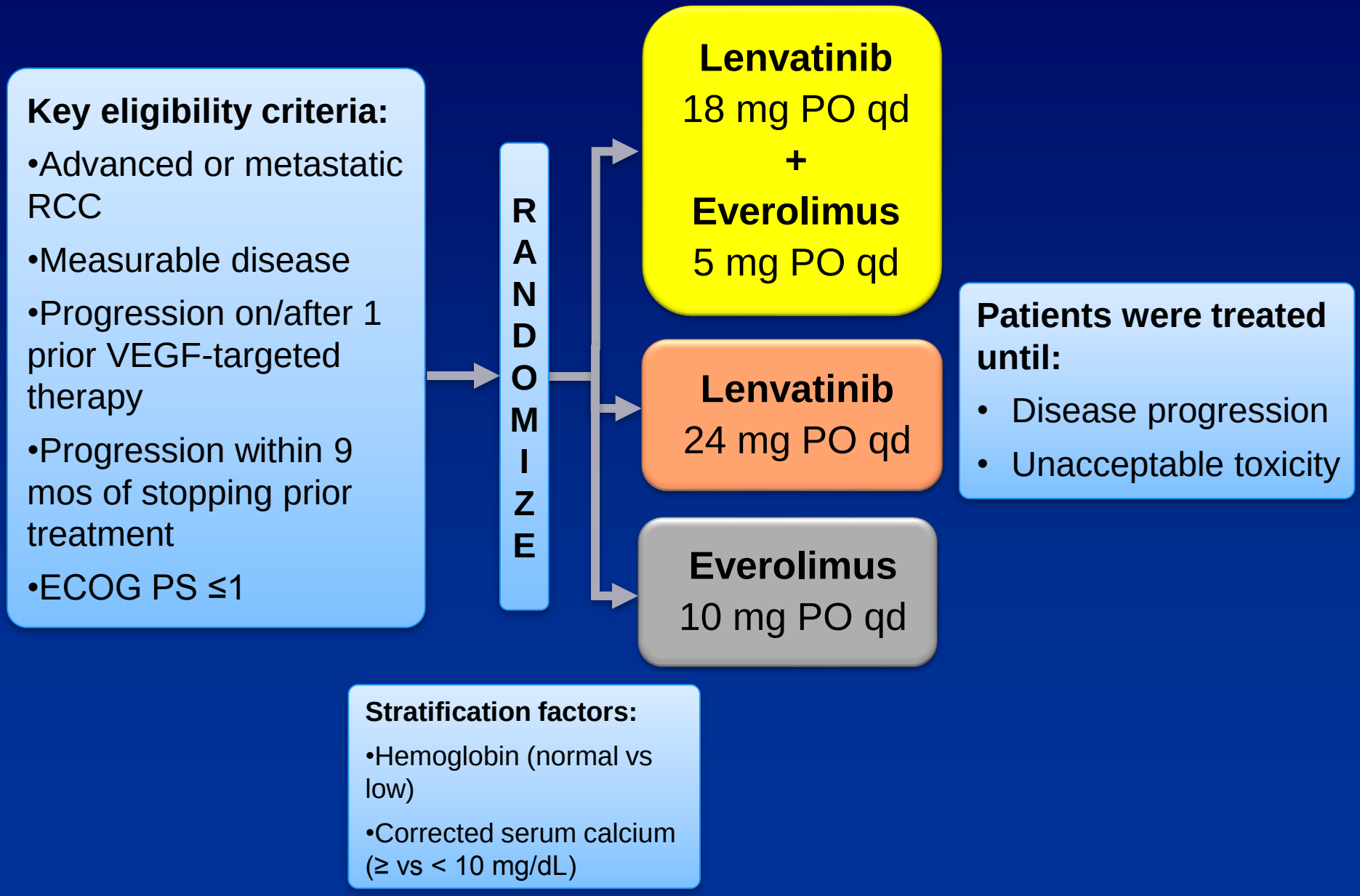
- Patients with metastatic NC-RCC treated with sunitinib had a statistically significantly prolonged PFS duration than patients treated with everolimus
  - Sunitinib resulted in improved PFS in good/intermediate risk, papillary, and unclassified subtypes
  - Everolimus resulted in improved PFS in poor risk and chromophobe subtypes
- Both agents resulted in short PFS times and low response rates
- Sunitinib and everolimus resulted in different rates of expected toxicities; more severe toxicities with sunitinib, but more discontinuations due to toxicity from everolimus.

Abstract No. 4506

Randomized phase 2 three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC)

R. Motzer, T. Hutson, H. Glen, M.D. Michaelson, A. Molina,
T. Eisen, J. Jassem, J. Zolnierek, P. Maroto, B. Mellado,
B. Melichar, J. Tomasek, H. Kim, K. Wood, C. Dutcus, J. Larkin

Study Design



Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

Robert J Motzer, Thomas E Hutson, Hilary Glen, M Dror Michaelson, Ana Molina, Timothy Eisen, Jacek Jassem, Jakub Zolnierek, Jose Pablo Maroto, Begoña Mellado, Bohuslav Melichar, Jiri Tomasek, Alton Kremer, Han-Joo Kim, Karen Wood, Corina Dutcus, James Larkin

Summary

Background Currently, metastatic renal cell carcinoma is treated with sequential single agents targeting VEGF or mTOR. Here, we aimed to assess lenvatinib, everolimus, or their combination as second-line treatment in patients with metastatic renal cell carcinoma.

Lancet Oncol 2015; 16: 1473–82

Published Online October 16, 2015 http://dx.doi.org/10.1016/

Conclusions

- **Progression-free survival was longer for lenvatinib/everolimus and lenvatinib compared with everolimus**
- **Response rate was higher in both lenvatinib-containing arms**
  - **The highest rate and longest duration of response was observed with the combination**
- **Study results suggest an overall survival benefit for lenvatinib/everolimus over everolimus**

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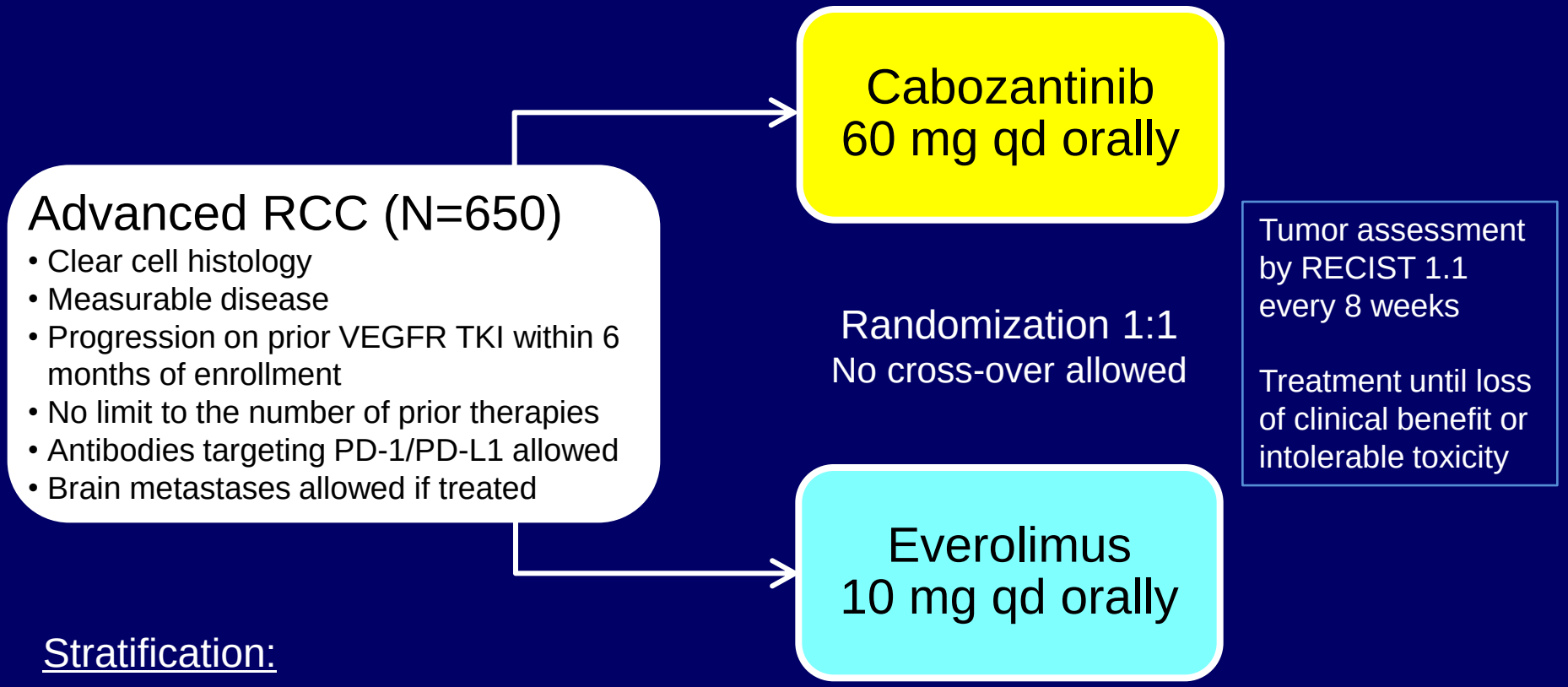
ORIGINAL ARTICLE

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*

Presented at the European Cancer Congress, Vienna, 26 September 2015

Study Design

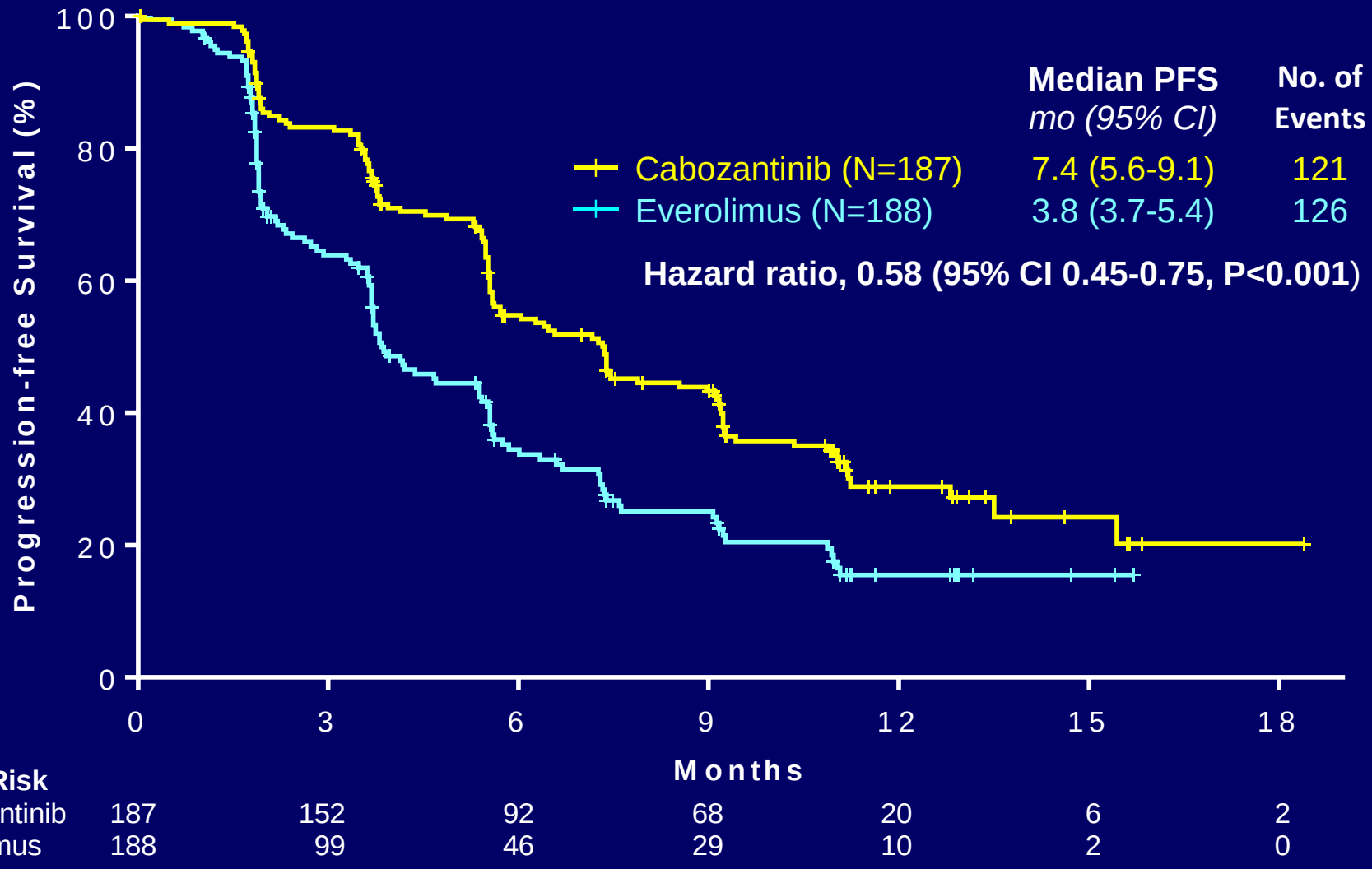


Stratification:

- MSKCC[1] risk groups: favorable, intermediate, poor
- Number prior VEGFR-TKIs: 1, 2 or more

[1] Motzer R. et al., J Clin Oncol, 2004

Progression-Free Survival
Independent Central Radiology Review



The NEW ENGLAND JOURNAL of MEDICINE

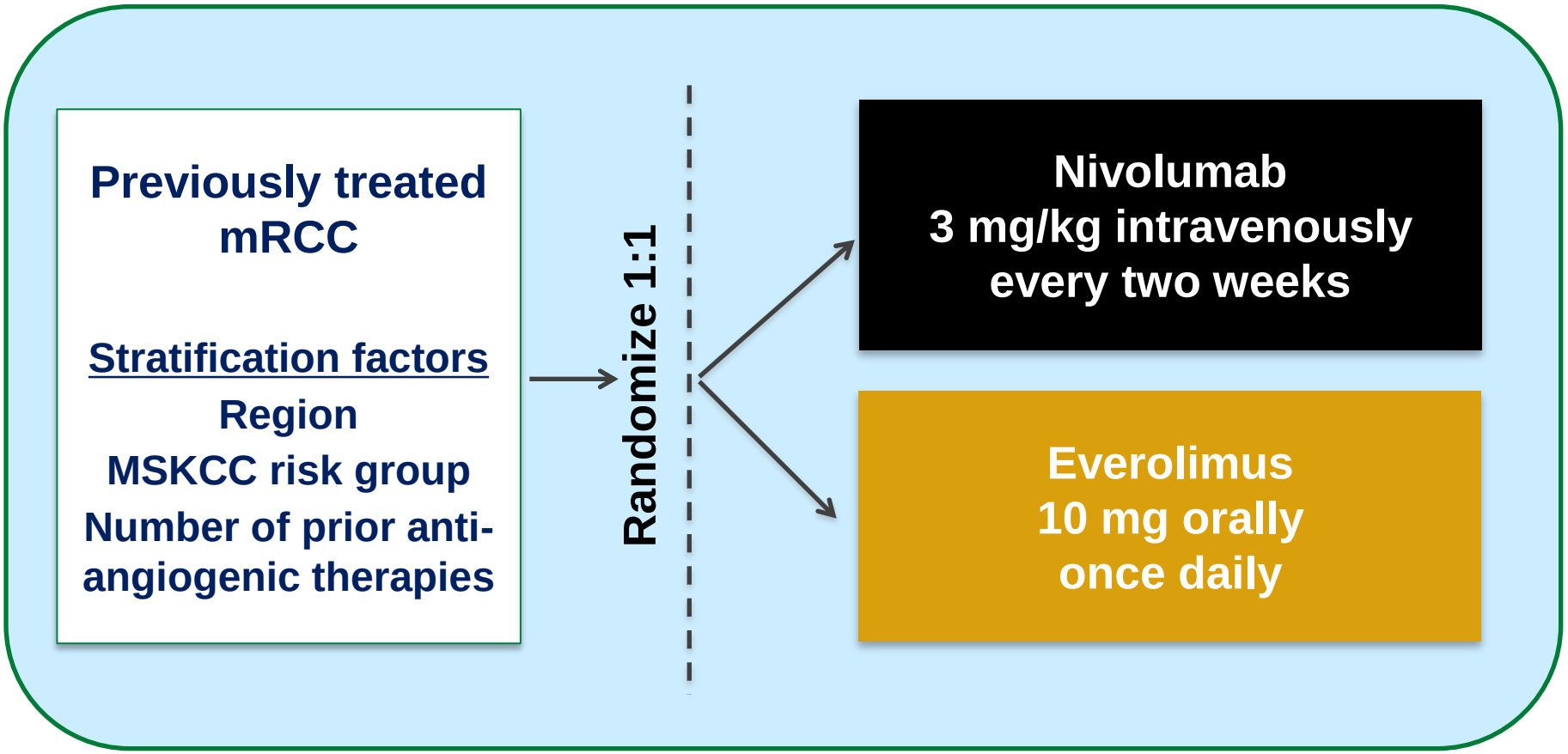
ORIGINAL ARTICLE

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Presented at the European Cancer Congress, Vienna, 26 September 2015

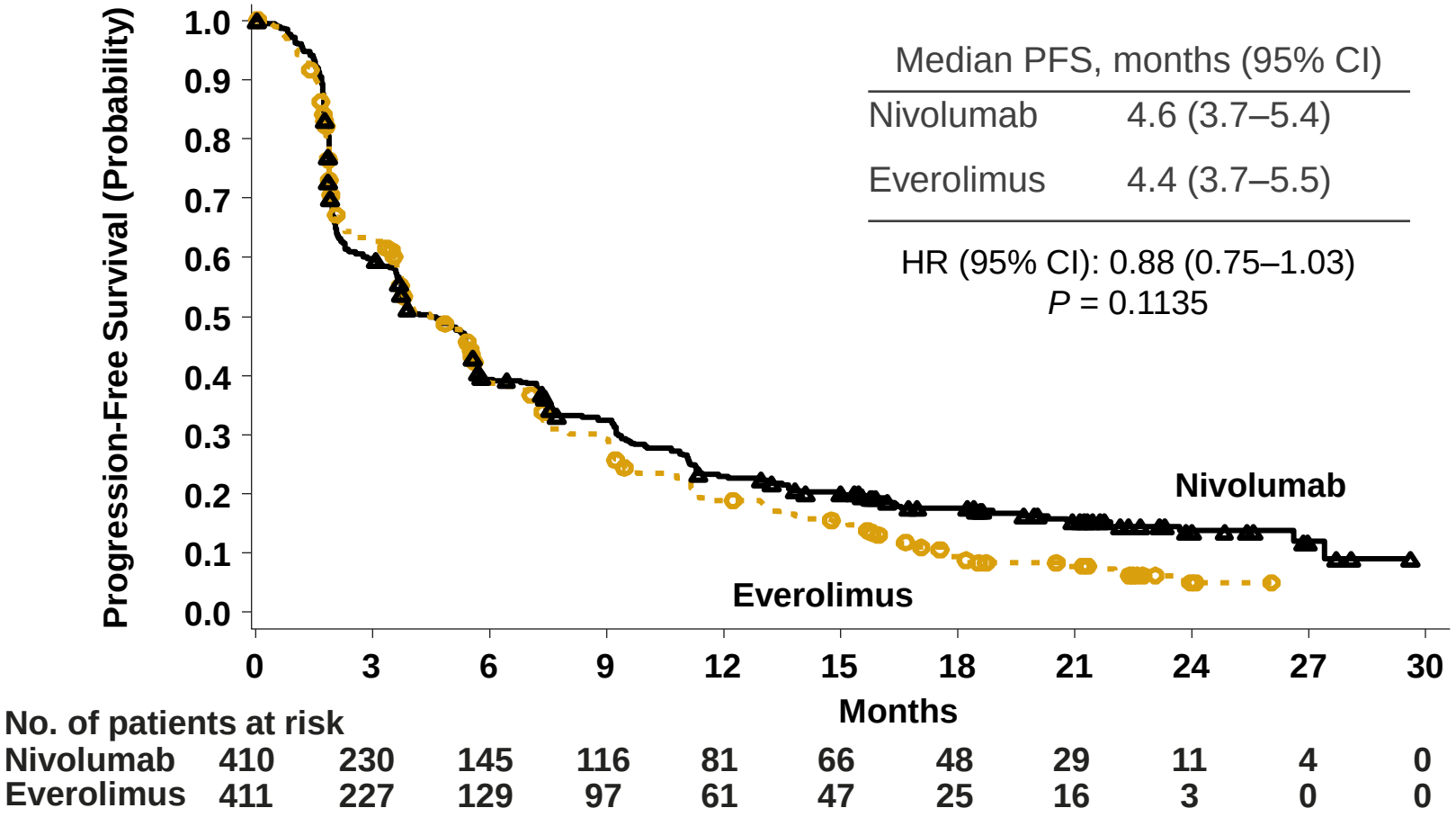
Checkmate-25 Study design



- **PRIMARY EDNPOINT: OS**
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

MSKCC, Memorial Sloan-Kettering Cancer Center.

Progression-free survival

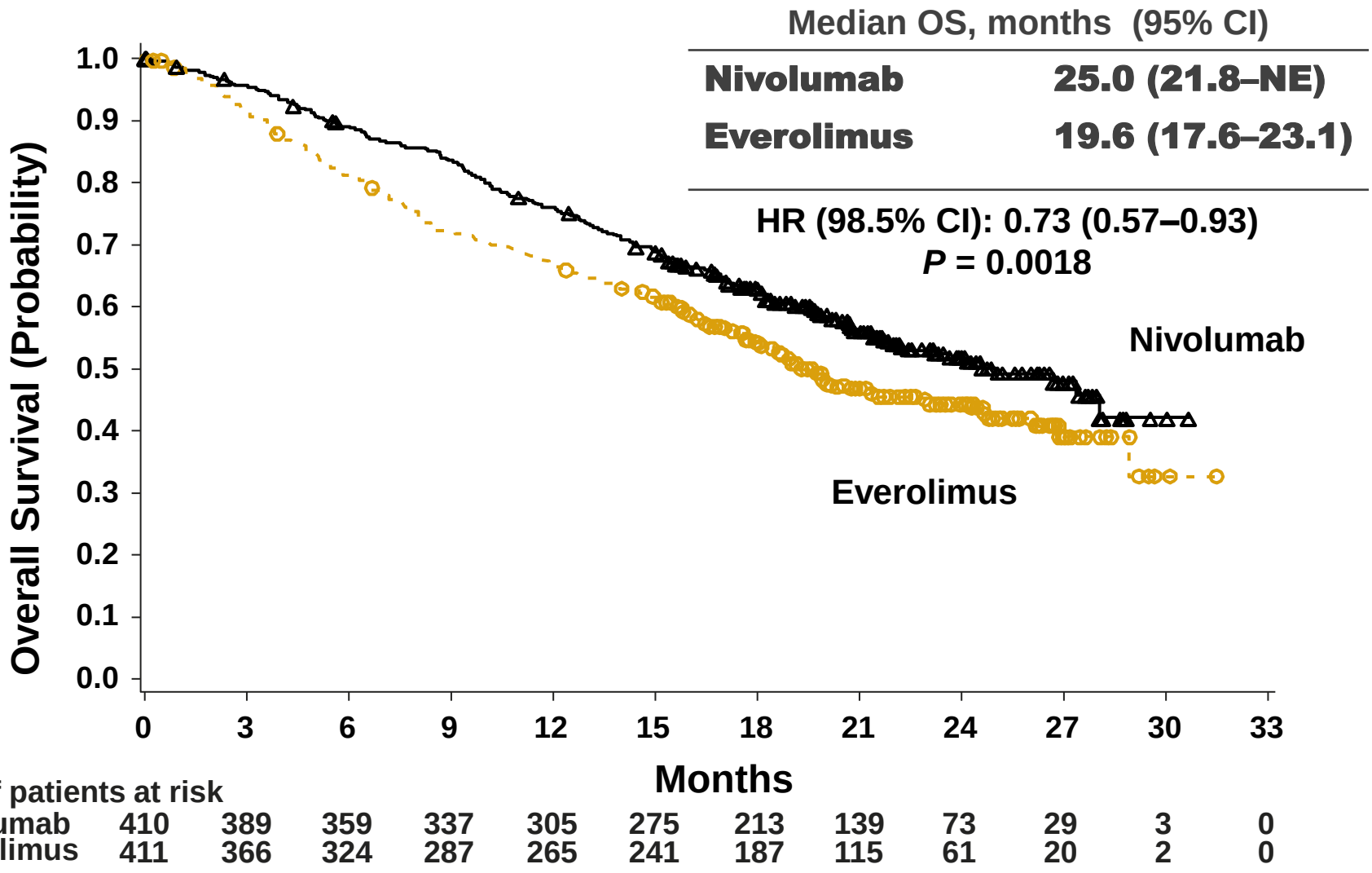


Median PFS, months (95% CI)	
Nivolumab	4.6 (3.7–5.4)
Everolimus	4.4 (3.7–5.5)

HR (95% CI): 0.88 (0.75–1.03)
P = 0.1135

- In a post-hoc analysis of patients who had not progressed or died at 6 months, median PFS was 15.6 months for nivolumab vs 11.7 months for everolimus (HR (95% CI): 0.64 (0.47–0.88))

Overall survival



Minimum follow-up was 14 months.

NE, not estimable.

Motzer, NEJM 2015

Outline Prostate

- Chemotherapy for HSPC
- COMET trial CRPC
- PCWG3
- Genomics
  - TCGA
  - StandUp2 Cancer: DNA repair and MSH mutations
- PARP inh in PCa

DANA-FARBER CANCER INSTITUTE
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL
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AUGUST 20, 2015

E3805 – CHAARTED Treatment

STRATIFICATION

Extent of Mets
-High vs Low
Age
≥70 vs < 70yo
ECOG PS
- 0-1 vs 2
CAB> 30 days
-Yes vs No
SRE Prevention
-Yes vs No
Prior Adjuvant ADT
≤12 vs > 12 months

→ RANDOMIZE

ARM A:
ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles
→ Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks

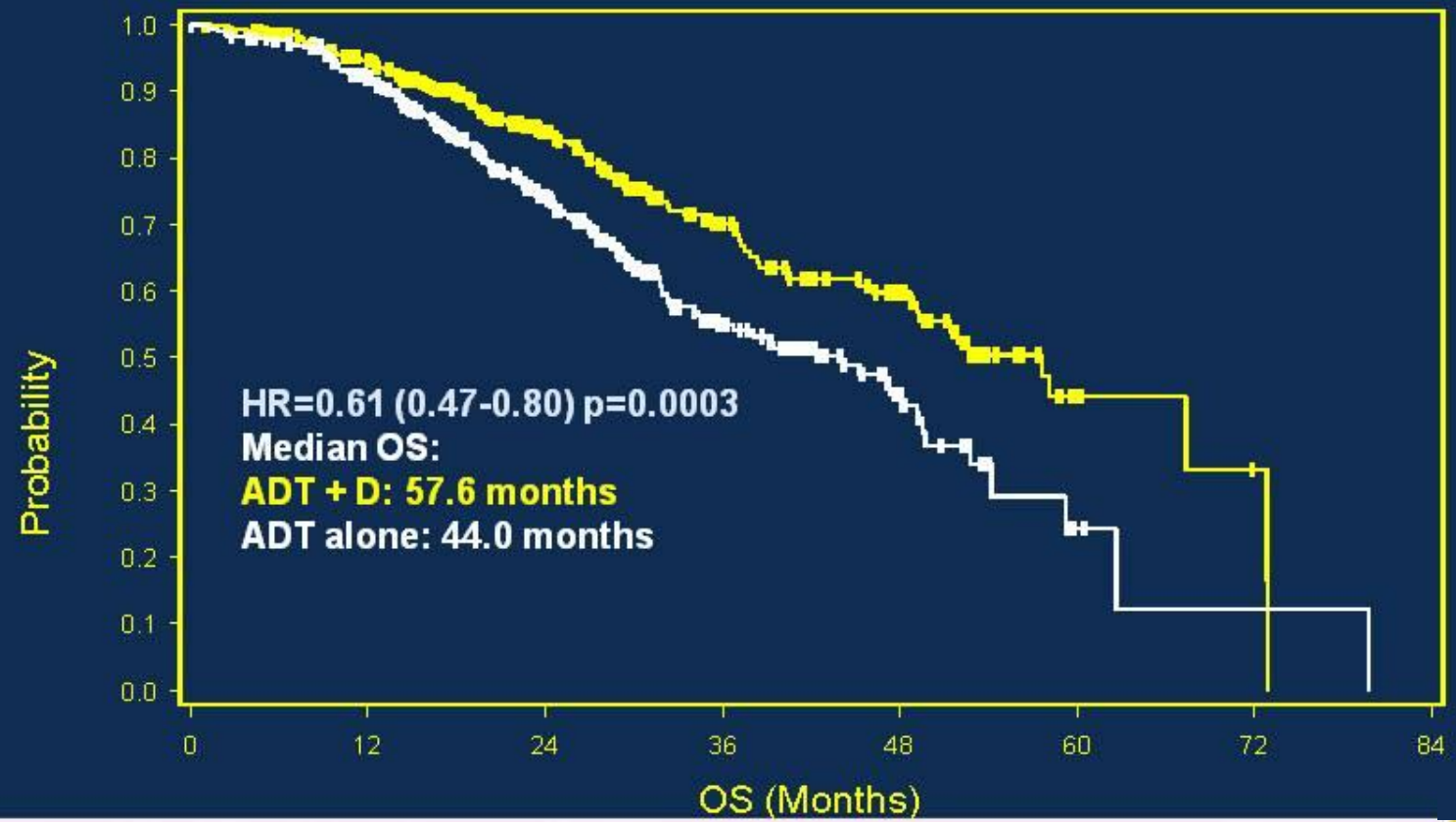
ARM B:
ADT (androgen deprivation therapy alone)
→ Evaluate every 12 weeks

→ Follow for time to progression and overall survival

Chemotherapy at investigator's discretion at progression

- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Primary endpoint: Overall survival



Sweeney et al *The* NEW ENGLAND JOURNAL *of* MEDICINE

AUGUST 20, 2015

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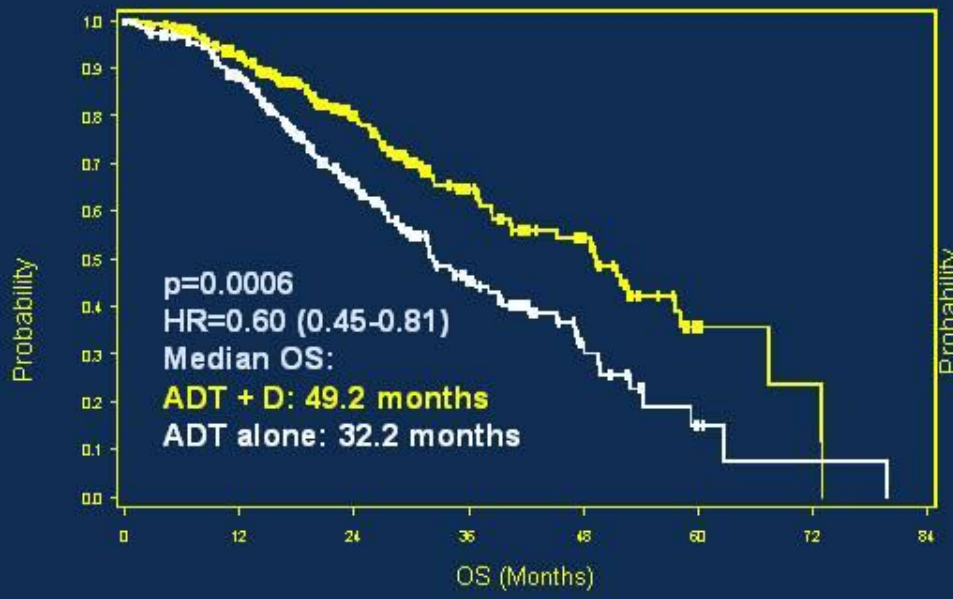
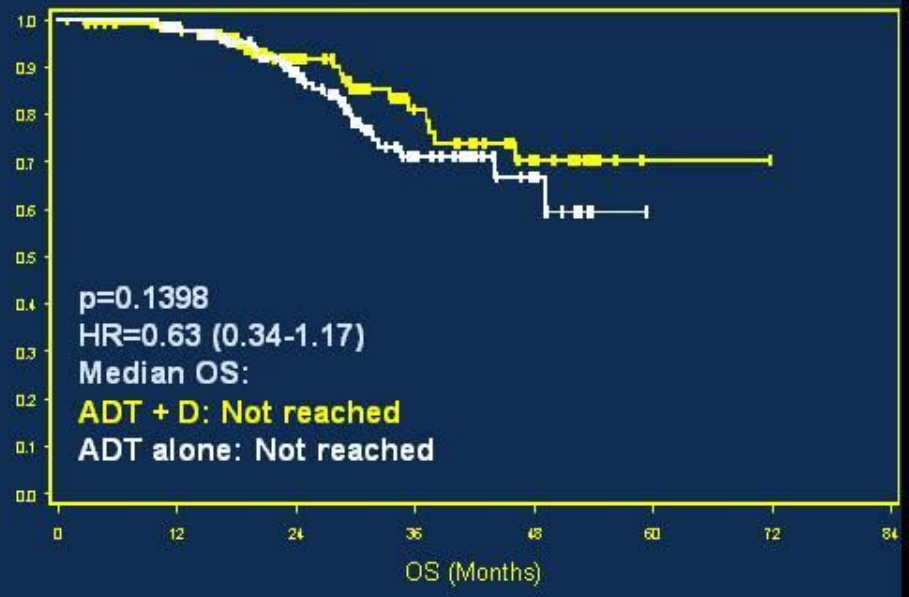
AUGUST 20, 2015

OS by extent of metastatic disease at start of ADT

High volume



Low volume



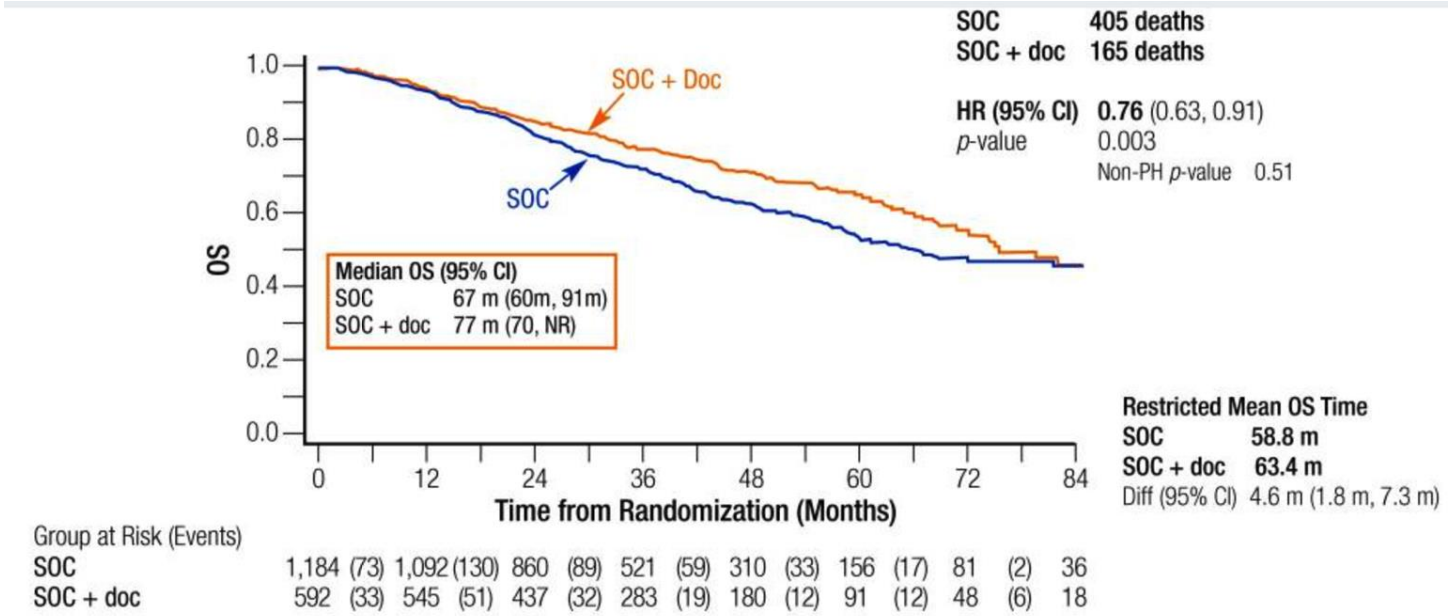
In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months

We projected 33 months in ADT alone arm with collaboration of SWOG9346 team

STAMPEDE

1184 men with metastatic (~75%) or high risk disease (~25%): randomized to ADT + docetaxel or ADT alone.

- OS: median 77 vs 67 months, hazard ratio [HR] 0.76, 95% CI 0.63-0.91. A similar benefit was observed for DFS
- **OS in M1 subset: median 65 versus 43 months, HR 0.73, 95% CI 0.59-0.89).**
- Failure-free survival in M1: HR 0.62, 95% CI 0.54-0.71; in M0 HR 0.57, 95% CI 0.42-0.76.



SOC = standard of care (androgen-deprivation therapy ± radiotherapy.

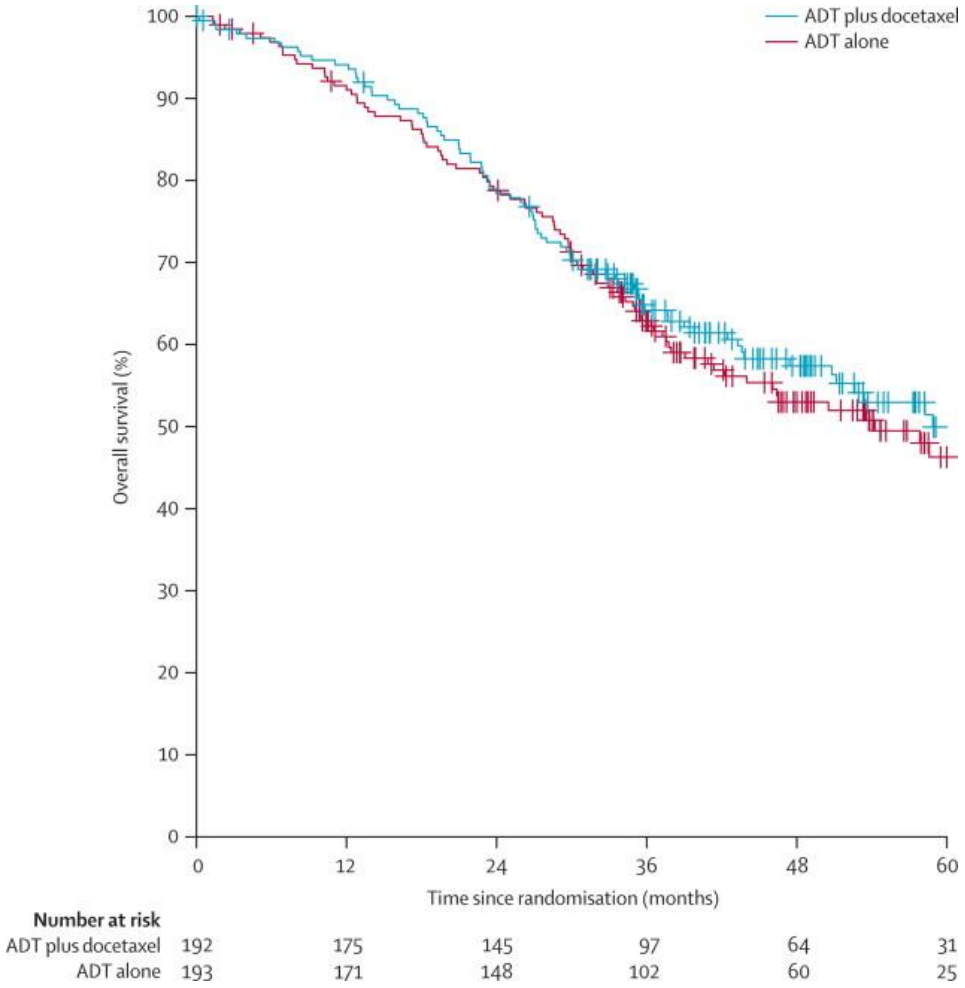
James et al, ASCO 2015, abstr 5001

GETUG-AFU 15

192 men randomized to ADT + docetaxel and 193 to receive ADT alone.

Median follow-up 50 months:
- Median OS 58.9 vs 54.2 months
- HR 1.01, 95% CI 0.75-1.36.
- 72 serious adverse events ADT + docetaxel
- Four treatment-related deaths in ADT + docetaxel

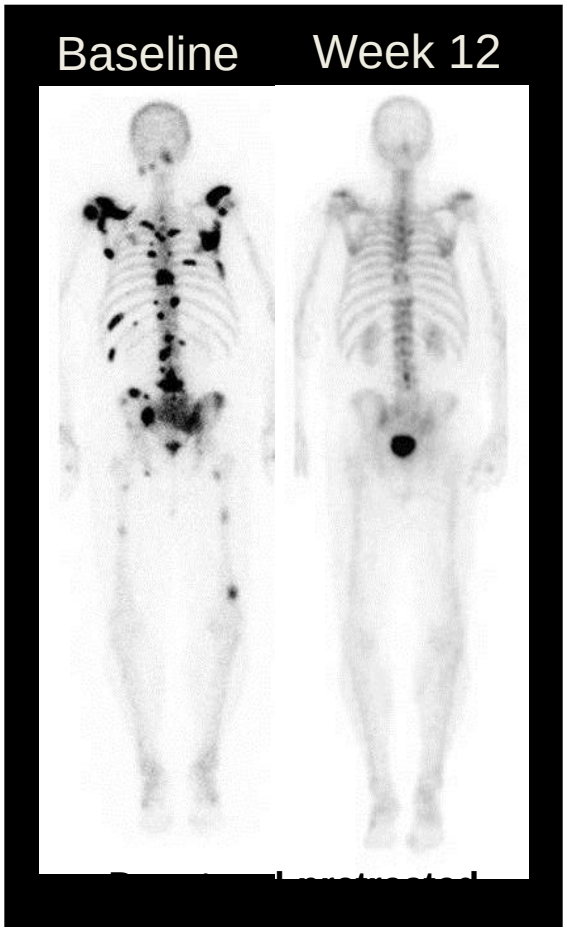
Median follow-up 83 months:
- Median OS 61 versus 47 months
  - HR 0.9, 95% CI 0.7-1.2
- PFS median 22.9 versus 12.9 months
  - HR 0.7, 95% CI 0.6-0.9
- PFS benefit seen in both high and low volume disease



Gravis et al, Lancet Oncol. 2013;14(2):149
Gravis et al, ASCO 2015, (suppl 7; abstr 140)

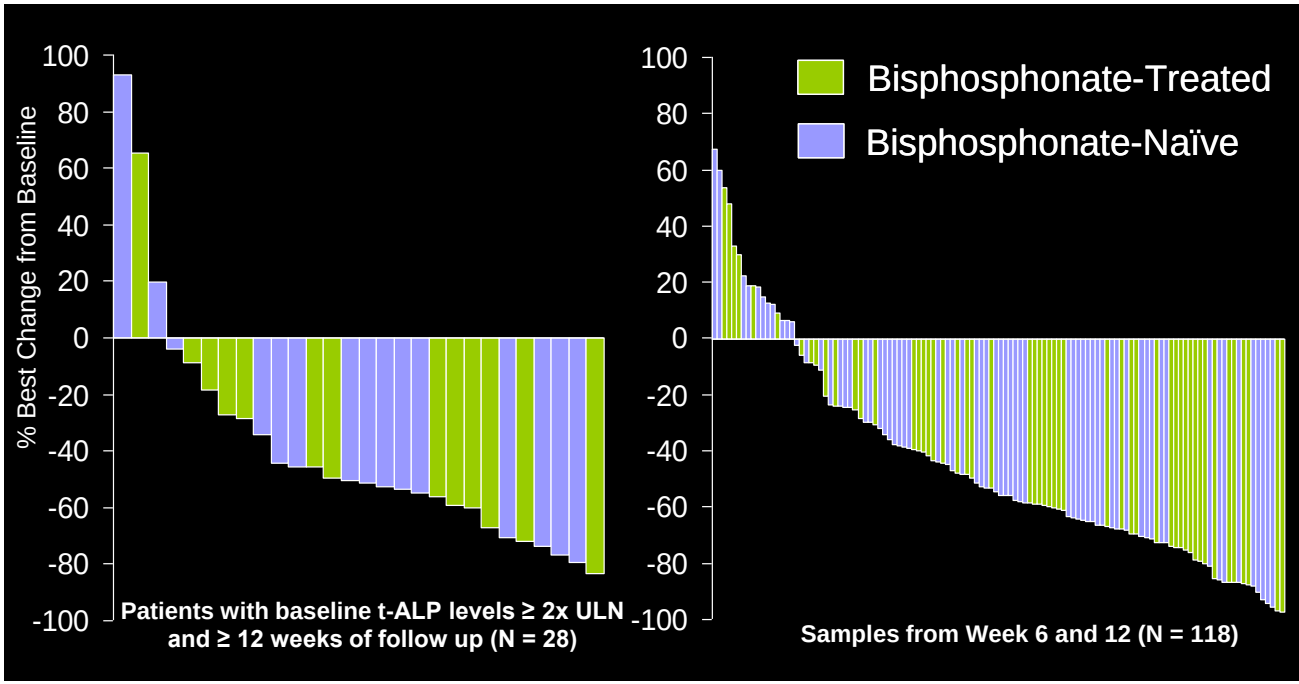
Cabozantinib (XL 184)

Bone effects



Bone scan evaluable (N=108)	n (%)
Complete resolution	21 (19)
Partial resolution	61 (56)
Stable	23 (21)
Progressive disease	3 (3)

Effects on osteoblast (t-ALP) and osteoclast (CTX) activity



Smith, et al JCO 2012

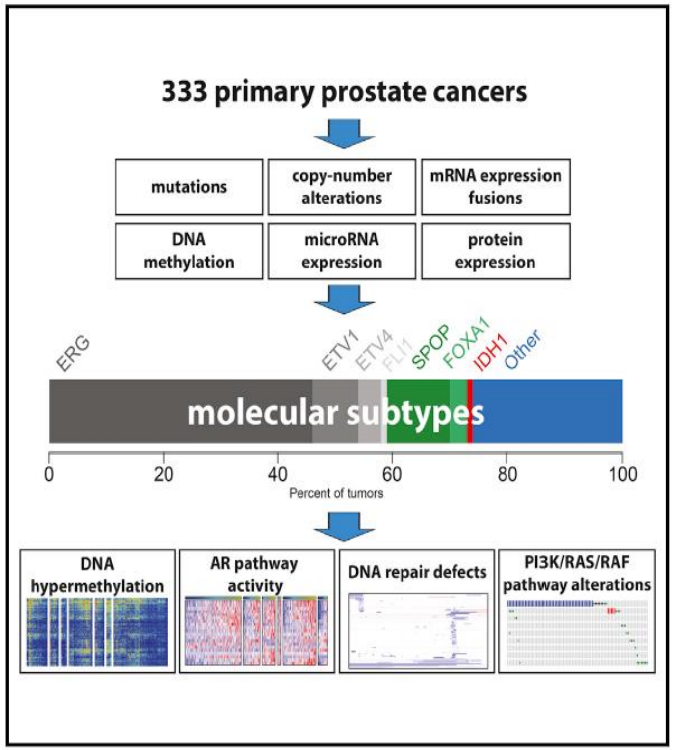
COMET-1: Final Analysis Abstr #139

- N = 1028, dose 60mg po
- Plan for 578 deaths to provided 90% power to detect HR 0.75
- Bone scan response at wk 12
- Based on 614 deaths: OS 11 mo vs 9.8, P=0.212
- BSR 41% for Cabo vs 3% for Pred
- Median PFS per investigator: 5.5 vs 2.8 mo, P<0.001
- Visceral dz*: OS 7.1 vs 4.8 mo

Cell

The Molecular Taxonomy of Primary Prostate Cancer

The Cancer Genome Atlas Research Network[1,*]
[1]The Cancer Genome Atlas Program Office, National Cancer Institute at NIH, 31 Center Drive, Building 31, Suite 3A20, Bethesda, MD 20892, USA
*Correspondence: schultz@cbio.mskcc.org (N.S.), massimo_loda@dfci.harvard.edu (M.L.), sander.research@gmail.com (C.S.)
http://dx.doi.org/10.1016/j.cell.2015.10.025



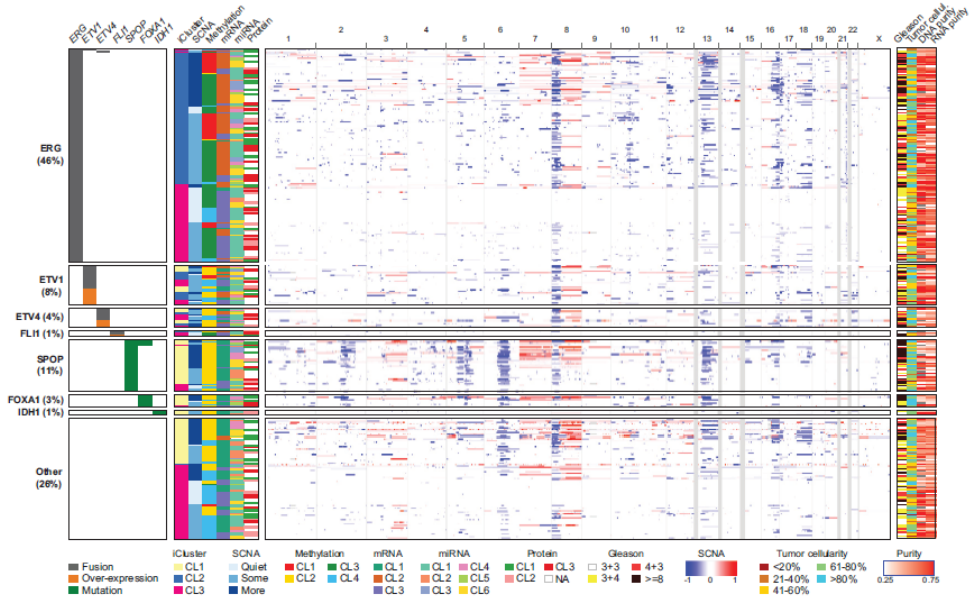


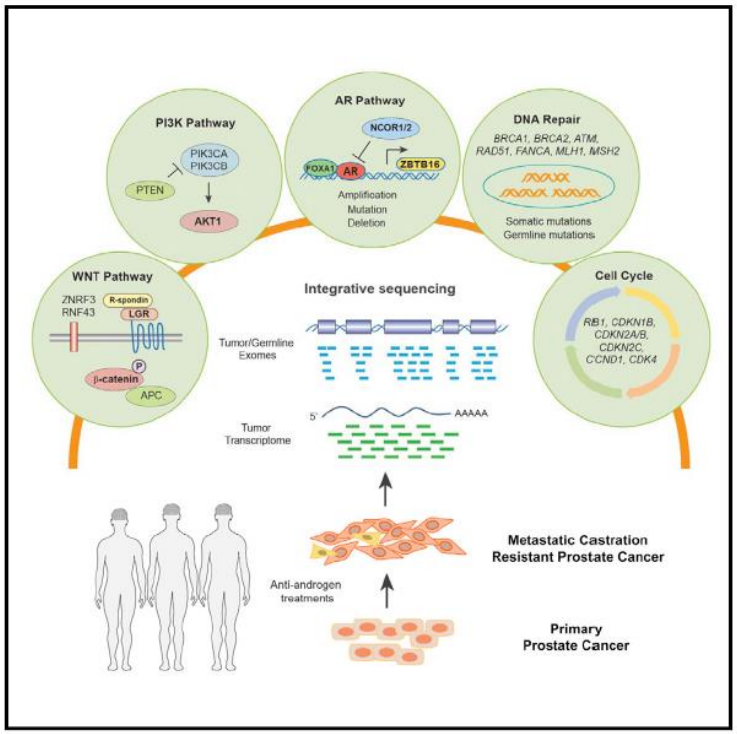
Figure 1. The Molecular Taxonomy of Primary Prostate Cancer

Comprehensive molecular profiling of 333 primary prostate cancer samples revealed seven genomically distinct subtypes, defined (top to bottom) by *ERG* fusions (46%), *ETV1/ETV4/FLI1* fusions or overexpression (8%, 4%, 1%, respectively), or by *SPOP* (11%), *FOXA1* (3%), and *IDH1* (1%) mutations. A subset of these subtypes was correlated with clusters computationally derived from the individual characterization platforms (somatic copy-number alterations, methylation, mRNA, microRNA, and protein levels from reverse phase protein arrays). The heatmap shows DNA copy-number for all cases, with chromosomes shown from left to right. Regions of loss are indicated by shades of blue, and gains are indicated by shades of red.
See also Figures S1, S2, S3, S4, S5, S6, and S7 and Tables S1A, S1B, S1E, and S2.

Cell

Integrative Clinical Genomics of Advanced Prostate Cancer

Dan Robinson,[1,2,43] Eliezer M. Van Allen,[3,4,43] Yi-Mi Wu,[1,2] Nikolaus Schultz,[5,40] Robert J. Lonigro,[1] Juan-Miguel Mosquera,[6,7,8,38] Bruce Montgomery,[9,10] Mary-Ellen Taplin,[3] Colin C. Pritchard,[26] Gerhardt Attard,[11,12] Himisha Beltran,[7,8,13,38] Wassim Abida,[14,20] Robert K. Bradley,[9] Jake Vinson,[15] Xuhong Cao,[1,42] Pankaj Vats,[1] Lakshmi P. Kunju,[1,2,17] Maha Hussain,[16,17,18] Felix Y. Feng,[1,17,19] Scott A. Tomlins,[1,2,17,18] Kathleen A. Cooney,[16,17,18] David C. Smith,[16,17,18] Christine Brennan,[1] Javed Siddiqui,[1] Rohit Mehra,[1,2] Yu Chen,[13,14,20] Dana E. Rathkopf,[13,20] Michael J. Morris,[13,20] Stephen B. Solomon,[21] Jeremy C. Durack,[21] Victor E. Reuter,[22] Anuradha Gopalan,[22] Jianjiong Gao,[40] Massimo Loda,[3,4,23,39] Rosina T. Lis,[3,23] Michaela Bowden,[3,23,39] Stephen P. Balk,[24] Glenn Gaviola,[25] Carrie Sougnez,[4] Manaswi Gupta,[4] Evan Y. Yu,[10] Elahe A. Mostaghel,[9,10] Heather H. Cheng,[9,10] Hyojeong Mulcahy,[27] Lawrence D. True,[28] Stephen R. Plymate,[10] Heidi Dvinge,[9] Roberta Ferraldeschi,[11,12] Penny Flohr,[11,12] Susana Miranda,[11,12] Zafeiris Zafeiriou,[11,12] Nina Tunariu,[11,12] Joaquin Mateo,[11,12] Raquel Perez-Lopez,[11,12] Francesca Demichelis,[7,29] Brian D. Robinson,[6,7,8,38] Marc Schiffman,[7,31,38] David M. Nanus,[7,8,13,38] Scott T. Tagawa,[7,8,13,38] Alexandros Sigaras,[7,30,32] Kenneth W. Eng,[7,30,32] Olivier Elemento,[30] Andrea Sboner,[6,7,30,38] Elisabeth I. Heath,[33,34] Howard I. Scher,[13,20] Kenneth J. Pienta,[35] Philip Kantoff,[3,44] Johann S. de Bono,[11,12,44] Mark A. Rubin,[6,7,8,38,44] Peter S. Nelson,[10,36,37,38,44] Levi A. Garraway,[3,4,44] Charles L. Sawyers,[14,41,44,*] and Arul M. Chinnaiyan[1,2,17,18,42,44,*]



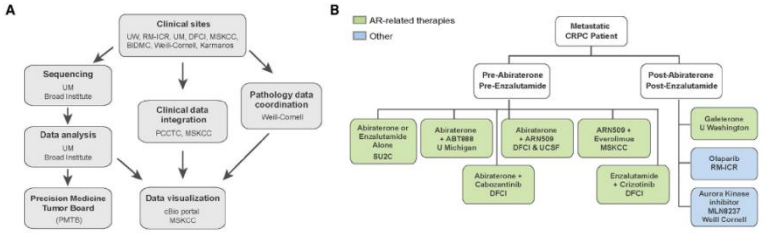


Figure 1. Overview of the SU2C-PCF IDT Multi-Institutional Clinical Sequencing of the mCRPC Project

(A) Schema of multi-institutional clinical sequencing project work flow.
(B) Clinical trials associated with the SU2C-PCF mCRPC project.
(C) Biopsy sites of the samples used for clinical sequencing.
(D) Histopathology of the cohort. Representative images of morphological analysis of mCRPC are shown along with prevalence in our cohort.

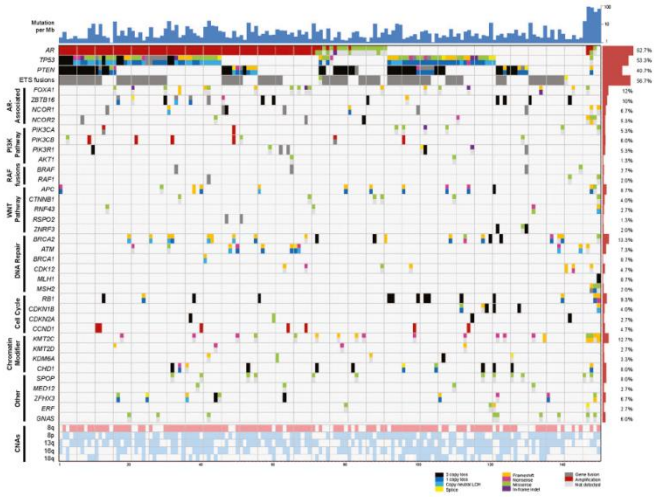
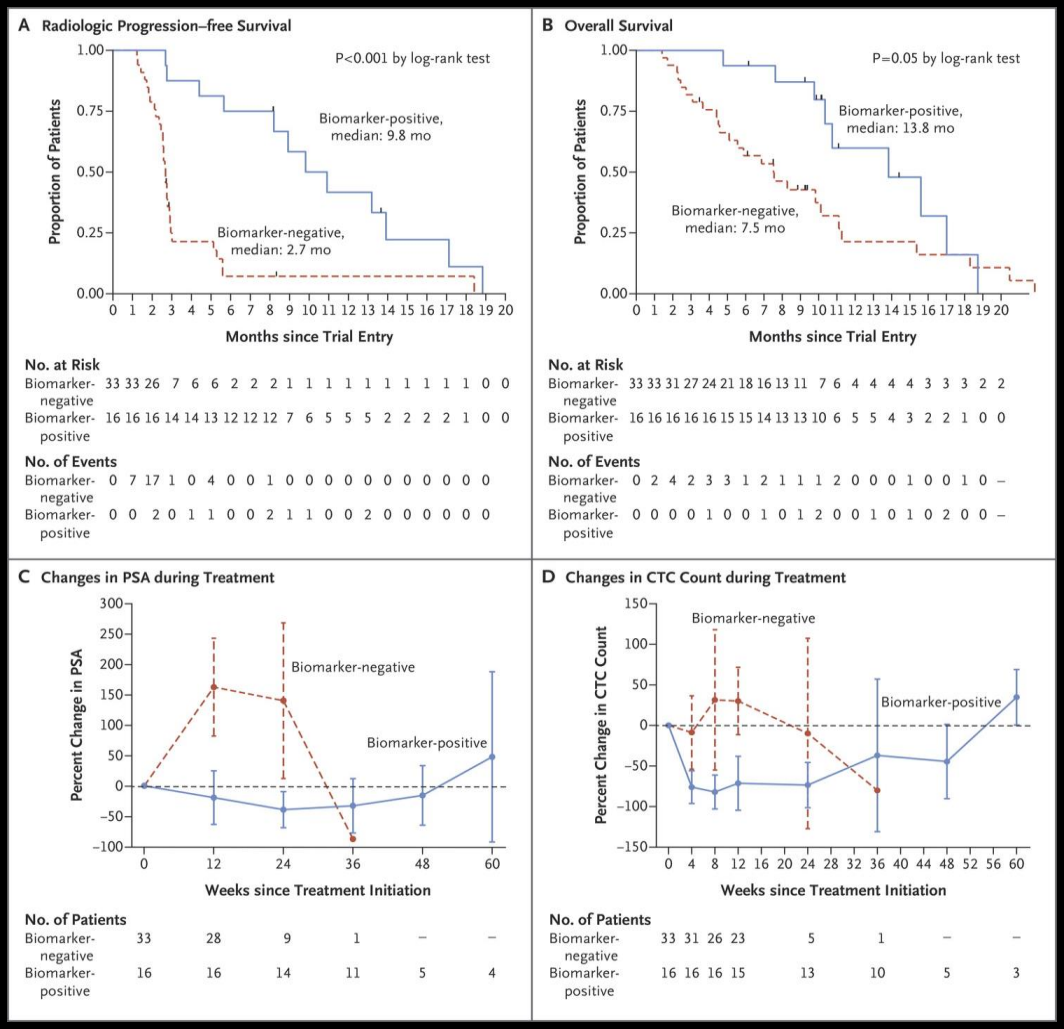


Figure 2. Integrative Landscape Analysis of Somatic and Germline Aberrations in Metastatic CRPC Obtained through DNA and RNA Sequencing of Clinically Obtained Biopsies

Columns represent individual affected individuals, and rows represent specific genes grouped in pathways. Mutations per Mb are shown in the upper histogram, and incidence of aberrations in the cohort is in the right histogram. Copy number variations (CNVs) common to mCRPC are shown in in the lower matrix, with pink representing gain and light blue representing loss. Color legend of the aberrations represented including amplification, two copy loss, one copy loss, copy neutral loss of heterozygosity (LOH), splice site mutation, frameshift mutation, missense mutation, in-frame indel, and gene fusion. Cases with more aberration in a gene are represented by split colors.

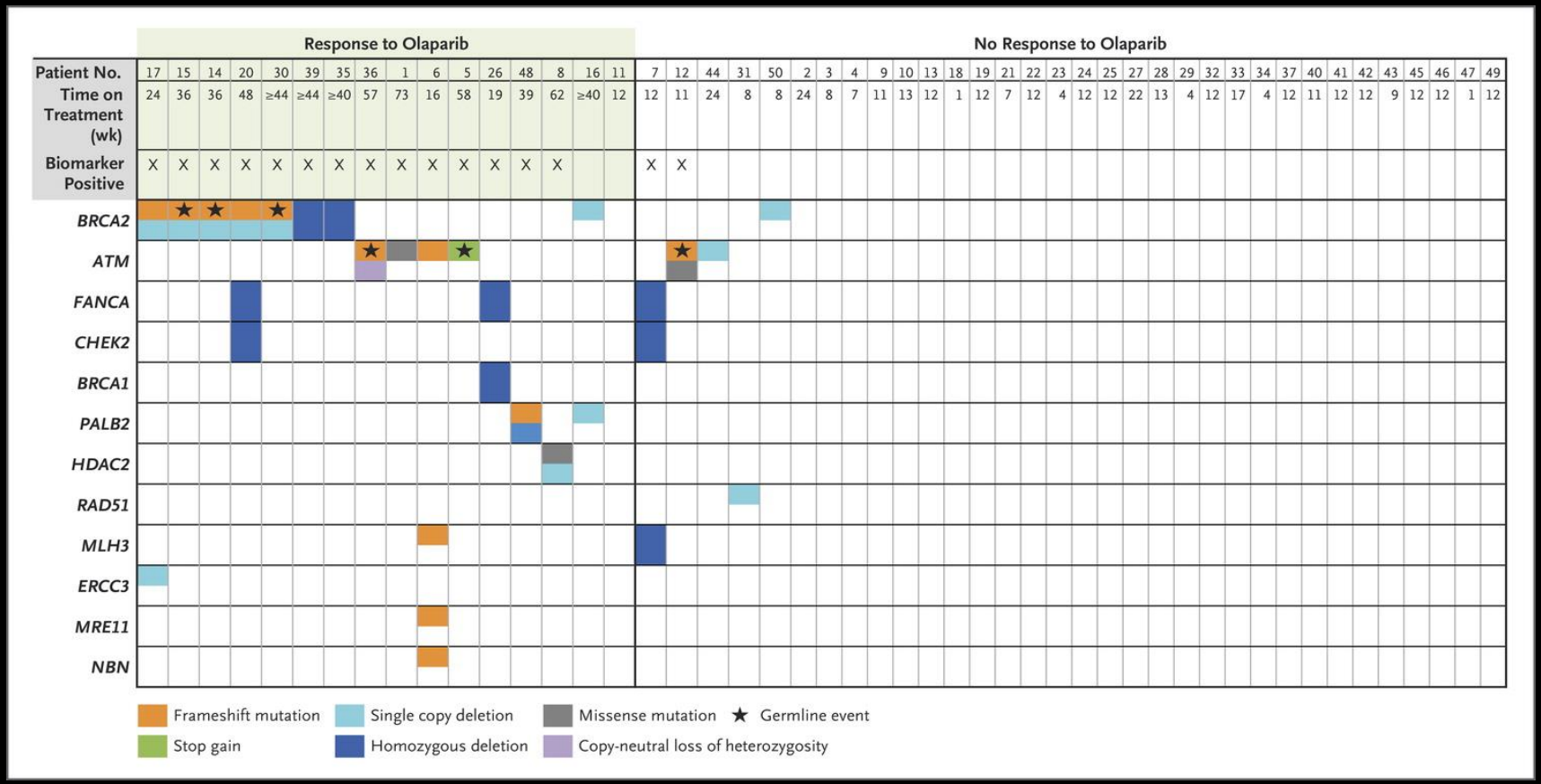
Antitumor Activity of Olaparib and Association with Defects in DNA-Repair Genes, According to Biomarker Status.



Mateo J et al. N Engl J Med 2015;373:1697-1708.

The NEW ENGLAND JOURNAL of MEDICINE

Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer.



Mateo J et al. N Engl J Med 2015;373:1697-1708.

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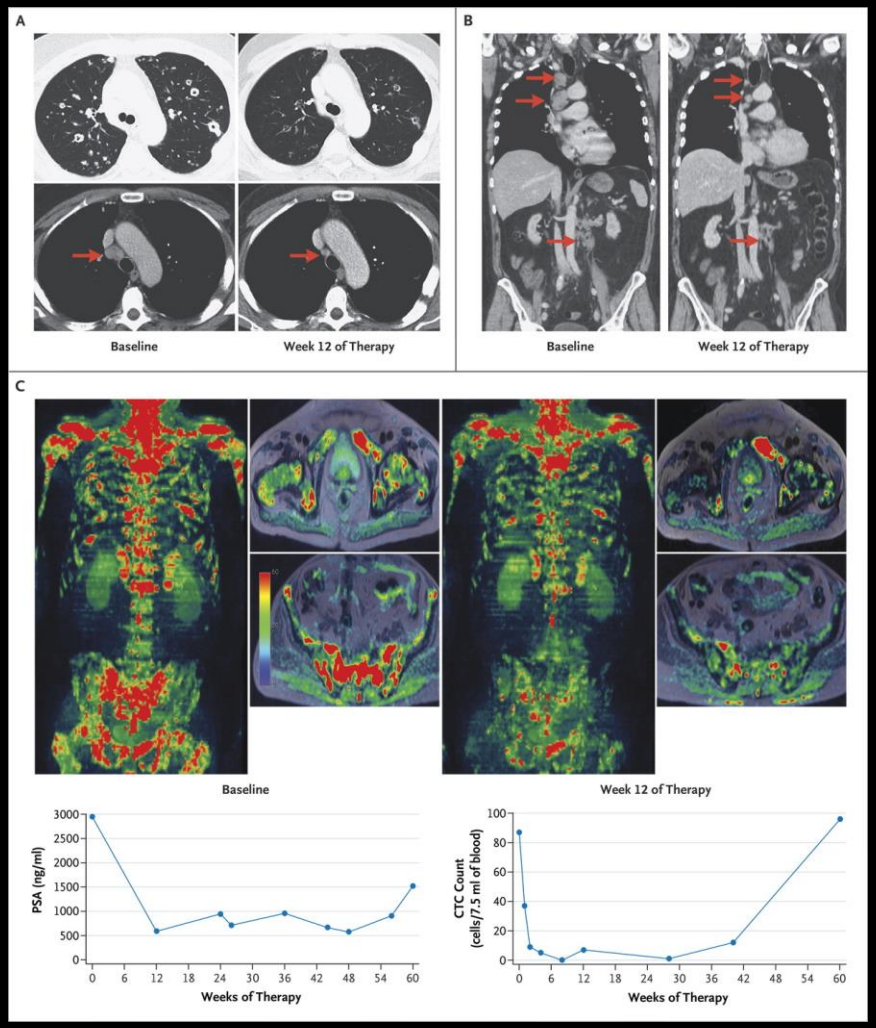
Radiologic Evidence of Tumor Responses to Olaparib at Week 12.



Mateo J et al. N Engl J Med 2015;373:1697-1708.

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GU Highlights 2015

- Failed role of lapatinib in maintenence
- Check point inhibitors are promising in bladder cancer
- Expression signatures might help to identify the best treatment option (chemo vs immuno)

- Adjuvant therapy in RCC an open question
- Nivolumab FDA approved for renal second line
- New promising role of cabozantanib in second line

- Established role of docetaxel in HSPC
- Genomic profiling in early and advance disease
- Translation to treatment with Olaparib