Advanced Bladder Cancer
In the era of targeted therapeutics

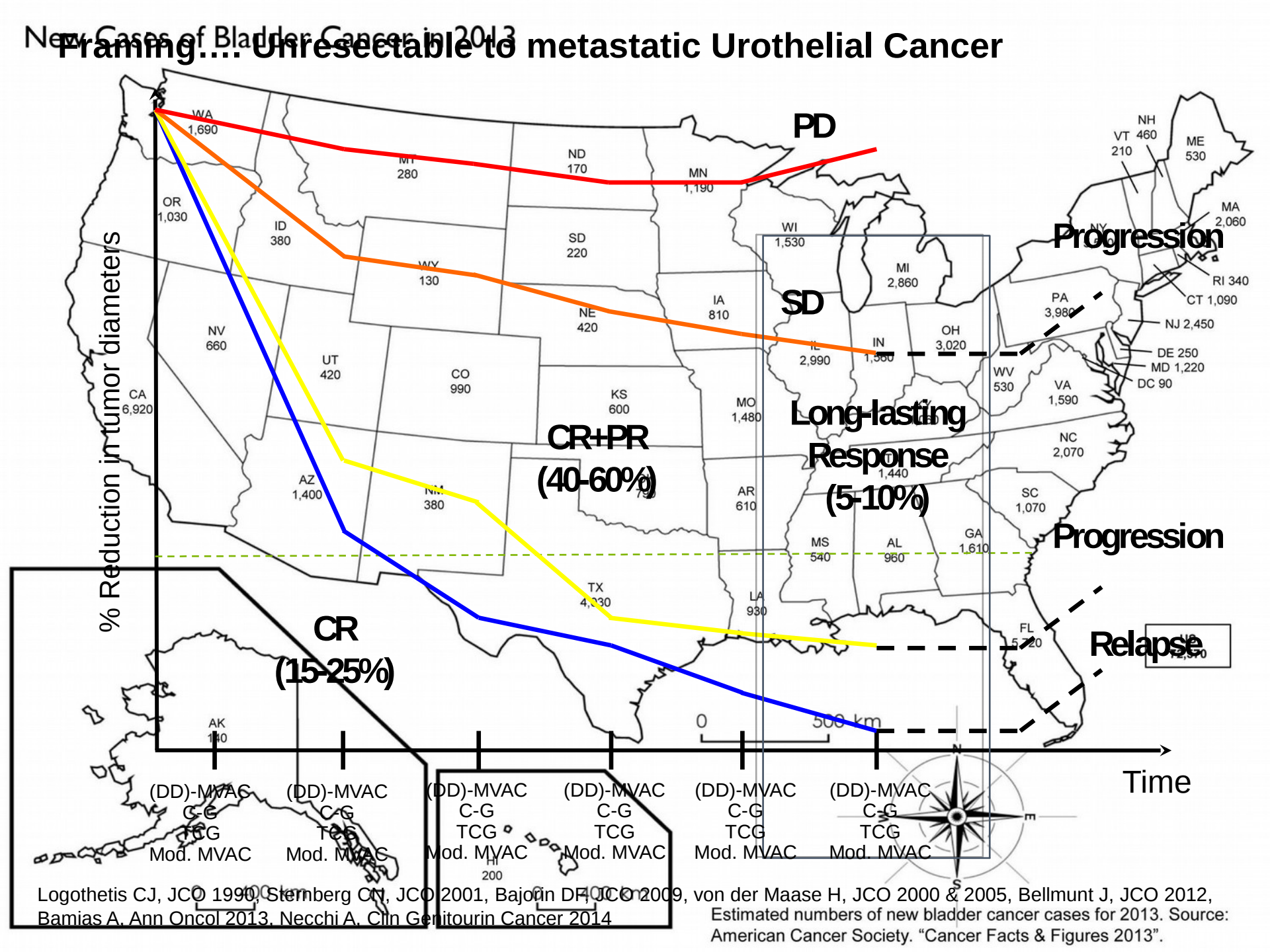
Andrea Necchi
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Disclosures

- Consultant and advisory role, GlaxoSmithKline (GSK)
- Research funding, Millennium
- Research funding, Pierre-Fabre Medicament
- Research funding, Amgen
- Consultant and advisory role, Celgene
- *Treasurer of the EORTC-GU Cancers Group*
- *Member of the EAU-YAU Bladder Cancer Working Group*

7th Pomeranian Uro-Oncology Meeting
„Bladder cancer - stagnation or progress?”

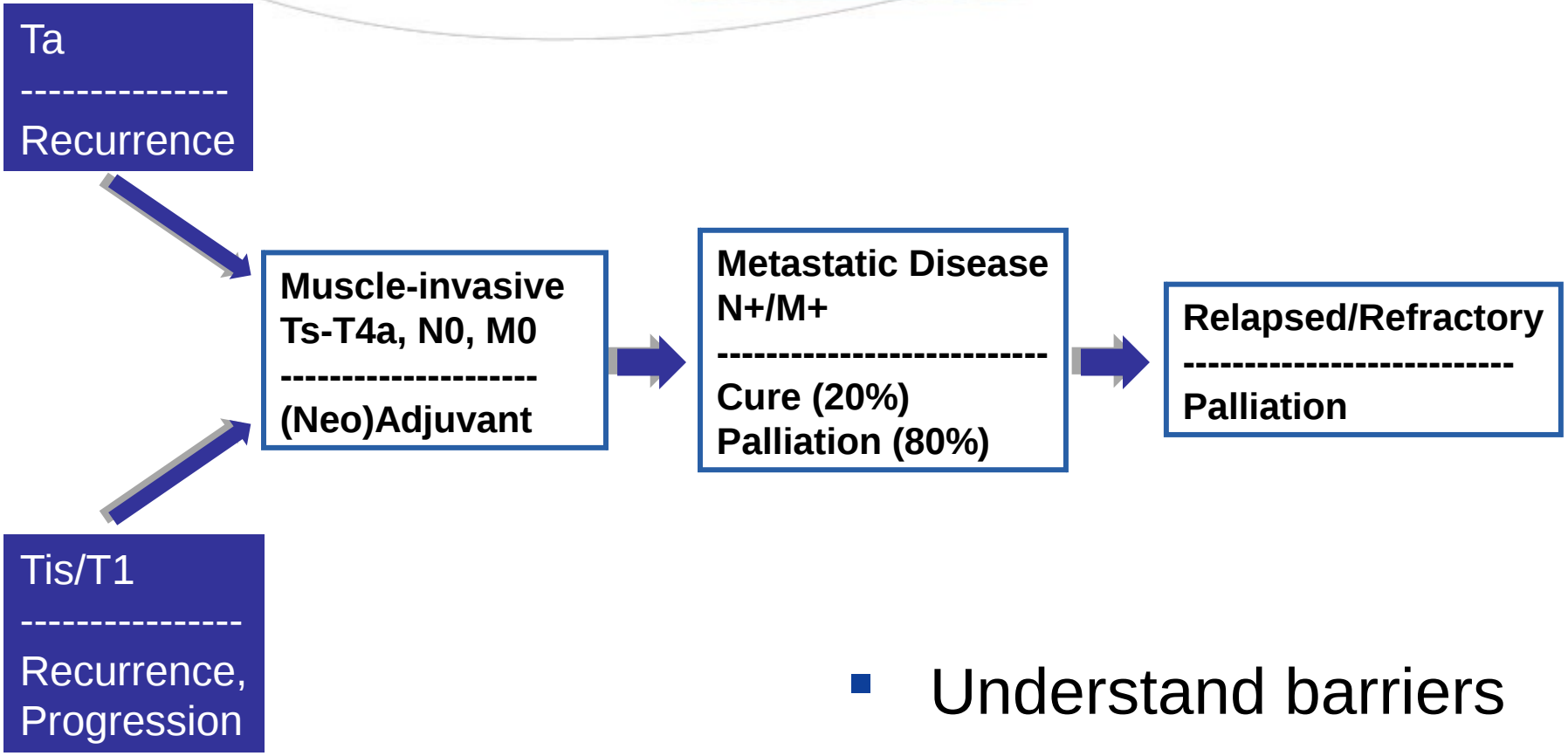
Framing…. Unresectable to metastatic Urothelial Cancer



Logothetis CJ, JCO 1990, Sternberg CN, JCO 2001, Bajorin DF, JCO 2009, von der Maase H, JCO 2000 & 2005, Bellmunt J, JCO 2012, Bamias A, Ann Oncol 2013, Necchi A, Clin Genitourin Cancer 2014

Estimated numbers of new bladder cancer cases for 2013. Source: American Cancer Society. "Cancer Facts & Figures 2013".

How can we do better?



- Understand barriers
- Improve therapies/patient selection
- Improve risk prediction and prognostic accuracy

How can we do better?

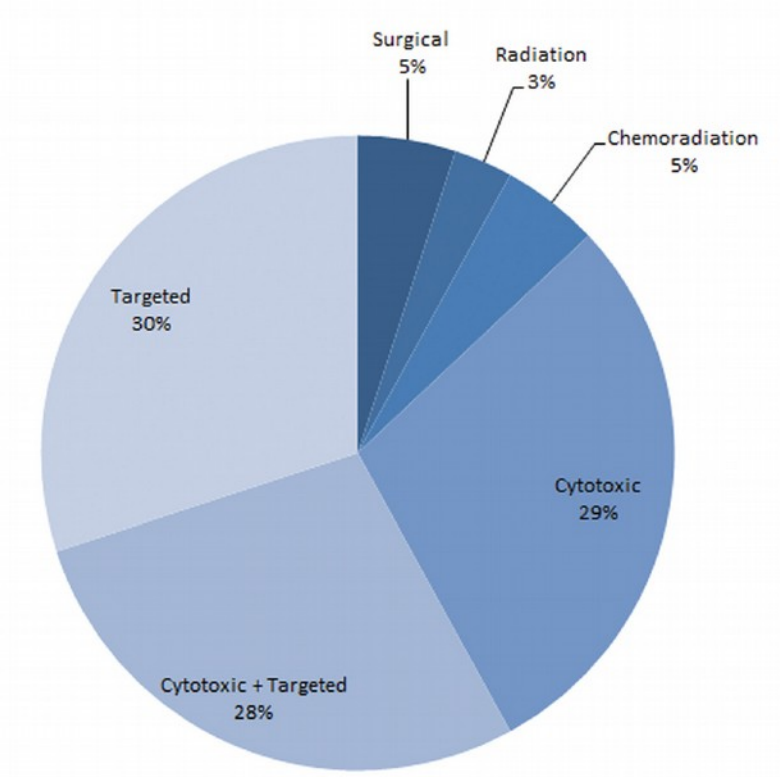
- Understand barriers

Critical Analysis of Contemporary Clinical Research in Muscle-Invasive and Metastatic Urothelial Cancer

A Report from the Bladder Cancer Advocacy Network Clinical Trials Working Group

TABLE 1. Trial Characteristics (n = 120)

Characteristic	Number of Trials (%)
Phase	
Phase 1	9 (8)
Phase 1/2	13 (11)
Phase 2	87 (73)
Phase 2/3	2 (2)
Phase 3	7 (6)
Unknown	2 (2)
Allocation	
Single-arm	87 (73)
Randomized	33 (27)
Sponsor	
Industry	62 (52)
National Cancer Institute	15 (13)
Institutional/other	42 (35)
Unknown	1 (1)
Recruitment status	
Active, not recruiting	29 (24)
Completed	27 (23)
Not yet recruiting	4 (3)
Recruiting	54 (45)
Suspended	2 (2)
Terminated/withdrawn	4 (3)
Number of study sites	
1	47 (39)
2	8 (7)
3	11 (9)
4	5 (4)
5	12 (10)
≥6	37 (31)
Location of sites	
United States	67 (56)
Outside United States	37 (31)
Both	16 (13)

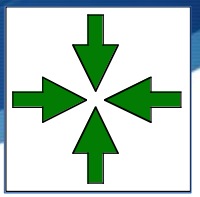


Galsky MD, Cancer 2013

Why is “translation” hard

- Patient selection and heterogeneity (tumor biology, host factors)
- Inaccuracy of clinical staging and risk assessment
- Gain access to patients with well annotated tissue
- Design early trials in which the desired therapeutic effect can be linked to a translational endpoint that reflects the biological activity of the agent under study
- Analyze, quantify, and integrate biomarkers generated by multiple platforms
- Cost and competing agendas

How can we do better?



- Improving therapeutic options
  - ***Searching for new agents: chemotherapy***

Unselecting patients across the second-line trials

	Previous perioperative therapy counted as first-line therapy	N	RR (%)	PFS (months)	OS (months)
Weekly paclitaxel	No	31	10	2·2	7·2
Paclitaxel q21d	Yes	14	7	-	.
Nab-paclitaxel	Yes	47	27.7	6.0	10.8
Eribulin	Yes	48	27	4.1	10.4
Irinotecan	No	40	5	2·1	5·4
Ixabepilone	Yes	42	11·9	2·7	8·0
Pemetrexed	Yes if <1 year	47	27·7	2·9	9·6
Oxaliplatin	Yes if <6 months	18	6		
Ifosfamide	NA	56	20		
Pralatrexate	NA	30	3·3	4·0	9·3
Pemetrexed	Yes	12	8	-	-
Docetaxel	Yes	30	13	-	9·0
Gemcitabine	NA	30	11	4·9	8·7
Gemcitabine	Yes	35	22·5	-	5·0
Topotecan	NA	44	9·1	1·5	6·3
Paclitaxel+gemcitabine	Yes	41	60	-	14·4
Ifosfamide+gemcitabine	NA	34	21	4·0	9·0
Carboplatin+paclitaxel	Yes if <1 year	44	16	4·0	6·0
Gemcitabine+Ifosfamide	No	43	22	3.5	4.8

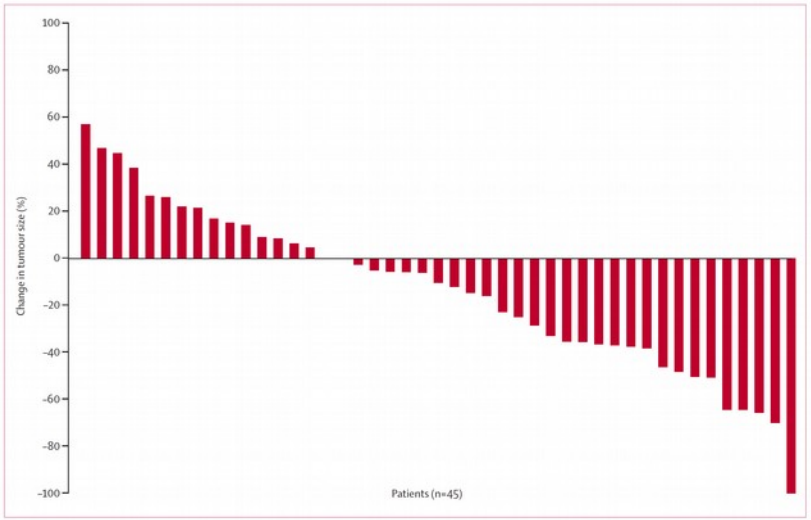
3 mos

6 mos

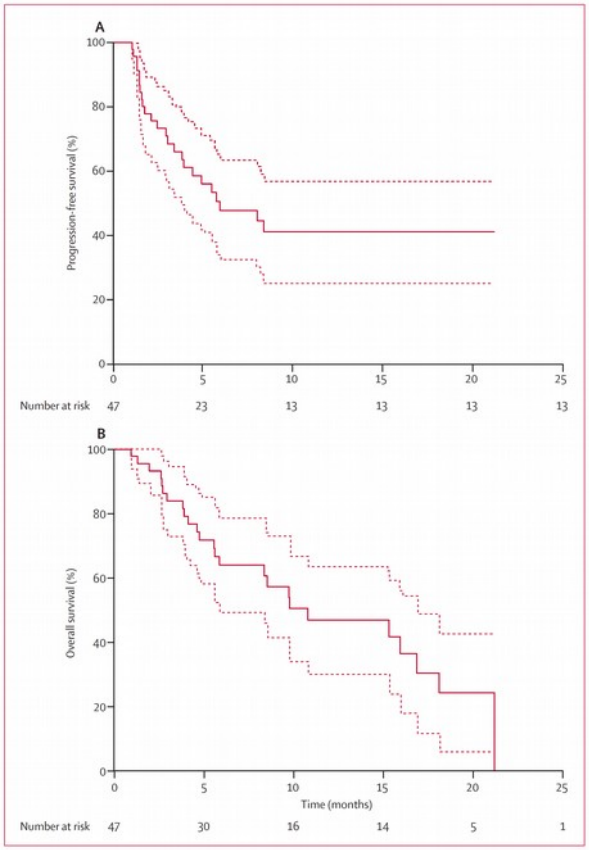
Vinflunine: Phase III, and EMA Approval

Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study

Yoo-Joung Ko, Christine M Canil, Som D Mukherjee, Eric Winquist, Christine Elser, Andrea Eisen, M Neil Reaume, Liying Zhang, Srikala S Sridhar



ORR: 28%



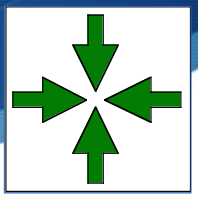
Median PFS: 6.0 mos

Median OS: 10.8 mos

Ko YJ, Lancet Oncol 2013

Ongoing: Nab-Paclitaxel vs Paclitaxel q21, ClinicalTrials.gov NCT02033993

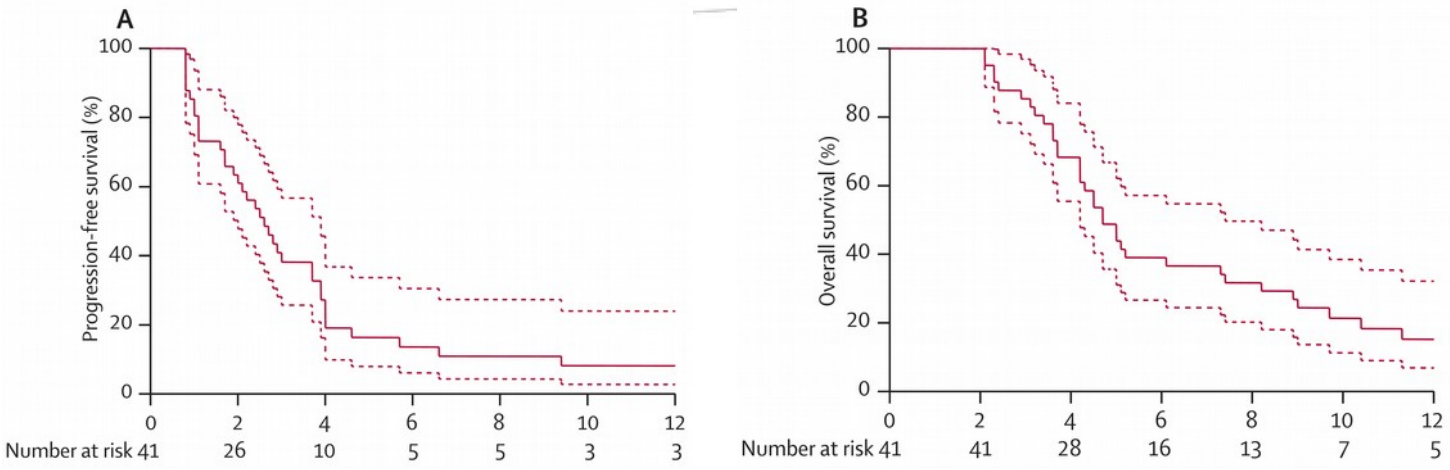
How can we do better?



- Improving therapeutic options
  - ***Targeting Angiogenesis***

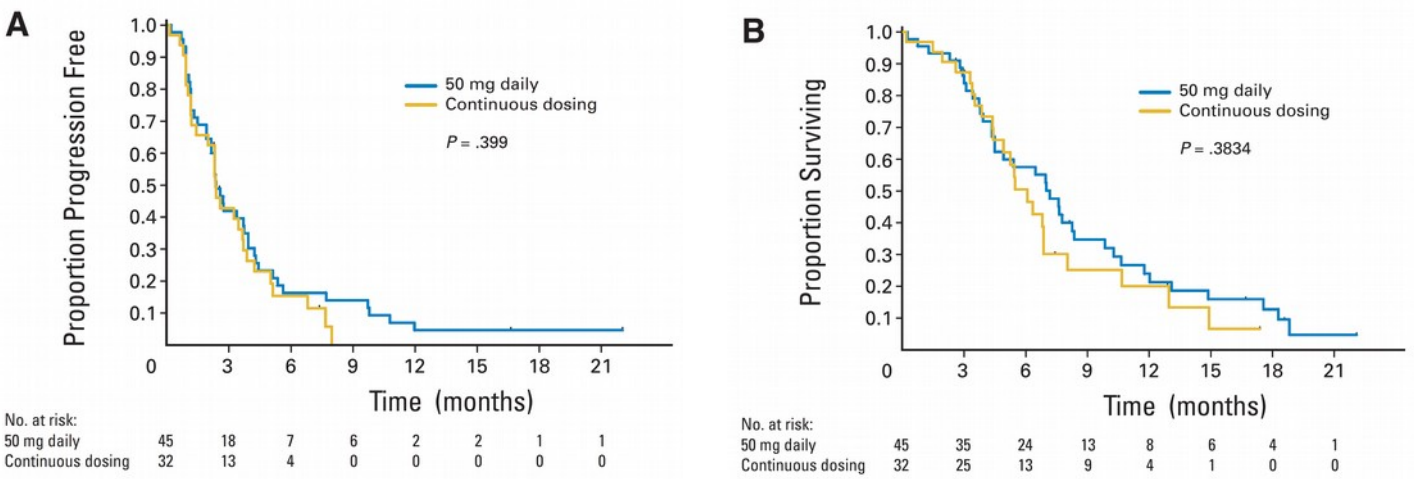
Pazopanib

Necchi A, Lancet Oncol 2012



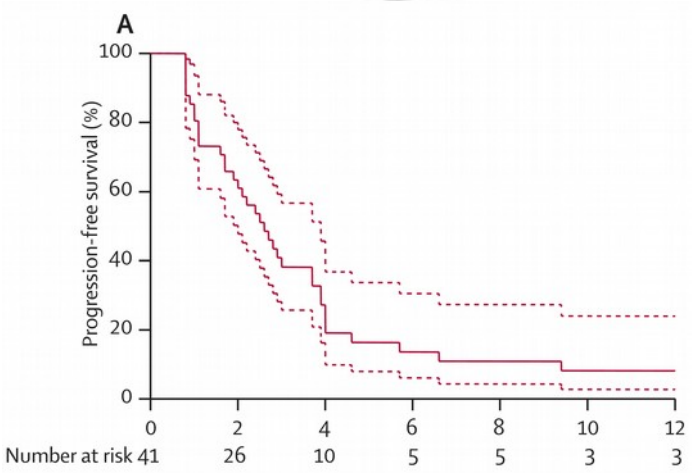
Sunitinib

Gallagher DJ, J Clin Oncol 2010



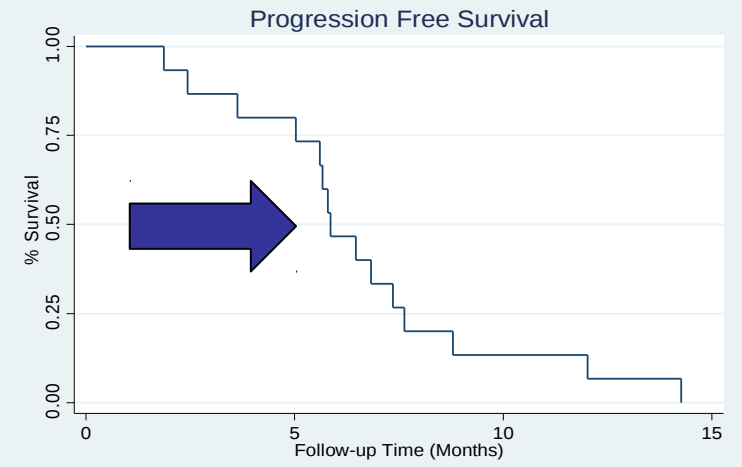
Pazopanib

Necchi A, Lancet Oncol 2012



PZP + weekly TXL

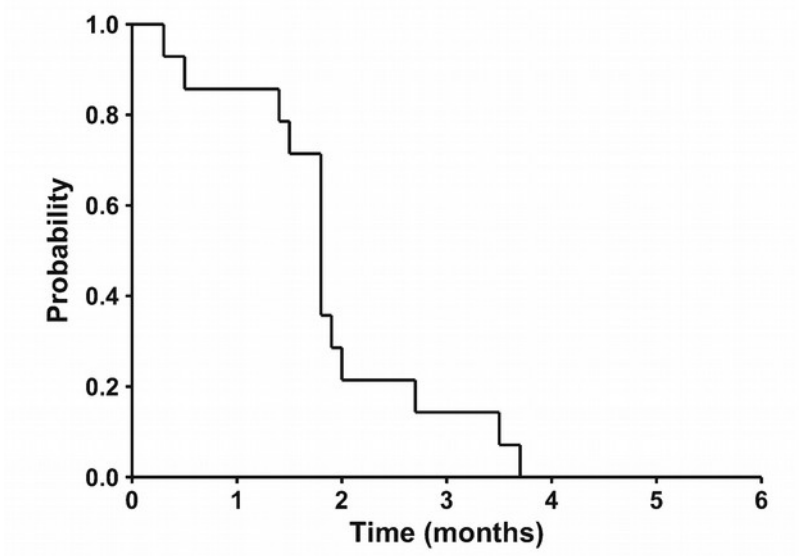
Srinivas S, ASCO-GU 2014



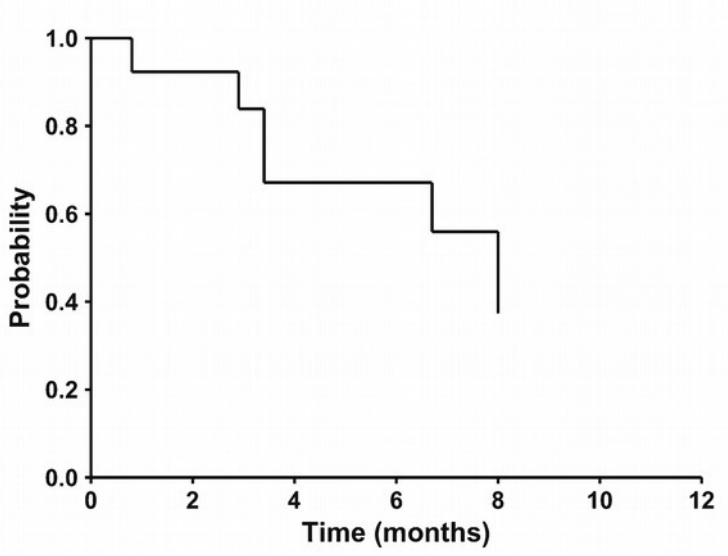
PF-03446962, a fully-human monoclonal antibody against transforming growth-factor β (TGFβ) receptor ALK1, in pre-treated patients with urothelial cancer: an open label, single-group, phase 2 trial

A. Necchi · P. Giannatempo · L. Mariani · E. Farè · D. Raggi · M. Pennati · N. Zaffaroni · F. Crippa · A. Marchianò · N. Nicolai · M. Maffezzini · E. Togliardi · M. G. Daidone · A. M. Gianni · R. Salvioni · F. De Braud

Median PFS: 1.8 months



Median OS: 8 months



Necchi A, Invest New Drugs 2014

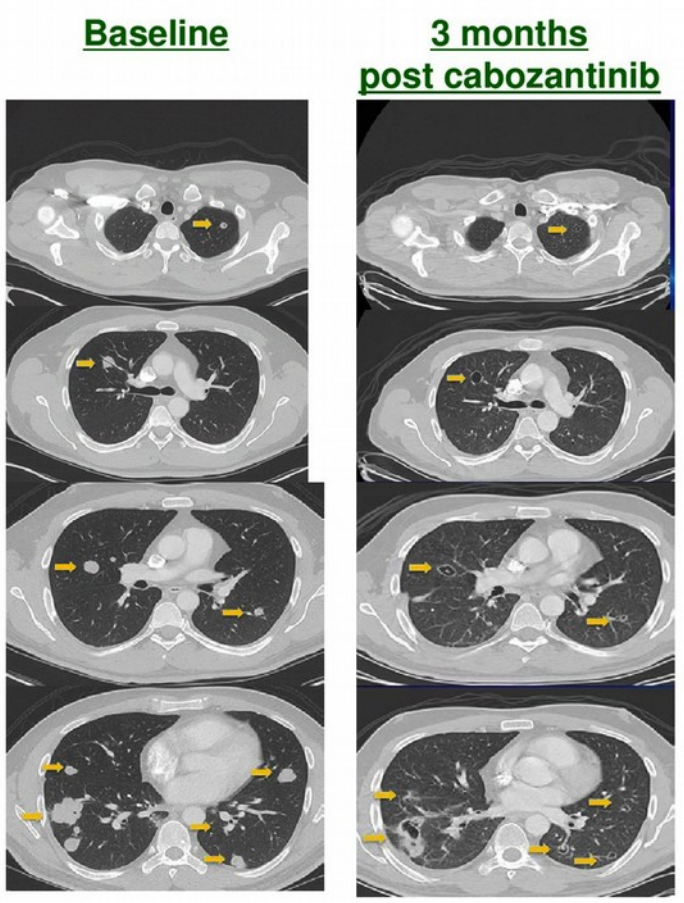
Phase 2 study of Cabozantinib (XL184) in refractory UC

Preliminary Results: Cohort 1

Cohort 1	N=21	%
Partial Response	3	14
Stable Disease	8	38
Clinical benefit	11	52
Progressive Disease	10	48

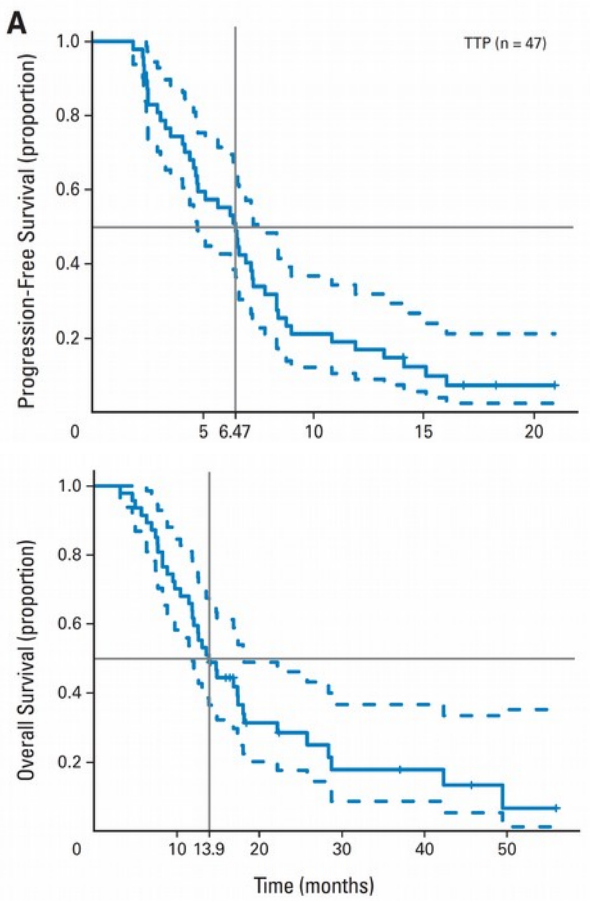
Preliminary Results: Cohort 2

Cohort 1	N=3	%
Partial Response	2	67
Stable Disease	0	0
Clinical benefit	2	67
Progressive Disease	1	33

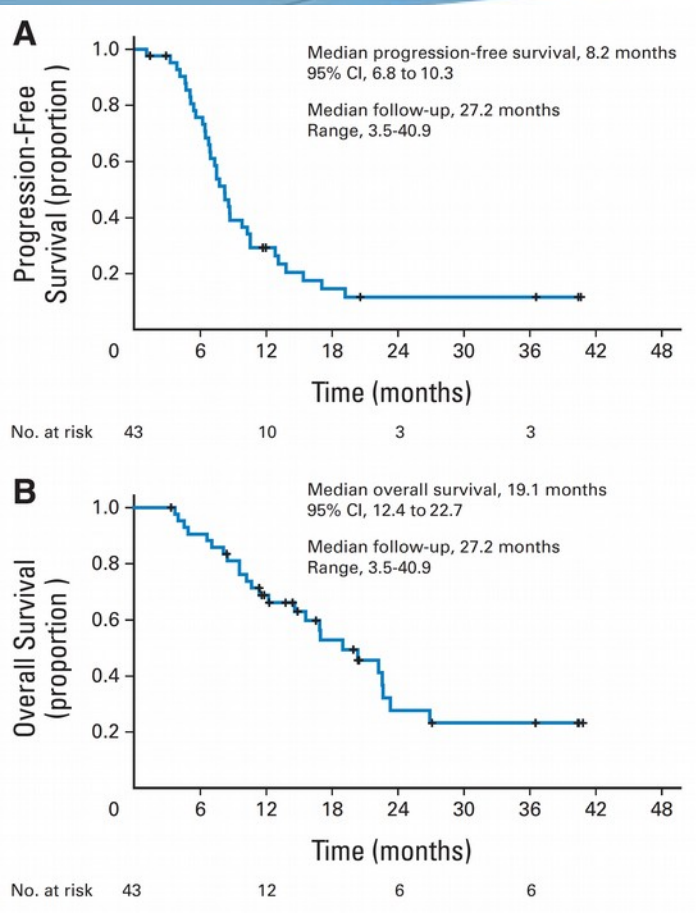


Apolo AB, ASCO-GU 2014

Unselecting patients across the clinical stages…



Bevacizumab-CBDCA/GEM
Balar AV, J Clin Oncol 2013



Bevacizumab-CDDP/GEM
Hahn NM, J Clin Oncol 2011

Ongoing: CG ± Bevacizumab Phase III, ClinicalTrials.gov NCT00942331

Unselecting patients across the clinical stages…

ARTICLE IN PRESS

Original Study

Gemcitabine, Cisplatin, and Sunitinib for Metastatic Urothelial Carcinoma and as Preoperative Therapy for Muscle-Invasive Bladder Cancer

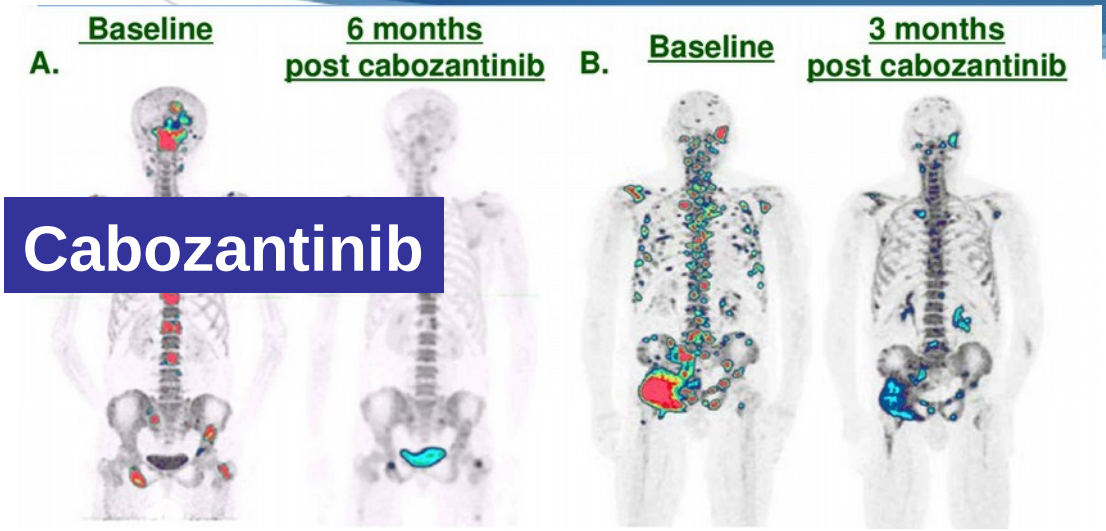
Matthew D. Galsky,[1,2] Noah M. Hahn,[3] Thomas Powles,[4] Beth A. Hellerstedt,[1,5] Seth P. Lerner,[6] Thomas A. Gardner,[7] Menggang Yu,[3] Mark O'Rourke,[1,8] Nicholas J. Vogelzang,[1,9] Darren Kocs,[1,10] Scott A. McKenney,[1,11] Anton M. Melnyk, Jr,[1,12] Thomas E. Hutson,[1,13] Mary Rauch,[1] Yunfei Wang,[1] Lina Asmar,[1] Guru Sonpavde[1,14,15]

Table 3 Treatment Emergent Grade 3 to 4 Adverse Events in ≥5% of the Study Population

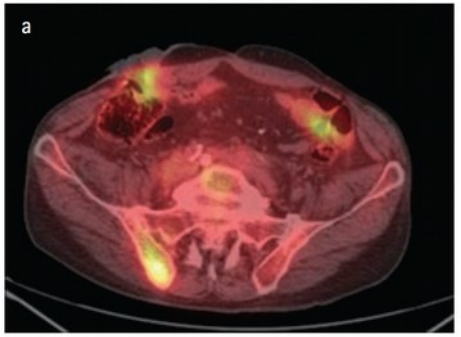
Adverse Event	Trial 1, No. (%) (n = 33)					Trial 2, No. (%) (n = 9)	
	Grade 3	Grade 4	Grade 3-4			Grade 3	Grade 4
			Overall (n = 33)	Initial Cohort (n = 15)	Reduced Cohort (n = 18)		
Anemia	7 (21)	3 (9)	10 (30)	5 (33)	5 (28)	0	1 (11)
Neutropenia	15 (46)	8 (24)	23 (70)	12 (80)	11 (61)	1 (11)	1 (11)
Thrombocytopenia	8 (24)	11 (33)	19 (58)	10 (67)	9 (50)	1 (11)	0
Anorexia	2 (6)	0	2 (6)	0	2 (11)	1 (11)	0
Diarrhea	2 (6)	0	2 (6)	1 (7)	1 (6)	0	0
Fatigue	1 (3)	0	1 (3)	0	1 (6)	1 (11)	0
Hand-Foot Syndrome	2 (6)	0	2 (6)	1 (7)	1 (6)	0	0
Headache	1 (3)	0	1 (3)	1 (7)	0	0	0
Hematuria	0	0	0	0	0	1 (11)	0
Hemorrhage	0	0	0	0	0	4 (44)	0
Hypertension	1 (3)	0	1 (3)	0	1 (6)	0	0
Hypomagnesemia	2 (6)	0	2 (6)	1 (7)	1 (6)	0	0
Infection	0	0	0	0	0	2 (22)	0
Nausea	0	0	0	0	0	1 (11)	0
Vomiting	0	0	0	0	0	2 (22)	0
Ulcer	0	0	0	0	0	1 (11)	0

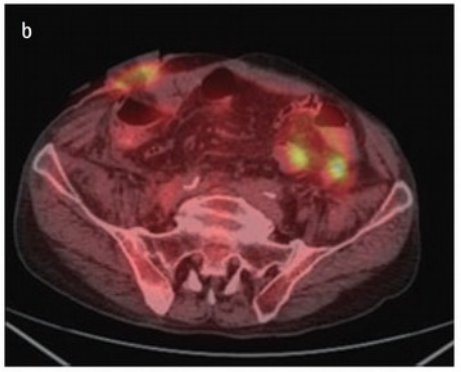
Galsky MD, Clin Genitourin Cancer 2013
See also: Balar AV, ASCO 2012
Toxicity: see also Lerner SP, ASCO 2011 and Galsky MD, ASCO 2010

Angiogenesis & the Dilemma of evaluating response

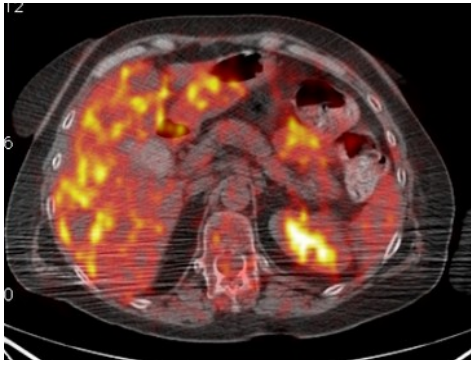


Cabozantinib

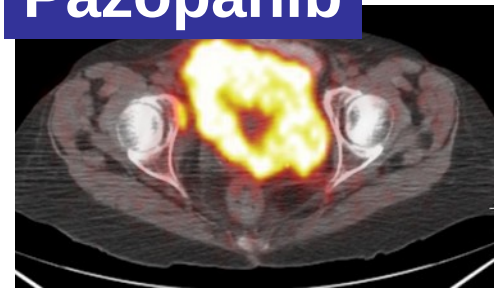


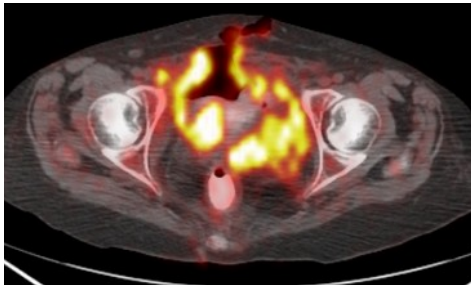


Sunitinib

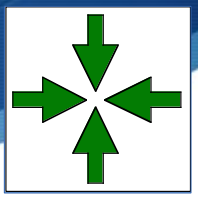


Pazopanib





How can we do better?



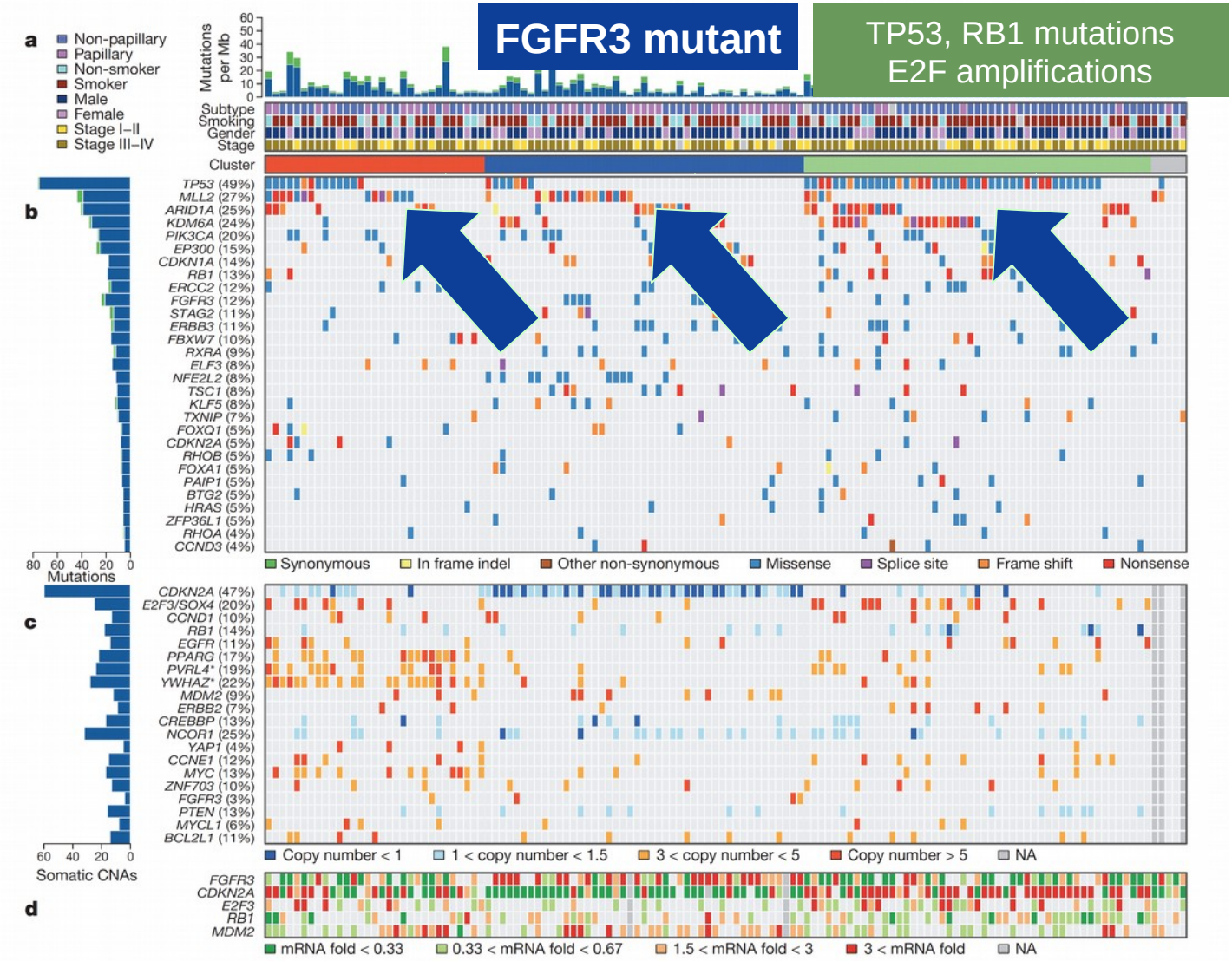
- Improving therapeutic options
  - ***A myriad of targetable genomic alterations***

Luminal Breast cancer
High HER2/ESR2 expression level

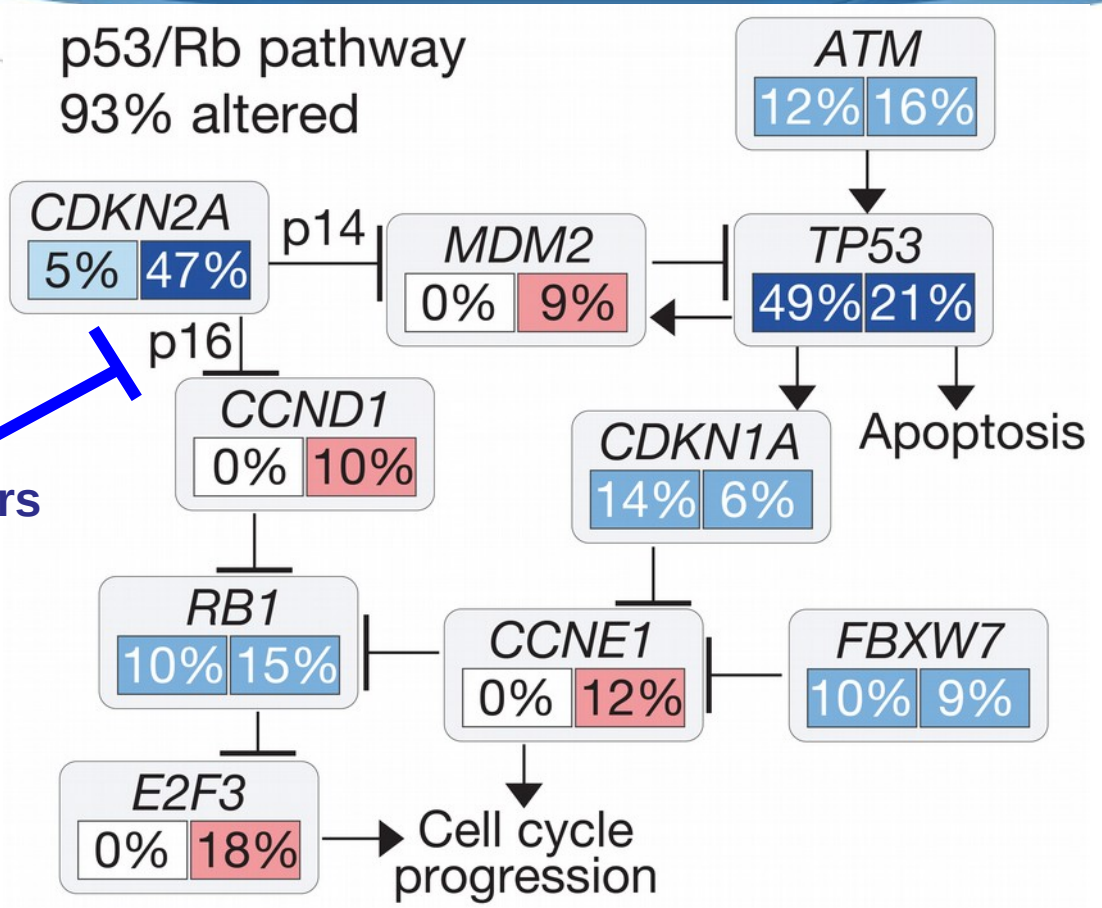
Basal-like breast cancer
HNSCC and Lung SCC

FGFR3 mutant

TP53, RB1 mutations
E2F amplifications

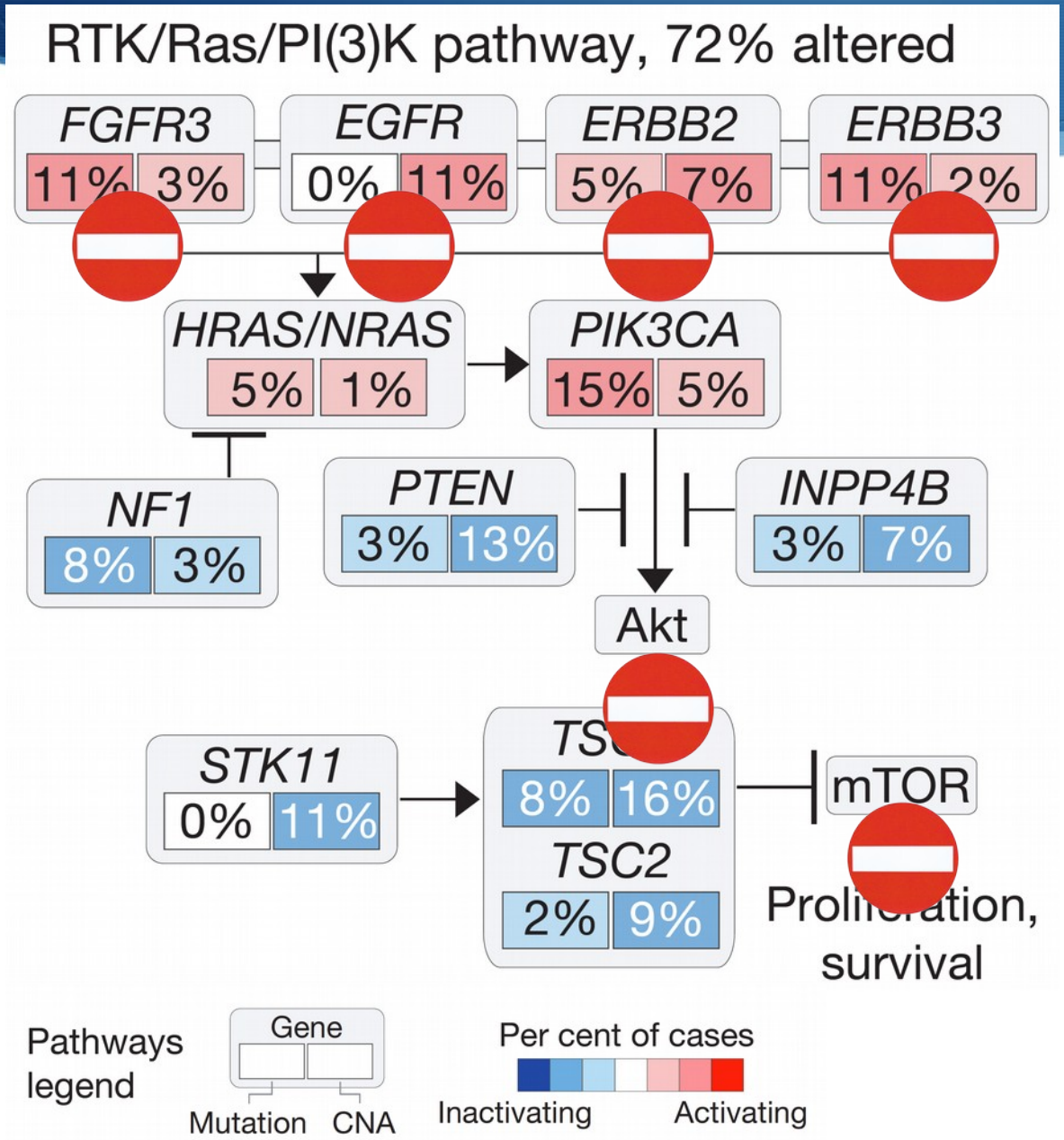


TCGA Network, Nature 2014



CDK4/6 Inhibitors (Palbociclib)

Study Title: A pre-clinical study of the selective CDK4_6 Inhibition PD0332991 (Palbociclib) in association with a selective MEK inhibitor PD-0325901 in transitional cell carcinoma (TCC) of the bladder.



The Cancer Genome Atlas

Final results of a multicenter, open-label phase 2 trial of dovitinib (TKI258) in patients with advanced urothelial carcinoma with either mutated or nonmutated *FGFR3*.

- **Median PFS (FGFR3mut):**

3.0 months (95% CI, 1.6-3.6) vs PFS (FGFR3non-mut): 1.8 months (95% CI, 1.6-3.2)

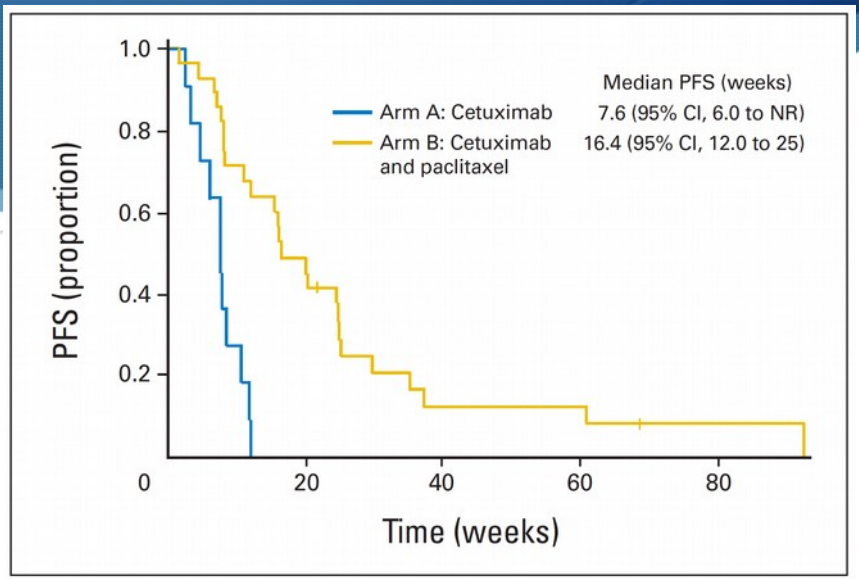
	FGFR3mut n=12	FGFR3non-mut n=31
Complete Response	0	0
Partial Response	0	1 (3.2)
Stable Disease	5 (41.7)	10 (32.3)
Progressive Disease	5 (41.7)	12 (38.7)
Unknown	2 (16.7)	8 (25.8)
Overall Response-Rate	0	1 (3.2)
Disease-control rate	3 (25.0)	8 (25.8)

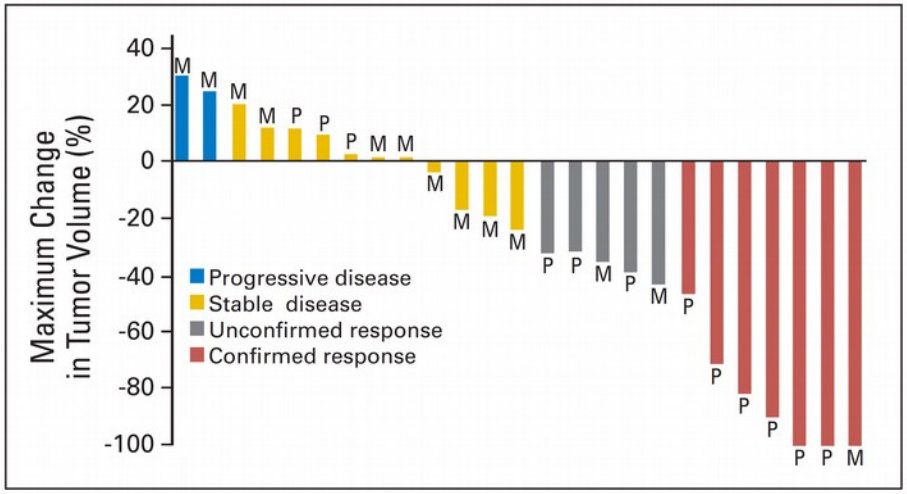
Dovitinib has limited single-agent activity in patients with advanced UC regardless of FGFR3 mutation status

Milowsky MI et al, GU ASCO 2013

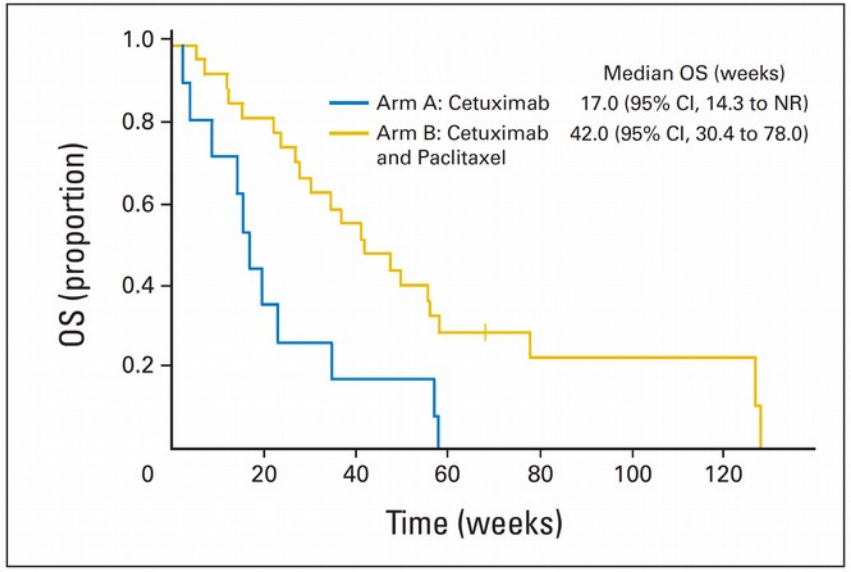
Cetuximab ± Paclitaxel in UC

PFS





OS



Wong YN, J Clin Oncol 2012

UC-EGFR_INT01: **An open label, randomized, phase 2 study of paclitaxel and Panitumumab compared to paclitaxel alone in patients with relapsed or refractory, epidermal growth-factor receptor positive urothelial cancer.**

- Histologically confirmed diagnosis of transitional cell tumors of the bladder or the urothelium.
- EGFR 2+ or 3+ at IHC
- ECOG PS: 0-2
- Metastatic disease.
- Measurable disease.
- **2nd and 3rd Line setting.**
- Neoadjuvant/adjuvant regimens will be counted provided that a relapse occurred within 6 months of the last cycle of chemotherapy.

PRIMARY ENDPOINT: PFS

The primary endpoint of the study is to evaluate and compare the progression-free survival.

Planned to start 07/2014

N=120
EGFR 2+/3+
UC

R

2:1

Panitumumab 6 mg/kg IV BW
+
Paclitaxel 80 mg/m2 IV d1,8,15 q28

Paclitaxel 80 mg/m2 IV d1,8,15 q28

Re-Staging:

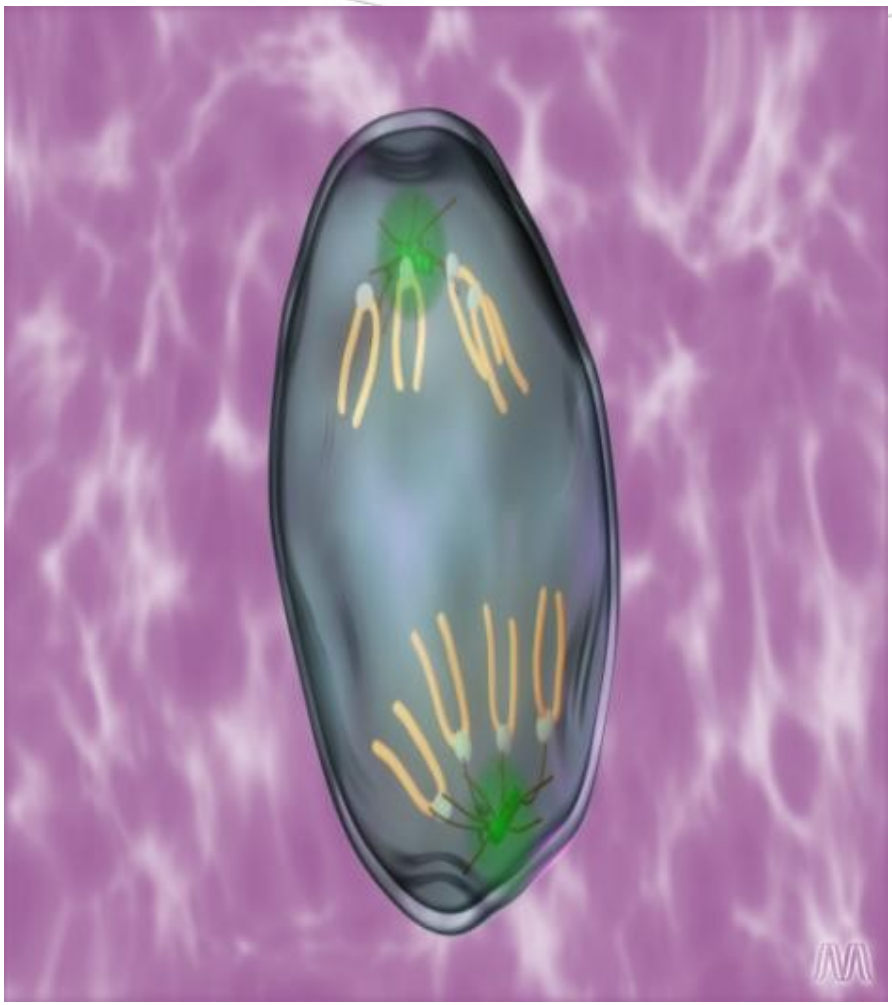
CT, (RECIST 1.1)
18FDG-PET/CT

→ Every 2 cycles until PD

Stratification factors:
1) TFPC
2) ECOG-PS
3) Hemoglobin
4) Liver mets

EudraCT: 2014-000857-35

MLN8237 (alisertib): Overview



- Investigational small molecule inhibitor of Aurora A kinase (AAK)
  - AAK regulates aspects of cell mitosis
  - Administered orally
  - Clinical studies are evaluating dosing schedules and pharmacodynamics
  - Phase 1 and 2 trials are ongoing in patients with solid tumors and hematologic malignancies
  - Phase 3 trial initiated in relapsed/refractory peripheral T-cell lymphoma (PTCL)

Nature Reviews Urology 10, 184 (2013); published online 5 March 2013; doi:10.1038/nrurol.2013.35

BLADDER CANCER

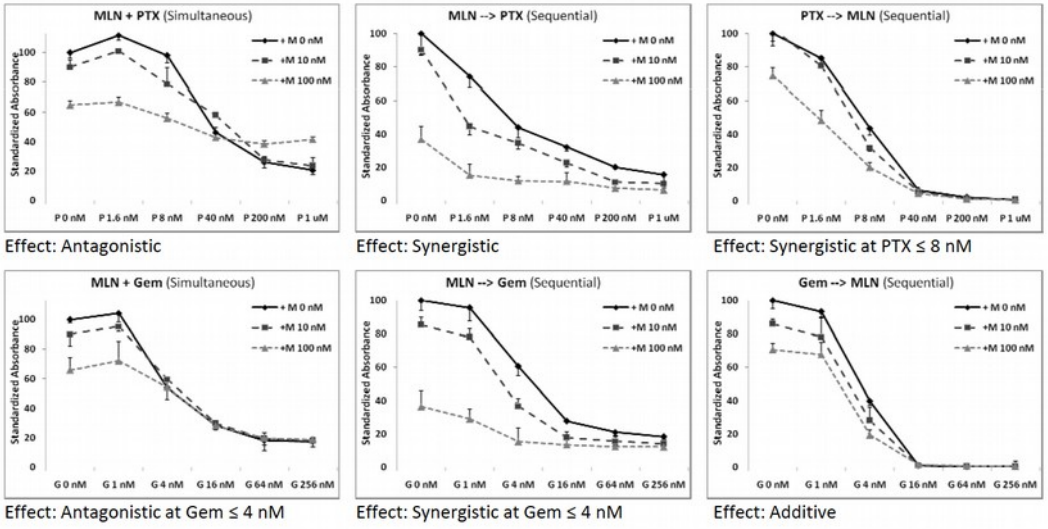
Aurora kinase inhibitors light up the therapeutic horizon in bladder cancer

Clinical Cancer Research

AACR

The investigational Aurora kinase A inhibitor MLN8237 induces defects in cell viability and cell cycle progression in bladder cancer cells in vitro and in vivo

Ning Zhou, Kamini Singh, Maria C Mir, et al.



Effect: Antagonistic | Effect: Synergistic | Effect: Synergistic at PTX ≤ 8 nM

Effect: Antagonistic at Gem ≤ 4 nM | Effect: Synergistic at Gem ≤ 4 nM | Effect: Additive

Zhou N et al, Clin Cancer Res 2013

UC-Aurora_INT01. A Phase 2 study of the Aurora kinase A inhibitor Alisertib (MLN8237) in patients with relapsed or refractory transitional-cell carcinoma of the bladder and urothelial tract *(ClinicalTrials.gov NCT02109328)*

INCLUSION	
Second-to-Third line	Pure Second line
PRIMARY ENDPOINT	
Response-Rate	Progression-free survival Median PFS (H0): 2.5 months to Median PFS (H1): 4.5 months [44% hazard rate reduction]

ALISERTIB (MLN8237)
50 mg BID orally for 7 days in a 21-day cycle

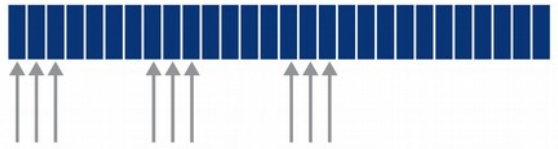
N=20 pts

R

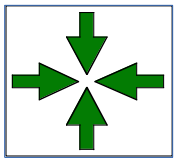
1:1

N=110 pts

Paclitaxel 60 mg/m2 weekly + MLN8237 (alisertib) 40 mg BID on days 1-3, 8-10 and 15-17.

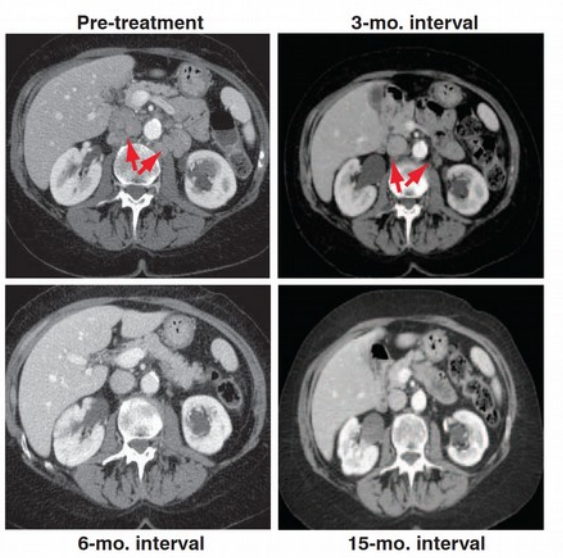


Paclitaxel 80 mg/m2 weekly + Placebo BID on days 1-3, 8-10 and 15-17.



Necchi A, ASCO 2014, #TPS4592

Phase 2 MSKCC trial of Everolimus (mTORC1 inhibitor) in UC – negative trial with 1 CR/1 PR in 45 patients. The pt with CR remains NED on drug for 36 months



Cystectomy (Tumor)

PBMCs (Normal)

Illumina HiSeq

Sequencing

Paired –end sequencing
2x100 bp mate pairs

Alignment

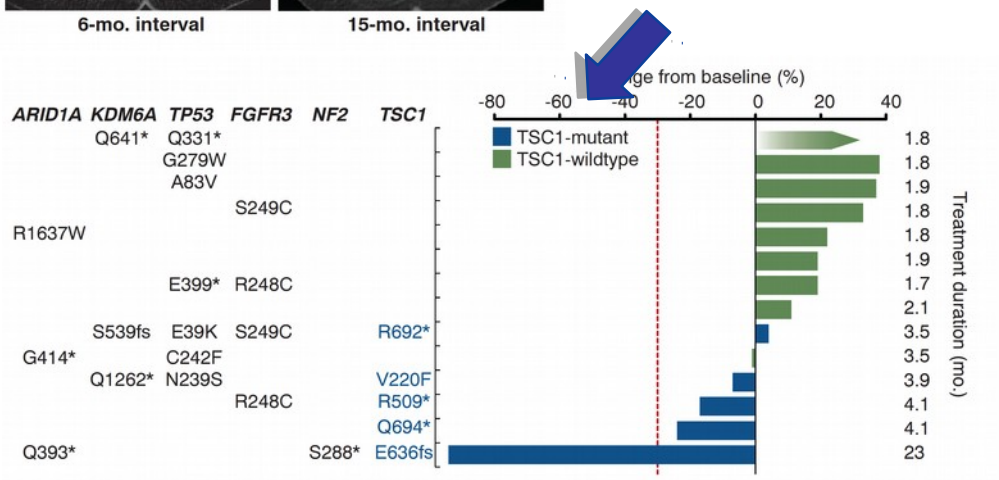
Multiple sequence realignment

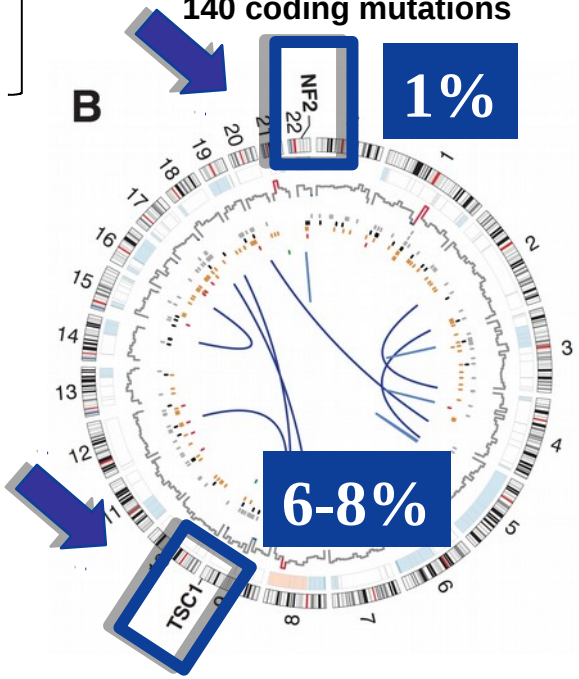
Base Quality recalibration

Mutation detection

MSK

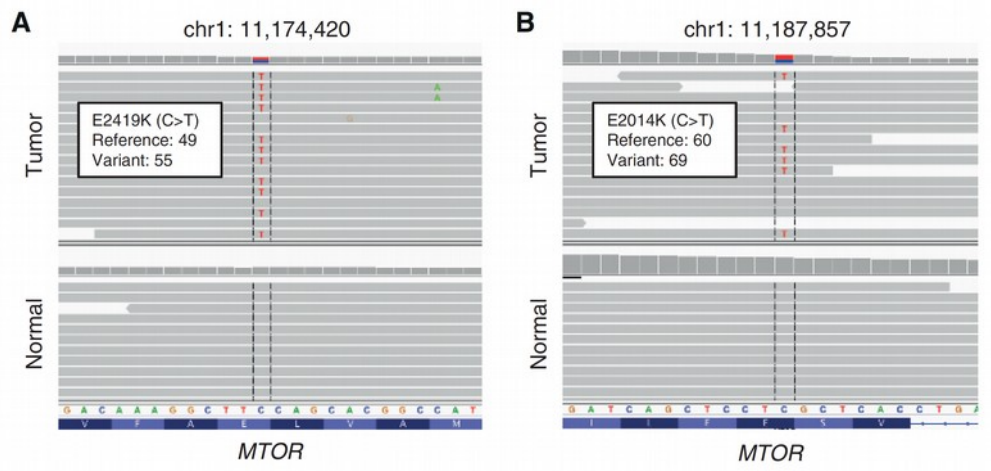
30X Coverage
89.1% genome
17,136 somatic mutations
140 coding mutations





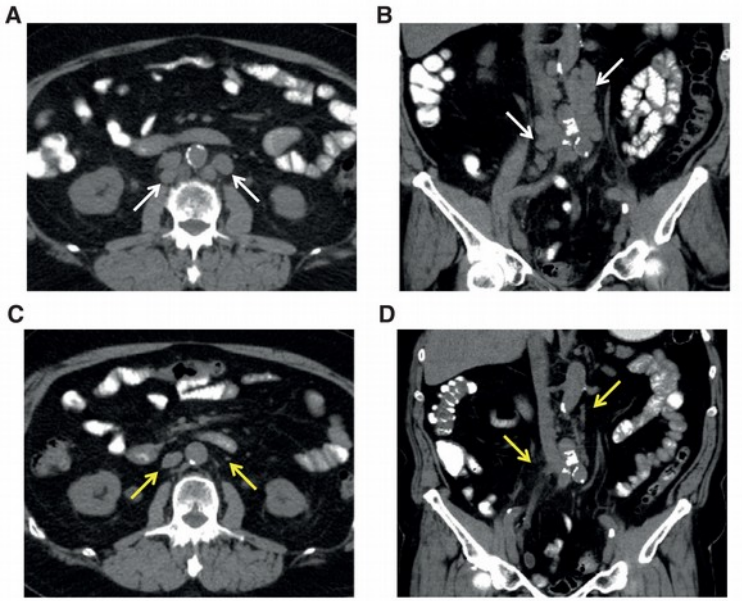
Iyer G et al. Science 2012

A 70-year-old man with metastatic urothelial carcinoma with a 14-month complete response to everolimus and pazopanib



Identification of two activating mTOR mutations in a patient with a complete response to everolimus and pazopanib.

Baseline



+2 months

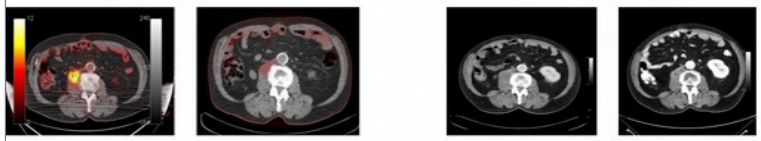
Wagle N et al, Cancer Discov 2014

- First-line Everolimus +/- Paclitaxel for cisplatin-ineligible patients with advanced Urothelial Carcinoma (NCT01215136)
- Gemcitabine and Split-Dose Cisplatin Plus Everolimus (RAD001) in patients with advanced solid tumor malignancies (NCT01182168)

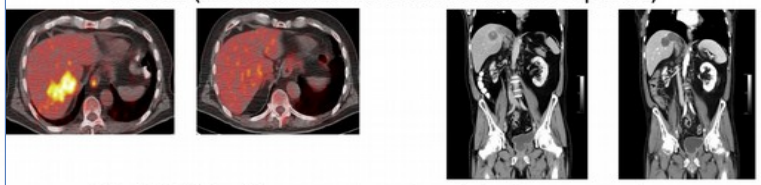
Phase 2 INT trial of Pazopanib in UC – positive trial with 17% PR in 41 patients. One pt with PR remains progression-free on drug for >30 months

Patient ID	# Prior Platinum-based cycles	# Prior Drugs	Treatment Line	Best Response (Centralized Review*)	Duration of response (months, centralized review)	^{18}FDG-PET/CT Response	Available Tissue for NGS	Blood/Urine available
01	10	6	3rd	**SD** with cavitation	3.7	Y	Archival FFPE (cystectomy); FFPE Liver Biopsy under PZP	**Y**; at baseline and q4wks until PD
03	10	8	4th	**SD** (borderline PR, -27%)	2.7	Y	Archival FFPE from cystectomy	**Y**; at baseline and q4wks until PD
04	12	6	3rd	**PR** with necrosis	19.2 (ongoing at +32 months)	Y	Archival FFPE from Nephroureterectomy; archival FFPE from retroperitoneal LAD	**Y**; at baseline and q4wks until PD
22	5	2	3rd	**SD** with necrosis	2.8	Y	FFPE + FFT of liver biopsy before and under PZP	**Y**; at baseline and q4wks until PD
30	3	3	4th	**SD** with necrosis	3.2	Y	FFPR + FFT from liver biopsy at baseline and under PZP	**Y**; at baseline and q4wks until PD
15	4	4	2nd	PD	≤1	N	Archival FFPE of cystectomy	Y; at baseline and q4wks until PD
16	4	3	2nd	PD	≤1	N	Archival FFPE from cystectomy; FFPE + FFT of pelvic relapse before PZP	**Y**; at baseline and q4wks until PD
18	6	3	3rd	PD	≤1	N	FFPE + FFT of liver biopsy before and under PZP	**Y**; at baseline and q4wks until PD

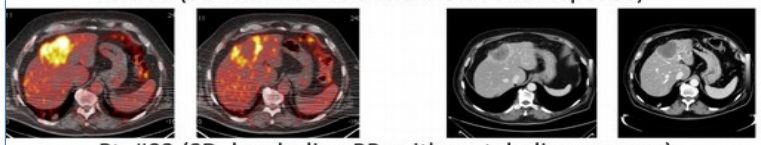
Pt. #04 (very long term PR, index case)



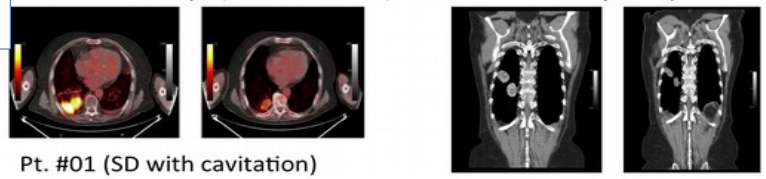
Pt. #22 (SD with necrosis and metabolic response)



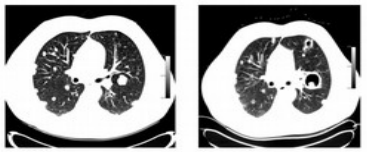
Pt. #30 (SD with necrosis and metabolic response)

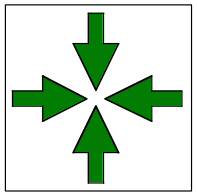


Pt. #03 (SD, borderline PR, with metabolic response)



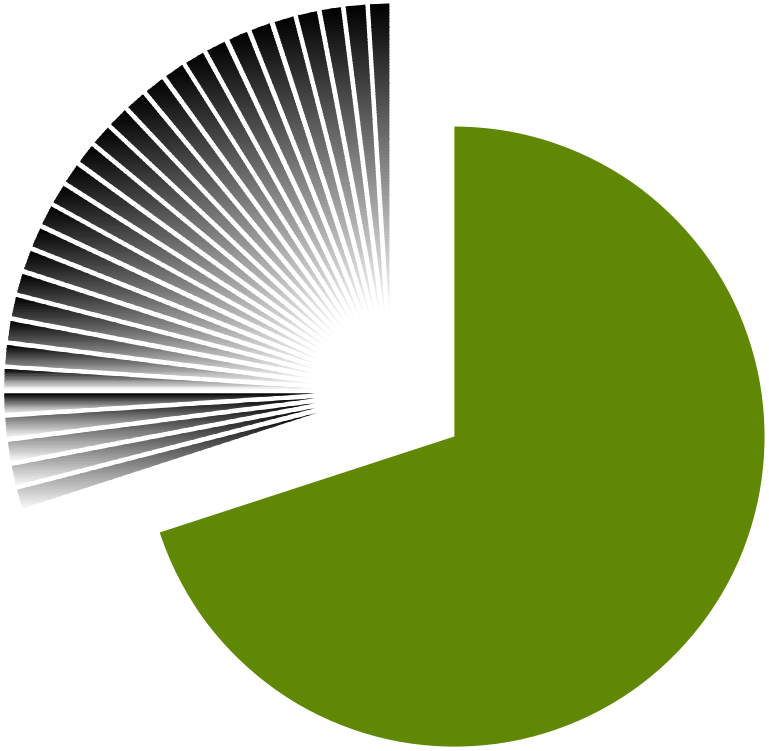
Pt. #01 (SD with cavitation)



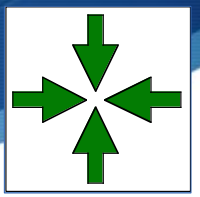


WIN
Worldwide Innovative Networking in personalized cancer medicine

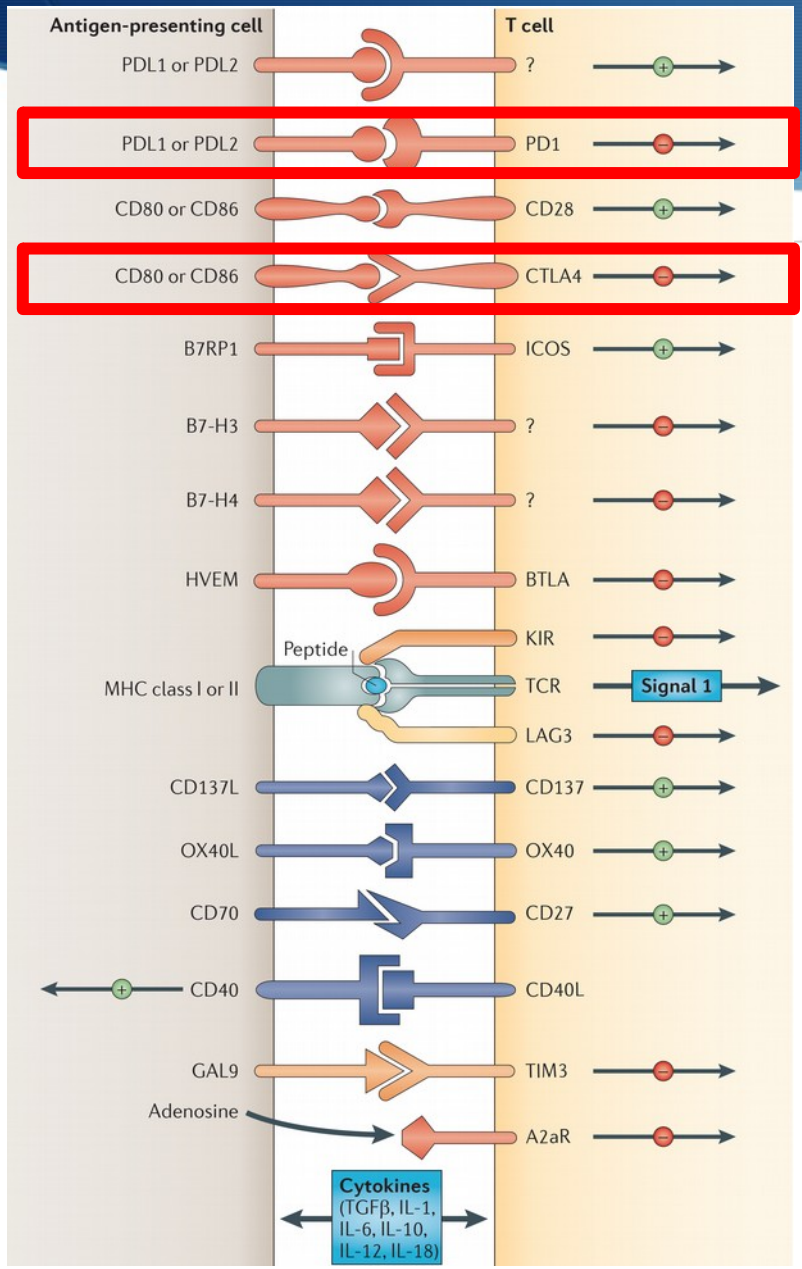
"Outlier" Approach to target sequencing analyses



How can we do better?



- Improving therapeutic options
  - ***Targeting the Immune System***

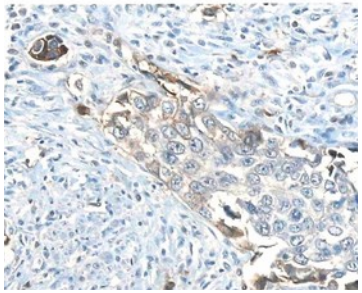


Pardoll DM, Nat Rev Cancer 2012

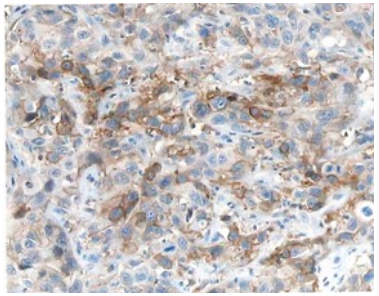
- Pre-operative Ipilimumab – window of opportunity trial *(Carthon BC et al, Clin Cancer Res 2010)*
- First-line IPI-Cis/Gem recruiting *(ClinicalTrials.gov NCT01524991)*

PD-L1

Membrane staining



Membrane and cytoplasmic 3+ staining

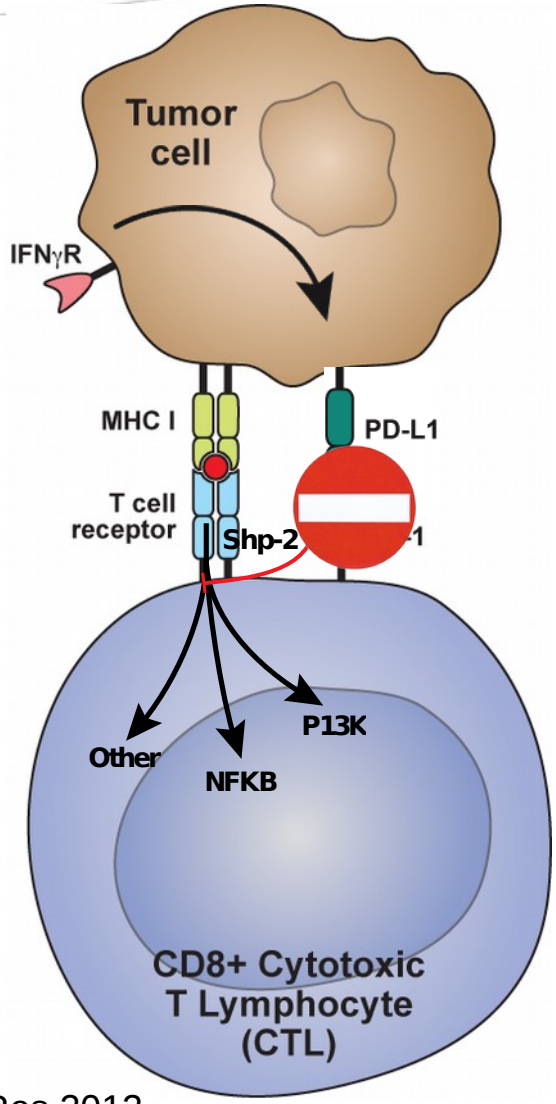


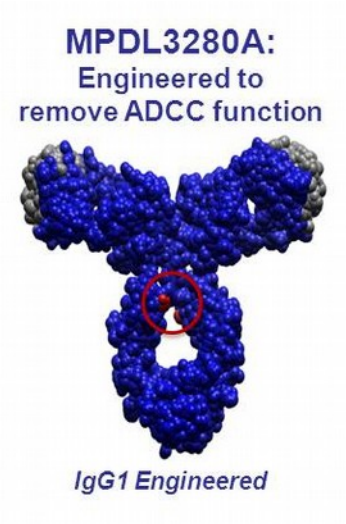
Overall PD-L1 IHC staining positivity=45% (30% 2+/3+)

Zhang J, ASCO 2013

Targeting PD-L1 by MPDL3280A (Hoffman-La Roche Ltd)

PD-L1 expression can render the T-cell inactivated through engagement of the inhibitory receptor PD-1





Adapted from Chen DS, et al., Clin Cancer Res 2012

GO29293:
A PHASE II, MULTICENTER, SINGLE-ARM STUDY OF MPDL3280A IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL BLADDER CANCER

Objectives:
Estimate RECIST v1.1 ORR of MPDL3280A in patients with UC who have 1) failed prior platinum 2) 1L patients unfit for platinum-containing regimen

Primary endpoint: Objective Response Rate (ORR)
Secondary endpoints: Overall Survival, Duration of Response

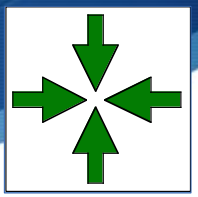
Key Eligibility
- TCC histology
- Archival tissue available at baseline; measurable disease
- ECOG PS 0-1
- Locally Adv/Metastatic

Cohorts
- 1L: Cisplatin-ineligible
- 2L+: Progression after prior platinum

→ MPDL3280A 1200 mg q3 wk x 16 cycles

Clinicaltrials.gov: NCT02108652
Study Sponsor: Hoffman-La Roche Ltd

How can we do better?



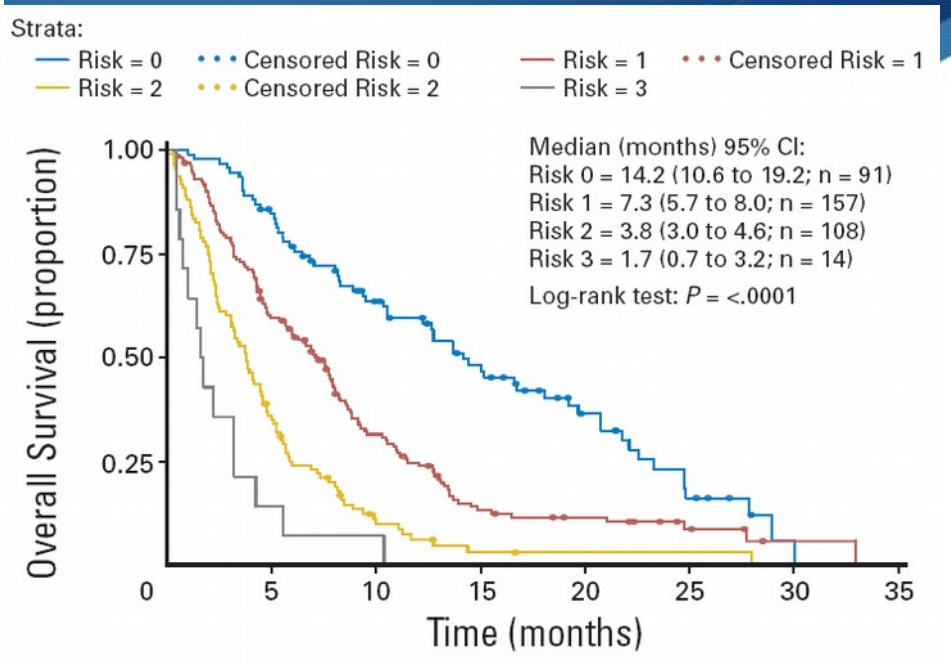
- Improving risk prediction/prognostic accuracy

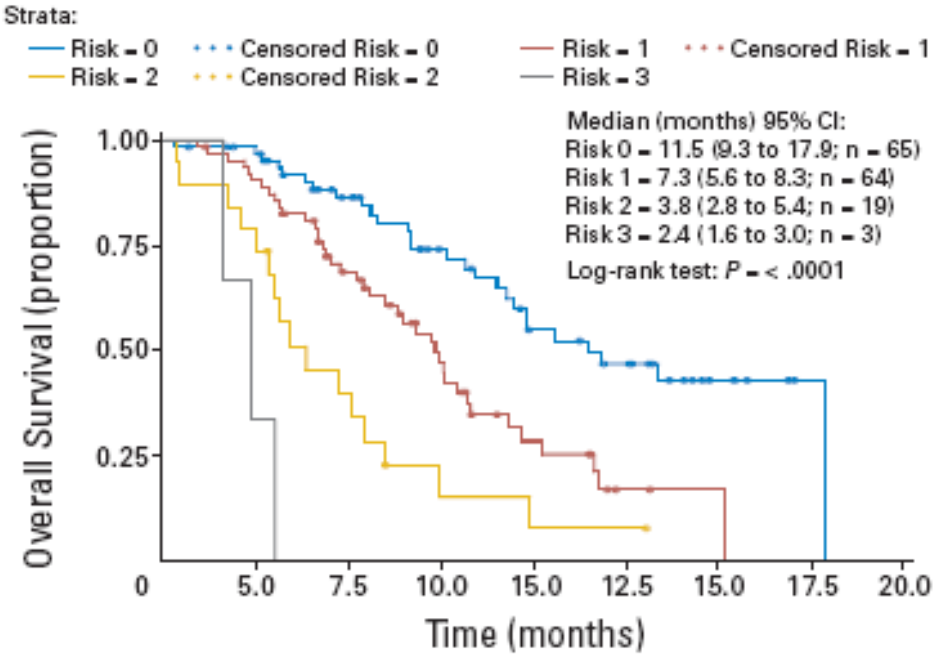
VOLUME 28 · NUMBER 11 · APRIL 10 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Prognostic Factors in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract Experiencing Treatment Failure With Platinum-Containing Regimens

Joaquim Bellmunt, Toni K. Choueiri, Ronan Fougeray, Fabio A.B. Schutz, Yacine Salhi, Eric Winquist, Stéphane Culine, Hans von der Maase, David J. Vaughn, and Jonathan E. Rosenberg

Prognostic Factor	Risk Group
Hb < 10 g/dL	0 No PF
Liver Mets	1 1 PF
ECOG PS ≥ 1	2 2 PF
	3 3 PF

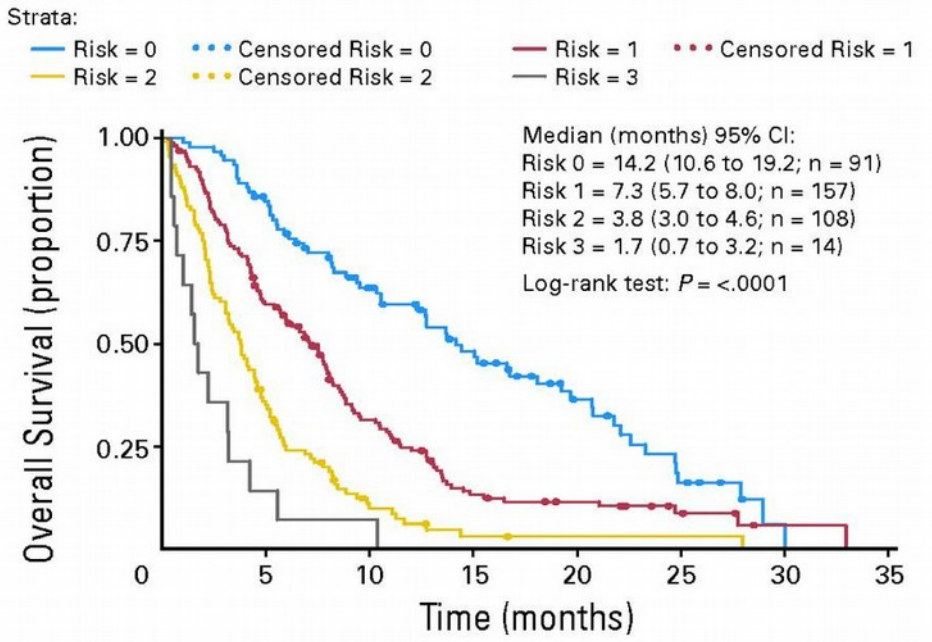


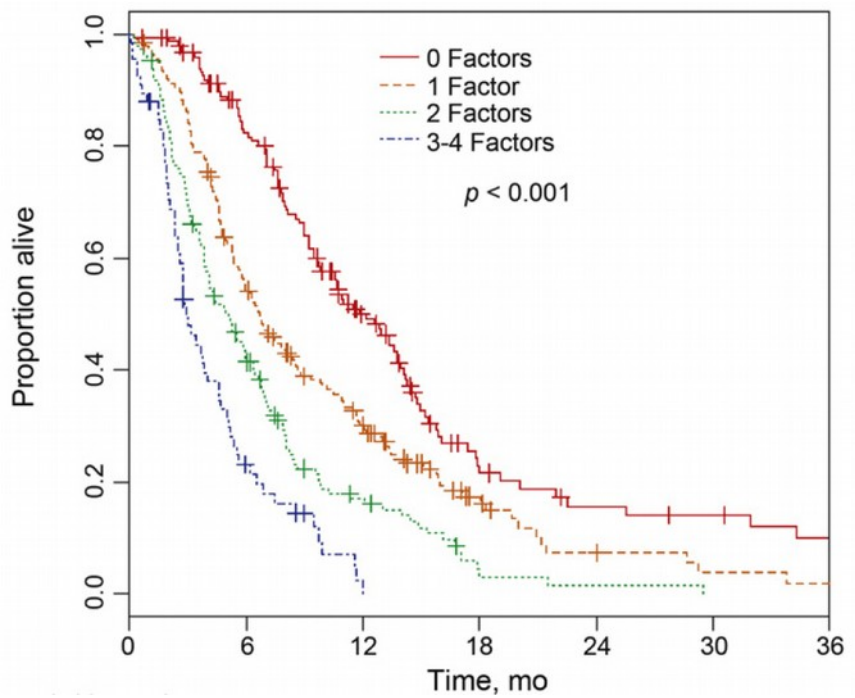


Bellmunt J et al. J Clin Oncol. 2010

Enhancing prognostic accuracy in second-line setting

Liver metastasis, Hb <10, ECOG-PS>0 + Time since prior CT





Bellmunt J et al, J Clin Oncol 2010

Sonpavde G et al, Eur Urol 2012

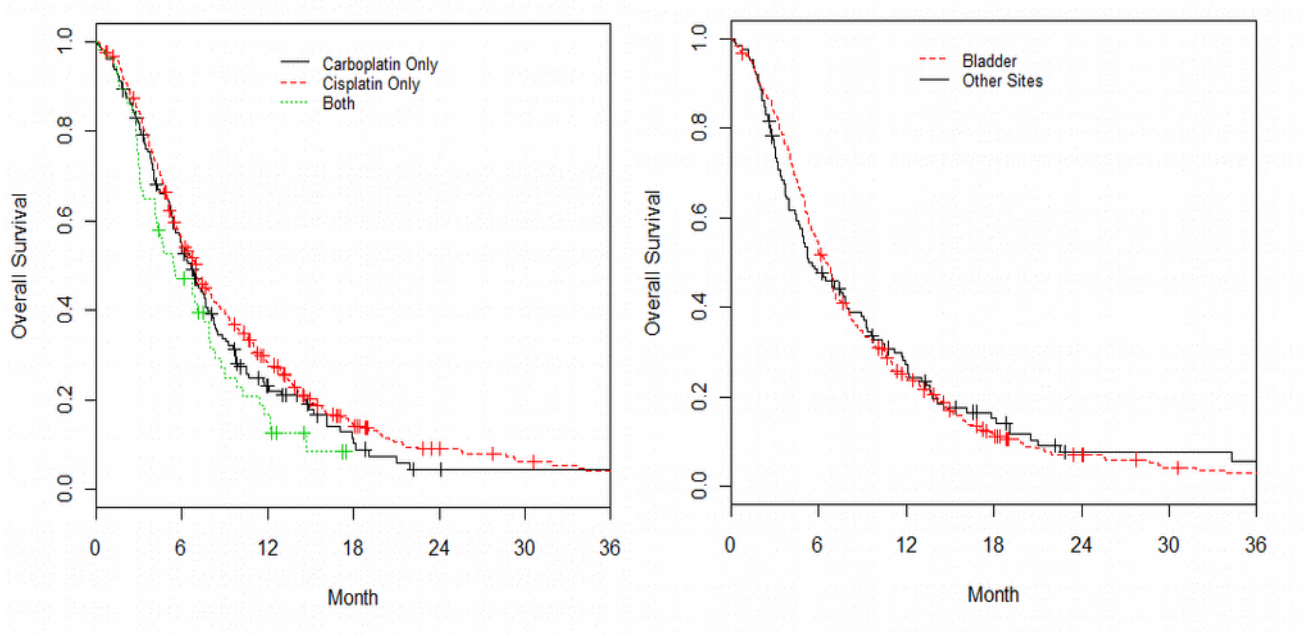
Impact of prior platinum agent and site of primary in patients with advanced urothelial carcinoma receiving salvage therapy

Sonpavde G, Bellmunt J, Rosenberg JE, Bajorin DF, Regazzi AM, Choueiri TK, Qu AQ, Niegisch G, Albers P, Necchi A, Di Lorenzo G, Fougeray R, Wong YN, Sridhar SS, Ko YJ, Milowsky MI, Galsky MD, Pond GR

731 patients overall, 663 evaluable for prior platinum regimen and 512 for site of primary.

Treatments:

vinflunine (N=151), docetaxel +/- vandetanib (N=148), paclitaxel-gemcitabine (N=98), sunitinib (N=77), volasertib (N=50), nab-paclitaxel (N=48), everolimus (N=45), pazopanib (N=43), cetuximab +/-paclitaxel (N=39) and paclitaxel-cyclophosphamide (N=32).



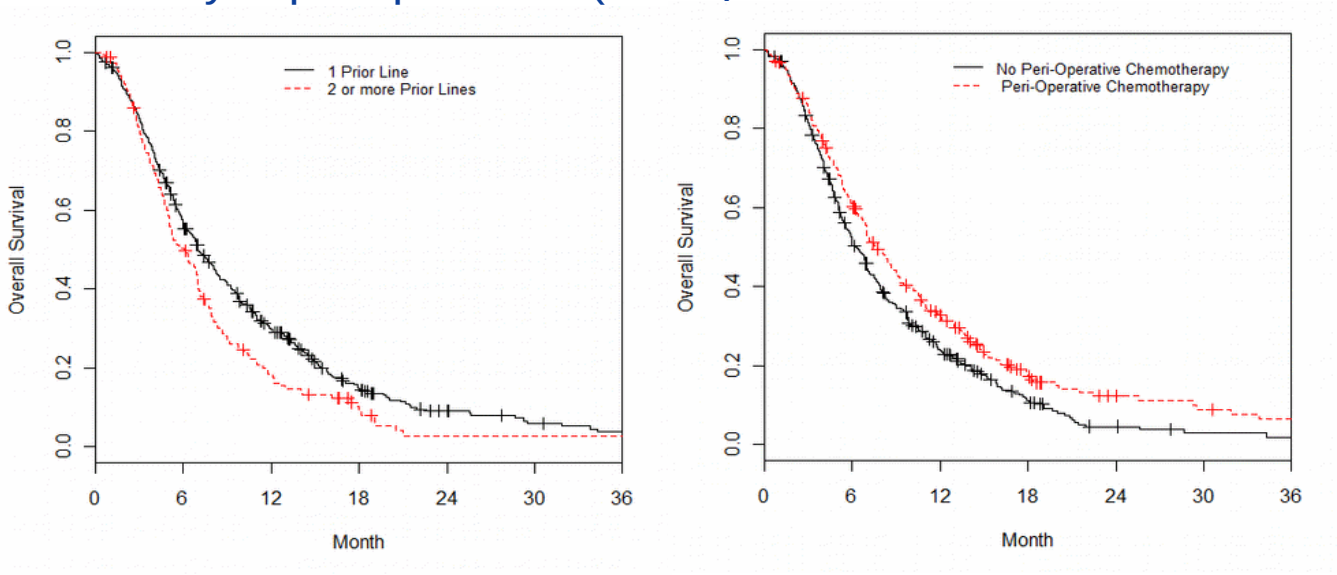
Sonpavde G, ASCO GU 2014

Impact of number of prior lines of therapy and prior perioperative chemotherapy in patients receiving salvage therapy for advanced urothelial carcinoma: implications for trial design

Pond GR, Bellmunt J, Rosenberg JE, Bajorin DF, Regazzi AM, Choueiri TK, Qu AQ, Niegisch G, Albers P, Necchi A, Di Lorenzo G, Fougeray R, Wong Y-N, Sridhar SS, Ko Y-J, Milowsky MI, Galsky MD, Sonpavde G

711 evaluable patients.

The trials evaluated vinflunine (N=151), docetaxel +/- vandetanib (N=147), paclitaxel-gemcitabine (N=83), sunitinib (N=77), nab-paclitaxel (N=48), volasertib (N=46), everolimus (N=45), pazopanib (N=43), cetuximab +/-paclitaxel (N=39) and paclitaxel-cyclophosphamide (N=32).



Sonpavde G, ASCO GU 2014

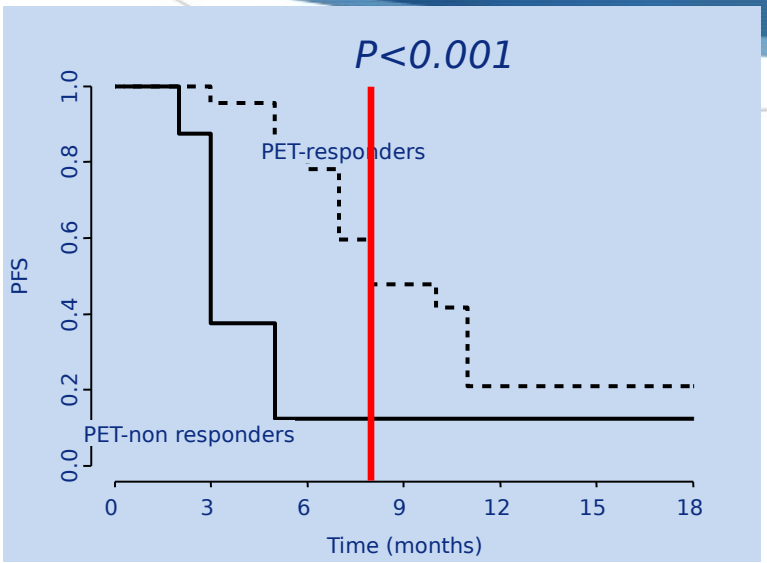
Recommendations for patient eligibility and trial design for the salvage therapy of advanced urothelial carcinoma

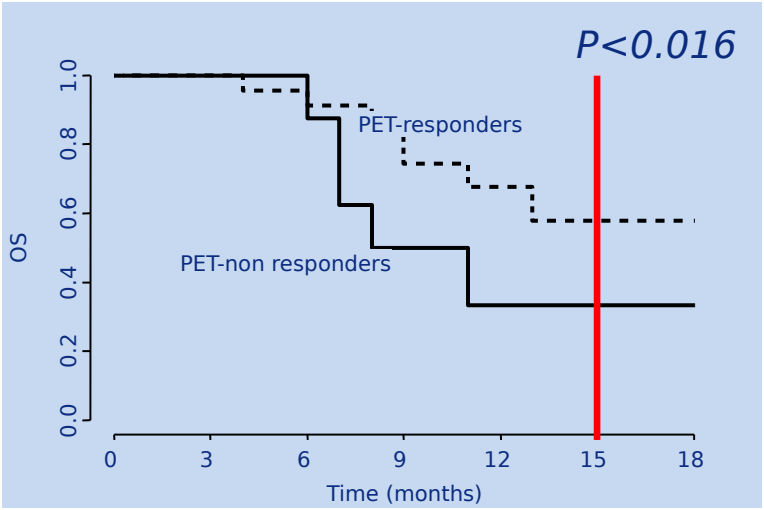
Pond GR, Bellmunt J, Rosenberg JE, Bajorin DF, Regazzi AM, Choueiri TK, Qu AQ, Niegisch G, Albers P, Necchi A, Di Lorenzo G, Fougeray R, Wong Y-N, Sridhar SS, Ko Y-J, Milowsky MI, Galsky MD, Sonpavde G

Eligibility criteria for all trials of salvage therapy for advanced UC	
Variable	**Eligibility**
Number of prior lines of therapy	≤2 including perioperative therapy
Prior perioperative therapy as only prior regimen	Yes if < 1 year earlier
Prior therapy for metastatic disease	Not required
Prior cisplatin or carboplatin	Required
Site of primary tumor: bladder or other	Both allowed
Primary refractory disease to first-line therapy	Allowed
Stratification factors in randomized trials	
Stratification factor	**Required?**
Performance status	Yes
Hemoglobin	Yes
Liver metastasis	Yes
Time from prior chemotherapy	Yes
Prior perioperative chemotherapy	No
Response to prior therapy	No
Number of prior lines of therapy	Not required up to 2 lines
Site of primary (bladder vs. other)	No
Prior platinum agent (cisplatin vs. carboplatin)	No

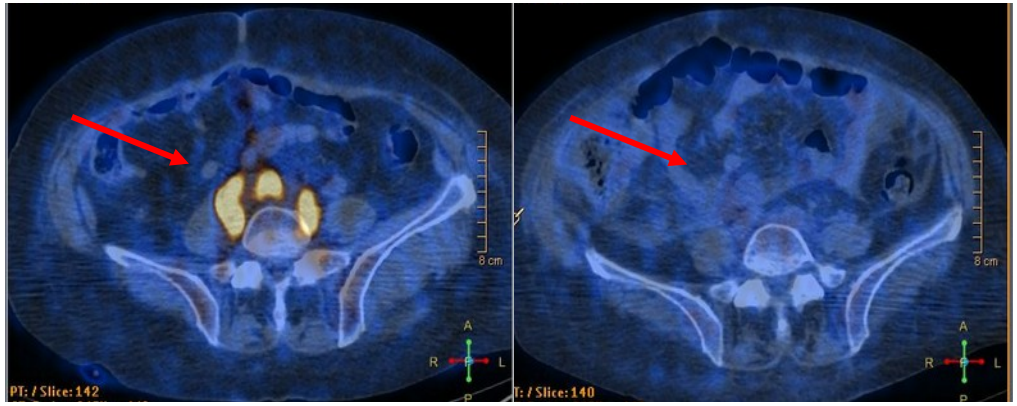
Clin Genitourin Cancer 2014 (in press)

Early FDG-PET (PET2) in advanced TCC (N=31)

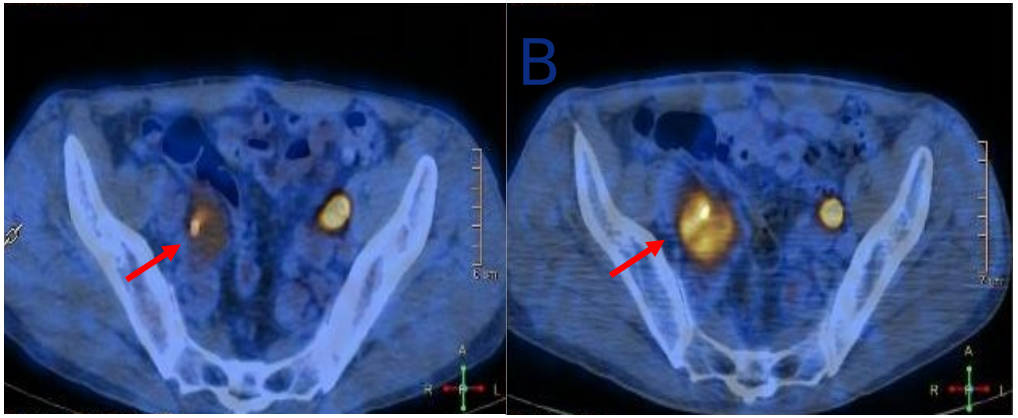




PET2 RESPONDER



PET2 NON RESPONDER



Giannatempo P et al. Clin Genitourin Cancer 2014 (Epub ahead of print)

Enumeration and molecular profiling of circulating tumor cells across the clinical stages

- **Size-based (ScreenCell) and EpCAM-based (AdnaTest) approaches**

Prevalence of circulating tumor cells in bladder cancer (baseline)

Clinical setting	AdnaTest	ScreenCell
Pts with MIBC (neoadjuvant setting, NA)	6/16 (**38%**)	11/12 (**92%**)
First-line setting (MVAC)	18/34 (**53%**)	15/20 (**75%**)
Second-line setting (Salvage PF-03446962)	9/14 (**64%**)	10/11 (**91%**)

Metastatic 1st line setting:

	Overall		CR+PR		SD+PD		CR		PR+SD	
	#cases (#events)	8-month PFS	#cases (#events)	8-month PFS	#cases (#events)	8-month PFS	#cases (#events)	8-month PFS	#cases (#events)	8-months PFS
CTC (ADNA test)										
Negative	13 (6)	48%	8 (2)	71%*	5 (4)	0%	3 (0)	3/3	7 (3)	50%**
Positive	16 (8)	25%	12 (5)	30%*	4 (3)	25%	3 (0)	3/3	11 (6)	0%**

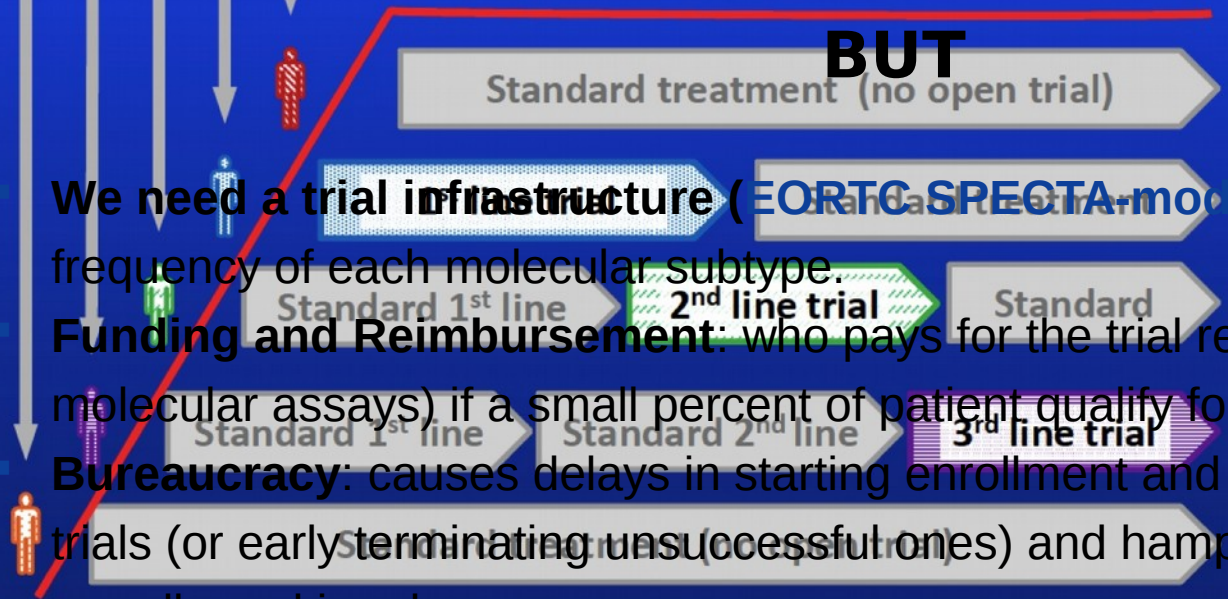
Necchi A et al, SUO 2013, ASCO-GU 2014, EAU 2014, ASCO 2014

Concluding remarks

It will be a good time for Bladder cancer specialists to:

- Improve the results in the advanced disease
- Improve the prognostic allocation and patient stratification
- Shape new treatment paradigms based on molecular understanding
- Investigate on novel trial design

Academia investment



- **We need a trial infrastructure (EORTC SPECTA-model)** due to low frequency of each molecular subtype.
- **Funding and Reimbursement**: who pays for the trial requirements (including molecular assays) if a small percent of patient qualify for a “targeted trial”?
- **Bureaucracy**: causes delays in starting enrollment and finalizing successful trials (or early terminating unsuccessful ones) and hampers recognition of groudbreacking drugs.

Industry cooperation

andrea.necchi@istitutotumori.mi.it

@AndreaNecchi