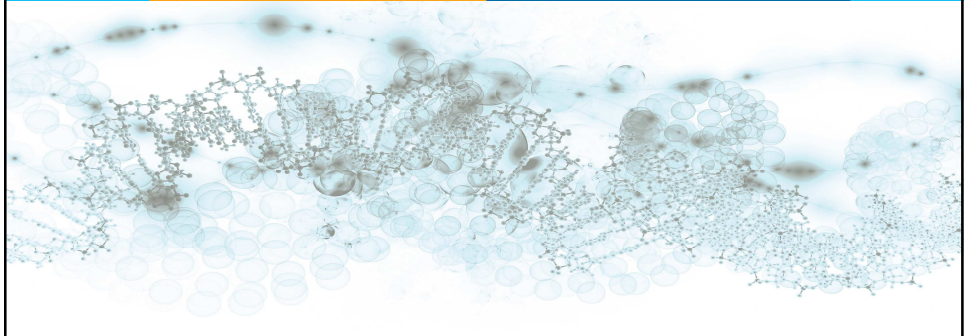


Molecular biomarkers for Genitourinary Cancers

Atish Choudhury, MD PhD

Senior Physician, Dana-Farber Cancer Institute

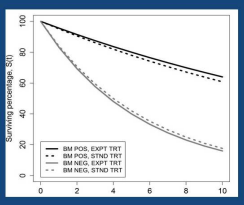
Disclosures

Honoraria: Bayer, Astellas Australia, Janssen Latin America, ANZUP, OncLive, MEDACorp, Oncology Learning Network, Aptitude Health, Targeted Oncology, Blackstone

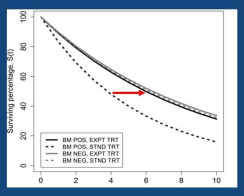
Advisory Board: Clovis, Dendreon, Bayer, Eli Lilly

Research Funding: Bayer

Molecular biomarkers in GU malignancies



- **Prognostic**
  - Identify patients more likely to have a particular outcome



- **Predictive Biomarker**
  - Experience a favorable or unfavorable effect from exposure

- **Tissue-based**
  - DNA sequencing
  - Gene expression / epigenetic profiling
  - IHC (protein expression / cellular composition [e.g. immune infiltration])
- **Blood-based**
  - CTCs (enumeration, gene expression, IHC [AR-v7], [epi-]genetic profiling)
  - ctDNA (screening, MRD [ctDNA+ → adjuvant therapy], [epi-]genetic profiling)

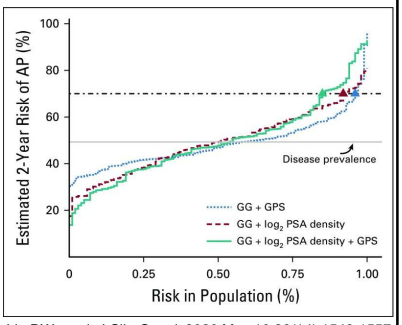
Commercially available gene expression-based diagnostics in primary prostate cancer

Test(s)	Company	List Price,* USD	Sample Requirement	Clinical Utility/Intended Use	Comments
Decipher PROSTATE GENOMIC CLASSIFIER	Decipher Biosciences (formally Genome Dx)	$5,150	FFPE tissue from prostate biopsy, or Prostate tissue after RP	Categorize patients into low/high risk to stratify patients to surveillance *v* treatment (and intensity of treatment) Postprostatectomy for patients with adverse pathologic features to guide whether surveillance, adjuvant, or salvage therapy may be warranted	Evaluates mRNA expression levels of 22 genes from FFPE tissue; generates score from 0 to 1.0 *cell cycle proliferation* *adhesion and motility* *immune modulation* *androgen signaling*
oncotype DX® Genomic Prostate Score	Genomic Health	$4,520	Tumor tissue from original biopsy in neutral buffered formalin; prostatectomy specimens not accepted	Biopsy-based likelihood of adverse pathologic features (Grade Group ≥ 3 or extracapsular extension); identify those who may benefit from surveillance *v* treatment	GPS ranges from 0 to 100 based on mRNA expression of 17 genes across four pathways *stromal response* *proliferation* *androgen signaling* *cellular organization*
MYRIAD Prolaris® Prostate Cancer	Myriad Genetic Laboratories	$3,900	FFPE tissue from: prostate tumor biopsy, or prostatectomy specimens	Aggressiveness of cancer; provides a 10-year risk of metastasis after definitive therapy, and disease-specific mortality under conservative management	mRNA expression of cell-cycle progression genes are used to calculate the score; clinical factors are subsequently added for risk assessment (31 genes) *cell cycle progression*

Eggener SE, et al. J Clin Oncol. 2020 May 1;38(13):1474-1494.

Clinical utility of genomic classifiers

- Decipher®, onco*type* DX® and Prolaris® all improve prognostic accuracy of multivariable models for PrCa-related outcomes in addition to clinicopathologic variables
- Role in decision making unclear → e.g. onco*type* DX® (GPS) did not add to model including Gleason Grade Group (GG) and PSA density in predicting adverse pathology in pts on active surveillance



Lin DW, et al. J Clin Oncol. 2020 May 10;38(14):1549-1557.

Recommendation 1.1

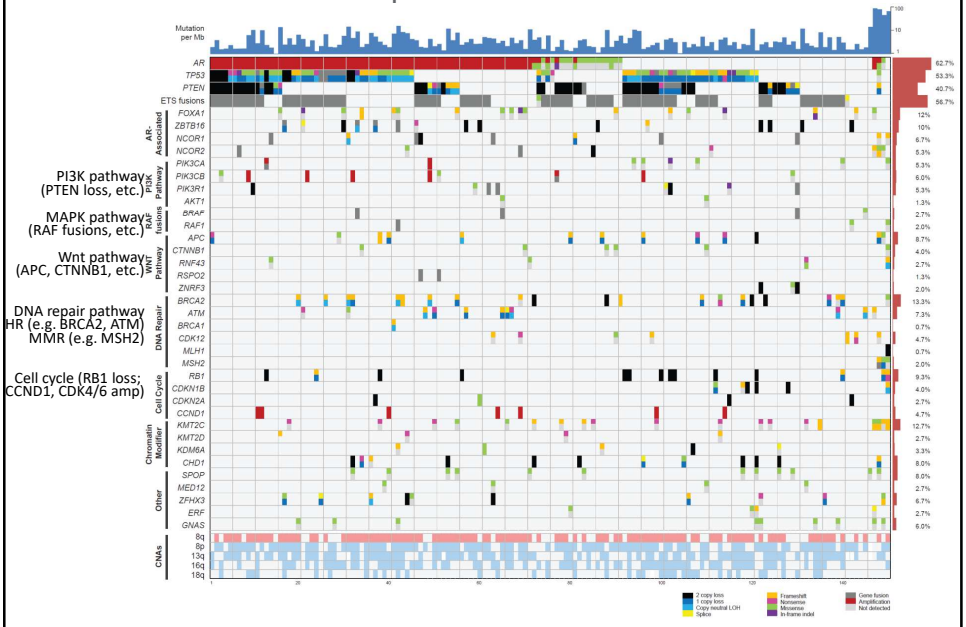
Commercially available molecular biomarkers (ie, onco*type* DX Prostate, Prolaris, Decipher) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is **likely to affect management**.

Routine ordering of molecular biomarkers is not recommended

(Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

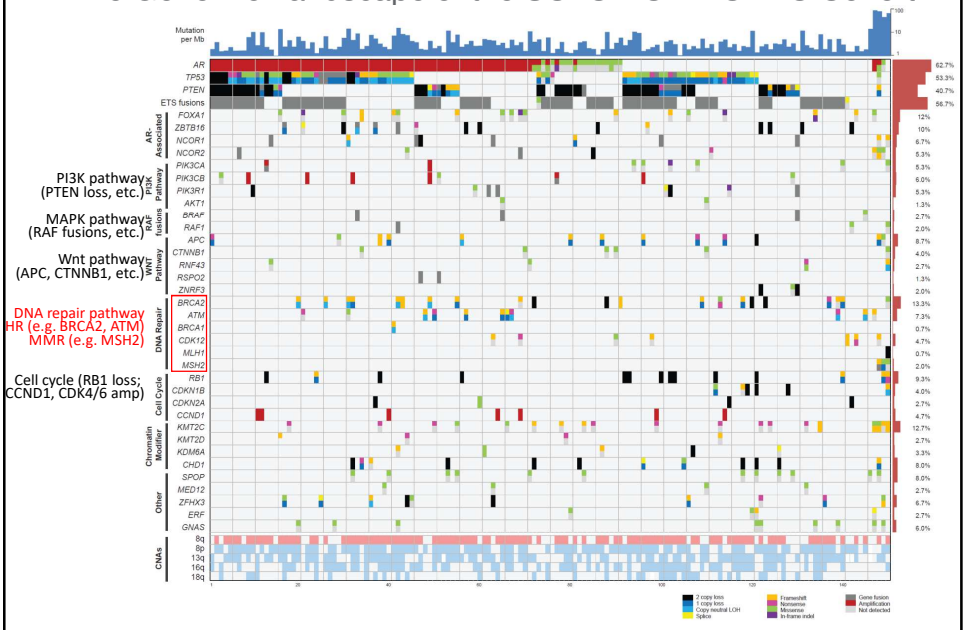
Eggener SE, et al. J Clin Oncol. 2020 May 1;38(13):1474-1494.

The Genomic Landscape of the SU2C-PCF mCRPC Cohort



Robinson D, Van Allen EM, et al. Cell. 2015 May 21;161(5):1215-1228.

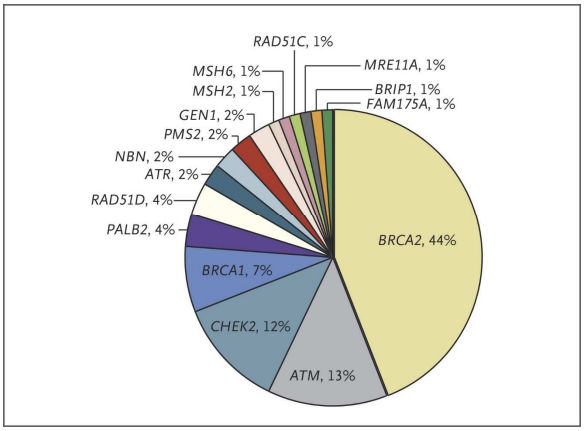
The Genomic Landscape of the SU2C-PCF mCRPC Cohort



Robinson D, Van Allen EM, et al. Cell. 2015 May 21;161(5):1215-1228.

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

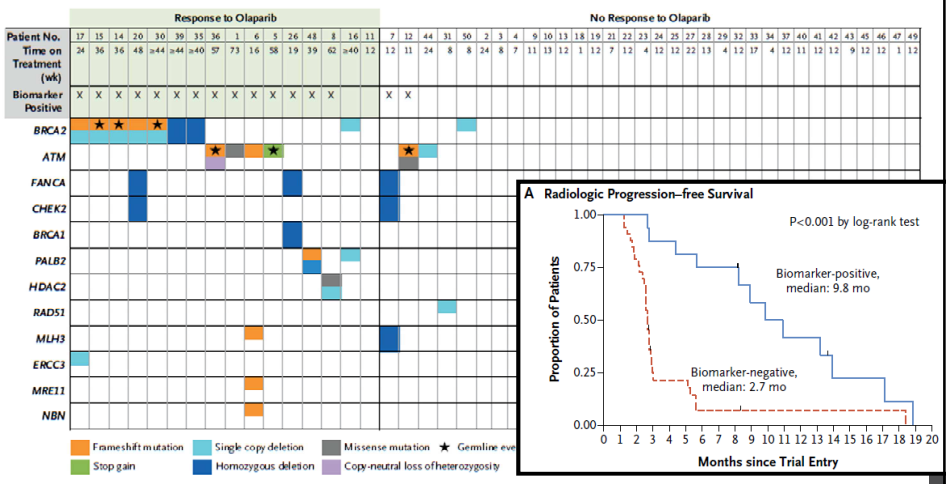
-A total of 84 germline DNA-repair gene mutations that were presumed to be deleterious were identified in 82/692 men (11.8%)
-Mutations were found in 16 genes



Pritchard CC, et al. N Engl J Med. 2016 Aug 4;375(5):443-53.

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer



Mateo J, et al. N Engl J Med. 2015 Oct 29;373(18):1697-708.

PROfound – Study Design

Key eligibility criteria
- mCRPC with disease progression on prior NHA, eg abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR*

Cohort A: *BRCA1*, *BRCA2* or *ATM* N=245
- Olaparib 300 mg bid n=162
- Physician's choice‡ n=83

Cohort B: Other alterations N=142
- Olaparib 300 mg bid n=94
- Physician's choice‡ n=48

2:1 randomization
Open-label

Upon BICR progression, physician's choice patients were allowed to cross over to olaparib

Stratification factors
- Previous taxane
- Measurable disease

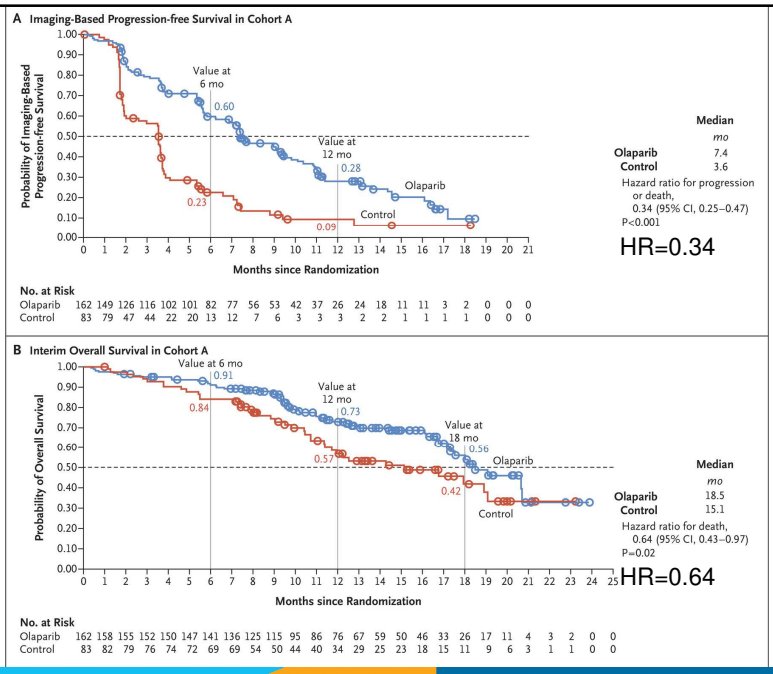
Primary Endpoint
Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

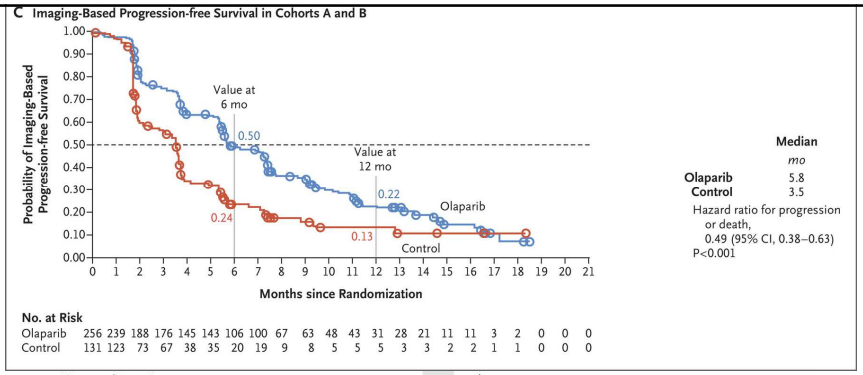
Key Secondary Endpoints
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

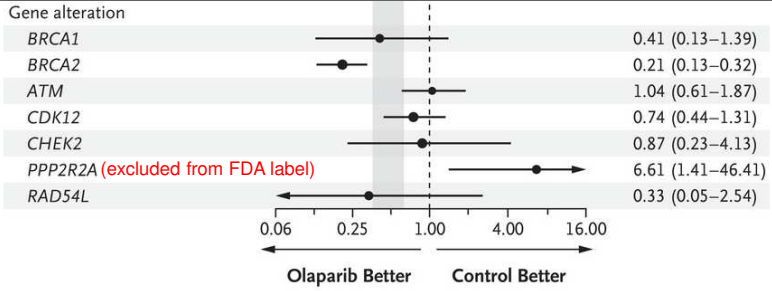
***An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test**
Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

‡Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid])
BICR, blinded independent central review

de Bono J, et al. N Engl J Med. 2020 May 28;382(22):2091-2102.


A Imaging-Based Progression-free Survival in Cohort A
Probability of Imaging-Based Progression-free Survival
Value at 6 mo
0.60
0.23
Value at 12 mo
0.28
0.09
Olaparib
Control
Months since Randomization
No. at Risk
Olaparib 162 149 126 116 102 101 82 77 56 53 42 37 26 24 18 11 11 3 2 0 0 0
Control 83 79 47 44 22 20 13 12 7 6 3 3 3 2 2 1 1 1 1 0 0 0
Median
mo
Olaparib 7.4
Control 3.6
Hazard ratio for progression or death, 0.34 (95% CI, 0.25–0.47)
P<0.001
HR=0.34
B Interim Overall Survival in Cohort A
Probability of Overall Survival
Value at 6 mo
0.91
0.84
Value at 12 mo
0.73
0.57
Value at 18 mo
0.56
0.42
Olaparib
Control
Months since Randomization
No. at Risk
Olaparib 162 158 155 152 150 147 141 136 125 115 95 86 76 67 59 50 46 33 26 17 11 4 3 2 0 0
Control 83 82 79 76 74 72 69 69 54 50 44 40 34 29 25 23 18 15 11 9 6 3 1 1 0 0
Median
mo
Olaparib 18.5
Control 15.1
Hazard ratio for death, 0.64 (95% CI, 0.43–0.97)
P=0.02
HR=0.64


C Imaging-Based Progression-free Survival in Cohorts A and B
Probability of Imaging-Based Progression-free Survival
Value at 6 mo
0.50
0.24
Value at 12 mo
0.22
0.13
Olaparib
Control
Months since Randomization
No. at Risk
Olaparib 256 239 188 176 145 143 106 100 67 63 48 43 31 28 21 11 11 3 2 0 0 0
Control 131 123 73 67 38 35 20 19 9 8 5 5 5 3 3 2 2 1 1 0 0 0
Median
mo
Olaparib 5.8
Control 3.5
Hazard ratio for progression or death, 0.49 (95% CI, 0.38–0.63)
P<0.001


Gene alteration
BRCA1 0.41 (0.13–1.39)
BRCA2 0.21 (0.13–0.32)
ATM 1.04 (0.61–1.87)
CDK12 0.74 (0.44–1.31)
CHEK2 0.87 (0.23–4.13)
PPP2R2A (excluded from FDA label) 6.61 (1.41–46.41)
RAD54L 0.33 (0.05–2.54)
0.06 0.25 1.00 4.00 16.00
Olaparib Better
Control Better

TRITON2: A Phase 2 Study of Rucaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Associated with Homologous Recombination Repair (HRR) Gene Alterations

Figure 5. Best Change from Baseline in PSA (n=84)

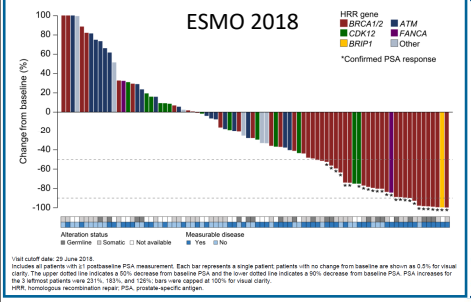


Figure 4. Best Change from Baseline in PSA in Rucaparib-Treated Patients with a *BRCA1/2* Alteration (n=96)

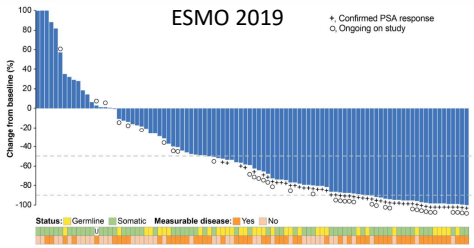
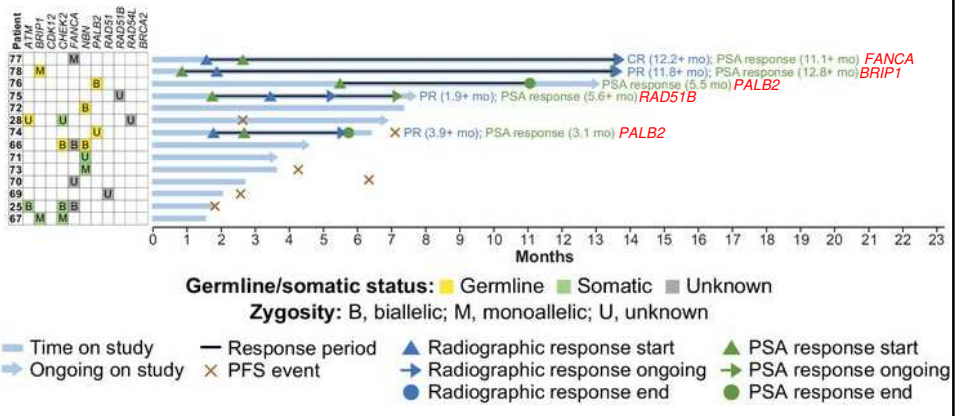


Table 4. Clinical Benefit Rates in Rucaparib-Treated Patients[a]

	DDR gene				
	BRCA1/2	***ATM***	***CDK12***	***CHEK2***	**Other**
6 mo, n/N (%) [95% CI]	47/84 (56.0) [44.7–66.8]	14/48 (29.2) [17.0–44.1]	3/14 (21.4) [4.7–50.8]	2/3 (66.7) [9.4–99.2]	6/12 (50.0) [21.1–78.9]
12 mo, n/N (%) [95% CI]	13/53 (24.5) [13.8–38.3]	2/25 (8.0) [1.0–26.0]	1/14 (7.1) [0.2–33.9]	0/1 (0) [0.0–97.5]	3/9 (33.3) [7.5–70.1]

Visit cutoff: 02 Jul 2019.
[a]Clinical benefit rate was the proportion of patients without radiographic progression per modified RECIST/PCWG3 criteria (per investigator assessment) who were ongoing with treatment through the indicated time interval.
CI, confidence interval; DDR, DNA damage repair; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Non-BRCA DNA Damage Repair Gene Alterations and Response to the Rucaparib: Analysis From the Phase II TRITON2 Study



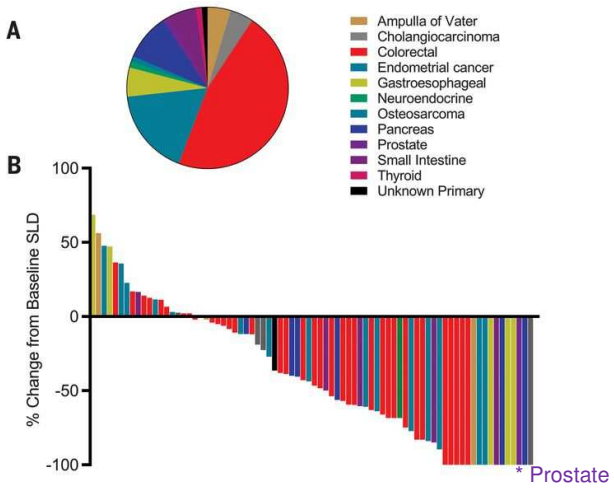
Abida W, et al. Clin Cancer Res. 2020 Jun 1;26(11):2487-2496.

PARP inhibitors - Conclusions

- Approved by the US Food and Drug Administration in May 2020
  - Olaparib - mCRPC patients (**post AR-directed therapy**) with deleterious or suspected deleterious germline or somatic **homologous recombination repair gene mutation**
  - Rucaparib - mCRPC patients (**post AR-directed therapy AND taxane**) with deleterious germline or somatic **BRCA gene mutation**

- Clear benefit to patients with mutations in *BRCA2* (and likely *BRCA1*)
- Unclear benefit in patients with mutations in *ATM*, *CHEK2*, *CDK12*
- ? Benefit in patients with mutations in genes canonically involved in HR (*PALB2*, *FANCA*, *RAD51C/D, RAD52, RAD54L*)

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

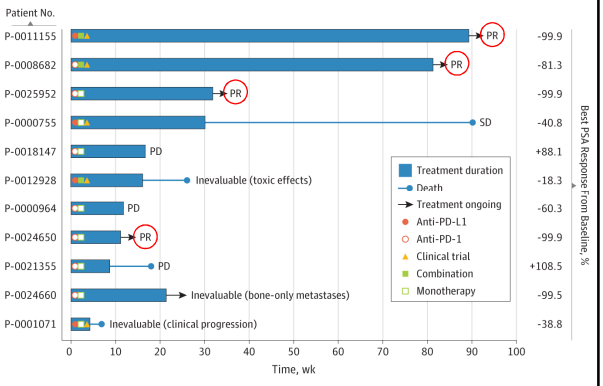


Le DL, *Science.* 2017 Jul 28;357(6349):409-413.

Analysis of the Prevalence of Microsatellite Instability in Prostate Cancer and Response to Immune Checkpoint Blockade

1346 PrCa pts underwent MSK-IMPACT testing

- 32 of 1033 patients (3.1%) with adequate tumor quality for analysis had MSI-H/dMMR disease
- 11 treated with anti-PD1/PD-L1 CPI
- 6 of 11 (54.5%) with PSA response, of whom 4 also had radiographic responses
- 5 of the 6 responders still on therapy for as long as 89 weeks



Abida W, et al. *JAMA Oncol.* 2019 Apr 1;5(4):471-478.

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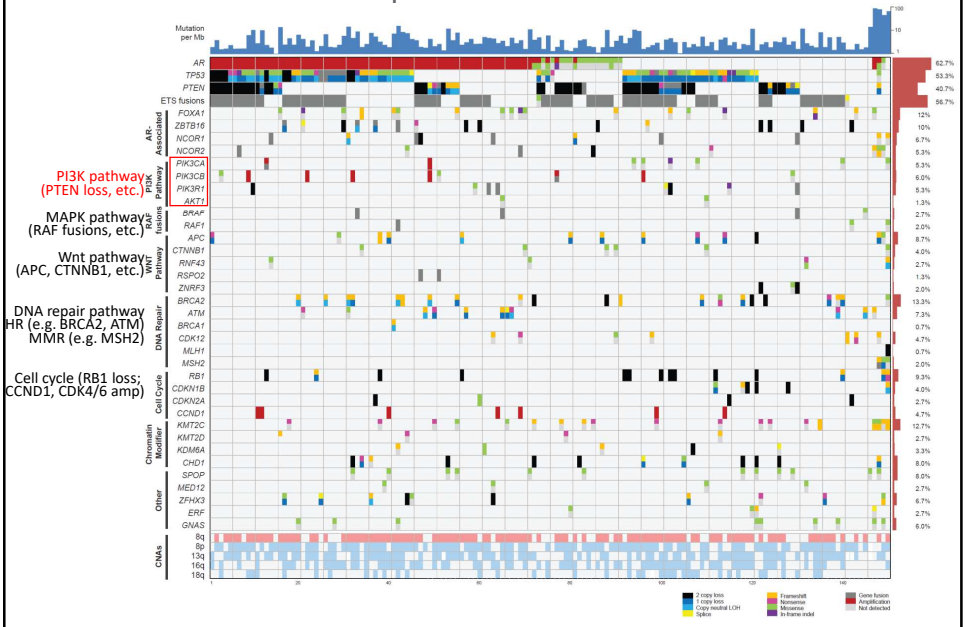
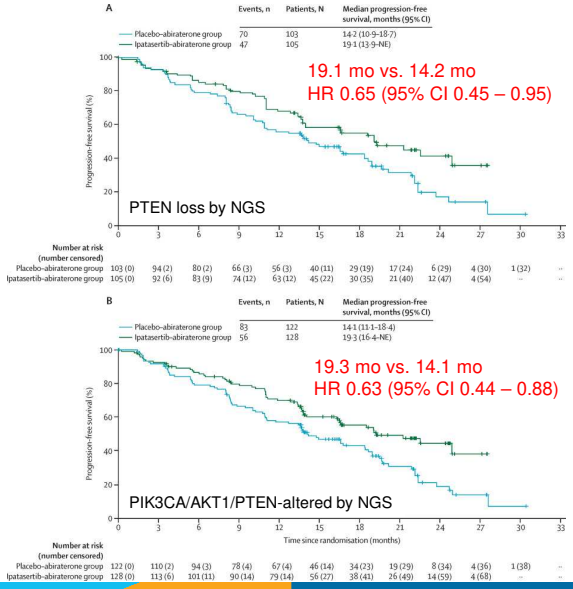


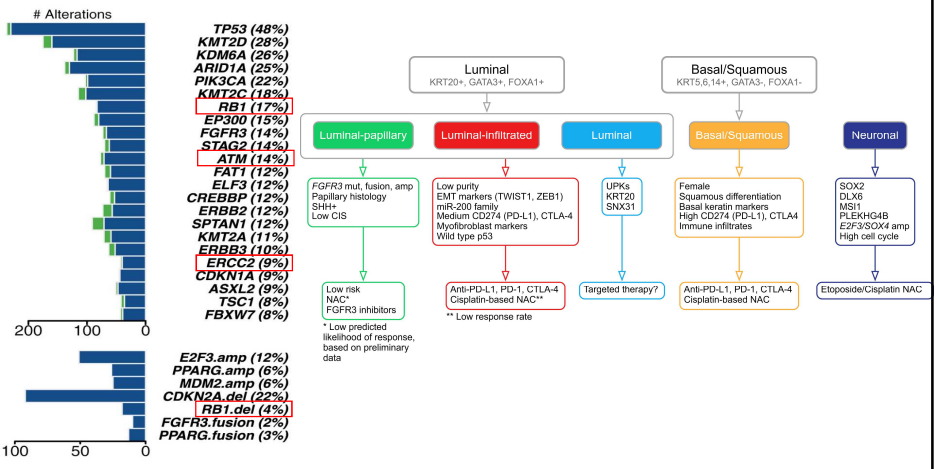
Robinson D, Van Allen EM, et al. Cell. 2015 May 21;161(5):1215-1228.

The AKT inhibitor ipatasertib with abiraterone prolongs radiographic progression-free survival compared to placebo



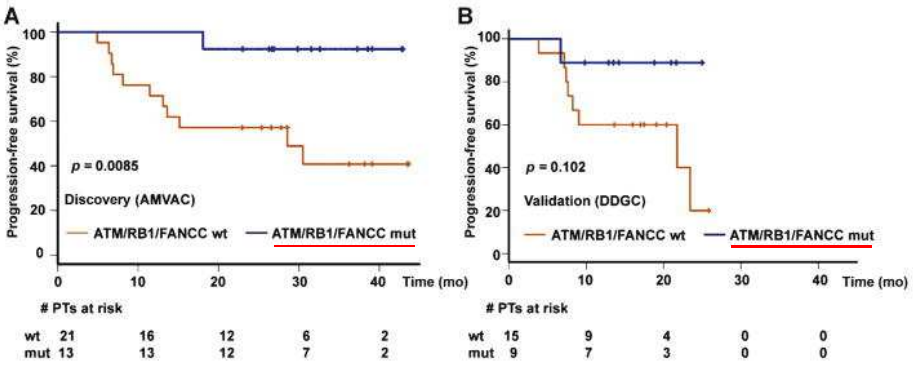
Sweeney CJ, et al. Lancet. 2021 Jul 10;398(10295):131-142.

Biology of Urothelial Carcinoma
Molecular heterogeneity but target-rich environment



Robertson AG et al. Cell. 2017;171(3):540-556.

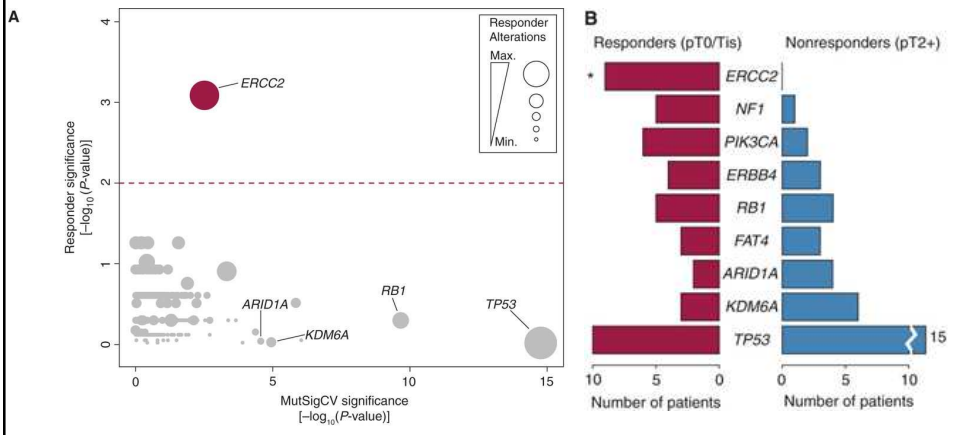
Association of molecular features with response to cisplatin-based chemotherapy



DNA repair gene variants associated with pCR and prolonged PFS

Plimack ER et al. Eur Urol. 2015;68(6):959-967

Association of molecular features with response to cisplatin-based chemotherapy

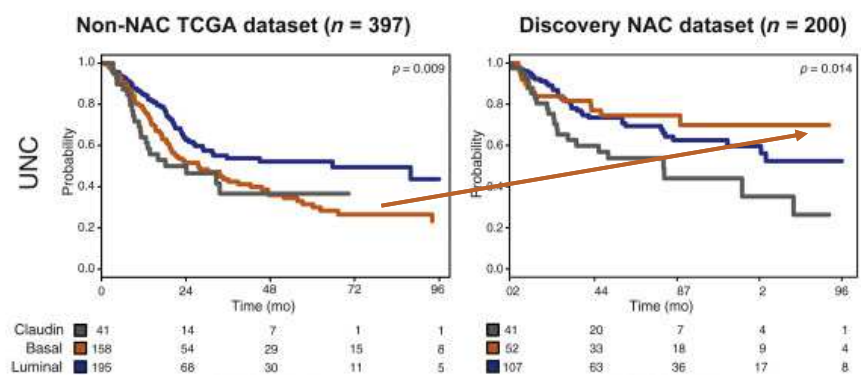


ERCC2 mutations associated with pCR → Bladder sparing approach for those with somatic ERCC2 mutations planned to be prospectively investigated

Van Allen EM et al. Cancer Discov. 2014;4(10):1140-1153

Association of molecular features with response to cisplatin-based chemotherapy

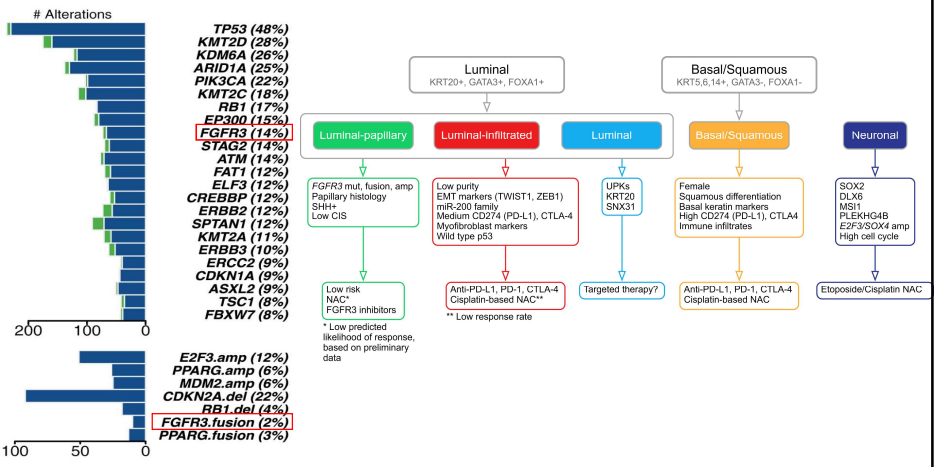
A



Basal gene expression subtype showed most improvement in OS with NAC

Seiler R et al. Eur Urol. 2017;72(4):544-554.

Biology of Urothelial Carcinoma
Molecular heterogeneity but target-rich environment



Robertson AG et al. Cell. 2017;171(3):540-556.

Erdafitinib: Antitumor Activity in Post-Platinum mUC With FGFR3/2 Activating Mutations/Fusions (RT-PCR)

		[95% CI]
Patients, n	99	
Response per investigator assessment[a], n (%)		
ORR	40 (40.4)	[30.7-50.1]
CR	3 (3.0)	
PR	37 (37.4)	
SD	39 (39.4)	
PD	18 (18.2)	
Unknown	2 (2.0)	
Median time to response	1.4 months	
Median duration of response	5.6 months	[4.2-7.2]
ORR among patient subgroups, n (%)		
Chemo-naïve	5/12 (41.7)	
Progressed or relapsed after chemo	35/87 (40.2)	
With visceral metastases	30/78 (38.5)	
Without visceral metastases	10/21 (47.6)	

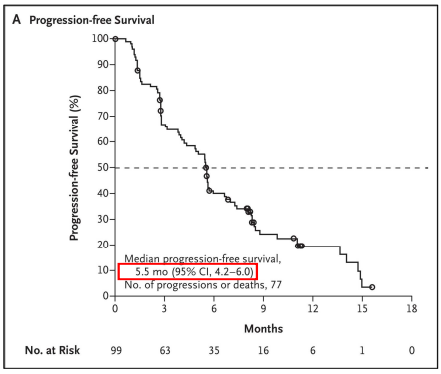
[a]Confirmed with second scan at least 6 weeks following the initial observation of response.

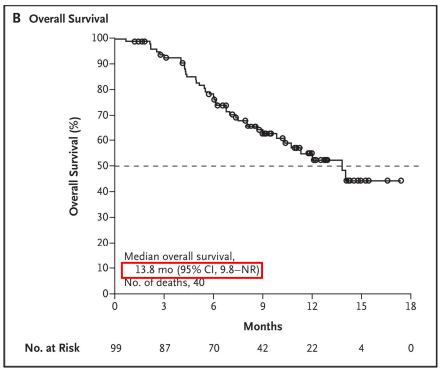
FGFR gene fusions (RT-PCR)
FGFR3-TACC3, FGFR3-BAIAP2L1 FGFR2-BICC1, FGFR2-CASP7 (n=6)

FGFR3 gene mutations (RT-PCR)
R248C, S249C, G370C, Y373C

Loriot Y et al. N Engl J Med. Jul 25 2019;381(4):338-348.

Erdafitinib: PFS and OS



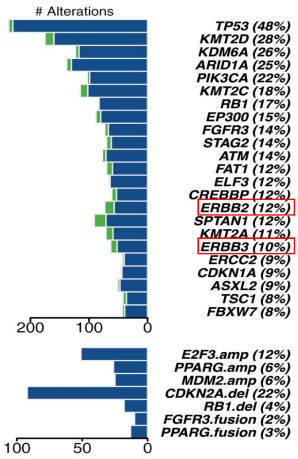


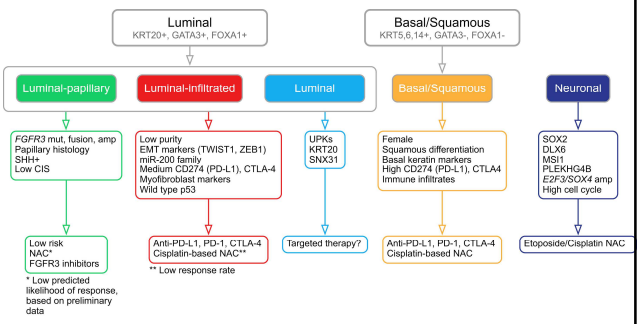
FDA-approved for locally advanced or metastatic urothelial carcinoma that has

- susceptible FGFR3 or FGFR2 genetic alterations and
- progressed during or following at least one line of prior platinum containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Loriot Y et al. N Engl J Med. Jul 25 2019;381(4):338-348.

Biology of Urothelial Carcinoma
Molecular heterogeneity but target-rich environment

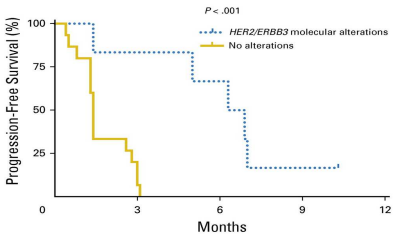




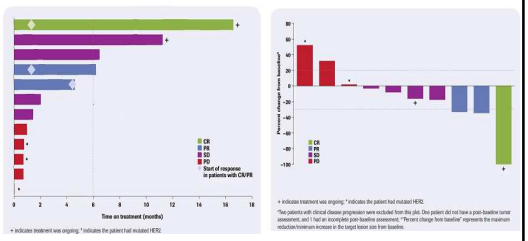
Robertson AG et al. Cell. 2017;171(3):540-556.

HER2/3 Kinase Inhibitors in Urothelial Carcinoma

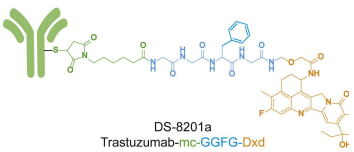
Afatinib (pan-HER TKI)[1]



Trastuzumab + Pertuzumab[2]



Trastuzumab-deruxtecan[3]



DS-8201a
Trastuzumab-mc-GGFG-Dxd

1. Choudhury NJ et al. J Clin Oncol. 2016;34:2165-2171
2. Bryce AH et al. J Clin Oncol. 2017;35(suppl 6S): 348
3. Doi T et al. Lancet Oncol. 2017;18:1512-1522.

Response rates and median overall survival with anti-PD-1/PD-L1 blockade in metastatic urothelial carcinoma

	Medication	Phase	# Patients	ORR (%)	PFS (m.)	OS (m.)	PD-L1 Response
Metastatic 2nd Line Therapy	*Atezolizumab*	I	100	21.0	–	8	–
		II	310	15.0	2.1	7.9	PD-L1 on IC > 5% associated with ORR, testing not required for treatment (1)
	Pembrolizumab	III P	270	21.6	2.1	10.3	PD-L1 TC and IC composite score > 10%, no difference in ORR or mOS (2)
		C	272	6.7	3.3	7.4	–
	Nivolumab	II	270	19.6	2.0	8.74	PD-L1 on TC > 1% not associated with ORR but associated with OS (3)
	Avelumab	Ib/II	241	17.6	1.6	7.0	PD-L1 on TC > 5% associated with improved ORR, no OS data as of yet (4)
	Durvalumab	Ib	191	17.8	–	–	Composite biomarker of PD-L1 > 25% on TC or IC predicts response rates, approved companion diagnostic (5)
Metastatic 1st Line*	*Atezolizumab*	II	100	23.0	2.7	15.9	PD-L1 on IC not associated with improved ORR or mOS (6)
	Pembrolizumab	II	370	29.0	–	–	PD-L1 TC and IC composite score with cutoff of 10%, no difference noted in ORR (7)

1. Rosenberg JE, et al. Lancet. 2016;387:1909–20.
2. Bellmunt J, et al. N Engl J Med. 2017;376:1015–26.
3. Sharma P, et al. Lancet Oncol. 2017;18:312–22.
4. Patel MR, et al. J Clin Oncol. 2017;35:330.
5. Massard C, et al. J Clin Oncol. 2016;34:3119–25.
6. Balar AV, et al. Lancet. 2017;389:67–76.
7. Balar A, et al. Ann Oncol. 2016;27:LBA32_PR-LBA_PR.

Aggen DH, Drake CG. J Immunother Cancer. 2017 Nov 21;5(1):94.

FDA update 6/19/18

FDA limited use of pembrolizumab and atezolizumab in 1st line due to decreased survival compared to platinum-based chemotherapy in patients with low PD-L1.

KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

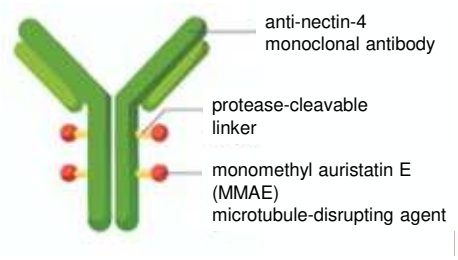
- Are **not eligible for cisplatin**-containing therapy and whose tumors express PD-L1 (Combined Positive Score ≥ 10 by Dako PD-L1 IHC 22C3 PharmDx Assay), or
- In patients who are **not eligible for any platinum**-containing chemotherapy regardless of PD-L1 status.

TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

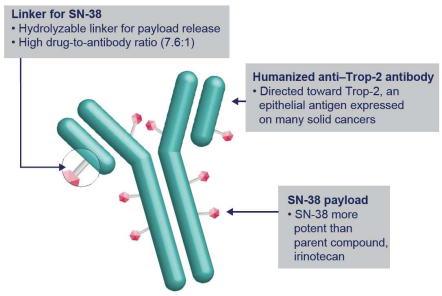
- Are **not eligible for cisplatin**-containing therapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area by Ventana PD-L1 [SP142] Assay)
- Are **not eligible for any platinum**-containing therapy regardless of PD-L1 status.

➢ Carboplatin-containing chemo preferred over pembro/atezo for 1st line tx if PD-L1 low

Antibody-drug conjugates (ADCs)



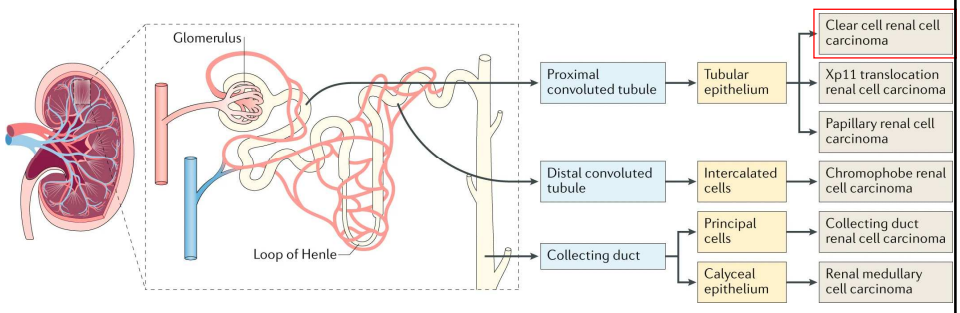
Enfortumab vedotin
(Nectin-4)



Sacituzumab Govitecan
(Trop-2)

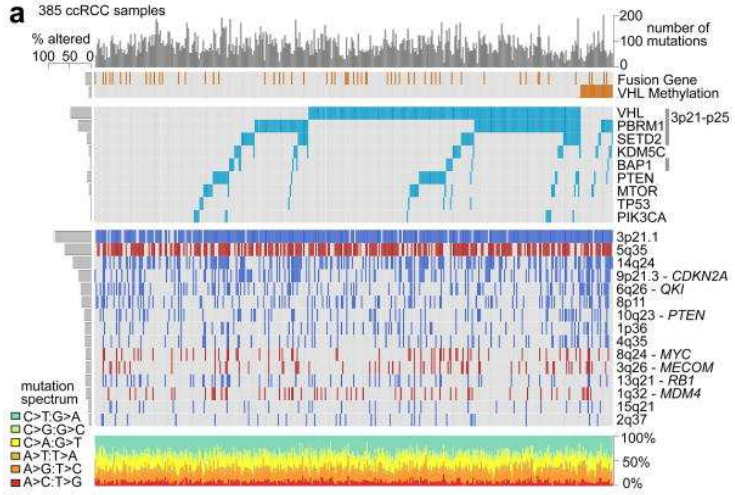
No biomarkers of response (Nectin-4 and Trop-2 levels not predictive)

Location and cell of origin of RCC histological subtypes



Dizman N, et al. Nat Rev Nephrol. 2020 Aug;16(8):435-451.

Comprehensive molecular characterization of clear cell renal cell carcinoma



Inactivation of von Hippel-Lindau (VHL) gene seen in familial and most sporadic clear cell RCC

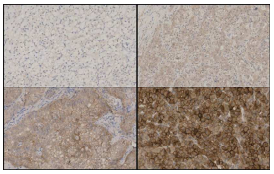
Leads to increased levels of hypoxia-inducible factors (HIF) and overexpression of HIF targets, such as VEGF

VEGF-targeted agents are standard in advanced clear-cell RCC, but biomarkers of activity are lacking

Cancer Genome Atlas Research Network. Nature. 2013 Jul 4;499(7456):43-9.
Choueiri TK, et al. Clin Cancer Res. 2013 Sep 15; 19(18): 5218–5226.

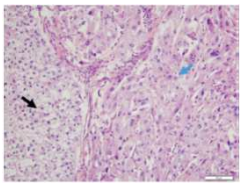
Current landscape of IO biomarker investigation in ccRCC

Immuno-histochemistry



PD-L1 IHC[1]

Histology



Sarcomatoid histology[2]

Benefit to 1st line IO combination over TKI alone regardless of PD-L1 status

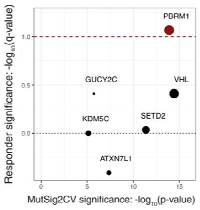
- IO-IO (ipilimumab+nivolumab)
- TKI-IO (axitinib+pembrolizumab, cabozantinib+nivolumab, lenavitinib+pembrolizumab)

Multiple retrospective studies suggest preferential benefit to IO with sarcomatoid histology

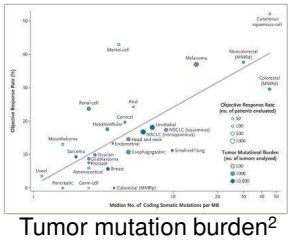
5. Choueiri et al., Clin Cancer Res, 2015. PMID: 25538263
6. Debien et al., Cancers, 2020. PMID: 31906050

Current landscape of IO biomarker investigation in ccRCC

Genomics

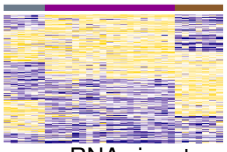


PBRM1 LOF mutations[1]

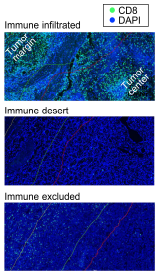


Tumor mutation burden[2]

Immune infiltration



Immune RNA signatures[3]

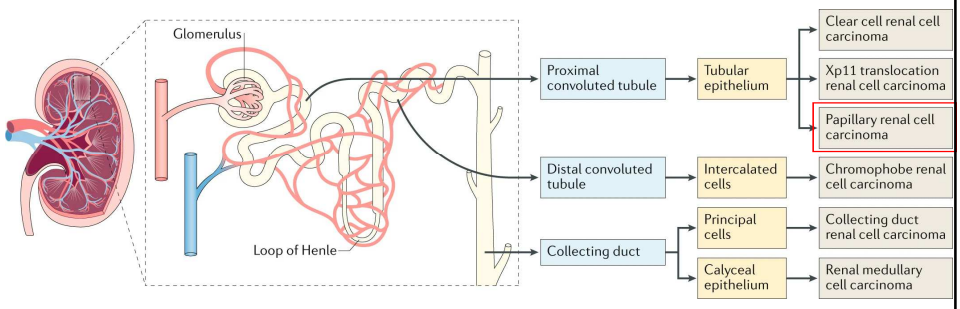


CD8⁺ infiltration[4]

Integration of biologically important features likely necessary to better predict benefit from IO in RCC

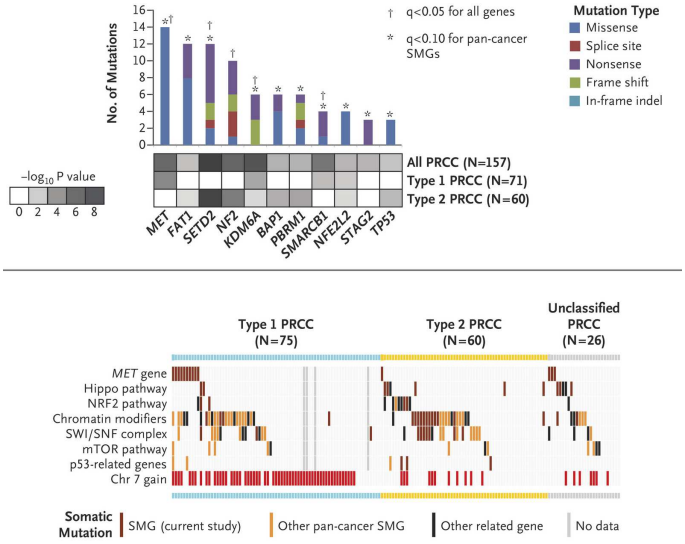
1. Miao et al., Science, 2018. PMID: 29301960; 2. Yarchoan et al., N Engl J Med, 2017. PMID: 29262275; 3. McDermott et al., Nature Med, 2018. PMID: 29867230. 4. Braun et al., Nature Med, 2020. PMID: 32472114

Location and cell of origin of RCC histological subtypes



Dizman N, et al. Nat Rev Nephrol. 2020 Aug;16(8):435-451.

Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma



The Cancer Genome Atlas Network. N Engl J Med 2016; 374:135-145.

Outcomes in clinical trials of MET-targeting agents in metastatic papillary renal cell carcinoma

Cohort size	Tissue source for analysis of *MET* mutations	Therapeutic agents	Overall PFS or TTF (months)	ORR (%)	Response in patients with *MET* alterations	Response in patients without *MET* alterations
74	Archival tumour tissue or liquid biopsy	Foretinib	9.3	13.5	Germline *MET* alterations: PR, 5/10; SD, 5/10	NA
					Patients with non-germline *MET* alterations: PR, 3/20; SD, 16/20	NA
50	Archival tumour tissue	Tivantinib or tivantinib–erlotinib	Tivantinib, 2; tivantinib–erlotinib, 3.9	0	PR or SD, 0/1	PR, 0/34; SD, 0/34
23	Archival tumour tissue	Crizotinib	5.8	17.4	PR, 2/4; SD, 1/4	PR, 1/16; SD, 11/16
109	Archival tumour tissue	Savolitinib	NA	7	PR, 8/44; SD, 22/44	PR, 0/46; SD, 11/46
37	Archival tumour tissue	Cabozantinib	6.9	32	PR, 4/10; SD, 4/10	PR, 7/27; SD, 15/27

Dizman N, et al. Nat Rev Nephrol. 2020 Aug;16(8):435-451.

Tissue-based molecular biomarkers in GU malignancies

- **Prostate cancer**
  - Gene expression-based genomic classifiers (Prolaris, onco*type* DX, Decipher)
  - Homologous recombination repair deficiency → olaparib or rucaparib (PARP inhibitor)
  - Mismatch repair deficiency → pembrolizumab (anti-PD1 checkpoint immunotherapy)
  - PTEN alteration → candidacy for trial of AKT inhibitor
- **Urothelial cancer**
  - PD-L1+ by IHC → CPI (rather than carboplatin-based chemo) for 1st tx in cisplatin-ineligible patients
  - Activating FGFR2/3 alteration → erdafitinib (FGFR inhibitor)
- **Kidney cancer**
  - MET alteration in papillary RCC → candidacy for trial of MET inhibitor

➢ Many others investigated but with limited clinical utility to date

➢ Targeted agents based on molecular biomarkers under study

FDA update 8/31/21

On 8/31/21, the FDA converted accelerated approval of pembrolizumab for first line treatment of locally advanced or metastatic urothelial carcinoma (UC) to full approval. Full approval was accompanied by a label change.

Previous accelerated approval was in the following patients:

- Those who are **not eligible for cisplatin**-containing therapy and whose tumors express PD-L1 (Combined Positive Score ≥ 10 by Dako PD-L1 IHC 22C3 PharmDx Assay), or
- Those who are **not eligible for any platinum**-containing chemotherapy regardless of PD-L1 status.

Current full approval:

- Those who are **not eligible for any platinum**-containing chemotherapy

Cisplatin-ineligible patients who are eligible for another platinum-containing chemo (i.e. carboplatin) are not included in full approval regardless of PD-L1 status.

➢ PD-L1 is no longer a relevant biomarker for selection of pembrolizumab for 1st line treatment of UC.

Acknowledgments

- David Braun
- Guru Sonpavde
- Mark Pomerantz
- Paul Nguyen
- Mark Preston