Markey Cancer Center
An NCI Comprehensive Cancer Center

Advancing GU Oncology: Clinically Actionable Biomarkers in Bladder Cancer

Zin Myint, MD
Associate Professor
Division of Medical Oncology

Patrick Hensley, MD
Assistant Professor
Departments of Urology & Pathology

Ninth Annual Precision Medicine Symposium
February 28, 2025

DISCLOSURES

- Patrick Hensley has no financial disclosures to report.
- Zin Myint – nothing to disclose

LEARNING OBJECTIVES

1. Review methods for predictive biomarker development in bladder cancer.
2. Recognize the role of predictive biomarkers to guide clinical decision making.
3. Review the clinical significance of FGFR3, HER2, HRR gene mutations and MSI-high in metastatic bladder cancer
4. Discuss how these biomarkers influence prognosis and therapeutic decision-making

Setting the Stage: Historical Treatment Paradigms & Novel Drug Development in Bladder Cancer

Bladder Cancer Epidemiology

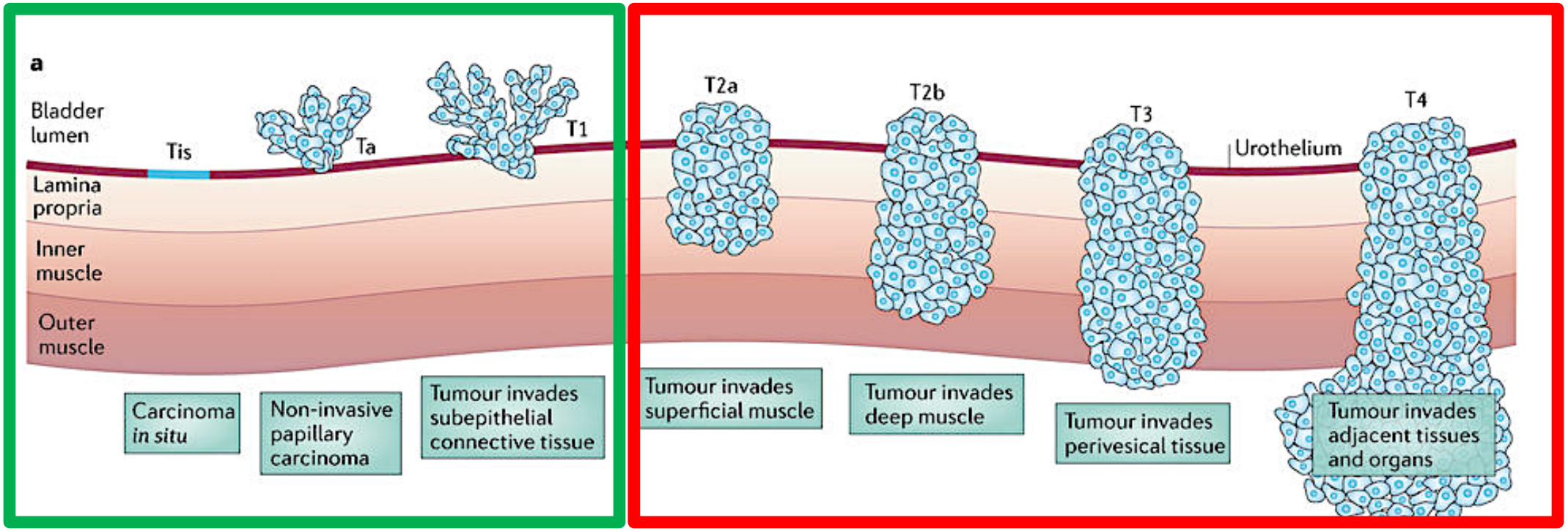
>80,000 new cases/year in North America

- 3 men:1 women ratio
- Cancer death: 8th leading cause in males, 11th in females
- At diagnosis, 70-80% localized to the superficial layers of wall (NMIBC)
- Remaining are muscle-invasive or metastatic
- > 600,000 patients alive with the disease
- Recurrence rate 70-80% within 2 years

Of all cancers, bladder cancer has the greatest lifetime treatment cost per patient diagnosed (US) → *$230,000*

$6 billion annually in US

TNM Staging



NMIBC:

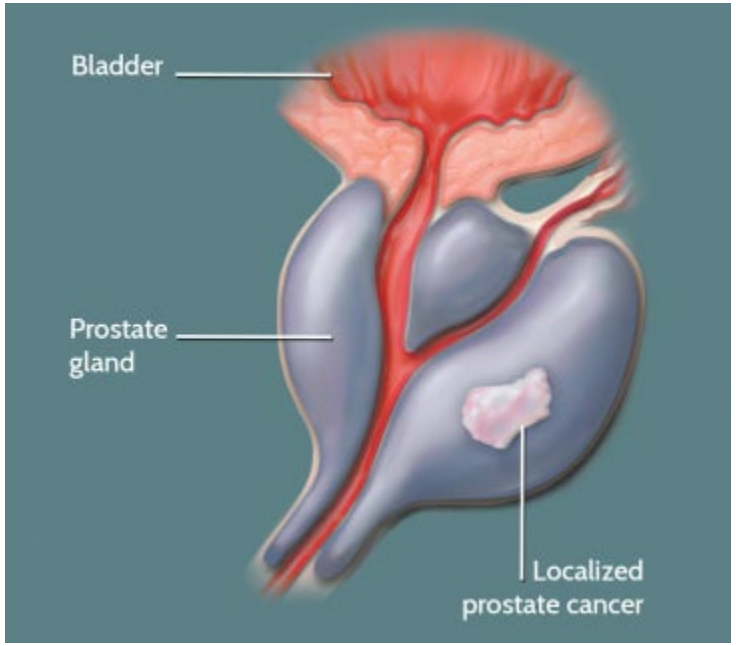
- ***Risk Stratification important***
  - Low- observation
  - Intermediate/high- intravesical tx
  - Very high- radical cystectomy

MIBC:

- ***One-size fits all***
  - Neoadjuvant chemo(immune)therapy → radical cystectomy
  - Chemoradiation for non-cystectomy candidates

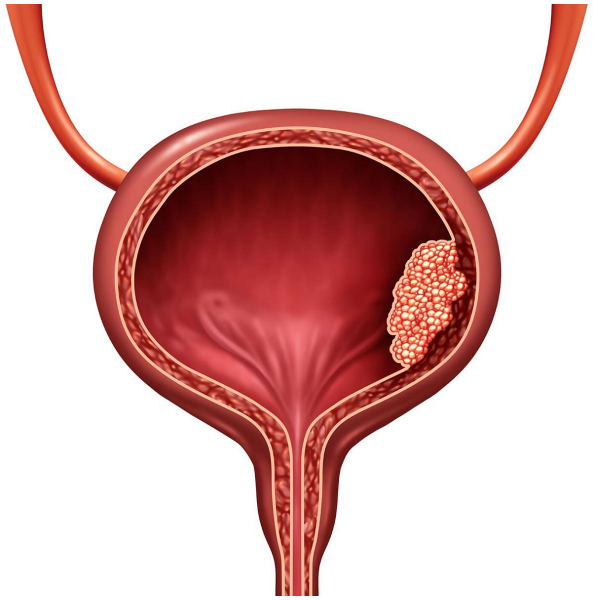
Prognosis

- 5-year CSS 80%



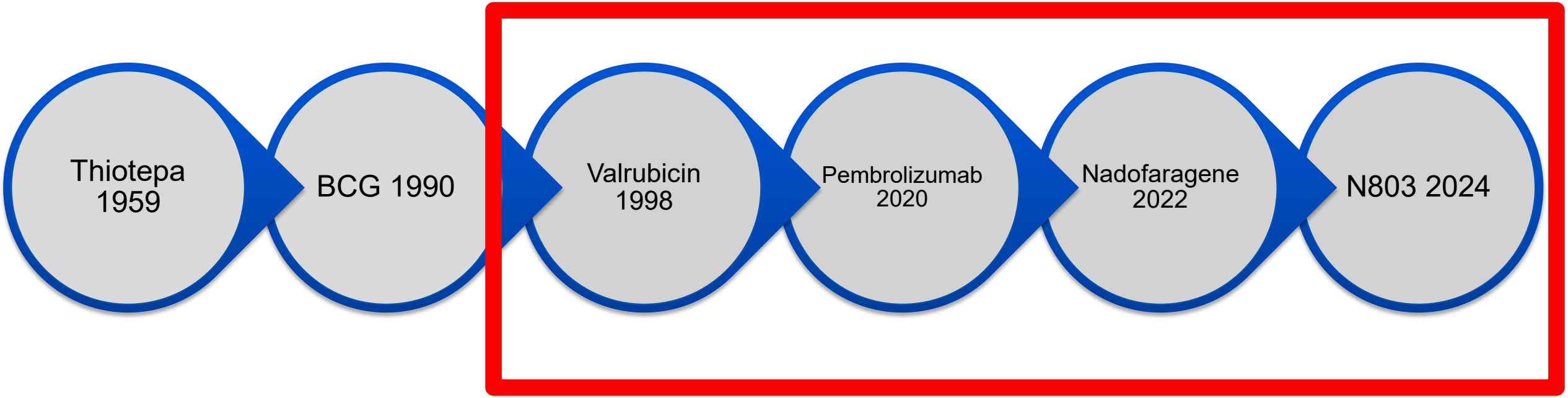
Gleason 5+5 Prostate Cancer (12/12 cores)

- 5-year CSS 80%

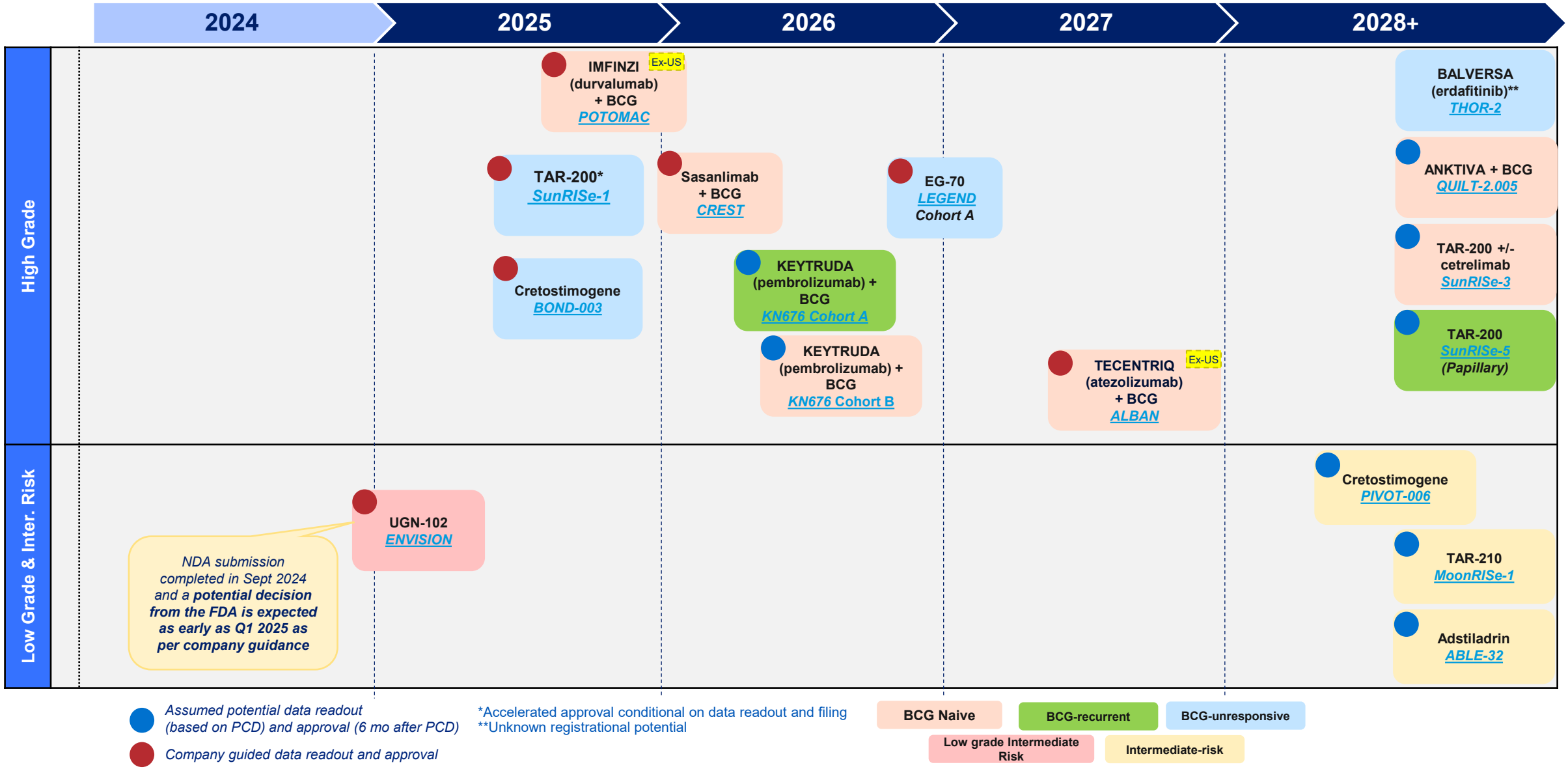


High Grade T1 Bladder Cancer

TIMELINE OF FDA APPROVALS FOR NMIBC

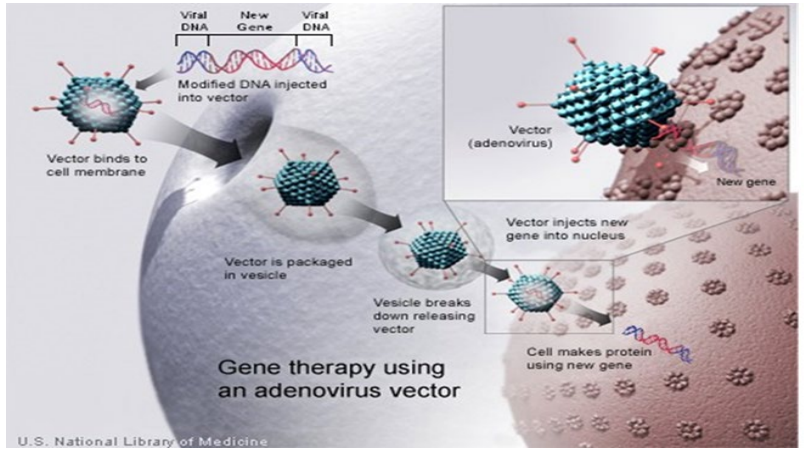


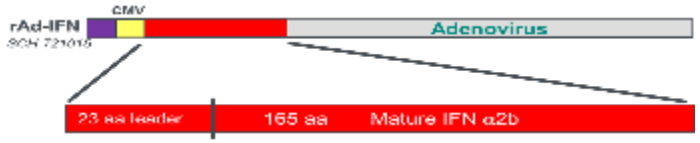
Pipeline of anticipated approvals



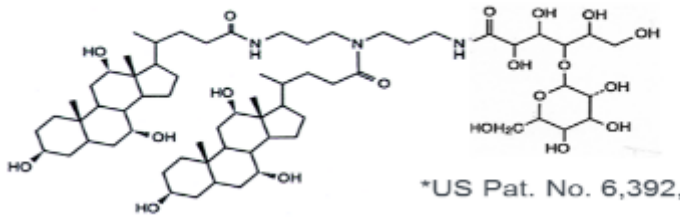
Trial	BOND-003	CORE-001	LEGEND	SunRISe-1	QUILT 3.032	NCT02773849	KEYNOTE-057
Agent	Cretostimogene [1]	Cretostimogene + Pembrolizumab [2,3]	EG-70 [4]	TAR-200 [5]	N-803 + BCG [6]	Nadofaragene [7-9]	Pembrolizumab [10-12]
MOA	Oncolytic Immunotherapy	Oncolytic Immunotherapy + Checkpoint inhibitor	RIG-1 Agonist + IL-12	Gemcitabine Delivery System	IL-15 + BCG	Gene Therapy Secreting IFN	Checkpoint Inhibitor
Route	Intravesical	Intravesical + Intravenous	Intravesical	Urinary placement catheter/ procedure	Intravesical	Intravesical	Intravenous
Stage	Phase 3 Enrollment Complete	Phase 2 Complete	Phase 1/2 Ongoing	Phase 2 Ongoing	Approved	Approved	Approved
Sample Size	N=112	N=35	N< 24 (Phase 1) N ≈ 100 (Phase 2)	N=85	N=77	N=98	N=96
CR at Any Time	**75% (79/105) [95% CI: 65% - 83%]**	83% (29/35) [95% CI: 70%-95%]	71% (15/21) [95% CI: not reported]	84% (71/85) [95% CI: 74% - 91%]	62% (48/77) [95% CI: 51% - 73%]	51% (50/98) [95% CI: 41% - 61%]	41% (39/96) [95% CI: 31% - 51%]
DoR of 12M (ITT)	Not Reported	66% (19/29) [95% CI: 46%-81%]	Not Reported	Not Reported	58%	46%	46%
DoR of 12M (K-M Est)	Not Reported	82% [95% CI: 61%-92%]	Not Reported	66% [95% CI: 45% - 80%]	Not Reported	Not Reported	Not Reported
Safety Profile	**0% Grade 3+ TRAE** **0% treatment-related discontinuation** **95% receive all protocol treatments**	0% Grade 3+ creto-related AE irAEs exclusively pembro-associated 5 unrelated treatment d/c	0% Grade 3+ TRAEs No treatment-related d/c	9% Grade 3 TRAE 6% serious TRAE 6% treatment-related d/c	16% SAE 7% treatment-related d/c	4% Grade 3+ TRAE 11% SAE 2% treatment-related d/c	13% Grade 3 or 4 TRAE 28% SAE 11% treatment-related d/c
Cost	?	?	?	?	$$$$	$$$$	$$$

ADSTILADRIN™ (NADOFARAGENE FIRADENOVEC)



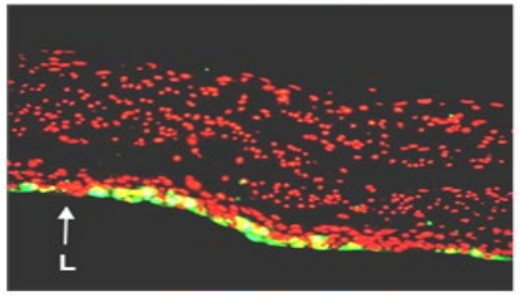


Syn3*



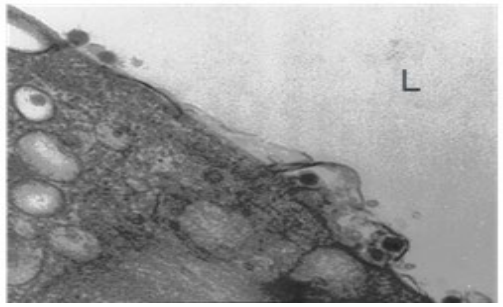
*US Pat. No. 6,392,069

rAd-IFN in Syn3



L – Lumen of bladder

Adenovirus particles on bladder epithelium and within vesicles using Syn3

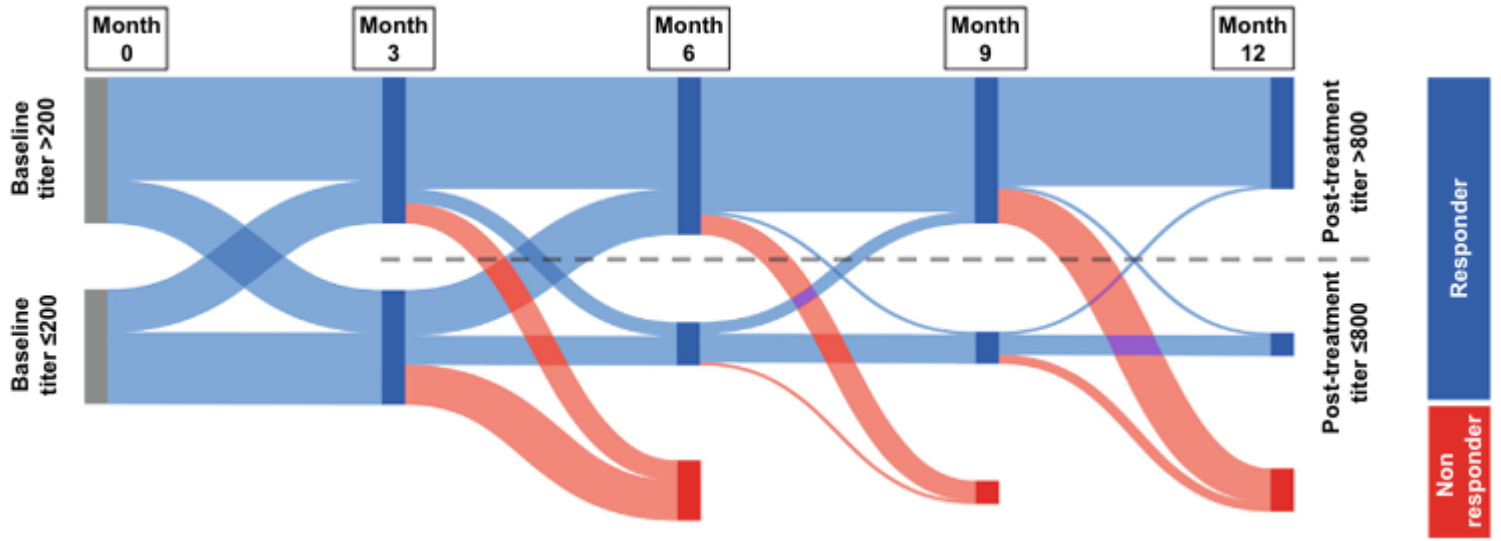


Protein active in transfected cells

Released into microenvironment

RATIONAL PREDICTIVE BIOMARKER DEVELOPMENT FOR EMERGING THERAPIES- PROOF OF CONCEPT

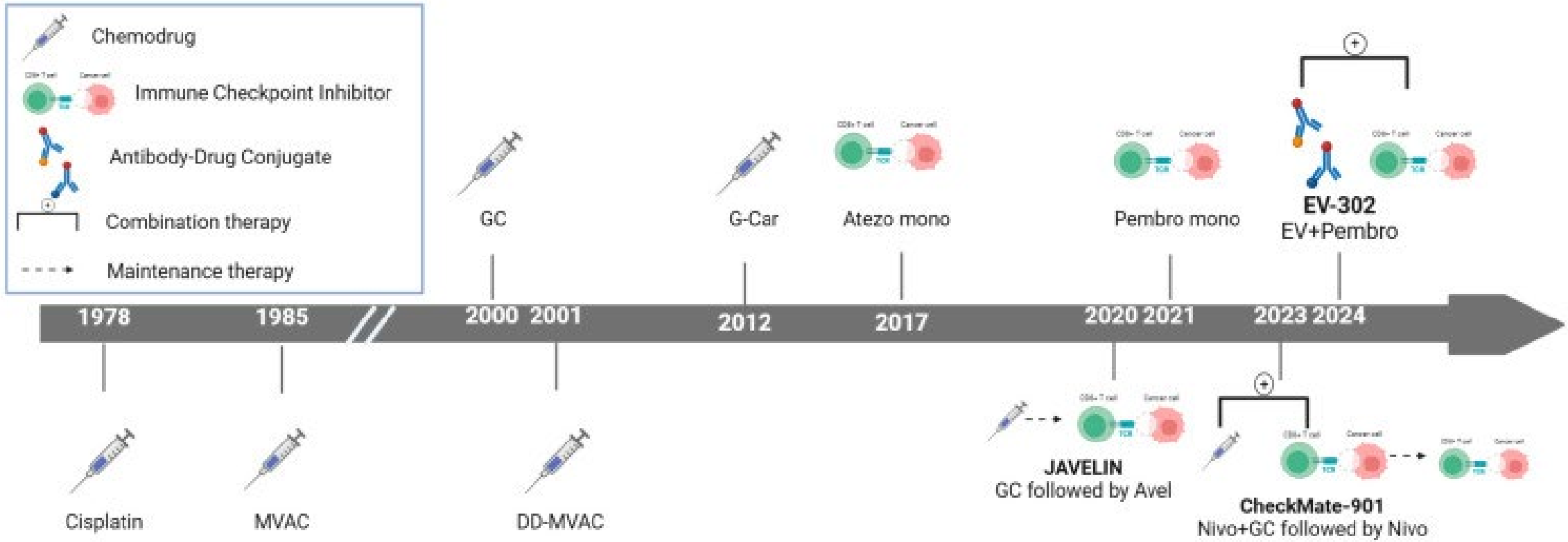
- Adstiladrin (nadofaragene firedenovec)- recombinant adenovirus + INFα
- Baseline and 3-month serum anti-adenoviral antibody titers predicted response



Markey Cancer Center

Mitra 2022

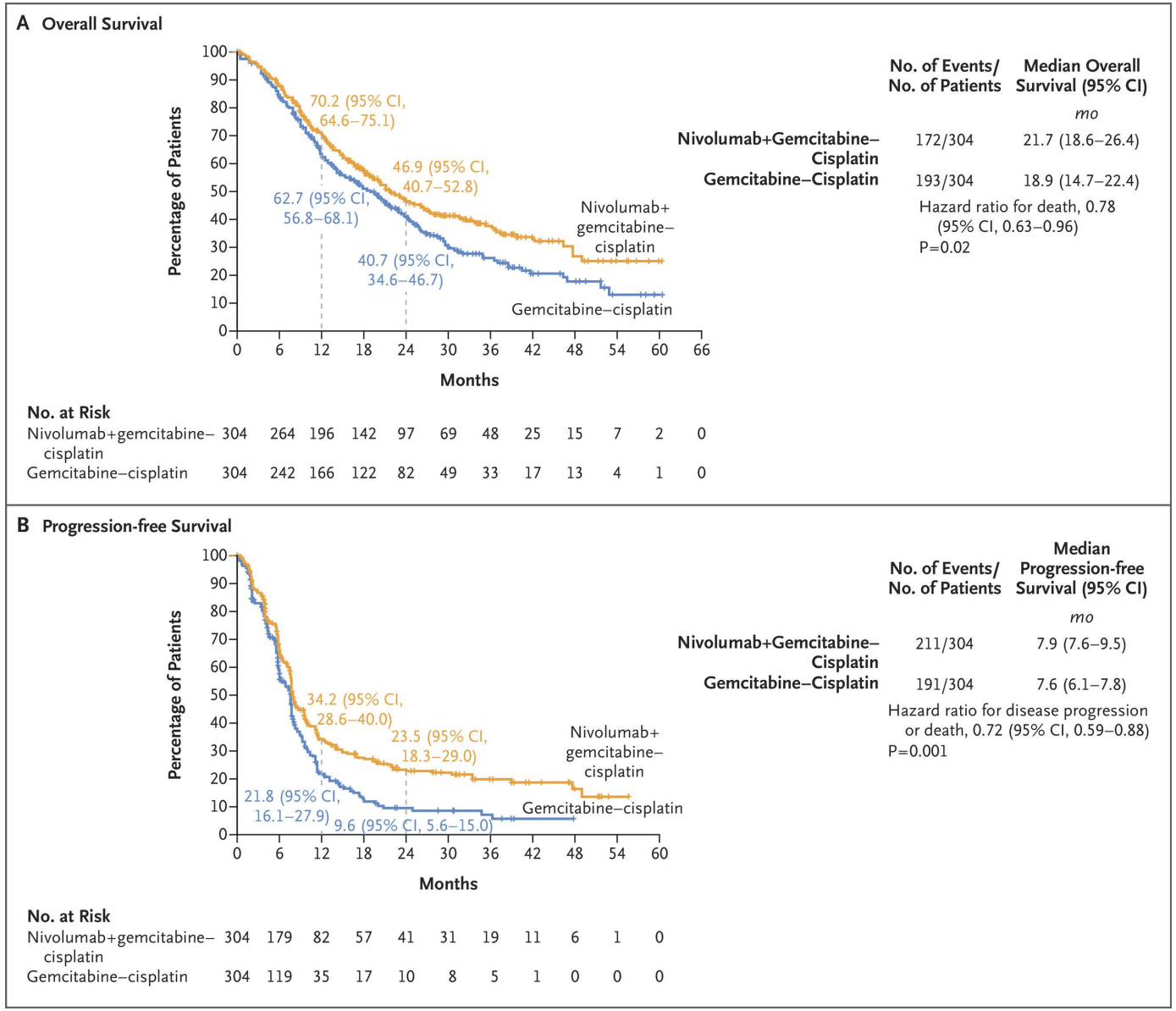
Treatment Landscape of Metastatic Urothelial Carcinoma



Markey Cancer Center

Kwon W & Lee M. Cancers. 2024 Dec 5;16(23):4078.

Checkmate 901

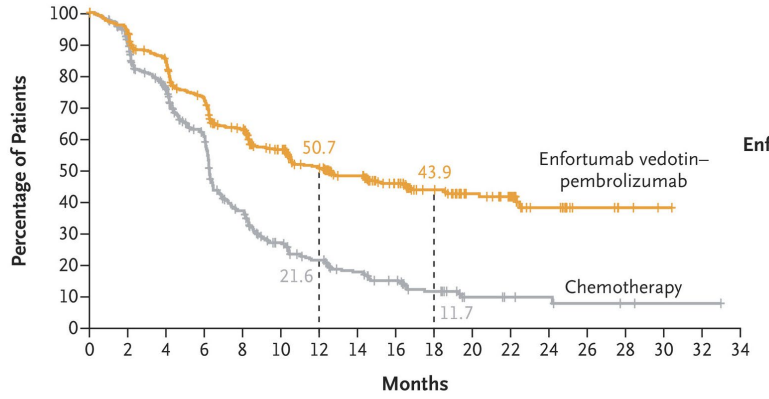


Markey Cancer Center

Van der Heijden MS et al. N Engl J Med 2023; 389:1778-1789

EV-302

Progression-free Survival

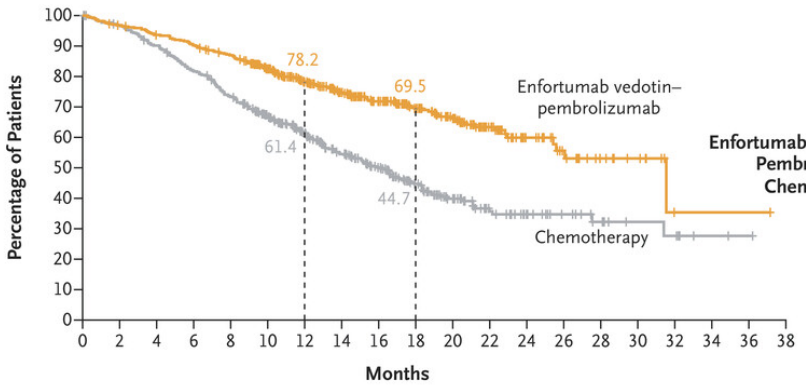


	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	223/442	12.5 (10.4–16.6)
Chemotherapy	307/444	6.3 (6.2–6.5)

Hazard ratio, 0.45 (95% CI, 0.38–0.54)
Two-sided P<0.001

No. at Risk																	
Enfortumab vedotin–pembrolizumab	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1	
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

Overall Survival



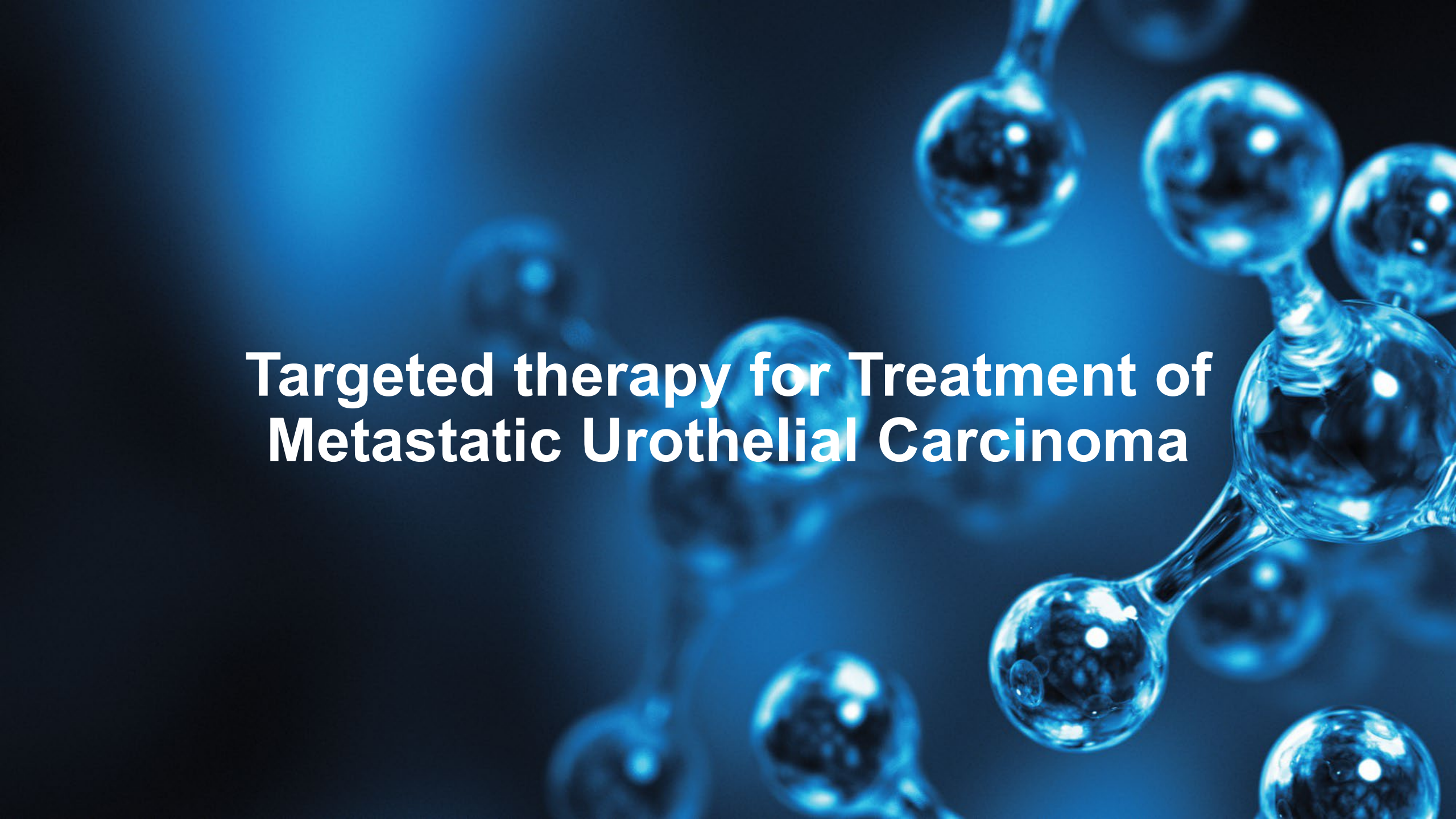
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	133/442	31.5 (25.4–NE)
Chemotherapy	226/444	16.1 (13.9–18.3)

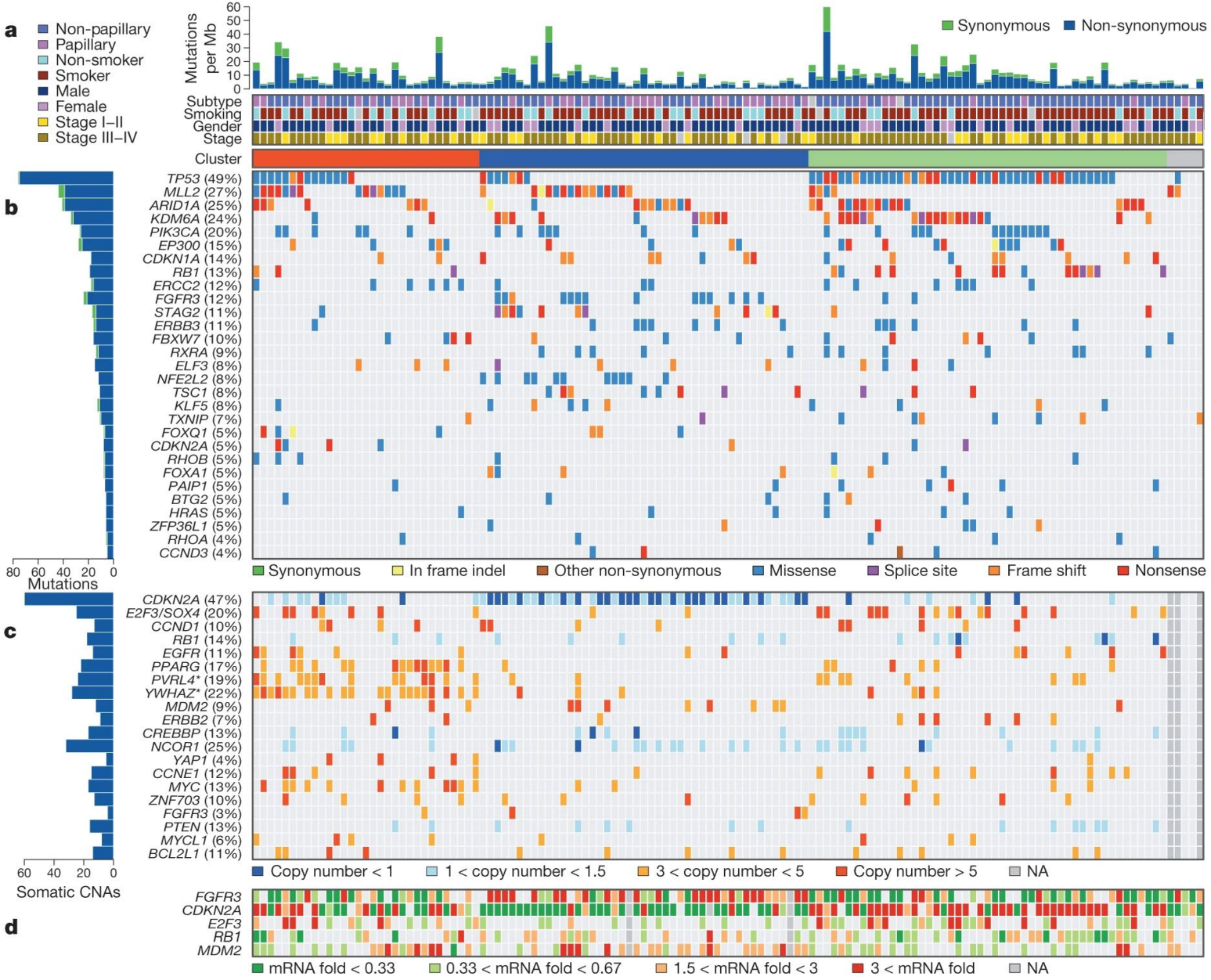
Hazard ratio, 0.47 (95% CI, 0.38–0.58)
Two-sided P<0.001

No. at Risk																	
Enfortumab vedotin–pembrolizumab	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

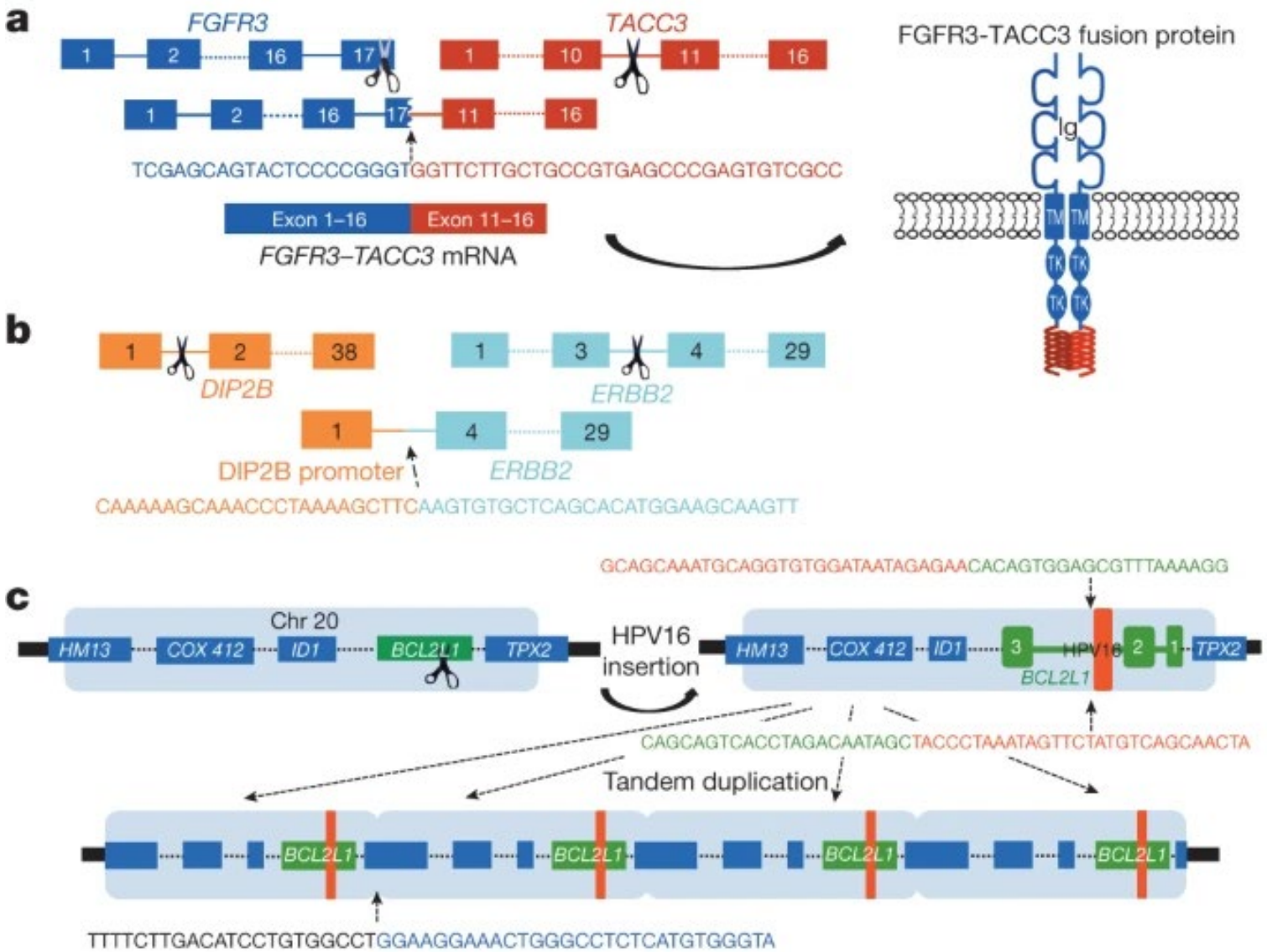
Markey Cancer Center

Powles T et al. N Engl J Med 2024;390:875-888

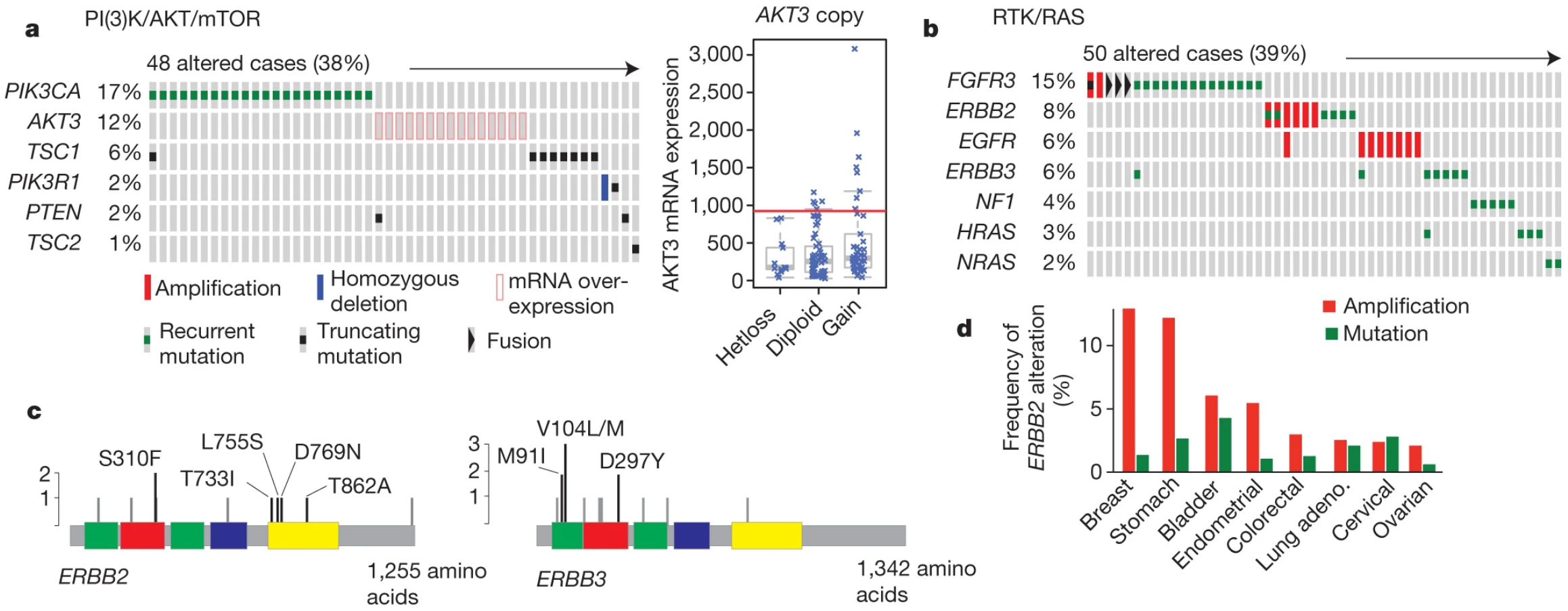

Targeted therapy for Treatment of
Metastatic Urothelial Carcinoma



The Cancer Genome Atlas Research Network. Nature. 507, 315-322 (2014)



The Cancer Genome Atlas Research Network. Nature. 507, 315-322 (2014)



The Cancer Genome Atlas Research Network. Nature. 507, 315-322 (2014)

Fibroblast growth factor receptors (FGFRs)

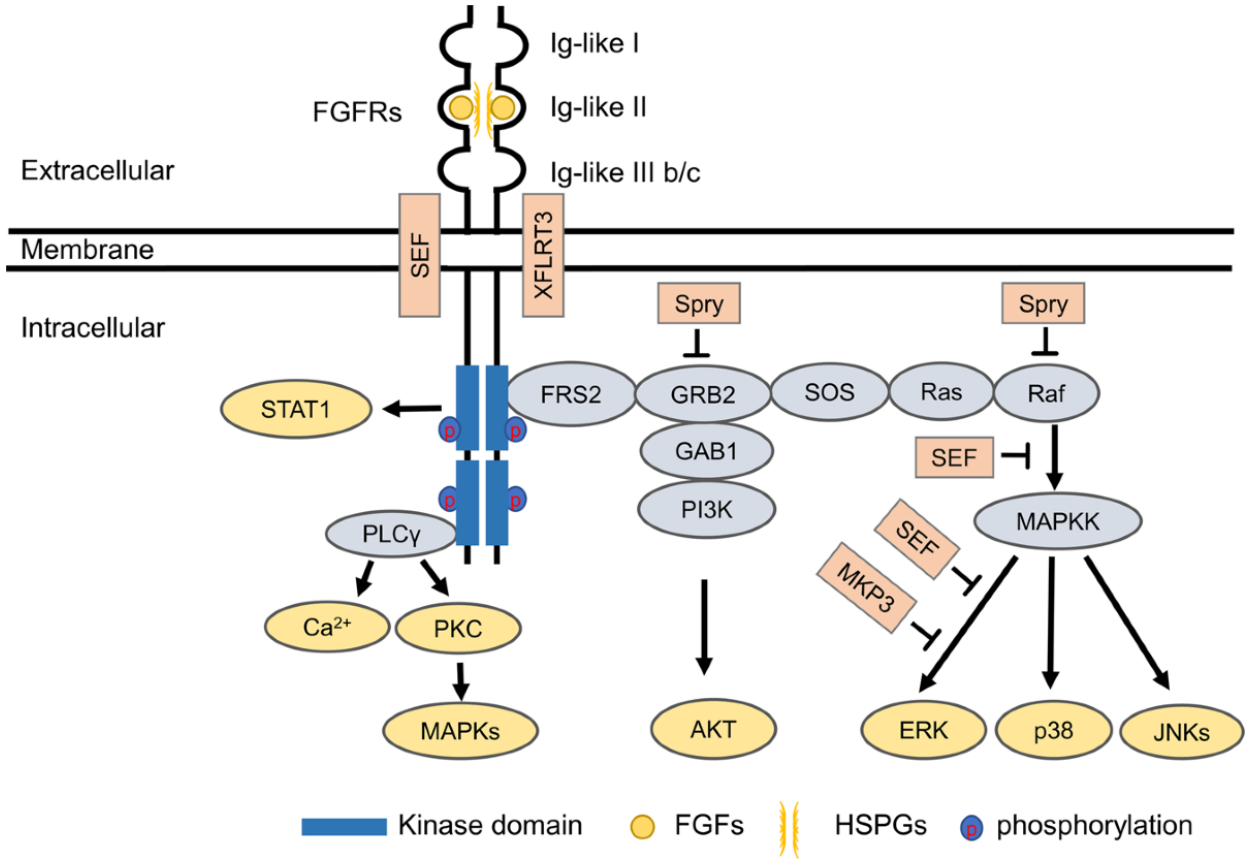
FGFR alterations are ubiquitous in UC

80% of the FGFR alterations in NMIBC and almost half of the alterations in MIBC

FGFR alterations occur in 20% of the patients with advanced urinary bladder UC and up to 37% of the upper tract

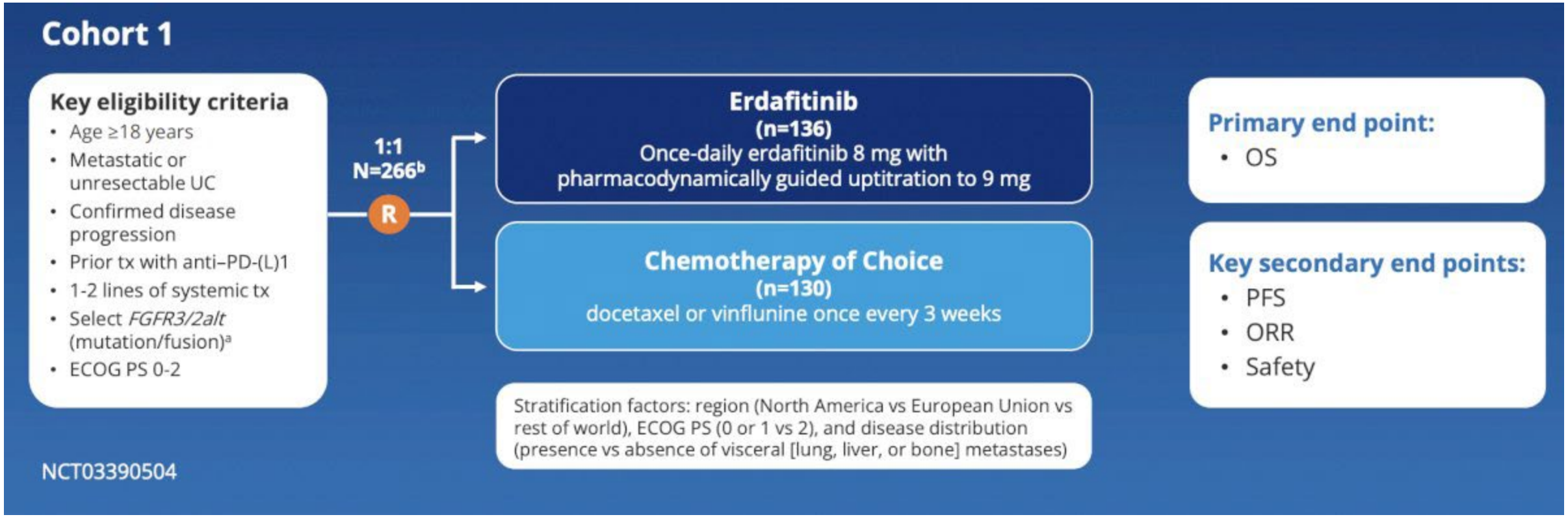
Of the *FGFR3* mutations, **S249C** is the most common, accounting for up to half of these mutations

Mutations in *FGFR*, which belongs to the family of tyrosine kinase receptors, downstream signaling via the *RAS/MAP3K/PI3K* pathway, ultimately leading to cell proliferation

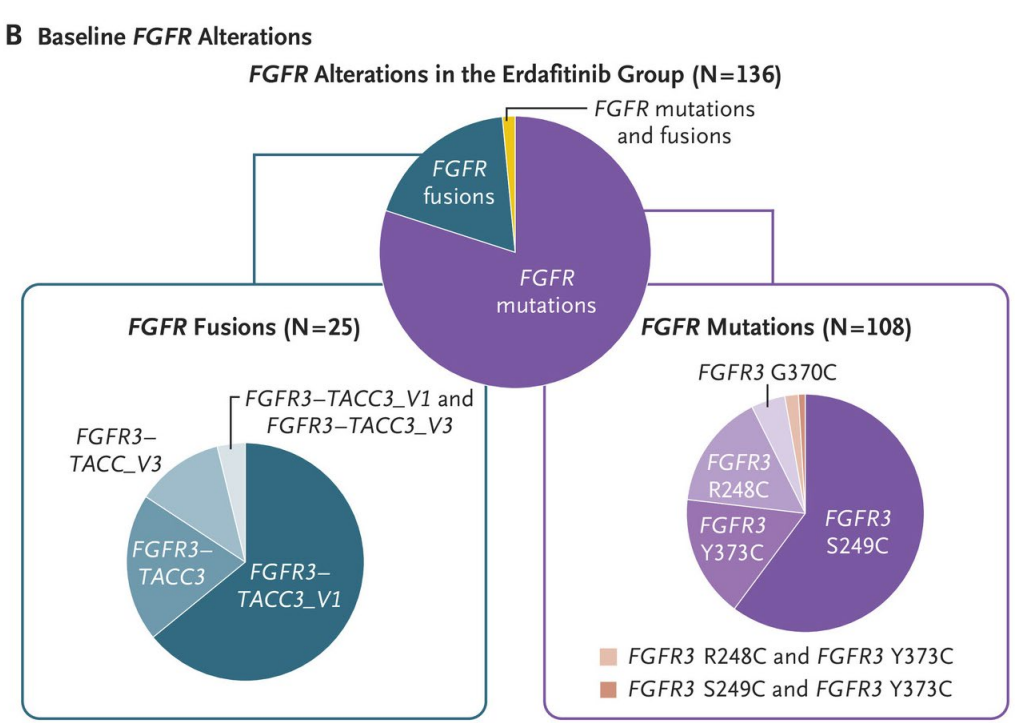


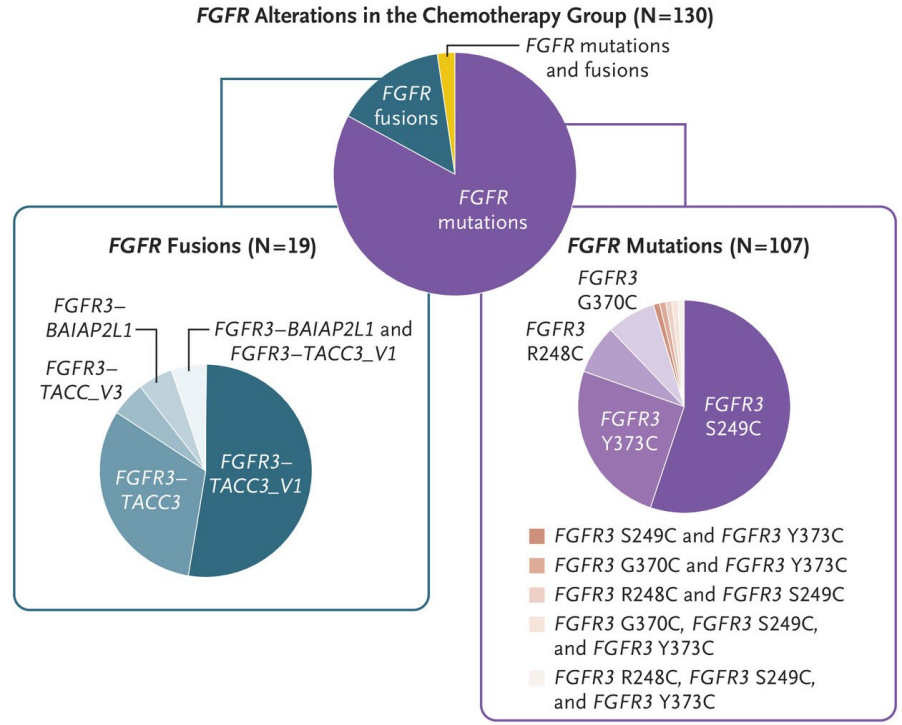
Mohanty SK et al. J Pers Med. 2023 Apr 28;13(5):756

Phase III THOR Study: Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Cancer



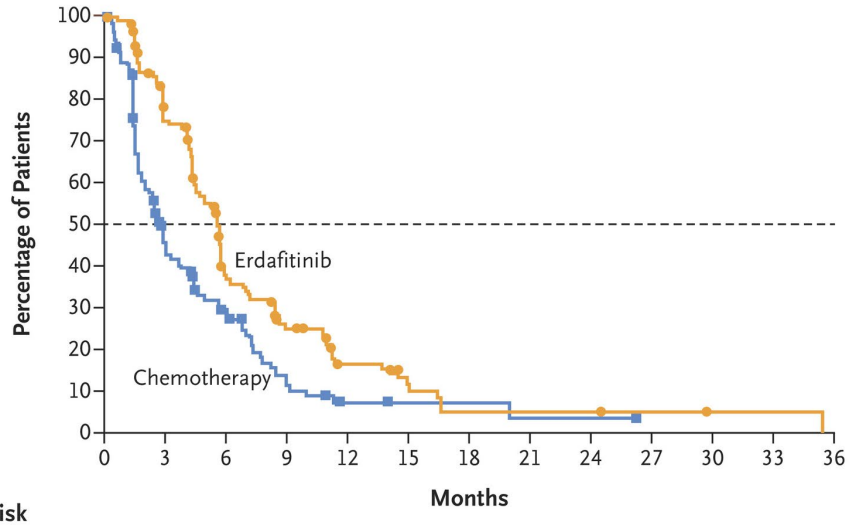
Loriot Y et al. N Engl J Med 2023; 389:1961-1971





Loriot Y et al. N Engl J Med 2023; 389:1961-1971

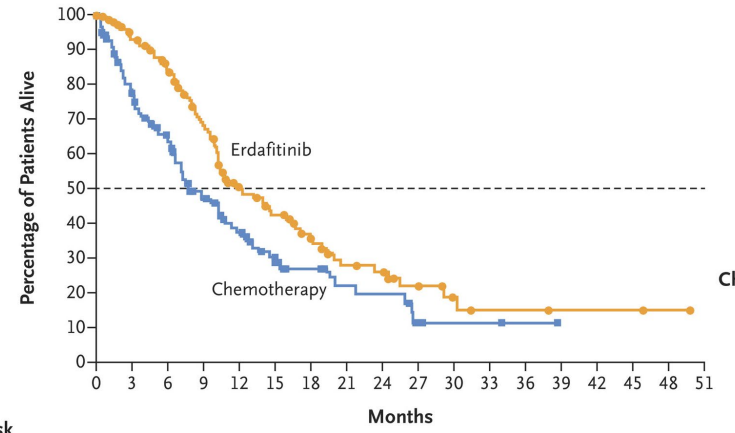
A Progression-free Survival



No. at Risk (no. with censored data)													
Erdafitinib	136	90	39	24	12	7	3	3	3	2	1	1	0
	(0)	(15)	(23)	(26)	(31)	(33)	(33)	(33)	(33)	(34)	(35)	(35)	(35)
Chemotherapy	130	43	23	9	4	2	2	1	1	0	0	0	0
	(0)	(28)	(33)	(35)	(37)	(39)	(39)	(39)	(39)	(40)	(40)	(40)	(40)

	No. of Progressions or Deaths/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Erdafitinib	101/136	5.6 (4.4–5.7)
Chemotherapy	90/130	2.7 (1.8–3.7)

Hazard ratio for disease progression or death, 0.58 (95% CI, 0.44–0.78)
P<0.001

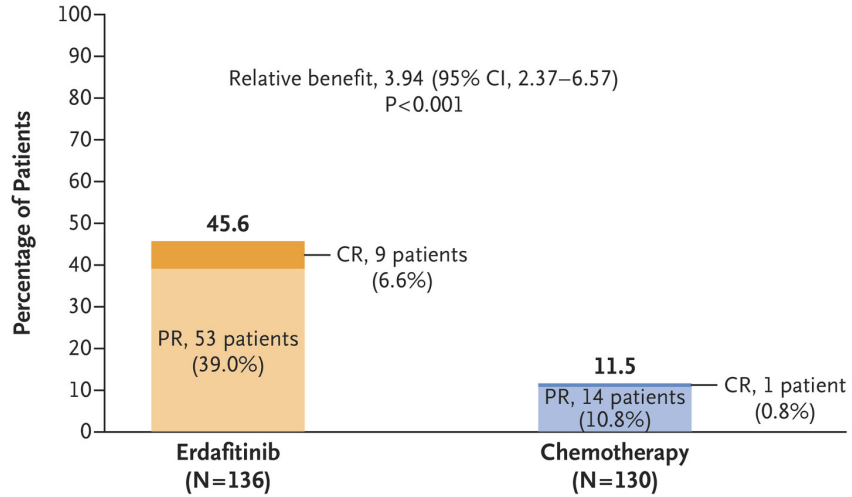


No. at Risk (no. with censored data)																	
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
	(0)	(10)	(20)	(25)	(35)	(39)	(44)	(47)	(48)	(52)	(55)	(56)	(56)	(57)	(57)	(57)	(58)	(59)
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0
	(0)	(17)	(25)	(30)	(35)	(41)	(45)	(47)	(47)	(49)	(50)	(50)	(51)	(52)	(52)	(52)	(52)	(52)

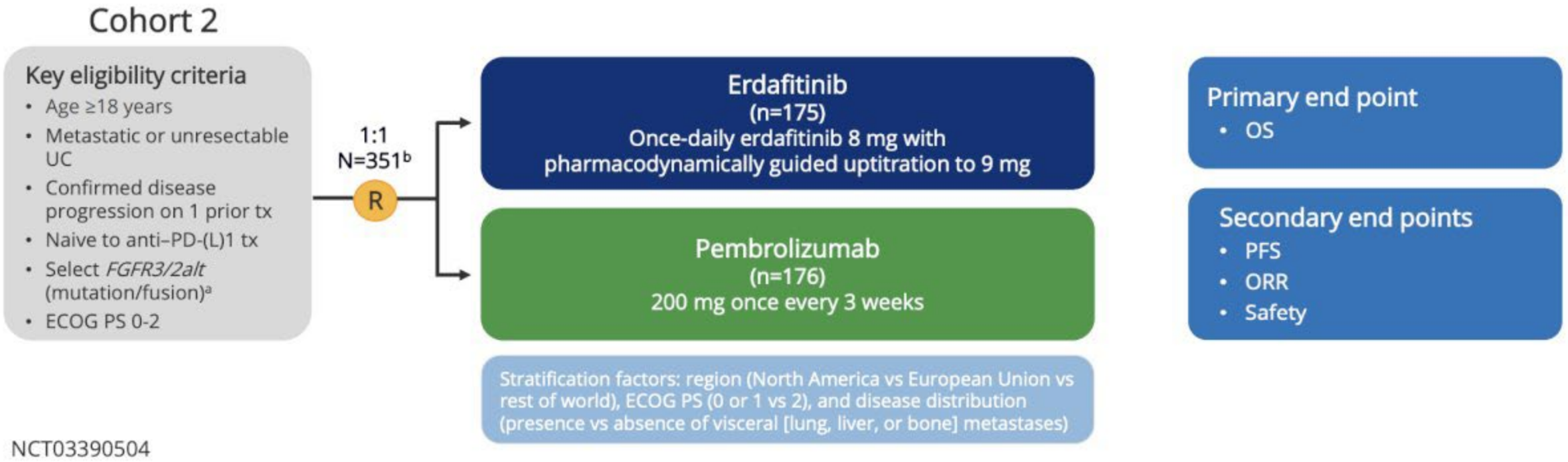
	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Erdafitinib	77/136	12.1 (10.3–16.4)
Chemotherapy	78/130	7.8 (6.5–11.1)

Hazard ratio for death, 0.64 (95% CI, 0.47–0.88)
P=0.005

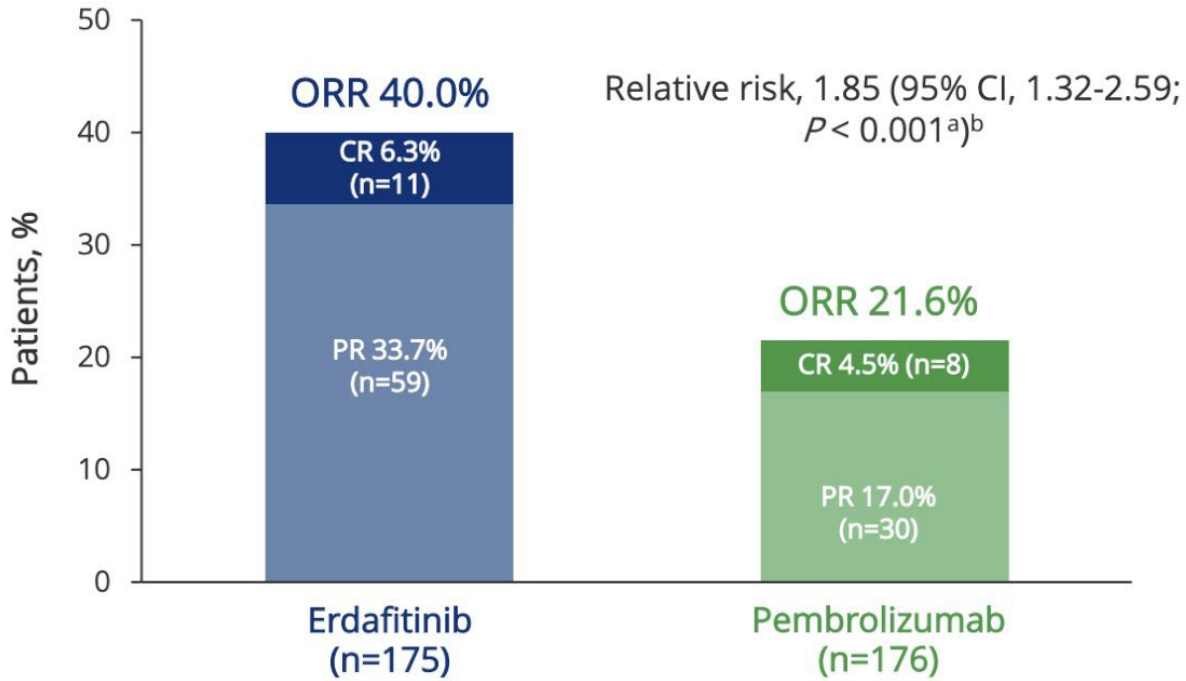
B Objective Response

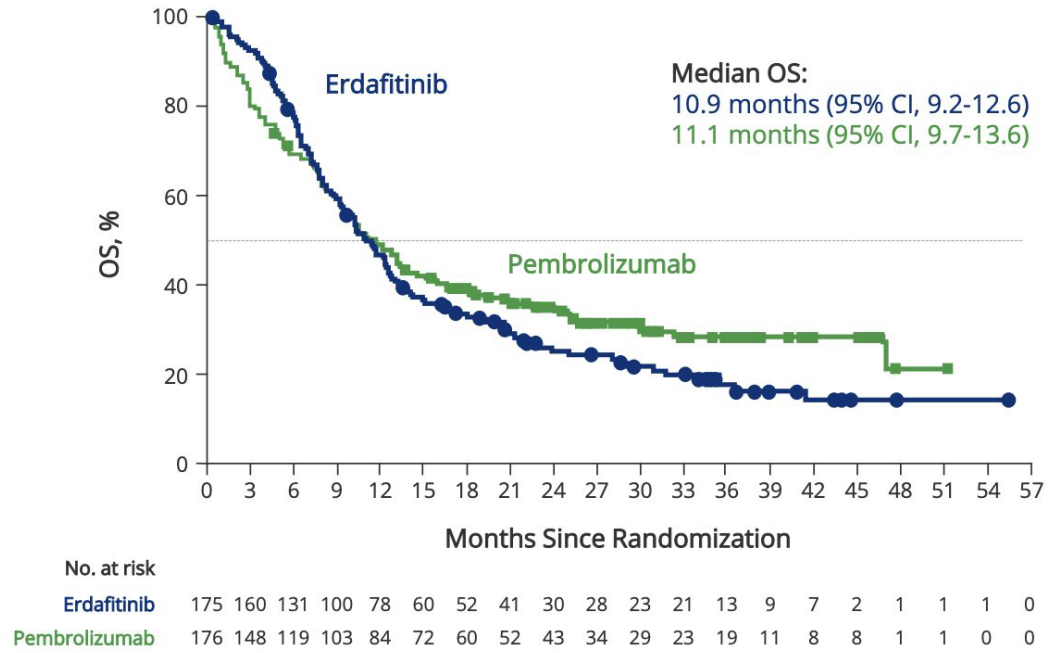


Loriot Y et al. N Engl J Med 2023; 389:1961-1971



Siefker-Radtke et al. Ann Oncol. 2024 Jan; 35(1):107-117





Siefker-Radtke et al. Ann Oncol. 2024 Jan; 35(1):107-117

FDA approves erdafitinib for locally advanced or metastatic urothelial carcinoma

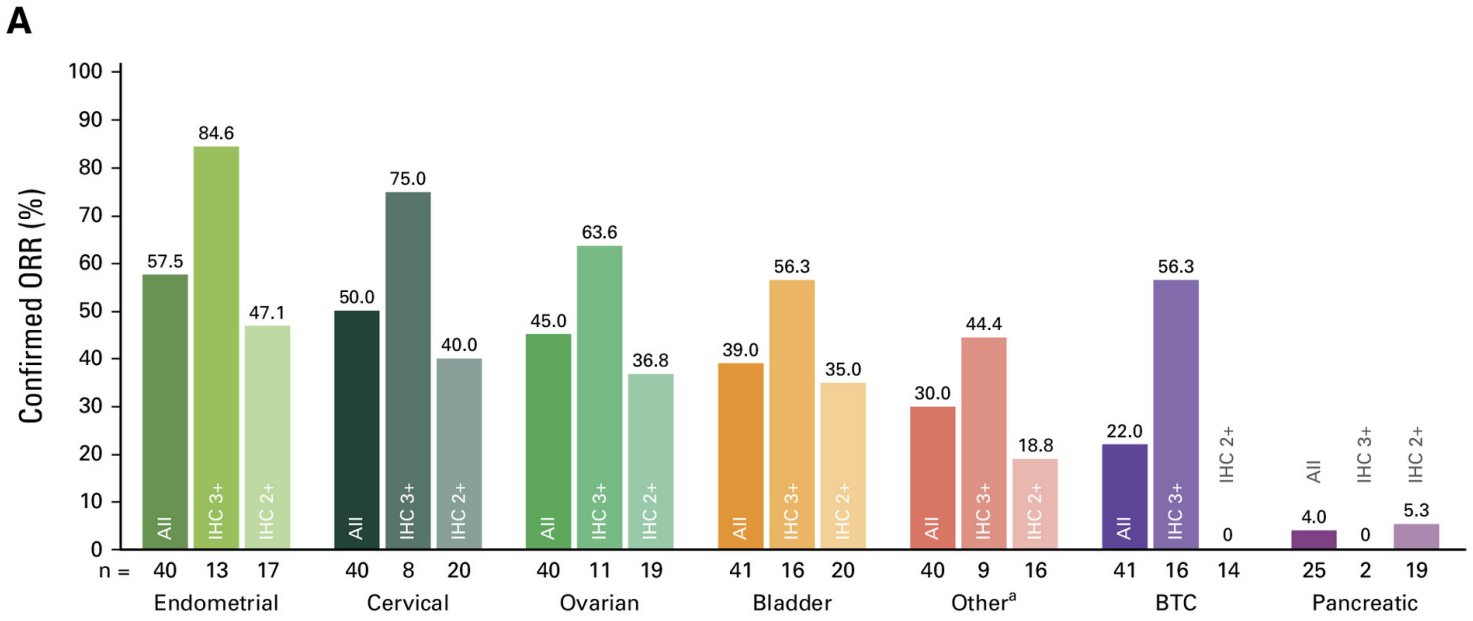
On January 19, 2024, the Food and Drug Administration approved erdafitinib (Balversa, Janssen Biotech) for adult patients with locally advanced or metastatic urothelial carcinoma (mUC) with susceptible FGFR3 genetic alterations, as determined by an FDA-approved companion diagnostic test, whose disease has progressed on or after at least one line of prior systemic therapy. Erdafitinib is not recommended for the treatment of patients who are eligible for and have not received prior PD-1 or PD-L1 inhibitor therapy. This approval amends the indication previously granted under accelerated approval for patients with mUC with susceptible FGFR3 or FGFR2 alterations after prior platinum-containing chemotherapy.

Human epidermal growth factor receptor 2 (HER2)

- Transmembrane tyrosine kinase receptor – cell proliferation, differentiation and survival
- Breast, gastric, biliary tract, bladder, pancreatic and gynecologic tumors
- Biologically aggressive tumor, poor prognosis, risk of disease recurrence
- SOC for unresectable metastatic breast, gastric, GEJ, non-small cell lung cancer

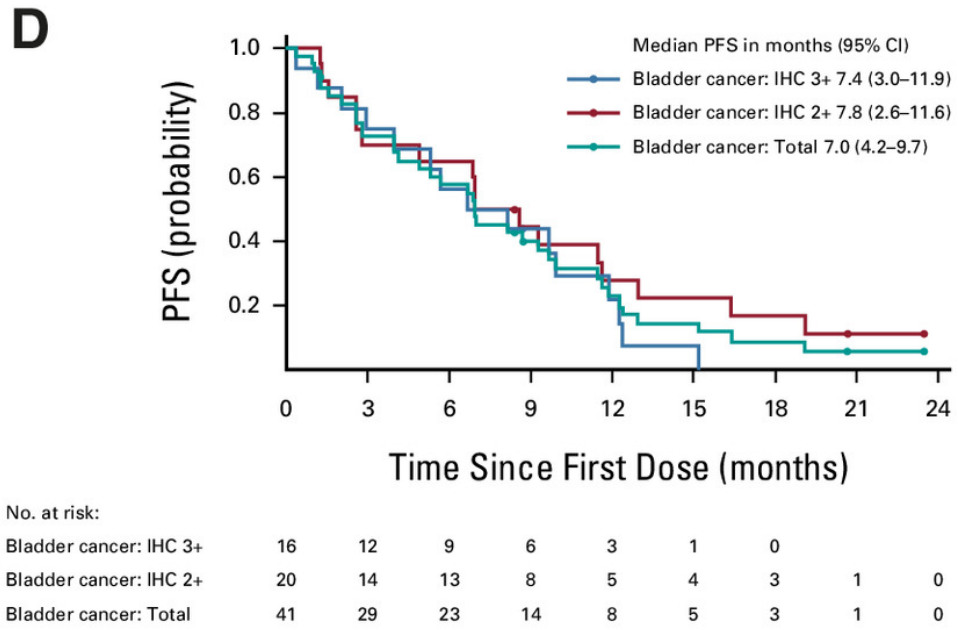
Meric-Bernstam et al. JCO Oct 2023

DESTINY-PanTumor-02

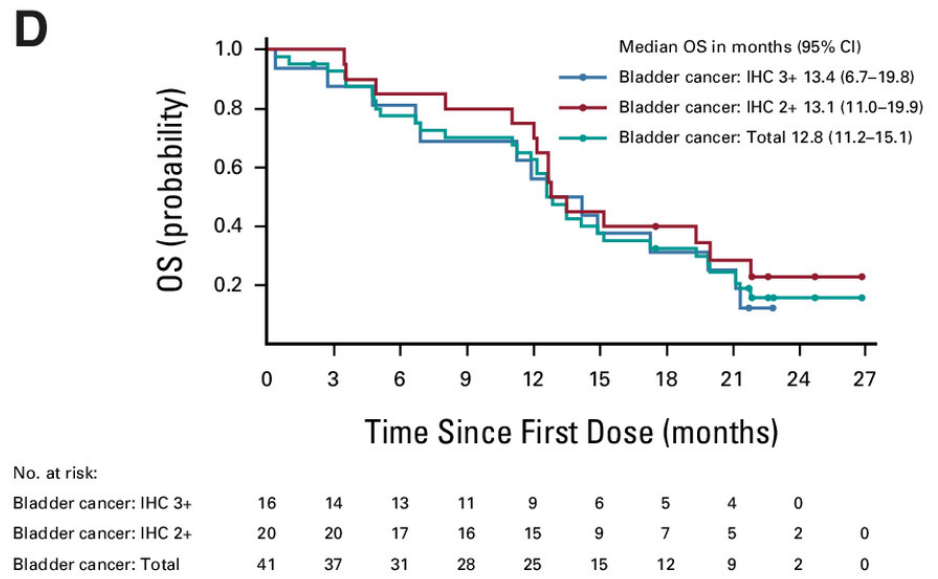


Meric-Bernstam F et al. *J Clin Oncol*. 2023 Oct 23;42(1):47-

DESTINY-PanTumor-02



Kaplan-Meier estimates of PFS, Bladder cancer



Kaplan-Meier estimates of OS; Bladder cancer

Meric-Bernstam F et al. *J Clin Oncol*. 2023 Oct 23;42(1):47-58

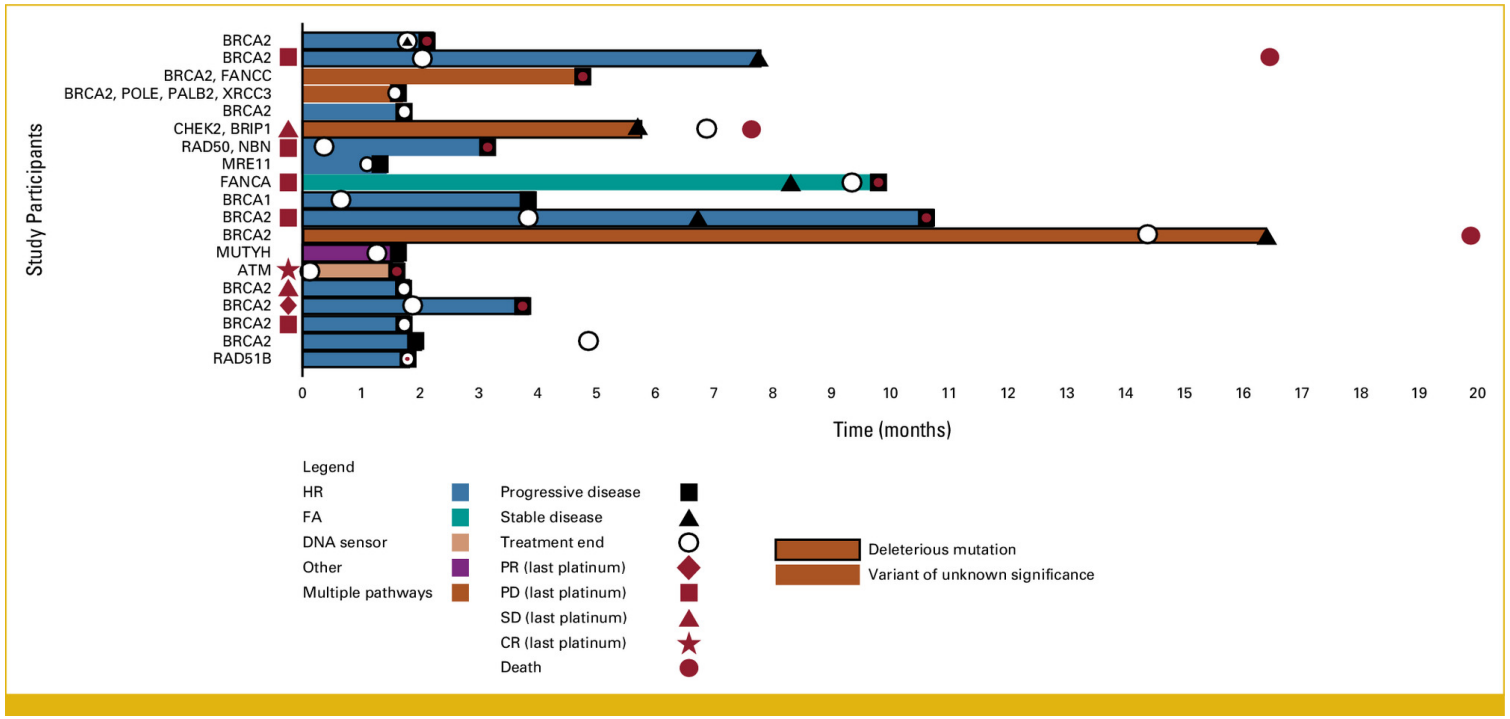
FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Homologous Recombination Repair (HRR)

- 10%-20% of urothelial carcinomas harbor mutations in HRR-related genes
- Somatic mutation (ERCC2) confers platinum sensitivity
- (HR-DDR) genes (*ARID1A, ATM, ATXR, BA1, BARD1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, WRN*)
- Bladder cancer had a 23.9% frequency of mutations in HR-DDR genes.
- *BRCA1* and *BRCA2* mutations >> 2.99% and 4.48% respectively.

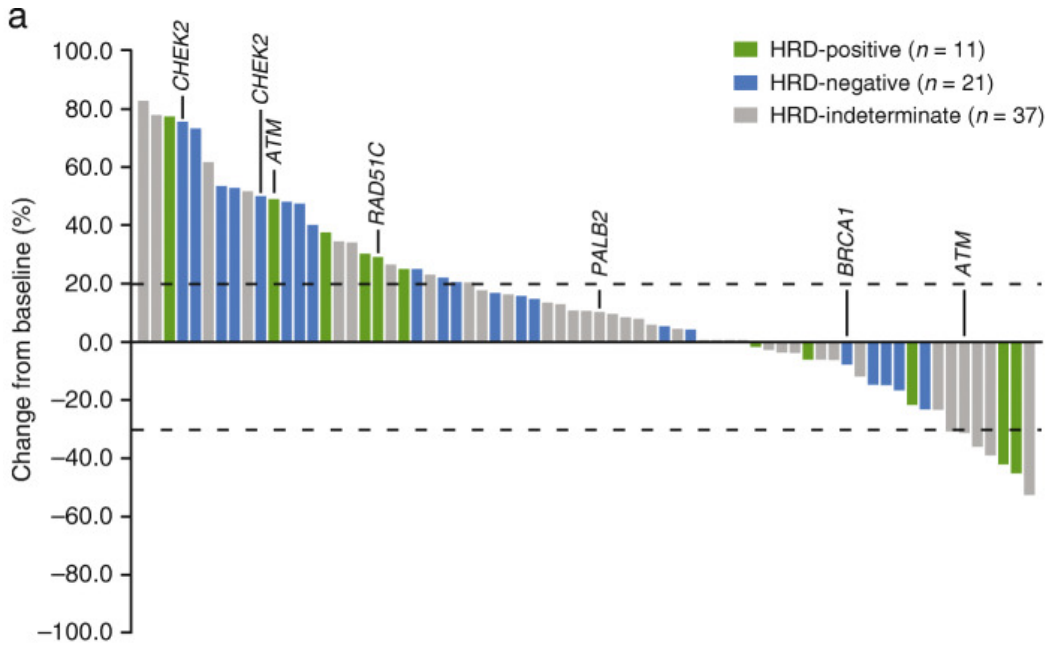
Phase II Trial of Olaparib in Patients With Metastatic Urothelial Cancer Harboring DNA Damage Response Gene Alterations

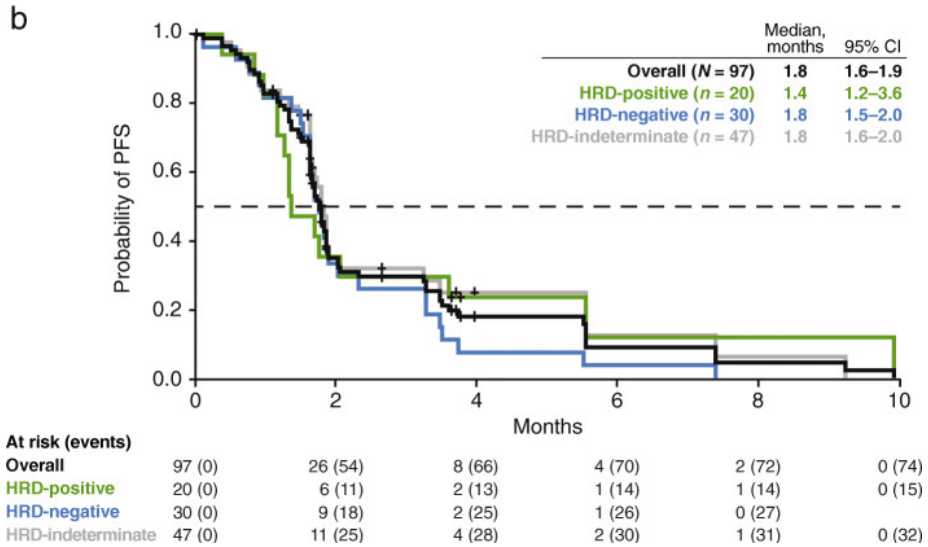


- N=19 with mUC
- Trial closed early before slow accrual
- 47% had previous cisplatin chemo
- 53% had HR gene alterations
- 42% had BRCA2 mutation
- No patients achievedPR
- The median PFS 1.9 months (0.8 – 16.1)
- The median OS 9.5 months (1.5 – 22.1)

Doroshow DB et al. JCO Precision Oncology. July 2023.

Efficacy and safety of rucaparib in previously treated, locally advanced or metastatic urothelial carcinoma from a phase 2, open-label trial (ATLAS)



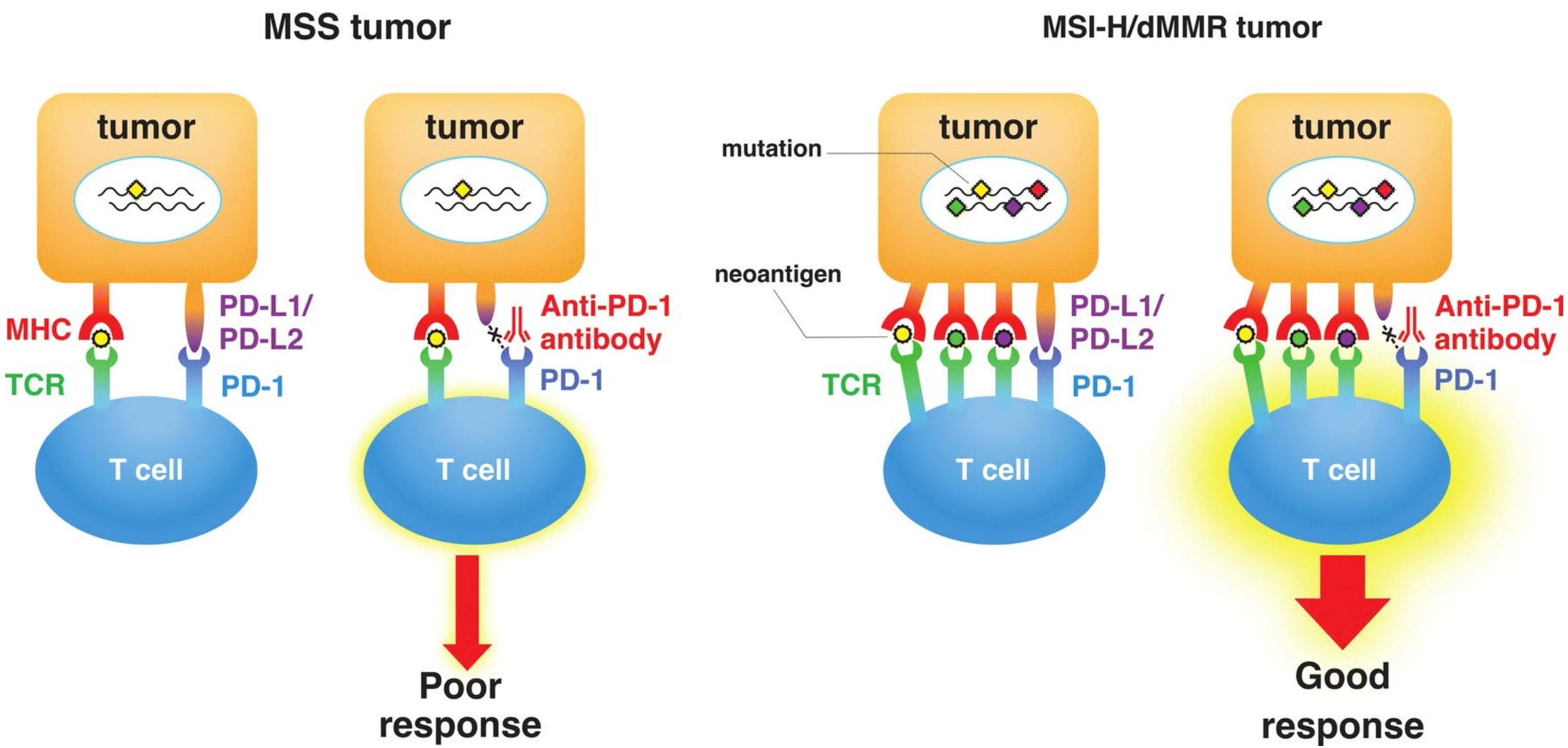


Grivas P et al. *BMC Cancer*. 2021 May 24;21:593.

The Meet-URO12 Randomized Phase 2 Trial

- To compare maintenance treatment with the PARP inhibitor niraparib plus best supportive care (BSC) versus BSC alone in patients with advanced UC without disease progression after first-line PBCT.
- Randomized (2:1) to experimental arm A (niraparib 300 or 200 mg or control arm B (BSC alone).
- The primary endpoint was progression-free survival (PFS)
- Fifty-eight patients were randomized (39 in arm A and 19 in arm B)
- The median PFS was 2.1 mo in arm A and 2.4 mo in arm B (hazard ratio 0.92; 95% confidence interval 0.49-1.75, p = 0.81)
- The 6-mo progression-free rates were 28.2% and 26.3%, respectively
- Addition of maintenance niraparib to BSC after first-line PBCT did not demonstrate a significant improvement in PFS in patients with UC.

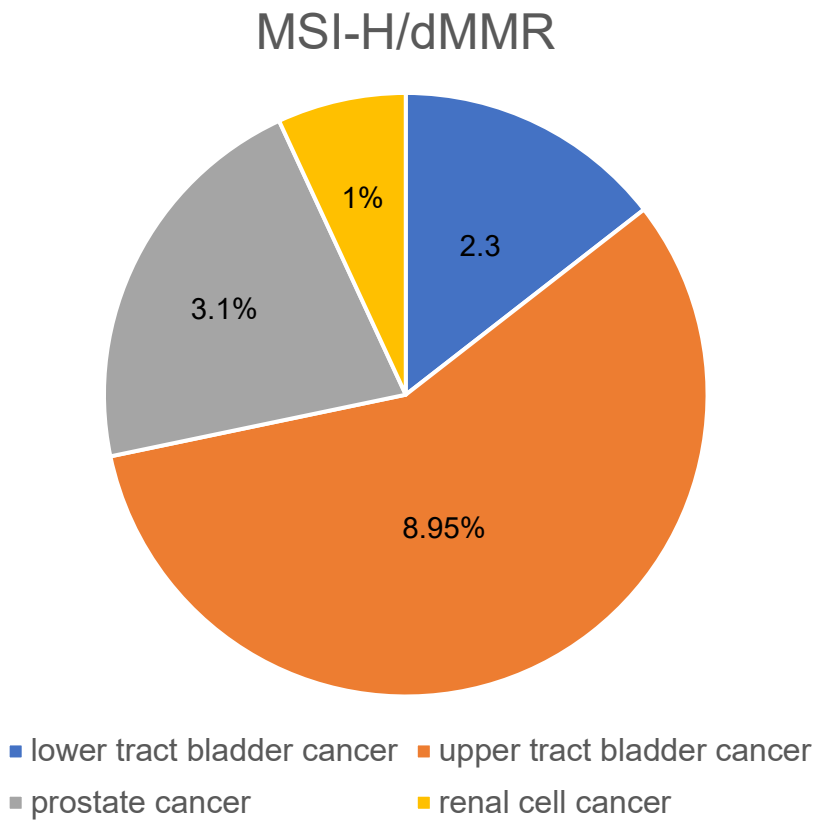
Vignani F et al. *Eur Urol*. 2023 Jan;83(1):82-89.



Eso Y et al. Journal of Gastroenterology, volume 55, pages 15-26, (202

Prevalence of dMMR/MSI/TMB-H in GU tumors

Tumor type	TMB high	MSI
Colorectal cancer (151)	23 (15.2%)	4 (2.6%)
Gastric cancer (116)	13 (11.2%)	1 (0.9%)
Sarcoma (60)	1 (1.7%)	0 (0%)
Biliary tract cancer (48)	7 (14.6%)	1 (2.1%)
Pancreatic cancer (42)	0 (0%)	0 (0%)
Genitourinary cancer (25)	9 (36.0%)	1 (4.0%)
Other GI tract cancer[a] (22)	1 (4.5%)	0 (0%)
Melanoma (21)	3 (14.3%)	0 (0%)
Hepatocellular carcinoma (12)	1 (8.3%)	0 (0%)
Rare cancers[b] (4)	0 (0%)	0 (0%)
Total 501	58 (11.6%)	7 (1.4%)



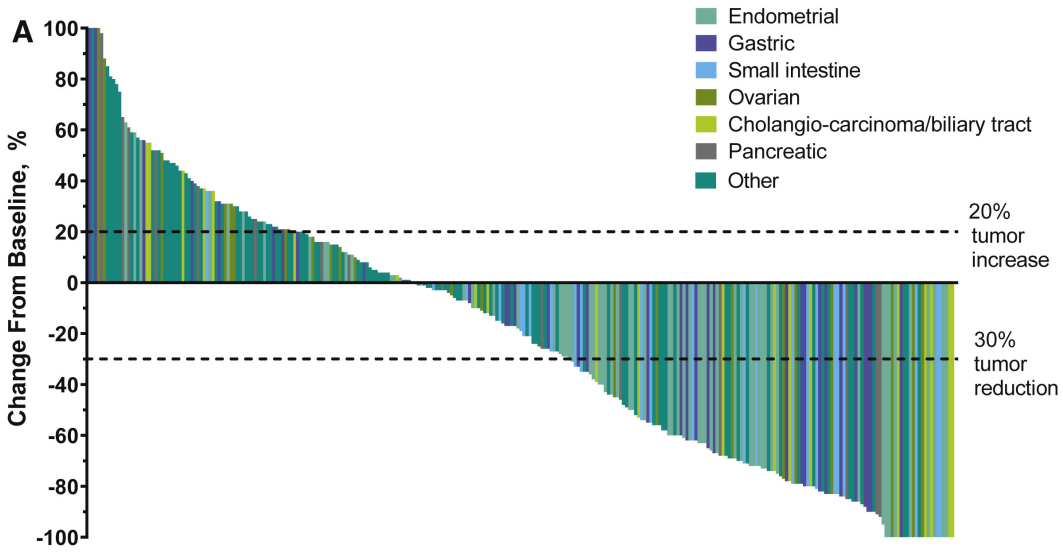
Chandran EBA et al. BMJ Oncology. 2024;3:e000335. Abida W et al. *JAMA Oncol.* 2019;5(4):471–478

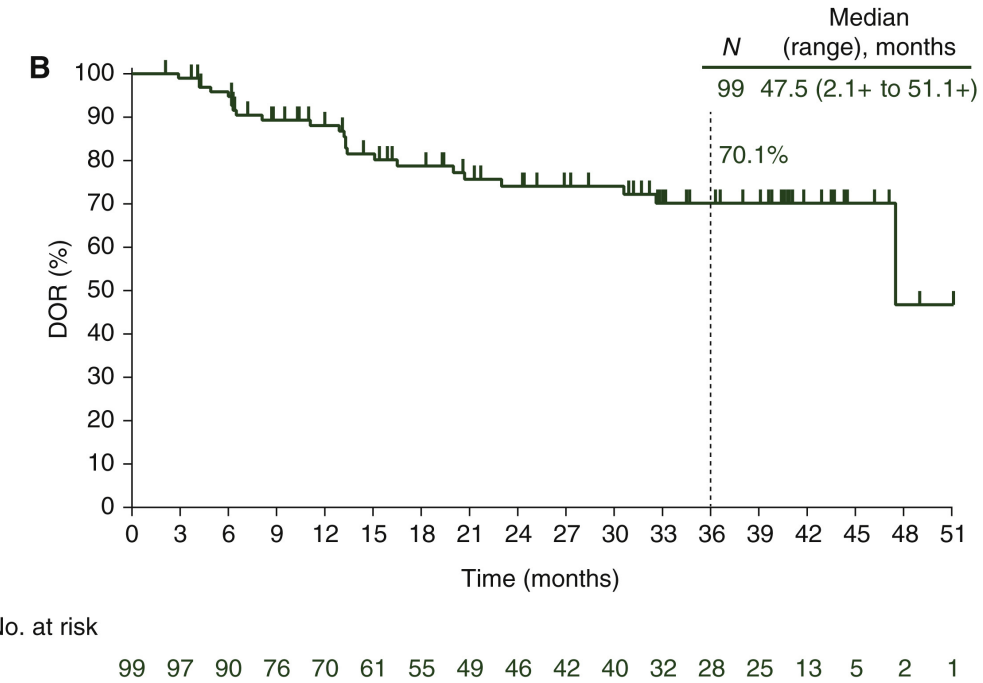
AUA Guidelines 2023

7. For patients with suspected/ diagnosed UTUC, clinicians should obtain a personal and family history to identify known hereditary risk factors for familial diseases associated with Lynch Syndrome (LS) (colorectal, ovarian, endometrial, gastric, biliary, small bowel, pancreatic, prostate, skin and brain cancer) for which referral for genetic counseling should be offered. *(Expert Opinion)*

8. Universal histologic testing of UTUC with additional studies, such as immunohistochemical (IHC) or microsatellite instability (MSI), should be performed to identify patients with high probability of Lynch-related cancers whom clinicians should refer for genetic counseling and germline testing. *(Strong Recommendation; Evidence Level: Grade B)*

KEYNOTE-158





Best objective response, *n* (%)	
CR	27 (8.4)
PR	72 (22.4)
SD	61 (19.0)
PD	131 (40.8)
Not evaluable	3 (0.9)
No assessment[b]	27 (8.4)
Time to response, median (range), months	2.1 (1.3-12.9)

Maio M et al. Annals of oncology Volume 33, Issue 9, Sep 2022

	Endometrial *n* = 68	Gastric *n* = 42	Small intestine *n* = 25	Ovarian *n* = 24	Cholangiocarcinoma/biliary tract *n* = 22	Pancreatic *n* = 22
ORR, % (95% CI)	48.5 (36.2-61.0)	31.0 (17.6-47.1)	48.0 (27.8-68.7)	33.3 (15.6-55.3)	40.9 (20.7-63.6)	18.2 (5.2-40.3)
Best objective response, *n* (%)						
CR	10 (14.7)	4 (9.5)	4 (16.0)	3 (12.5)	3 (13.6)	1 (4.5)
PR	23 (33.8)	9 (21.4)	8 (32.0)	5 (20.8)	6 (27.3)	3 (13.6)
SD	13 (19.1)	7 (16.7)	7 (28.0)	2 (8.3)	3 (13.6)	3 (13.6)
PD	19 (27.9)	15 (35.7)	5 (20.0)	12 (50.0)	8 (36.4)	8 (36.4)

Maio M et al. Annals of oncology Volume 33, Issue 9, Sep 2022

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

FDA approves pembrolizumab for adults and children with TMB-H solid tumors

On June 16, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by a test, that have progressed following prior treatment and who have no s alternative treatment options.

Today, the FDA also approved the FoundationOneCDx assay (Founda Inc.) as a companion diagnostic for pembrolizumab.

FDA Grants Full Approval to Pembrolizumab for Certain Adult and Pediatric Patients With Advanced MSI-H or dMMR Solid Tumors

Case

51 yr old M with history of prostate cancer in 2020 s/p surgery with Gleason 4+5=9, pT3b pN0. Six months after surgery, met to pelvic nodes. Started him on Lupron and enzalutamide. PSA became undetectable.

NGS >> Mismatch repair deficient, **MSI high and TMB 23 mut/Mb**. Germline positive.

Sep 2023: surveillance CT scan showed a partially calcified polypoid filling defect within the left renal collectin system measuring 1.4 cm x 0.7 cm

underwent left ureteroscopy and biopsy. Path confirmed high grade papillary urothelial carcinoma

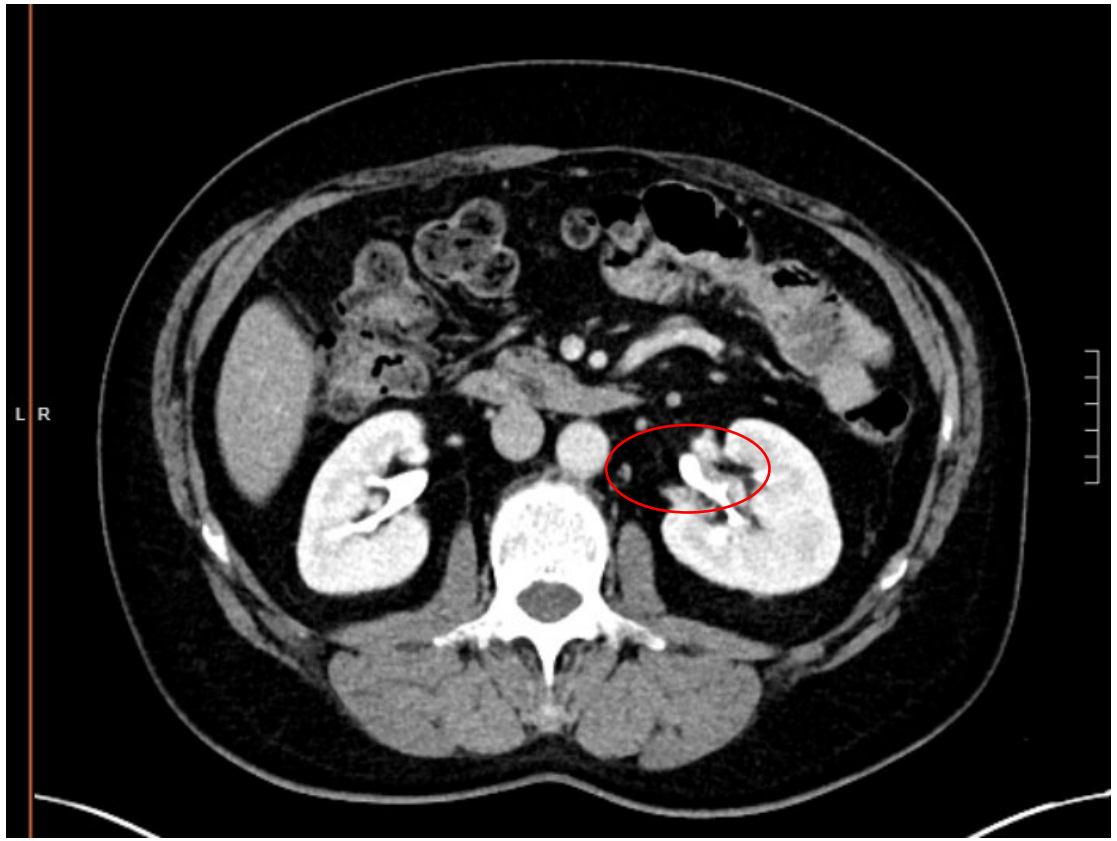
Pembrolizumab was given for one year

underwent left ureteroscopy with biopsy >> normal without concerning masses or lesions

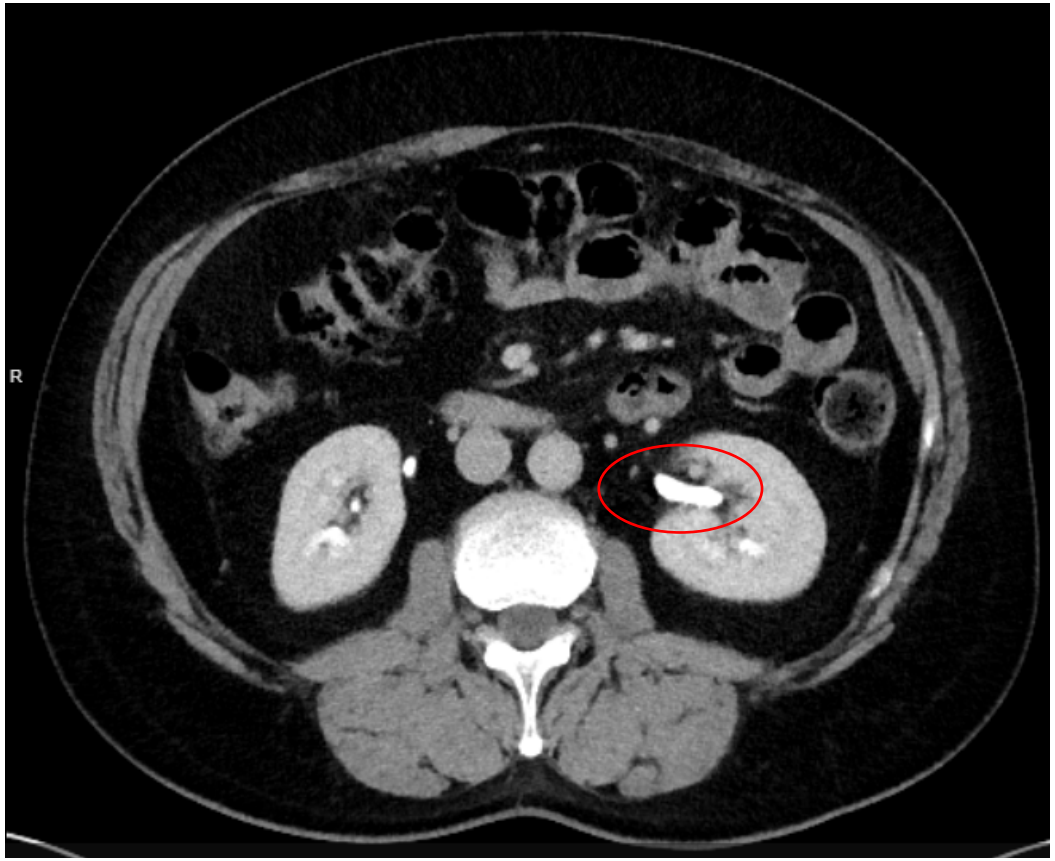
CT scan >> complete remission

ctDNA was negative

Before Immunotherapy

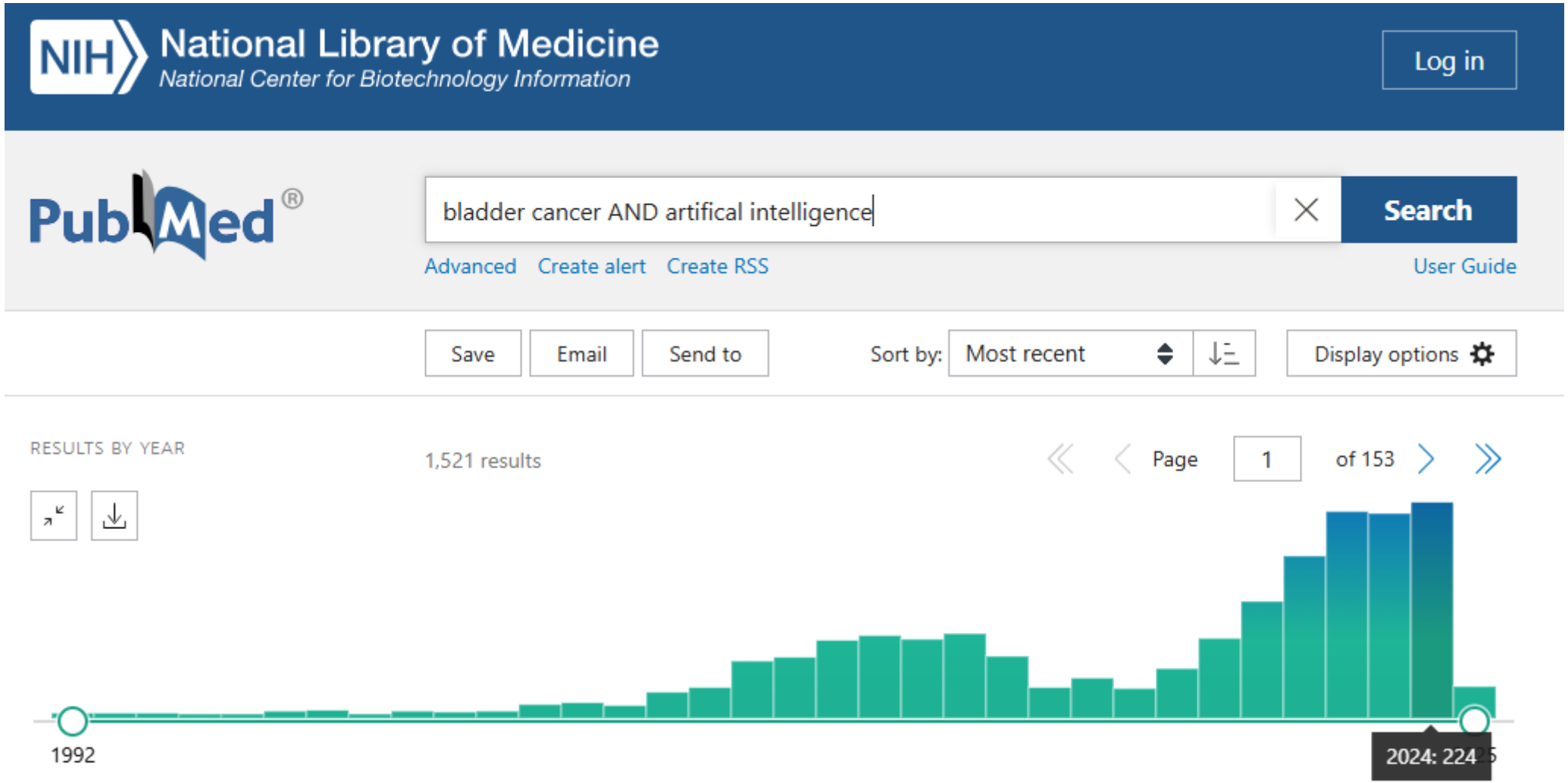


After Immunotherapy



Neoadjuvant PD-1 Blockade in Mismatch Repair-Deficient, Localized High-grade Urothelial Carcinoma

Artificial Intelligence Histopathology in Bladder Cancer



Markey Cancer Center

USE OF AI IN BLADDER CANCER

Detection

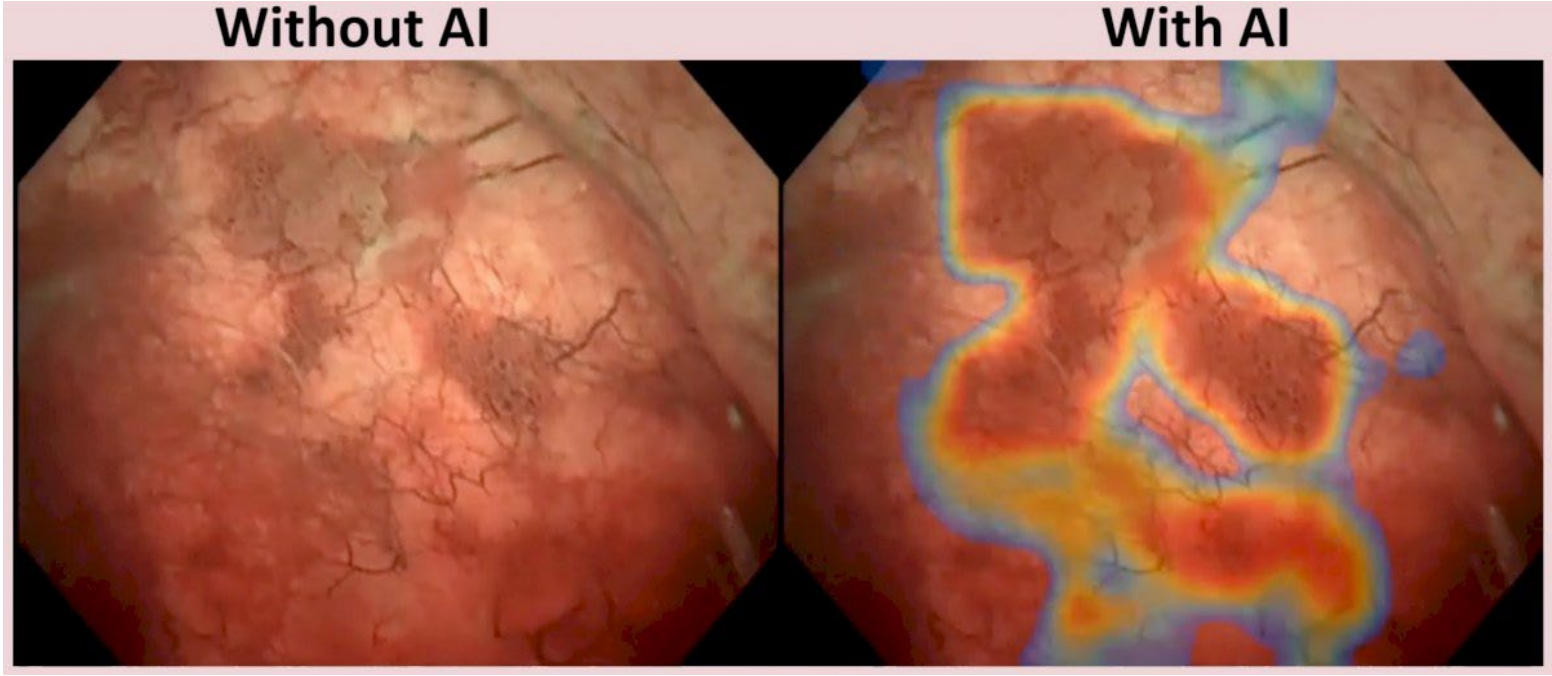
- Cystoscopy
- Imaging (CT, MRI, US)

Diagnosis

- Histopathology & cytology
- Molecular biomarkers

Outcomes Prediction

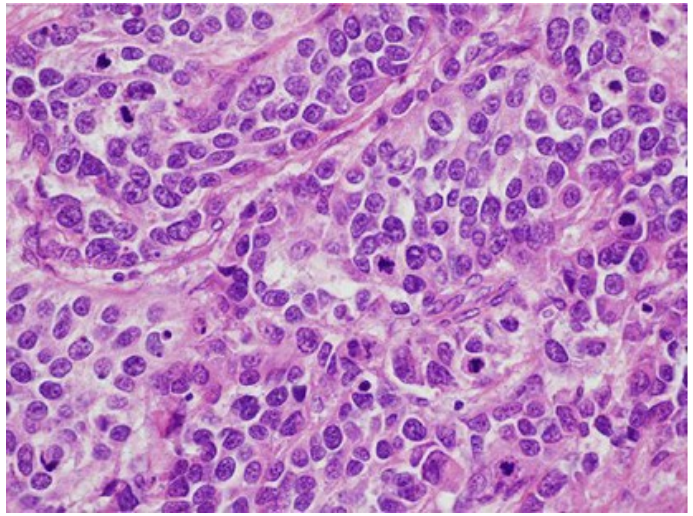
- Post-operative morbidity/mortality

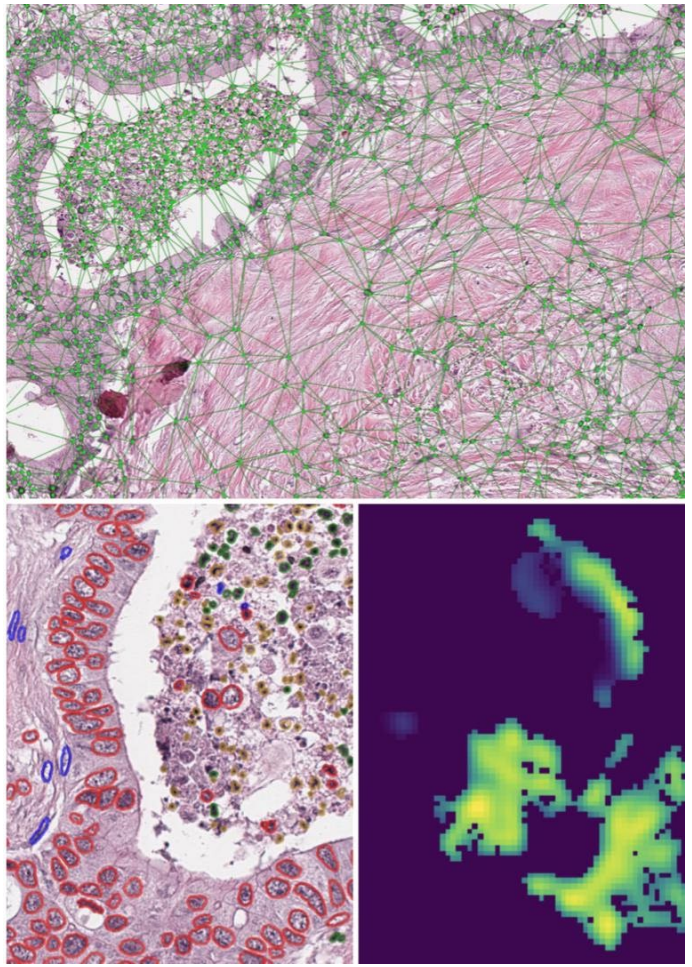


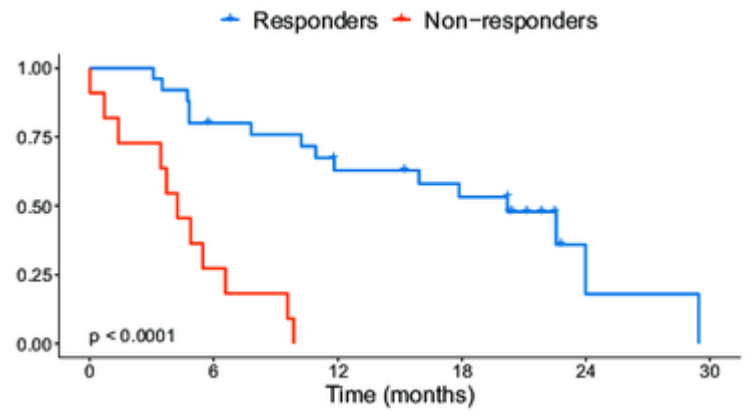
GOAL: risk-stratification, optimizing patient selection for effective agents, minimize morbidity

Ikeda EAU 2023; Laurie 2023

AI Histopathology: How it Works



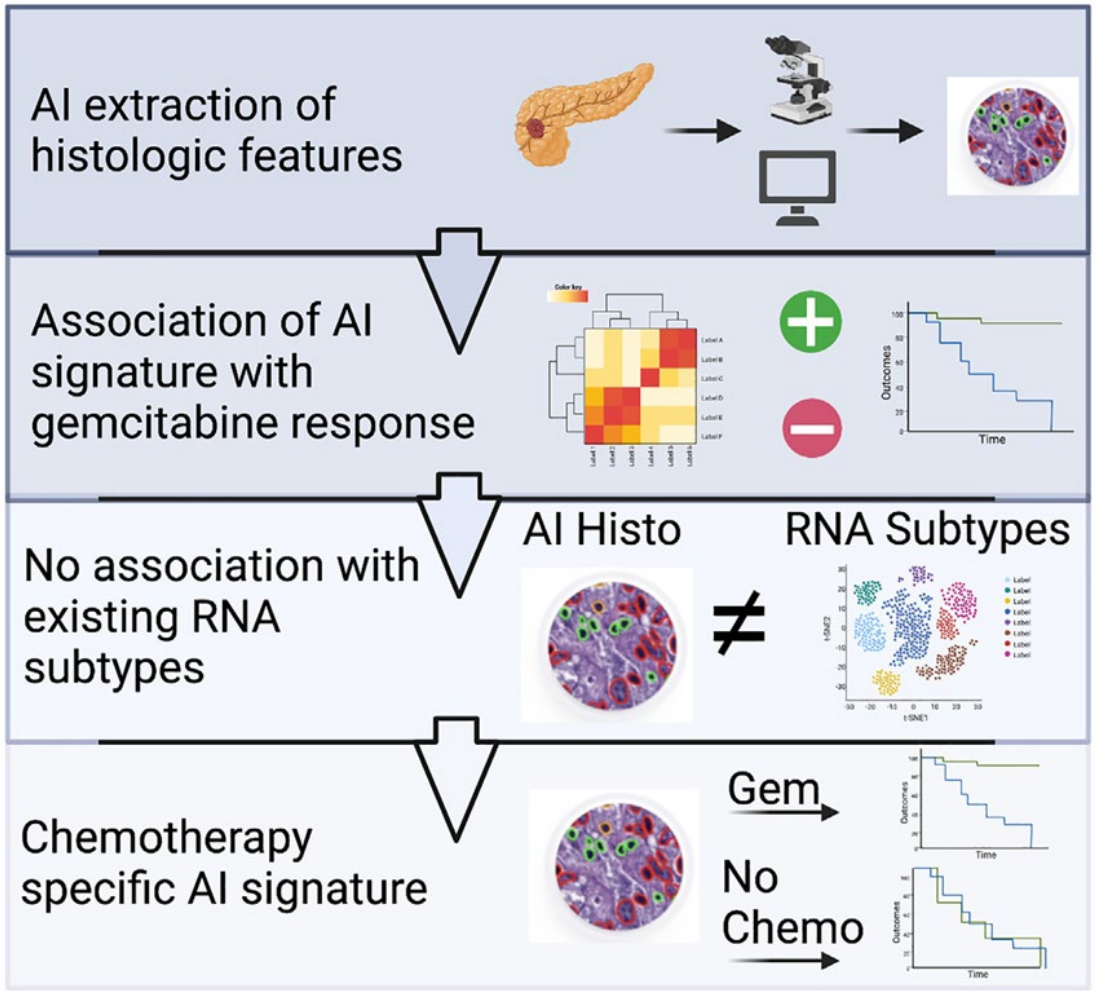




Development of an artificial intelligence-derived histologic signature associated with adjuvant gemcitabine treatment outcomes in pancreatic cancer

Proof of Concept- Pancreatic Cancer

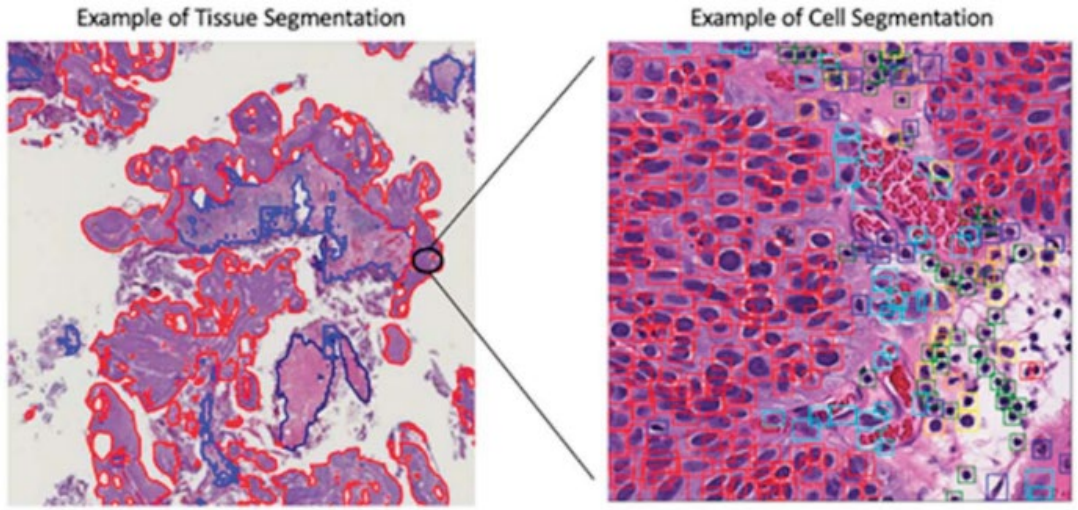
- Pancreatic cancer lacks actionable biomarkers for precision therapy
- Evaluated AI-path vs. RNA-based subtypes to predict response to AC in PDAC:
  - Training set + external validation of AI-path signature
  - AI-path outperformed 3 established RNA subtypes
  - Not prognostic in an untreated cohort

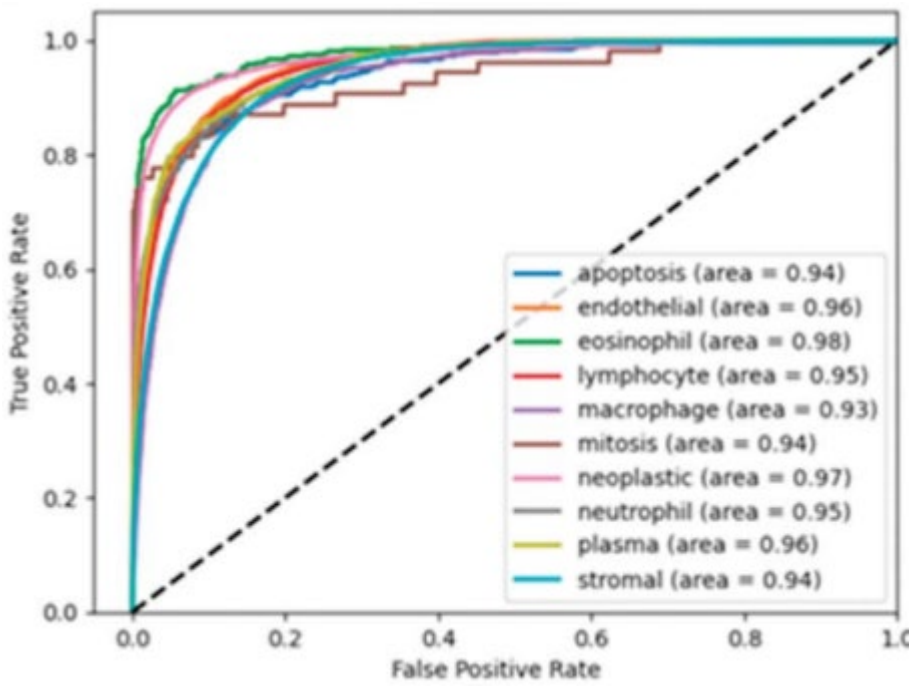


Markey Cancer Center

Nimgaonkar 2023

Predicting Response to Intravesical Bacillus Calmette-Guerin in HR-NMIBC Using an Artificial Intelligence–Powered Pathology Assay: Development and Validation in an International Cohort



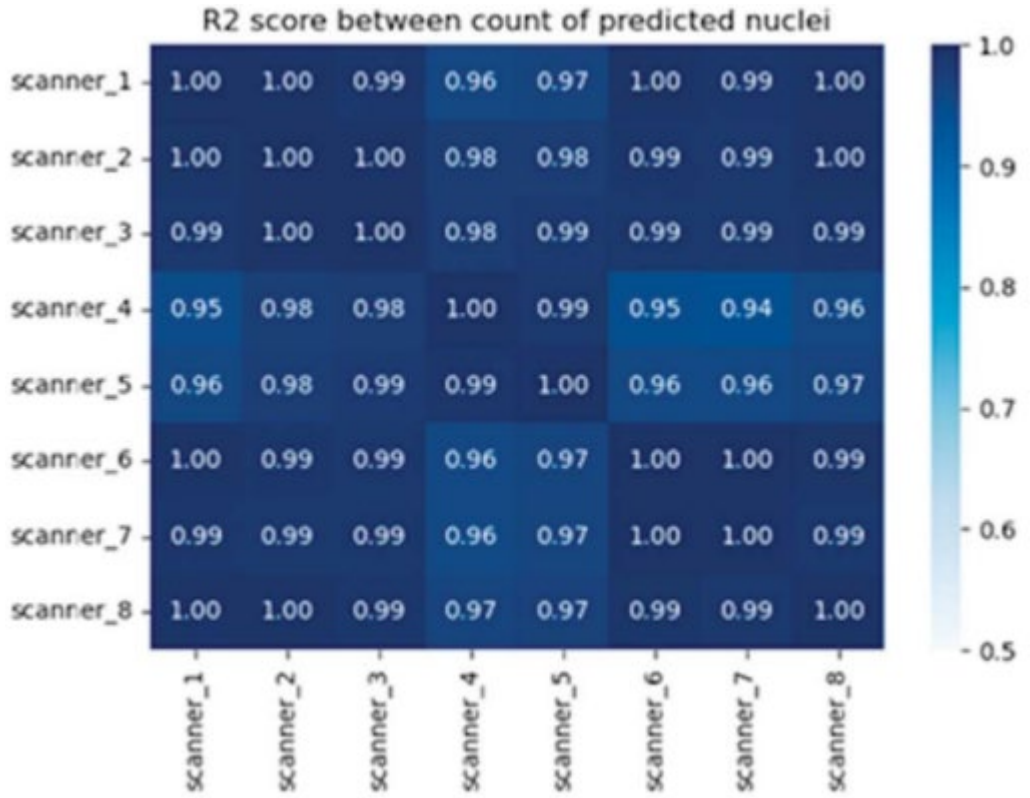


Computational Histology AI (CHAI) accurately identifies specific cell/tissue types

Markey Cancer Center

Lotan et al., J Urol 2024

Predicting Response to Intravesical Bacillus Calmette-Guerin in HR-NMIBC Using an Artificial Intelligence–Powered Pathology Assay: Development and Validation in an International Cohort

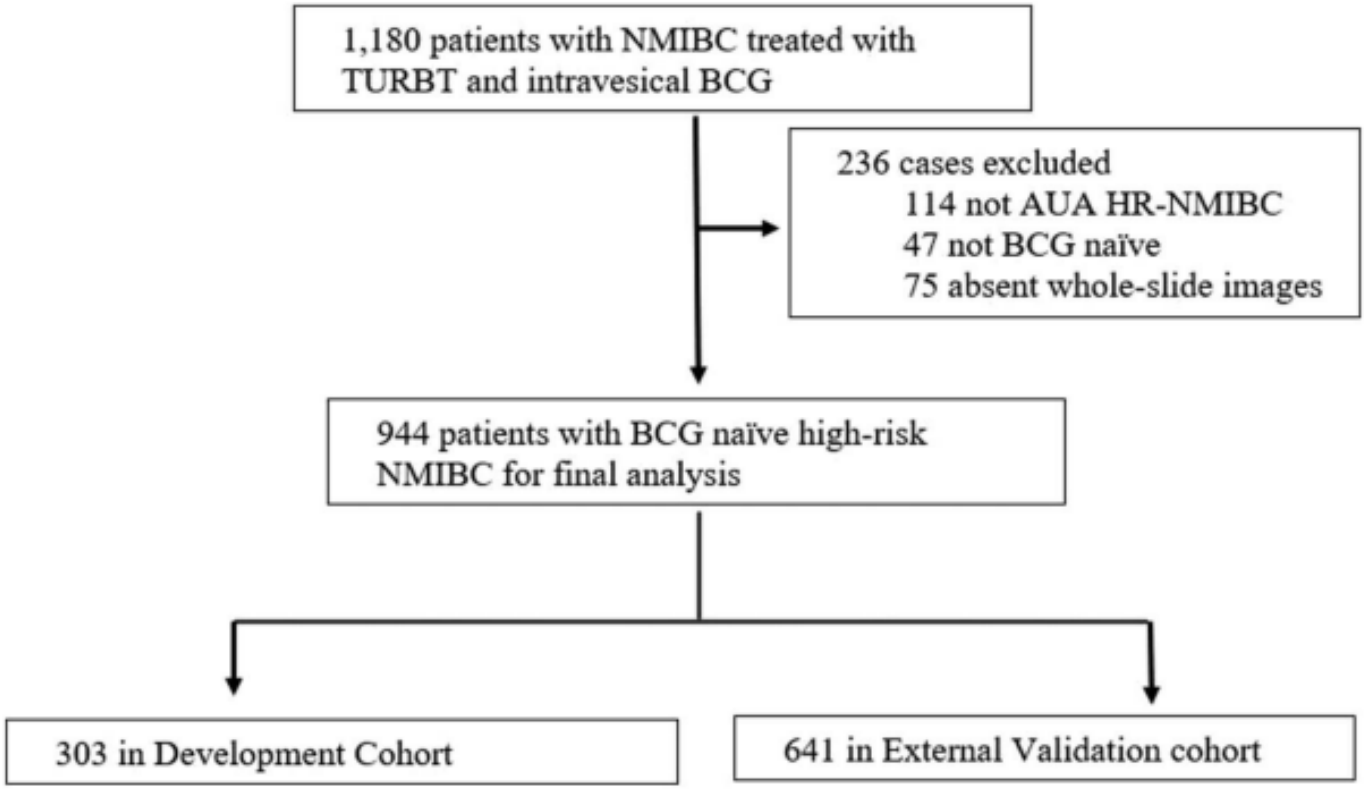


Cell/tissue segmentation agnostic to slide scanner (8 models)

Markey Cancer Center

Lotan et al., J Urol 2024

Predicting Response to Intravesical Bacillus Calmette-Guerin in HR-NMIBC Using an Artificial Intelligence–Powered Pathology Assay: Development and Validation in an International Cohort



Markey Cancer Center

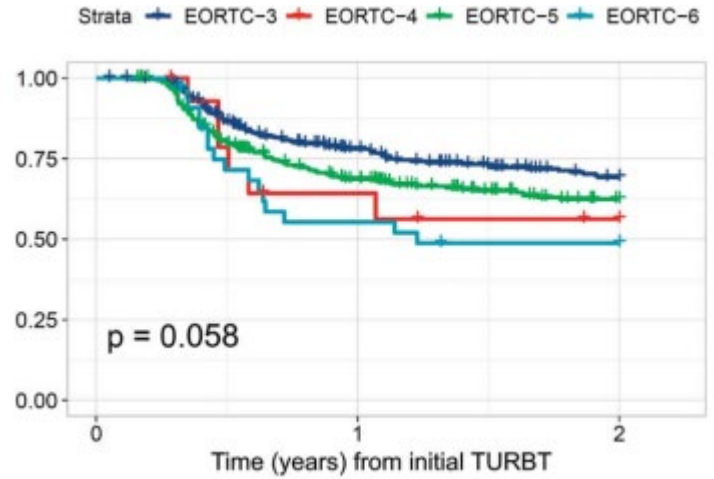
Lotan et al., J Urol 2024

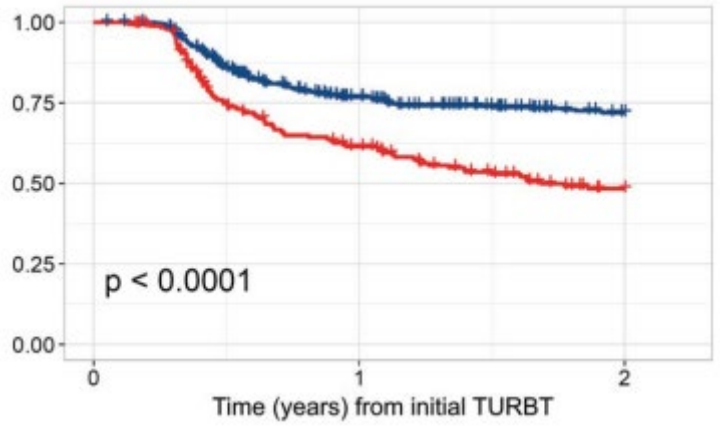
Predicting Response to Intravesical Bacillus Calmette-Guerin in HR-NMIBC Using an Artificial Intelligence–Powered Pathology Assay: Development and Validation in an International Cohort

EORTC Risk Strata

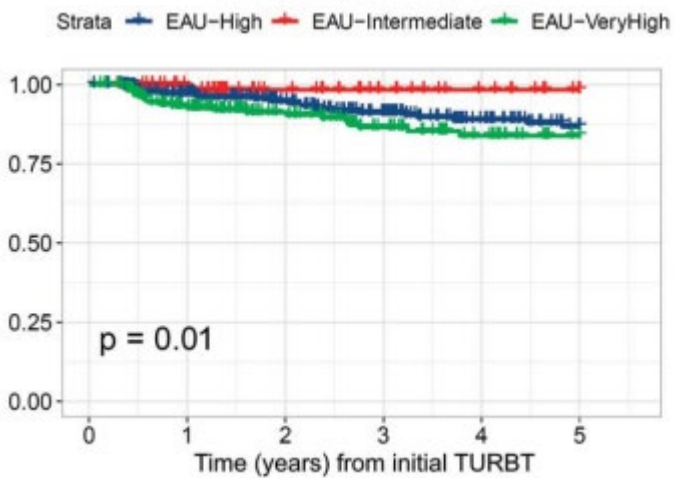
CHAI Risk Strata

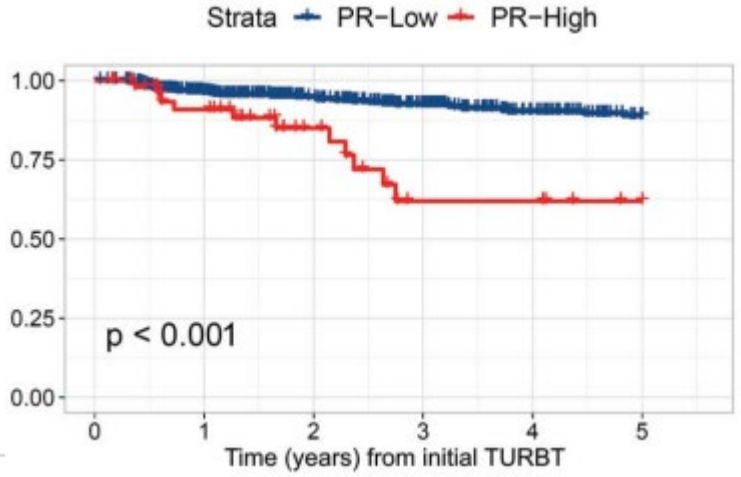
hgRFS

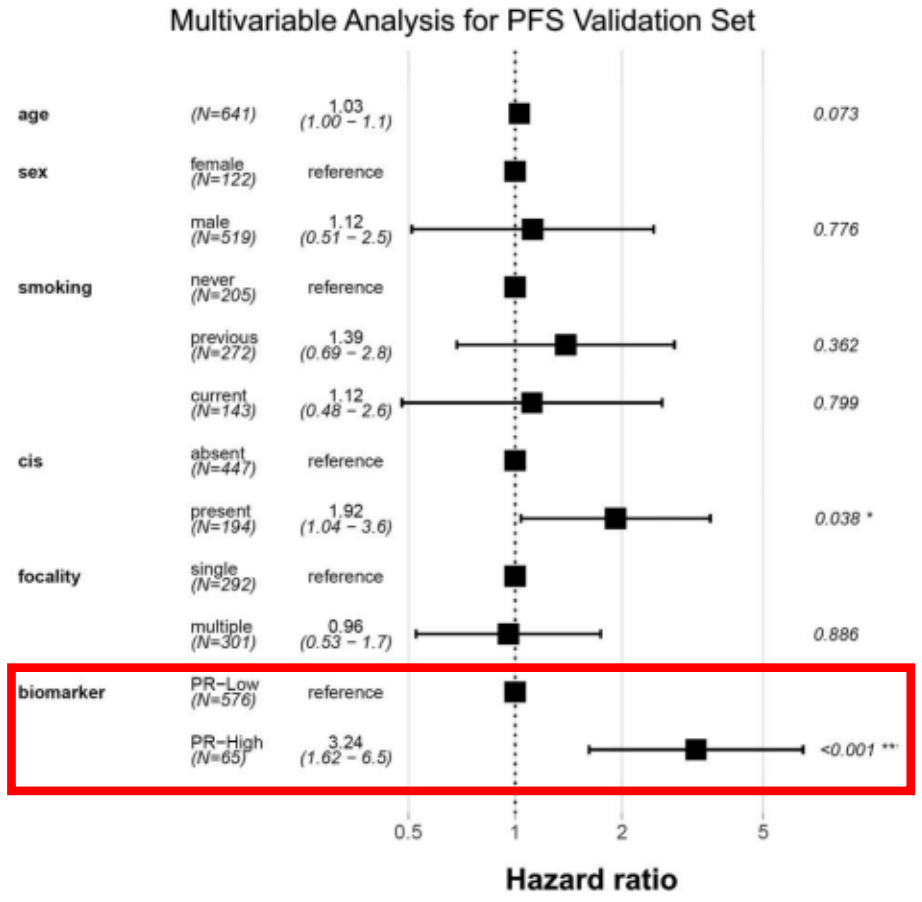




PFS







Markey Cancer Center

Computational Histology AI (CHAI) outperforms clinical risk stratification for NMIBC response to BCG

Lotan et al., J Urol 2024

Vesta (CHAI) is the only bladder cancer diagnostic that predicts response to BCG using histology

Valar Labs | Vesta

Patient [redacted] [redacted]

PATIENT

Name [redacted]
Date of Birth
Medical Record #
Sex
Disease

PHYSICIAN

Ordering Physician: Patrick Hensley
Medical Facility: University of Kentucky
Pathologist: Molly Tovar
Pathology Lab: undefined
Additional Recipient: N/A

SPECIMEN

Specimen Source [redacted]
Case ID
Date of Collection
Date Received
Diagnosis: HGTa

VESTA BIOMARKER®

BIOMARKER ABSENT

This patient does not have the Vesta Biomarker and will likely have an expected response to BCG therapy. This patient should be monitored as per the treating physician's discretion.

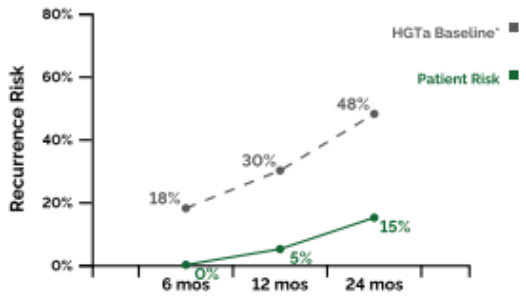
VESTA PROGNOSIS REPORT

Risk of Recurrence

Vesta Score 3

0 10 20 30 40 50 60 70 80 90 100

This patient is in the 3rd percentile of risk of recurrence.



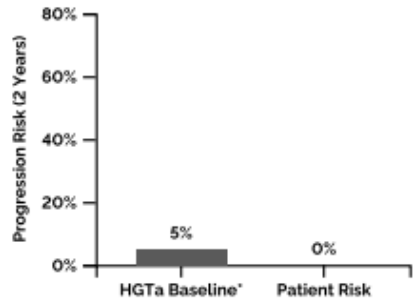
This patient is at a reduced risk of recurrence when compared to the HGTa baseline population from a cohort of nationally recognized cancer centers. In the chart above, this patient has a 5% risk of recurrence compared to a baseline of 30% at 12 months. This represents a 83% reduced relative risk of recurrence when compared to the baseline population.

Risk of Progression

Vesta Score 4

0 10 20 30 40 50 60 70 80 90 100

This patient is in the 4th percentile of risk of progression.



This patient is at a reduced risk of progression when compared to the HGTa baseline population from a cohort of nationally recognized cancer centers. In the chart above, this patient has a 0% risk of progression compared to a baseline of 5% at 2 years. This represents a 100% reduced relative risk of progression when compared to the baseline population.

SUMMARY

This patient does NOT have the Vesta Biomarker and will likely have a typical response to BCG therapy. Additionally, this patient is at a reduced risk of recurrence and a reduced risk of progression.

Valar Labs | Vesta

Patient [redacted] [redacted]

PATIENT

Name [redacted]
Date of Birth
Medical Record #
Sex

PHYSICIAN

Ordering Physician: Patrick Hensley
Medical Facility: University of Kentucky
Pathologist: Allison Derek
Pathology Lab: UK Laboratories

SPECIMEN

Specimen Source [redacted]
Case ID
Date of Collection
Date Received
Diagnosis: HGTaCIS*

VESTA® BIOMARKER

BIOMARKER PRESENT
At Risk of not responding to BCG therapy

This patient has the Vesta Biomarker and is at risk of not responding to BCG therapy. Alternative treatment modalities may be considered for this patient based on this result.

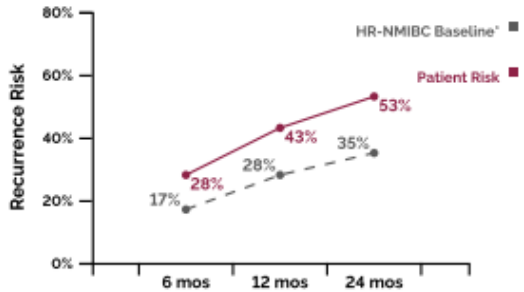
VESTA PROGNOSIS REPORT

Risk of Recurrence

Vesta Score 92

0 10 20 30 40 50 60 70 80 90 100

This patient has a risk of recurrence that is higher than 92% of HR-NMIBC patients.[1]



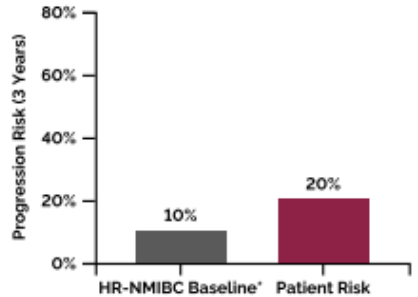
This patient has an elevated risk of recurrence when compared to the HR-NMIBC baseline population from a cohort of international academic cancer centers.[1] In the chart above, this patient has an estimated 43% risk of recurrence compared to a baseline of 28% at 12 months.

Risk of Progression

Vesta Score 97

0 10 20 30 40 50 60 70 80 90 100

This patient has a risk of progression that is higher than 97% of HR-NMIBC patients.[1]



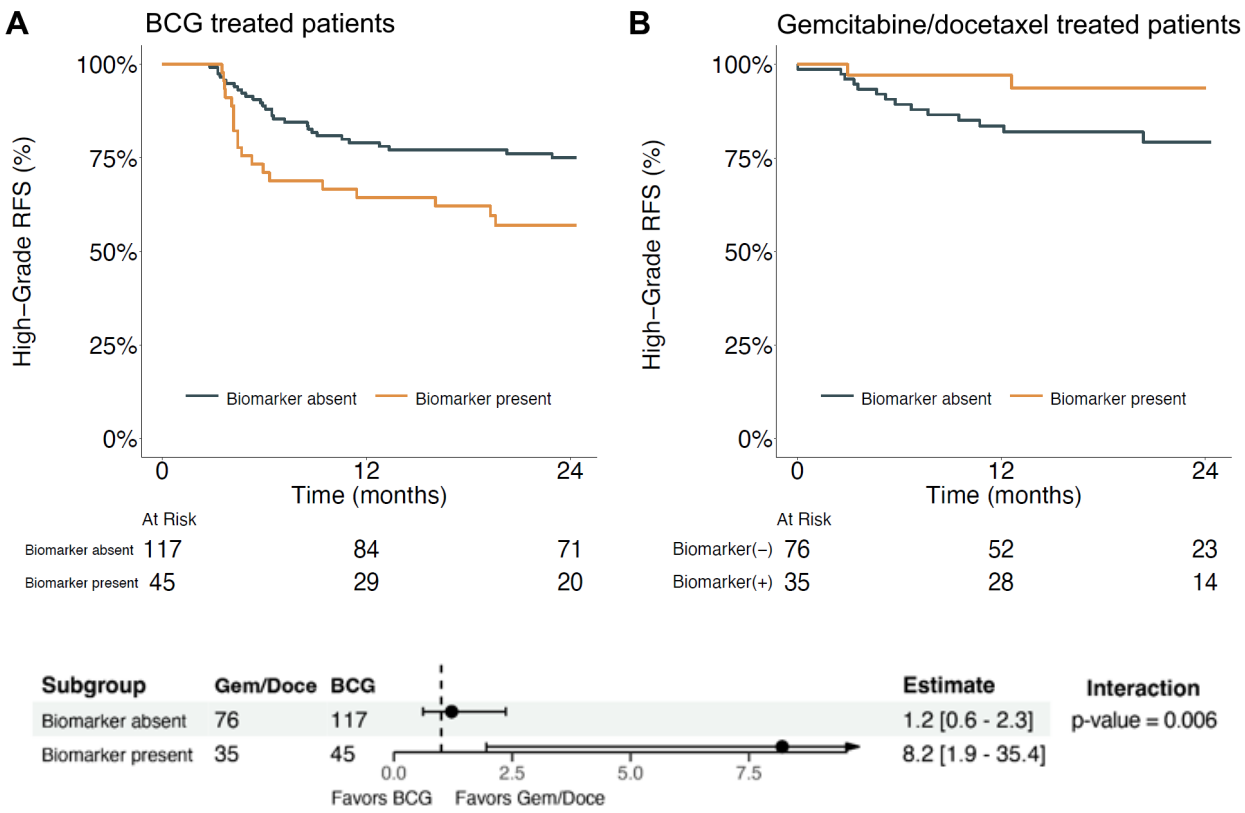
This patient has an elevated risk of progression when compared to the HR-NMIBC baseline population from a cohort of international academic cancer centers.[1] In the chart above, this patient has an estimated 20% risk of progression compared to a baseline of 10% at 3 years.

SUMMARY

This patient has the Vesta Biomarker and is at risk for not responding to BCG therapy. Additionally, this patient has an elevated risk of recurrence and has an elevated risk of progression compared to the HR-NMIBC baseline population. Alternative treatment modalities may be considered for this patient based on this result.

An Artificial Intelligence-Powered Predictive Biomarker Identifies Poor Response to Intravesical BCG and Relative Clinical Benefit to Sequential Gemcitabine and Docetaxel in HG-NMIBC

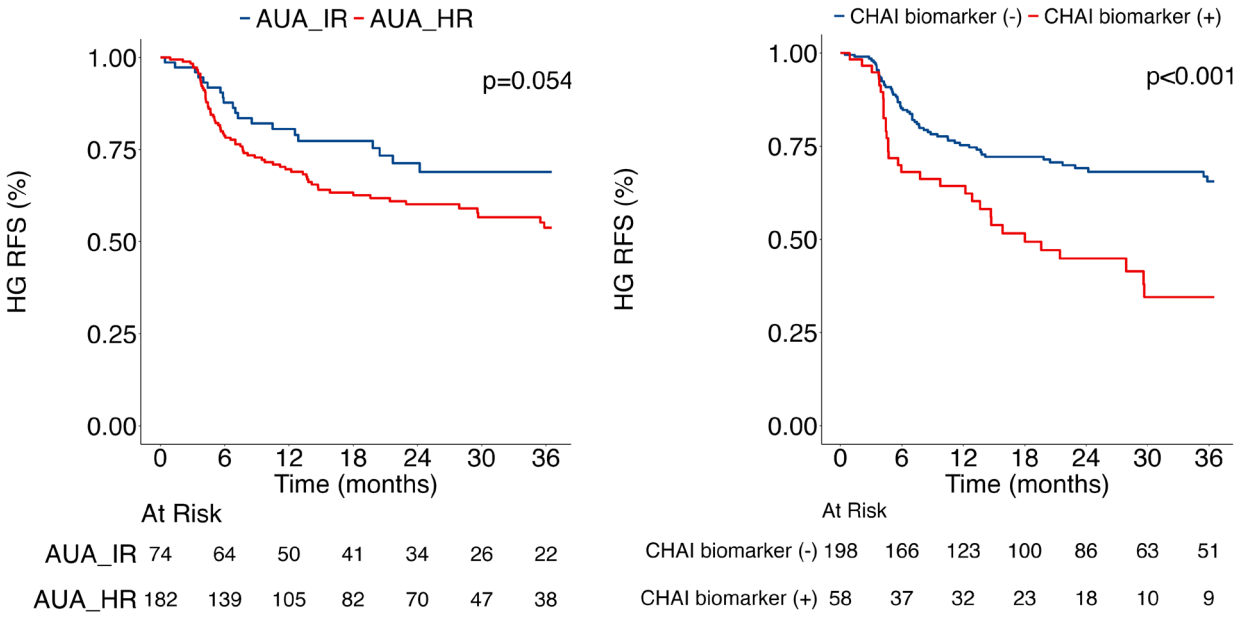
- Two SOC intravesical therapy regimens exists for high-risk NMIBC:
  - BCG
  - Gemcitabine/docetaxel
- In a multi-institutional cohort of N=272 HG NMIBC cases, CHAI (+) patients respond poorly to BCG and favorably to GME/DOCE
- **CHAI can be used to guide initial therapy in treatment naïve HG-NMIBC**



Markey Cancer Center

Packiam & Hensley, in press

Computational Histology AI (CHAI) Biomarker improves risk stratification of high-grade Ta NMIBC over existing clinical guidelines



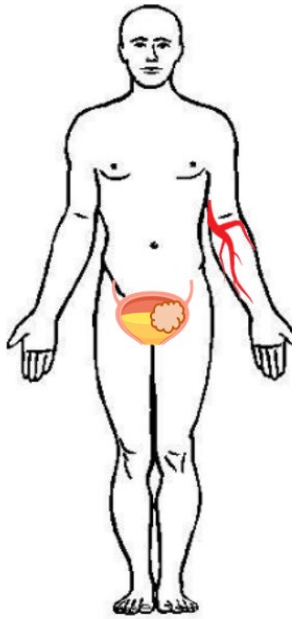
- High-grade Ta disease is heterogeneous with risk-stratification systems varying considerably between available guidelines (NCCN, AUA, EAU)
  - Therapeutic implications
  - Surgical implications
- In a multi-institutional cohort of N=256 HG Ta cases, the CHAI biomarker outperformed the AUA risk-stratification when predicting recurrence and progression

Markey Cancer Center

Chang et al., AUA 2025

Conclusions and Unmet Needs

Treating MIBC: Current Paradigm



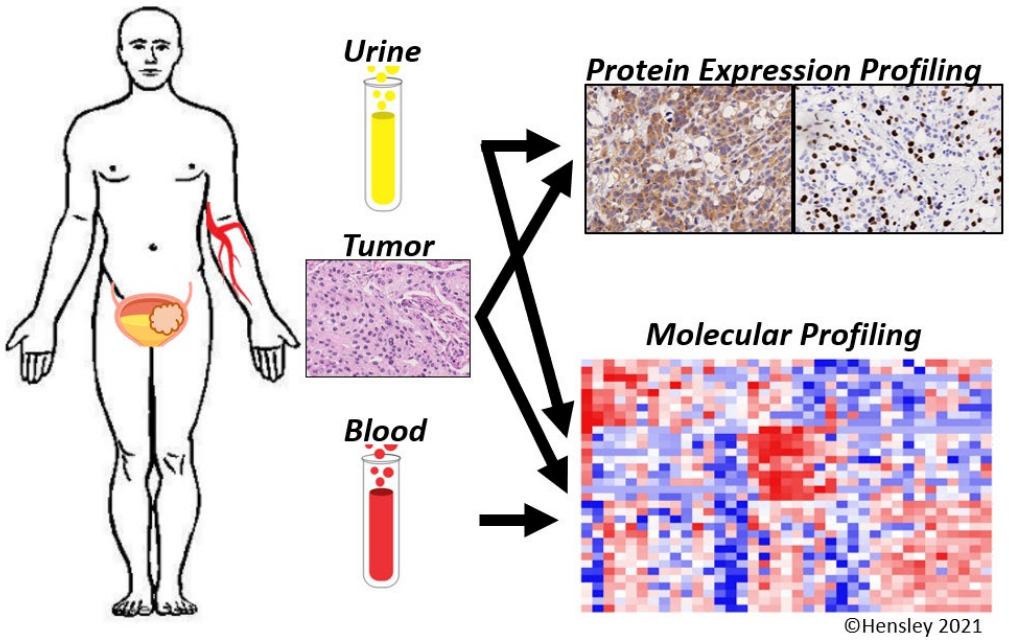
Neoadjuvant Chemotherapy

+

Radical Cystectomy

One size fits all

Treating MIBC: Future Directions



Upfront radical cystectomy
Cis-neoadjuvant therapy
IO/ADC-neoadjuvant therapy
Bladder preservation after clinical response

Risk-stratified, tumor-informed treatment patient selection for NAC
→ improve clinical outcomes, avoid over-treatment

Conclusions

- Historical treatment paradigms are shifting in the treatment of UC:
  - NMIBC:
    - BCG → intravesical alternatives
    - Novel treatments with novel MOA
    - Systemic tx
  - MIBC:
    - Bladder preservation
    - Optimization of neoadjuvant and adjuvant therapy approaches
  - Metastatic:
    - Platinum → targeted tx and ADCs
    - Durable radiographic responses in mUC
- Need for rational biomarker development for therapeutic sequencing of utmost importance

Markey Cancer Center

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

BEST HOSPITALS U.S.News & WORLD REPORT CANCER 2024-2025

THANK **YOU**

For more information contact us

Zin Myint

zin.myint@uky.edu

(410)236-8095

Patrick Hensley

patrick.hensley@uky.edu

(614)582-1337

Derek Allison

derek.allison@uky.edu

(865)256-5482