Modern Radiation Oncology. Innovation in personalized oncology: back to the future.

Back to Future: Old and new drugs in genitourinary tumors: what have we not to forget?

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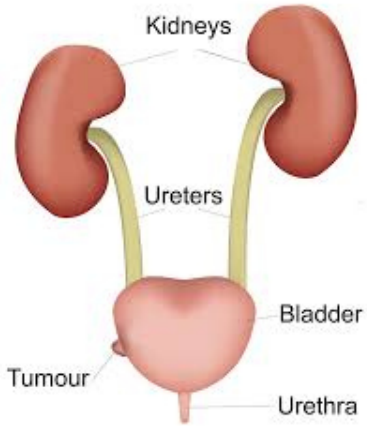
Conflicts of interest

Type of support	Sponsor
Advisory board	AAA, Astellas, BMS, Ipsen, Janssen, Merk, MSD, Pfizer, Sanofi, Bayer, EISAI.
Consultant	Astellas, Ipsen, Merk, MSD, Pfizer, EISAI
Research support (inst)	BMS, MSD, Pfizer
PI clinical trial	BMS, Exelixis, Ipsen, Lilly, MSD, Seagen.

New approaches for Genitourinary Tumors

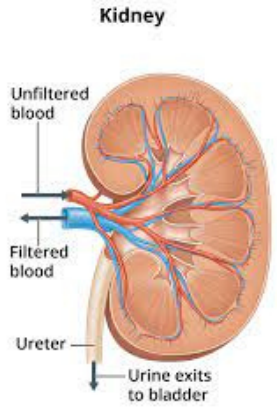
Agenda

Urothelial cancer



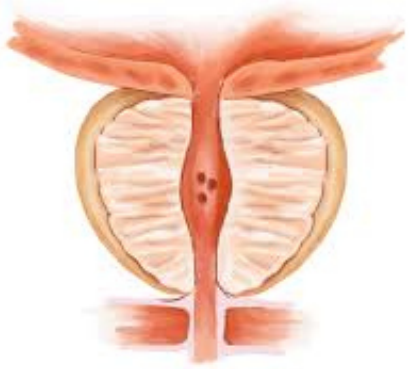
- New approaches for first line
- New targets

Renal cell carcinoma



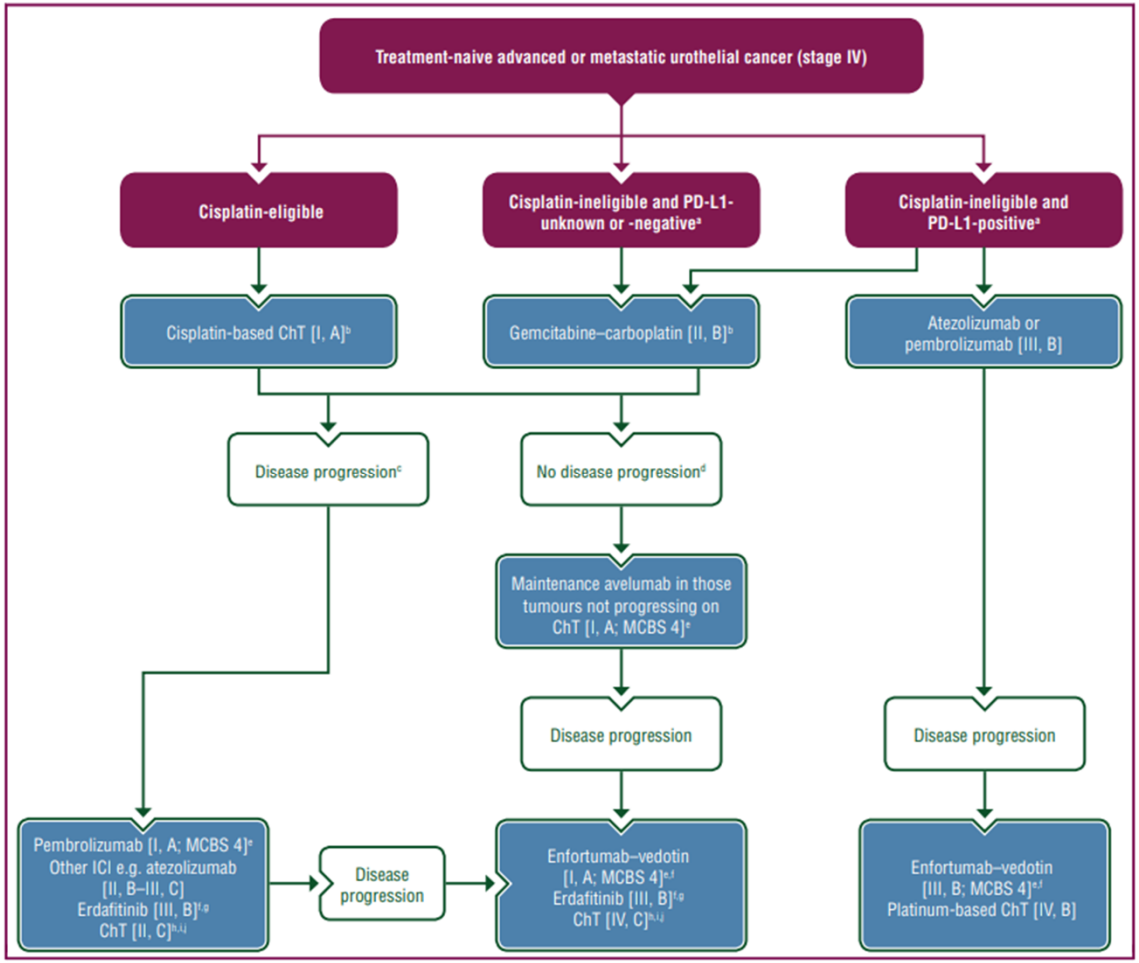
- New approaches for first line
- New targets
- What's news for adjuvant Tx?
- Microbiome & immunotherapy

Prostate cancer



New approaches for Genitourinary Tumors: *Urothelial cancer*

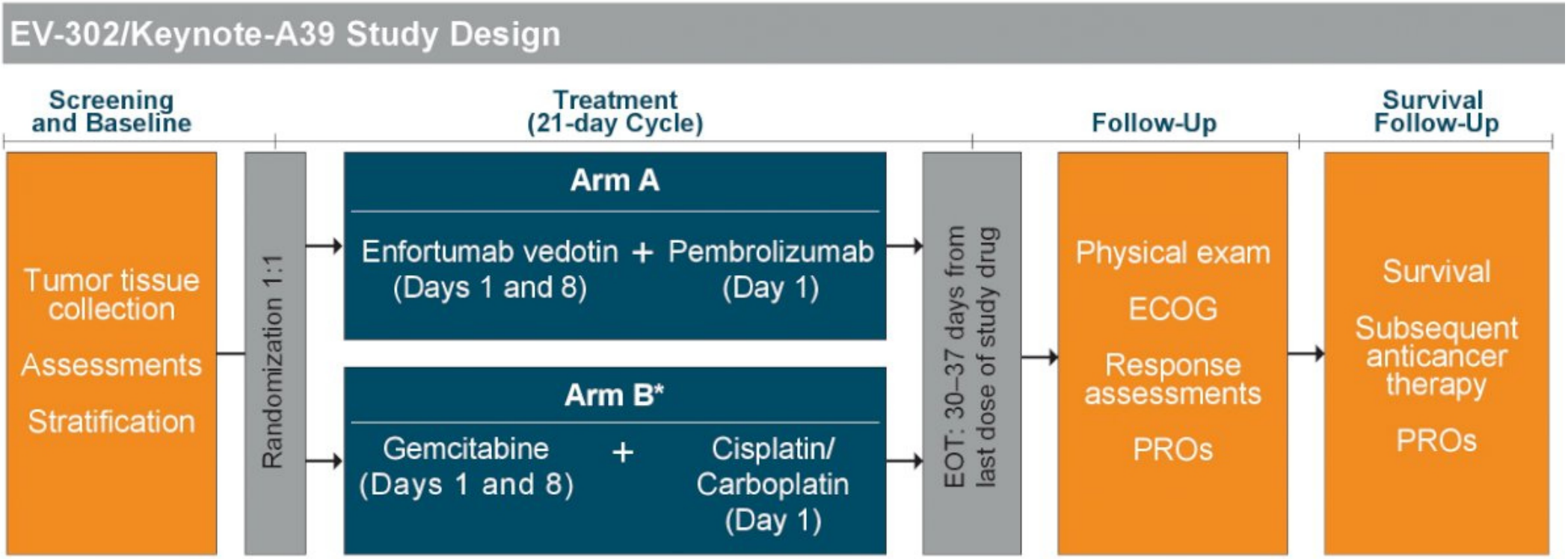
Current approach



Powles T, et al. Ann Oncol. 2022;33:244-258.

New approaches for Genitourinary Tumors: *Urothelial cancer*

New approaches for first line: EV+pembro



New approaches for Genitourinary Tumors: *Urothelial cancer*

New approaches for first line: EV+pembro

September 22nd, 2023

Merck Announces Phase 3 KEYNOTE-A39/EV-302 Trial Met Dual Primary Endpoints of Overall Survival (OS) and Progression-Free Survival (PFS) in Certain Patients With Previously Untreated Locally Advanced or Metastatic Urothelial Cancer

New approaches for Genitourinary Tumors: *Urothelial cancer*

New targets: *role of FGFR*

Erdafitinib is a Pan-FGFR Inhibitor With Activity in Metastatic Urothelial Carcinoma

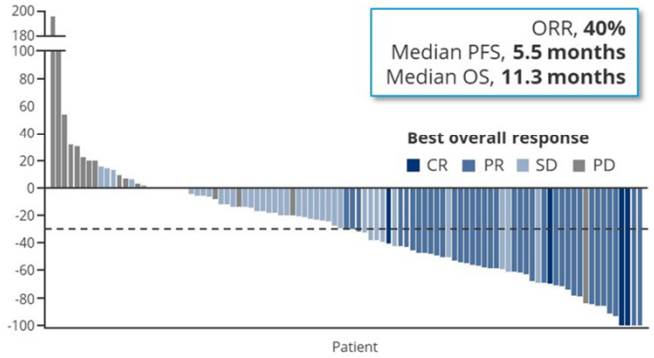
- ***FGFRalt*** are observed in **~20% of advanced or mUC** and may function as oncogenic drivers[1,2]

Erdafitinib is an oral selective pan-FGFR tyrosine kinase inhibitor[3]

- Erdafitinib was granted accelerated approval in the United States and is approved in 17 other countries to treat locally advanced or mUC in adults with susceptible *FGFR3/2alt* who have progressed after platinum-containing chemotherapy[4-6]

- **THOR** is a confirmatory, randomized phase 3 study:
  - Cohort 1 assessed whether erdafitinib improved survival over chemotherapy in patients with *FGFRalt* mUC who progressed on or after ≥1 prior treatment that included anti–PD-(L)1

In the single-arm phase 2 BLC2001 trial, erdafitinib showed a benefit in patients with *FGFR-altered* advanced urothelial cancer[4]



Patients received erdafitinib 8 mg/d with pharmacodynamically guided uptitration to 9 mg/d.

FGFR, fibroblast growth factor receptor; *FGFRalt*, *FGFR* alterations; mUC, metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
[a]Patients received erdafitinib 8 mg/d with pharmacodynamically guided uptitration to 9 mg/d.

1. Necchi A, et al. *Eur Urol Focus*. 2019;5:853-586; 2. di Martino E, et al. *Future Oncol*. 2016;12:2243-2263; 3. Perera TPS, et al. *Mol Cancer Ther*. 2017;16:1010-1020; 4. Loriot Y, et al. *N Engl J Med*. 2019;381:338-348; 5. BALVERSA® (erdafitinib) [package insert]. Horsham, PA: Janssen Products, LP; 2023; 6. Siefker-Radtke AO, et al. *Lancet Oncol*. 2022;23:248-258.

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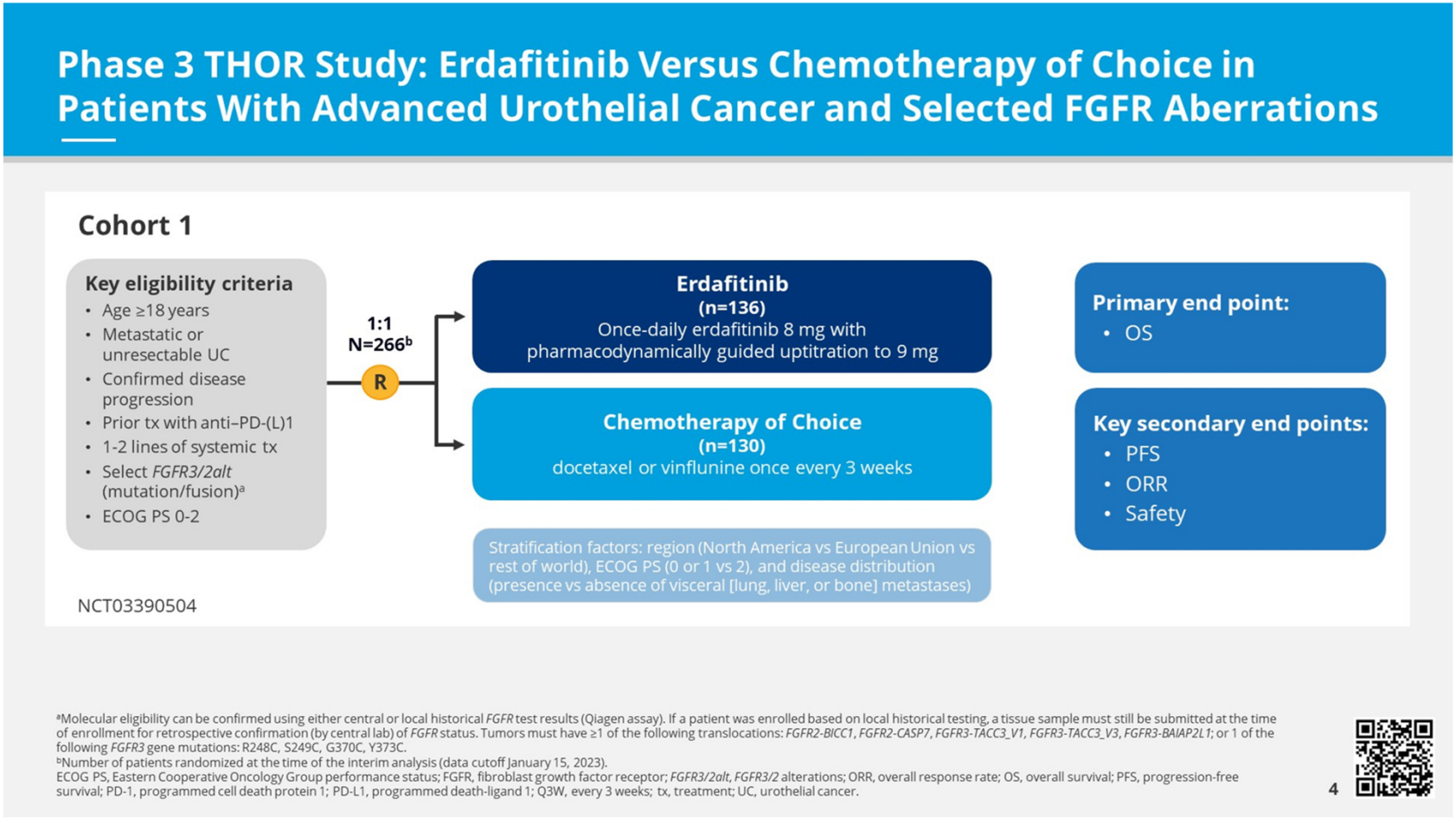
New approaches for Genitourinary Tumors: *Urothelial cancer*

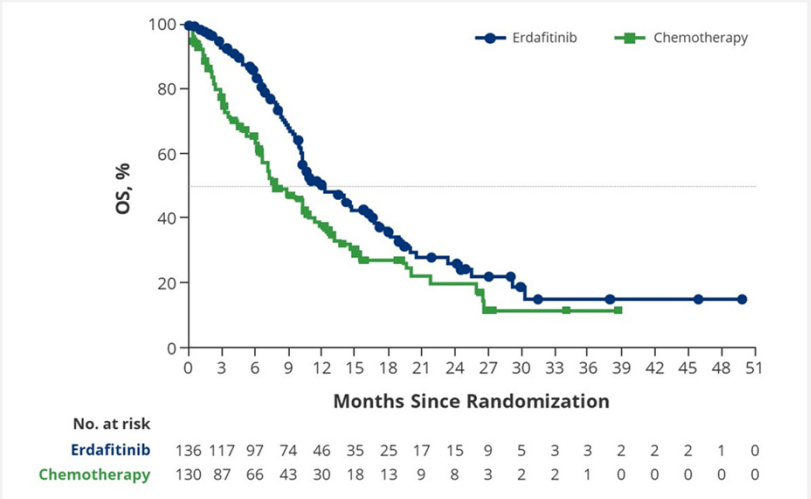
New targets: *role of FGFR*



New approaches for Genitourinary Tumors: *Urothelial cancer*

New targets: *role of FGFR*

Overall Survival for Erdafitinib Was Superior to Investigator's Choice of Chemotherapy



- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; *P* = 0.005)[a]
- Based on these interim analysis results, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; OS, overall survival.
[a]The significance level for stopping for efficacy was p=0.019, corresponding to a HR of 0.69.

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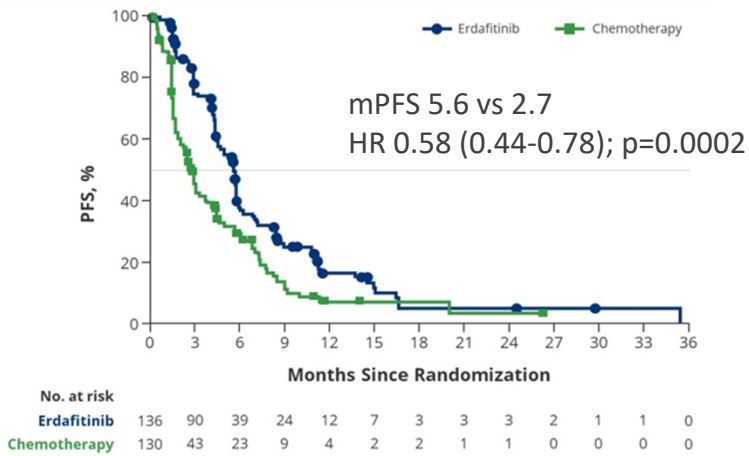
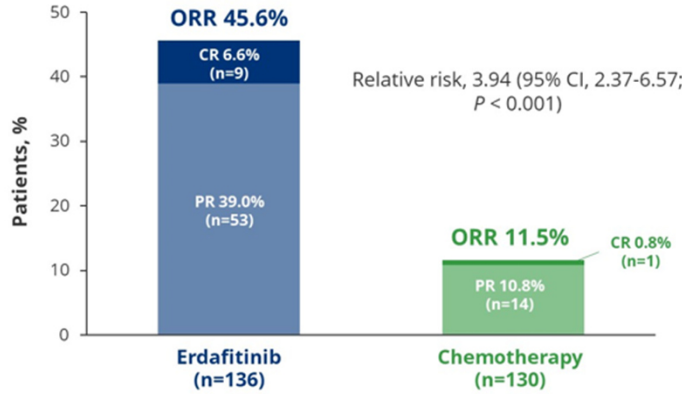


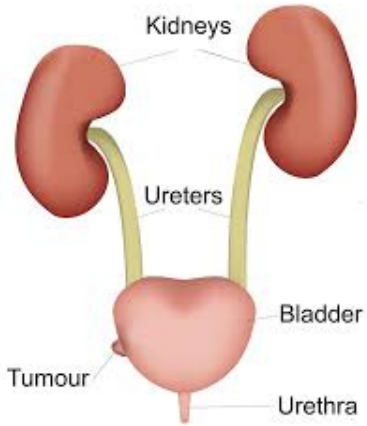
mPFS 5.6 vs 2.7
HR 0.58 (0.44-0.78); p=0.0002



New approaches for Genitourinary Tumors

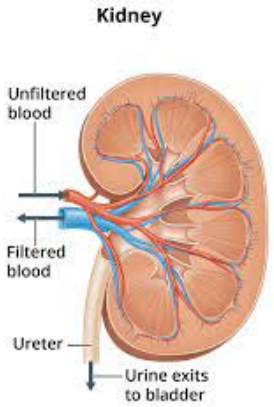
Agenda

Urothelial cancer



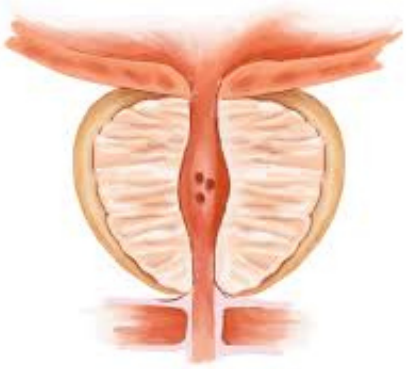
- New approaches for first line
- New targets
- Use of ctDNA for adjuvant Tx

Renal cell carcinoma



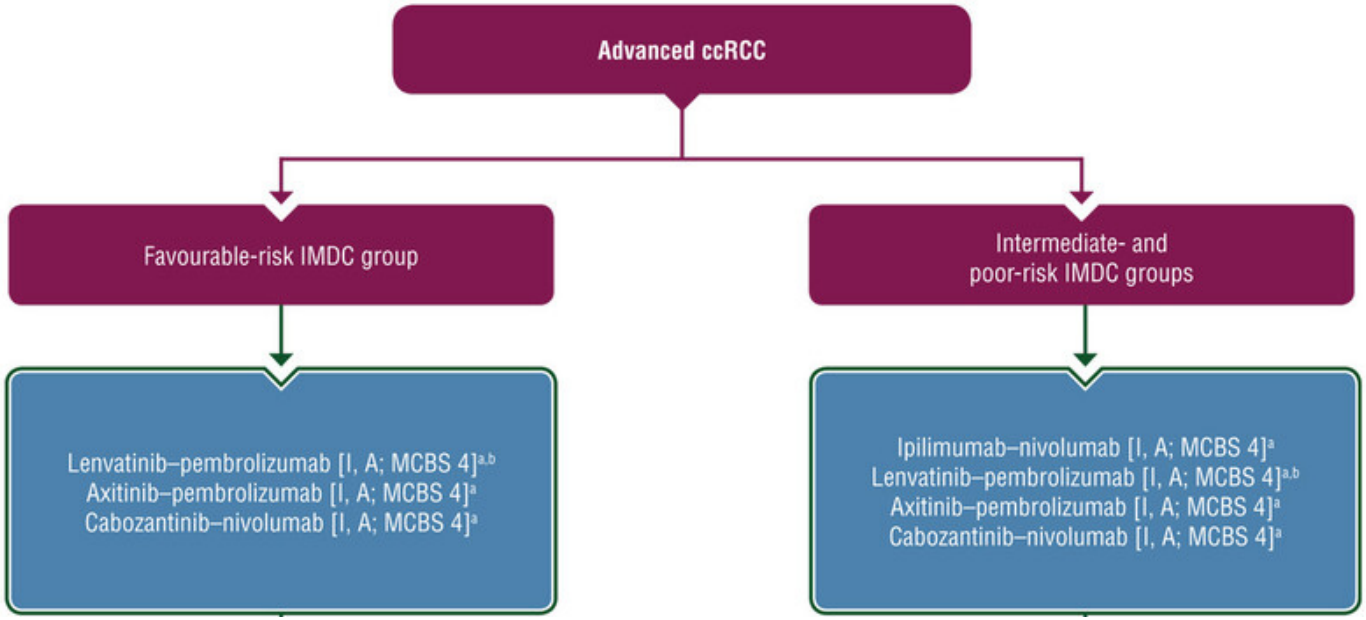
- New approaches for first line
- New targets
- What's news for adjuvant Tx?
- Microbiome & immunotherapy

Prostate cancer



New approaches for Genitourinary Tumors: *Renal cell carcinoma*

Current approach

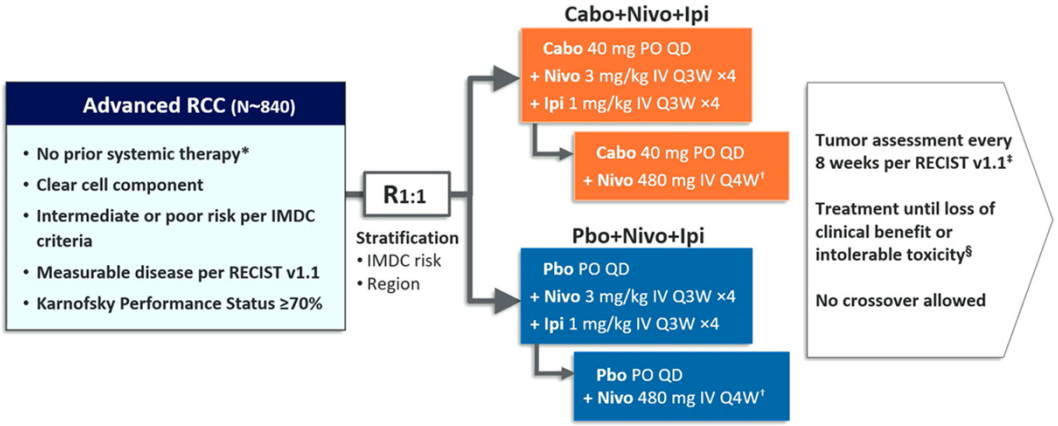


eUpdate – Renal Cell Carcinoma Treatment Recommendations
Published: 28 September 2021. Authors: ESMO Guidelines Committee available at esmo.org

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

New approaches for first line: *intensification*

COSMIC-313 Study Design



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

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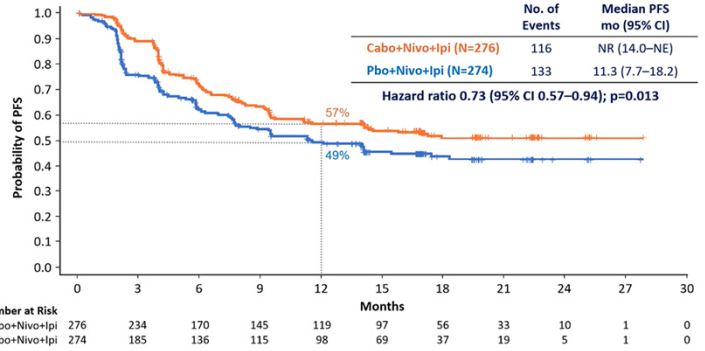
Progression-Free Survival: Final Analysis (PITT Population)



PFS per RECIST v1.1 by BIRC.

Date of the 249th event: Aug 23, 2021

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Summary of Adverse Events (Safety Population)

	Cabo+Nivo+Ipi (N=426)		Pbo+Nivo+Ipi (N=424)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse events				
Any event,* %	99	73	91	41
Alanine aminotransferase increased	46	26	17	6
Aspartate aminotransferase increased	44	20	16	5
Diarrhea	41	4	18	3
Palmar-plantar erythrodysesthesia	28	3	4	0
Hypothyroidism	24	<1	15	0
Hypertension	23	8	5	2
Fatigue	22	2	21	1
Lipase increased	22	9	13	6
Amylase increased	20	5	12	2
Rash	20	2	20	1
Pruritus	20	0	26	<1

- Grade 5 TRAEs occurred in 3 patients (1%) with Cabo+Nivo+Ipi (gastrointestinal hemorrhage, hepatic failure, and respiratory failure) and 3 patients (1%) with Pbo+Nivo+Ipi (renal failure, myocarditis, and sudden death) ≤30 days after last dose; through 100 days after last dose, two additional patients had grade 5 TRAEs with Cabo+Nivo+Ipi (immune-mediated hepatitis and acute hepatic failure) and one additional patient with Pbo+Nivo+Ipi (perforated ulcer)
- Use of high-dose corticosteroids (≥40 mg of prednisone or equivalent) for AEs was 58% with Cabo+Nivo+Ipi and 35% with Pbo+Nivo+Ipi

*Occurring in ≥20% of either treatment group.

Data cut-off: Jan 31, 2022

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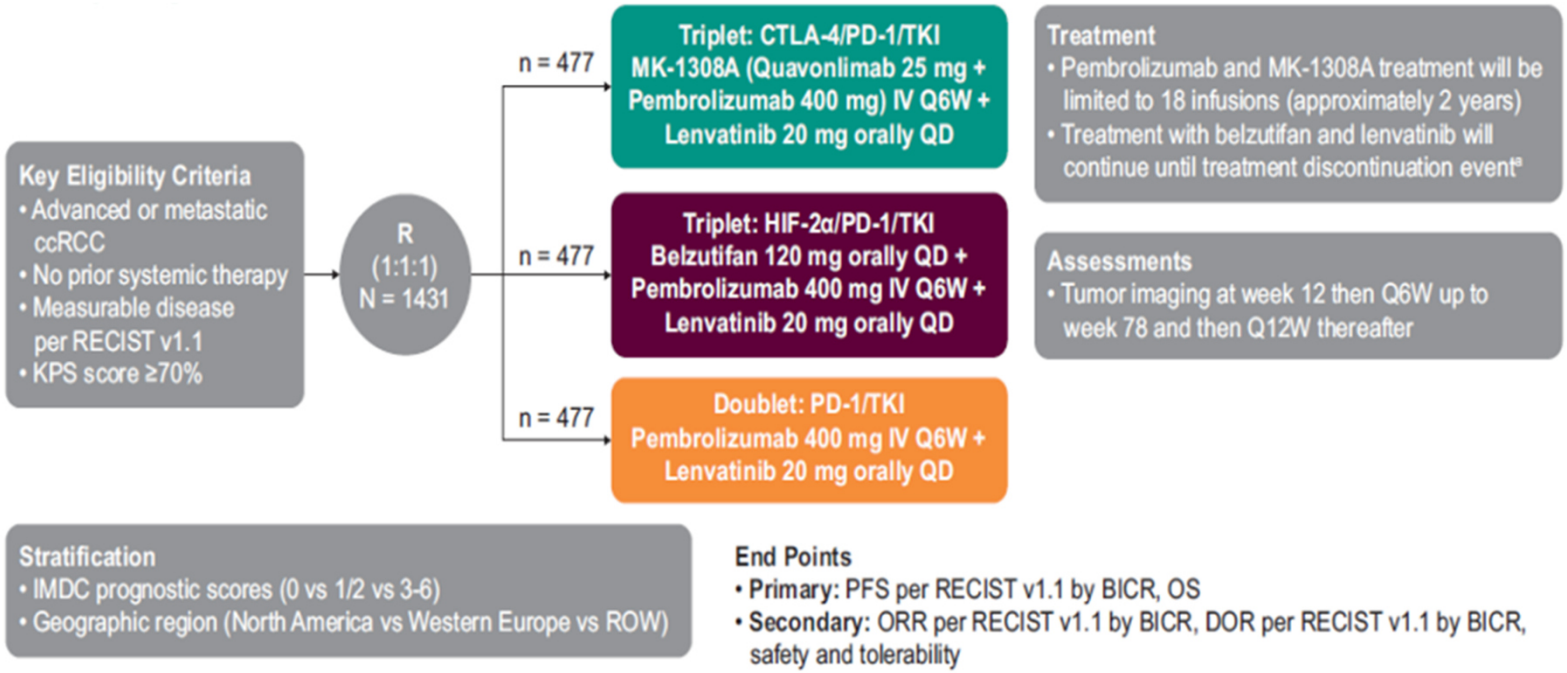
Choueiri TK, et al. N Engl J Med 2023; 388:1767-1778

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

New approaches for first line: *intensification*

LITESPARK-012 study

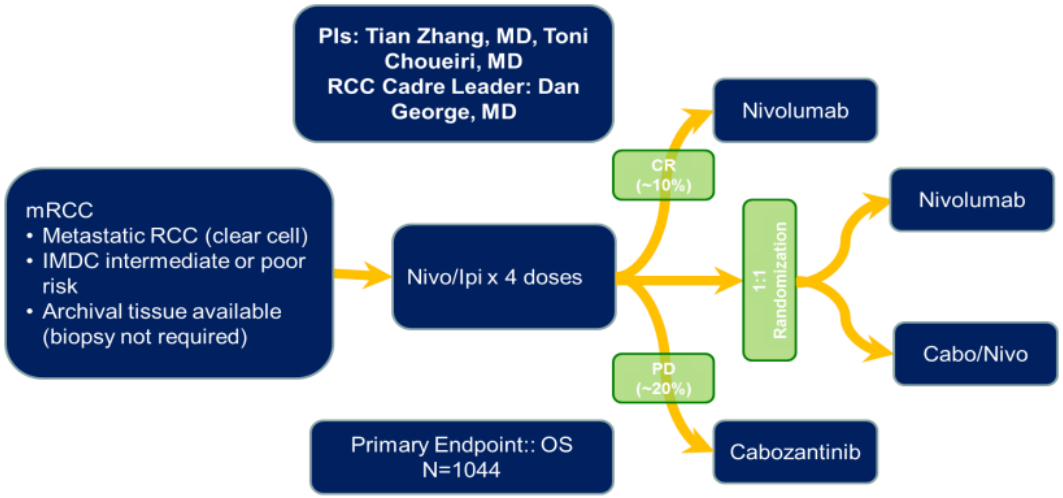


NCT04736706

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

New approaches for first line: (alternative) *intensification*

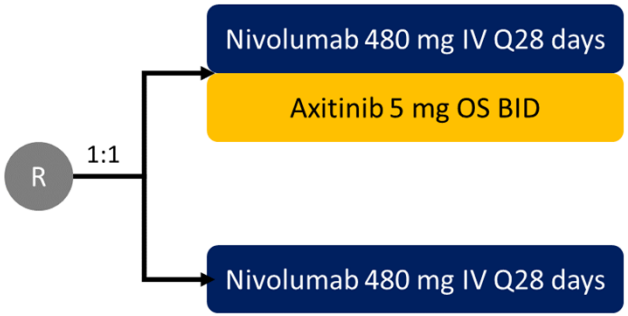
ALLIANCE PDIGREE Trial



NCT03793166

AXIN trial

118 mRCC patients **after ipi/nivo induction** with
- ECOG=0-1
- Metastatic disease
- No PD & No RC
- No Immune tox ≥ G2

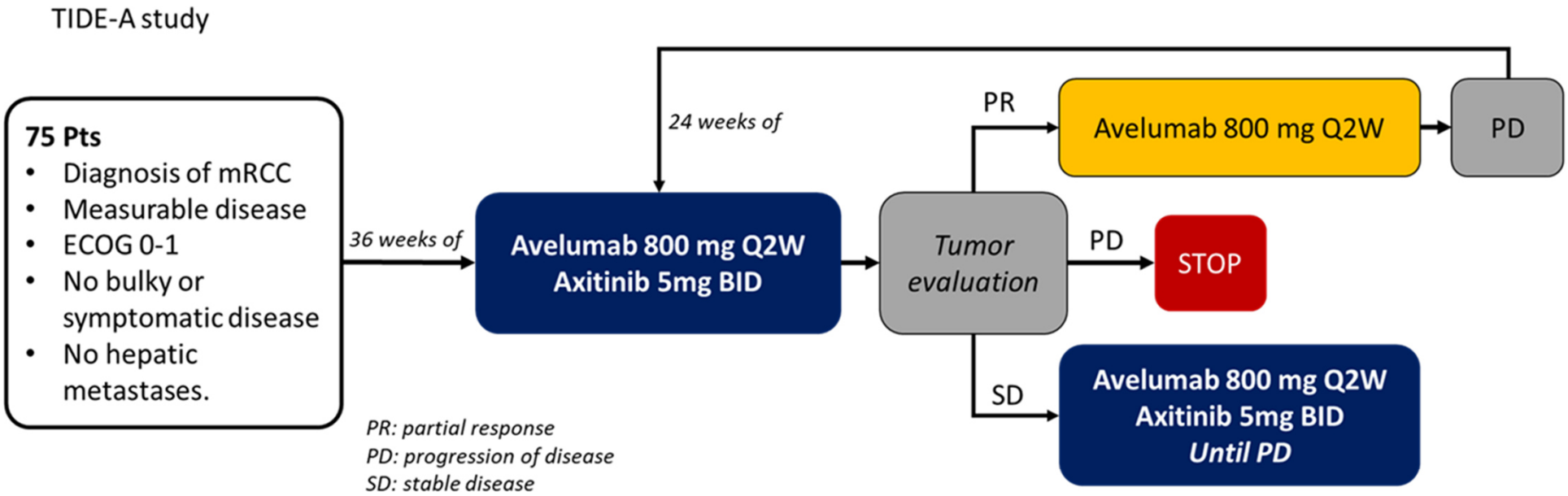


Endpoints:
Primary: *ORR*
Secondary: *mPFS, mOS; deepth of response, DOR, QoL, safety*

NCT05817903

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

New approaches for first line: de-*intensification*

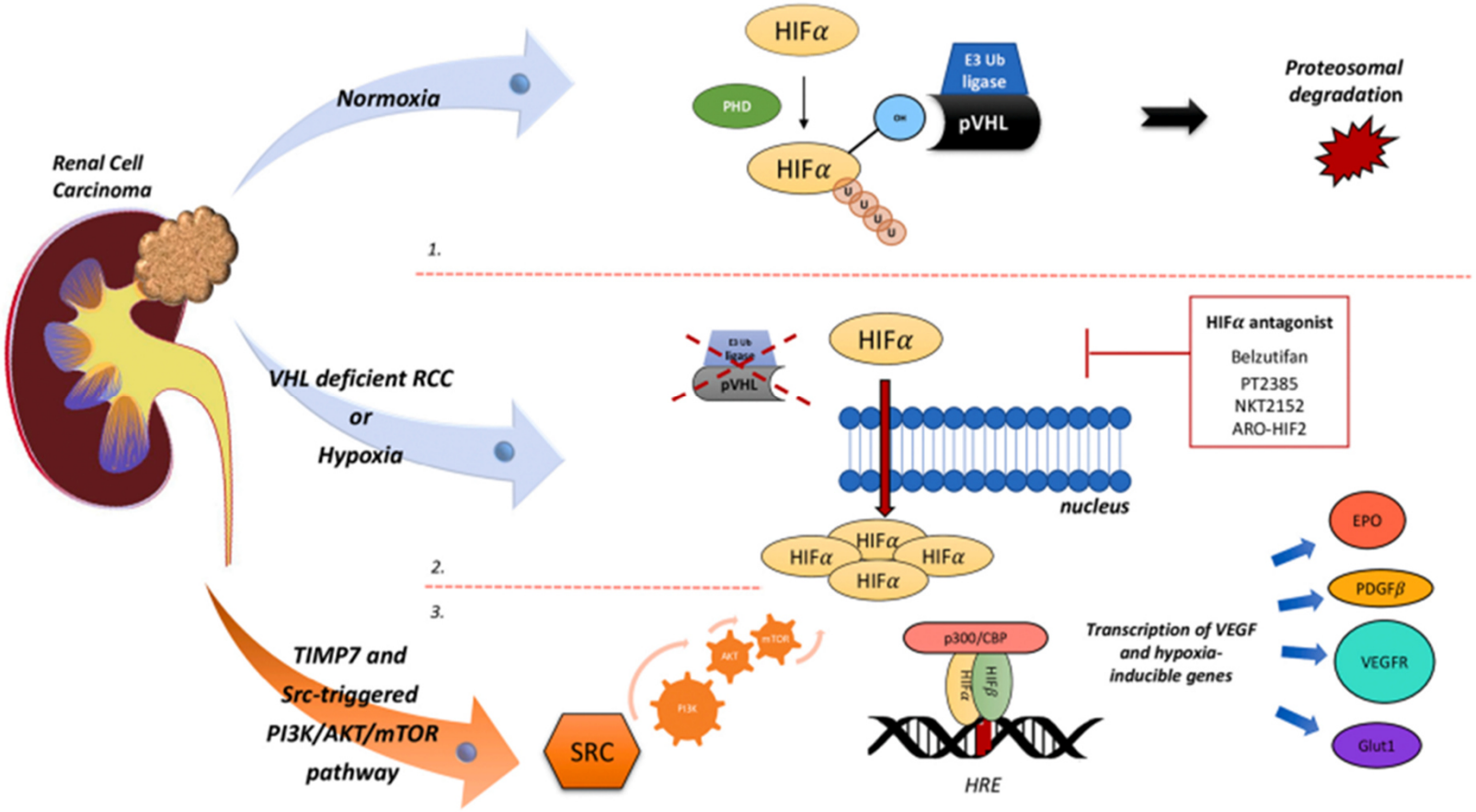


Iacovelli et al. Presented at ASCO GU 2020 TPS762

Eudract CT number: 2019-004098-23
ClinicalTrials.gov Identifier: NCT04698213

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

New targets: HIF



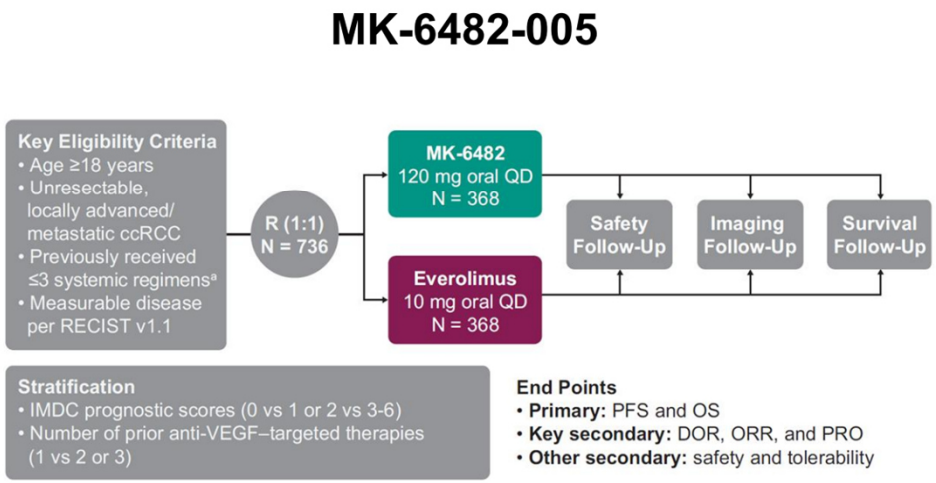
Iacovelli R, et al. Crit Rev Oncol Hematol. 2022;176:103750.

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

New targets: HIF

Merck Announces WELIREG® (belzutifan) Phase 3 LITESPARK-005 Trial Met Primary Endpoint of Progression-Free Survival in Certain Previously Treated Patients With Advanced Renal Cell Carcinoma

August 18, 2023 6:45 am ET



First positive Phase 3 results for WELIREG from LITESPARK-005 showed statistically significant improvements in PFS versus everolimus in these patients

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced topline results from LITESPARK-005, the first positive Phase 3 trial investigating WELIREG, Merck's oral hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor. LITESPARK-005 is evaluating WELIREG for the treatment of adult patients with advanced renal cell carcinoma (RCC) that has progressed following PD-1/L1 checkpoint inhibitor and vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKI) therapies. In the trial, WELIREG showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to everolimus, based on a pre-specified interim analysis conducted by an independent Data Monitoring Committee. A statistically significant improvement in the trial's key secondary endpoint of objective response rate (ORR) was also demonstrated. A trend toward improvement in overall survival (OS), a dual primary endpoint, was observed; however, this result did not reach statistical significance. OS will be tested at a subsequent analysis. The safety profile of WELIREG in this trial was consistent with that observed in previously reported studies. Results will be presented at an upcoming medical meeting and shared with regulatory authorities.

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

What's news for adjuvant Tx?

A Study of Belzutifan (MK-6482) Plus Pembrolizumab (MK-3475) Versus Placebo Plus Pembrolizumab in Participants With Clear Cell Renal Cell Carcinoma Post Nephrectomy (MK-6482-022)

1600 Patients with
- Histologically confirmed diagnosis of ccRCC
- Intermediate-high risk RCC
  - pT2, Grade 4 or sarcomatoid, N0, M0
  - pT3, Any Grade, N0, M0
- High Risk RCC
  - pT4, Any Grade, N0, M0
  - pT Any stage, Any Grade, N+, M0
  - M1 NED
- No prior systemic therapy
- BICR-verified tumor free (CT or MRI) of brain, chest, abdomen, pelvis and bone scan

1:1

Belzutifan 120 mg/day for 54 wks
+
Pembrolizumab 400 mg Q6 wks for 9 cycles

Placebo 120 mg/day for 54 wks
+
Pembrolizumab 400 mg Q6 wks for 9 cycles

Stratification factors:
- Intermediate-high Risk vs High Risk vs M1 NED
- Tumor Grade 1 or 2 vs Tumor Grade 3 or 4

Primary Endpoint: DFS by investigator
Key Secondary Endpoint: OS

NCT05239728

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

What's news for adjuvant Tx?

A Phase 2, Randomized, Double-blind, Clinical Study of V940 (mRNA-4157) Plus Pembrolizumab (MK-3475) Versus Placebo Plus Pembrolizumab in the Adjuvant Treatment of Participants With Renal Cell Carcinoma

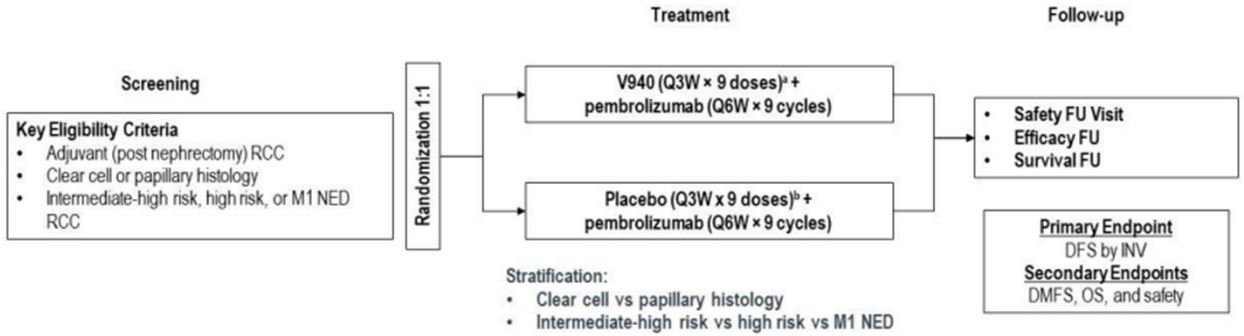
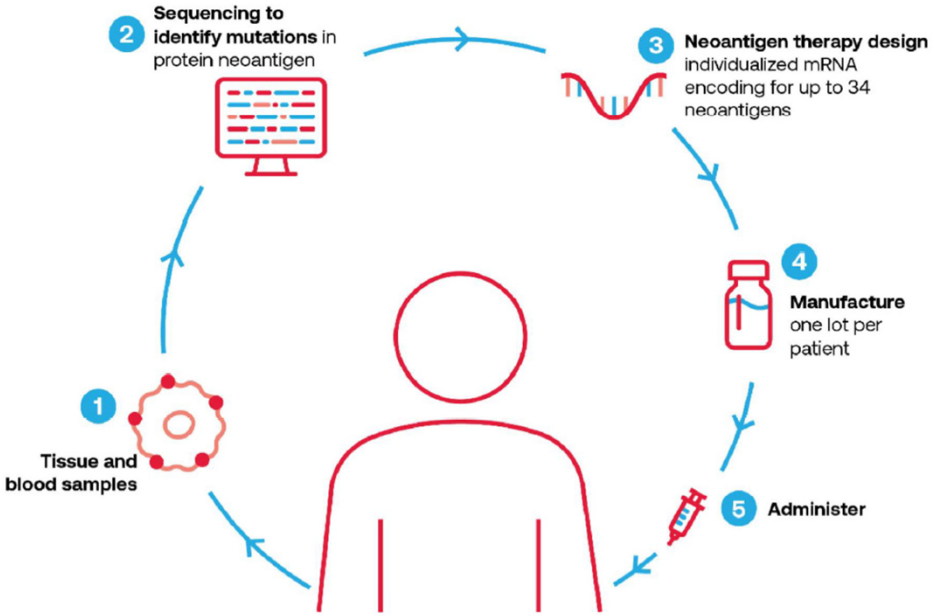


Figure 2 Schematic Representation of Generation of V940



New approaches for Genitourinary Tumors: *Renal cell carcinoma*

Microbiome & Cancer

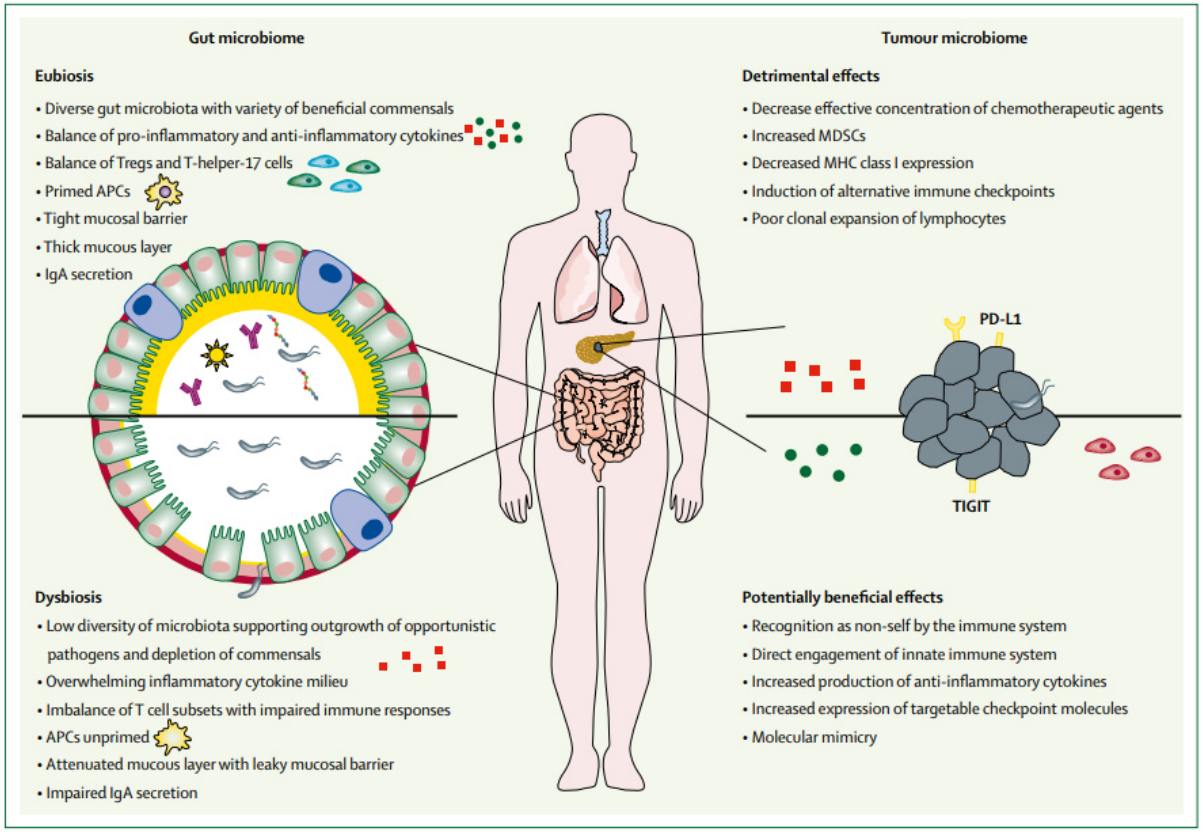
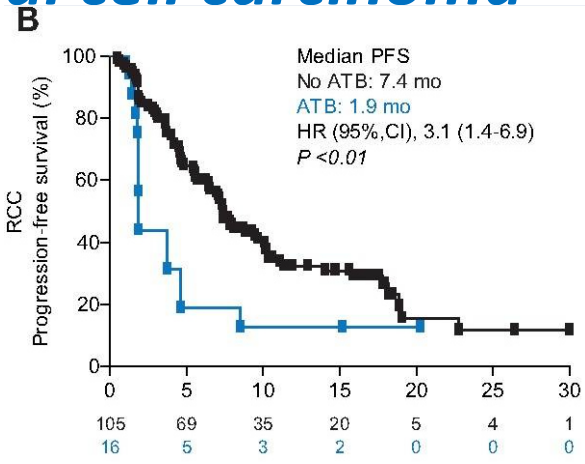
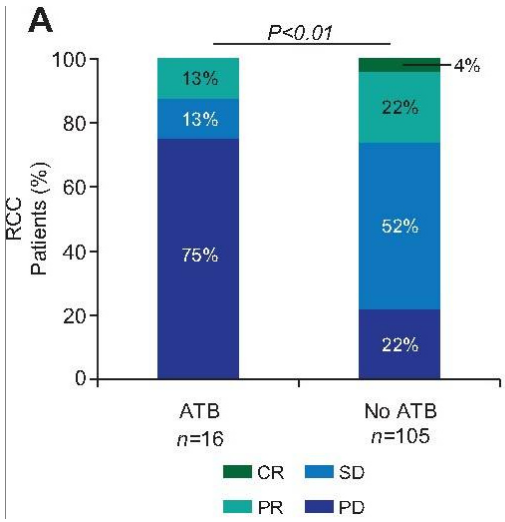


***Figure 1*: Complex interplay of the gut and tumour microbiome and the host immune system**
APCs=antigen-presenting cells. IgA=immunoglobulin A. MHC=major histocompatibility complex. Tregs=regulatory T cells. MDSCs=myeloid-derived suppressor cells. PD-L1=programmed death ligand 1.





McQualde JL. et al. Lancet Oncol . 2019 Feb;20(2):e77-e91.
Derosa L, et al. Ann Oncol. 2018 Jun 1;29(6):1437-1444.

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

Microbiome & Cancer

Studies evaluating gut microbiome composition and treatment response in mRCC patients.

Study	Patient Population	Microorganism Associated with Response/Clinical Benefit	Treatment
Routy et al, Science (2018) [50]	Patients with metastatic RCC or NSCLC	*Akkermansia muciniphila*, *Ruminococcus*, *Alistipes*, and *Eubacterium*	Anti PD-L1
Derosa et al, European Urology, (2020) [85]	Patients with advanced RCC	*Akkermansia muciniphila*, *Bacteroides salyersiae*, and *Eubacterium siraeum*	Nivolumab
Salgia European Urology (2020) [86]	Patients with metastatic RCC	*Akkermansia municiphila*, *Prevotella copri*, *Feacalibacterium rumino Bifidobacterium adolescentis*, and *Barnesiella intestinihominis*	Nivolumab or nivolumab with ipilimumab
Dizman et al, Cancer Medicine (2021) [90]	Patients with metastatic RCC	*Akkermansia muciniphila*, *Barnesiella intestinihominis and Bacteroides caccae*	VEGF-TKI therapy
Dizman et al, Nature Medicine (2022) [91]	Patients with metastatic RCC	*Bifidobacterium* spp.	Nivolumab with ipilimumab +/− CBM588

Meza L, et al. J Clin Med. 2023 Feb; 12(4): 1502.

New approaches for Genitourinary Tumors: *Renal cell carcinoma*

Microbiota transplantation: The TACITO Trial (FPG study)

50 Patients with
- Renal cancer
- Measurable disease
- Eligible to axi-pembro

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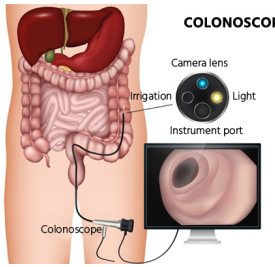
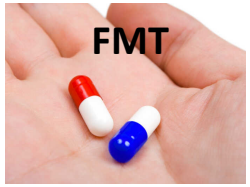
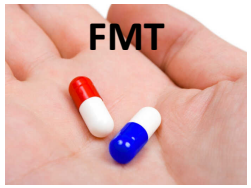
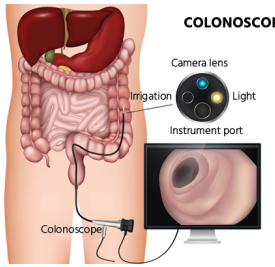


+ FMT





Axitinib + pembrolizumab per SOC



+ Placebo

Within 8 weeks from the start of A/P

After 12 weeks from colonoscopy

After 24 weeks from colonoscopy

FMT: Fecal microbiota transplantation;
SOC: standard of care.

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New approaches for Genitourinary Tumors:
CONCLUSIONS

Urothelial cancer:

- The medical treatment of mUC is changing by the introduction of a new standard of care in first line that will change the current landscape. *Everything should be redrawn!*
- The use of the FGFRi erdafitinib offers a new chance of cure even if availability molecular test and toxicity might affect is large use.

Renal cell carcinoma:

- In the medium-term, it is unlikely that new therapies can improve survival like that immunotherapy.
- New strategies can improve current management offering intensification for the “low-responders” and deintensification for the “super-responders”.
- Belzutifan is a fascinating drug, but its values should be unequivocally reported in clinical trials.
- mRNA vaccination and microbiome representing interesting approaches highlighting the complex relationship between host and immune system that warrant future investigations.