# Updates in Kidney and Bladder Cancers

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SCHOOL OF MEDICINE
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# Disclosure of Conflicts of Interest

Pedro C. Barata, MD MSc has the following financial relationships to disclose:

**Consultant (Institutional):** Astellas; Eisai; Janssen, EMD Serono; Dendreon; Pfizer, Seattle Genetics, BMS, Bayer, Guardant Health
**Contracted Research (Institutional):** AstraZeneca, Merck, Caris Life Sciences
**Research Grant (Institutional):** BlueEarth Diagnostics, Merck,
**Speaker's Bureau (Unbranded, Institutional):** Bayer, Caris Life Sciences, Natera, Pfizer

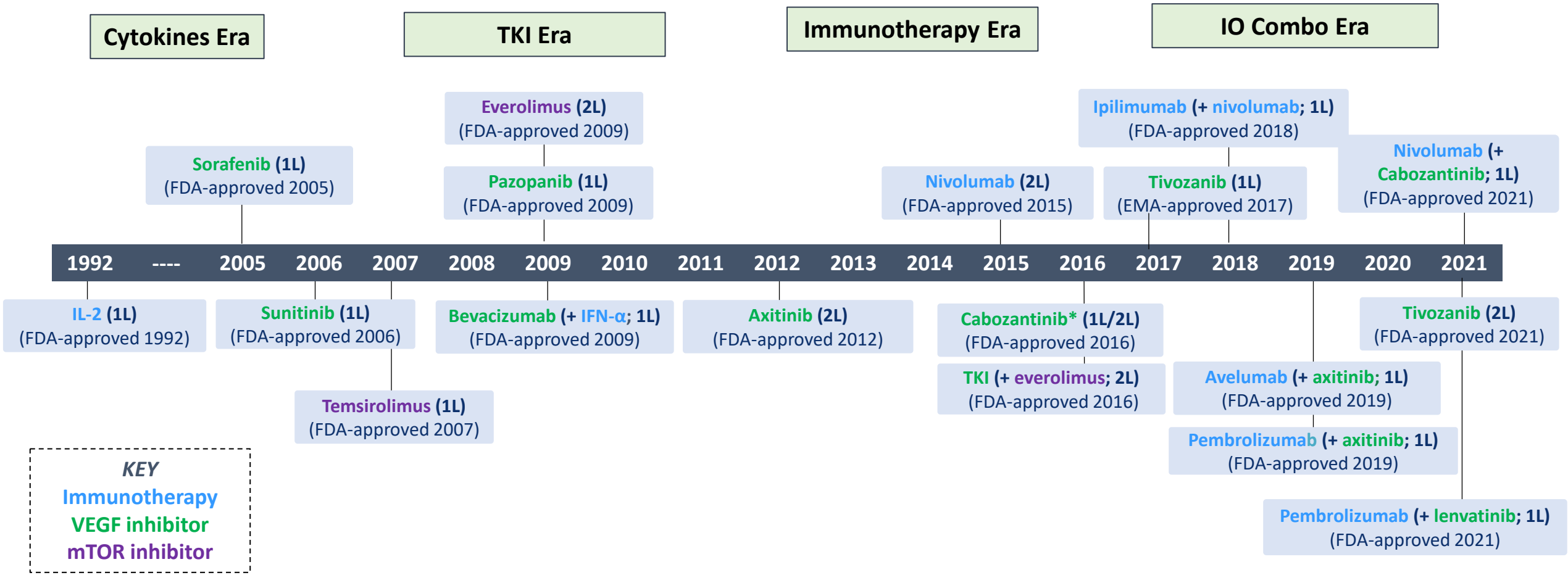
# Unlabeled/Investigational Use

I plan on discussing the following unlabeled/investigational use of the following products:

Axitinib/avelumab, Enfortumab Vedotin, Sacituzumab govitecan, and Tivozanib

# Renal Cell Cancer

# Evolution of Systemic Therapy in Metastatic RCC




*1L = first line; 2L= second line; IFN-α = interferon alpha; IL = interleukin; IO = immunotherapy; mTOR, mammalian target of rapamycin;TKI = tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR-2 = VEGF receptor-2*

*Cabozantinib inhibits VEGFR-2, but also c-MET and AXL.22.

Dizman N, et al. *Nature Reviews Nephrol.* 2020;16:435–451.

Food and Drug Administration. Drug Approvals and Databases. https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases.

# Advanced Renal Cancer – First Line

# Updated Results From Front-Line IO-Combination Trials

| | CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546) | KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429) | CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328) | CLEAR (Len/Pembro)[4] (N=355 vs n=357) |
|---|---|---|---|---|
| HR<br>mOS, months | **0.72**<br>55.7 vs 38.4 | **0.73**<br>45.7 vs 40.1 | **0.70**<br>37.7 vs 34.3 | **0.72**<br>NR vs NR |
| Landmark OS 12 mo<br>Landmark OS 24 mo | **83%** vs. 78%<br>**71%** vs. 61% | **90%** vs. 79%<br>**74%** vs. 66% | **86%** vs. 76%<br>**70%** vs 60% | **90%** vs 79% (est.)<br>**79%** vs. 70% |
| HR<br>mPFS, months | **0.86**<br>**12.3** vs 12.3 | **0.68**<br>**15.7** vs 11.1 | **0.56**<br>**16.6** vs 8.3 | **0.39**<br>**23.9** vs 9.2 |
| ORR, % | **39** vs 32 | **60** vs 40 | **56** vs 28 | **71** vs 36 |
| CR, % | **12** vs 3 | **10** vs 4 | **12** vs 5 | **16** vs 4 |
| Med f/u, months | **67.7** | **42.8** | **32.9** | **33.7** |
| Primary PD, % | **18** | **11** | **6** | **5** |

1. Consistent OS benefit; medians immature for IO/TKIs
2. IO/TKIs with more tumor shrinkage; higher ORR, longer PFS and less early PD
3. Ipi/Nivo has the most durable benefit at 5 years -IO/TKI data immature

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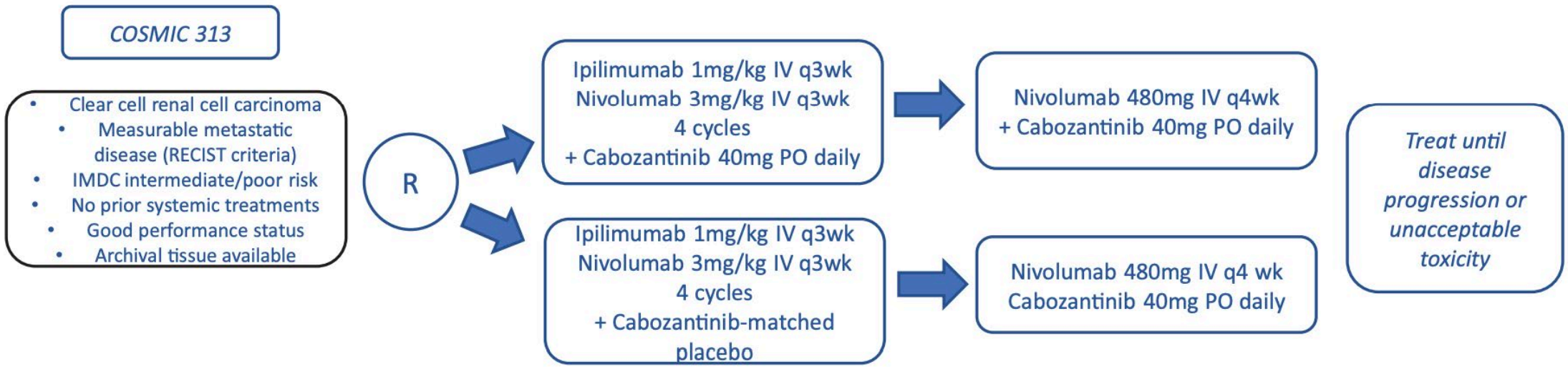
# HRQoL Summary of Randomized Phase 3 First-Line Combination Studies in cc Renal Cell Carcinoma

| HRQoL Tools | CHECKMATE-214[1] | | KEYNOTE-426[2] | | CHECKMATE-9ER[3] | | CLEAR[4] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N=847 | | N=861 | | N=651 | | N=1069 | | | |
| | Nivolumab + Ipilimumab | vs. Sunitinib | Axitinib + Pembrolizumab | vs. Sunitinib | Cabozantinib + Nivolumab | vs. Sunitinib | Lenvatinib + Pembrolizumab | vs. Sunitinib | Lenvatinib + Everolimus | vs. Sunitinib |
| | Intermediate and Poor Risk Only | | All Risk Groups | | All Risk Groups | | All Risk Groups | | | |
| FKSI-19 | ✓ | | | | ✓ | | | | | |
| FKSI-DRS | | | = | | | | = | | = | |
| EORTC QLQ-C30 | | | = | | | | = | | = | |
| FACT-G | ✓ | | | | | | | | | |
| EQ-5D-3L | ✓ | | = | | ✓ | | = | | = | |

1. Lancet Oncol 2019; 20: 297–310; 2. Bedke J. et al., 35th Annual EAU Congress -July 2020 (via https://www.urotoday.com)3. Cella D et al., JCO 39, no. 6_suppl (February 20, 2021) 285; 4. Motzer R et al., JCO 39, 2021 (suppl 15; abstr 4502).

Presented By: Andrea B. Apolo, MD
@apolo_andrea

# PIVOT-09 and COSMIC 313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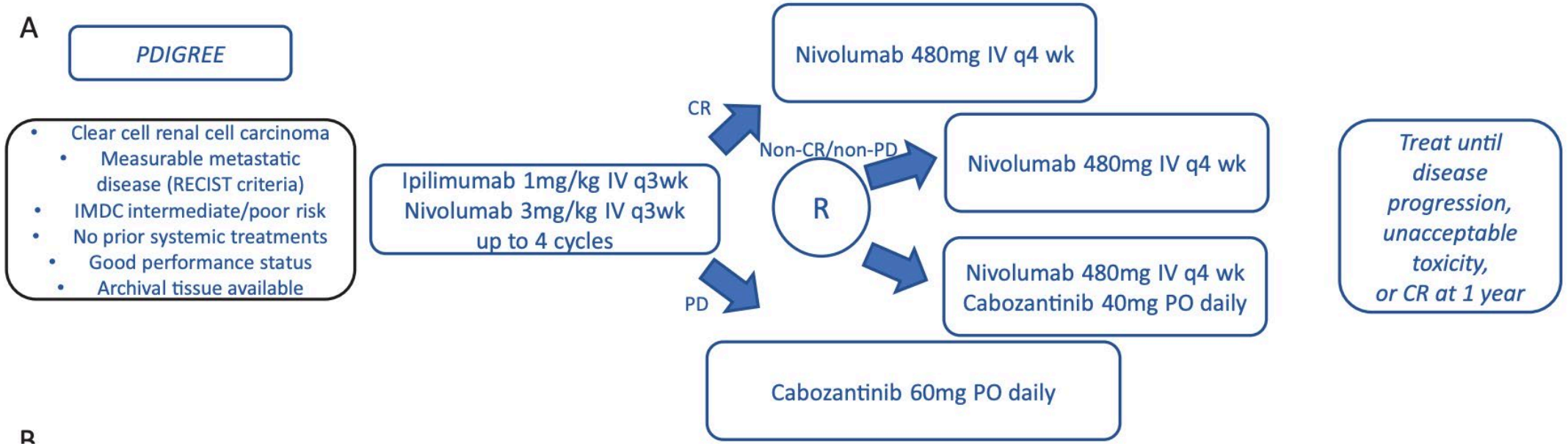
# PDIGREE and MK3475-03A

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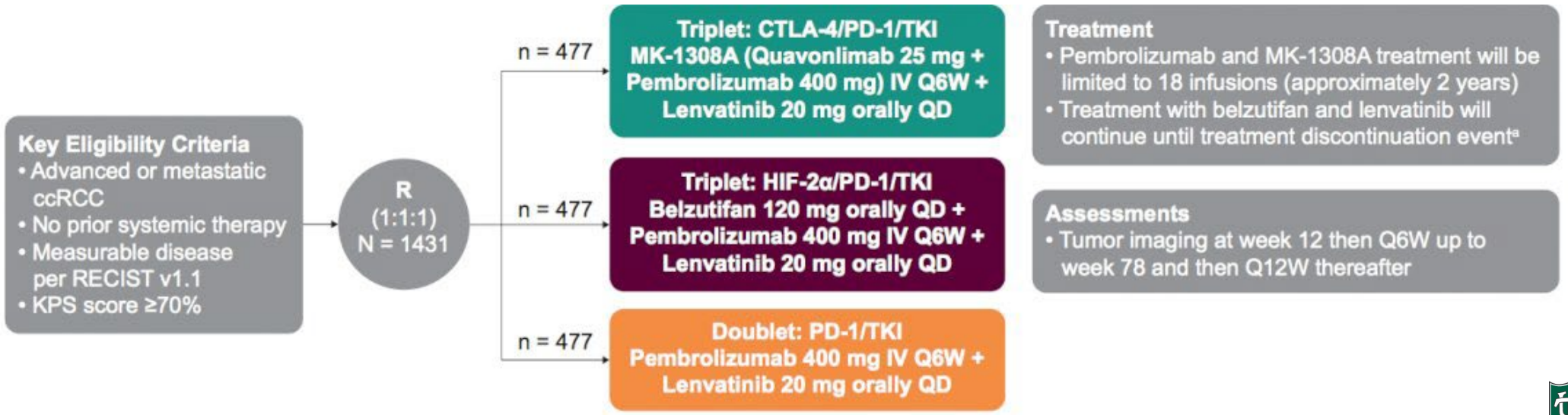


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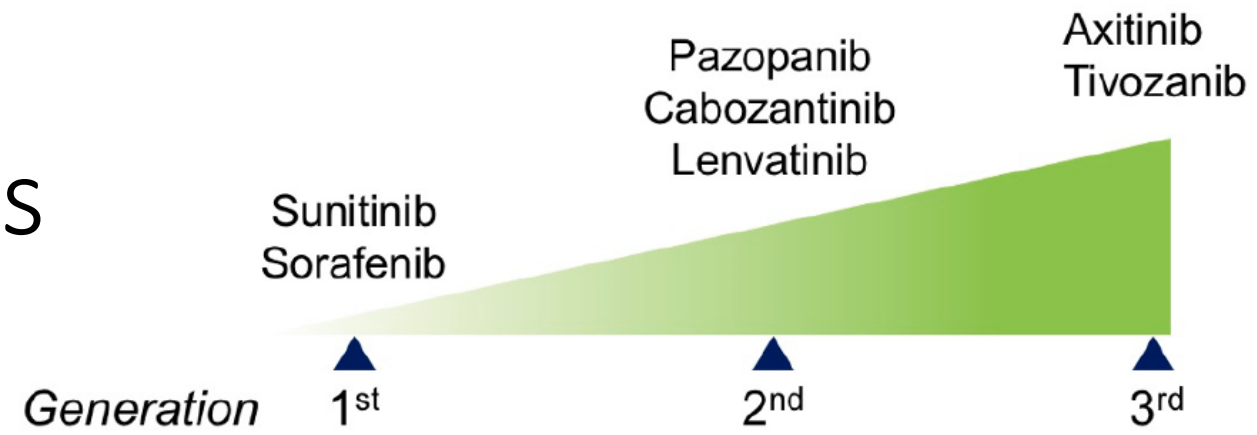
# Second Line and Beyond

# VEGF-TKI Properties




- Increased potency
- and/or VEGFR selectivity
- Favorable PK

Higher generation

**PD Properties**

| Drug name | Selectivity | Generation | Potency ($IC_{50}$, nM) | | | | | | Other targets |
|---|---|---|---|---|---|---|---|---|---|
| | | | VEGFR-1 | VEGFR-2 | VEGFR-3 | PDGFR-β | c-Kit | FGFR-1 | |
| Tivozanib | Yes | III | 0.2–30 | 0.2–6.5 | 0.2–15 | 1.7–49 | 1.6–78 | 530 | RET, FGFR-2/3 |
| Axitinib | Yes | III | 0.1–1.2 | 0.2–0.3 | 0.1–0.3 | 1.6–1.7 | 1.6–1.7 | 231 | PDGFRα |
| Pazopanib | Yes | II | 7–15 | 8–30 | 2–47 | 14–215 | 2.4–74 | 14–80 | PDGFRα |
| Lenvatinib | No | II | 1.3 | 0.74 | 0.71 | NR | 11 | 22 | PDGFRα, RET, FGFR-2/4 |
| Cabozantinib | No | II | 12.2 | 0.04–14.0 | 6 | 575 | 4.6–752 | NA | c-MET, RET, AXL, FLT3, TRKB, TIE-2 |
| Sunitinib | No | I | 2–21 | 10–38 | 3–30 | 8–75 | 1–40 | 437–880 | PDGFRα, RET, FLT3, CSF-1R |
| Sorafenib | No | I | 9 | 28–90 | 7–20 | 68 | 68–1862 | 64–580 | RET, FLT3, RAF |

$IC_{50}$: concentration required for 50% inhibition. The comparison of the pharmacological potencies among VEGFR-TKIs should be done with caution due to different assays and conditions used (e.g., inhibition of recombinant receptor tyrosine kinase activity in cell-free kinase assays or VEGF-induced phosphorylation of intracellular VEGFR in cell-based assays). NR: not reported. References: [16,18,44,94–98].

Fogli S, et al. Cancer Treat Rev. 2020;84:101966.

# Second-Line Therapy: Preferred NCCN Recommendations

| | Nivolumab vs evero[2]<br>N = 821 | Cabozantinib vs evero[3]<br>N = 658 | Lenvatinib + evero vs lenvatinib or evero[4]<br>N = 153 |
|---|---|---|---|
| **Trial** | Phase 3 CM-025 | Phase 3 METEOR | Phase 2 Study 205 |
| **Patient population** | TKI-refractory<br>(72% 1 prior) | TKI-refractory<br>(71% 1 prior) | TKI-refractory<br>(100% 1 prior) |
| **Primary end point** | OS | PFS (IRC) | PFS (INV) |
| **Risk, favorable/int/poor** | 35/49/16 | 45/42/12 | 24/37/39 |
| **ORR, %** | 25 | 17 | 43 |
| **PFS, mo** | 4.6 | 7.4 (HR 0.51; 95% CI, 0·41–0·62; P <.0001) | 14.6 (HR, 0.40; 95% CI, 0.24-0.68; P = .0005 vs evero) |
| **OS, mo** | 25.0 (HR, 0.73; 95% CI, 0.57-0.93; P =.002) | 21.4 | 25.5 |
| **Dose reductions** | N/A | 62% | 71% |
| **AE discontinuation** | 8% | 12% | 24% |
| **Toxicity** | 18% G3<br>1% G4 (tx-related) | 71% G3/4 | 57% G3<br>14% G4 |

AE, adverse event; discontinuation; evero, everolimus; tx, treatment.

1. Rini et al., *Lancet*. 2011;378:1931; 2. Motzer et al., *N Engl J Med*. 2015;373:1803;
3. Choueiri et al., *Lancet Oncol.* 2016;17:917-927; 4. Motzer et al., *Lancet Oncol*. 2015;16:1473

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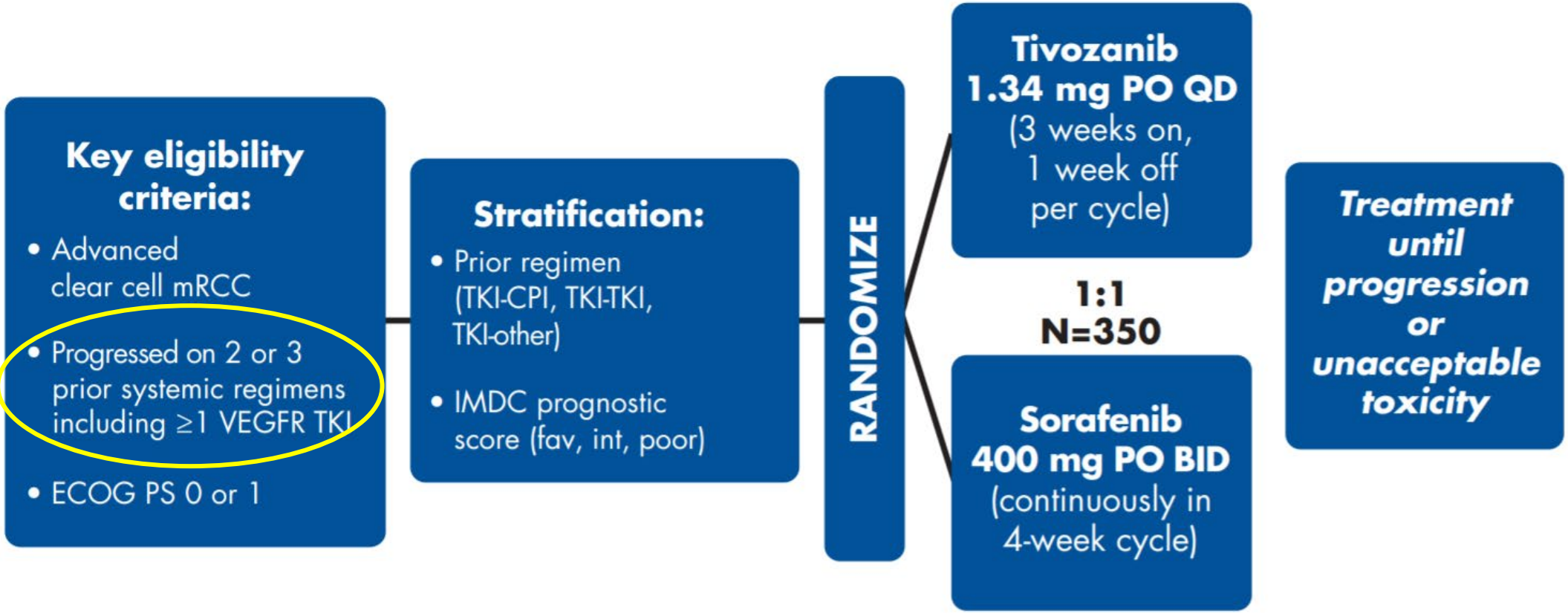
# Phase 3 TIVO-3: Study Design




**Primary endpoint: PFS (BICR)**
**Secondary endpoints: OS, ORR, DOR, and safety**

Verzoni E, et al. ASCO 2021. Abstract 4546.

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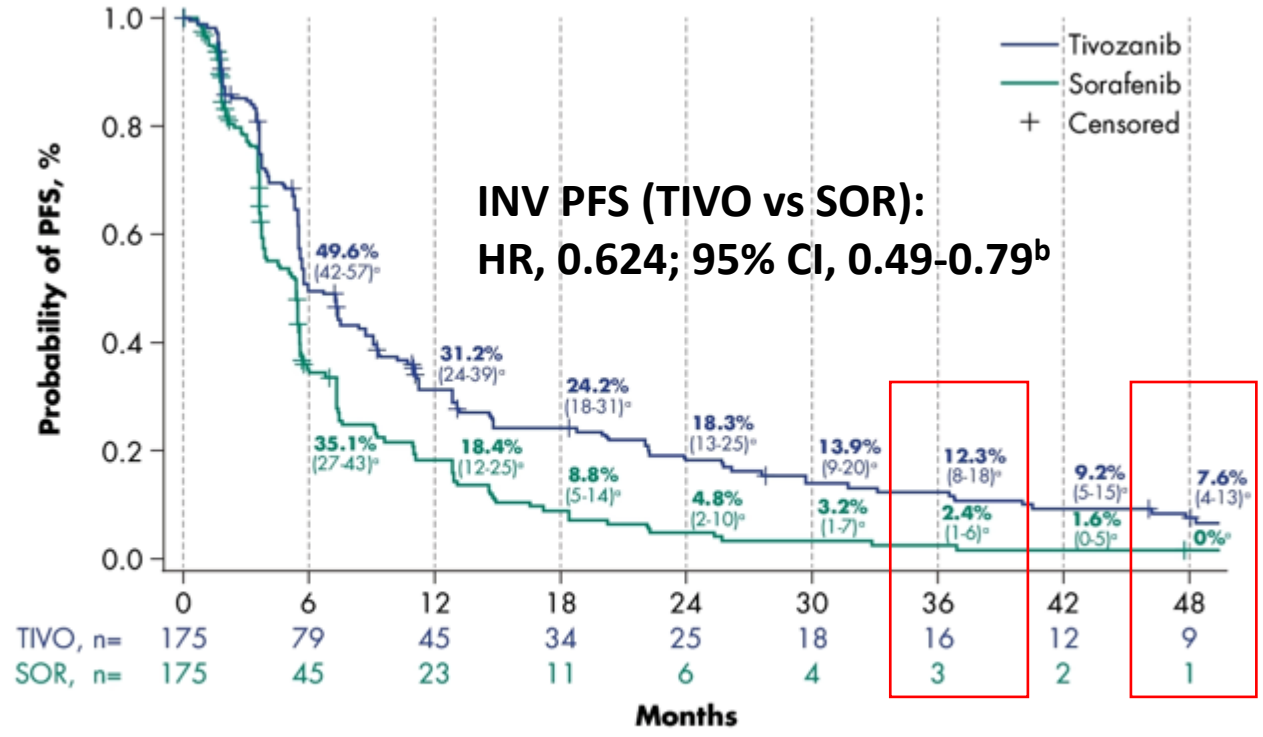
# TIVO-3: Landmark Rates of Long-Term PFS (ITT[a])— INV Assessment




**INV PFS (TIVO vs SOR):**
**HR, 0.624; 95% CI, 0.49-0.79[b]**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| LT-PFS Δ (TIVO–SOR) | 0% | 14.5% | 12.8% | 15.4% | 13.5% | 10.7% | 9.9% | 7.6% | 7.6% |
| Odds ratio (TIVO:SOR) | N/A | 1.81 | 2.02 | 3.32 | 4.46 | 4.88 | 5.73 | N/A[b] | N/A[b] |

**A clinically relevant proportion of patients were alive and progression free at 3 and 4 years after initiating TIVO therapy compared with SOR, and this difference was consistent across all clinical and demographic subgroups evaluated**

| Subgroup | TIVO n | SOR n | 12-month PFS, % | | 24-month PFS, % | | 36-month PFS, % | | 48-month PFS, % | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | TIVO | SOR | TIVO | SOR | TIVO | SOR | TIVO | SOR |
| **Prior treatment** | | | | | | | | | | |
| Any immunotherapy | 47 | 44 | 27.0 | 18.6 | 19.1 | 3.7 | 9.8[a] | NE | 6.5 | NE |
| TKI-TKI only | 79 | 80 | 31.6 | 9.8 | 18.6 | 2.0 | 13.5 | NE | NE | NE |
| No immunotherapy | 128 | 131 | 32.7 | 18.3 | 18.1 | 5.1 | 13.0 | 2.0 | 7.9 | NE |

**a.** Results include the ITT population, with censoring for missing assessments and discontinuation without PD.
**b.** Data cut-off: May 24, 2021.

Atkins MB, et al. ASCO GU 2022. Abstract 362.

# TIVO-3: Safety

| | Tivozanib (n=173)* | | | Sorafenib (n=170)* | | |
|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 1–2 | Grade 3 | Grade 4 |
| Hypertension | 46 (27%) | 35 (20%) | 0 | 23 (14%) | 23 (14%) | 0 |
| Diarrhoea | 57 (33%) | 3 (2%) | 0 | 81 (48%) | 15 (9%) | 1 (1%) |
| Fatigue | 50 (29%) | 6 (4%) | 0 | 28 (16%) | 8 (5%) | 0 |
| Decreased appetite | 42 (24%) | 6 (4%) | 0 | 35 (21%) | 3 (2%) | 1 (1%) |
| Dysphonia | 40 (23%) | 1 (1%) | 0 | 13 (8%) | 0 | 0 |
| Asthenia | 36 (21%) | 8 (5%) | 0 | 28 (16%) | 6 (4%) | 0 |
| Nausea | 33 (19%) | 0 | 0 | 21 (12%) | 4 (2%) | 0 |
| Stomatitis | 32 (18%) | 3 (2%) | 0 | 28 (16%) | 4 (2%) | 0 |
| Palmar-plantar erythrodysesthesia syndrome | 27 (16%) | 1 (1%) | 0 | 61 (36%) | 17 (10%) | 0 |
| Hypothyroidism | 23 (13%) | 1 (1%) | 0 | 10 (6%) | 0 | 0 |
| Vomiting | 13 (8%) | 1 (1%) | 0 | 17 (10%) | 3 (2%) | 0 |
| Decreased weight | 14 (8%) | 1 (1%) | 0 | 23 (14%) | 3 (2%) | 0 |
| Rash | 6 (4%) | 0 | 0 | 31 (18%) | 12 (7%) | 1 (1%) |
| Alopecia | 5 (3%) | 0 | 0 | 35 (21%) | 1 (1%) | 0 |
| Pruritus | 1 (1%) | 0 | 0 | 17 (10%) | 0 | 0 |

Rini BI, et al. *Lancet Oncol*. 2020;21:95-104.

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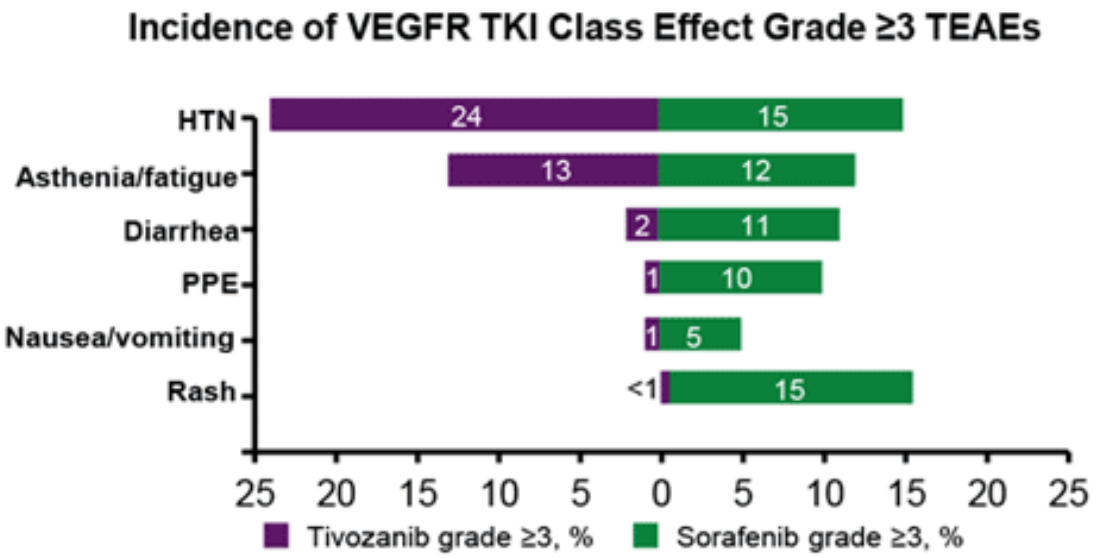
# TIVO-3: Safety (cont.)




| | TIVO (n = 173) | SOR (n = 170) |
|---|---|---|
| Exposure (mean cycles) | 11.9 | 6.7 |
| Dose interruption, % | 50 | 64 |
| Dose reduction, % | 25 | 39 |
| Dose discontinuation, % | 21 | 30 |
| Grade 3/4 TRAE, % | 46 | 55 |

**Compared with sorafenib, tivozanib was associated with:**

- ↑ tolerability, regardless of age or prior CPI treatment.
- ↑ duration of exposure
- ↓ all-grade and grade ≥ TEAEs
- ↓ dose modifications and time to dose modifications

Most frequent AEs leading to discontinuation (T vs S): malignant neoplasm progression (3% vs 1%) and fatigue (1% vs 4%. No TRAE-related deaths.

Rini B, et al. Lancet Oncol. 2020;21:95-104. Pal SK, et al. ASCO 2021. Abstract 4567. Escudier B, et al. ASCO 2021. Abstract e16553.

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## Key Inclusion Criteria

- Metastatic clear cell RCC
- Measurable disease per irRECIST[1]
- Disease progression after PD-1/PD-L1 treatment:
  - ≥ 2 doses of anti-PD-1/PD-L1
  - Defined by RECIST v1.1; confirmed ≥ 4 weeks

## Study Treatment

**Lenvatinib[a]**
20 mg/day PO
+
**Pembrolizumab[b]**
200 mg/3 weeks IV

## Primary End Point[c]

- Objective response rate at week 24

## Secondary End Points

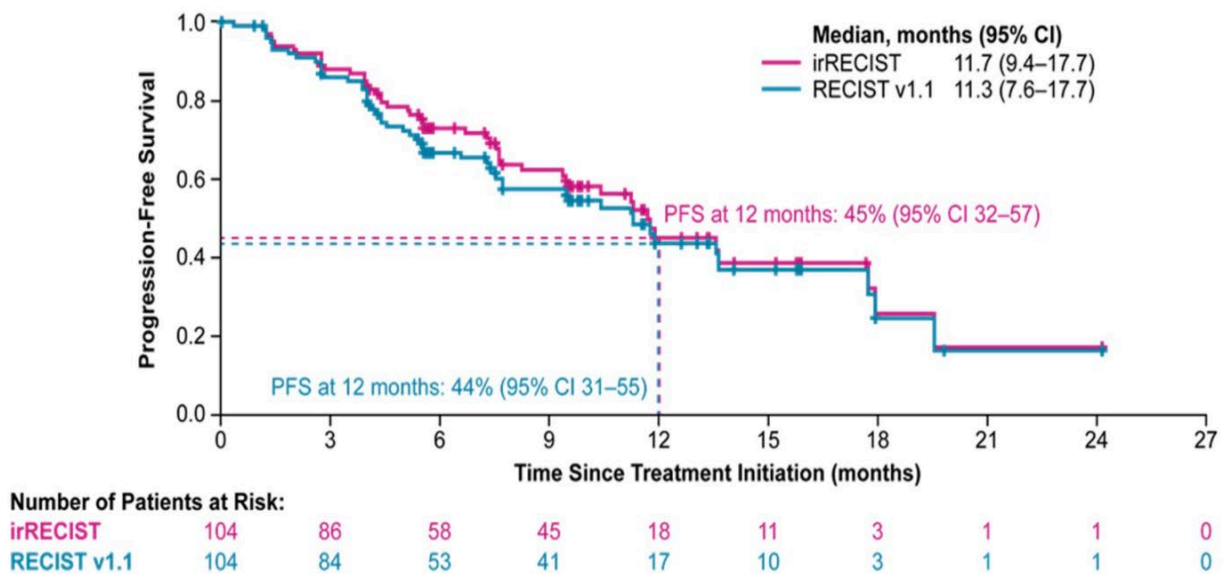
- Objective response rate[c]
- Progression-free survival[c]
- Overall survival
- Safety and tolerability

## Tumor Response by Investigator Assessment

| Parameter | irRECIST N = 104 | RECIST v1.1[a] N = 104 |
|---|---|---|
| **ORR at week 24, %** (95% CI) | 51 (41–61) | – |
| **ORR, %** (95% CI) | 55 (45–65) | 52 (42–62) |
| **Best objective response, %** | | |
| Partial response | 55 | 52 |
| Stable disease | 36 | 38 |
| Progressive disease | 5 | 6 |
| Not evaluable | 5 | 5 |
| **Median DOR, months** (95% CI) | 12 (9–18) | 12 (9–18) |

[a] Up to 10 target lesions could be selected (up to 5 per organ).

## PFS Kaplan–Meier Curves by irRECIST[a] and RECIST v1.1[a,b]




Lee at al, ASCO 2021

# CONTACT-03 and TINIVO-2

- Histologically confirmed advanced, metastatic ccRCC or nccRCC
- Radiographic progression during or following ICI treatment

R
1:1

N ≈ 500

**Atezolizumab** *IV*
*1200 mg q3w*
+
**Cabozantinib** *po*
*60 mg qd*

**Cabozantinib** *po*
*60 mg qd*

*No crossover allowed*

Treatment until loss of clinical benefit or unacceptable toxicity

Survival follow-up

## N = 326

- Histologically / cytologically confirmed recurrent/metastatic RCC
- ECOG PS 0 or 1
- Progressed following immediate prior immunotherapy treatment in first or second line
- Stratified by IMDC and prior TKI

**Randomize 1:1**

Tivozanib + Nivolumab

Tivozanib

## Treatment Until Progression

### Endpoints

- Primary: PFS
- Secondary: OS, ORR, DoR, Safety and Tolerability

# Renal Cell Cancer – NeoAdjuvant

# Patients and Methods I



**Major eligibility criteria**

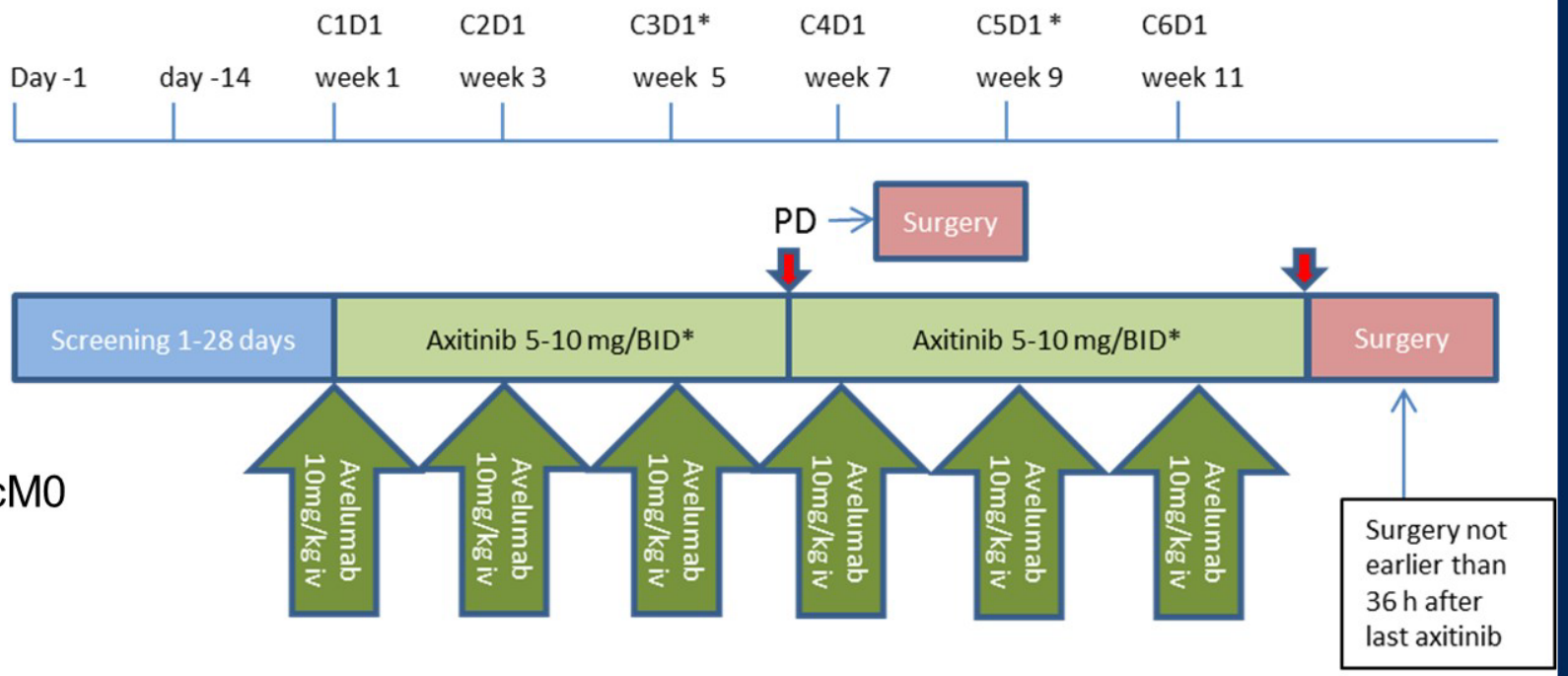
Age ≧ 18 years

Clinical high-risk clear-cell RCC by cTNM/biopsy Fuhrman grade

- cT1b-T2a $G_4$ cN0 cM0
- cT2b-T3a $G_{3-4}$ cN0 cM0
- cT3b-T4 $G_{any}$ cN0 cM0
- $cT_{any}$ cN1 (fully resectable) $G_{any}$ cM0

WHO performance status 0-1

No comorbidities precluding systemic therapy or surgery



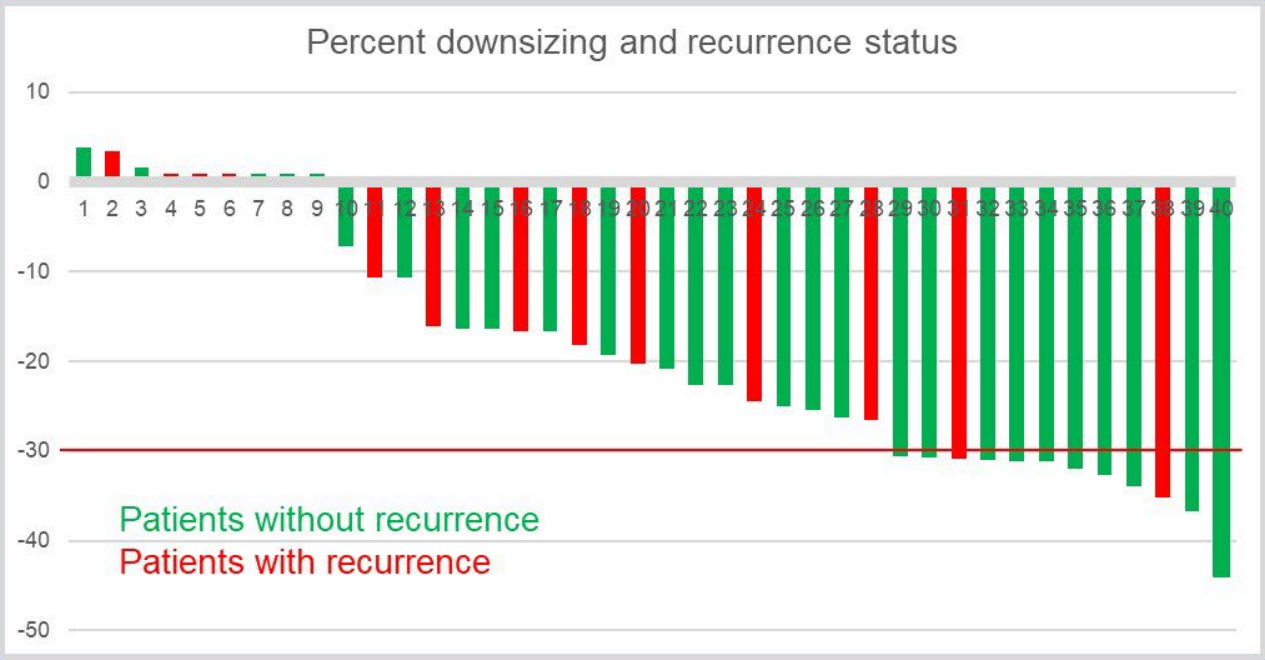

*after week 4: if tolerated well, switch to 7 mg Axitinib BID
after week 8: if tolerated well, switch to 10 mg Axitinib BID

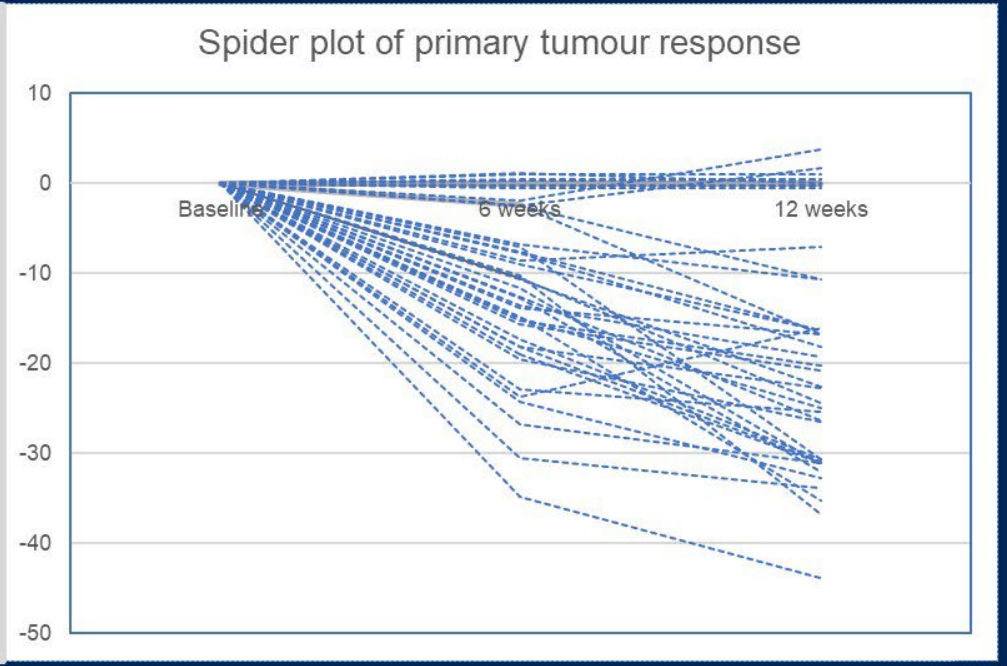
Neoavax (NCT03341845) is an open label, single arm, phase II trial, investigating 12 weeks of neoadjuvant avelumab/axitinib prior to nephrectomy in patients with high-risk non-metastatic clear-cell RCC.



PRESENTED BY: Axel Bex, MD, PhD

# Primary tumour response




Twelve patients (30%) had a partial response (PR) of their primary tumour. Median primary tumour downsizing was 20 % (+3.8--43.5). Of the 12 patients with PR of the primary tumour, 10 (83%) are disease-free. None of the primary tumours progressed by RECIST 1.1.





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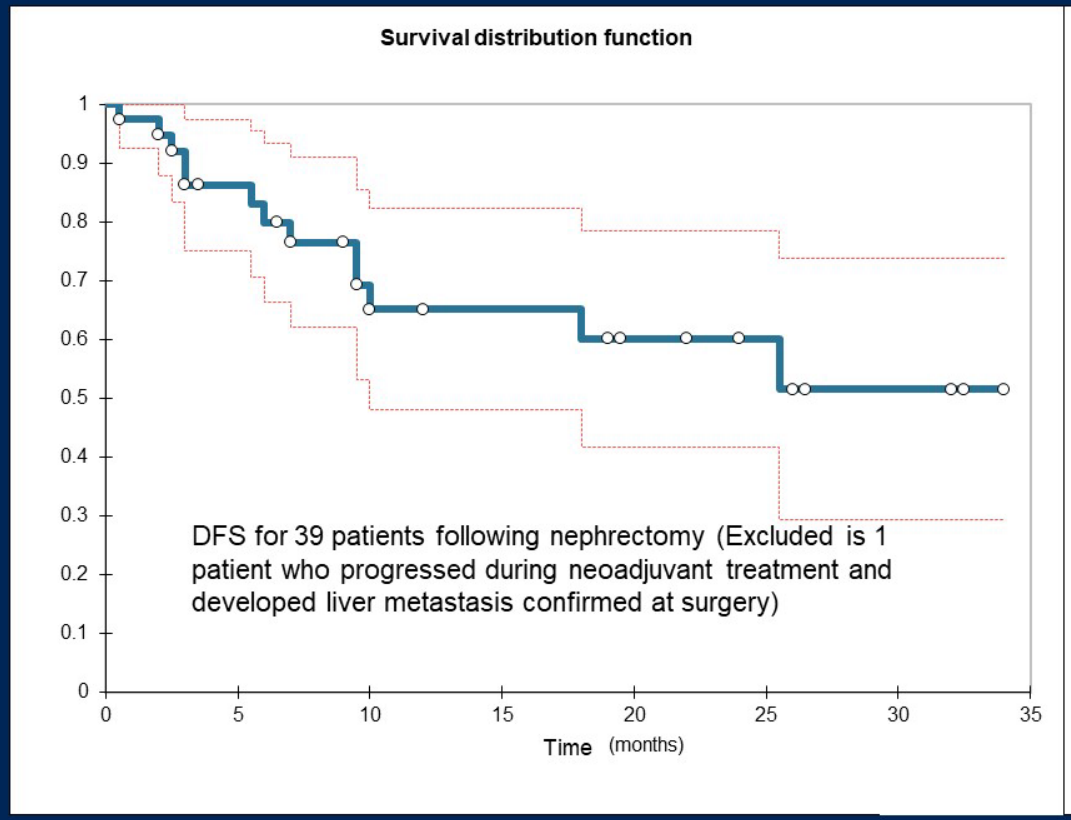
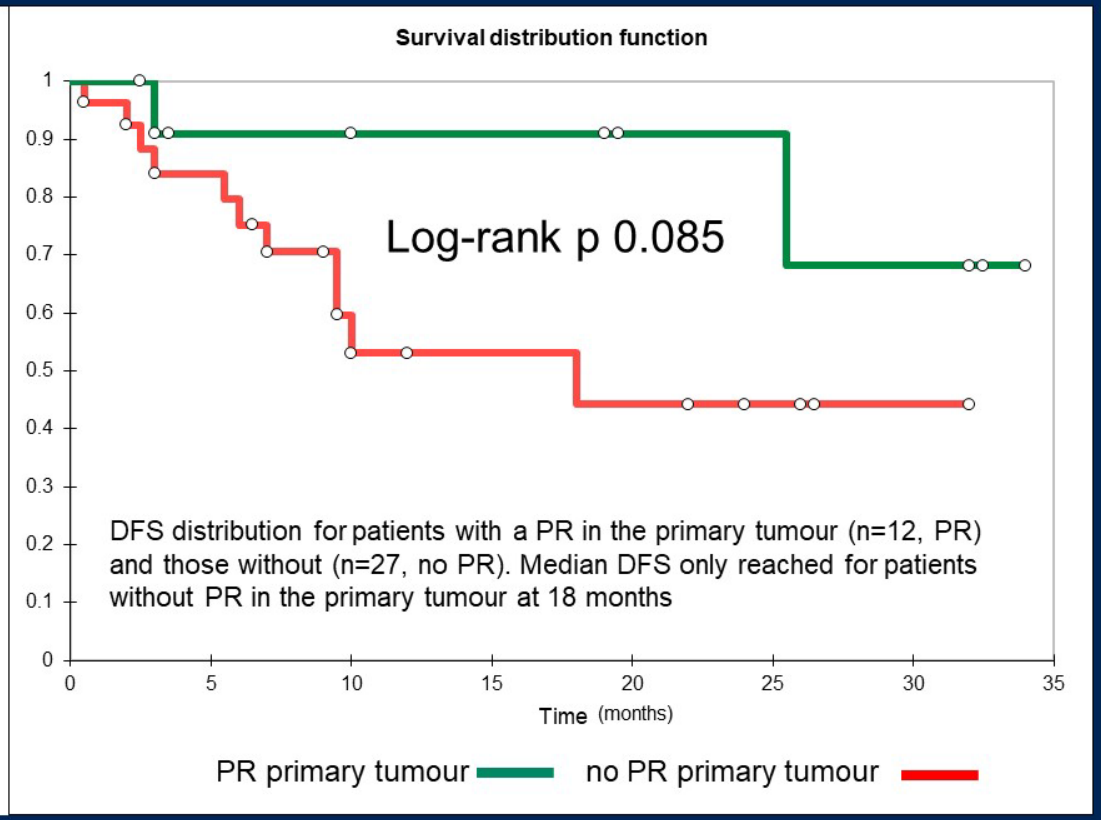
# Disease-Free Survival

At a median follow-up of 23.5 months, recurrence occurred in 13 (32.5%) patients and 3 died of disease. Median DFS and OS were not reached.





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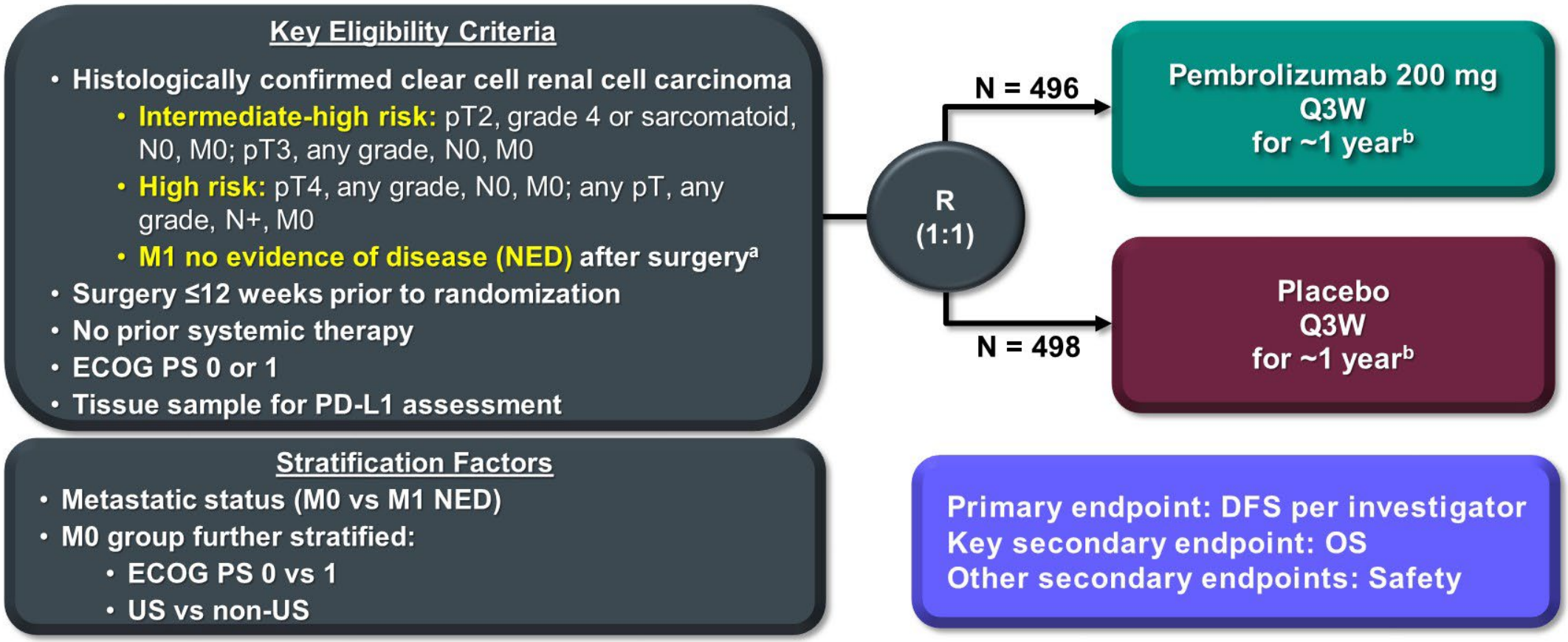
# Renal Cell Cancer – Adjuvant

# KEYNOTE-564 (NCT03142334) Study Design




- Median (range) time from randomization to cutoff: 30.1 (20.8−47.5) months

Q3W, every 3 weeks.
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.
Data cutoff date: June 14, 2021.

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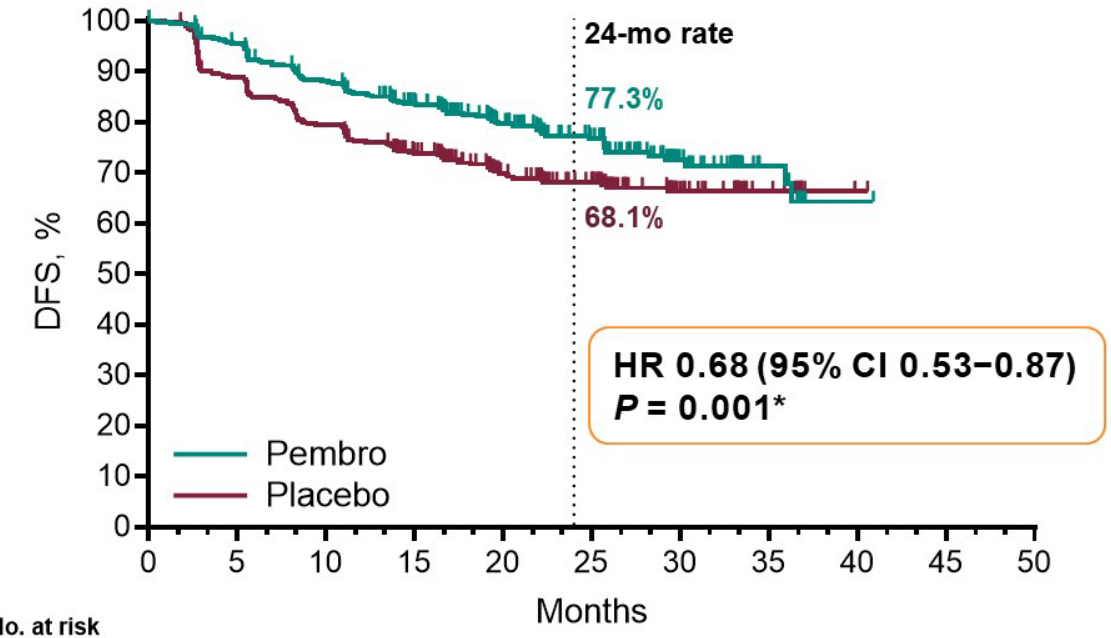
# Primary Endpoint: DFS, ITT Population

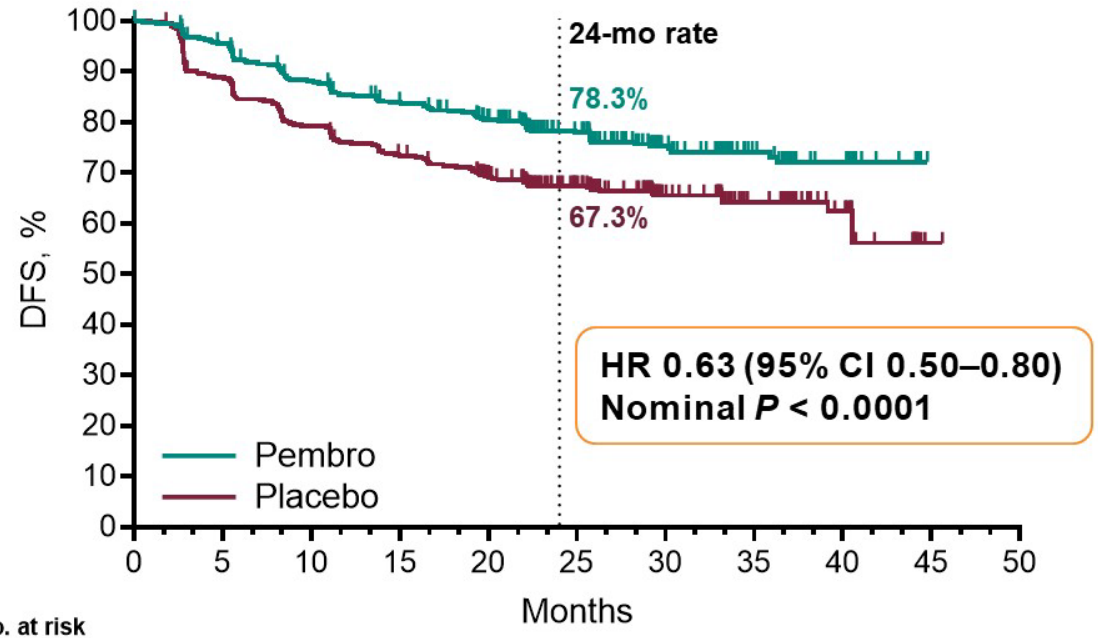
**Primary Analysis: 24.1 mo Follow-Up**




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro | 496 | 457 | 414 | 371 | 233 | 151 | 61 | 21 | 1 | 0 | 0 |
| Placebo | 498 | 436 | 389 | 341 | 209 | 145 | 56 | 19 | 1 | 0 | 0 |

| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| **Pembro** | 109 | NR (NR–NR) |
| **Placebo** | 151 | NR (NR–NR) |

**Updated Analysis: 30.1 mo Follow-Up**




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro | 496 | 458 | 416 | 389 | 361 | 255 | 135 | 77 | 37 | 0 | 0 |
| Placebo | 498 | 437 | 389 | 356 | 325 | 230 | 125 | 74 | 33 | 1 | 0 |

| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| **Pembro** | 114 | NR (NR–NR) |
| **Placebo** | 169 | NR (40.5–NR) |

* denotes statistical significance.

ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.



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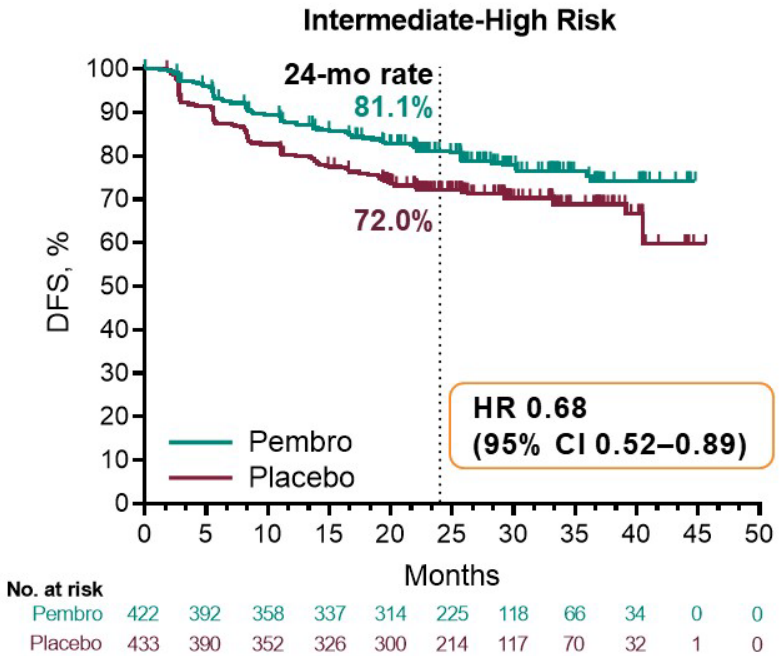
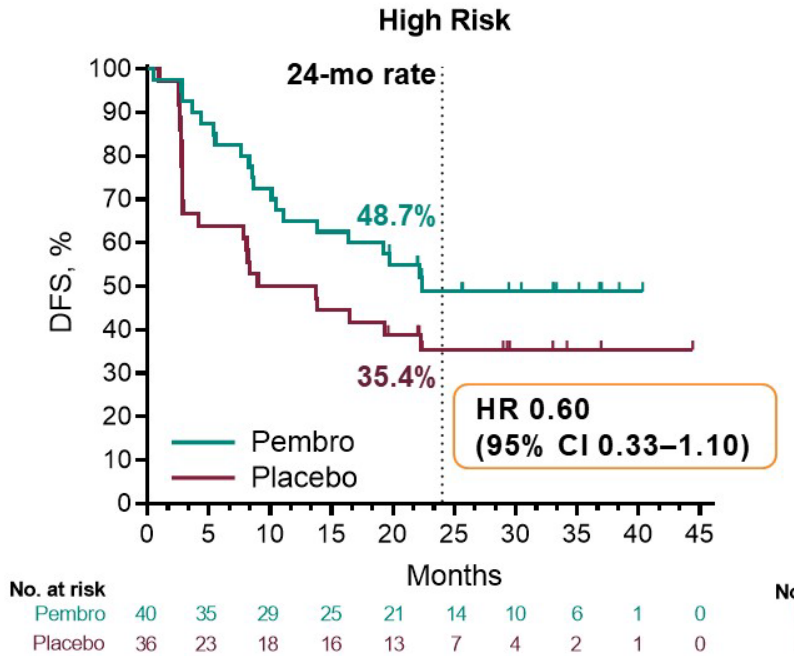
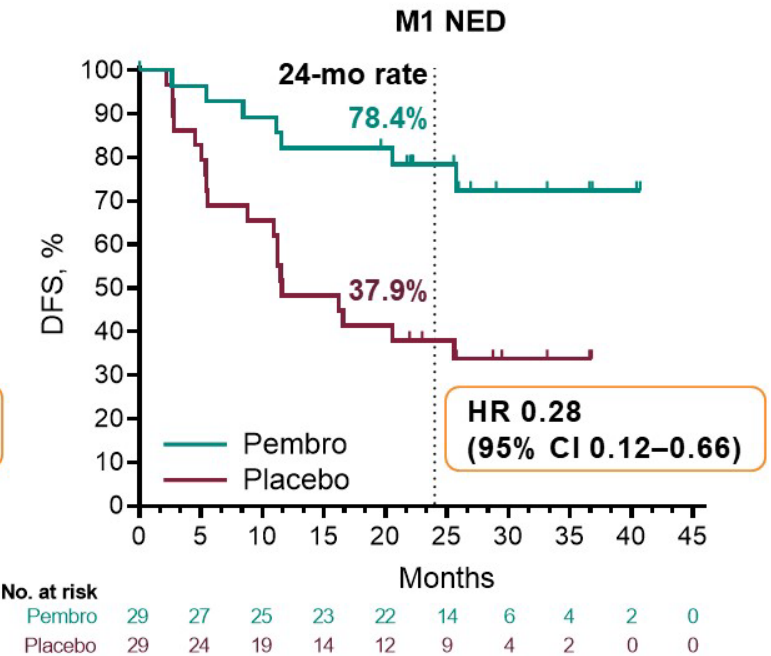
# DFS by Recurrence Risk Subgroups




| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| **Pembro** | 87 | NR (NR–NR) |
| **Placebo** | 127 | NR (40.5–NR) |




| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| **Pembro** | 20 | 22.4 (11.1–NR) |
| **Placebo** | 23 | 11.4 (2.9–NR) |




| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| **Pembro** | 7 | NR (25.7–NR) |
| **Placebo** | 19 | 11.6 (5.6–NR) |

**Intermediate-high risk**: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0;
**High risk**: pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0;
**M1 NED**: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy.
DFS, disease-free survival; NR, not reached. Data cutoff date: June 14, 2021.



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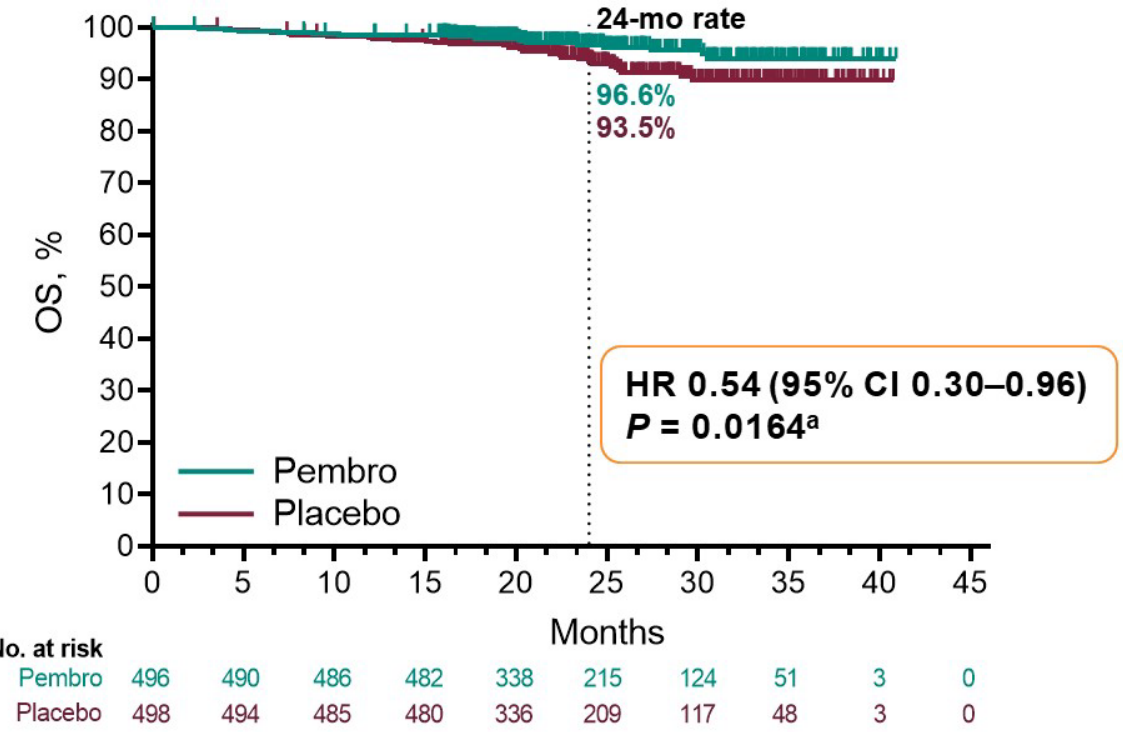
# Key Secondary Endpoint: OS, ITT Population

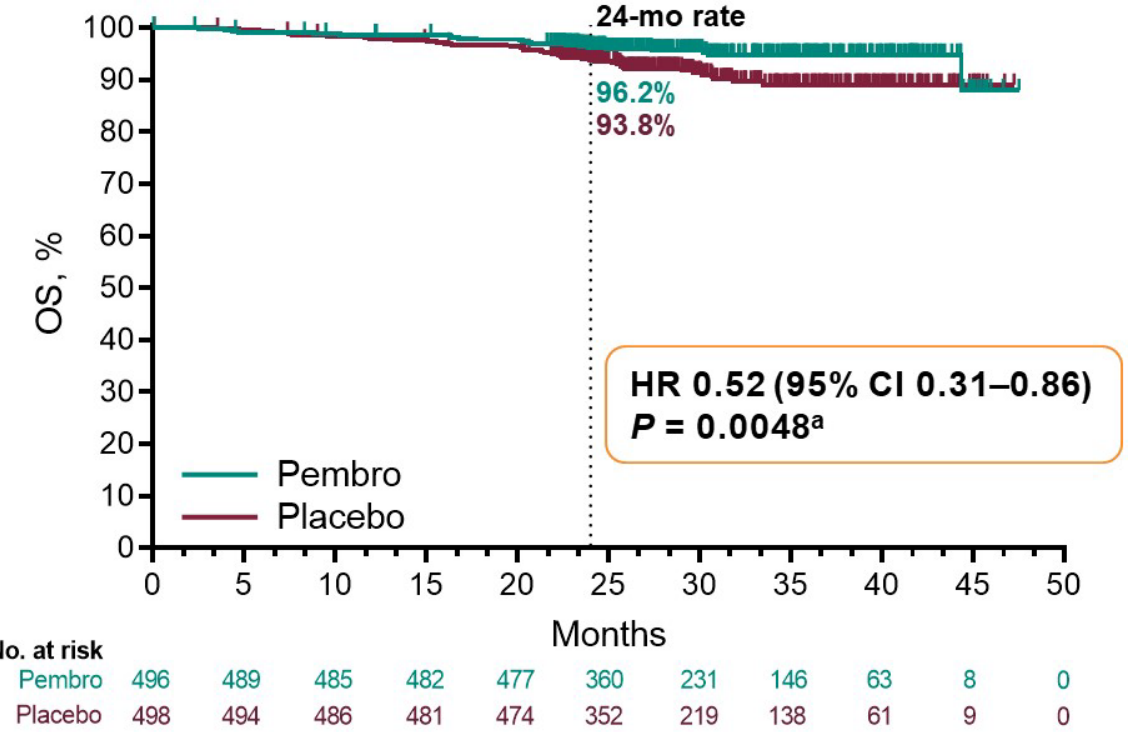
## Primary Analysis: 24.1 mo Follow-Up




| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pembro | 496 | 490 | 486 | 482 | 338 | 215 | 124 | 51 | 3 | 0 |
| Placebo | 498 | 494 | 485 | 480 | 336 | 209 | 117 | 48 | 3 | 0 |

| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| Pembro | 18 | NR (NR–NR) |
| Placebo | 33 | NR (NR–NR) |

## Updated Analysis: 30.1 mo Follow-Up




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro | 496 | 489 | 485 | 482 | 477 | 360 | 231 | 146 | 63 | 8 | 0 |
| Placebo | 498 | 494 | 486 | 481 | 474 | 352 | 219 | 138 | 61 | 9 | 0 |

| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| Pembro | 23 | NR (NR–NR) |
| Placebo | 43 | NR (NR–NR) |

[a]Did not cross prespecified p-value boundary for statistical significance.
ITT population included all randomized participants. NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

# Studies of Adjuvant IO in RCC

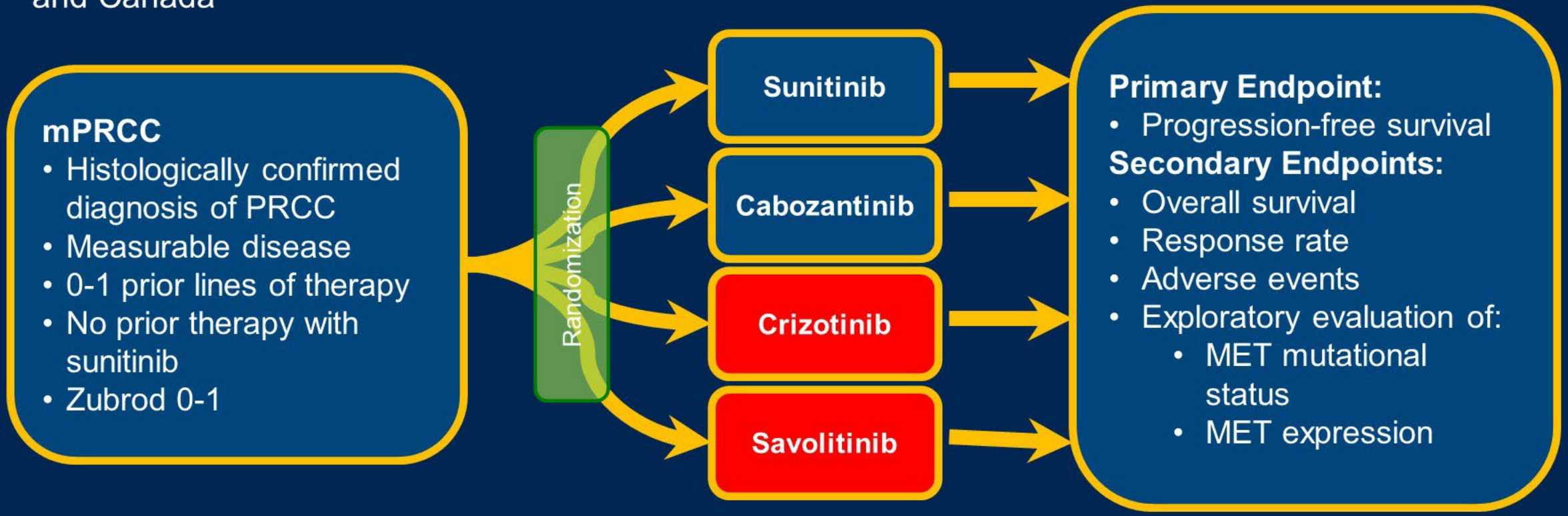
| Trial | Sample Size | Inclusion Criteria | Treatment | Primary Endpoint | Expected Results |
|---|---|---|---|---|---|
| **Keynote-564**[1] | 994 | pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell | Pembrolizumab vs placebo | DFS | **ASCO 2021 ASCO GU 2022** |
| **IMmotion010**[2] | 778 | pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell | Atezolizumab vs placebo | DFS | 1/2022 |
| **CheckMate-914**[3] | 1600 | pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell | Nivolumab + ipilimumab vs. nivolumab + placebo vs placebo *(6 months)* | DFS | 1/2023 |
| **PROSPER RCC**[4] | 766 | T2Nx, TxN1, TxNxM1 (resected to NED); any RCC histology | Nivolumab vs observation | EFS | 11/2023 |
| **RAMPART**[5] | 1750 | Leibovich score 3-11; any RCC histology | Durvalumab + tremelimumab vs durvalumab vs observation | DFS, OS | 7/2024 |

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy.
DFS, disease-free survival; EFS, event-free survival; NED, no evidence of disease; RCC, renal cell carcinoma; OS, overall survival.
1. Choueiri TK et al. *N Engl J Med*. 2021;385:683-694. 2. NCT03024996. 3. NCT03138512. 4. NCT03055013. 5. NCT03288532.

# Non-Clear Cell Renal Cell Carcinoma

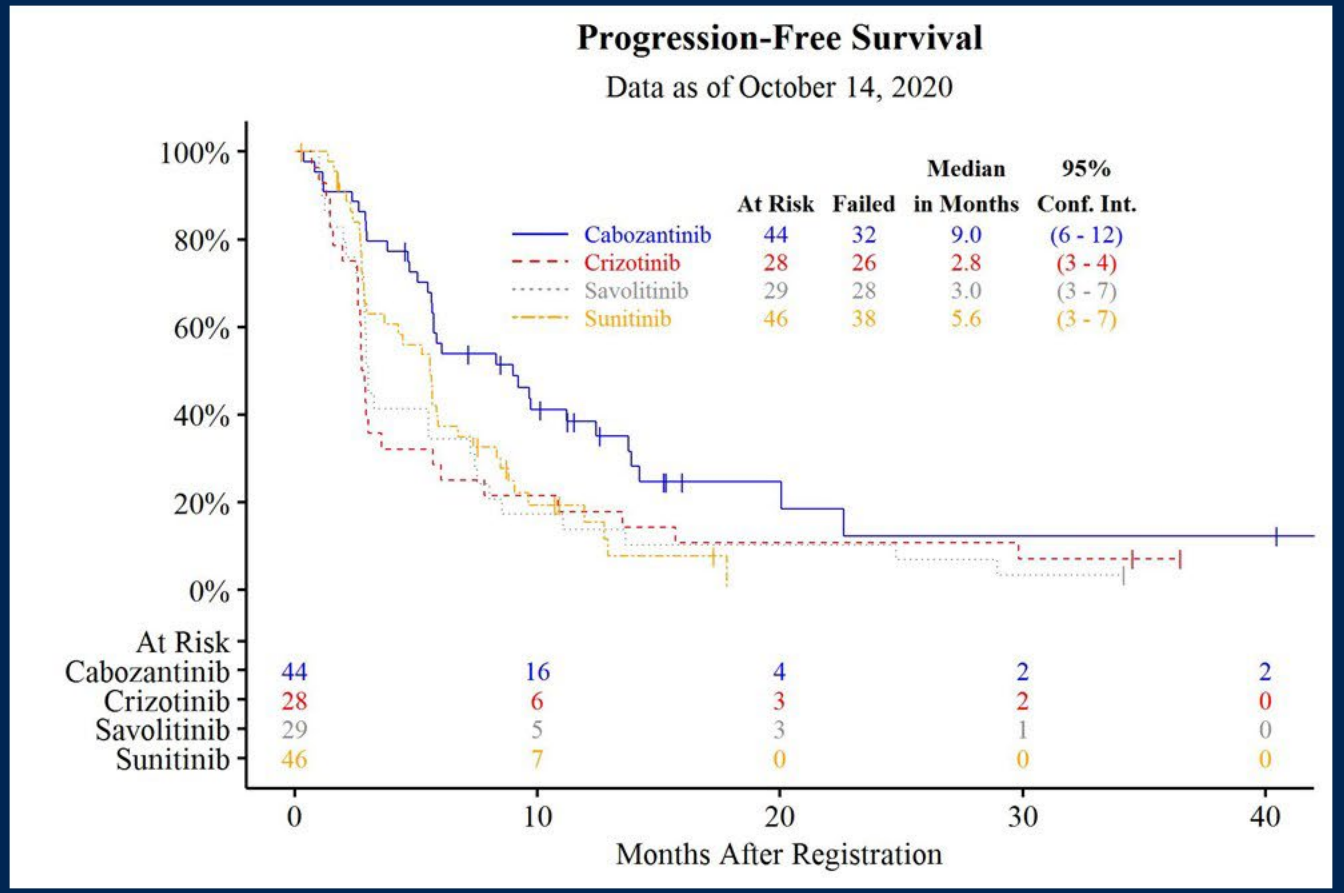
# Results: Accrual and Futility Analysis

- From April 2016 to December 2019, 152 patients were enrolled at 65 centers throughout the US and Canada




- Savolitinib and crizotinib arms closed for futility in December of 2018

# Results: Progression-Free Survival




- Cabozantinib significantly prolonged PFS relative to sunitinib (HR 0.60 (95%CI 0.37-0.97 [1-sided P-value=0.019])

# Study Design

**Key Inclusion Criteria**
- Advanced or metastatic ncRCC
- Measurable disease per RECIST v1.1
- 0–1 prior lines of systemic therapy

## Study Treatment

**Cabozantinib**
40 mg PO daily

+

**Nivolumab**
240 mg IV every 2 weeks
(or 480 mg IV 4 weeks)

**Primary Endpoint**
- ORR by RECIST

**Secondary Endpoints**
- PFS by RECIST
- PFS by irRECIST
- OS
- Safety and tolerability

**This is a single center, open-label, phase 2 study (NCT03635892) including patients treated with 0 or 1 prior systemic therapies in non-clear cell RCC with select histologies[1]:**

- Cohort 1: papillary[2], unclassified, or translocation-associated RCC (N=40)
- Cohort 2: chromophobe RCC (N=7)

**Cohort 1 was a single-stage design that met its primary endpoint (N=20) and was expanded to produce more precise estimates of ORR (total N=40). Cohort 2 was a Simon two-stage design that closed early.**

[1]Histopathology was prospectively reviewed at MSKCC and retrospectively reviewed/confirmed by dedicated GU pathologist (YC)
[2]Papillary included unclassified with papillary features, high grade/type 1 papillary, and FH-deficient/type 2 papillary

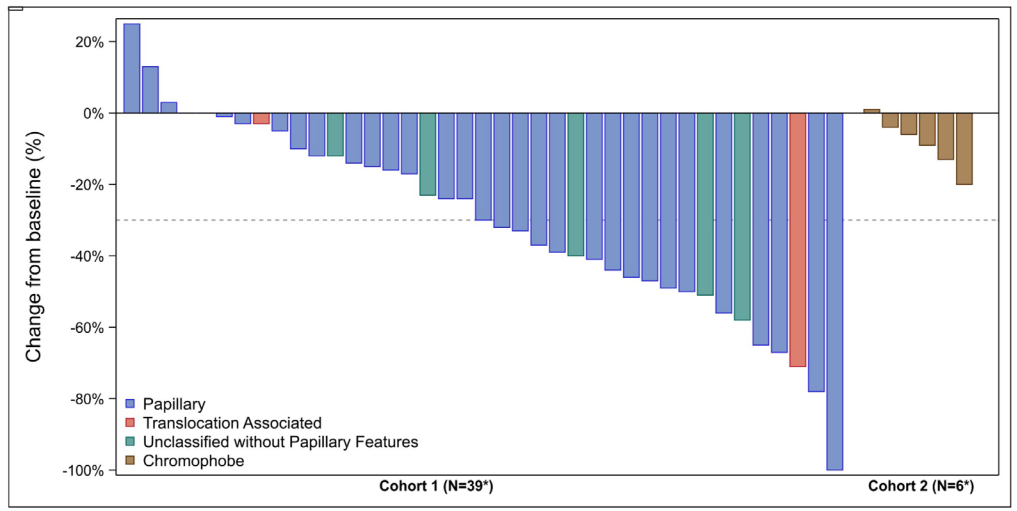
ncRCC, non-clear cell renal cell carcinoma, ORR, objective response rate; RECIST, Response Evaluation Criteria In Solid Tumors v1.1; irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; PO, orally; IV, intravenously; PFS, progression-free survival; OS, overall survival

## Summary of Efficacy Outcomes

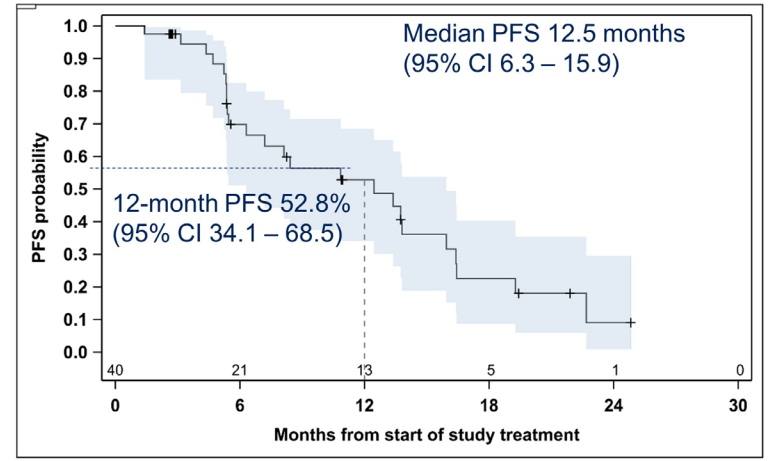
| | Cohort 1 (N=40) | Cohort 2 (N=7) |
|---|---|---|
| Objective response rate (95% CI) | 47.5% (31.5, 63.9) | 0% (0, 41.0) |
| Best response – n (%) | | |
| Partial response | 19 (47%) | 0 (0%) |
| Stable disease | 20 (50%) | 5 (71%) |
| Progressive disease | 1 (3%) | 1 (14%) |
| Not Evaluable | 0 (0%) | 1 (14%) |
| Disease control rate (95% CI) | 97.5% (86.8, 99.9) | 71.4% (29.0, 96.3) |
| Clinical benefit rate (95% CI) | 75.0% (58.8, 87.3) | 57.1% (18.4, 90.1) |
| Median progression-free survival, months (95% CI) | 12.5 (6.3, 15.9) | * |
| Median duration of response, months (95% CI) | 13.6 (9.7, 19.8) | † |

*Median PFS not calculated due to small numbers of patients.
†No responders in cohort to calculate DOR

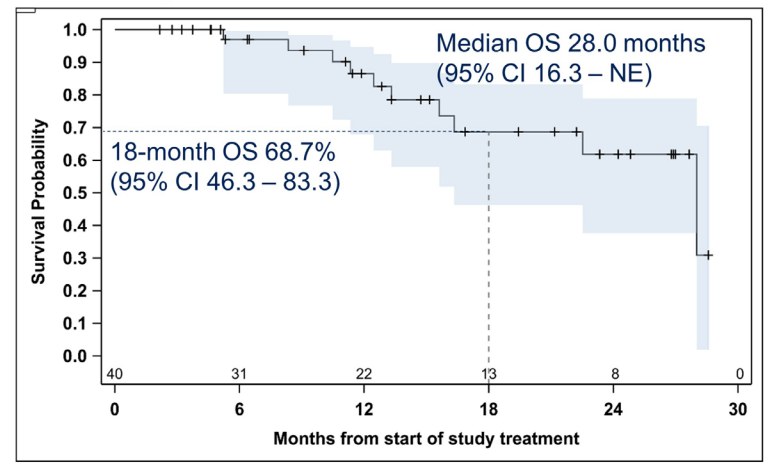
## Maximum Change in Target Lesions by Histology




## PFS by RECIST Kaplan-Meier Curve of Cohort 1 (Papillary/unclassified/translocation-associated)




## OS Kaplan-Meier Curve of Cohort 1



# Summary Points

- Primary renal tumors respond to systemic therapy with IO-based therapy (but less than metastatic sites)
- The gold-standard for mRCC is an IO-based combination (TKI monotherapy is the exception, not the rule!)
- TKI is the current SOC (includes novel agents, ie tivozanib). IO rechallenge might play a role: CONTACT3 and TINIVO2 will confirm
- nccRCC (papillary, uncl, transl ++) might benefit from IO-TKI (cabo/nivo)
- The benefit of adjuvant IO seems associated with the higher risk of recurrence/progression

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# *Urothelial Carcinoma*

# Platinum and Cisplatin Eligibility Criteria[1-4]

| Platinum-Ineligible 10% to 15% | Platinum-Eligible (85-90%) |
|---|---|

| Platinum-Ineligible Criteria | Cisplatin-Ineligible Criteria (~35%) |
|---|---|
| **Proposed consensus definition (Gupta JCO 2019)[2]**<br><br>One of the following 5 parameters to be used to define "platinum-ineligible"<br>• ECOG PS ≥3<br>• CrCl <30 ml/min<br>• Peripheral neuropathy ≥ grade 3<br>• NYHA Class III heart failure<br>• ECOG PS 2 and CrCl <30 ml/min | **Proposed working group cisplatin ineligibility criteria (Galsky JCO 2011)[3]**<br><br>At least one of the following<br>• WHO or ECOG PS of 2 or Karnofsky PS of 60% to 70%<br>• CrCl <60 mL/min<br>• CTCAE v4 grade ≥2 audiometric hearing loss<br>• CTCAE v4 grade ≥2 peripheral neuropathy<br>• NYHA Class III heart failure |

1. Internal resource: 1L UC Landscape and Patient Journey: US Report 07.30.2019. 2. Gupta S. et al, *J Clin Oncol.* 2019;37(Suppl 7s):abst 451. 3. Galsky MD, et al, *J Clin Oncol.* 2011;29: 2432-2438. 4. Kantar Health, Utilization and number of months of first-line systemic therapy, metastatic bladder cancer, United States, 2019

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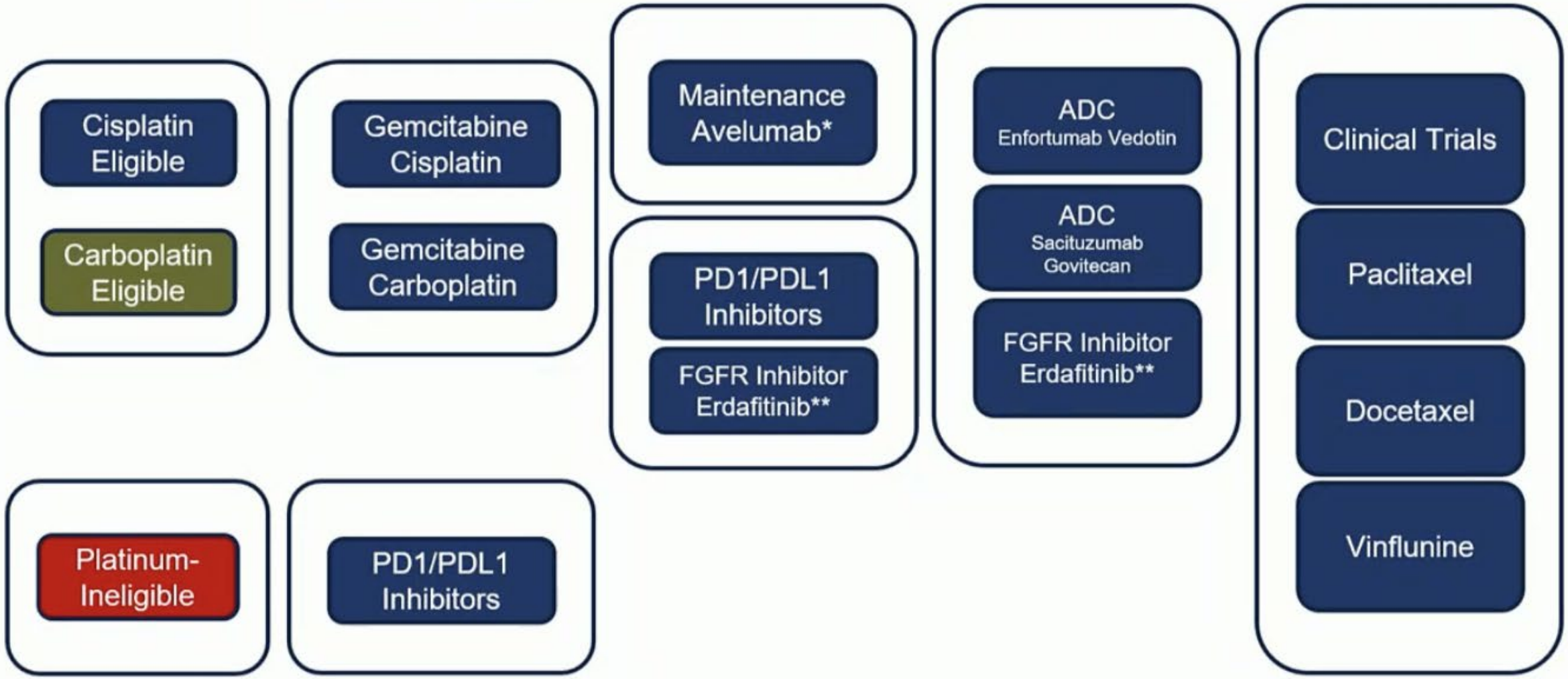
# Treatment Landscape of mUC in 2021




*Disease control on platinum-based chemotherapy; ** FGFR 2/3 alterations, no prior Erdafitinib. ADC - Antibody Drug Conjugates

# *First-line mUC – platin-eligible*

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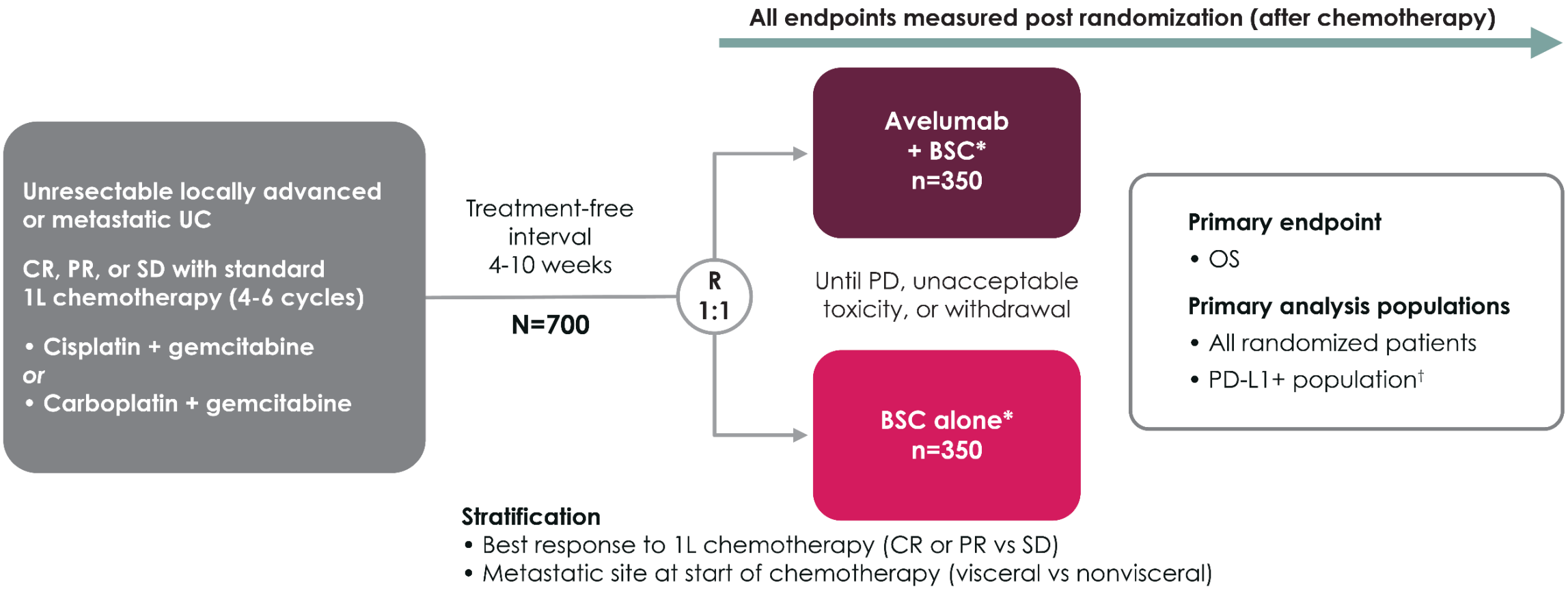
# JAVELIN Bladder 100 Phase III Study



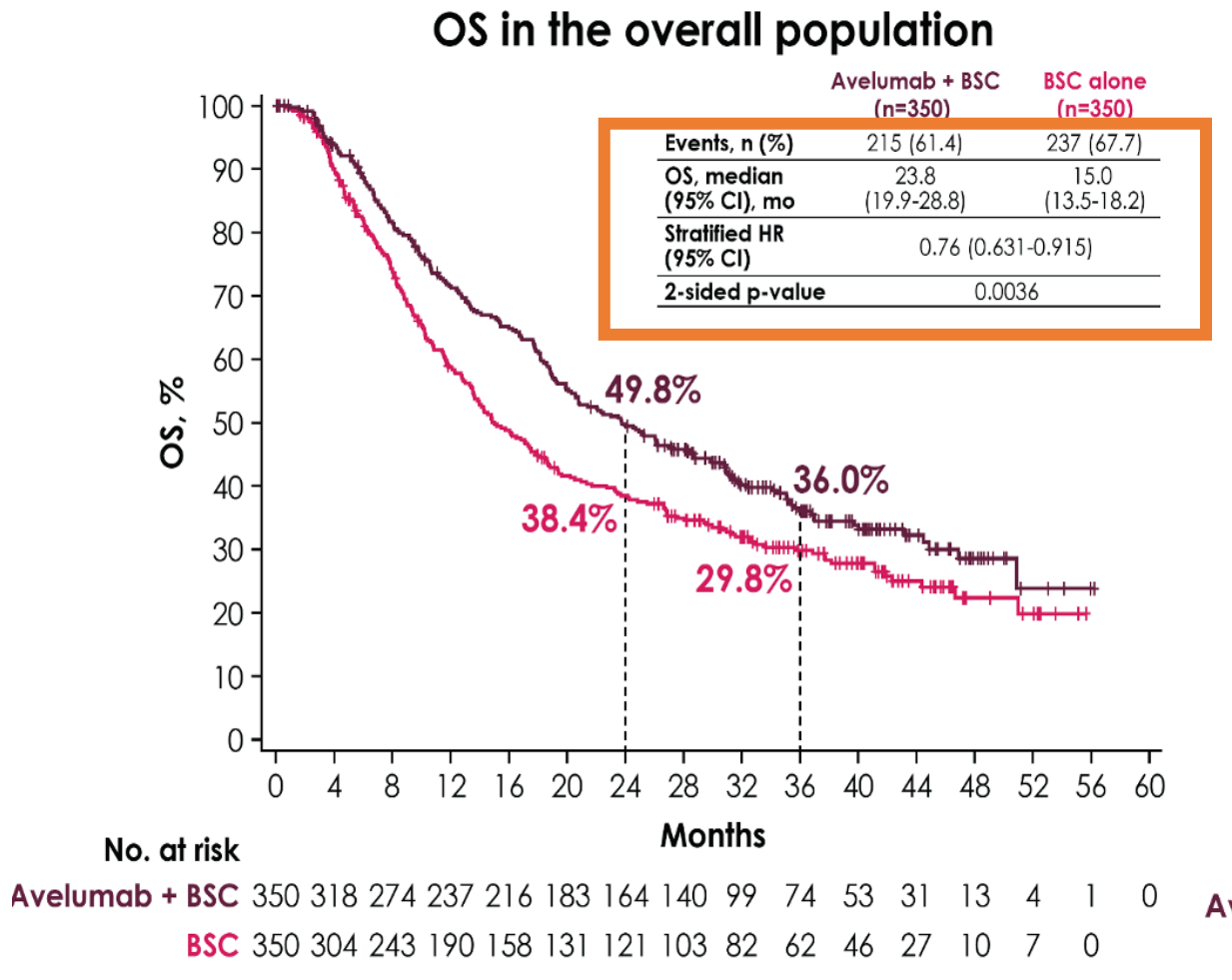

Data cutoff date: June 2021

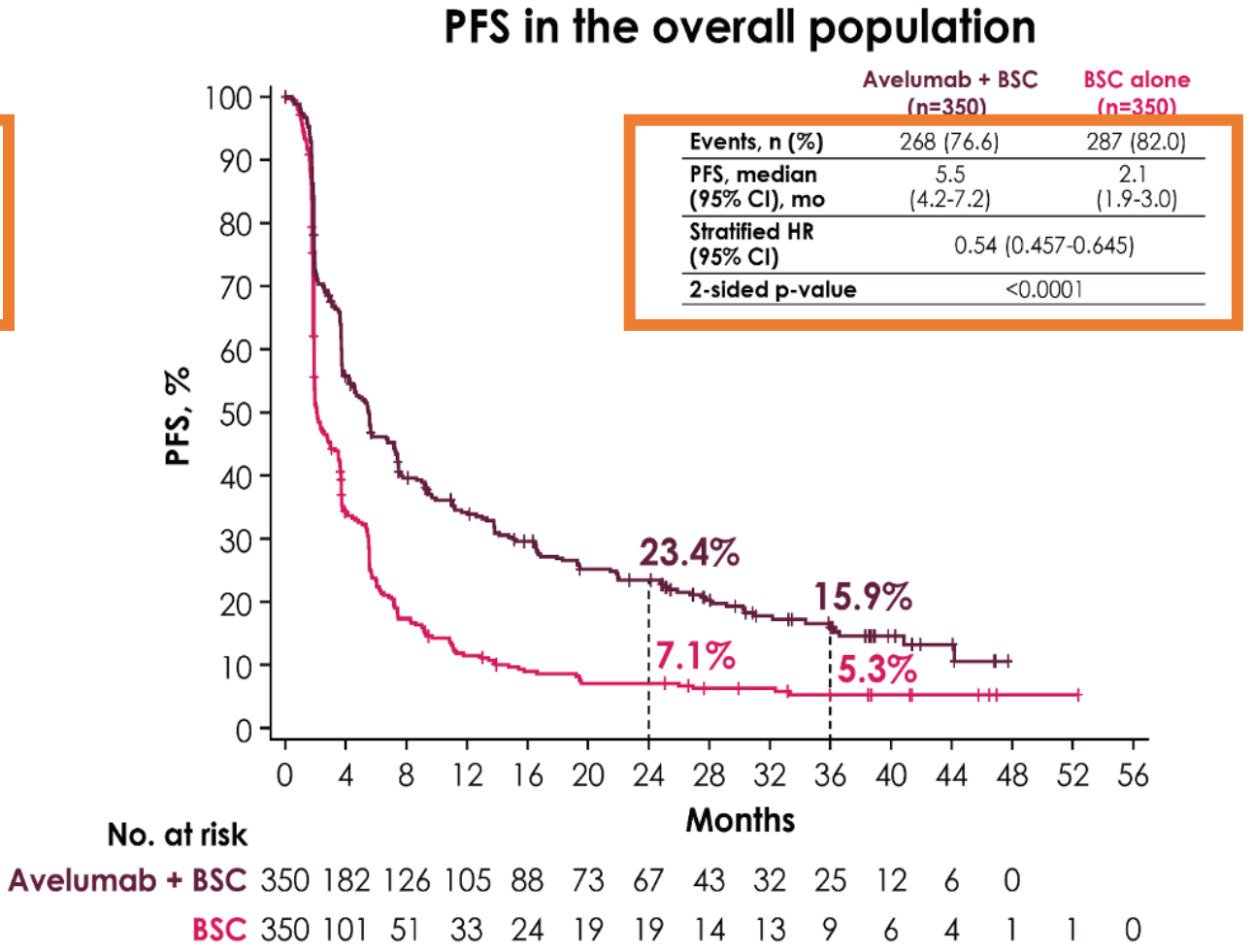
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. †Assessed using the Ventana SP263 assay.

1L, first line; BSC, best supportive care; CR, complete response; PR, partial response; OS, overall survival; PD, progressive disease; R, randomization; SD, stable disease; UC, urothelial carcinoma.

Presented by Srikala Sridhar at ASCO 2021 Annual Meeting June 4-8, 2021. Abstract 4527.

# OS and PFS in the Overall Population: 38m Follow-up

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# JAVELIN Bladder 100:Updated Subsequent Anticancer Therapy: 38 mo Follow-up

| | All patients (N=700) | | Subgroup that discontinued study treatment due to PD (n=484) | |
|---|---|---|---|---|
| | Avelumab + BSC (n=350) | BSC alone (n=350) | Avelumab + BSC (n=209) | BSC alone (n=275) |
| **Discontinued and received subsequent drug therapy, n (%)** | 185 (52.9) | 252 (72.0) | 158 (75.6) | 225 (81.8) |
| PD-1 or PD-L1 inhibitor | 40 (11.4) | 186 (53.1) | 27 (12.9) | 166 (60.4) |
| FGFR inhibitor | 10 (2.9) | 13 (3.7) | 10 (4.8) | 11 (4.0) |
| Any other drug | 177 (50.6)* | 156 (44.6)† | 151 (72.2) | 139 (50.5) |
| **Study treatment ongoing, n (%)** | 43 (12.3) | 10 (2.9) | – | – |

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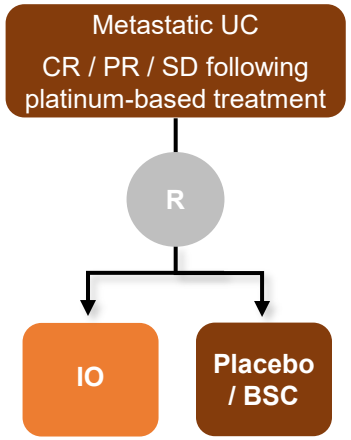
# Current First-line Metastatic UC Maintenance and Combination Trials

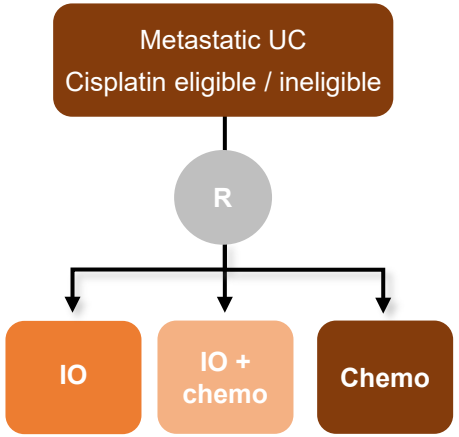
## Treatment Strategies with the Potential to Impact Standard of Care

### Maintenance



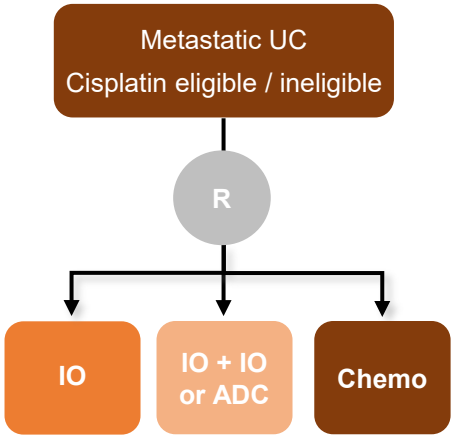

| | | | |
|---|---|---|---|
| **JB100** [NCT02603432] | avelumab | BSC | OS |
| **HOOSIER** [NCT02500121] | pembro | placebo | 6-mo PFS |

### Chemo + IO




| | | | | |
|---|---|---|---|---|
| ~~**KN361**~~ [NCT02853305] | pembro | pembro + chemo | chemo | OS, PFS |
| **CM901** [NCT03036098] | -- | nivo + chemo* | chemo | OS, PFS |
| ~~**IMvigor130**~~ [NCT02807636] | atezo | atezo + chemo | chemo | OS, PFS, safety |
| **NILE**† [NCT03682068] | durva | durva + chemo | chemo | OS, PFS |

### IO + IO/ IO + ADC




| | | | | |
|---|---|---|---|---|
| ~~**DANUBE**~~ [NCT02516241] | durva | durva + treme | chemo | OS |
| **CM901** [NCT03036098] | -- | nivo + ipi | chemo | OS, PFS |
| **EV-302** [NCT04223856] | pembro | pembro + EV + chemo | chemo | OS, PFS |
| **NILE**† [NCT03682068] | durva | durva + treme + chemo | chemo | OS, PFS |

~~Study~~ has read out with negative results on one or more endpoints

†NILE is a 3-arm trial comparing durva + CT to durva + treme + CT to CT alone; including features of IO + CT, as well as IO doublet therapy.

*For cisplatin-eligible patients only.

1L, first-line; ADC, antibody-drug conjugate; atezo, atezolizumab; BSC, best supportive care; EV, enfortumab vedotin; chemo, chemotherapy; CR, complete response; durva, durvalumab; IO, immuno-oncology; ipi, ipilimumab; OS, overall survival; nivo, nivolumab; pembro, pembrolizumab; PFS, progression-free survival; PR, partial response; R, randomisation; SD, stable disease; SoC, standard of care; treme, tremelimumab; UC, urothelial carcinoma. NCT entries available at https://clinicaltrials.gov/ [Accessed August 2020].

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# *First-line mUC – cisplatin ineligible*

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# Enfortumab vedotin + Pembrolizumab (EV-103)

## Long Term Results and Durability Updates from ASCO 2021

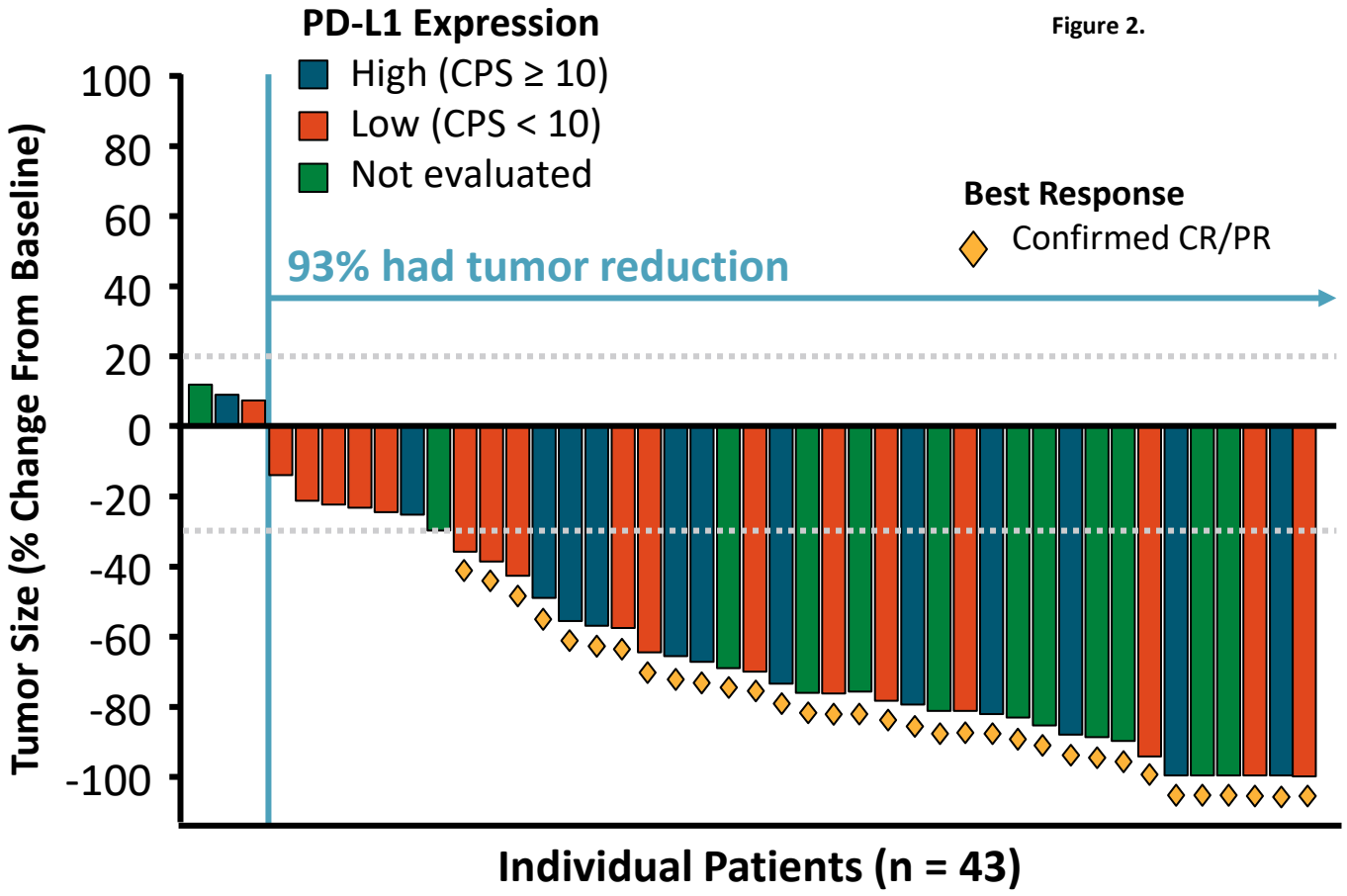
- Updated data with 24.9 months median follow-up (Data cut-off: October 2020)

**Figure 1.**

| Best Overall Response | All Patients (N = 45) |
|---|---|
| **Confirmed ORR, n (%) [95% CI]**<br>CR, n (%)<br>PR, n (%) | **33 (73.3) [58.1–85.4]**<br>7 (15.6)<br>26 (57.8) |
| SD | 9 (20.0) |
| PD | 1 (2.2) |
| ORR in patients with liver metastasis, n/N (%) | 8/14 (57.1) |
| **ORR by PD-L1 status, n/N (%)**<br>High expression<br>Low expression | <br>11/14 (78.6)<br>12/19 (63.2) |
| **Additional Efficacy @ ASCO 2021** | **All Patients (N = 45)** |
| Median DOR, months, (95% CI) | 25.6 (8.3, –) |
| DCR, % | 93.3 |
| Median PFS, months, (95% CI) | 12.3 (8.0, –) |
| 24 mo. OS Rate, %, (95% CI) | 56.3 (39.8-69.9) |

1. Presented by TW Friedlander at ASCO 2021 Annual Meeting June 4-8, 2021. Abstract 4528.

**Figure 2.**




2. Rosenberg. ASCO 2020. Abstr 5044. Rosenberg. ASCO GU 2020. Abstr 441.

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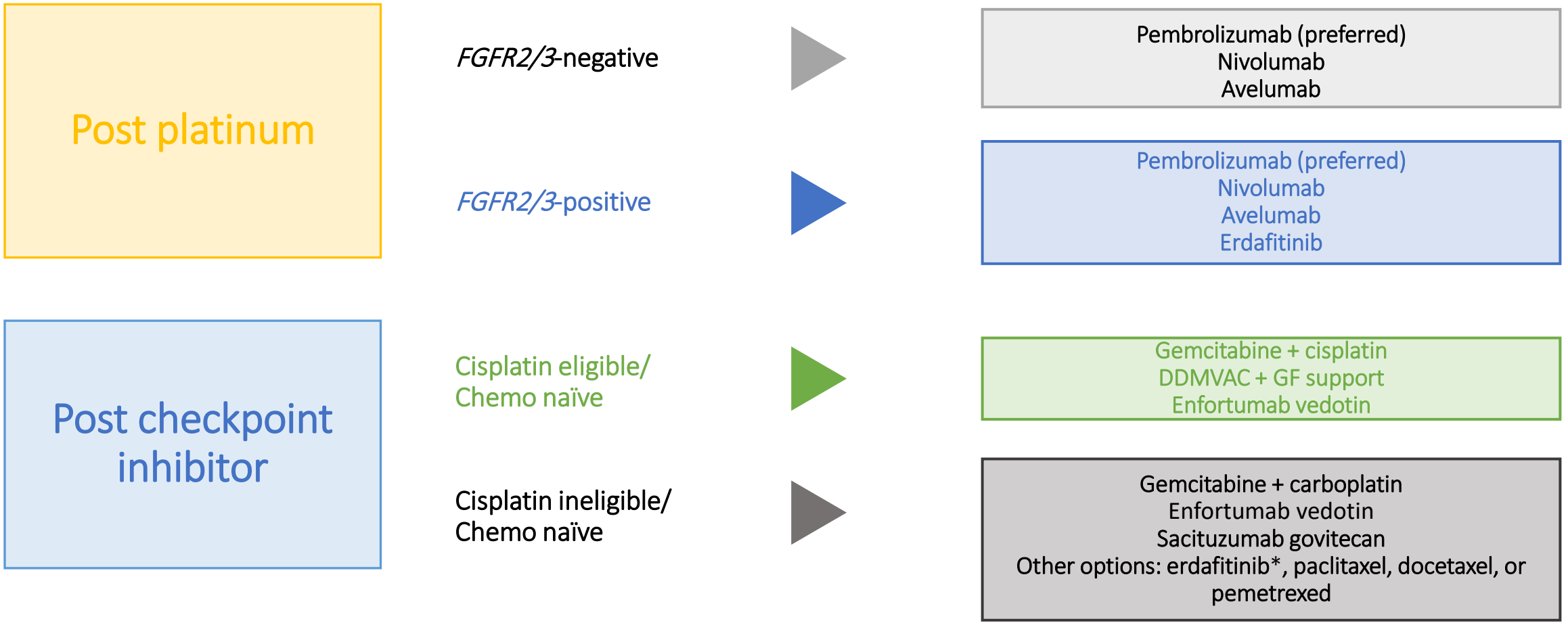
# Second-Line Systemic Treatment for mUC




* If *FGFR2/3* positive

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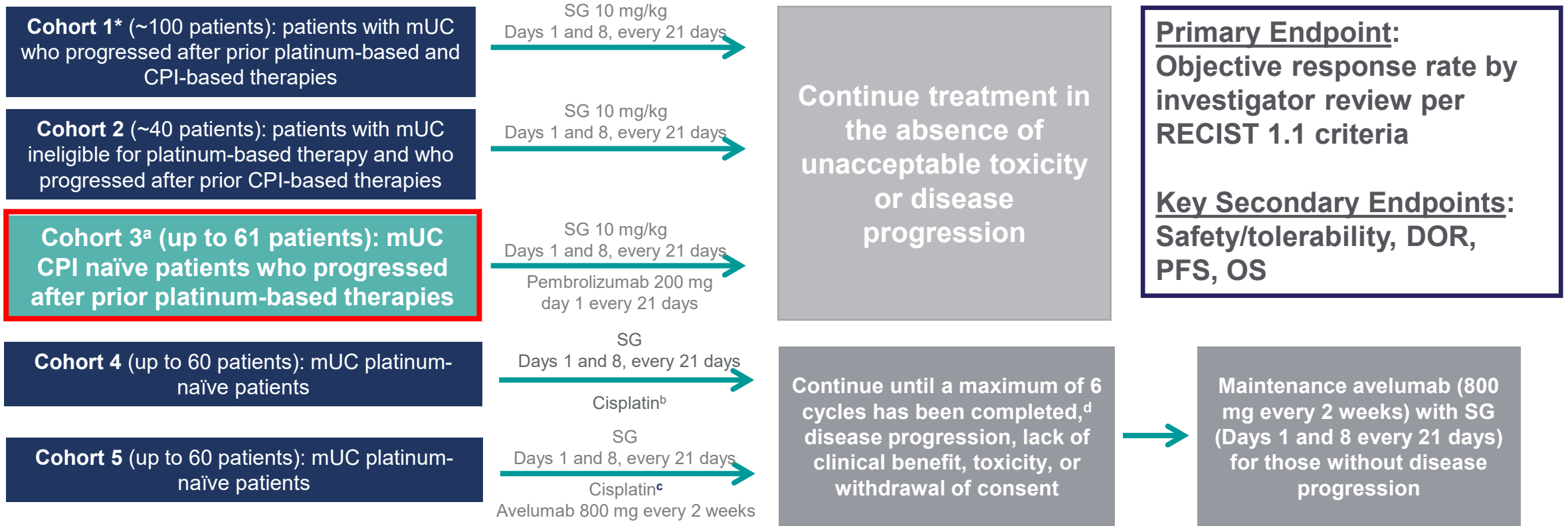
# TROPHY-U-01 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC




**Key Inclusion Criteria**: Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,[b,c] adequate hepatic function
**Key Exclusion Criteria**: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

***Accelerated FDA approval for treatment of patients with locally advanced or mUC who previously received platinum-containing chemotherapy and PD-1/L1 inhibitor[1]**

[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min; [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days.
CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

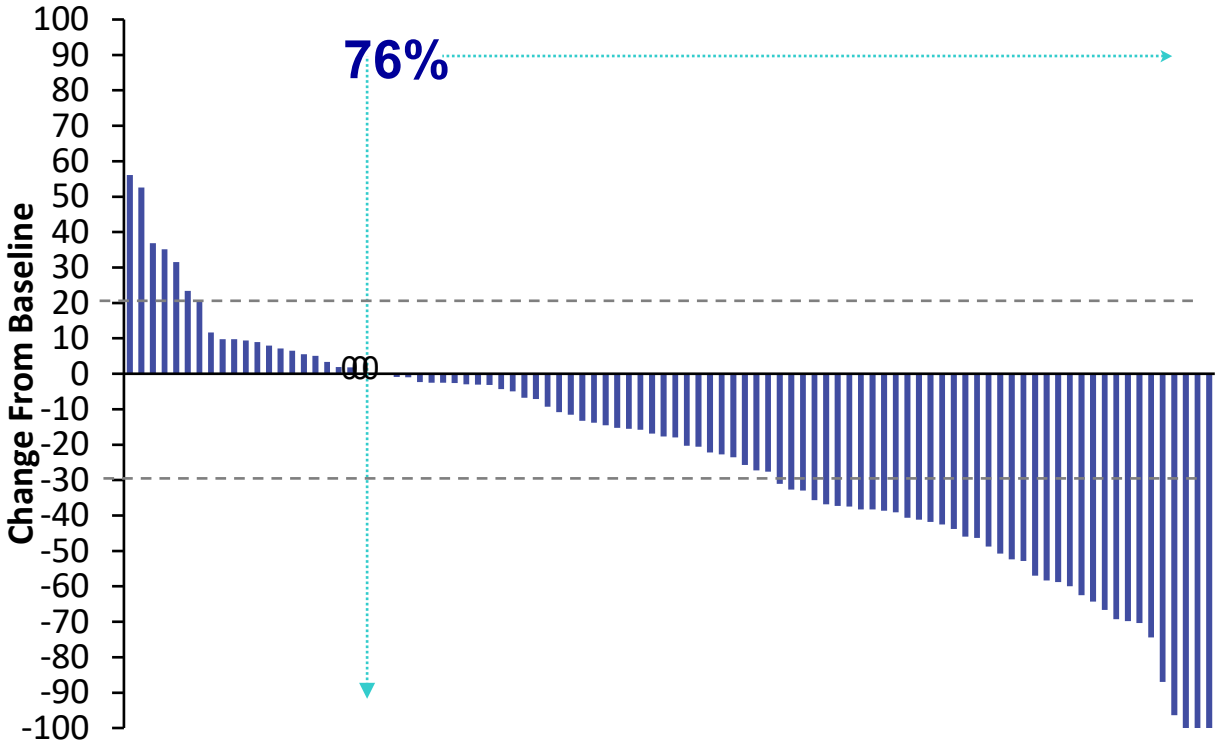
1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

Grivas, P. Abstract 434. Presented at ASCO GU 2022; February 17 – 19; San Francisco, CA.

# TROPHY-U-01 Cohort 1: Response and Reduction in Tumor Size

| Endpoint | Cohort 1 (N=113) |
|---|---|
| ORR, No. (%) [95% CI] | 31 (27) [19, 37] |
| CR, No. (%) | 6 (5) |
| PR, No. (%) | 25 (22) |
| Median duration of response, mo [95% CI] (range) | 5.9 [4.70, 8.60] (1.4–11.7) |
| Median time to onset of response, mo (range) | 1.6 (1.2–5.5) |

Assessments were per Blinded Independent Review Assessment, RECIST v1.1.




71/94 patients with at least one post-baseline target lesion measurement and accepted for central review. Fourteen patients had no post-treatment imaging, 1 patient lacked measurable lesions by central review, and 4 patients had poor image quality.

Loriot Y, et al. *Annal Oncol*. 2020;31(suppl 4):S1142-S1215 (LBA24).

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# TROPHY-U-01 Cohort 1: Response and Reduction in Tumor Size

| Endpoint |
| --- |
| ORR, No. (%) [95 |
| CR, No. (%) |
| PR, No. (%) |
| Median duration [95% CI] (range) |
| Median time to (range) |

**FDA grants accelerated approval to sacituzumab govitecan for advanced urothelial cancer**

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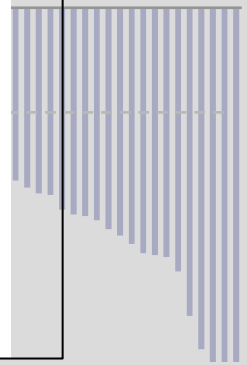
On April 13, 2021, the Food and Drug Administration granted accelerated approval to sacituzumab govitecan ([redacted]) for patients with locally advanced or metastatic urothelial cancer (mUC) who previously received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor.



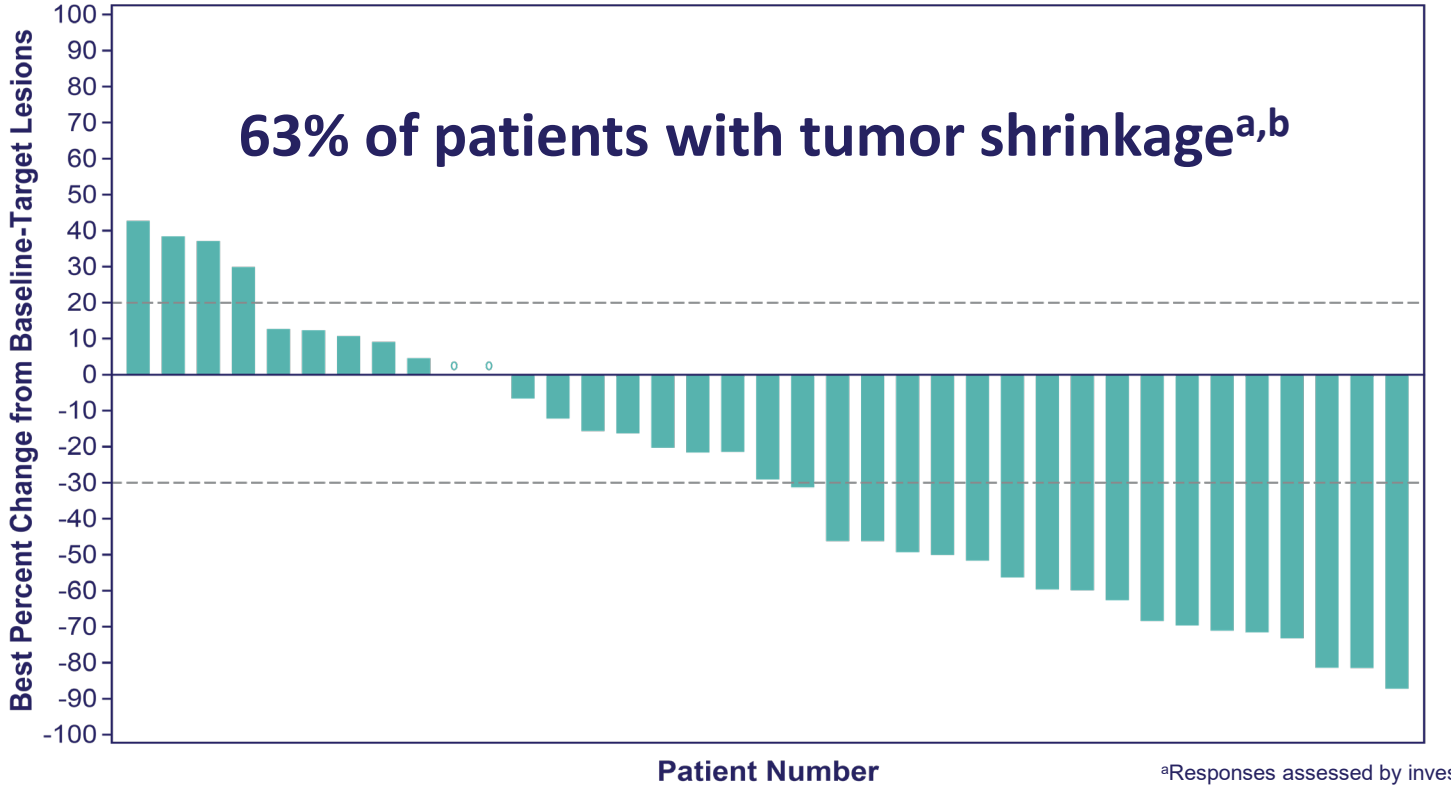
Assessments were per Blinded Independent Review Assessment, RECIST v1.1.

71/94 patients with at least one post-baseline target lesion measurement and accepted for central review. Fourteen patients had no post-treatment imaging, 1 patient lacked measurable lesions by central review, and 4 patients had poor image quality.

Loriot Y, et al. *Annal Oncol*. 2020;31(suppl 4):S1142-S1215 (LBA24).

# TROPHY-U-01 Cohort 3: Overall Response and Best % Change From Baseline in Tumor Size

- Median follow-up: 5.8 months (data cutoff date: 2021-09-24)
- Median time to response: 2 months (1.3–2.8; n=14)
- Median DOR not yet reached: N/A (2.80-N/A)
- Median PFS (95% CI), 5.5 months (1.7–NR); median OS, not reached




| | Cohort 3[a] (N=41) |
|---|---|
| **Objective response rate (CR + PR), n (%) [95%CI]** | **14 (34) [20.1-50.6]** |
| **Objective response rate (CR + PR), evaluable patients, n (%)** | 14 (38) |
| **Best overall response, n (%)** | |
| **CR** | 1 (2) |
| **PR** | 13 (32) |
| **SD** | 11 (27) |
| ***SD ≥ 6 months*** | *4 (10)* |
| **PD** | 12 (29) |
| **Not assessed** | 4 (10) |
| **Clinical Benefit Rate (CR + PR + SD), n (%) [95%CI]** | 25 (61) [44.5-75.8] |

[a]Responses assessed by investigator in the intent-to-treat population. [b]Patients without post-baseline assessments are not shown here.
CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

Grivas, P. Abstract 434. Presented at ASCO GU 2022; February 17 – 19; San Francisco, CA.

# Localized UC

# CheckMate 274

## Study design

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

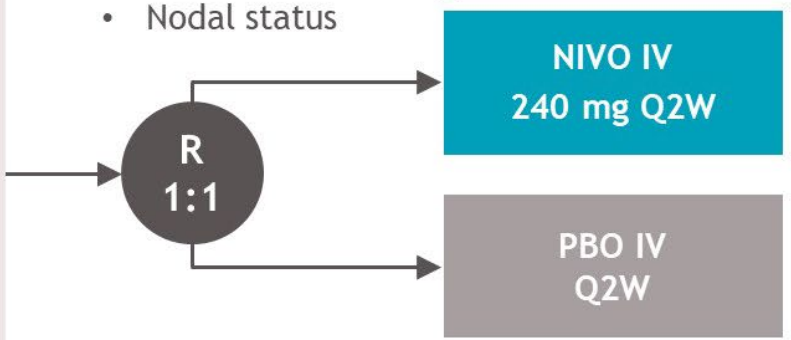
**N = 709**

**Key inclusion criteria**

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

**Stratification factors**

- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status




*Treat for up to 1 year of adjuvant therapy*

**Minimum follow-up,** 5.9 months
**Median follow-up in ITT population,** 20.9 months (NIVO) and 19.5 months (PBO)

**Primary endpoints:** DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
**Secondary endpoints:** NUTRFS, DSS, and OS[b]
**Exploratory endpoints included:** DMFS, safety, HRQoL

[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

# Select baseline demographic and disease characteristics in all randomized patients

| | NIVO (N = 353) | PBO (N = 356) |
|---|---|---|
| **Mean age (range), years** | 65.3 (30-92) | 65.9 (42-88) |
| **Male, %** | 75.1 | 77.2 |
| **Region, %** | | |
| United States | 13.9 | 14.9 |
| Europe | 48.2 | 48.0 |
| Asia | 22.7 | 20.8 |
| Rest of the world | 15.3 | 16.3 |
| **ECOG PS,[a] %** | | |
| 0 | 63.5 | 62.1 |
| 1 | 34.6 | 35.1 |
| 2[b] | 2.0 | 2.5 |
| **Tumor origin at initial diagnosis, %** | | |
| Urinary bladder | 79.0 | 78.9 |
| Upper tract disease | 21.0 | 21.1 |
| **Minor histological variants present, %** | 41.1 | 39.6 |
| **PD-L1 ≥ 1% by IVRS, %** | 39.7 | 39.9 |
| **Prior neoadjuvant cisplatin, %** | 43.3 | 43.5 |
| **Pathologic T stage at resection,[c,d] %** | | |
| pT0-2 | 22.7 | 24.2 |
| pT3 | 58.4 | 57.3 |
| pT4a | 16.1 | 17.4 |
| Other | 2.5 | 0.8 |
| **Nodal status at resection,[d] %** | | |
| N+ | 47.3 | 47.2 |
| N0/x with < 10 nodes removed | 26.6 | 27.8 |
| N0 with ≥ 10 nodes removed | 25.8 | 24.7 |

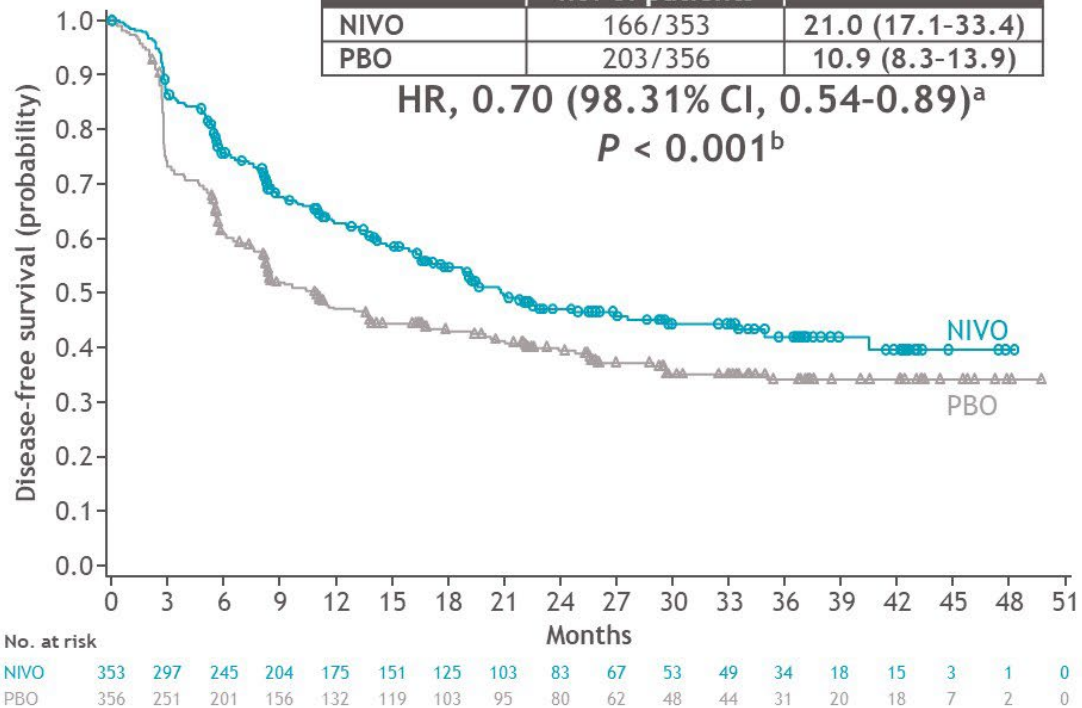
[a]Not reported for 1 patient in the PBO arm. [b]ECOG PS of 2 was permitted only for patients who did not receive cisplatin-based neoadjuvant chemotherapy and are ineligible for adjuvant cisplatin-based chemotherapy. [c]The T staging included patients with N+, N0, or NX. [d]Not reported for 1 patient in each arm.
ECOG PS, Eastern Cooperative Oncology Group performance status; IVRS, interactive voice-response system.

# Disease-free survival

## ITT

| | No. of events/ no. of patients | Median (95% CI), months |
|---|---|---|
| NIVO | 166/353 | 21.0 (17.1-33.4) |
| PBO | 203/356 | 10.9 (8.3-13.9) |

HR, 0.70 (98.31% CI, 0.54-0.89)[a]
*P* < 0.001[b]



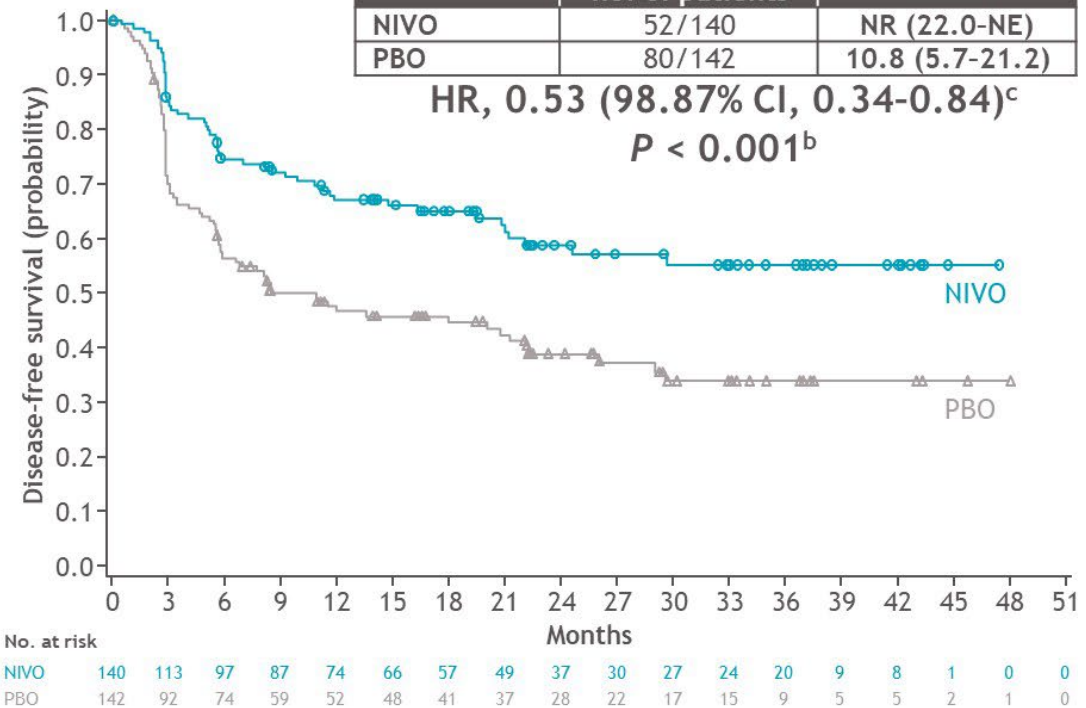

No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 353 | 297 | 245 | 204 | 175 | 151 | 125 | 103 | 83 | 67 | 53 | 49 | 34 | 18 | 15 | 3 | 1 | 0 |
| PBO | 356 | 251 | 201 | 156 | 132 | 119 | 103 | 95 | 80 | 62 | 48 | 44 | 31 | 20 | 18 | 7 | 2 | 0 |

## PD-L1 ≥ 1%

| | No. of events/ no. of patients | Median (95% CI), months |
|---|---|---|
| NIVO | 52/140 | NR (22.0-NE) |
| PBO | 80/142 | 10.8 (5.7-21.2) |

HR, 0.53 (98.87% CI, 0.34-0.84)[c]
*P* < 0.001[b]




No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 140 | 113 | 97 | 87 | 74 | 66 | 57 | 49 | 37 | 30 | 27 | 24 | 20 | 9 | 8 | 1 | 0 | 0 |
| PBO | 142 | 92 | 74 | 59 | 52 | 48 | 41 | 37 | 28 | 22 | 17 | 15 | 9 | 5 | 5 | 2 | 1 | 0 |

Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

## Disease-free survival

# FDA approves nivolumab for adjuvant treatment of urothelial carcinoma



On August 19, 2021, the Food and Drug Administration approved nivolumab [redacted] for the adjuvant treatment of patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection.

Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

# Summary Points

- PD(L)-1 play a role in localized and advanced UC
- ADC-IO combinations are promising
- Long-term Fup data supports the use of IO earlier in the course of the disease
- Optimal sequencing is unclear

# Thank You!!

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