# Immunotherapy for the Treatment of Kidney and Bladder Cancer

Alan J. Koletsky, MD

Genitourinary Cancer Research Program, Lynn Cancer Institute
Clinical Asistant Professor of Biomedical Science
The Charles E. Schmidt College of Medicine, Boca Raton, FL

# Immunotherapy for Kidney and Bladder Cancer

## Overview

Update of Recently Approved Therapies in First and Second Line Settings

Rationale for New Combination Therapies

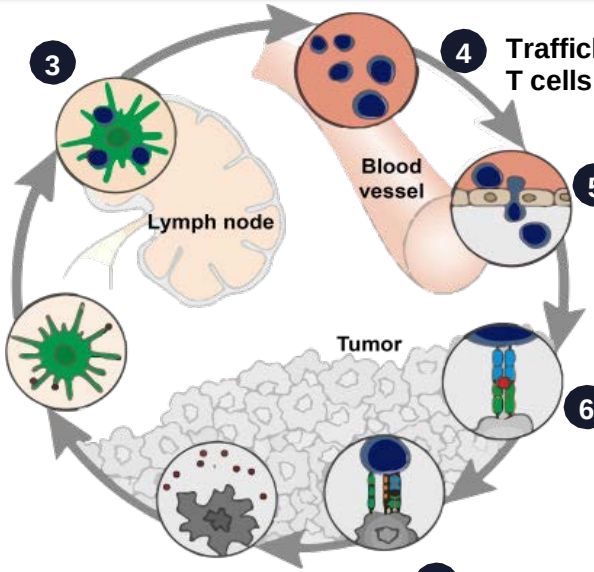
Future Strategies

# Multiple Steps Required for Anticancer Activity[1]

**Priming and activation**
- Anti–CTLA-4
- Anti-CD137 (agonist)
- Anti-OX40 (agonist)
- Anti-CD27 (agonist)
- IL-2
- IL-12

**Cancer antigen presentation**
- Vaccines
- IFN-α
- GM-CSF/T-VEC
- Anti-CD40 (agonist)
- TLR agonists

**Release of cancer cell antigens**
- Chemotherapy
- Radiation therapy
- Targeted therapy




**Trafficking of T cells to tumors**

**Infiltration of T cells into tumors**
- Anti-VEGF
- Anti-CXCR4

**Recognition of cancer cells by T cells**
- CAR-T cell therapy
- HDAC inhibitors

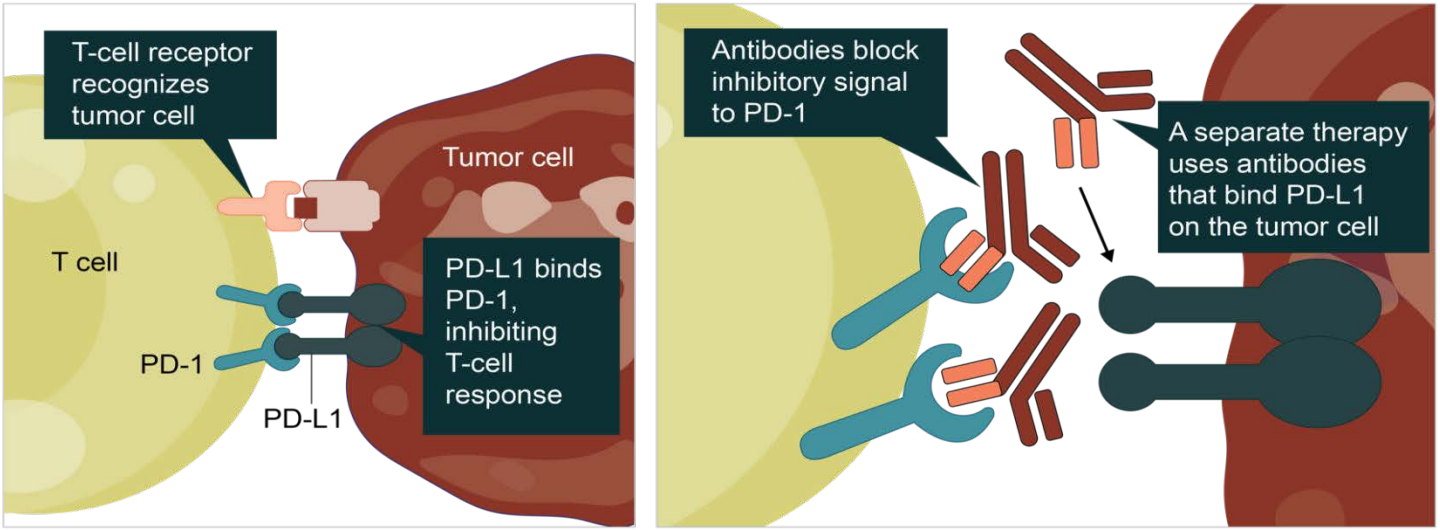
**Killing of cancer cells and tolerance**
- Anti–PD-1/PD-L1
- IDO inhibitors
- Anti–LAG-3

- **Multiple processes are required to establish and maintain an effective immune response**
- **Determinants of sensitivity and resistance not clearly defined yet**

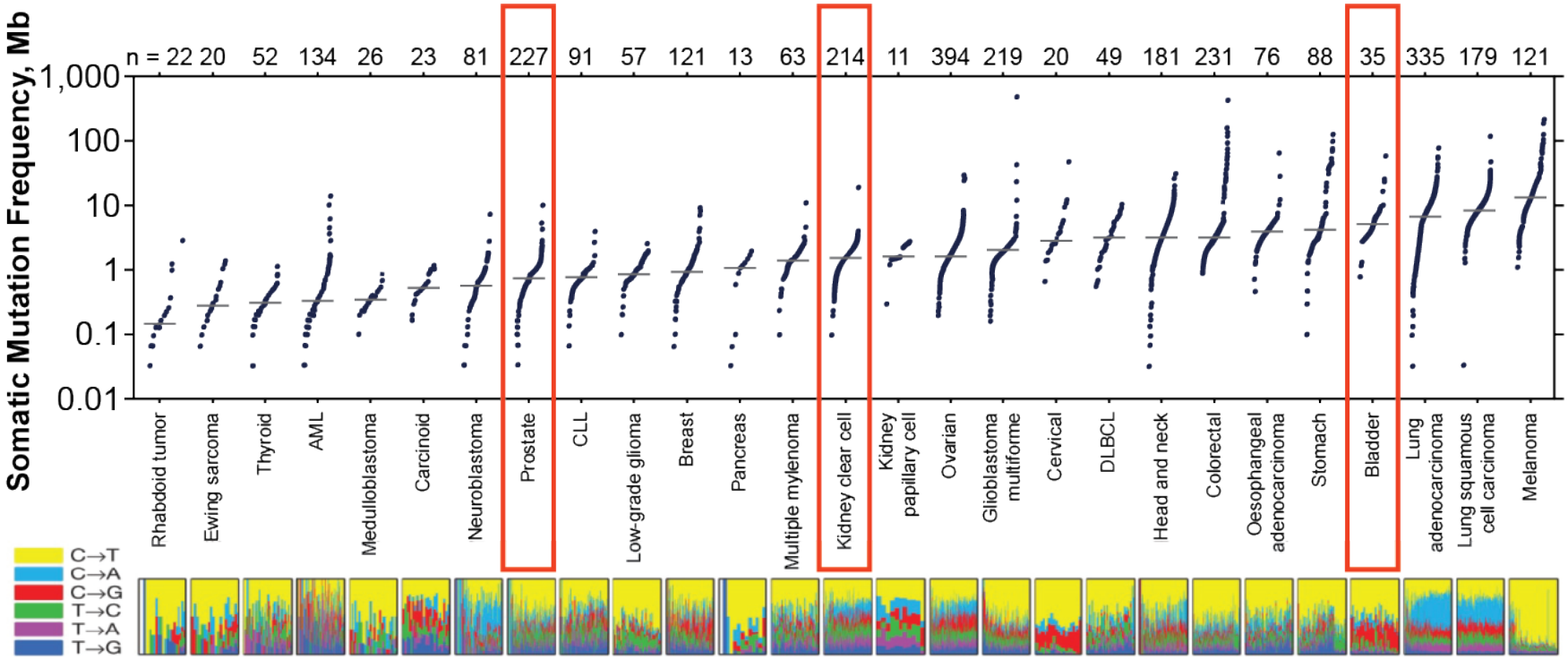
1. Chen DS et al. *Immunity*. 2013;39:1-10.

# Immune Checkpoint Blockade in Cancer

**Tumor cells can inhibit the body's immune response by binding to proteins, such as PD-1, on the surface of T cells; antibody therapies that block this binding reactivate the immune response**

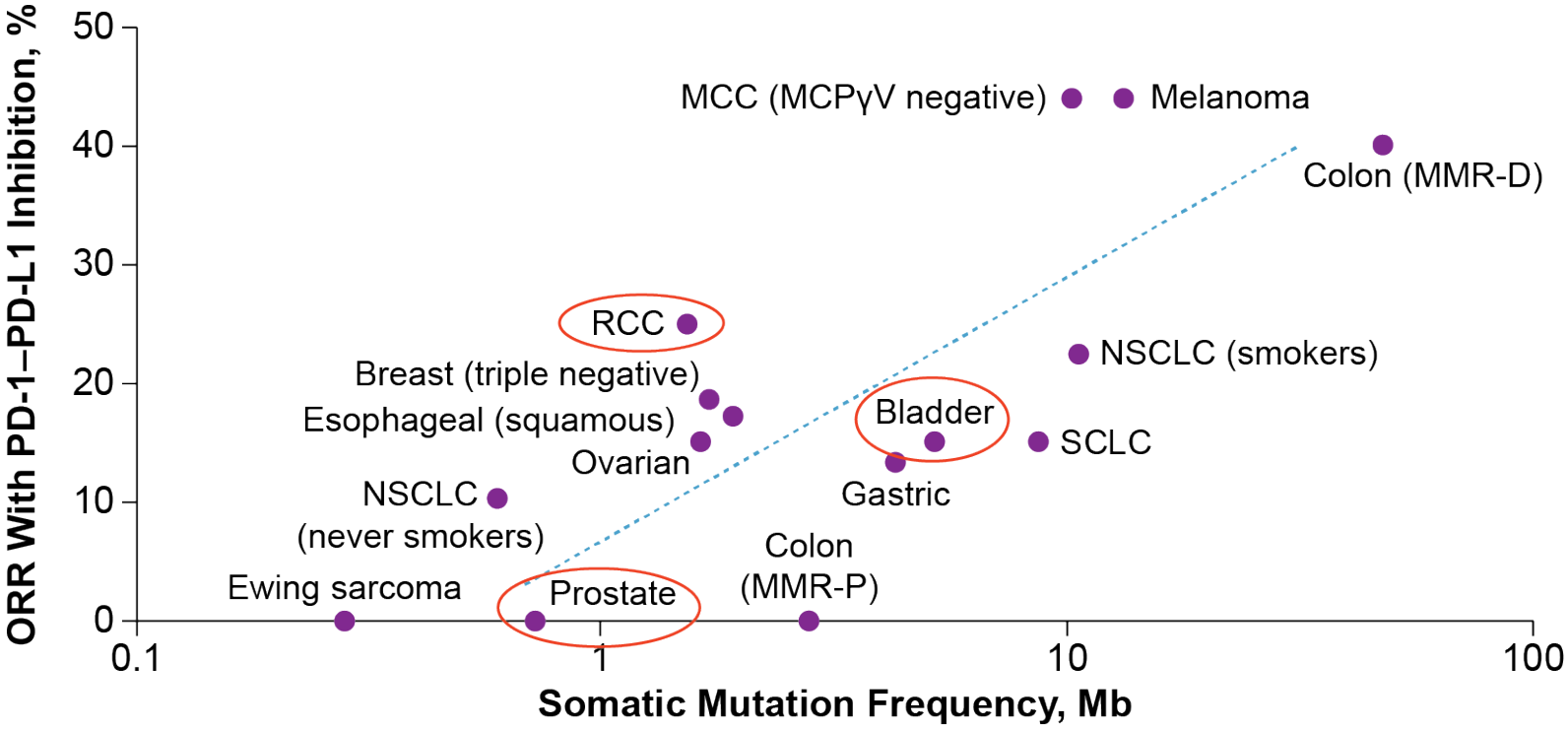


# Mutational Burden[1]




1. Lawrence MS et al. *Nature*. 2013;499:214-218.

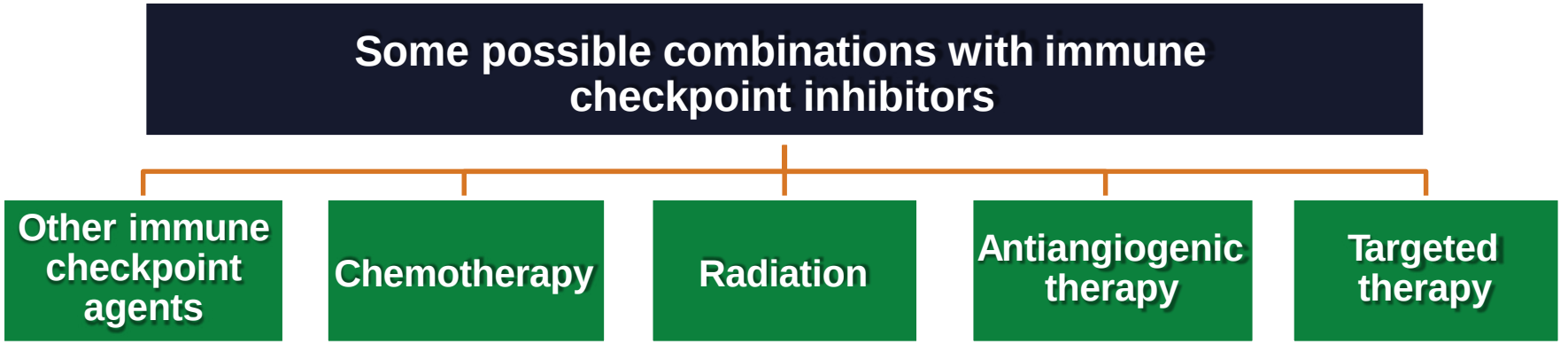
# Response Rate and Tumor Mutational Burden[1]




1. Yarchoan M et al. *Nature Rev Cancer*. 2017;17:209-222.

# Overcoming Immunotherapy Resistance

- Multiple strategies may be considered
- Tip balance away from tumor-protective mechanisms and towards antitumor immunity
- Rational combinations are required to move the field forward
- Some are leading to improved survival



# Targeting the PD-1/PD-L1 Axis Has Activity in GU Cancers

**5 anti–PD-1/anti–PD-L1 drugs now approved for advanced urothelial carcinoma**

Atezolizumab, nivolumab, durvalumab, avelumab, pembrolizumab

**Nivolumab approved for kidney cancer**

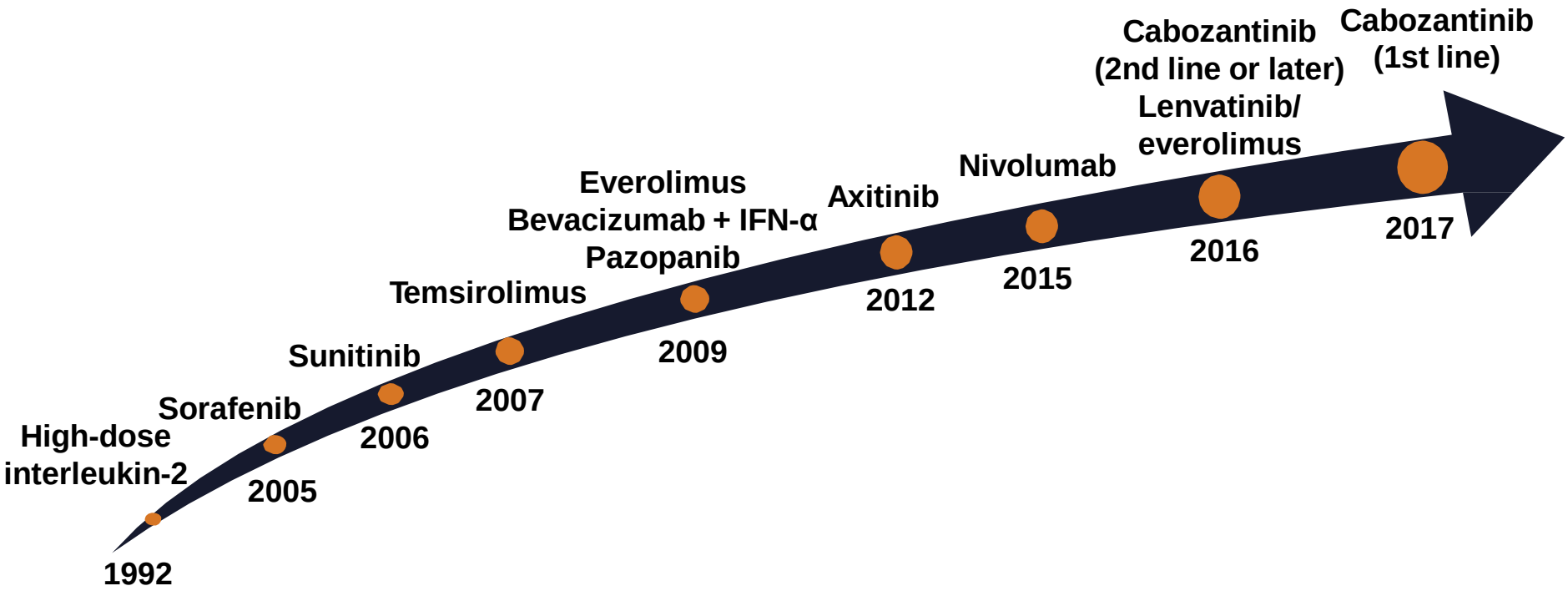
Two positive phase 3 trials for combination therapy:

- Ipilimumab/nivolumab in first-line therapy
- Atezolizumab/bevacizumab as first-line therapy in PD-L1–positive tumors

**Provocative data with enzalutamide-resistant cancers responding to pembrolizumab**

Multiple large trials ongoing

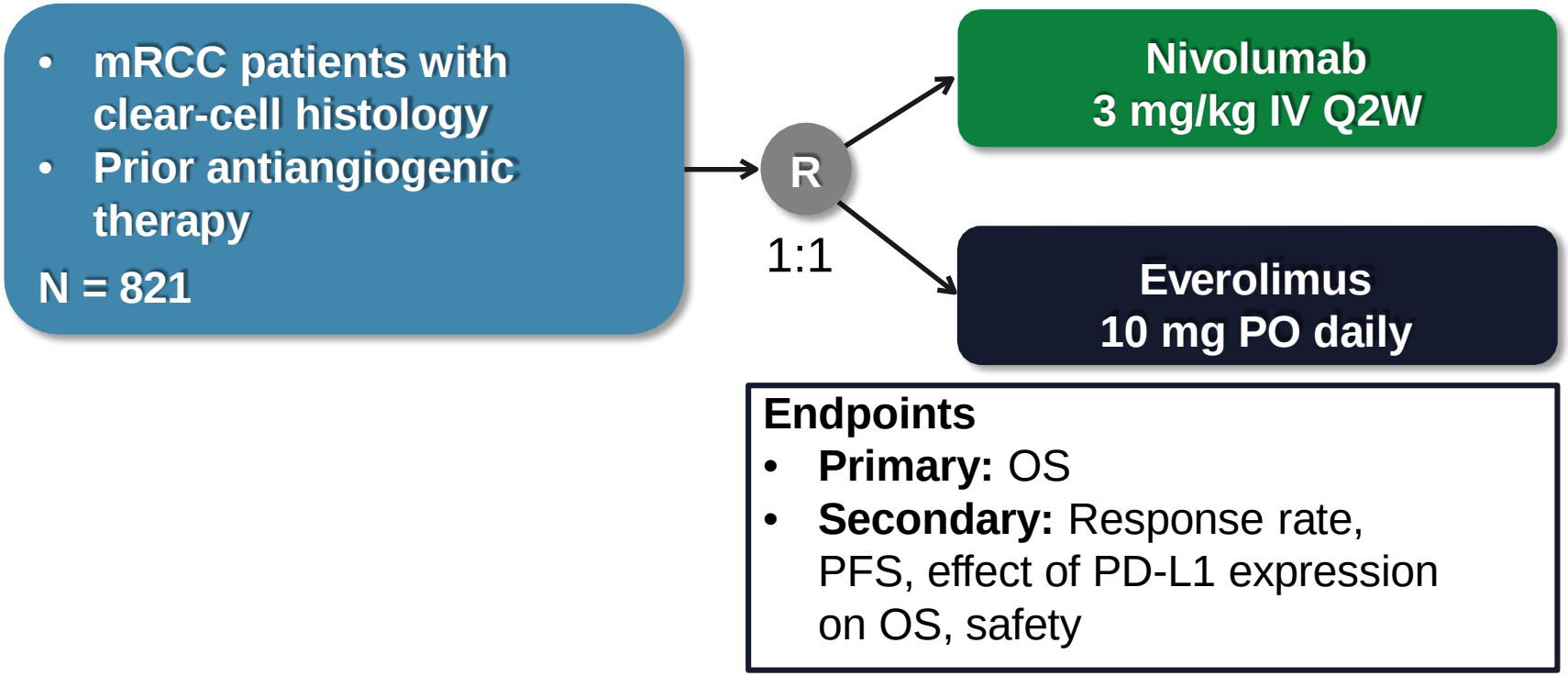
# Approved Therapies for Renal Cell Carcinoma[1]




1. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 26, 2018.

# New Options for Pretreated Patients

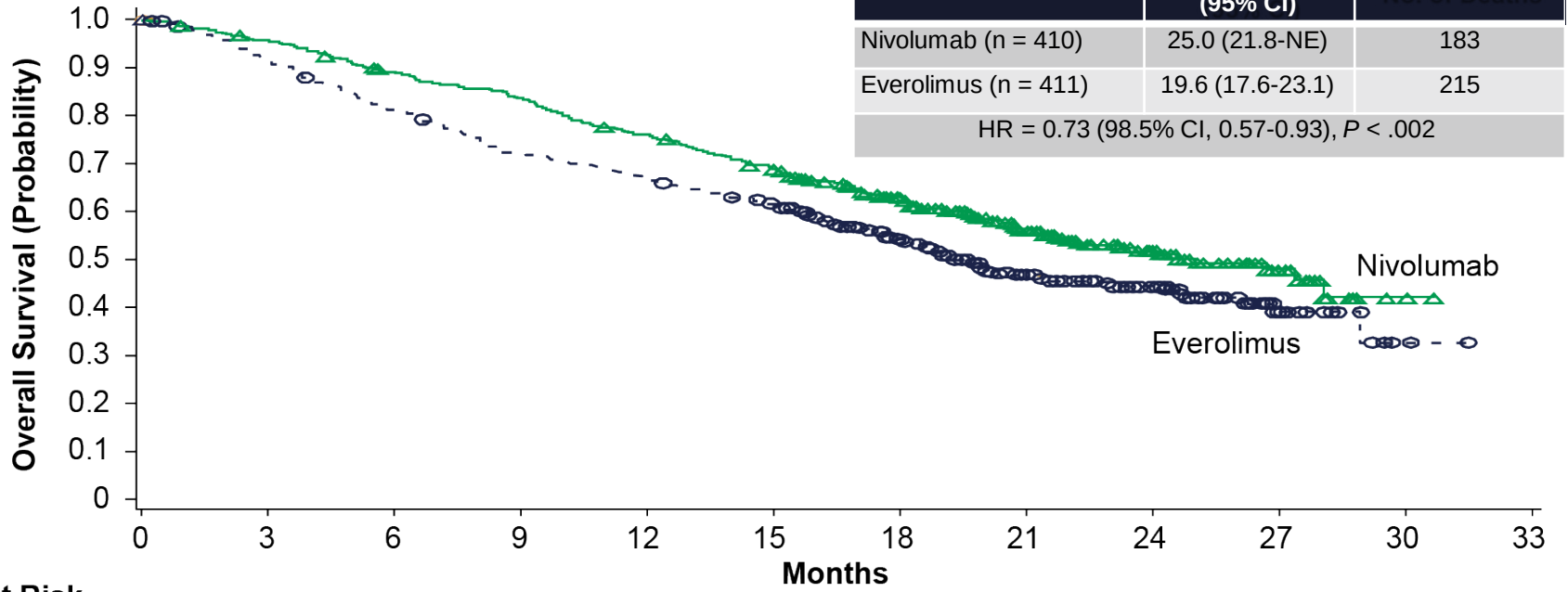
# CheckMate-025: Phase 3 Study of Nivolumab vs Everolimus[1]




1. Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

# CheckMate-025: Overall Survival[1]

| | Median OS, mo (95% CI) | No. of Deaths |
|---|---|---|
| Nivolumab (n = 410) | 25.0 (21.8-NE) | 183 |
| Everolimus (n = 411) | 19.6 (17.6-23.1) | 215 |
| HR = 0.73 (98.5% CI, 0.57-0.93), *P* < .002 | | |



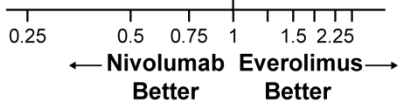

**No. at Risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 410 | 389 | 359 | 337 | 305 | 275 | 213 | 139 | 73 | 29 | 3 | 0 |
| Everolimus | 411 | 366 | 324 | 287 | 265 | 241 | 187 | 115 | 61 | 20 | 2 | 0 |

1. Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

# CheckMate-025: Subgroup Analysis of OS[1]

| Subgroup | Nivolumab | Everolimus | Unstratified Hazard Ratio for Death (95% CI) |
|---|---|---|---|
| **Overall** | 183/410 | 215/411 | 0.76 (0.62-0.92) |
| **MSKCC risk group** | | | |
| Favorable | 45/145 | 52/148 | 0.89 (0.59-1.32) |
| Intermediate | 101/201 | 116/203 | 0.76 (0.58-0.99) |
| Poor | 37/64 | 47/60 | 0.47 (0.30-0.73) |
| **Prior anti-angiogenic regimens** | | | |
| 1 | 128/294 | 158/297 | 0.71 (0.56-0.90) |
| 2 | 55/116 | 57/114 | 0.89 (0.61-1.29) |
| **Region** | | | |
| US/Canada | 66/174 | 87/172 | 0.66 (0.48-0.91) |
| Western Europe | 78/140 | 84/141 | 0.86 (0.63-1.16) |
| Rest of the world | 39/96 | 44/98 | 0.78 (0.51-1.20) |
| **Age, years** | | | |
| <65 | 111/257 | 118/240 | 0.78 (0.60-1.01) |
| ≥65 to <75 | 53/119 | 77/131 | 0.64 (0.45-0.91) |
| ≥75 | 19/34 | 20/40 | 1.23 (0.66-2.31) |
| **Sex** | | | |
| Female | 48/95 | 56/107 | 0.84 (0.57-1.24) |
| Male | 135/315 | 159/304 | 0.73 (0.58-0.92) |




1. Adapted from: Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

# ORR by Risk Level[1]

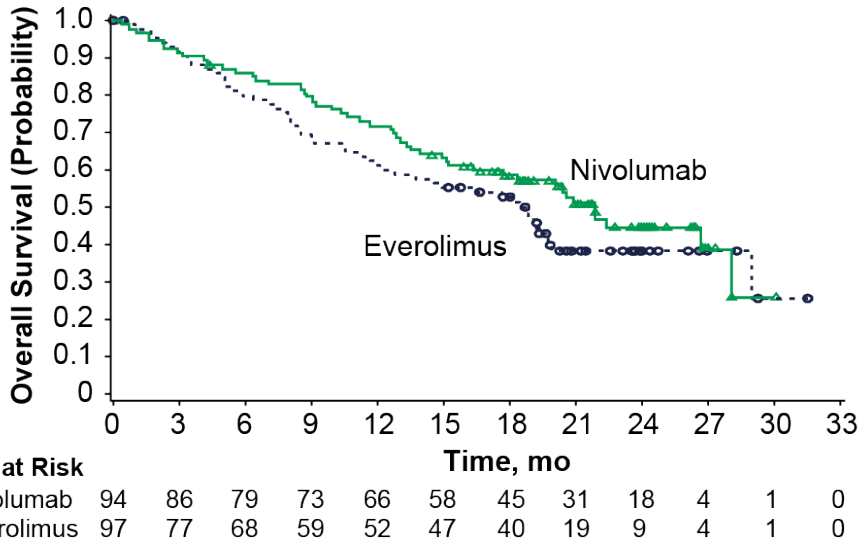
| MSKCC Risk Group | Nivolumab, % | Everolimus, % |
|---|---|---|
| Favorable | 24 | 8 |
| Intermediate | 25 | 5 |
| Poor | 27 | 3 |

1. Escudier B et al. *Eur Urol*. 2017;72:962-971.

# Overall Survival by Tumoral PD-L1 Expression[1]

## Patients With ≥1% PD-L1 Expression

| | Median OS, mo (95% CI) | No. of Deaths |
|---|---|---|
| Nivolumab (n = 94) | 21.8 (16.5-28.1) | 48 |
| Everolimus (n = 87) | 18.8 (11.0-19.9) | 51 |

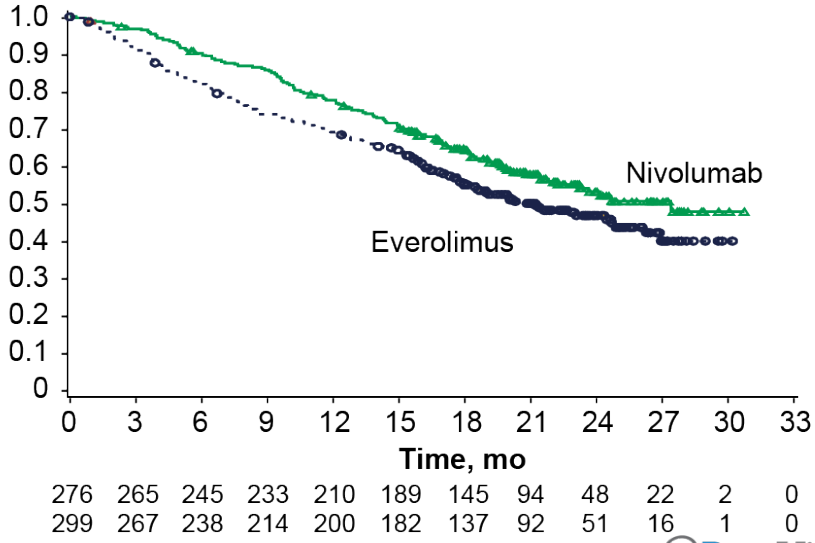



**No. at Risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 94 | 86 | 79 | 73 | 66 | 58 | 45 | 31 | 18 | 4 | 1 | 0 |
| Everolimus | 97 | 77 | 68 | 59 | 52 | 47 | 40 | 19 | 9 | 4 | 1 | 0 |

## Patients With <1% PD-L1 Expression

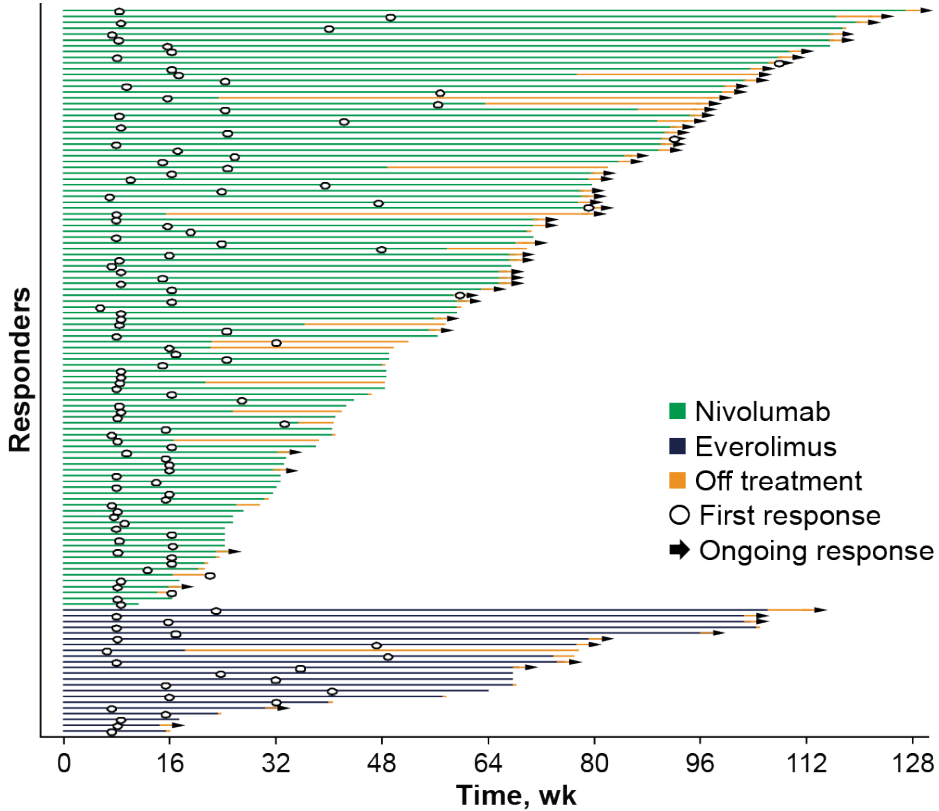
| | Median OS, mo (95% CI) | No. of Deaths |
|---|---|---|
| Nivolumab (n = 276) | 27.4 (21.4-NE) | 118 |
| Everolimus (n = 299) | 21.2 (17.7-26.2) | 150 |




| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 276 | 265 | 245 | 233 | 210 | 189 | 145 | 94 | 48 | 22 | 2 | 0 |
| Everolimus | 299 | 267 | 238 | 214 | 200 | 182 | 137 | 92 | 51 | 16 | 1 | 0 |

1. Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

# CheckMate-025: Duration of Response[1]




**Response Rate**
Nivolumab 21.5%
Everolimus 3.9%

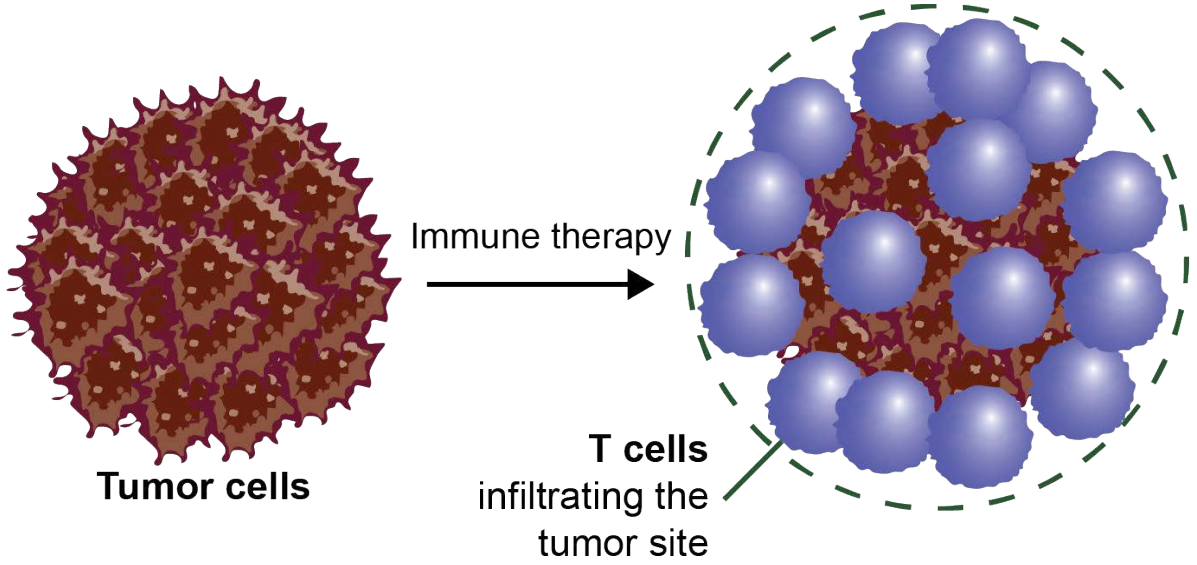
**DOR**
Nivolumab 23.0 months
Everolimus 13.7 months

Number of patients with durable benefit off therapy

Optimal duration of therapy unknown

1. Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

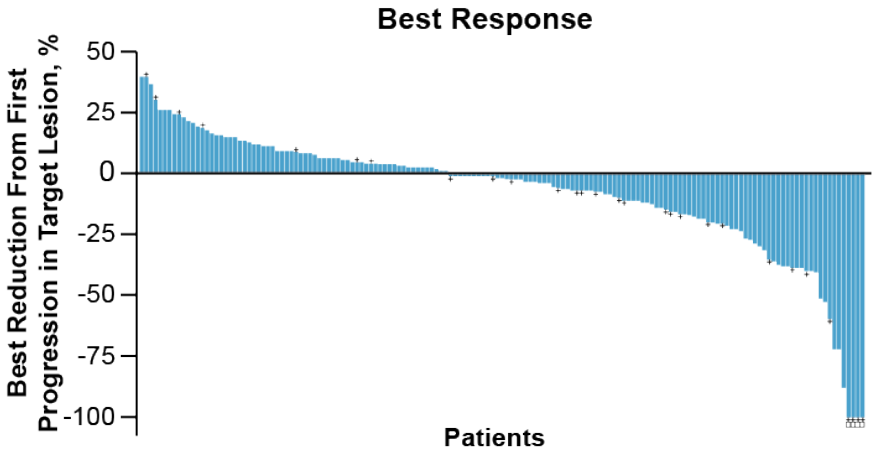
# Tumor Flare With Immunotherapy[1]

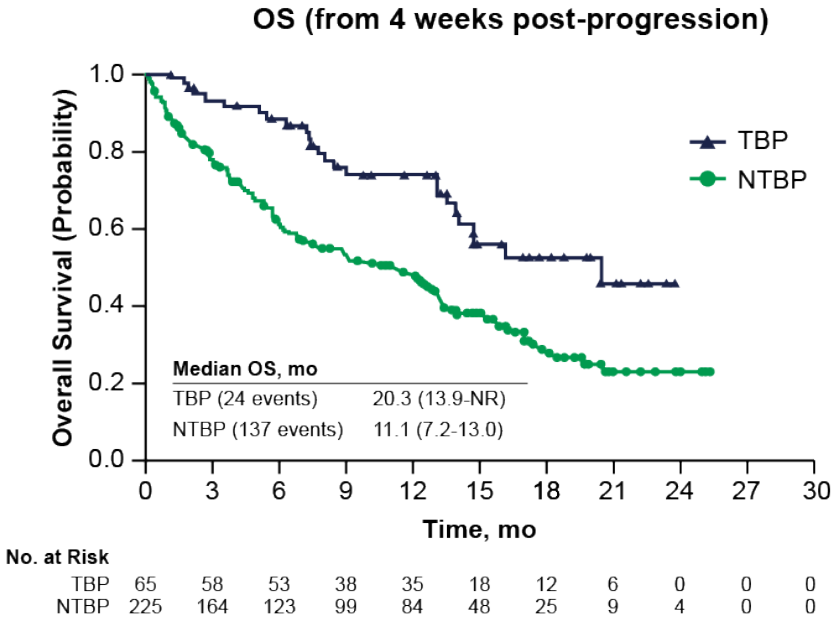



- In patients on immunotherapy, tumor flare or the appearance of new lesions may precede antitumor effects
  - This phenomenon may be characterized as a RECIST-defined progression and may result in premature discontinuation of therapy

1. Wolchok JD et al. *Clin Cancer Res*. 2009;15:7412-7420.

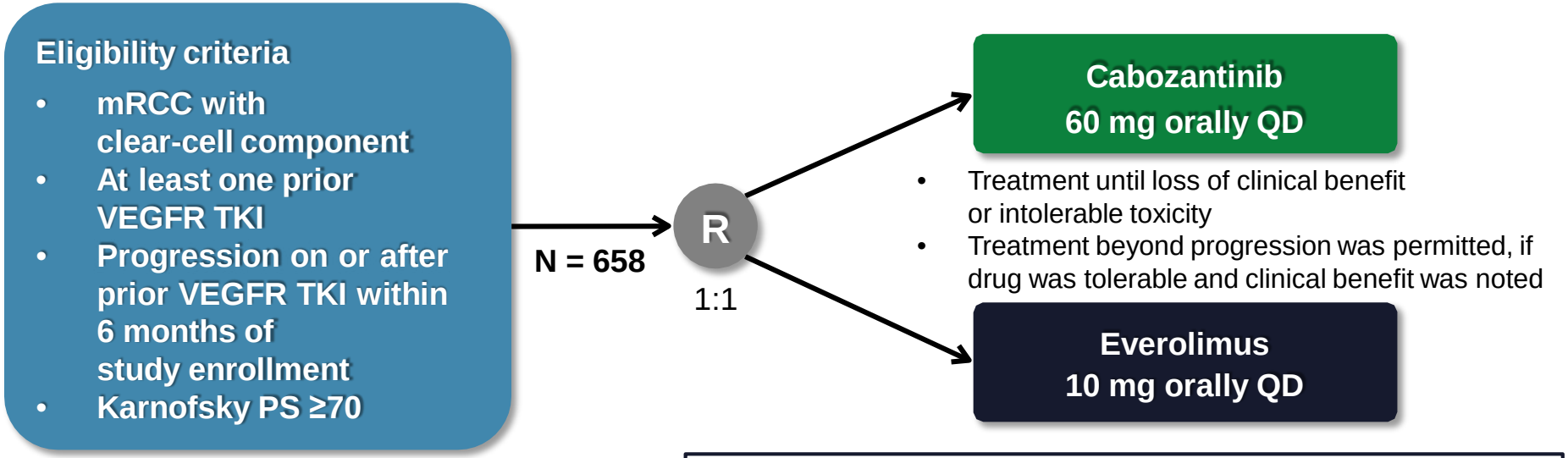
# CheckMate-025: Treatment Beyond Progression[1]




1. Escudier B et al. *Eur Urol*. 2017;72:368-376.

# METEOR: Phase 3 Study of Cabozantinib vs Everolimus[1]

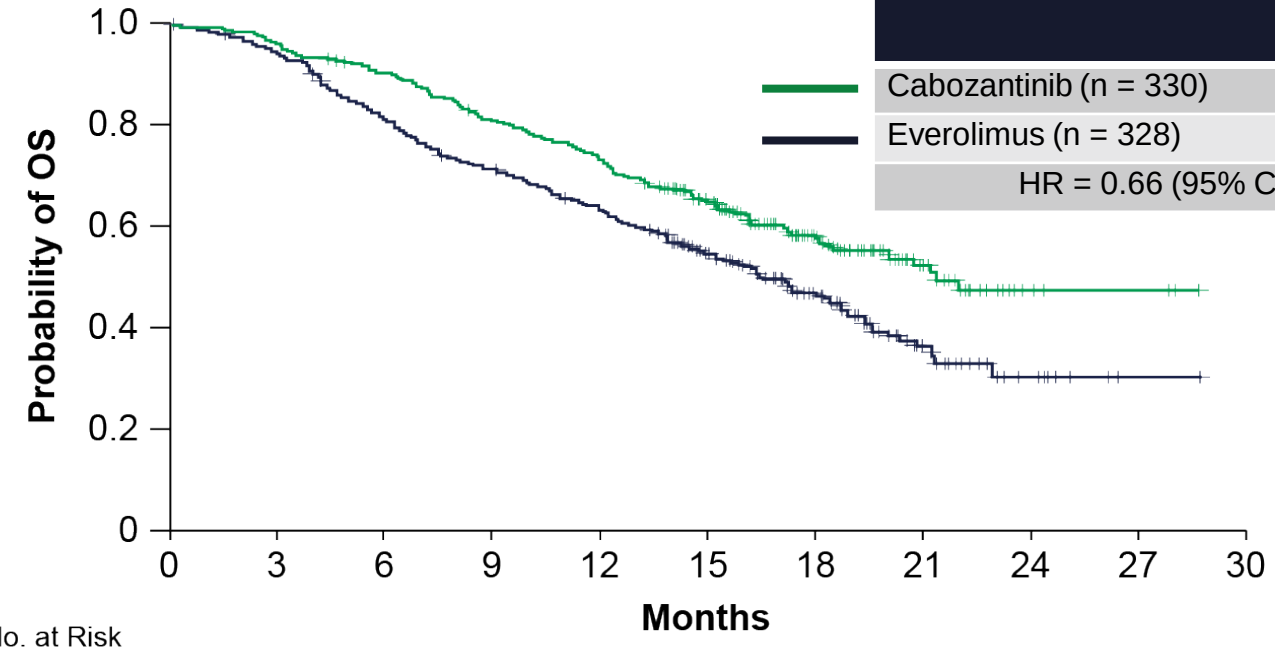



**Stratification:** MSKCC risk criteria; number of prior VEGFR TKIs

- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR
- **Exploratory endpoints:** Safety, tolerability, tumour MET status, circulating tumour cells, serum bone markers and plasma biomarkers, skeletal-related events, and HRQOL

1. Choueiri TK et al. *N Engl J Med.* 2015;373:1814-1823.

# METEOR: OS[1,a]



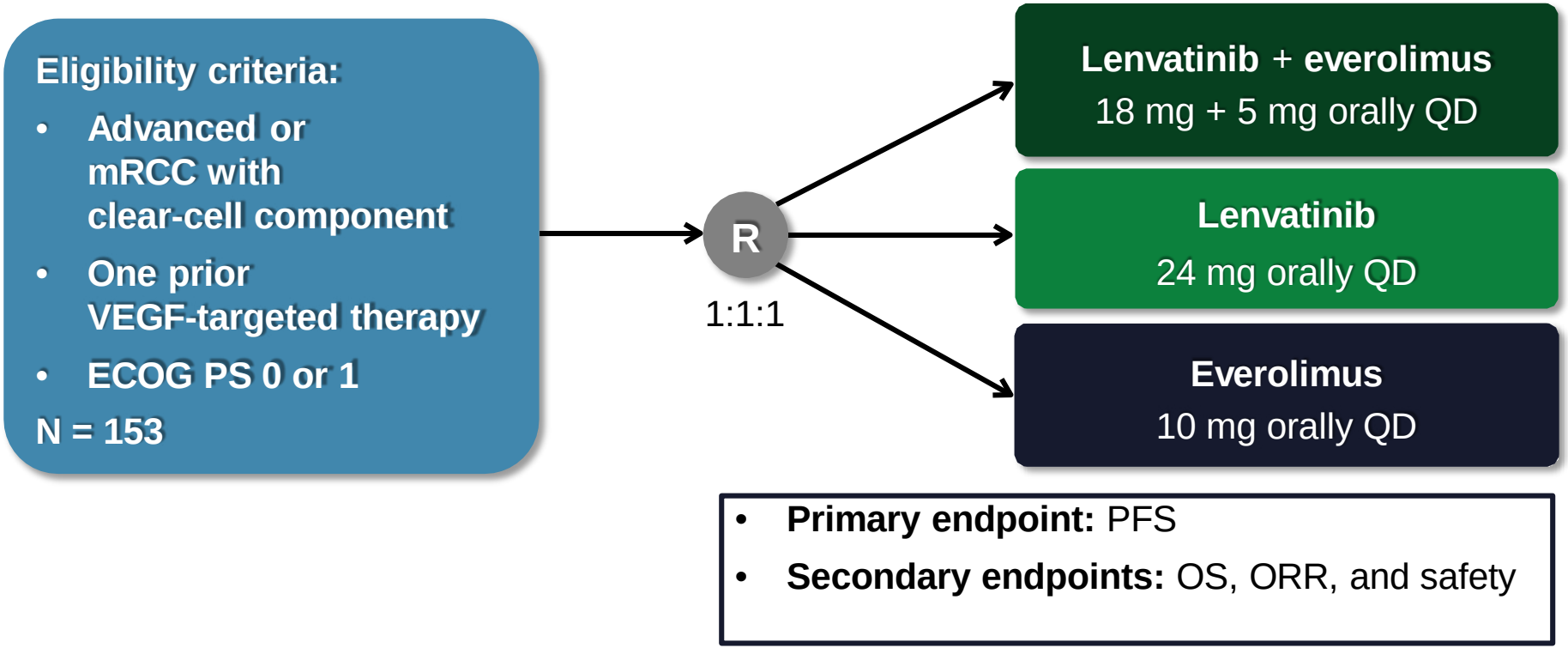

| | Median OS, mo (95% CI) | No. of Deaths |
|---|---|---|
| Cabozantinib (n = 330) | 21.4 (18.7-NE) | 140 |
| Everolimus (n = 328) | 16.5 (14.7-18.8) | 180 |
| HR = 0.66 (95% CI, 0.53-0.83) , *P* = .00026 | | |

| No. at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cabozantinib | 330 | 318 | 296 | 264 | 239 | 178 | 105 | 41 | 6 | 3 | 0 |
| Everolimus | 328 | 307 | 262 | 229 | 202 | 141 | 82 | 32 | 8 | 1 | 0 |

[a] Cut-off: December 31, 2015.

1. Choueiri TK et al. *Lancet Oncol*. 2016;17:917-927.

# Lenvatinib Alone or Plus Everolimus vs Everolimus Randomized Phase 2 Trial[1]




1. Motzer RJ et al. *Lancet Oncol*. 2016;17:e4-e5.

# Phase 2 Lenvatinib Plus Everolimus: Efficacy

| Primary Analysis | Lenvatinib + Everolimus (n = 51) | Lenvatinib (n = 52) | Everolimus (n = 50) |
|---|---|---|---|
| Median PFS, mo (95% CI)[1,a] | 12.8 (7.4-17.5) | 9.0 (5.6-10.2) | 5.6 (3.6-9.3) |
| Median OS, mo (95% CI)[2] | 25.5 (20.8-25.5) | 18.4 (13.3-NE) | 17.5 (11.8-NE) |
| ORR, n (%)[1,a] | 18 (35) | 20 (39) | 0 (0) |
| Median duration of response, mo (95% CI)[2] | 13.1 (3.8-NE) | 7.5 (3.8-NE) | 8.5 (7.5-9.4) |
| Median number of cycles (range)[2] | 9.0 (1-25) | 8.5 (1-25) | 5.0 (1-22) |

[a] As assessed by an independent radiologic review.

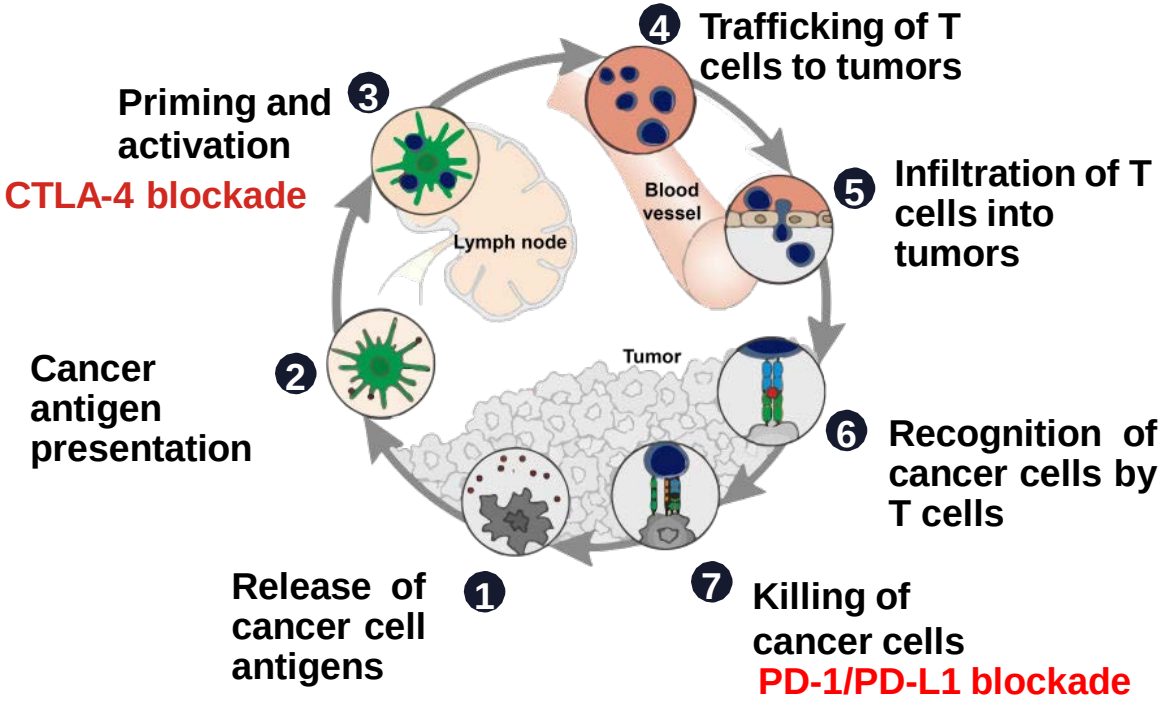
1. Motzer RJ et al. *Lancet Oncol.* 2016;17:e4-e5. 2. Motzer RJ et al. *Lancet Oncol*. 2015;6:1473-1482.

# Key Points: Second-Line Therapy

- Level 1 data supports use of nivolumab OR cabozantinib
- Toxicities vary between VEGF pathway– versus PD-1 pathway–directed therapy
- No clear evidence for clinical choice
- No definitive biomarkers
- Role of additional combinations being tested
- Phase 3 confirmatory trial of lenvatinib + everolimus pending

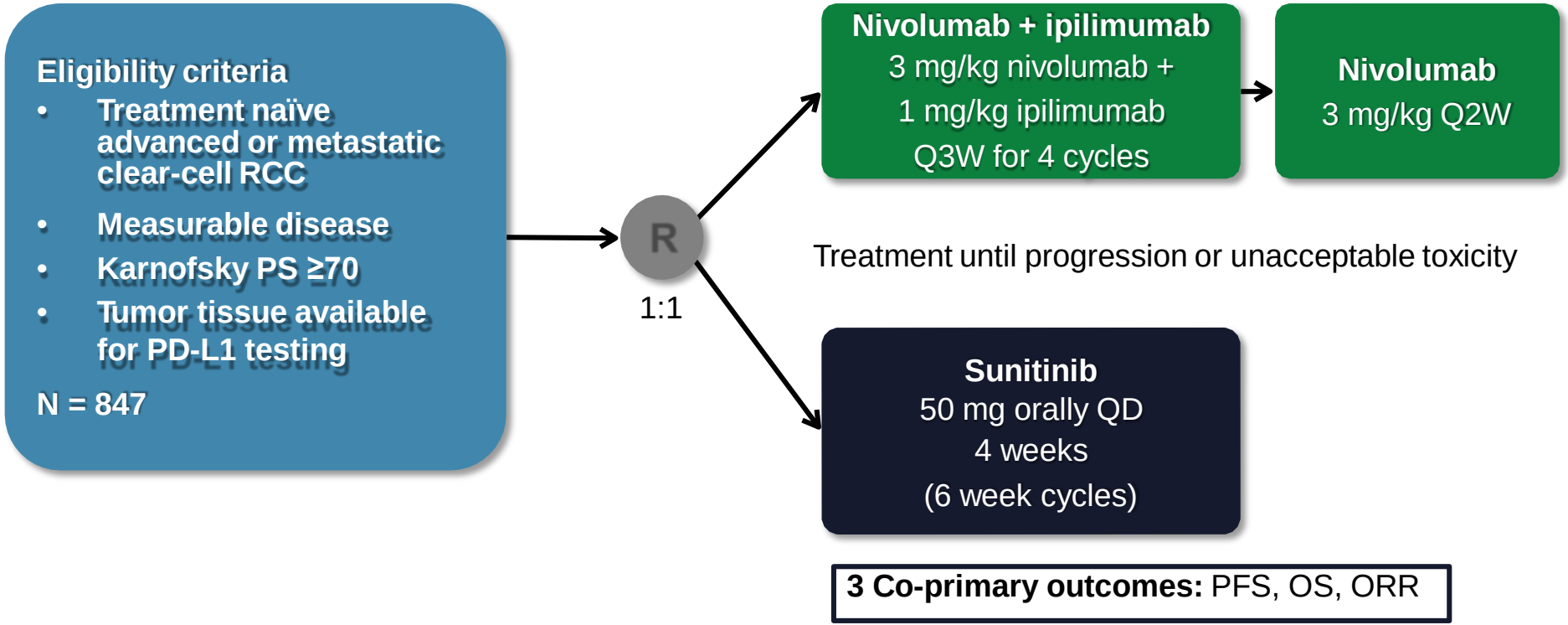
# What About Front-Line Therapy?

# Is CTLA-4 Blockade Synergistic With Anti–PD-1?[1]




1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10.

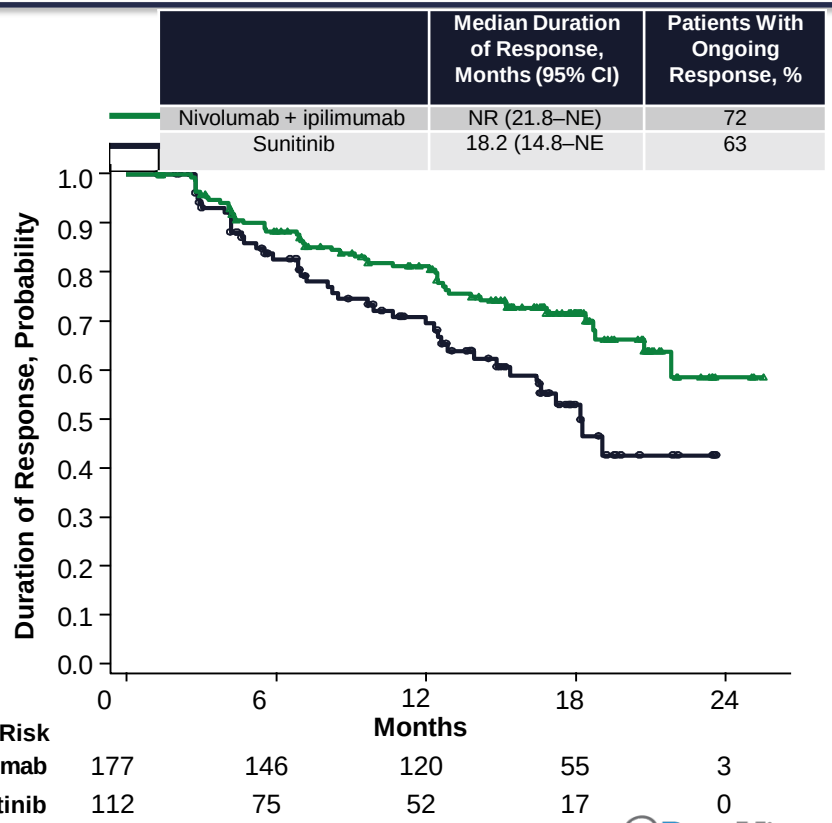
# CheckMate-214: Phase 3 Trial[1]




1. Escudier B et al. ESMO 2017. Abstract LBA5.

# CheckMate-214: ORR per IRCC
## IMDC Intermediate-Risk/Poor-Risk Patients[1]

| Outcome (N = 847) | Nivolumab + ipilimumab (n = 425) | Sunitinib (n = 422) |
|---|---|---|
| Confirmed ORR,[a] % (95% CI) | 42 (37–47) | 27 (22–31) |
| | *P* < .0001 | |
| Confirmed BOR,[a] % | | |
| Complete response | 9[b] | 1[b] |
| Partial response | 32 | 25 |
| Stable disease | 31 | 45 |
| Progressive disease | 20 | 17 |
| Unable to determine/not reported | 8 | 12 |

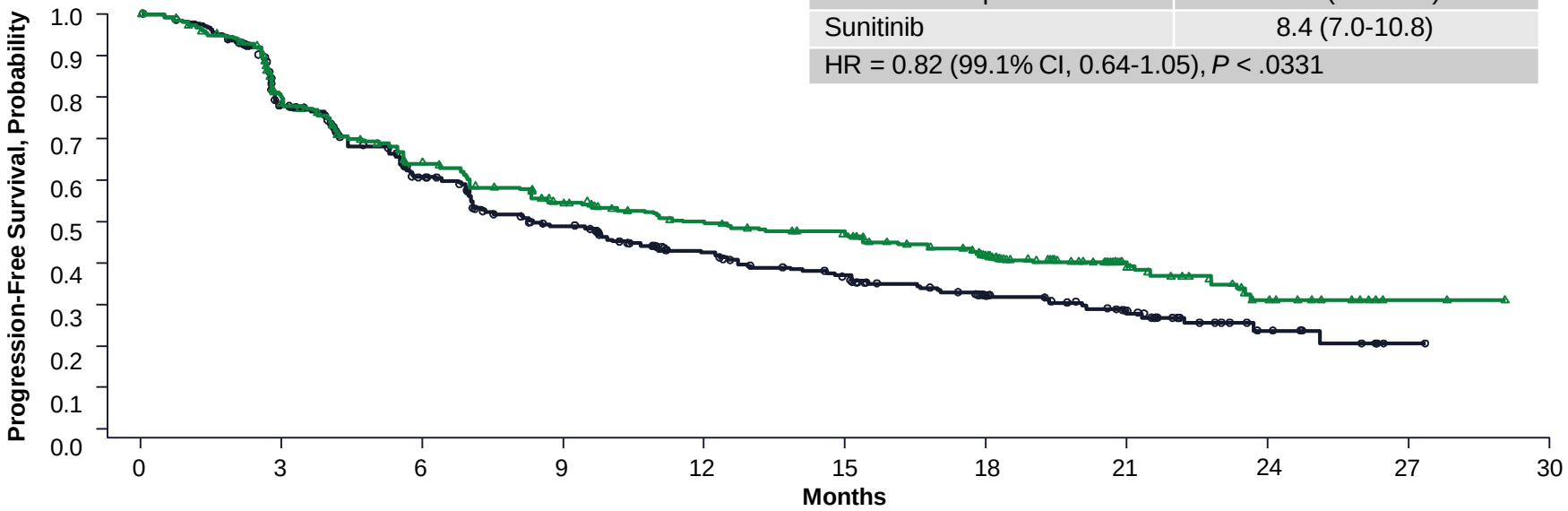



[a] IRRC-assessed ORR and BOR by RECIST v1.1. [b] *P* < 0.0001.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

# CheckMate-214: PFS per IRRC
## IMDC Intermediate-Risk/Poor-Risk Patients[1]

| | Median PFS (95% CI), mo |
|---|---|
| Nivolumab + ipilimumab | 11.6 (8.7-15.5) |
| Sunitinib | 8.4 (7.0-10.8) |
| HR = 0.82 (99.1% CI, 0.64-1.05), *P* < .0331 | |



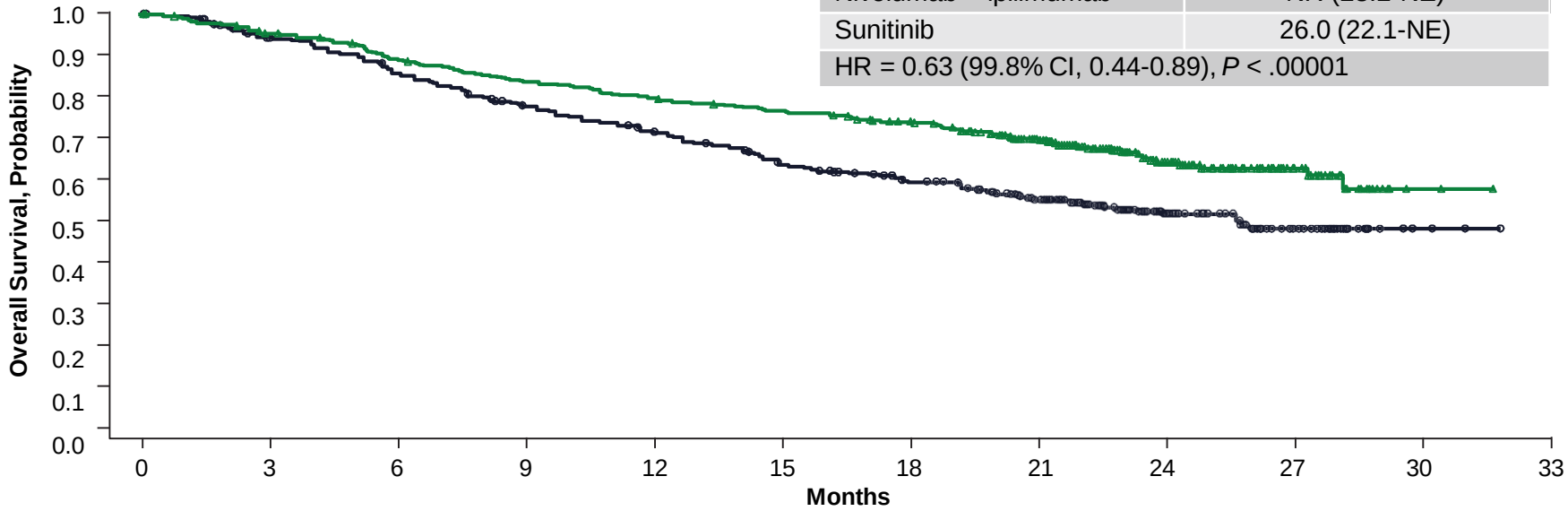

| No. at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + ipilimumab | 425 | 304 | 233 | 187 | 163 | 149 | 118 | 46 | 17 | 3 | 0 |
| Sunitinib | 422 | 282 | 191 | 139 | 107 | 86 | 57 | 33 | 11 | 1 | 0 |

1. Escudier B et al. ESMO 2017. Abstract LBA5.

# CheckMate-214: OS

## IMDC Intermediate-Risk/Poor-Risk Patients[1]

| | Median OS (95% CI), mo |
|---|---|
| Nivolumab + ipilimumab | NR (28.2-NE) |
| Sunitinib | 26.0 (22.1-NE) |
| HR = 0.63 (99.8% CI, 0.44-0.89), *P* < .00001 | |




| No. at Risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + ipilimumab | 425 | 399 | 372 | 348 | 332 | 318 | 300 | 241 | 119 | 44 | 2 | 0 |
| Sunitinib | 422 | 387 | 352 | 315 | 288 | 253 | 225 | 179 | 89 | 34 | 3 | 0 |

1. Escudier B et al. ESMO 2017. Abstract LBA5.

# CheckMate 214: ORR and PFS per IRRC
## IMDC Favorable Risk[1]

| Outcome, N = 249[a] | Nivolumab + Ipilimumab (n = 125) | Sunitinib (n = 124) |
|---|---|---|
| Confirmed ORR,[b] % (95% CI) | 29 (21–38) | 52 (43–61) |
| | *P* = .0002 | |
| PFS,[c] median (95% CI), months | 15.3 (9.7–20.3) | 25.1 (20.9–NE) |
| | HR (99.1% CI) 2.18 (1.29–3.68)<br>*P* < .0001 | |

[a] 11% of patients in both arms had tumor PD-L1 expression ≥1%. [b] IRRC assessed by RECIST v1.1. [c] IRRC assessed.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

# CheckMate-214: Treatment-Related Adverse Events[1]

| Event, % | Nivolumab + Ipilimumab (n = 547) | | Sunitinib (n = 535) | |
|---|---|---|---|---|
| | Any Grade | Grade 3–5 | Any Grade | Grade 3–5[a] |
| Treatment-related adverse events in ≥25% of patients | 93 | 46 | 97 | 63 |
| Fatigue | 37 | 4 | 49 | 9 |
| Pruritus | 28 | <1 | 9 | 0 |
| Diarrhea | 27 | 4 | 52 | 5 |
| Nausea | 20 | 2 | 38 | 1 |
| Hypothyroidism | 16 | <1 | 25 | <1 |
| Decreased appetite | 14 | 1 | 25 | 1 |
| Dysgeusia | 6 | 0 | 33 | <1 |
| Stomatitis | 4 | 0 | 28 | 3 |
| Hypertension | 2 | <1 | 40 | 16 |
| Mucosal inflammation | 2 | 0 | 28 | 3 |
| Palmar-plantar erythrodysesthesia syndrome | 1 | 0 | 43 | 9 |
| Treatment-related AEs leading to discontinuation, % | 22 | 15 | 12 | 7 |
| Treatment-related deaths | n = 7[b] | | n = 4[c] | |

[a] Two patients had grade 5 cardiac arrest. [b] Pneumonitis, immune-mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c] Cardiac arrest (n = 2), heart failure, multiple organ failure.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

# CheckMate-214: Treatment-Related Adverse Events[1]

| Event, % | Nivolumab + Ipilimumab (n = 547) | | Sunitinib (n = 535) | |
|---|---|---|---|---|
| | Any Grade | Grade 3–5 | Any Grade | Grade 3–5[a] |
| Treatment-related adverse events in ≥25% of patients | 93 | 46 | 97 | 63 |
| Fatigue | 37 | 4 | 49 | 9 |
| Pruritus | 28 | <1 | 9 | 0 |
| Diarrhea | 27 | 4 | 53 | 5 |
| Nausea | 26 | 1 | 48 | 1 |
| Hypothyroidism | 16 | <1 | 25 | <1 |
| Decreased appetite | 14 | 1 | 25 | 1 |
| Dysgeusia | 9 | 0 | 33 | <1 |
| Stomatitis | 4 | 0 | 28 | 3 |
| Hypertension | 2 | <1 | 40 | 16 |
| Mucosal inflammation | 2 | 0 | 28 | 3 |
| Palmar-plantar erythrodysesthesia syndrome | 1 | 0 | 43 | 9 |
| Treatment-related AEs leading to discontinuation, % | 22 | 15 | 12 | 7 |
| Treatment-related deaths | n = 7[b] | | n = 4[c] | |

**60% of patients treated with nivolumab + ipilimumab required systemic corticosteroids,**

**45% high dose steroids for an adverse event**

[a] Two patients had grade 5 cardiac arrest. [b] Pneumonitis, immune-mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c] Cardiac arrest (n = 2), heart failure, multiple organ failure.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

# CABOSUN: Randomized Phase 2 Assessment of Front-Line Cabozantinib[1]

**Multicenter, randomized, phase 2 study**

- Clear-cell RCC
- Intermediate or poor risk
- No prior systemic therapy

N = 157

R

**Cabozantinib 60 mg/d (Continuous dosing) (n = 79)**

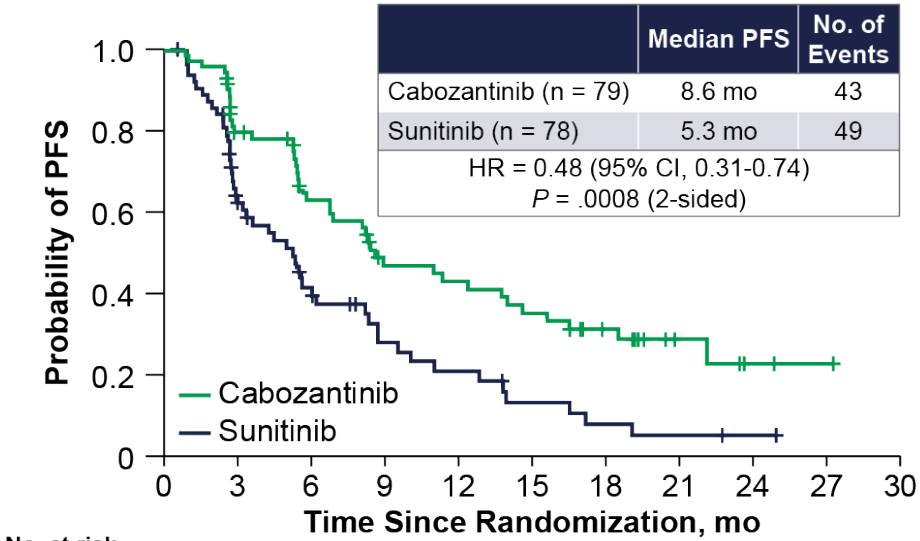
**Sunitinib 50 mg/d (4/2 dosing) (n = 78)**

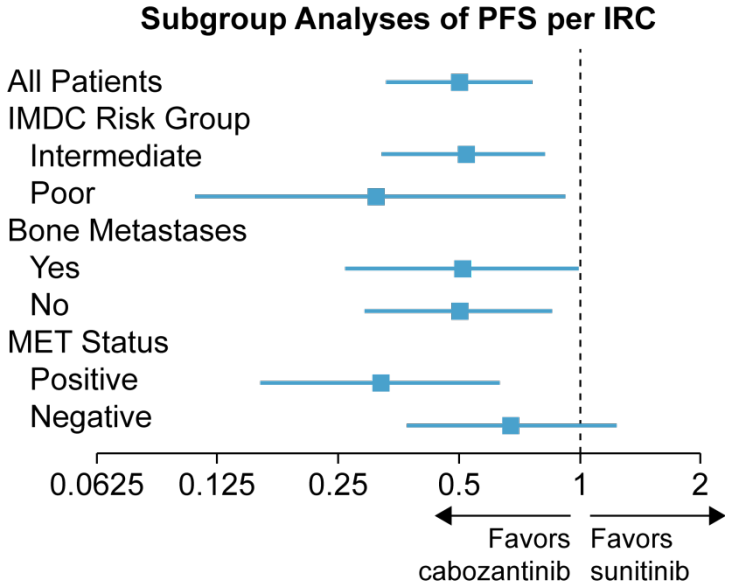
**Stratified by:**
- International Metastatic Renal Cell Carcinoma Database Consortium risk group (intermediate vs poor)
- Bone metastasis (yes/no)

**Primary endpoint:** PFS

1. Choueiri TK et al. *J Clin Oncol.* 2016;35:591-597.

# CABOSUN: PFS per IRC and OS[1,a]



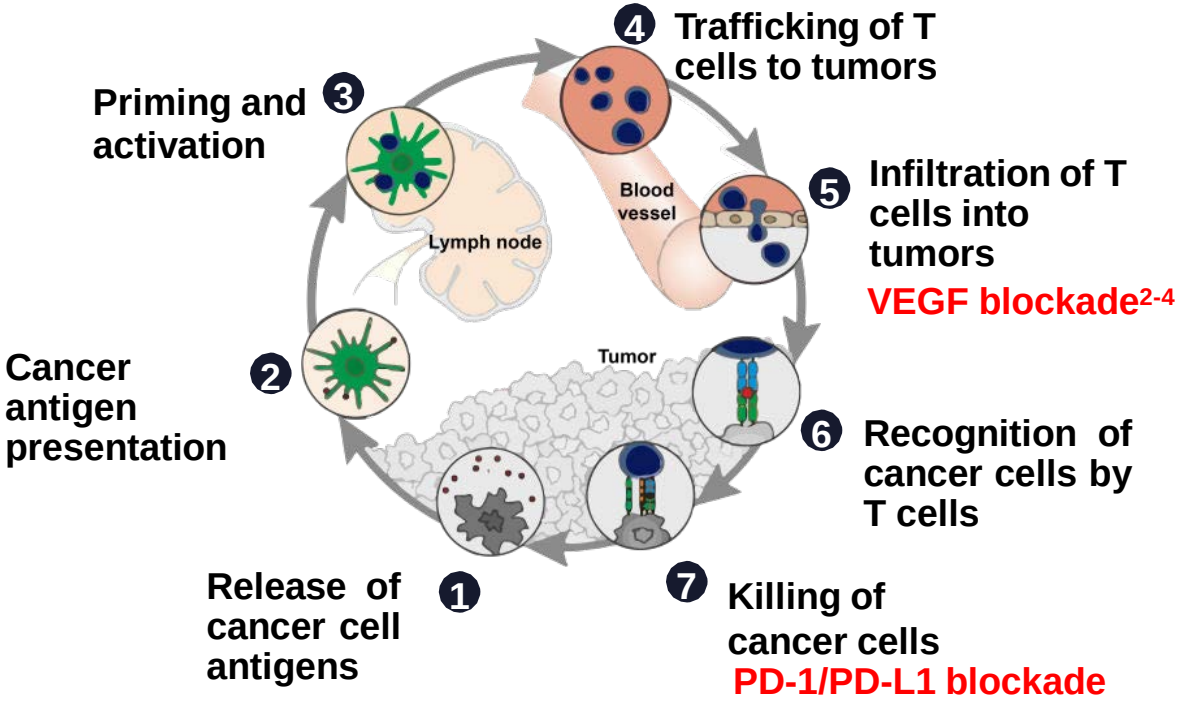




**OS**
HR = 0.80 (95% CI, 0.53-1.21)
*P* = .29 (2-sided)
Median OS: cabozantinib, 26.6 mo; sunitinib, 21.2 mo

[a] Data cutoff: PFS, September 15, 2016; OS, July 1, 2017.

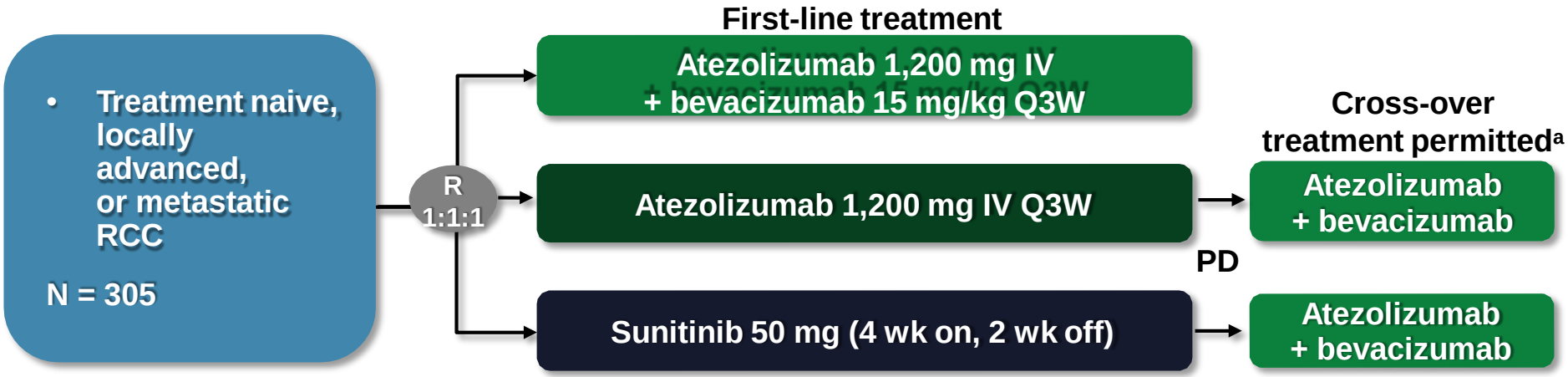
1. Choueiri TK et al. ESMO 2017. Abstract LBA38.

# Is VEGF Inhibition Synergistic With Anti–PD-1?[1]




1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10. 2. Shrimali RK et al. *Can Res.* 2010;70:6171-6180. 3. Manning EA et al. *Clin Cancer Res.* 2007;13:3951-3959. 4. Motz GT et al. *Nat Med.* 2014;20:607-615.

# Phase 2 IMmotion150 Trial Design[1,2]

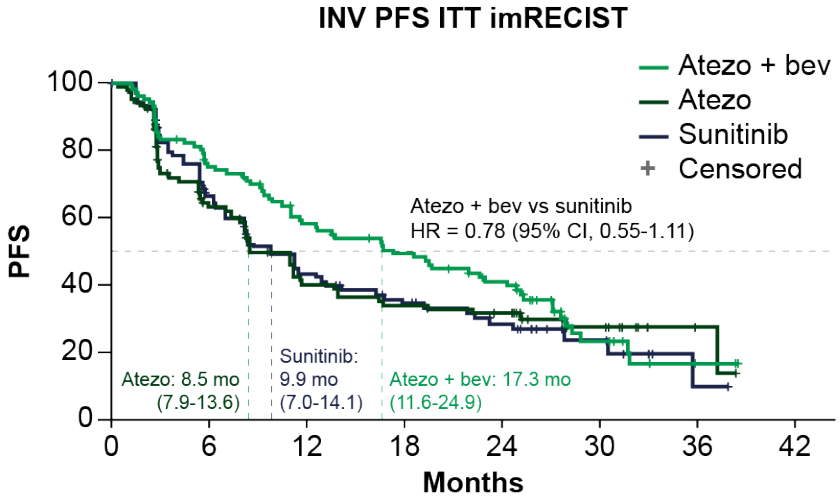



- IMmotion150 was designed to be hypothesis generating and inform the phase 3 study IMmotion151
- Co-primary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with ≥1% of IC expressing PD-L1
- Exploratory endpoints included interrogation of the association between outcome and TME gene signatures[3]

[a] Crossover from atezolizumab monotherapy not allowed in Europe.

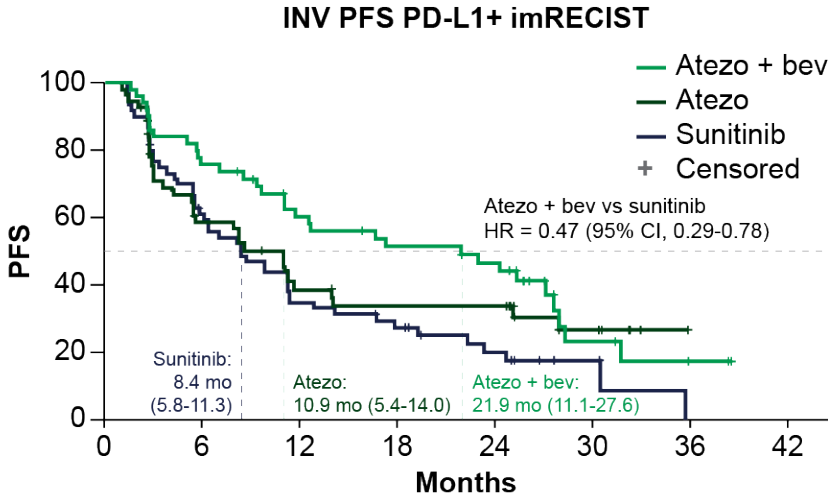
1. McDermott DF et al. *J Clin Oncol.* 2016;34:833-842. 2. McDermott DF et al. American Society for Clinical Oncology 2017 Genitourinary Symposium (ASCO GU 2017). Abstract 431. 3. McDermott D et al. American Association for Cancer Research Annual Meeting 2017 (AACR 2017). Abstract CT081.

# Bevacizumab + Atezolizumab – Phase 2 Efficacy[1]




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Atezo + bev | 101 | 73 | 54 | 44 | 33 | 10 | 2 |
| Atezo | 103 | 56 | 34 | 28 | 25 | 11 | 2 |
| Sunitinib | 101 | 59 | 37 | 26 | 18 | 7 | 1 |




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Atezo + bev | 50 | 37 | 27 | 22 | 19 | 5 | 2 |
| Atezo | 54 | 28 | 17 | 14 | 14 | 6 | – |
| Sunitinib | 60 | 35 | 20 | 14 | 8 | 3 | – |

1. Pal SK et al.16th International Kidney Cancer Symposium 2017.

# IMmotion151: Phase 3 Assessment of Bevacizumab/Atezolizumab[1]

- Treatment-naïve advanced or metastatic RCC
- Clear-cell and/or sarcomatoid histology
- KPS ≥ 70
- Tumor tissue available for PD-L1 staining

N = 915

R

1:1

**Atezolizumab 1200 mg IV**
**+**
**Bevacizumab 15 mg/kg Q3W**

**Sunitinib 50 mg**
**(4 wk on, 2 wk off)**

**Stratification:**
- MSKCC risk score

**Co-primary endpoints:** Investigator-assessed PFS in patients with PD-L1 expression ≥1;

## Increases in CD8+ T cells are observed with treatments

Patient 3, Female, 62 years old

# IMmotion151: Efficacy and Safety[1]

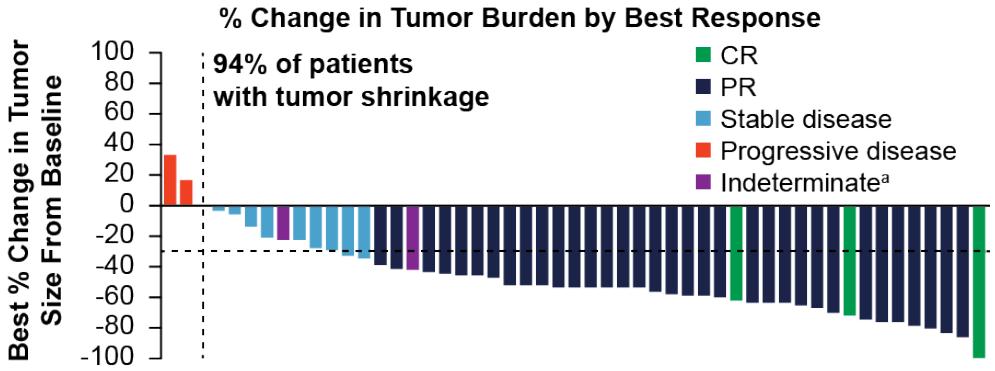
| | PD-L1+, (n = 362)[a] | | ITT (N = 915) | |
|---|---|---|---|---|
| | Sunitinib (n = 184) | Atezolizumab + Bevacizumab (n = 178) | Sunitinib (n = 461) | Atezolizumab + bevacizumab (n = 454) |
| mPFS (95% CI) | 7.7 (6.8-9.7) | 11.2 (8.9-15.0) | 8.4 (7.5-9.7) | 11.2 (9.6-13.3) |
| HR (95% CI), *P* | 0.74 (0.57-0.96), 0.0217 | | 0.83 (0.70-0.97), 0.219[b] | |
| ORR, % | 35 (28-42) | 43 (35-50) | 33 (29-38) | 37 (32-41) |
| DOR, months (95% CI) | 1.29 (9.8-NE) | NE (12.4-NE) | 14.2 (11.3-NE) | 16.6 (15.4-NE) |

Treatment-related grade 3-4 AEs: 40% atezolizumab/bevacizumab; 54% sunitinib
Treatment-related any grade AE leading to discontinuation: 12% atezolizumab/bevacizumab; 8% sunitinib

[a] PD-L1 expression on ≥1% on tumor infiltrating immune cells, SP142 IHC assay. [b] Descriptive purposes only.

1. Motzer RJ et al. ASCO GU. 2018. Abstract 578.

# VEGFR-TKI + Anti–PD-1: Axitinib + Pembrolizumab—Efficacy[1]




- Median PFS was 15.1 mo (11.4-NR) in overall population
- **UPDATED PFS: 20.9 months[2]**
- Of 11 pts enrolled in the dose-finding phase, median PFS not yet reached
- 9 of 48 (18.8%) evaluable tumor specimens were PD-L1–positive

| N = 52 | Axitinib + Pembrolizumab |
|---|---|
| Pts with baseline assessment | 52 (100) |
| Pts with measurable disease at BL | 52 (100) |
| Best overall response, n (%) | |
| CR | 3 (5.8) |
| PR | 34 (65.4) |
| Stable disease | 10 (19.2) |
| Progressive disease | 2 (3.8) |
| Indeterminate[b] | 3 (5.8) |
| ORR (CR + PR) | 37 (71.2) |
| 95% exact CI | 56.9-82.9 |
| **UPDATED ORR[2]** | **73.1%** |

[a] Stable disease or PR not confirmed. [b] 2 patients indeterminate and 1 patient with no follow-up assessment.

1. Atkins MB et al. *Ann Oncol.* 2016;27:266-295. 2. Atkins MB et al. ASCO GU 2018. Abstract 579.

# VEGFR-TKI + Anti–PD-1: Axitinib + Pembrolizumab—Safety[1]

| Dosage[a] (N = 52) | Pembrolizumab Average Dose per Cycle, mg/kg | Axitinib Average Daily Dose, mg | Days on Treatment |
|---|---|---|---|
| Mean (SD) | 1.9 (0.1) | 8.5 (1.7) | 318.5 (124.7) |
| Median | 2.0 | 8.9 | 316.0 |
| Range | 1.6-2.1 | 4.7-13.8 | 22.0-656.0 |

Update[2]

- Most common grade ≥ 3 AEs
  - Hypertension (23%), diarrhea (10%) fatigue (10%)
- Immune-related AEs
  - Diarrhea (29%), increased ALT 17%, increased AST(13%), hypothyroidism (13%), fatigue (12%)

| | AEs in ≥20% of Pts, n (%) | Immune-Related AEs, n (%)[b] |
|---|---|---|
| Any AE | 34 (65.4) | 10 (19.2) |
| Diarrhea | 5 (9.6) | 4 (7.7) |
| Fatigue | 3 (5.8) | 2 (3.8) |
| Decreased appetite | 1 (1.9) | 0 |
| Hypertension | 9 (17.3) | 0 |
| Increased ALT | 3 (5.8) | 2 (3.8) |
| Hypothyroidism | 0 | 2 (3.8) |
| Nausea | 1 (1.9) | 0 |
| PPE syndrome | 2 (3.8) | 0 |
| Increased AST | 2 (3.8) | 2 (3.8) |
| Headache | 4 (7.7) | 0 |
| Dizziness | 1 (1.9) | 0 |
| Dyspnea | 2 (3.8) | 0 |
| Weight loss | 3 (5.8) | 1 (1.9) |
| Vomiting | 1 (1.9) | 0 |
| Oral pain | 1 (1.9) | 0 |
| Proteinuria | 1 (1.9) | 0 |
| Hyperthyroidism | 1 (1.9) | 0 |
| Colitis | 2 (3.8) | 2 (3.8) |

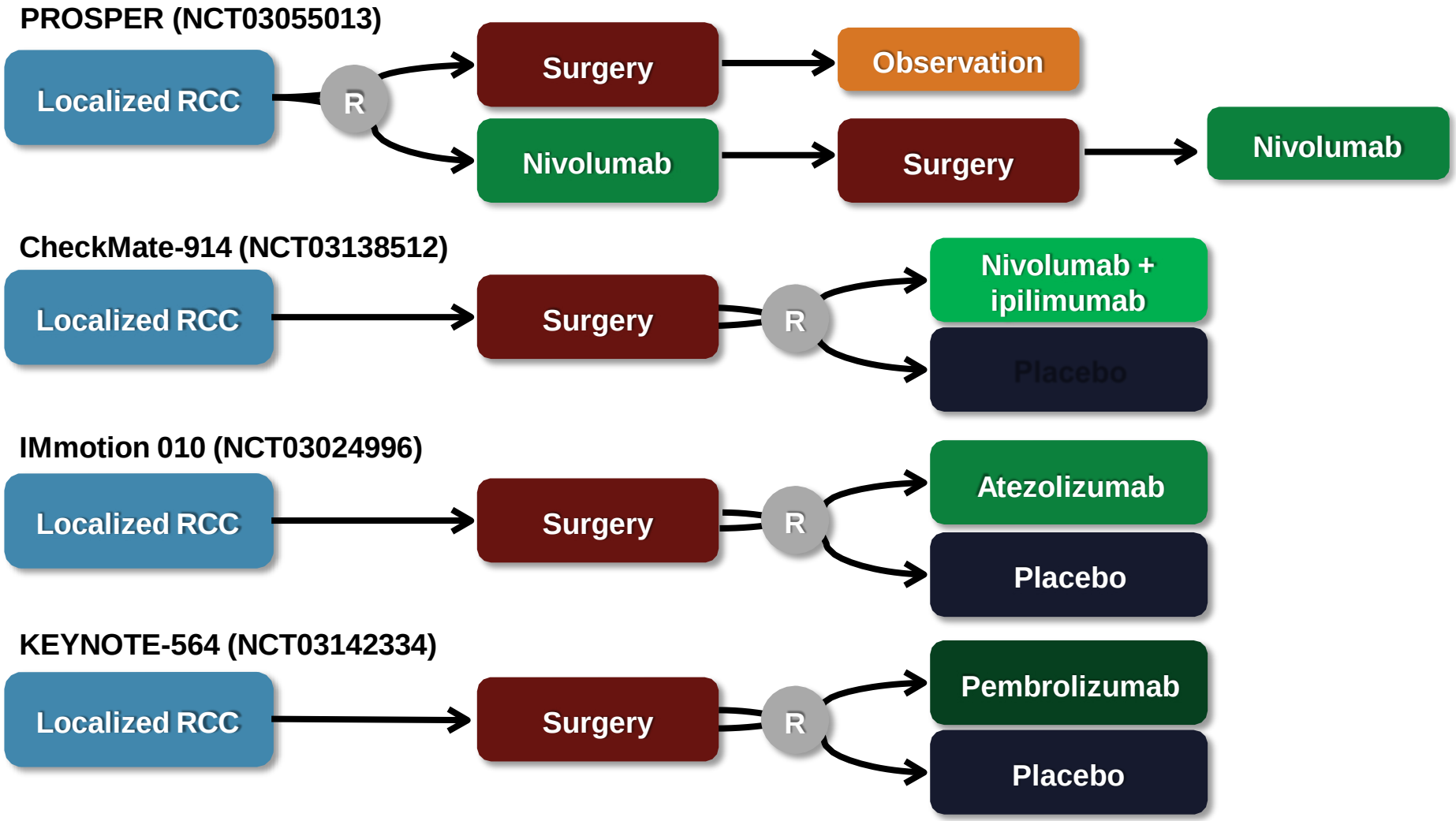
[a] Dosage: 2 mg/kg IV pembrolizumab every 3 weeks + 5 mg axitinib twice daily. [b] No immune-related grade ≥4 AEs reported.

1. Atkins MB et al. *Ann Oncol.* 2016;27:266-295. 2. Atkins MB et al. ASCO GU 2018. Abstract 579.

# First-Line Phase 3 Trials in Advanced RCC[1]

| Experimental Arm | Primary Endpoint | Estimated N | Trial | ClinicalTrials.gov ID |
|---|---|---|---|---|
| Axitinib + avelumab | PFS | 583 | JAVELIN Renal 101 | NCT02684006 |
| Axitinib + pembrolizumab | PFS, OS | 840 | KEYNOTE-426 | NCT02853331 |
| Bevacizumab + atezolizumab | PFS, OS in PD-L1–detectable tumors | 900 | IMmotion151 | NCT02420821 |
| Nivolumab + ipilimumab | PFS, OS | 1,070 | CheckMate 214 | NCT02231749 |
| Nivolumab + cabozantinib or nivolumab + ipilimumab + cabozantinib | PFS in intermediate-risk/ poor-risk patients | 1,014 | CheckMate 9ER | NCT03141177 |
| Lenvatinib/pembrolizumab or lenvatinib/everolimus | PFS | 735 | CLEAR | NCT02811861 |
| Sunitinib + AGS-003 | OS | 450 | ADAPT | NCT01582672 |

1. www.clinicaltrials.gov. Accessed February 6, 2018.


PROSPER (NCT03055013)
Localized RCC
R
Surgery
Observation
Nivolumab
Surgery
Nivolumab
CheckMate-914 (NCT03138512)
Localized RCC
Surgery
R
Nivolumab + ipilimumab
Placebo
IMmotion 010 (NCT03024996)
Localized RCC
Surgery
R
Atezolizumab
Placebo
KEYNOTE-564 (NCT03142334)
Localized RCC
Surgery
R
Pembrolizumab
Placebo

# Immunotherapy for the Treatment of Bladder Cancer

# Immune Checkpoint Blockade Has Revolutionized the Treatment of Advanced Urothelial Carcinoma[1]

- Before 2016, cytotoxic chemotherapy was the only option for patients with locally advanced or metastatic urothelial carcinoma
- Cisplatin-based combination chemotherapy remains the standard of care for eligible patients
- Outcomes with carboplatin-based chemotherapy are poor, with median survival about 9 months in phase 3 trials
- After failure of platinum-based chemotherapy, survival was short, and available treatments (taxanes, pemetrexed, vinflunine [EU]) were toxic

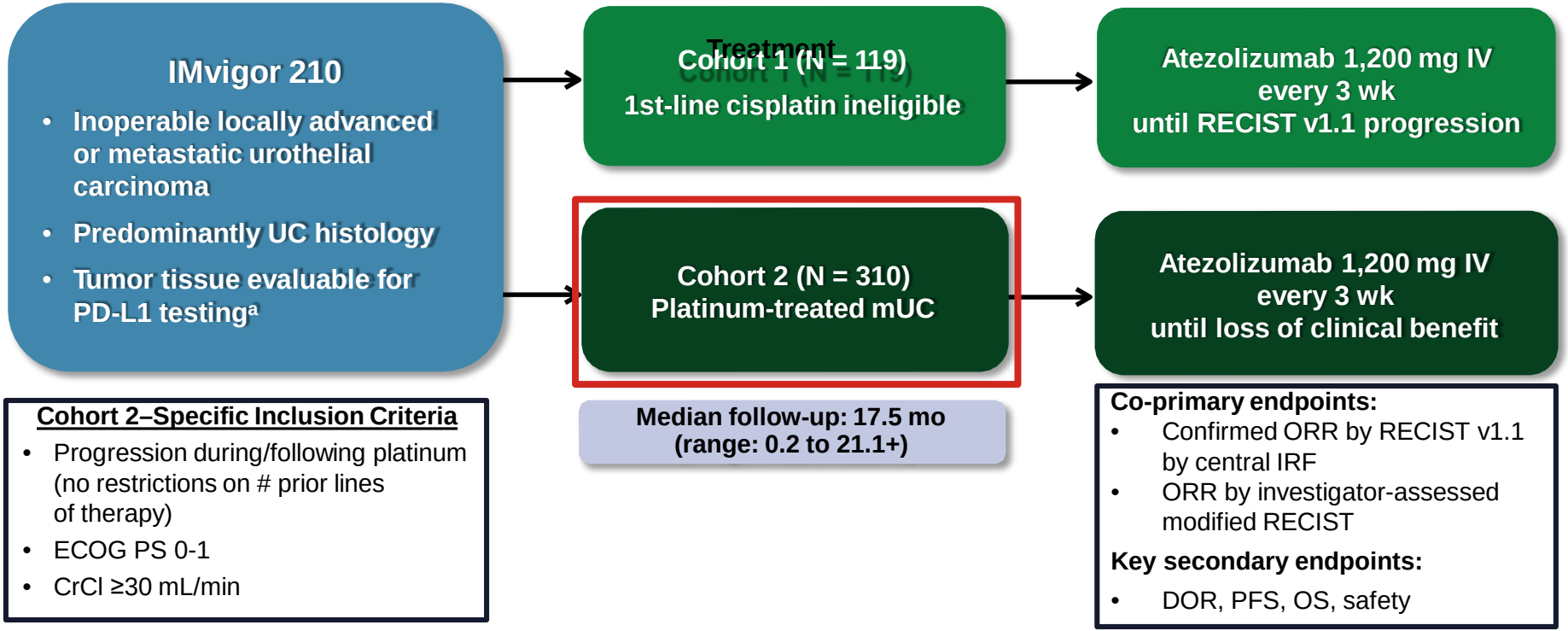
1. Abida W et al. *Hematol Oncol Clin North Am*. 2015;29:319-328.

# Approved Checkpoint Inhibitors for Platinum-Refractory mUC

M Ornstein JTT online Feb 13, 2018 with permission

| | *Atezolizumab* | *Nivolumab* | *Pembrolizumab* | *Avelumab* | *Durvalumab* |
|---|---|---|---|---|---|
| **Phase (no. of pts)** | **Phase II (310)** | **Phase II (265)** | **Phase III (270)** | **Phase 1b (241)** | **I/II (191)** |
| **Dosing** | **1200 mg Q 3wk** | **240 mg Q 2wk** | **200 mg Q 3wk** | **10mg/kg Q 2wk** | **10 mg/kg Q 2w** |
| **ORR** | **15%** | **20%** | **21%** | **18%** | **18%** |
| **mPFS/OS (months)** | **2.1/7.9** | **2.0/8.7** | **2.1/10.3** | **1.5/7.0** | **2.2/18.2** |
| ***Grade 3/4 Rx-Related AEs*** | **16%** | **18%** | **15%** | **8%** | **7%** |
| **Most Common Rx-related AEs** | **Fatigue (30%)**<br>**Nausea (14%)**<br>**Pruritis (10%)** | **Fatigue (17%)**<br>**Pruritis (9%)**<br>**Diarrhea (9%)** | **Pruritis (19.5%)**<br>**Fatigue (13.9%)**<br>**Nausea (10.9%)** | **Infusion-related reaction (22.8%)**<br>**Fatigue (12%)** | **Fatigue (19.4%)**<br>**Decrease appetite (9%)**<br>**Diarrhea 8.4%)** |
| FDA Approval | May18,2016 (accelerated) | February 2, 2017 (accelerated) | May 18, 2017 (regular approval) | May 9, 2017 (accelerated) | May 1, 2017 (accelerated) |

# IMvigor210 Cohort 2 Study Design: Basis for Accelerated Approval[1,2]

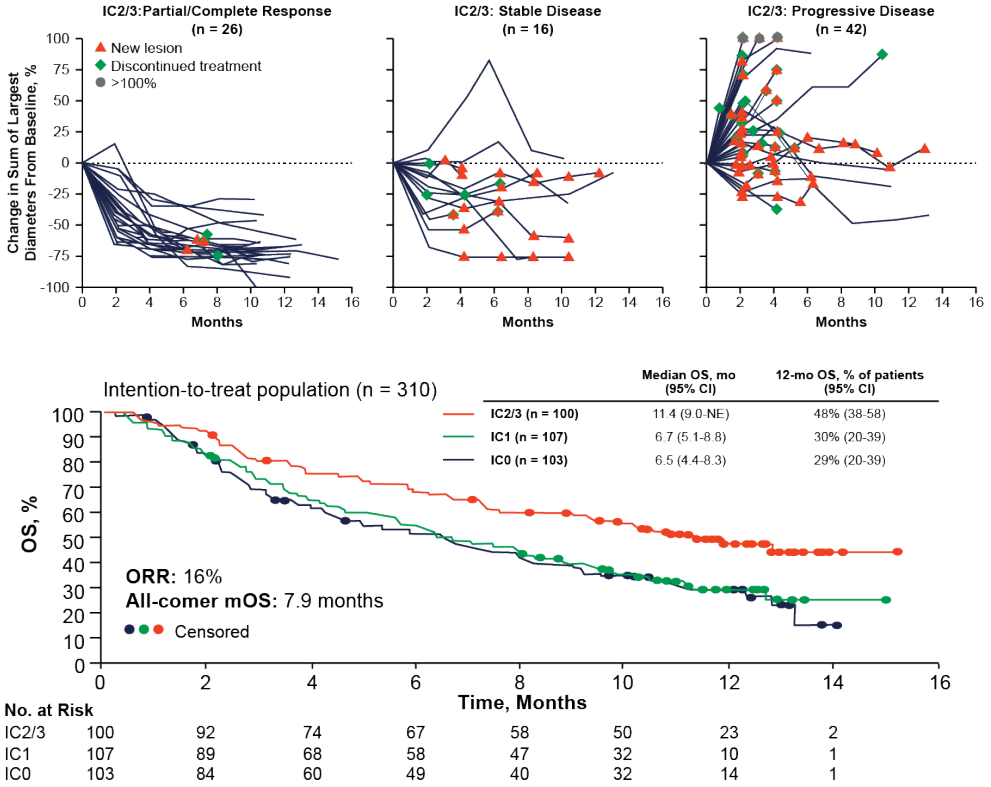



[a] PD-L1 prospectively assessed by a central laboratory, with patients and investigators blinded.

1. Dreicer R et al. ASCO 2016. Abstract 4515. 2. Rosenberg JE et al. *Lancet*. 2016;387:1909-1920.

# IMvigor210: Atezolizumab Approved for Prior Platinum-Treated Patients[1]

- 40% had 2 or more prior regimens
- ORR: 14.8%
- Median OS: 7.9 mo
- Modest toxicity
- Higher levels of PD-L1 staining on immune cells are associated with higher response rate and longer survival (SP142 assay)




1. Rosenberg JE et al. *Lancet*. 2016;387:1909-1920.

# IMvigor211 Trial in Previously Treated Urothelial Cancer[1]

**Phase 3**

**Patients with previously treated relapsed UBC (n = 931 [234 PD-L1+])**

PD-L1 testing by SP142 assay on immune cells

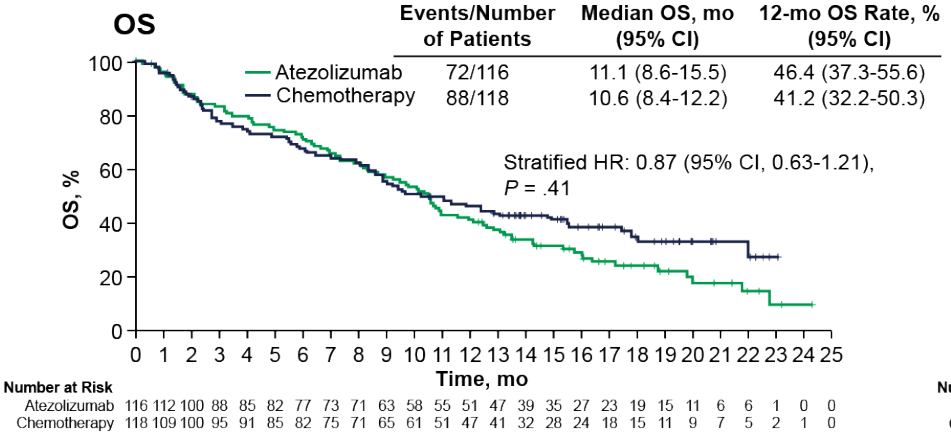
**Atezolizumab 1,200 mg IV Q3W**

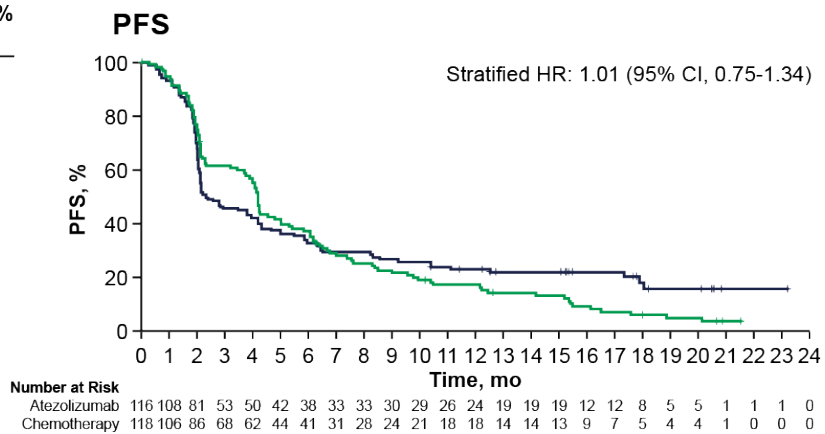
**Vinflunine, paclitaxel, or docetaxel IV Q3W until progression**

- **Primary endpoint**: OS in IHC 2/3→1/2/3→ITT
- **Secondary endpoints**: PFS, ORR, DOR

1. Powles T et al. *Lancet*. 2017 Dec 18 [Epub ahead of print].

# Atezolizumab Did Not Improve OS in the PD-L1–Positive Population[1]

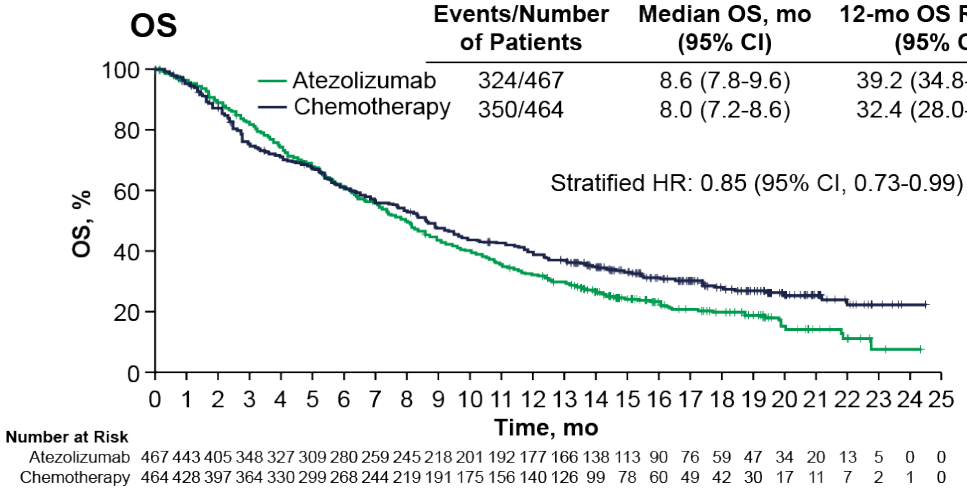


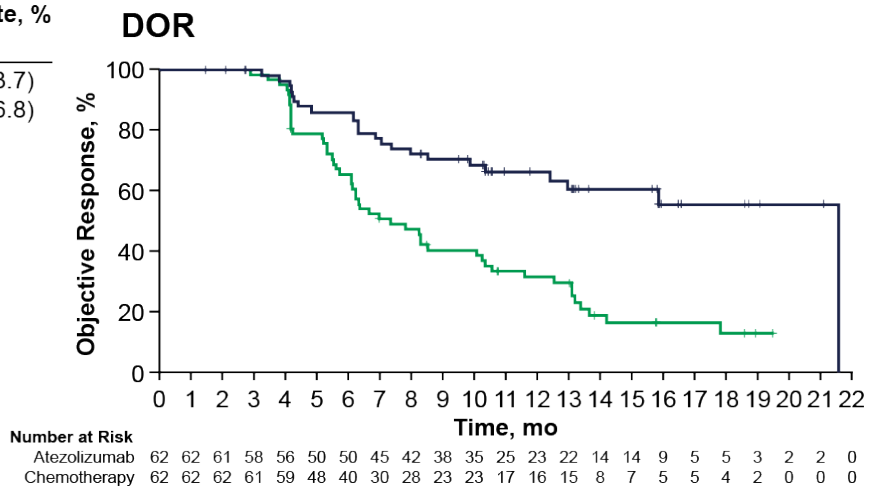




**PD-L1 staining enriched for response and survival for both chemotherapy and atezolizumab**

1. Powles T et al. *Lancet*. 2017 Dec 18 [Epub ahead of print].

# IMvigor211:Outcomes in the ITT Population[1]

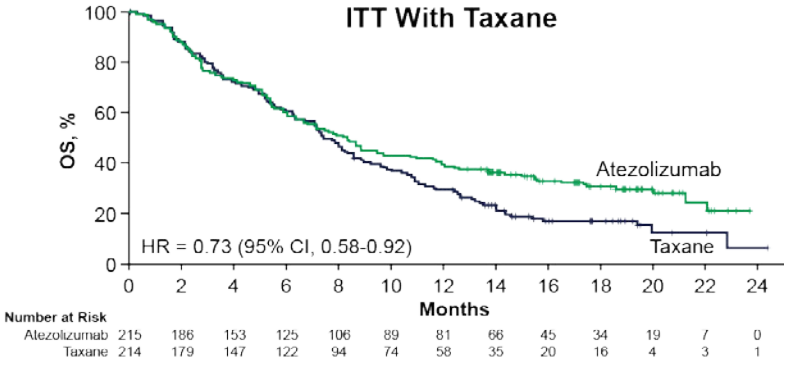


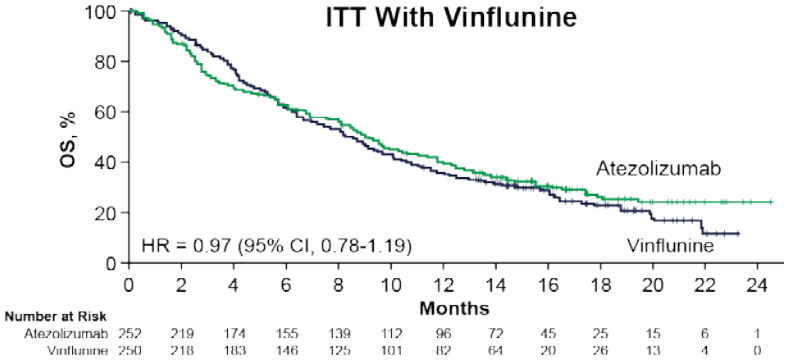




- Study design did not allow formal assessment of OS in the entire study population
  - HR and long-term survival favored atezolizumab
- DOR was dramatically longer in patients treated with atezolizumab

1. Powles T et al. *Lancet*. 2017 Dec 18 [Epub ahead of print].

# IMvigor211: Subgroup Analysis by Chemotherapy Type[1]




**OS was also examined in subgroups based on chemotherapy type at randomization**

- **Improved OS was observed with atezolizumab vs taxanes**

| Subgroup | Median OS, mo (95% CI) |
|---|---|
| Atezolizumab | 8.3 mo (6.6-9.8) |
| Taxane | 7.5 mo (6.7-8.8) |

| Subgroup | Median OS, mo (95% CI) |
|---|---|
| Atezolizumab | 9.2 mo (7.9-10.4) |
| Vinflunine | 8.3 mo (6.9-9.6) |

1. Adapted from Powles T et al. European Association for Cancer Research, American Association for Cancer Research, and Italian Cancer Society (EACR-AACR-SIC) 2017 Special Conference. Abstract 606.

# What Does This Mean?

**Atezolizumab is an active drug**

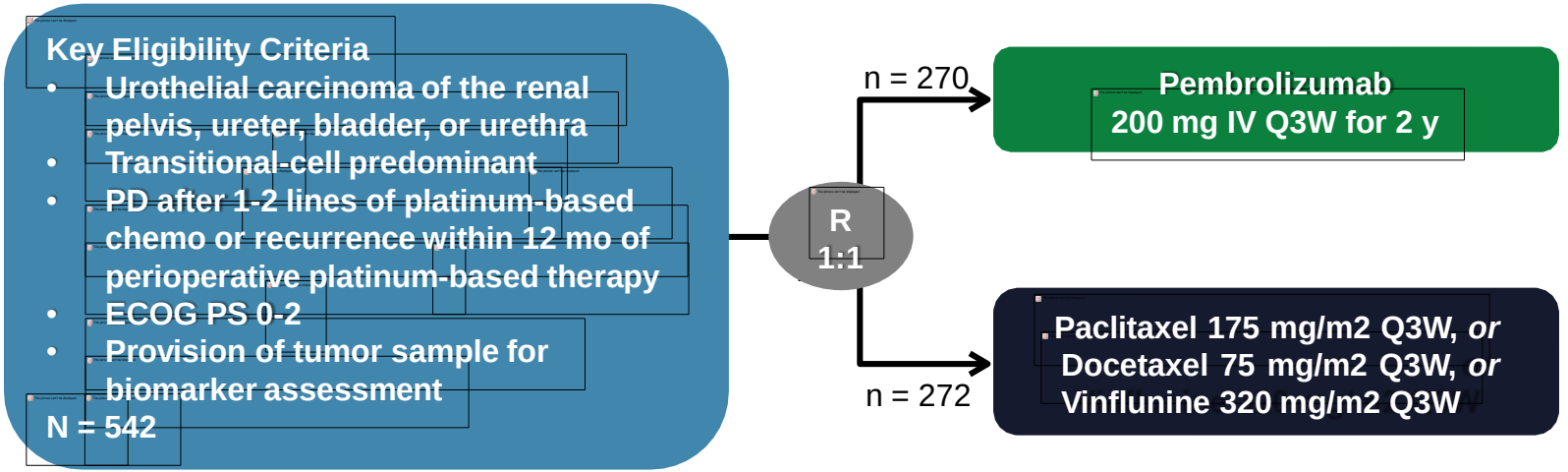
- Phase 3 trial showed that vinflunine is a more active agent than previously thought
- Atezolizumab activity recapitulated earlier data

**SP142 PD-L1 biomarker did not perform as predicted**

- IC2/3 predicted both chemotherapy and immunotherapy response

**Level 1 evidence (randomized phase 3 trial) supports pembrolizumab as second-line therapy**

# KEYNOTE-045 Phase 3 Trial (NCT02256436)[1]




**Stratification Factors**

- ECOG PS (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 mo)

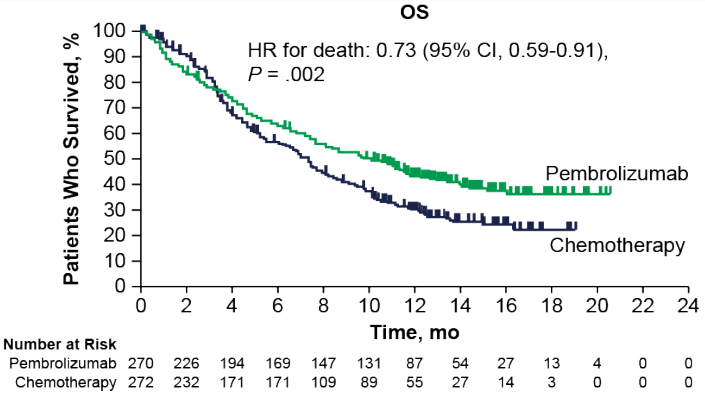
**Key Endpoints**

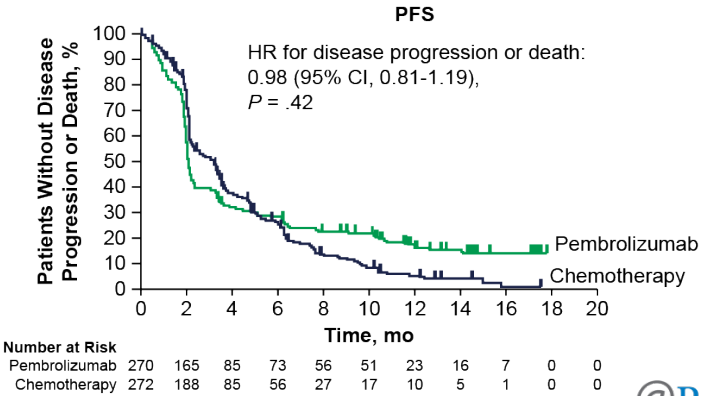
- **Primary:** OS and PFS in total and in PD-L1 combined positive score ≥10% populations
- **Secondary:** ORR and DOR in total and in PD-L1 combined positive score ≥10% populations; safety in total population

1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

# KEYNOTE-045: Pembrolizumab Improves OS vs Chemotherapy in the Second or Third Line[1]

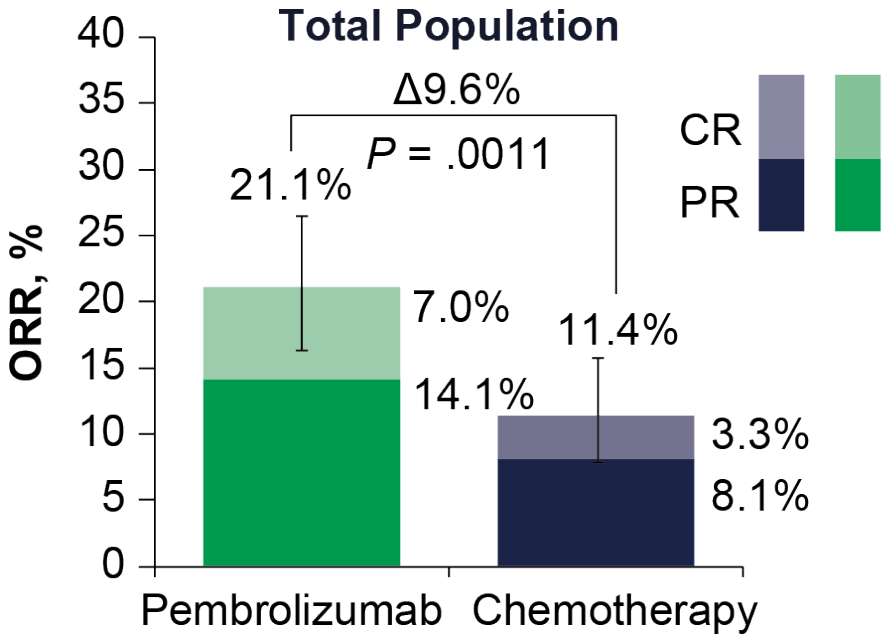
- Median OS 10.3 months for pembrolizumab vs 7.4 for chemo (HR = 0.73)
- **Updated: 10.3 mo vs 7.3 mo (HR = 0.70)[2]**
- PFS short, and not different between the two arms
- PD-L1 expression with this assay was a poor prognostic biomarker and does not help with patient selection

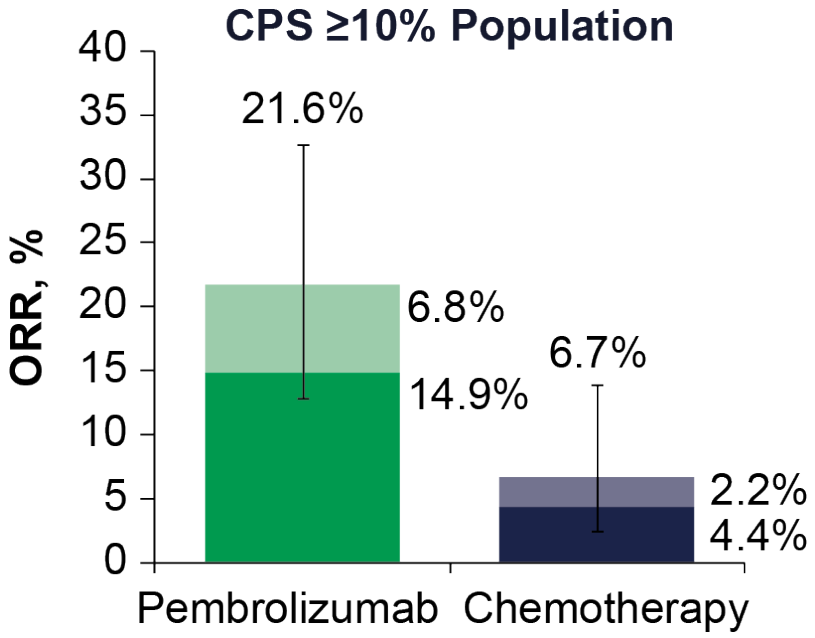



1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026. 2. Bellmunt J et al. ASCO GU 2018. Abstract 410.

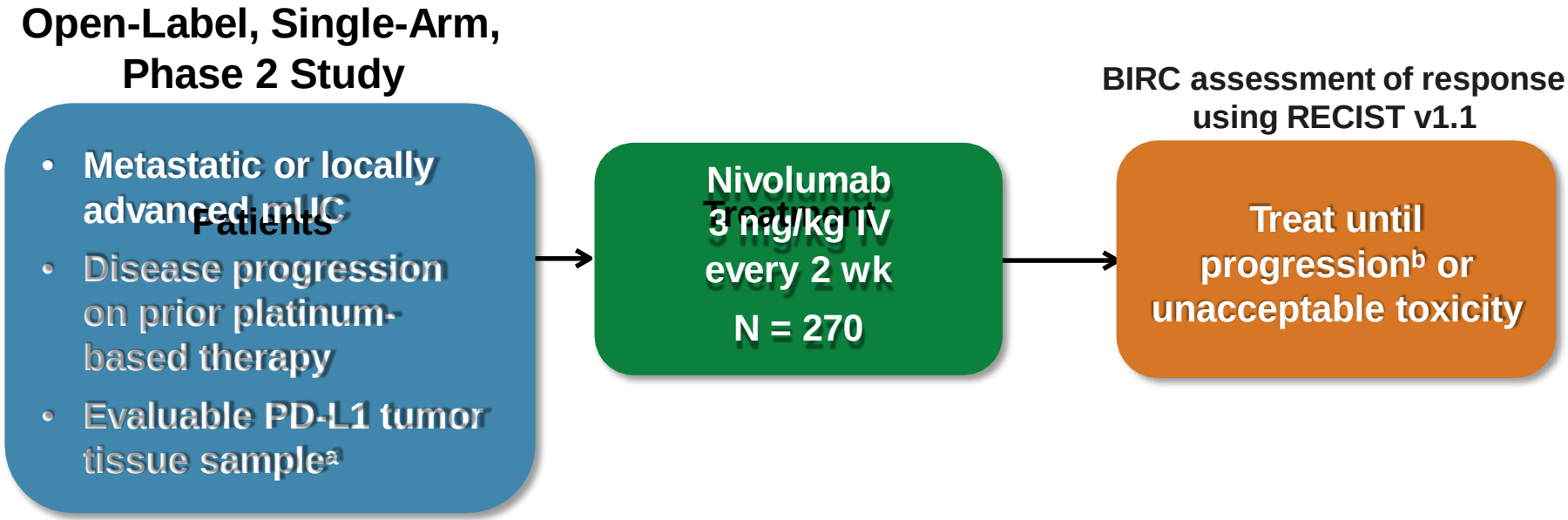
# KEYNOTE-045: Confirmed Objective Response Rate[1]




1. Bellmunt J et al. *J Immunother Cancer*. 2016;4(suppl. 2):O2.

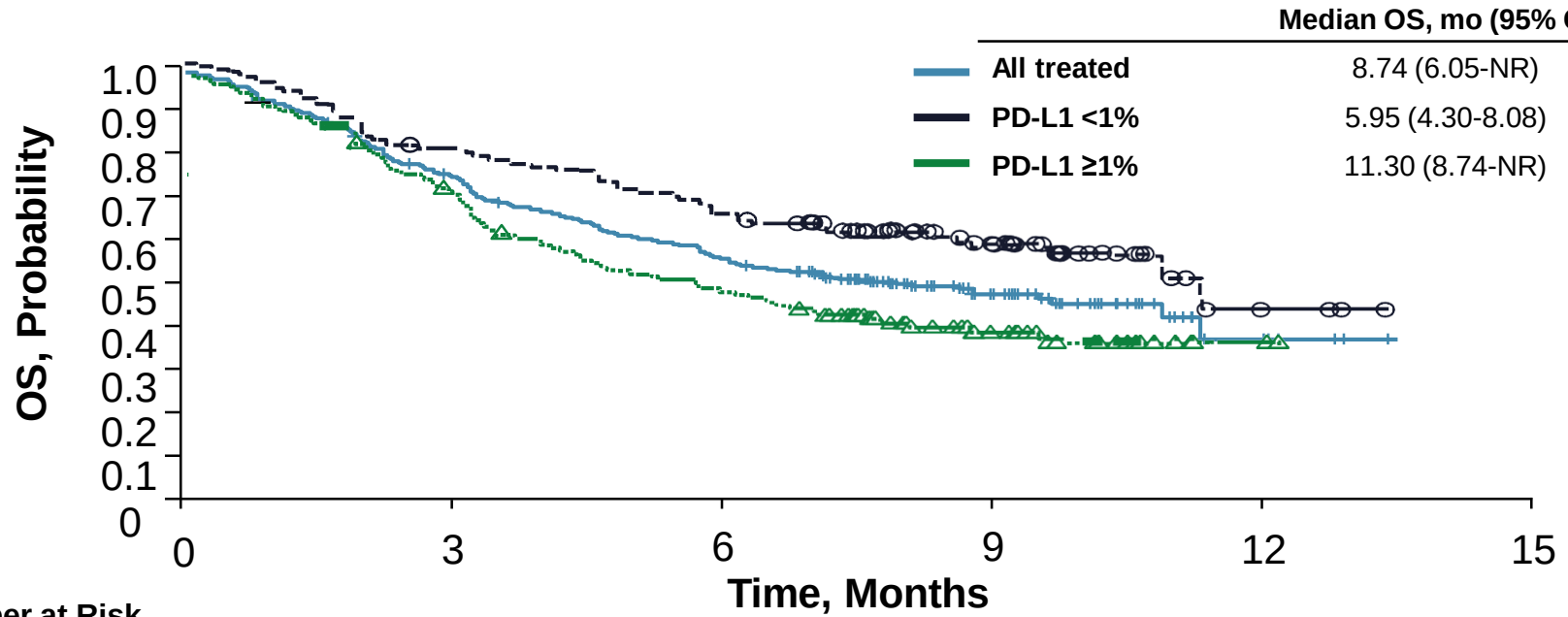
# CheckMate-275: Study Design[1,2]




[a] Patients were required to have an evaluable tumor tissue sample for PD-L1 expression testing at screening, but were not excluded based on PD-L1 status. [b] Patients could have been treated beyond progression under protocol-defined circumstances.

1. Galsky MD et al. European Society for Medical Oncology 2016 Congress (ESMO 2016). Abstract LBA31_PR.
2. Sharma P et al. *Lancet Oncol*. 2017;18:312-322.

# CheckMate-275: Overall Survival[1,2]




**Number at Risk**

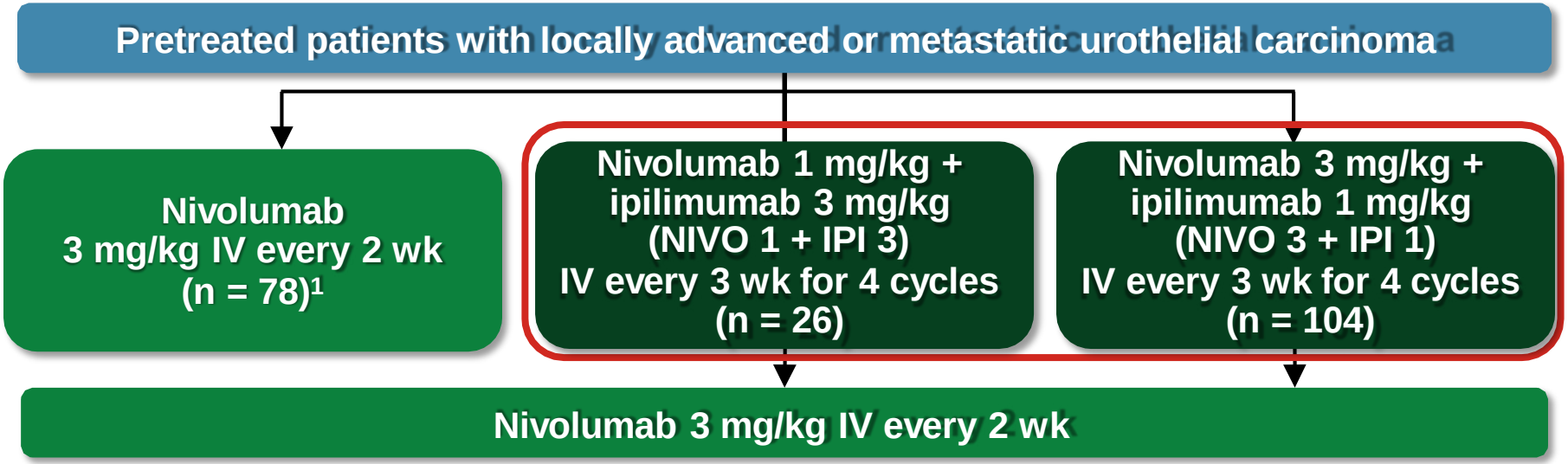
| | | | | | | |
|---|---|---|---|---|---|---|
| All treated patients | 265 | 198 | 148 | 63 | 5 | 0 |
| PD-L1 <1% | 143 | 101 | 69 | 26 | 2 | 0 |
| PD-L1 ≥1% | 122 | 97 | 79 | 37 | 3 | 0 |

[a] Similar results were seen using the 5% PD-L1 tumor expression cut-off.

1. Galsky MD et al. ESMO 2016. Abstract LBA31_PR. 2. Sharma P et al. *Lancet Oncol*. 2017;18:312-322.

# Anti–CTLA-4 and Anti–PD-1: CheckMate-032: Study Design[1,2]

**Open-label, multicenter, phase 1/2 study**




- Treatment beyond progression was permitted if treatment was tolerated and prespecified clinical benefit was noted
- Tumor measurements: CT or MRI every 6 wk (±1 wk) from first dose for the first 24 wk, then every 12 wk (±1 wk)

1. Sharma P et al. *Lancet Oncol*. 2016;17:1590-1598. 2. https://clinicaltrials.gov/ct2/show/NCT01928394. Accessed January 28, 2018.

# Anti–CTLA-4 and Anti–PD-1: CheckMate-032: Antitumor Activity[1]

| Outcome, % | Nivolumab 1 + Ipilimumab 3 (n = 26) | Nivolumab 3 + Ipilimumab 1 (n = 104) | Nivolumab Monotherapy (n = 78) |
|---|---|---|---|
| **Confirmed ORR, %** | 38.5 | 26.0 | 24.4 |
| 95% CI | 20.2-59.4 | 17.9-35.5 | 15.3-35.4 |
| **Best overall response, %** | | | |
| Complete response | 3.8 | 2.9 | 6.4 |
| Partial response | 34.6 | 23.1 | 17.9 |
| Stable disease | 19.2 | 25.0 | 28.2 |
| Progressive disease | 26.9 | 41.3 | 38.5 |

1. Sharma P et al. 31st Annual Meeting & Associated Programs of the Society for Immunotherapy of Cancer (SITC 2016). Abstract O3.

# Immune–Immune Combinations Hold Significant Promise

- CTLA-4, PD-1 pathway combinations have significant toxicity
- Identification of agents with less toxicity in combination is warranted
  - Advanced bladder cancer patients tend to be older and sicker
- Multiple different classes of agents are being tested

# Future Strategies

# Indoleamine 2,3-Dioxygenase 1 (IDO1)[1]

Resistance to PD-1 pathway inhibition may be mediated in part by IDO1 activity

IDO1:
- Depletes tryptophan and increases kynurenine levels
- Leads to an immunosuppressive tumor microenvironment

This leads to:
- Decreased effector T-cell function
- Differentiation of regulatory T cells

Inhibitors of this pathway are being tested in mUC

1. Mellor AL et al. *Front Immunol*. 2017;8:1360.

# Epacadostat and Pembrolizumab[1]

40 patients treated in expansion cohort at 100 mg PO BID

ORR is 35%

Tolerability appears similar to PD-1 therapy alone

80% had 1 or fewer prior regimens in metastatic setting

- Relatively lightly pretreated cohort compared with IMvigor210 (59%), but similar to KEYNOTE-045 (80%) and Checkmate-275 (71%)

Promising ORR worthy of further investigation in a planned large randomized trial

1. Smith DC et al. ASCO 2017. Abstract 4503.

# Nivolumab and BMS986205[1]

25 bladder cancer patients treated in a multicohort phase 1/2a dose-escalation and expansion study (CA017-003)

ORR was 32%

Kynurenine levels were decreased in pre- and on-treatment tumor biopsies

Toxicity seemed similar to single agent therapy

1. Luke JJ et al. SITC 2017. Abstract O41.