# Pacientes inelegíveis a cisplatina: quando quimio e quando imunoterapia?

**Denis F. Jardim, MD, PhD**

Oncologista Titular Hospital Sírio Libanês-SP

# Conflitos de interesse

| | PALESTRANTE | ELABORAR MATERIAL TÉCNICO-CIENTIFICO | APOIO CIENTIFICO PARA PARTICIPAR EM EVENTOS | PESQUISA CLÍNICA FINANCIADA | ADVISORY BOARD |
|---|---|---|---|---|---|
| ASTELLAS | X | | X | X | |
| JANSSEN | X | | X | | X |
| ROCHE | X | | X | | |
| LIBBS | X | X | | | X |
| RECEPTA | | | | X | |
| BMS | X | | X | X | |
| MSD | X | | | | |
| ASTRA ZENECA | X | | | | |

# Cisplatin Ineligible definition

| Criteria for Patients Entering Clinical Trials With Metastatic Urothelial Carcinoma<br>Deemed "Unfit" for Cisplatin-Based Chemotherapy* |
|---|
| ▪ WHO or ECOG PS ≥ 2 or Karnofsky PS 60% to 70% |
| ▪ Measured or calculated creatinine clearance < 60 mL/min |
| ▪ CTCAE v4 grade ≥ 2 audiometric hearing loss |
| ▪ CTCAE v4 grade ≥ 2 peripheral neuropathy |
| ▪ NYHA Class III heart failure |

*≥ 1 must be present.

Galsky MD, et al. J Clin Oncol. 2011;29:2432-2438.

# Carboplatin+Gencitabine

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in Patients With Advanced Urothelial Cancer "Unfit" for Cisplatin-Based Chemotherapy: Phase II—Results of EORTC Study 30986

✓Fase 2/3 - reportados dados do fase 2

✓ Paciente "unfit" - inelegíveis para cisplatina (30< TFG < 60 ou ECOG 2)

✓ Avaliação de Taxa de Resposta e Toxicidades Agudas Graves (TAG)

**1:1**

**Randomização**

**n = 178**

**Metotrexato 30 mg/m2 d1, d15, d22**

**Carboplatina AUC 4,5 d1**

**Vimblastina 3mg/m2 d1, d15, d22**

**Carboplatina AUC 4,5**

**Gemcitabina 1000mg/m2 D1 e D8**

J Clin Oncol, 2012 Jan 10;30(2)

# Carboplatin+Gencitabine

Less response and higher toxicity when more than 1 adverse factor is present

- Cisplatin-inegible
- Chemotherapy-inegible

**Table 3.** Impact of Reason Ineligible (unfit) for Cisplatin and Bajorin Risk Groups by Treatment Group (severe acute toxicity, response rate, survival)

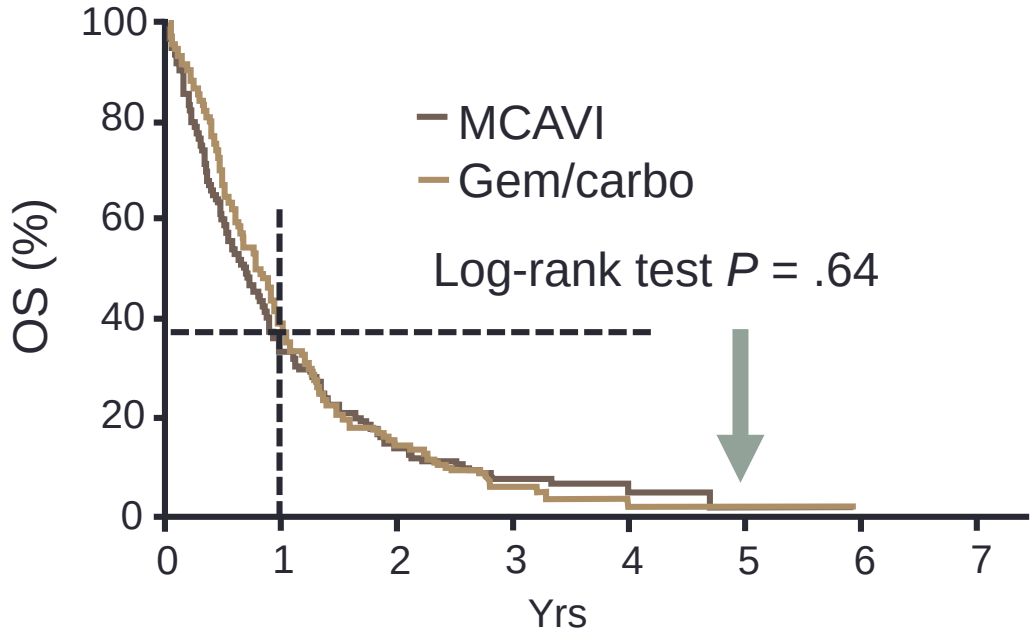
| | GC | | | | | | M-CAVI | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | WHO PS ≥ 2 (n = 21) | | GFR (< 60 mL/min) (n = 66) | | Both (n = 32) | | WHO PS ≥ 2 (n = 21) | | GFR (< 60 mL/min) (n = 65) | | Both (n = 33) | |
| Variable | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Severe acute toxicity | | | | | | | | | | | | |
| No | 20 | 95.2 | 60 | 90.9 | 28 | 87.5 | 19 | 90.5 | 51 | 78.5 | 24 | 72.7 |
| Yes | 1 | 4.8 | 6 | 9.1 | 4 | 12.5 | 2 | 9.5 | 14 | 21.5 | 9 | 27.3 |
| Best overall response | | | | | | | | | | | | |
| Complete response | 0 | 0.0 | 4 | 6.1 | 0 | 0.0 | 0 | 0.0 | 4 | 6.2 | 0 | 0.0 |
| Confirmed | 0 | | 3 | | 0 | | 0 | | 3 | | 0 | |
| Unconfirmed | 0 | | 1 | | 0 | | 0 | | 1 | | 0 | |
| Partial response | 10 | 47.6 | 27 | 40.9 | 8 | 25.0 | 4 | 19.0 | 19 | 29.2 | 9 | 27.3 |
| Confirmed | 9 | | 26 | | 5 | | 3 | | 14 | | 5 | |
| Unconfirmed | 1 | | 1 | | 3 | | 1 | | 5 | | 4 | |
| Stable disease | 6 | 28.6 | 24 | 36.4 | 9 | 28.1 | 7 | 33.3 | 23 | 35.4 | 11 | 33.3 |
| Progression | 3 | 14.3 | 8 | 12.1 | 7 | 21.9 | 7 | 33.3 | 9 | 13.8 | 1 | 3.0 |
| Early death | 1 | 4.8 | 2 | 3.0 | 1 | 3.1 | 0 | 0.0 | 4 | 6.1 | 6 | 18.1 |
| Not assessable | 1 | 4.8 | 1 | 1.5 | 7 | 21.9 | 3 | 14.3 | 6 | 9.2 | 6 | 18.2 |

J Clin Oncol, 2012 Jan 10;30(2)

# Cisplatin but Not Carboplatin Can Yield Durable and Complete Responses in the Frontline

## Gemcitabine/Carboplatin[1]

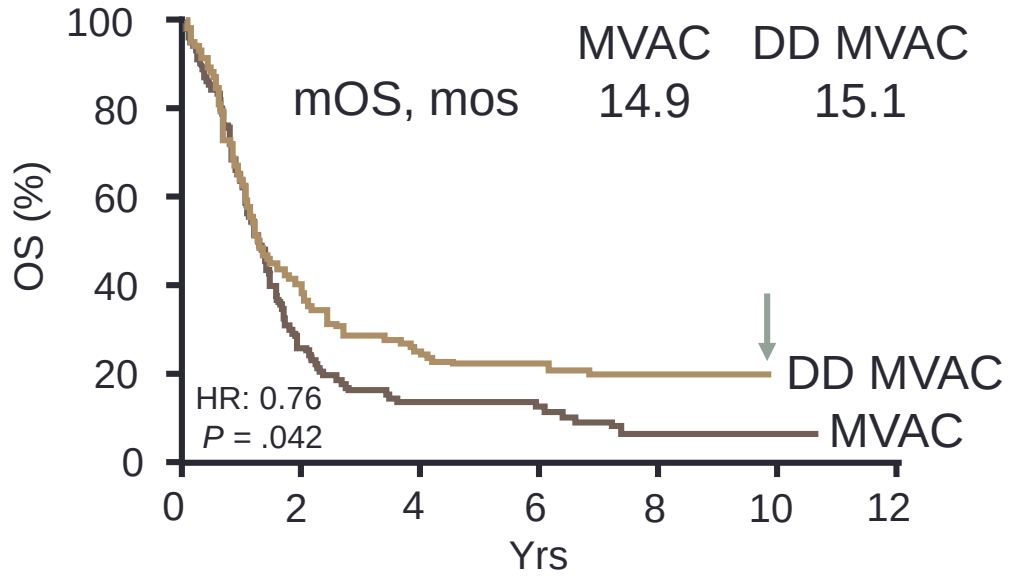
mOS: 9.3 mos




| Patients at Risk, n | | | | | | |
|---|---|---|---|---|---|---|
| MCAVI (n = 119) | 37 | 13 | 7 | 3 | 1 | 1 |
| Gem/carbo (n = 119) | 44 | 15 | 5 | 2 | 2 | 1 |

## DD MVAC (Cisplatin)[2]

mOS: 15.1 mos




| Patients at Risk, n | | | | | |
|---|---|---|---|---|---|
| MVAC (n = 129) | 32 | 15 | 11 | 4 | 2 |
| DD MVAC (n = 134) | 45 | 29 | 23 | 8 | 0 |

1. De Santis M, et al. J Clin Oncol. 2012;30:191-199. 2. Sternberg CN, et al. Eur J Cancer. 2006;42:50-54.

# Pembrolizumabe

Keynote-052

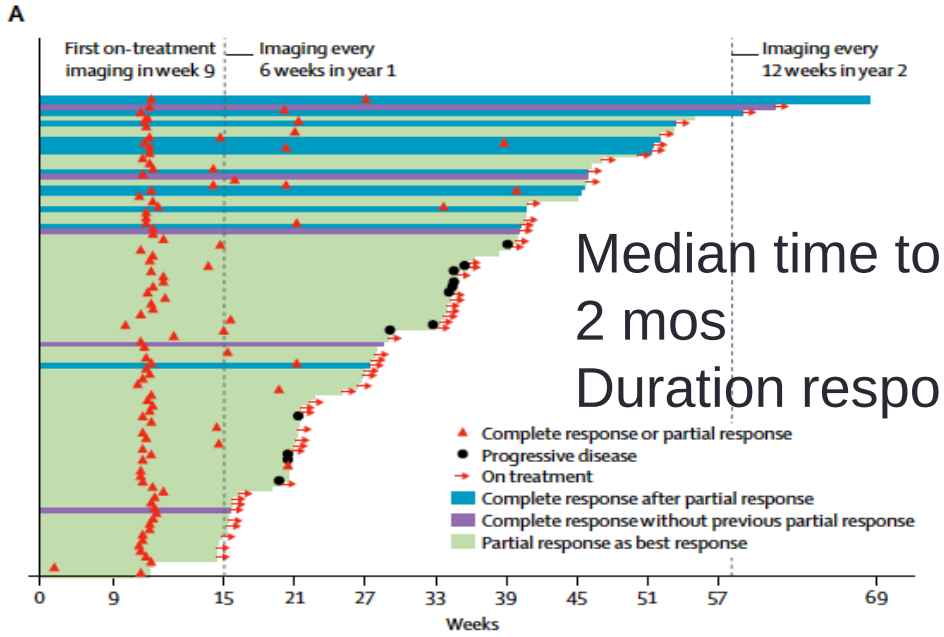
Fase 2


# Atezolizumab

ImVigor 210-coorte 1

Fase 2

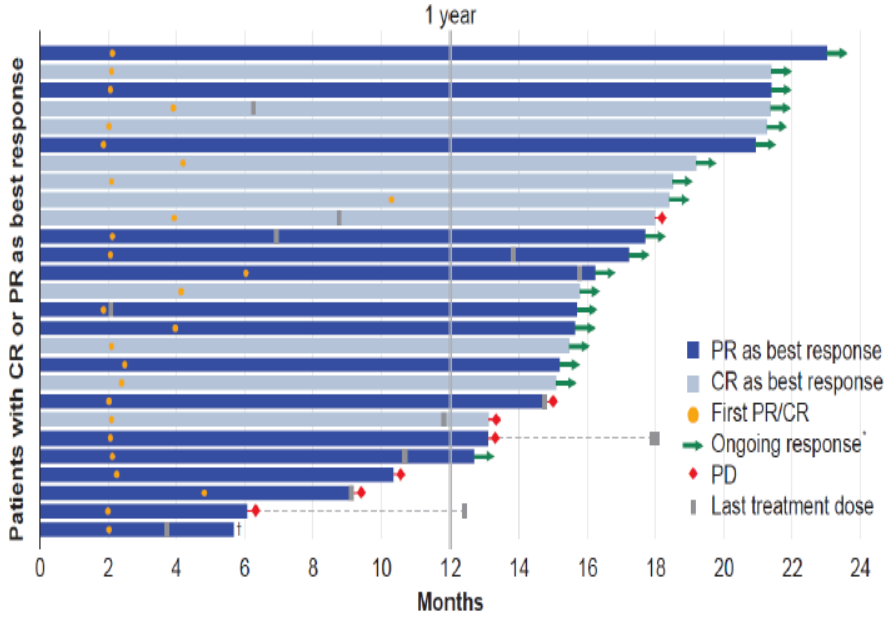
# Resposta




Median time to response: 2 mos
Duration response: NR


58% w/ decrease target lesions

ORR: 28.9%




Median time to response: 2.1 mos
Duration response: NR

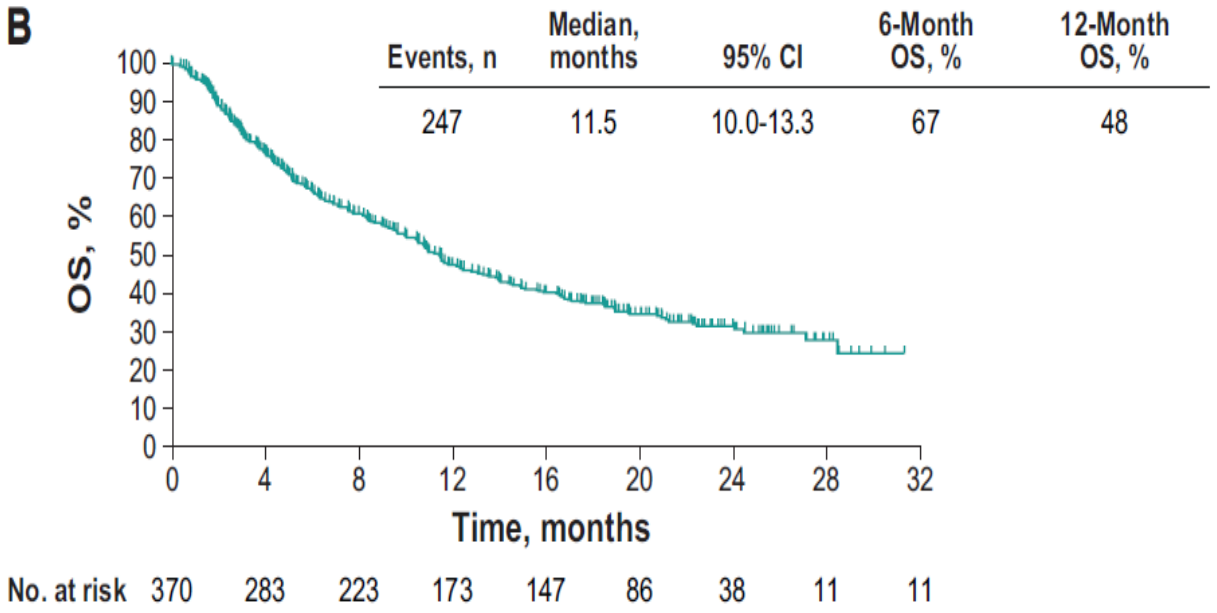
- ORR: 24%
  - CR rate: 8%
  - No difference by PD-L1 status

Keynote052 and ImVigor 2010 Balar et al Lancet Oncol 2017;

# OS

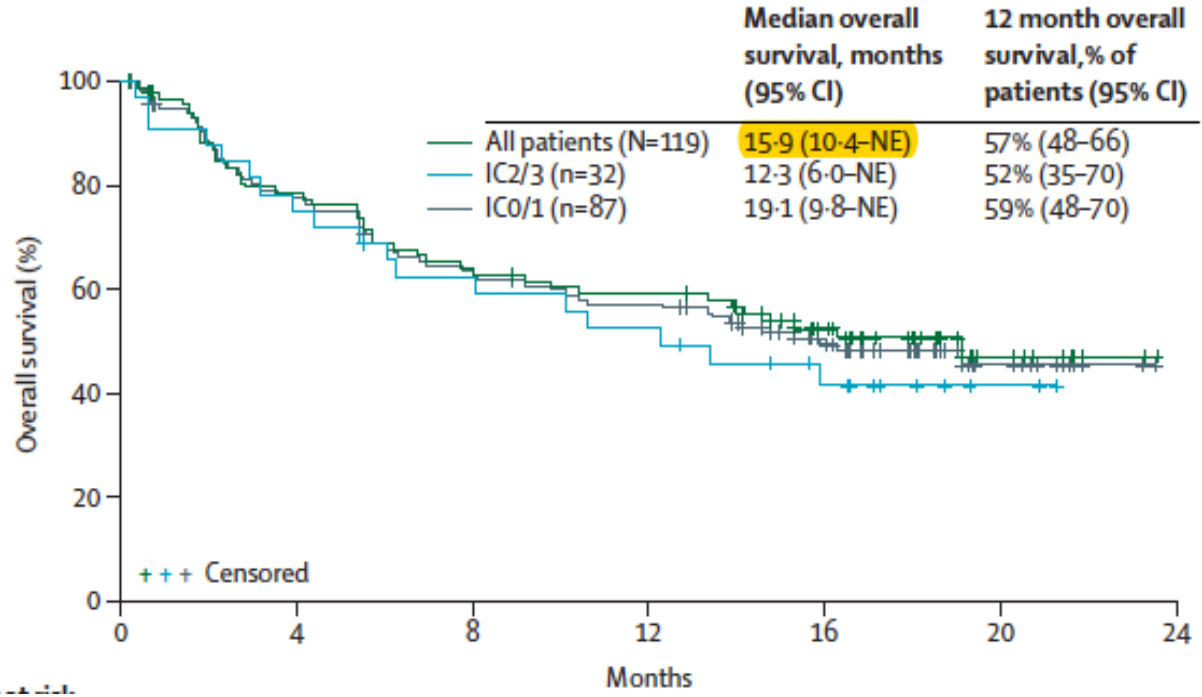
## Pembrolizumab

- Median OS 11.5 mos (95% CI 10-13.3 mos)




## Atezolizumab

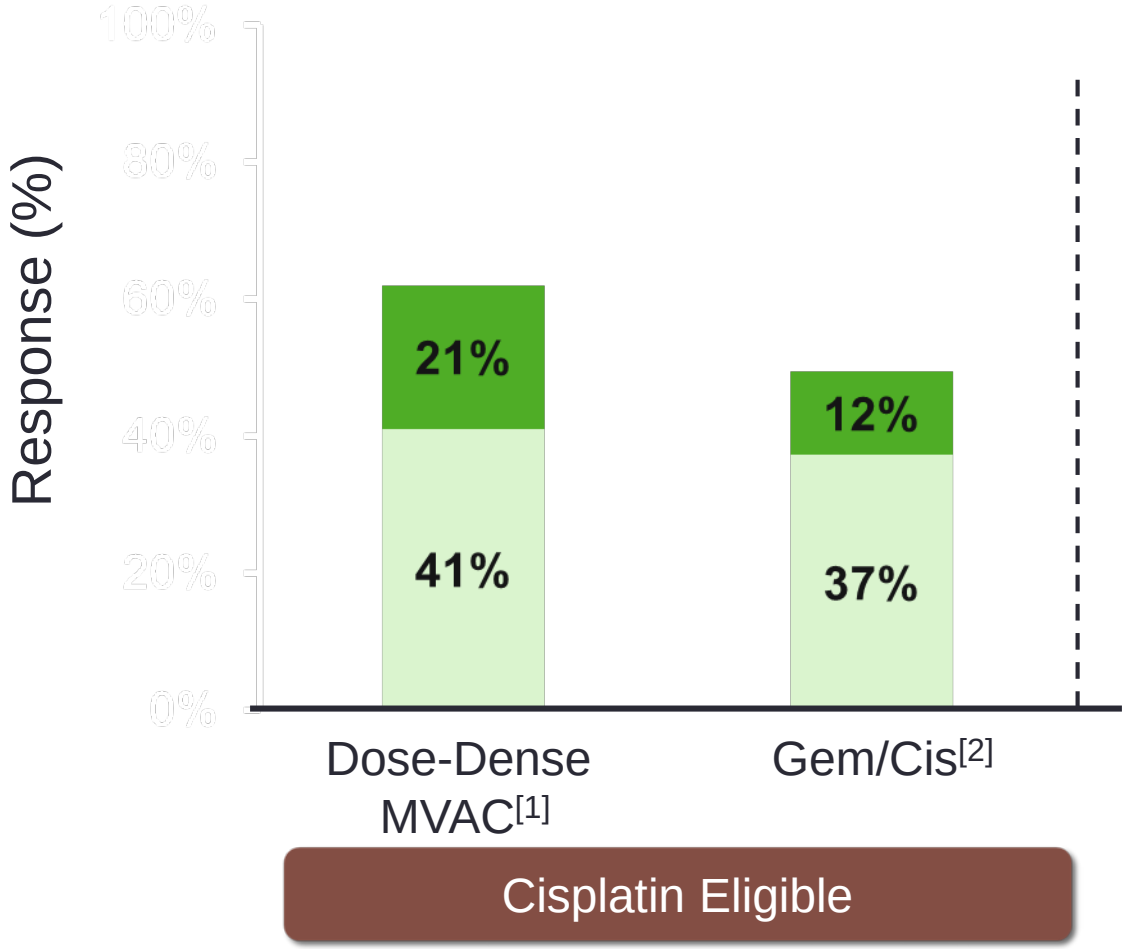
- Median OS 16.3 mos (95% CI 10.4-24.5)




Keynote052 and ImVigor 2010 Balar et al Lancet Oncol 2017; update ASCO 2017 by O-Donnel and ASCO 2018 by Vuky and Balar

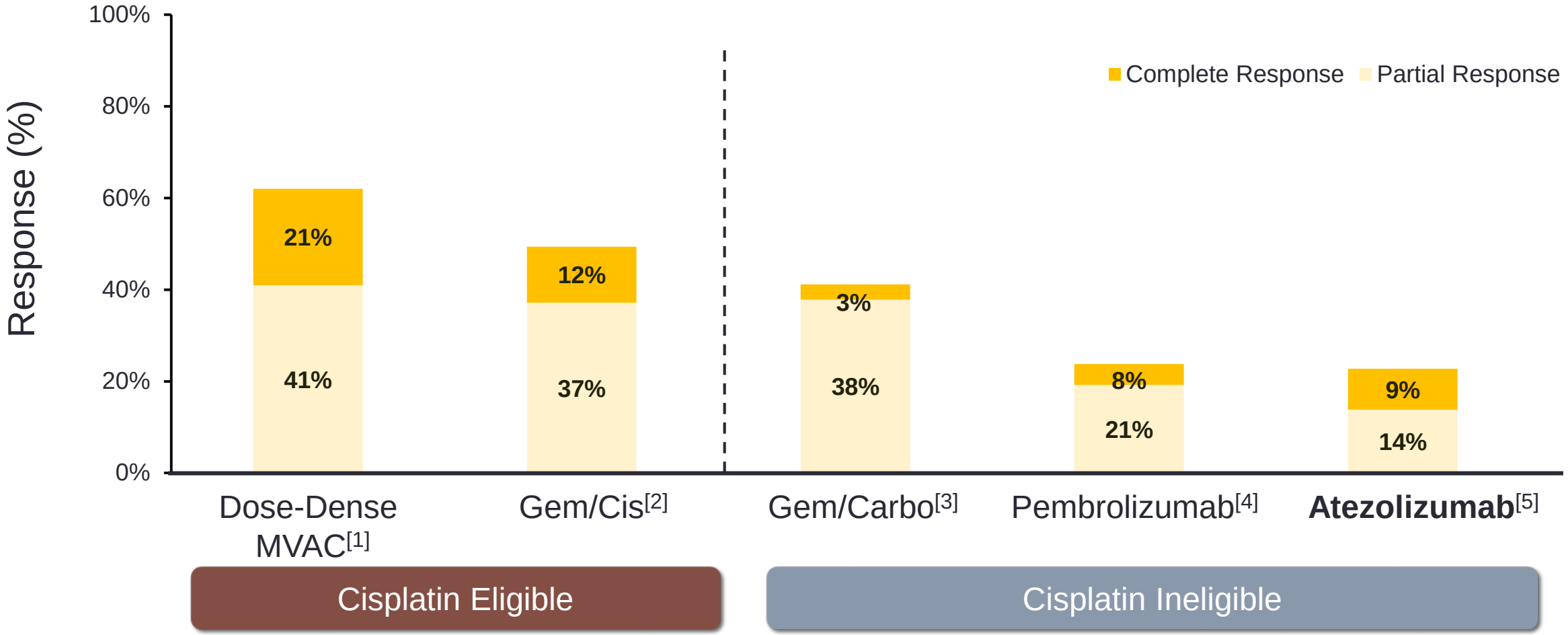
**Atezolizumab** and **Pembrolizumab** received accelerated approval for the treatment of cisplatin-ineligible mUC

# Response Rates to First-line Therapy for Metastatic Urothelial Carcinoma




1. Sternberg CN, et al. Eur J Cancer. 2006;42:50-54. 2. von der Maase H, et al. J Clin Oncol. 2000;18:3068-3077. 3. De Santis M, et al. J Clin Oncol. 2012;30:191-199. 4. Balar AV, et al. Lancet Oncol. 2017;18:1483-1492.
5. Balar AV, et al. Lancet. 2017;389:67-76.

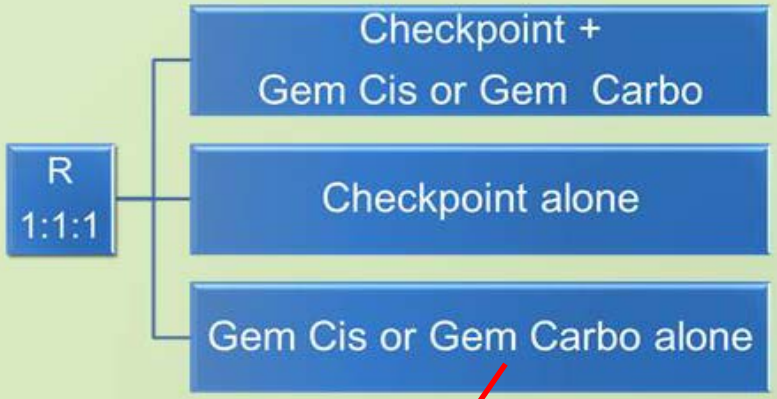
# Response Rates to First-line Therapy for Metastatic Urothelial Carcinoma




1. Sternberg CN, et al. Eur J Cancer. 2006;42:50-54. 2. von der Maase H, et al. J Clin Oncol. 2000;18:3068-3077. 3. De Santis M, et al. J Clin Oncol. 2012;30:191-199. 4. Balar AV, et al. Lancet Oncol. 2017;18:1483-1492.
5. Balar AV, et al. Lancet. 2017;389:67-76.

# But...

The studies cited compare monotherapy to platinum chemotherapy




The control arm of these studies used platinum combinations for patients with reasonable clinical status

## FDA Warns Against Single-Agent Checkpoint Inhibition for PD-L1-Low Untreated Urothelial Carcinoma

Silas Inman @silasinman
**Published:** Saturday, May 19, 2018

The FDA has issued a drug safety notification warning against the use of frontline single-agent immune checkpoint inhibition for patients with PD-L1–low expressing platinum-eligible urothelial carcinoma, following a demonstration of lower overall survival with pembrolizumab (Keytruda) and atezolizumab (Tecentriq) compared with platinum-based chemotherapy.

The FDA warning was based on an assessment conducted by a data monitoring committee (DMC) for the phase III KEYNOTE-361 study and the phase III IMvigor130 study. The KEYNOTE-361 (NCT02853305) and the IMvigor130 (NCT02807636) studies are exploring pembrolizumab and atezolizumab, respectively, with or without chemotherapy compared with chemotherapy or the immunotherapy alone.

# But...

**Press release**

**01/06/2018**

## EMA restricts use of Keytruda and Tecentriq in bladder cancer

### Data show lower survival in some patients with low levels of cancer protein PD-L1

Early data from two clinical trials[1] show reduced survival with Keytruda (pembrolizumab) and Tecentriq (atezolizumab) when used as first-line treatments for urothelial cancer (cancer of the bladder and urinary tract) in patients with low levels of a protein called PD-L1. The data indicate that Keytruda and Tecentriq may not work as well as chemotherapy medicines in this group of patients.

As a result, the European Medicines Agency (EMA) has recommended restricting the use of these medicines as first line-treatments for urothelial cancer.

Keytruda and Tecentriq should now only be used for first-line treatment of urothelial cancer in patients with high levels of PD-L1 (see full indications below).

There are no changes to how these medicines should be used in patients with urothelial cancer who have had chemotherapy or in patients with other cancers for which these medicines are approved.

The two clinical trials are continuing but no new patients with low levels of PD-L1 will be given only Keytruda or Tecentriq. Patients in the trials who have any questions should speak to the doctor treating them.

The review of data on Keytruda and Tecentriq was carried out by EMA's Committee for Medicinal Products for Human Use (CHMP).

**Keytruda**

"Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (see section 5.1).

Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and **whose tumours express PD-L1 with a combined positive score (CPS) ≥10** (see section 5.1)."

**Tecentriq**

"Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:

- after prior platinum-containing chemotherapy, or
- who are considered cisplatin ineligible, and **whose tumours have a PD-L1expression ≥5%** (see section 5.1)."

- There are no changes to the use of Keytruda or Tecentriq in patients who have had chemotherapy for urothelial cancers or in patients with other cancers for which these medicines are approved.
- Healthcare professionals in the EU will be sent a letter with details of these recommendations and the two ongoing studies.

FDA U.S. FOOD & DRUG ADMINISTRATION

August 16th, 2018

## Pembrolizumab

Pembrolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

## Atezolizumab

- Are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1–stained tumor-infiltrating immune cells covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or
- Are not eligible for any platinum-containing therapy regardless of level of tumor PD-L1 expression.

# Biomarkers – cisplatin ineligible ASCO18

Vuky # 4524

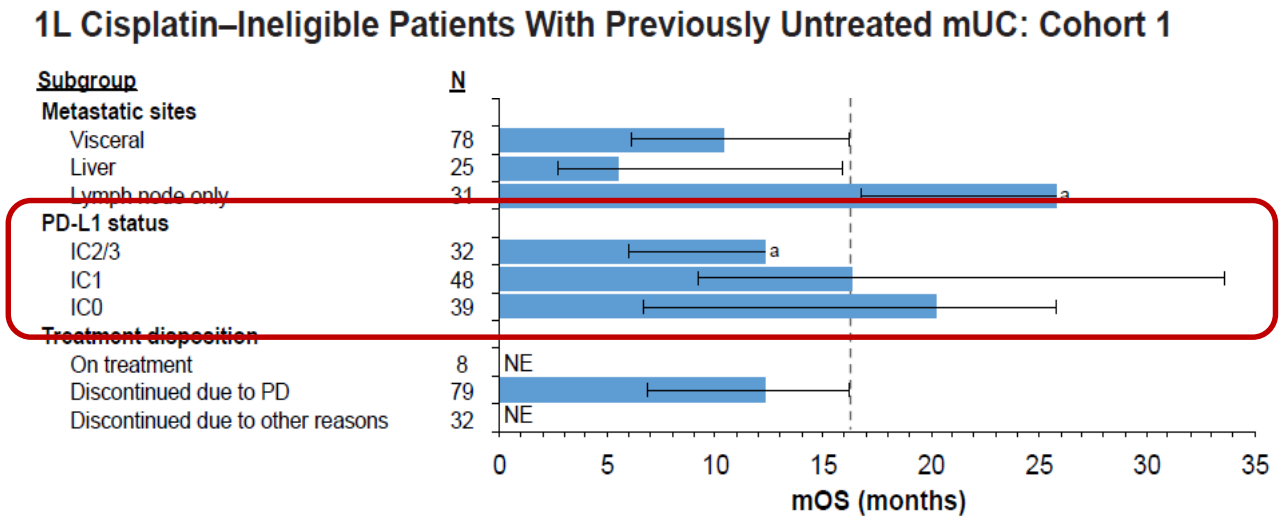
In KN052 – Cisplatin ineligible front line **pembrolizumab**, low PDL1 (CPS <10) patients were 74% of the study population and had worse median OS.

Table 3. Overall Survival by Subgroups

| Response | N | Events, n (%) | Median OS (95% CI), mo |
|---|---|---|---|
| PD-L1 subgroup | | | |
| PD-L1 CPS <10 | 251 | 186 (74) | 10.0 (7.8-11.6) |
| PD-L1 CPS ≥10 | 110 | 57 (52) | 18.5 (12.2 to NR) |

Balar # 4523

In contrast, in IMvigor210 – Cisplatin ineligible front line **atezolizumab** - low PDL1 (IC0/1) patients were 70% of the study population and had similar to slightly better median OS.



# Biomarcadores para prática

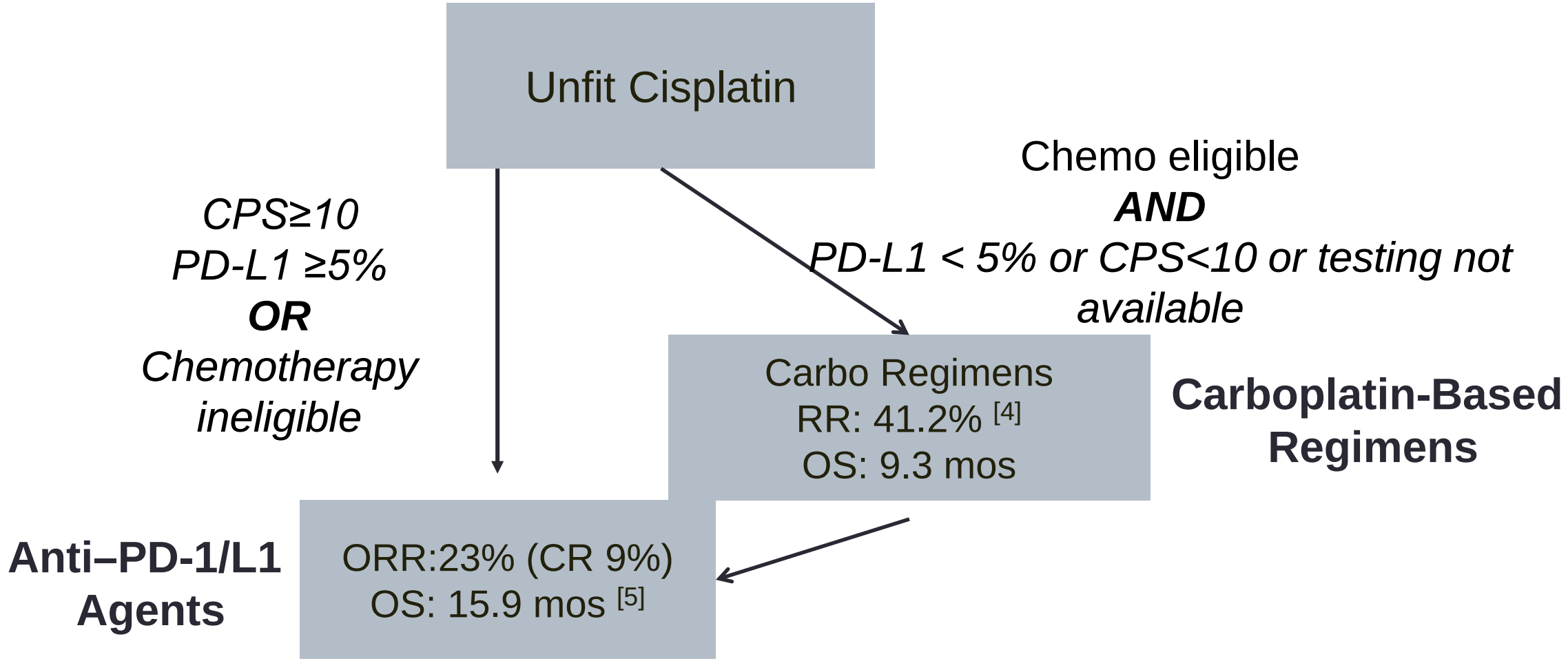
## Pembrolizumab

- Dako PD-L1 22C3 PharD Assay
- Score = CPS (positividade tumor + células imunes)
- Corte = CPS ≥10

## Atezolizumab

- Ventana PD-L1 SP142 Assay
- Score = % PD-L1 expresso células imune
- Corte = PD-L1≥5%

# Advanced Bladder Cancer Landscape: 2019 Standard of Care




1. von der Maase H, et al. J Clin Oncol. 2000;18:3068-3077. 2. Sternberg CN, et al. Eur J Cancer. 2006;42:50-54. 3. Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026. 4. de Santis M, et al. J Clin Oncol 2012. 5. Balar AV et al. Lancet Oncol 2017

# OBRIGADO

jardimde@gmail.com

@jardim_denis