AIGOM
ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

**19 GIUGNO 2023**
*ore 15.00 - 18.00*

# LE NOVITA' DA CHICAGO 2023:
## l'evoluzione delle conoscenze in oncologia...

CLICCA QUI
**VIRTUAL MEETING**

**NEOPLASIE GENITO-URINARIE: Tumori renali e uroteliali**

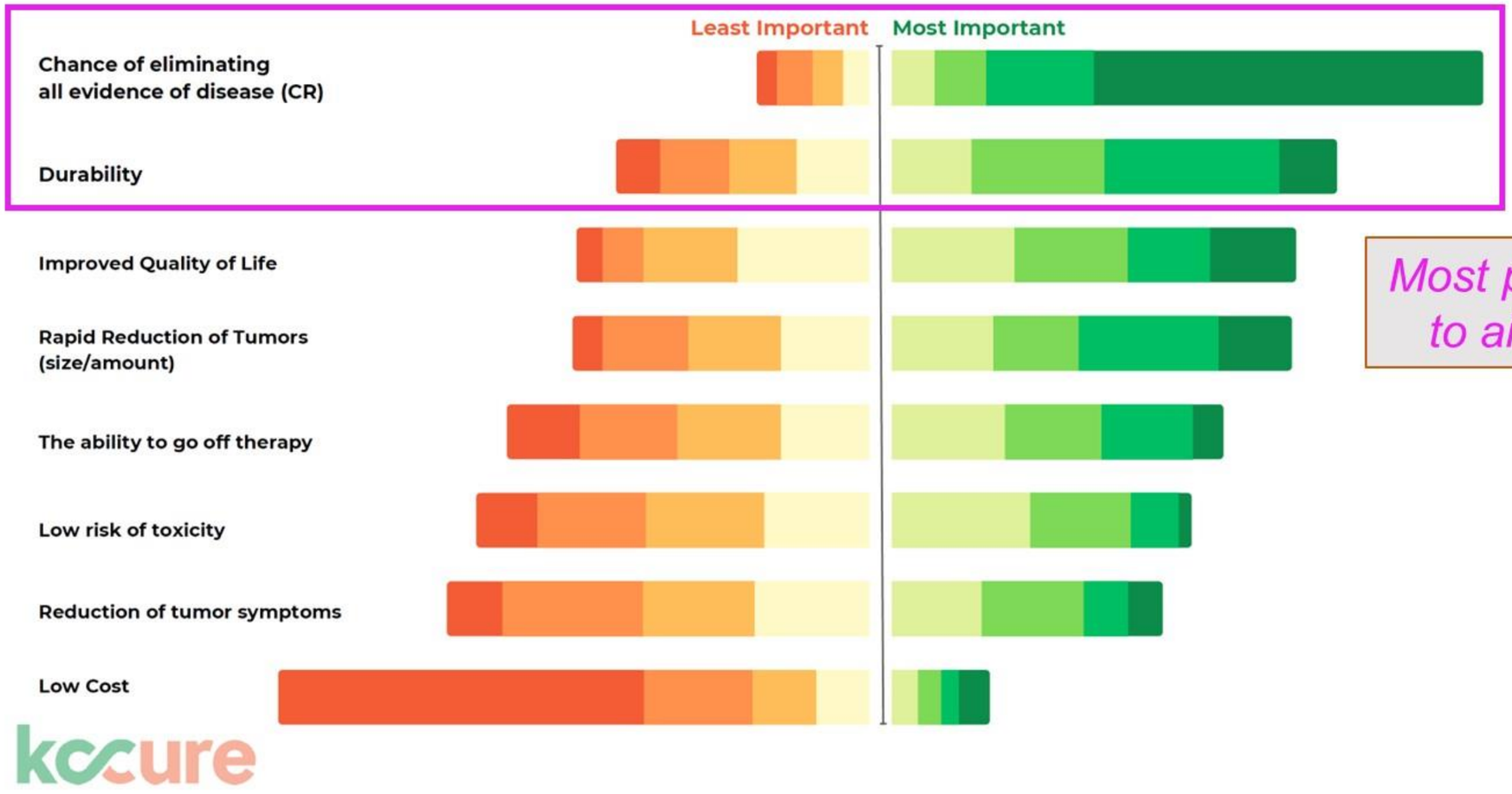
Dott.ssa Grazia Sirgiovanni
Azienda Ospedaliera Santa Maria - Terni

# GENITOURINARY CANCER: RCC

## ADVANCED DISEASE:

- **Criticità e conferme nelle combinazioni TKI-IO: *Final prespecified overall survival (OS) analysis of CLEAR study***
- Ruolo del rechallenge dell'ICI in linee successive: *Primary PFS analysis from the CONTACT-03 study*

# What's next? Patient perspective on goals of systemic therapy for advanced RCC




*Most patients want to aim for **cure***

Battle, ASCO 2023.

# Prior results of the primary analysis

***Key eligibility criteria***

- Advanced clear-cell RCC
- Treatment-naïve
- KPS ≥ 70
- Measurable disease
- Adequate organ function

***Stratification factors***

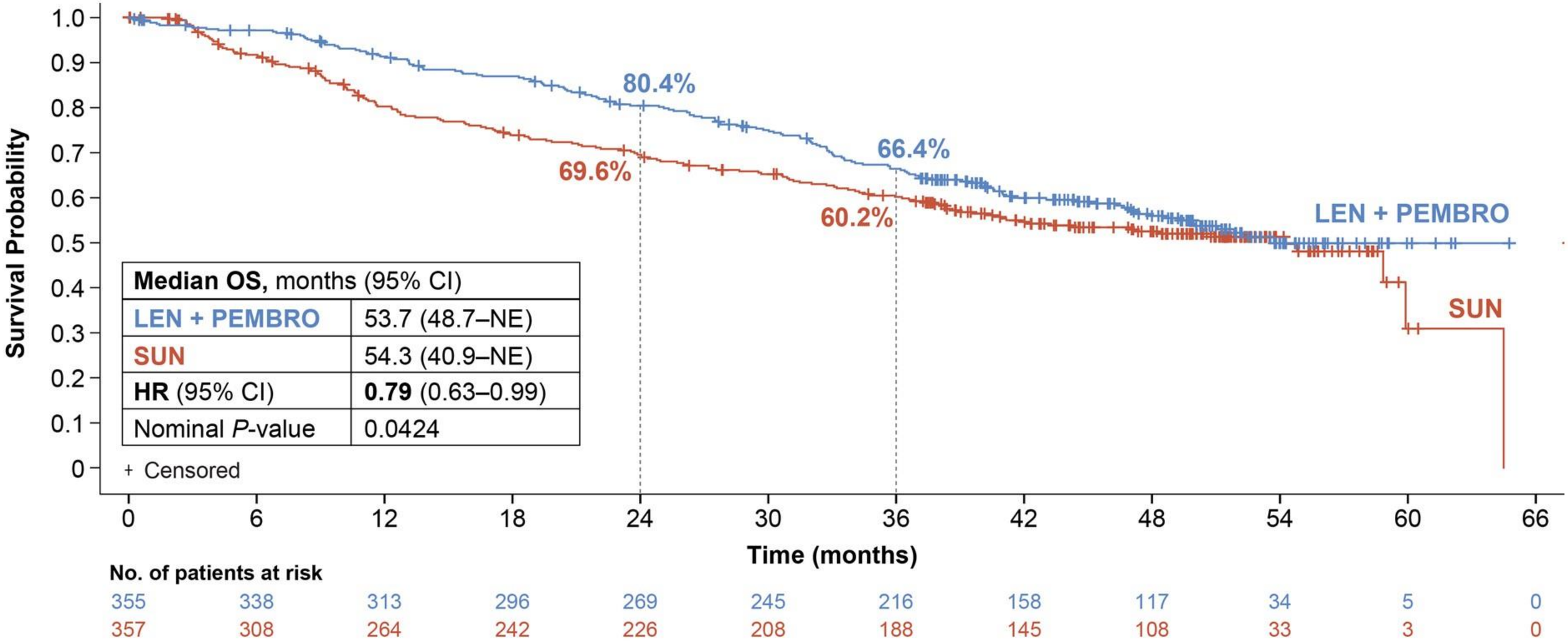
- Region
- MSKCC risk groups

**R 1:1:1**

| Median follow-up: **26.6** mos | **LEN** 20 mg oral QD + **PEMBRO**[a] 200 mg IV Q3W | **LEN** 18 mg oral QD + **EVE** 5 mg oral QD | **SUN** 50 mg oral QD 4 weeks on / 2 weeks off |
|---|---|---|---|
| **PFS**,[b] median (95% CI) — mos | 23.9 (20.8–27.7) | 14.7 (11.1–16.7) | 9.2 (6.0–11.0) |
| HR (95% CI) vs SUN; *P*-value | **0.39** (0.32–0.49); **<0.001** | 0.65 (0.53–0.80); <0.001 | |
| **OS**, median (95% CI) — mos | NR (33.6–NE) | NR (NE–NE) | NR (NE–NE) |
| HR (95% CI) vs SUN; *P*-value | **0.66** (0.49–0.88); **0.005** | 1.15 (0.88–1.50); 0.30 | |
| **ORR** (95% CI)[b] — % | **71.0** (66.3–75.7) | 53.5 (48.3–58.7) | 36.1 (31.2–41.1) |
| Complete response — % | **16.1** | 9.8 | 4.2 |

Reference: Motzer R, Alekseev B, Rha SY, et al. N Engl J Med. 2021;384(14):1289-1300. a: Patients could receive a maximum of 35 pembrolizumab treatments. b: per independent imaging review by RECIST v1.1.

# Final OS analysis




| **Median OS,** months (95% CI) | |
|---|---|
| LEN + PEMBRO | 53.7 (48.7–NE) |
| SUN | 54.3 (40.9–NE) |
| **HR** (95% CI) | **0.79** (0.63–0.99) |
| Nominal *P*-value | 0.0424 |

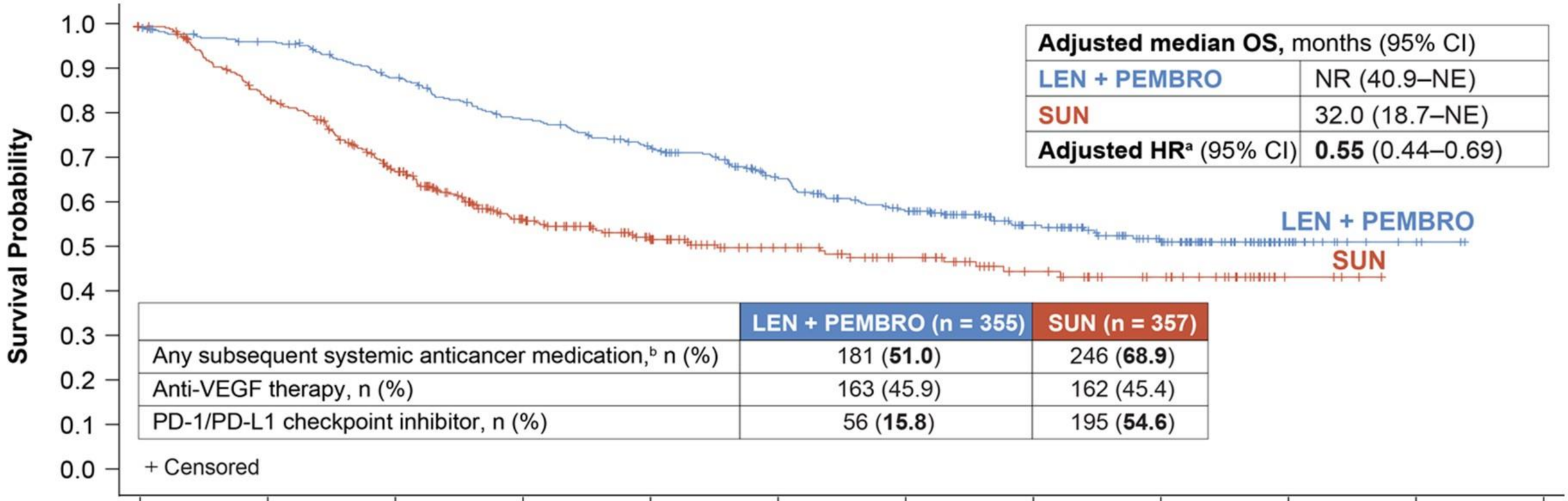
**No. of patients at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 355 | 338 | 313 | 296 | 269 | 245 | 216 | 158 | 117 | 34 | 5 | 0 |
| 357 | 308 | 264 | 242 | 226 | 208 | 188 | 145 | 108 | 33 | 3 | 0 |

At median OS follow-up time (IQR) of **49.8 months** (41.4–53.1) in the lenvatinib plus pembrolizumab group and **49.4 months** (41.6–52.8) in the sunitinib group, 308 target OS events had occurred (lenvatinib plus pembrolizumab, 149 events; sunitinib, 159 events). The HR and 2-sided 95% CI for lenvatinib plus pembrolizumab vs sunitinib were estimated by a stratified Cox proportional hazards model with Efron's method for ties, stratified by geographic region and MSKCC prognostic groups.

# Final OS analysis adjusted for subsequent anticancer medications

| **Adjusted median OS,** months (95% CI) | |
|---|---|
| LEN + PEMBRO | NR (40.9–NE) |
| SUN | 32.0 (18.7–NE) |
| **Adjusted HR**[a] (95% CI) | **0.55** (0.44–0.69) |




| | LEN + PEMBRO (n = 355) | SUN (n = 357) |
|---|---|---|
| Any subsequent systemic anticancer medication,[b] n (%) | 181 (**51.0**) | 246 (**68.9**) |
| Anti-VEGF therapy, n (%) | 163 (45.9) | 162 (45.4) |
| PD-1/PD-L1 checkpoint inhibitor, n (%) | 56 (**15.8**) | 195 (**54.6**) |

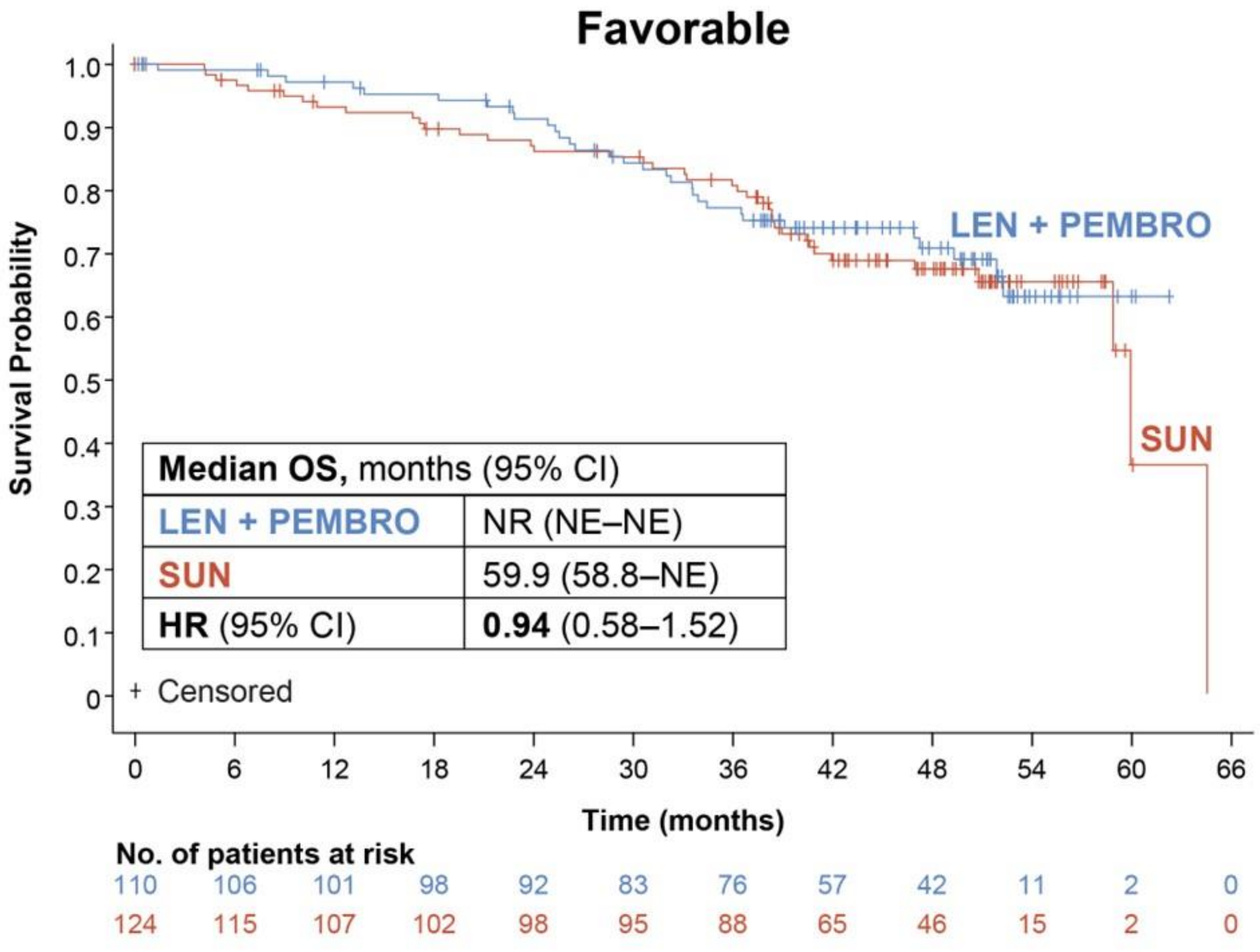
**No. of patients at risk (adjusted):**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LEN + PEMBRO | 355 | 336 | 303 | 266 | 240 | 193 | 159 | 107 | 68 | 19 | 3 | 0 |
| SUN | 357 | 282 | 212 | 140 | 100 | 72 | 56 | 37 | 26 | 4 | 0 | 0 |

a: A 2-stage estimation post-hoc method of adjusting overall survival for any effects of subsequent anticancer medications was used. b during survival follow-up


PRESENTED BY: Thomas E. Hutson

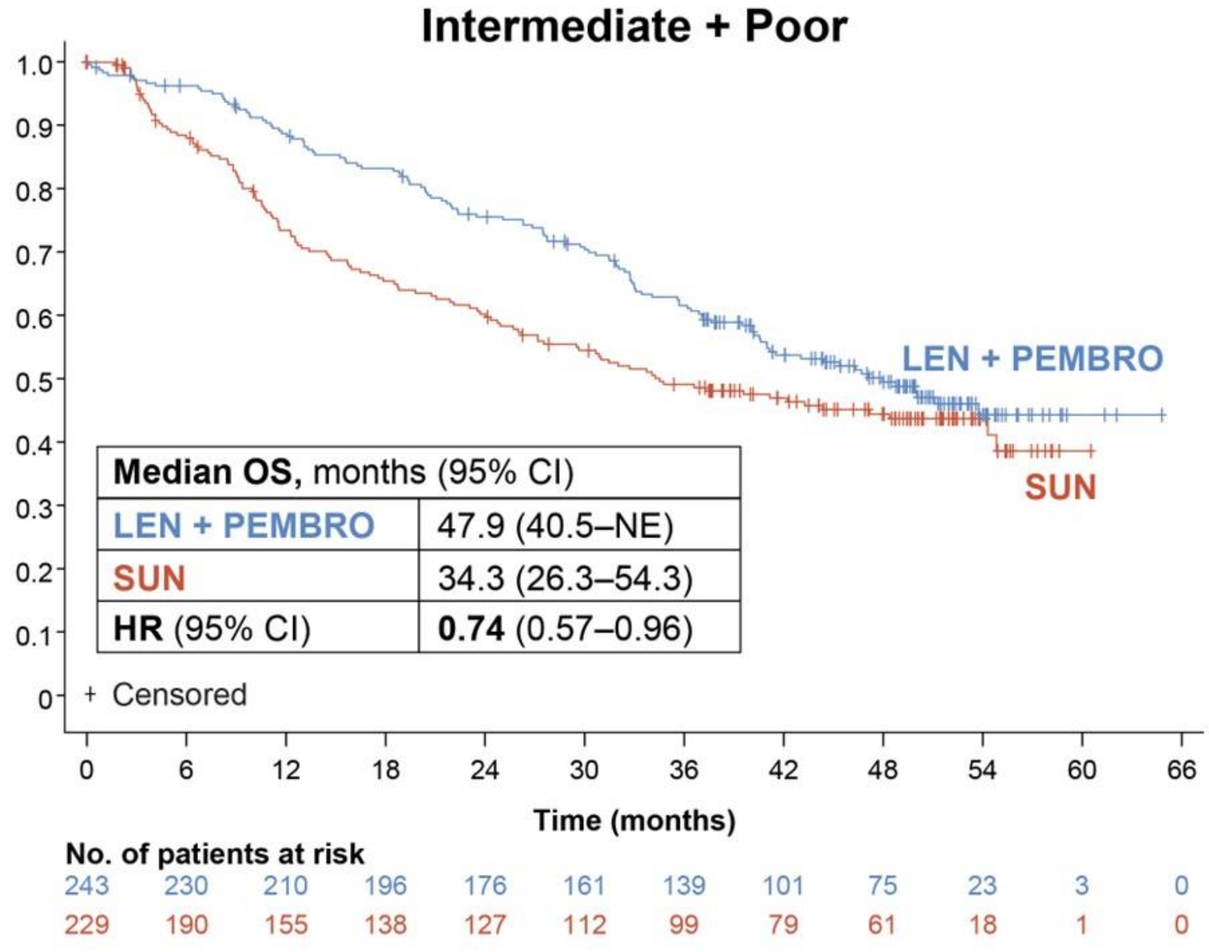
# Final OS analyses in IMDC risk subgroups




| **Median OS**, months (95% CI) | |
|---|---|
| LEN + PEMBRO | NR (NE–NE) |
| SUN | 59.9 (58.8–NE) |
| **HR** (95% CI) | **0.94** (0.58–1.52) |

**No. of patients at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 110 | 106 | 101 | 98 | 92 | 83 | 76 | 57 | 42 | 11 | 2 | 0 |
| 124 | 115 | 107 | 102 | 98 | 95 | 88 | 65 | 46 | 15 | 2 | 0 |




| **Median OS**, months (95% CI) | |
|---|---|
| LEN + PEMBRO | 47.9 (40.5–NE) |
| SUN | 34.3 (26.3–54.3) |
| **HR** (95% CI) | **0.74** (0.57–0.96) |

**No. of patients at risk**

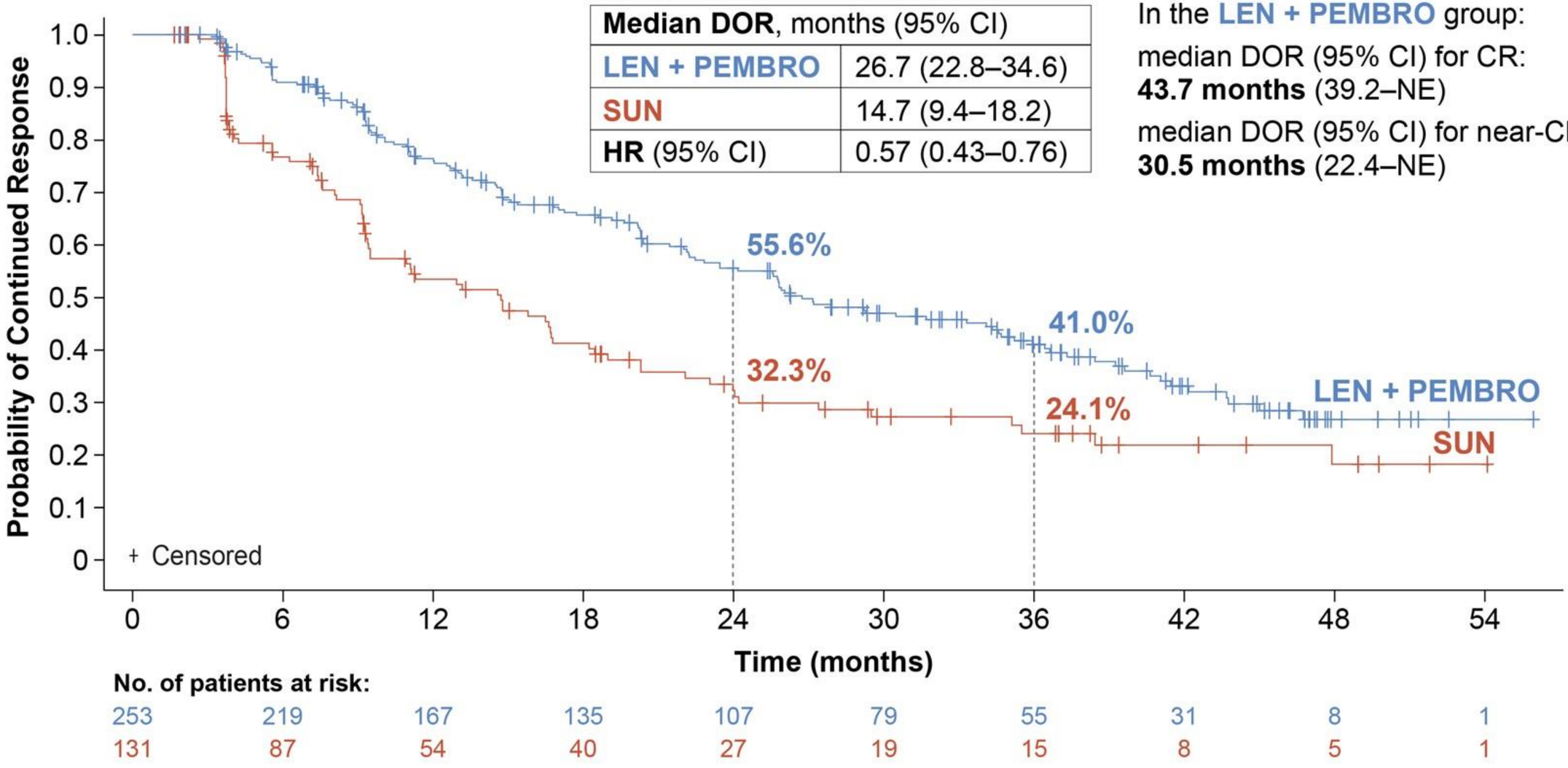
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 243 | 230 | 210 | 196 | 176 | 161 | 139 | 101 | 75 | 23 | 3 | 0 |
| 229 | 190 | 155 | 138 | 127 | 112 | 99 | 79 | 61 | 18 | 1 | 0 |

IMDC risk group was not a stratification factor and relevant data were derived programmatically. Hazard ratio is for lenvatinib + pembrolizumab vs sunitinib based on a Cox regression model with treatment as a factor. The Efron method was used for correction of tied events. Medians were estimated by the Kaplan-Meier method, and the 95% CIs were estimated with a generalized Brookmeyer and Crowley method.

# Duration of response[a]

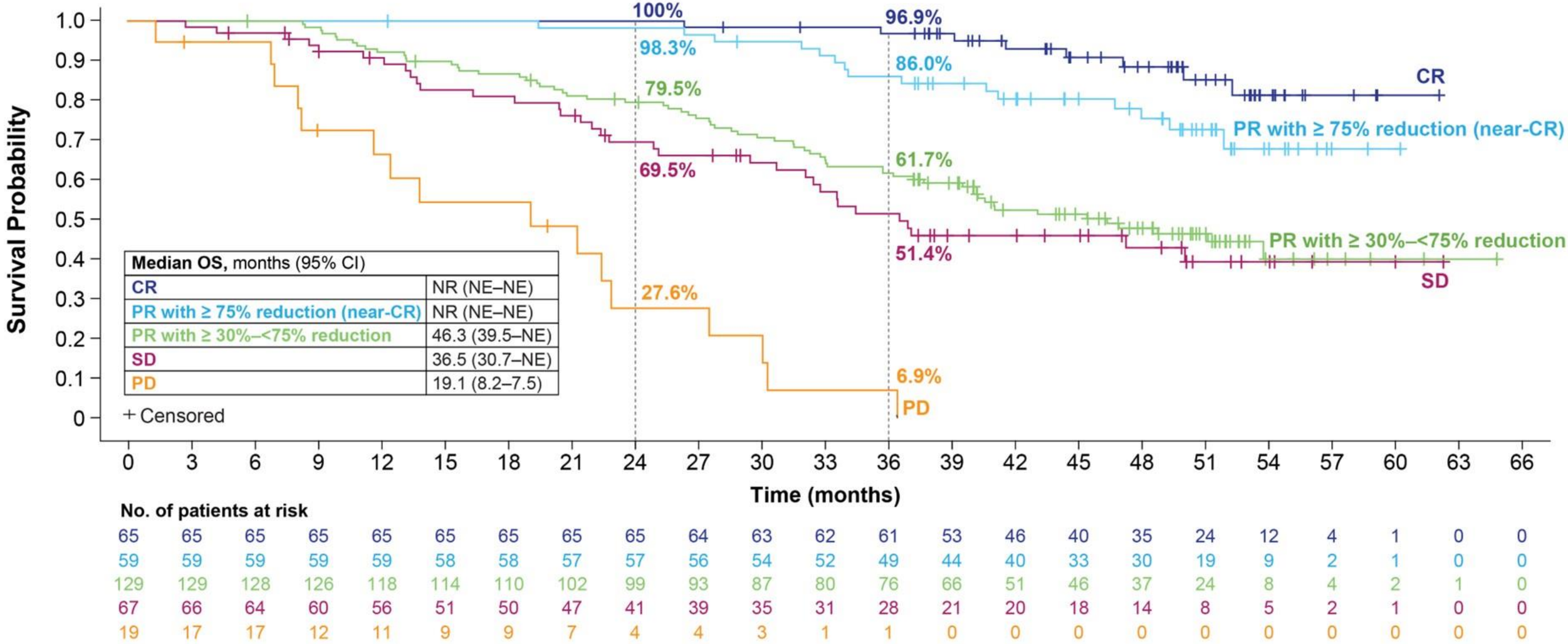
| **Median DOR**, months (95% CI) | |
|---|---|
| LEN + PEMBRO | 26.7 (22.8–34.6) |
| SUN | 14.7 (9.4–18.2) |
| **HR** (95% CI) | 0.57 (0.43–0.76) |

In the LEN + PEMBRO group:
median DOR (95% CI) for CR:
**43.7 months** (39.2–NE)
median DOR (95% CI) for near-CR[b]:
**30.5 months** (22.4–NE)




a: DOR was by IIR per RECIST v1.1. b: Near-CR refers to partial responders who showed a maximum tumor reduction of ≥ 75%.
The 95% CIs are estimated with a generalized Brookmeyer and Crowley method. Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties and stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS. 95% CI were constructed using the method of Normal Approximation.

# Final OS analyses by best overall response:
## LEN + PEMBRO




| **Median OS,** months (95% CI) | |
|---|---|
| CR | NR (NE–NE) |
| PR with ≥ 75% reduction (near-CR) | NR (NE–NE) |
| PR with ≥ 30%–<75% reduction | 46.3 (39.5–NE) |
| SD | 36.5 (30.7–NE) |
| PD | 19.1 (8.2–7.5) |

**No. of patients at risk**

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 64 | 63 | 62 | 61 | 53 | 46 | 40 | 35 | 24 | 12 | 4 | 1 | 0 | 0 |
| 59 | 59 | 59 | 59 | 59 | 58 | 58 | 57 | 57 | 56 | 54 | 52 | 49 | 44 | 40 | 33 | 30 | 19 | 9 | 2 | 1 | 0 | 0 |
| 129 | 129 | 128 | 126 | 118 | 114 | 110 | 102 | 99 | 93 | 87 | 80 | 76 | 66 | 51 | 46 | 37 | 24 | 8 | 4 | 2 | 1 | 0 |
| 67 | 66 | 64 | 60 | 56 | 51 | 50 | 47 | 41 | 39 | 35 | 31 | 28 | 21 | 20 | 18 | 14 | 8 | 5 | 2 | 1 | 0 | 0 |
| 19 | 17 | 17 | 12 | 11 | 9 | 9 | 7 | 4 | 4 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Near-CR refers to partial responders who showed a maximum tumor reduction of ≥ 75%.


PRESENTED BY: Thomas E. Hutson

# *Take-home messages*

- OS meno entusiasmante di quanto ci si potesse aspettare sulla base dei dati di PFS
- Impatto del rischio favorevole sulla sopravvivenza? Non beneficio nel gruppo a buona prognosi
- Ragione della maggior durata di risposta: ruolo dell'anti-CTLA4? Discontinuazione dell'immunoterapia dopo 2 anni di trattamento?

# GENITOURINARY CANCER: RCC

## ADVANCED DISEASE:

- Criticità e conferme nelle combinazioni TKI-IO: *Final prespecified overall survival (OS) analysis of CLEAR study*
- **Ruolo del rechallenge dell'ICI in linee successive: *Primary PFS analysis from the CONTACT-03 study***

# Phase III CONTACT-03 study

**Key eligibility criteria**

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

R
1:1
N=522

**Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO**

**Cabozantinib 60 mg daily PO**

**Stratification factors**

- **IMDC risk group**
  0 vs 1-2 vs ≥3
- **Histology**
  Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid[b]
- **Most recent line of ICI**
  Adjuvant vs 1L vs 2L

**Primary endpoints**

- Independent centrally-assessed PFS[c]
- OS

**Key secondary endpoints**

- Investigator-assessed PFS[c]
- ORR (per central review and per investigator)[c]
- Duration of response (per central review and per investigator)[c]
- Safety

ClinicalTrials.gov ID, NCT04338269. IMDC, International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021.
[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation). [b] Clear cell or non-clear cell. [c] Assessed according to RECIST 1.1.

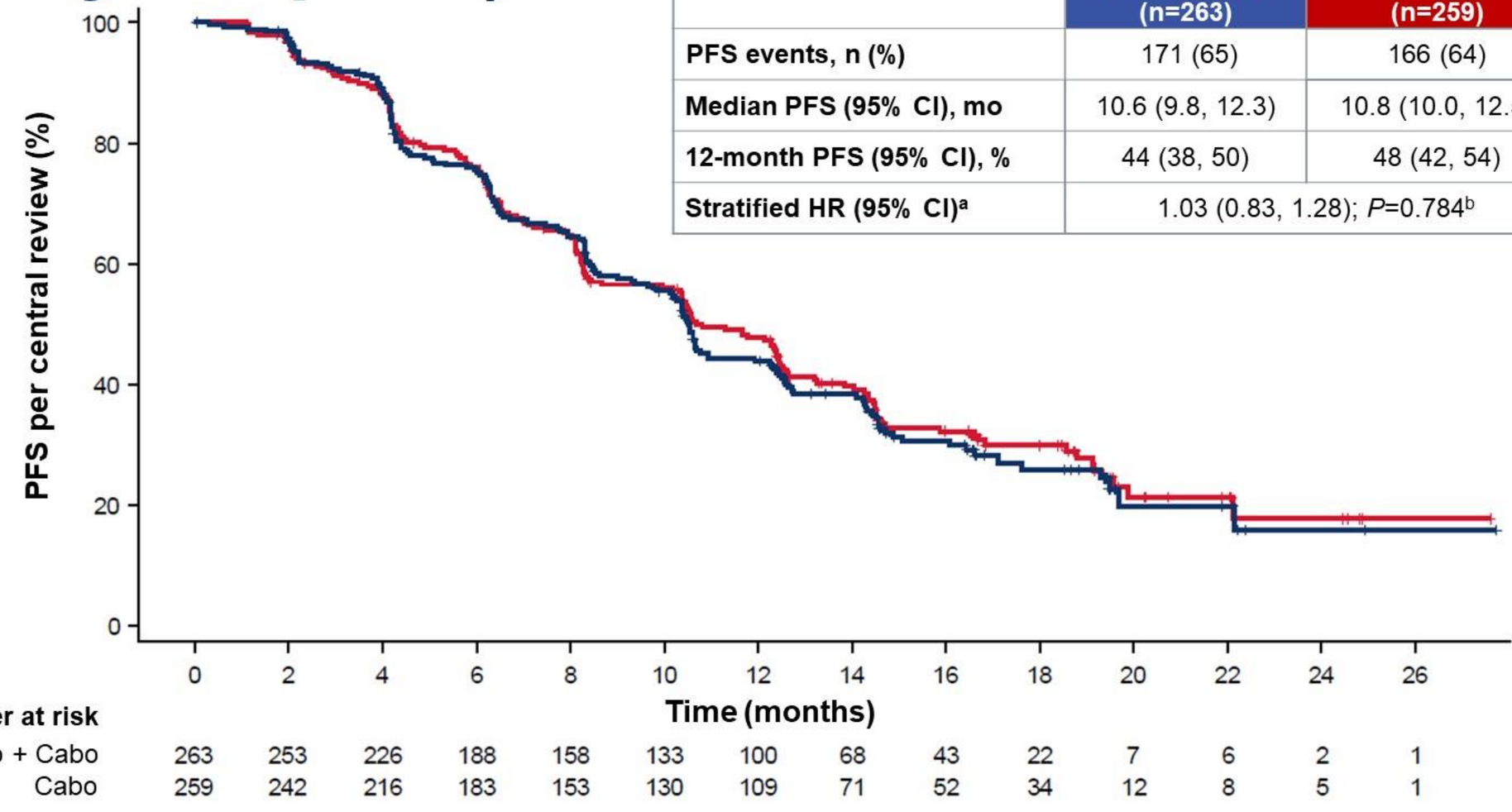
# Baseline demographics and characteristics

| Characteristic | Atezo + Cabo (n=263) | Cabo (n=259) |
|---|---|---|
| **Age, median (range), y** | 62 (20-85) | 63 (18-89) |
| **Male sex, n (%)** | 204 (77.6) | 197 (76.1) |
| **Race, n (%)** | | |
| White | 219 (83.3) | 213 (82.2) |
| Asian | 33 (12.5) | 23 (8.9) |
| Other | 11 (4.2) | 23 (8.9) |
| **Most recent line of immune checkpoint inhibitor therapy, n (%)[a]** | | |
| Adjuvant | 1 (0.4) | 1 (0.4) |
| Locally advanced or metastatic; first line | 144 (54.8) | 132 (51.0) |
| Locally advanced or metastatic; second line | 118 (44.9) | 124 (47.9) |
| **Histology, n (%)[b]** | | |
| Dominant clear cell without sarcomatoid | 207 (78.7) | 200 (77.2) |
| Dominant non-clear cell without sarcomatoid | 30 (11.4) | 31 (12.0) |
| Any sarcomatoid | 25 (9.5) | 28 (10.8) |
| **IMDC score, n (%)[c]** | | |
| 0 | 49 (18.6) | 69 (26.6) |
| 1-2 | 172 (65.4) | 153 (59.1) |
| ≥3 | 41 (15.6) | 36 (13.9) |
| **Prior VEGFR-TKI use, n (%)** | | |
| 0 | 93 (35.4) | 95 (36.7) |
| 1 | 166 (63.1) | 159 (61.4) |
| 2 | 4 (1.5) | 5 (1.9) |

[a] In the Cabo arm, 2 patients had no most recent ICI. [b] In the Atezo + Cabo arm, 1 patient had missing histology. [c] In each arm, there was 1 patient with missing IMDC score.

# Primary analysis of centrally reviewed PFS (primary endpoint)

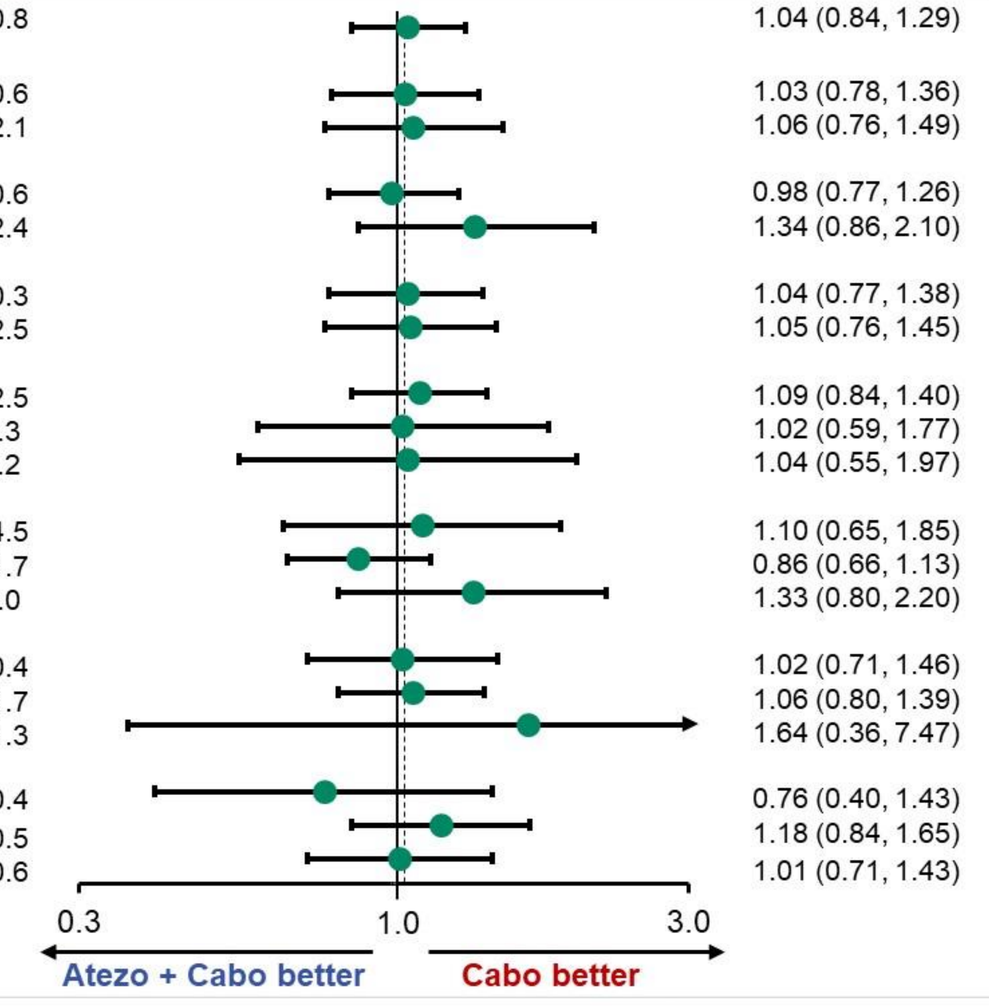
| | Atezo + Cabo (n=263) | Cabo (n=259) |
|---|---|---|
| **PFS events, n (%)** | 171 (65) | 166 (64) |
| **Median PFS (95% CI), mo** | 10.6 (9.8, 12.3) | 10.8 (10.0, 12.5) |
| **12-month PFS (95% CI), %** | 44 (38, 50) | 48 (42, 54) |
| **Stratified HR (95% CI)[a]** | 1.03 (0.83, 1.28); *P*=0.784[b] | |




[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

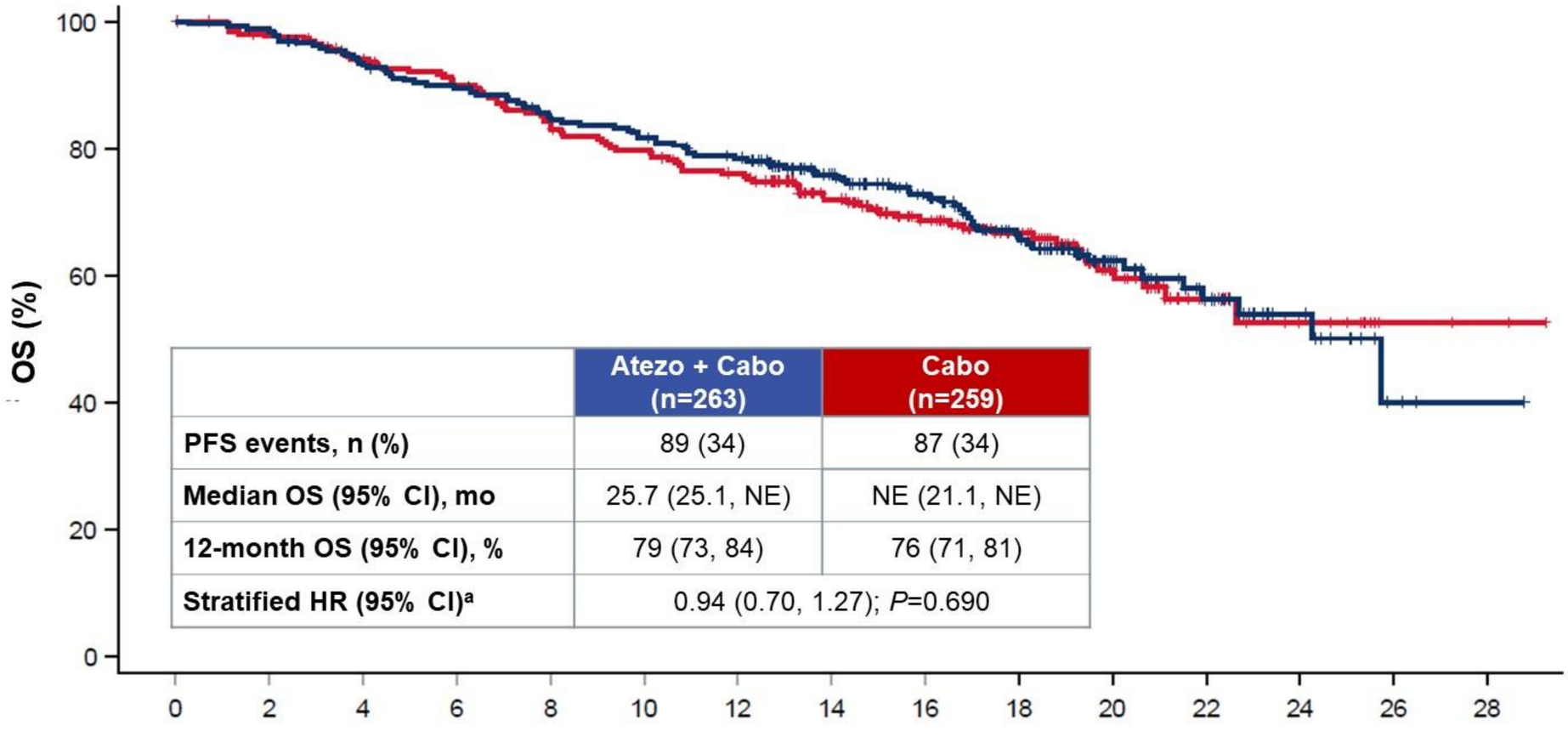
# Centrally reviewed PFS by subgroup

| Characteristic[a] | Atezo + Cabo: No. of PFS events/patients | Atezo + Cabo: Median PFS, mo | Cabo: No. of PFS events/patients | Cabo: Median PFS, mo | PFS HR (95% CI)[b] |
|---|---|---|---|---|---|
| **All patients** | 171/263 | 10.5 | 166/259 | 10.8 | 1.04 (0.84, 1.29) |
| **Age** | | | | | |
| <65 y | 104/153 | 10.4 | 96/144 | 10.6 | 1.03 (0.78, 1.36) |
| ≥65 y | 67/110 | 10.6 | 115/225 | 12.1 | 1.06 (0.76, 1.49) |
| **Sex** | | | | | |
| Male | 130/204 | 10.6 | 197/401 | 10.6 | 0.98 (0.77, 1.26) |
| Female | 41/59 | 10.1 | 62/121 | 12.4 | 1.34 (0.86, 2.10) |
| **Most recent ICI therapy** | | | | | |
| First line | 98/144 | 9.9 | 87/132 | 10.3 | 1.04 (0.77, 1.38) |
| Second line | 72/118 | 12.4 | 77/124 | 12.5 | 1.05 (0.76, 1.45) |
| **Histology** | | | | | |
| Dominant clear cell | 128/207 | 10.7 | 117/200 | 12.5 | 1.09 (0.84, 1.40) |
| Dominant non-clear cell | 25/30 | 6.3 | 27/31 | 8.3 | 1.02 (0.59, 1.77) |
| Any sarcomatoid component | 18/25 | 8.3 | 22/28 | 8.2 | 1.04 (0.55, 1.97) |
| **IMDC score** | | | | | |
| 0 | 25/49 | 14.3 | 34/69 | 14.5 | 1.10 (0.65, 1.85) |
| 1-2 | 109/172 | 10.8 | 104/153 | 11.7 | 0.86 (0.66, 1.13) |
| 3-6 | 36/41 | 4.9 | 28/36 | 6.0 | 1.33 (0.80, 2.20) |
| **Prior lines of VEGFR-TKI** | | | | | |
| 0 | 61/93 | 9.7 | 60/95 | 10.4 | 1.02 (0.71, 1.46) |
| 1 | 107/166 | 10.6 | 102/159 | 11.7 | 1.06 (0.80, 1.39) |
| 2 | 3/4 | 6.7 | 4/5 | 11.3 | 1.64 (0.36, 7.47) |
| **Best response to most recent ICI** | | | | | |
| CR/PR | 25/47 | 11.9 | 16/30 | 10.4 | 0.76 (0.40, 1.43) |
| SD | 70/104 | 10.5 | 65/97 | 10.5 | 1.18 (0.84, 1.65) |
| PD | 63/92 | 10.4 | 63/95 | 10.6 | 1.01 (0.71, 1.43) |




CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Categories with ≤2 patients are not shown. [b] Unstratified.

# Interim analysis of OS (primary endpoint)




| | Atezo + Cabo (n=263) | Cabo (n=259) |
|---|---|---|
| **PFS events, n (%)** | 89 (34) | 87 (34) |
| **Median OS (95% CI), mo** | 25.7 (25.1, NE) | NE (21.1, NE) |
| **12-month OS (95% CI), %** | 79 (73, 84) | 76 (71, 81) |
| **Stratified HR (95% CI)[a]** | 0.94 (0.70, 1.27); *P*=0.690 | |

**Number at risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezo + Cabo | 263 | 259 | 240 | 229 | 215 | 207 | 196 | 157 | 127 | 91 | 50 | 31 | 15 | 3 | 1 |
| Cabo | 259 | 247 | 235 | 221 | 207 | 195 | 182 | 145 | 113 | 88 | 50 | 22 | 11 | 3 | 2 |

[a] Stratified for IMDC risk group.

# Safety summary

| Adverse event, n (%) | Atezo + Cabo (n=262) | Cabo (n=256) |
|---|---|---|
| **Any-cause AE** | 262 (100) | 254 (99.2) |
| Any-cause treatment-related AE | 252 (96.2) | 249 (97.3) |
| **Grade 3 or 4 AE** | 177 (67.6) | 158 (61.7) |
| Grade 3 or 4 treatment-related AE | 145 (55.3) | 121 (47.3) |
| **Death due to AE** | 17 (6.5) | 9 (3.5) |
| Death due to treatment-related AE | 3 (1.1)[a] | 0 |
| **Serious AE** | 126 (48.1) | 84 (32.8) |
| Serious treatment-related AE | 63 (24.0) | 30 (11.7) |
| **AE leading to withdrawal from a trial drug** | 41 (15.6) | 10 (3.9) |
| AE leading to withdrawal from atezo | 29 (11.1) | – |
| AE leading to withdrawal from cabo | 25 (9.5) | 10 (3.9) |
| **AE leading to interruption or reduction of a trial drug** | 240 (91.6) | 223 (87.1) |
| AE leading to interruption of atezo[b] | 159 (60.7) | – |
| AE leading to interruption or reduction of cabo | 234 (89.3) | 223 (87.1) |

[a] Treatment-related AEs leading to death were immune-mediated enterocolitis and renal failure (both related to atezo) and intestinal perforation (related to cabo). [b] Dose reduction of atezo was not permitted.

# *Take Home Messages*

- Lo studio CONTACT-03 non può stabilire in modo definitivo il ruolo del rechallenge dell'immunoterapia nel setting post-ICI
- Rimane da chiarire il ruolo di un rechallenge «delayed» e del trattamento ottimale dopo terapia adiuvante
- Debolezza del partner scelto per cabozantinib

# GENITOURINARY CANCER: UROTHELIAL CARCINOMA

EARLY STAGE:

- Regime chemioterapico peri-operatorio: *Overall Survival (OS) data at 5 years in the GETUG/AFU V05 VESPER Trial*

ADVANCED DISEASE:

- Terapie target: *Primary analysis of phase III THOR study*

# GENITOURINARY CANCER: UROTHELIAL CARCINOMA

## EARLY STAGE:

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ADVANCED DISEASE:

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# Trial design (1)

## Chemotherapy

- **4 cycles of GC** — Gemcitabine 1250 mg/m$^2$ d1 and d8; Cisplatin 70 mg/m$^2$ d1 — **every 3 weeks**
- **6 cycles of ddMVAC** — Methotrexate 30 mg/m$^2$ d1; Vinblastine 3 mg/m$^2$ d2; Doxorubicin 30 mg/m$^2$ d2; Cisplatin 70 mg/m$^2$ d2; ***+ G-CSF support from d3 to d9*** — **every 2 weeks**

# Trial design (2)

## Inclusion criteria

- Pure or mixed urothelial bladder cancer *(neuroendocrine excluded)*
- ECOG PS < 2 and all criteria for cisplatin eligibility
- Written informed consent

**AND**

- ≥ T2, N0 *(LN ≤ 10 mm on CT scan)*, M0 (Neoadjuvant CT)
- > pT2 or pN+ and M0 (Adjuvant CT)

# Trial design (3)

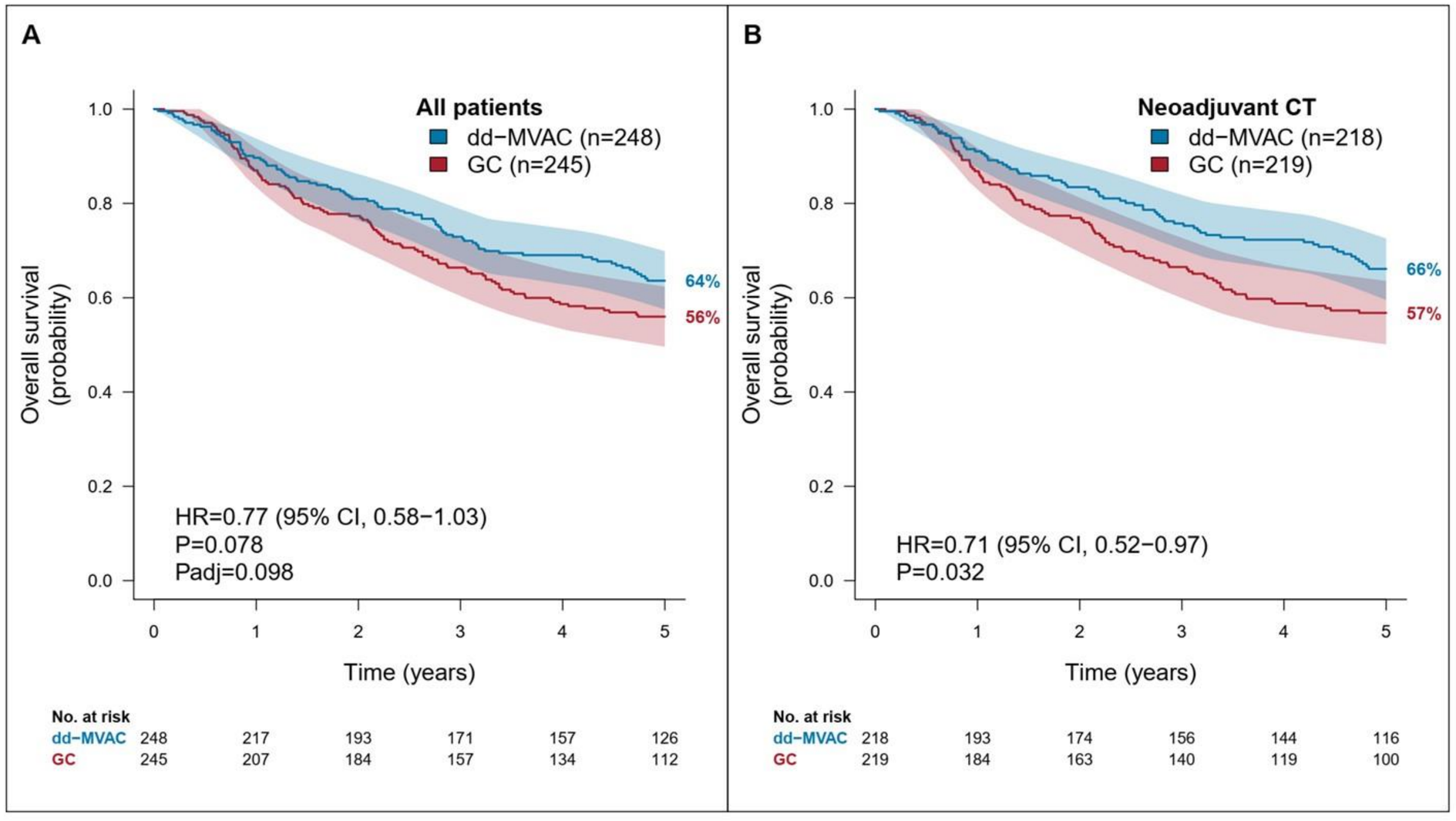
- **500 patients included in 28 centers from 2013 to 2018**

  *(493 patients available for intent-to-treat analysis)*

- **Adjuvant** (n=56) **and Neoadjuvant** (n=437) (88%)
- **Primary end-point :** Progression Free Survival at 3 years
- **Final analysis :** Overall and Specific Survival at 5 years

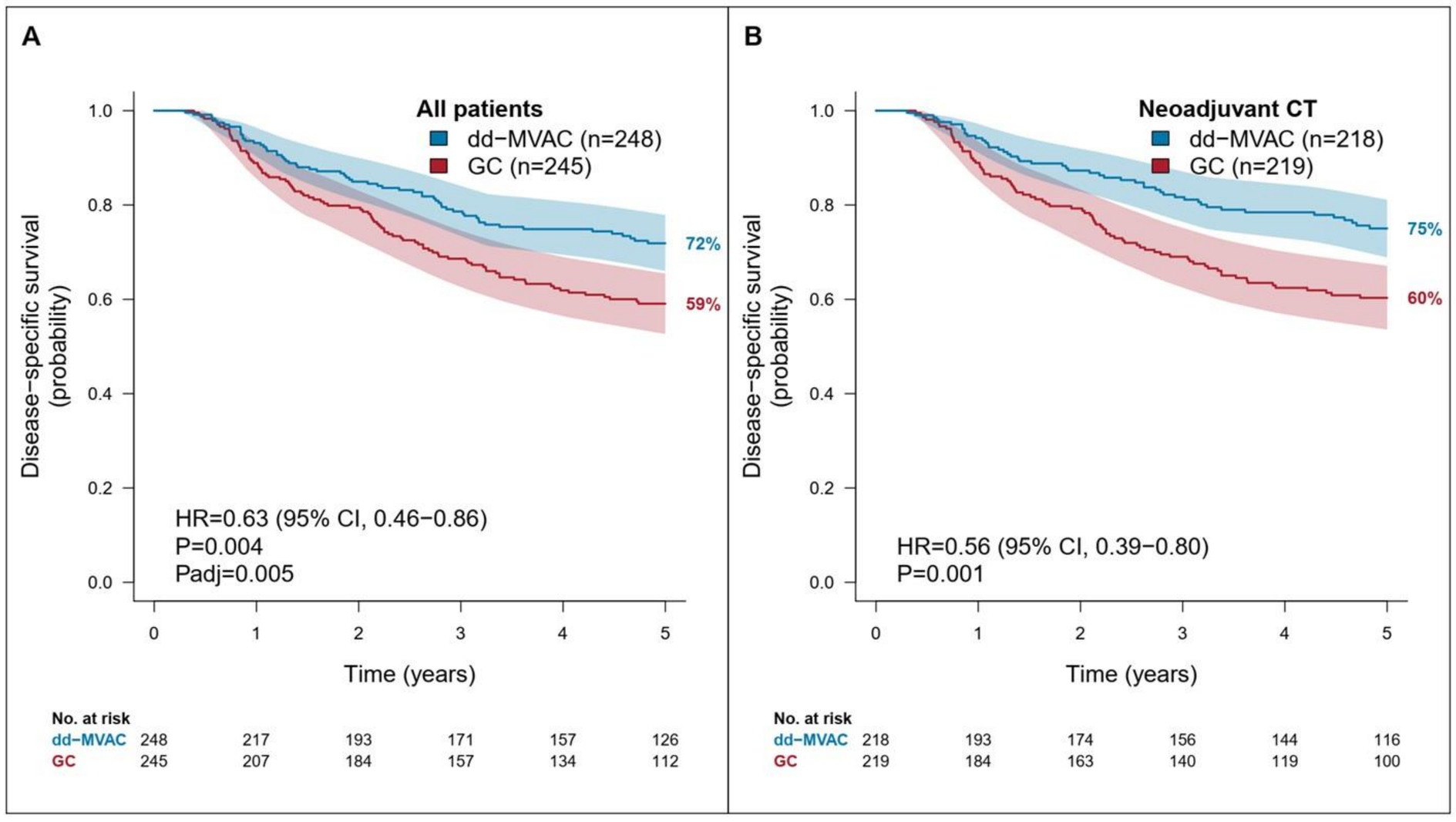
# Results (1)

## Overall Survival at 5 years



# Results (2)

## Disease-specific Survival



# Results (5)

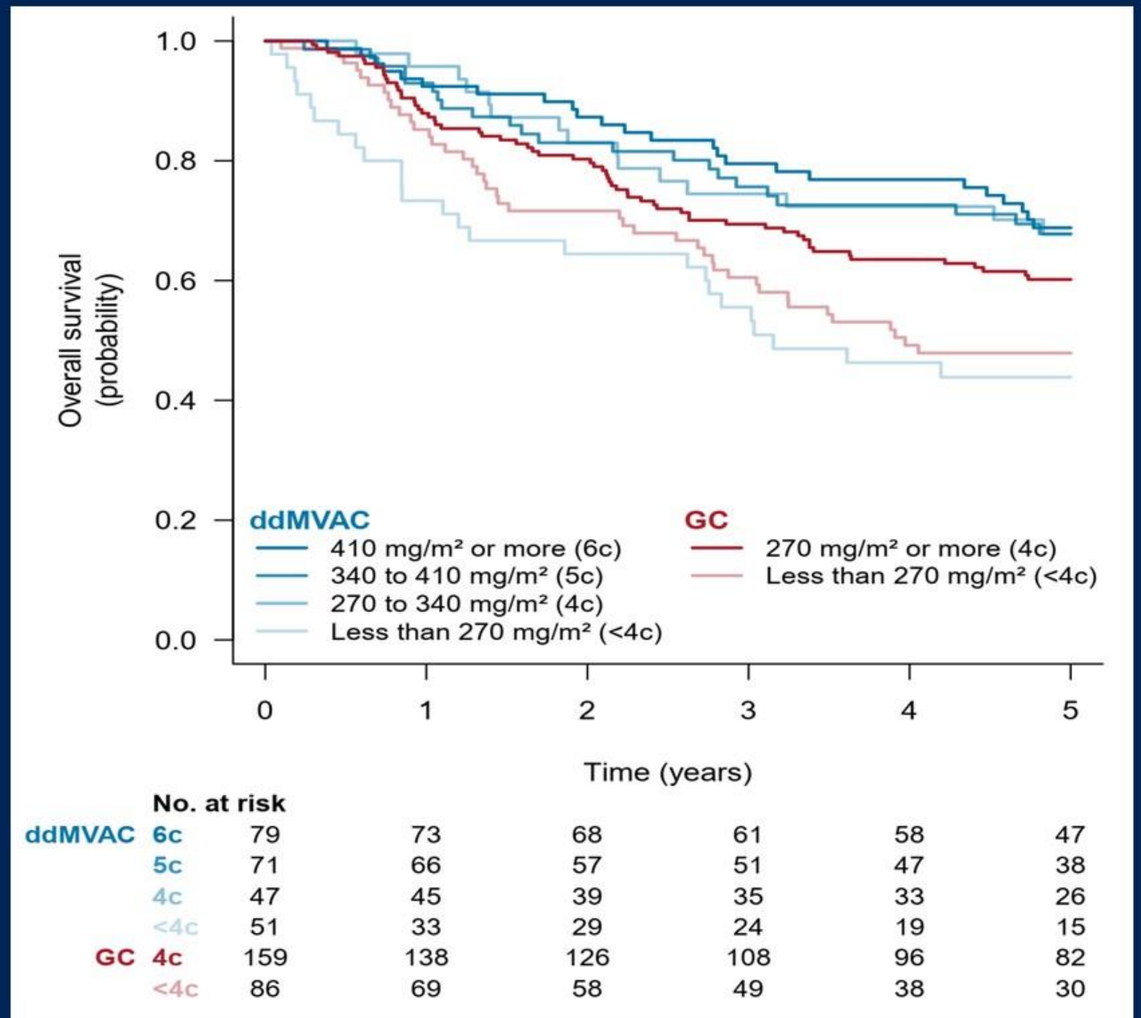
## OS stratified by CT arm and number of cycles delivered

**Importance of cumulative cisplatin dose**

**Poor OS** *< 4 full doses cisplatin*

**Median OS** *GC arm 4 full doses cisplatin*

**High OS** *dd-MVAC arm > 4 full doses cisplatin*




| | No. at risk | | | | | | |
|---|---|---|---|---|---|---|---|
| ddMVAC | 6c | 79 | 73 | 68 | 61 | 58 | 47 |
| | 5c | 71 | 66 | 57 | 51 | 47 | 38 |
| | 4c | 47 | 45 | 39 | 35 | 33 | 26 |
| | <4c | 51 | 33 | 29 | 24 | 19 | 15 |
| GC | 4c | 159 | 138 | 126 | 108 | 96 | 82 |
| | <4c | 86 | 69 | 58 | 49 | 38 | 30 |

# *Take Home Messages*

- Ruolo CENTRALE della chemioterapia neoadiuvante con l'obiettivo di raggiungere un valido surrogato della sopravvivenza: la risposta patologica completa
- La dose cumulativa di cisplatino rappresenta un fattore rilevante che impatta sulla sopravvivenza
- 4 o 6 dosi di ddMVAC?

# GENITOURINARY CANCER: UROTHELIAL CARCINOMA

EARLY STAGE:

- Regime chemioterapico peri-operatorio: *Overall Survival (OS) data at 5 years in the GETUG/AFU V05 VESPER Trial*

**ADVANCED DISEASE:**

- **Terapie target:** ***Primary analysis of phase III THOR study***

# Phase 3 THOR Study: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Selected FGFR Aberrations

## Cohort 1

**Key eligibility criteria**

- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression
- Prior tx with anti–PD-(L)1
- 1-2 lines of systemic tx
- Select *FGFR3/2alt* (mutation/fusion)[a]
- ECOG PS 0-2

**1:1**
**N=266[b]**

R

**Erdafitinib**
**(n=136)**
Once-daily erdafitinib 8 mg with pharmacodynamically guided uptitration to 9 mg

**Chemotherapy of Choice**
**(n=130)**
docetaxel or vinflunine once every 3 weeks

Stratification factors: region (North America vs European Union vs rest of world), ECOG PS (0 or 1 vs 2), and disease distribution (presence vs absence of visceral [lung, liver, or bone] metastases)

**Primary end point:**
- OS

**Key secondary end points:**
- PFS
- ORR
- Safety

NCT03390504

[a]Molecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have ≥1 of the following translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; or 1 of the following *FGFR3* gene mutations: R248C, S249C, G370C, Y373C.
[b]Number of patients randomized at the time of the interim analysis (data cutoff January 15, 2023).
ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; *FGFR3/2alt*, *FGFR3/2* alterations; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; tx, treatment; UC, urothelial cancer.

# Demographics and Disease Characteristics

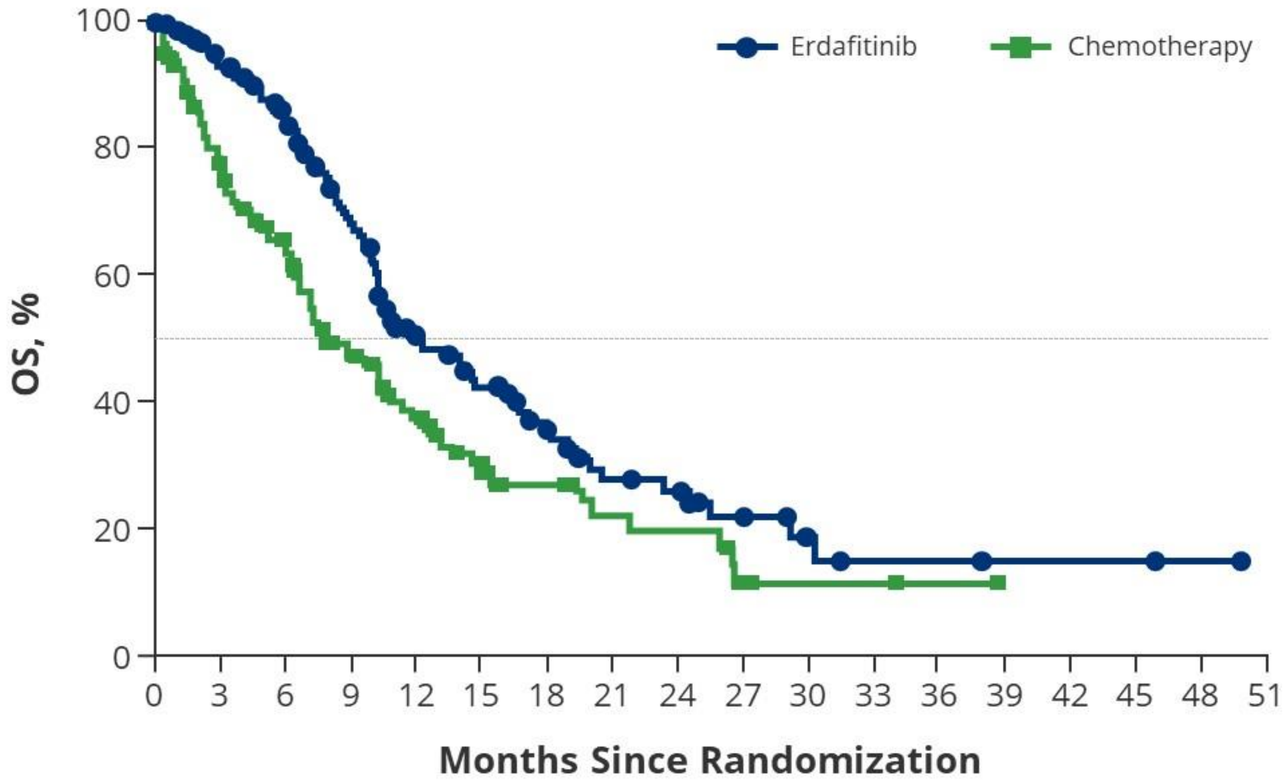
| Characteristic | Erdafitinib (n=136) | Chemotherapy (n=130) |
|---|---|---|
| Age, median (range), years | 66 (32-85) | 69 (35-86) |
| Men, n (%) | 96 (70.6) | 94 (72.3) |
| Race, n (%) | | |
| White | 81 (59.6) | 63 (48.5) |
| Asian | 37 (27.2) | 40 (30.8) |
| Black or African American | 0 | 1 (0.8) |
| Multiple | 0 | 1 (0.8) |
| Not reported | 18 (13.2) | 25 (19.2) |
| Presence of visceral metastases, n (%) | 101 (74.3) | 97 (74.6) |
| Liver | 31 (22.8) | 38 (29.2) |

| Characteristic | Erdafitinib (n=136) | Chemotherapy (n=130) |
|---|---|---|
| ECOG PS 0-1, n (%) | 124 (91.2) | 117 (90) |
| Primary tumor upper tract, n (%) | 41 (30.1) | 48 (36.9) |
| PD-L1 low (CPS <10), n (%) | 89 (92.7)[a] | 68 (86.1)[a] |
| *FGFRalt*, n (%)[b] | (n=135) | (n=129) |
| Mutations | 108 (79.4) | 107 (82.3) |
| Fusions | 25 (18.4) | 19 (14.6) |
| Mutations and fusions | 2 (1.5) | 3 (2.3) |
| Prior lines of systemic therapy[c] | | |
| 1 line | 45 (33.1) | 33 (25.4) |
| 2 lines | 90 (66.2) | 97 (74.6) |

- Patient baseline characteristics were generally balanced between treatment arms

[a]For PD-L1 status, percentage is based on patients with available data (n=96 for erdafitinib and n=79 for chemotherapy).
[b]All patients enrolled had *FGFR3alt*. 2 patients were subsequently identified as false positives; they were included in the intent-to-treat population.
[c]1 patient in the erdafitinib group had 3 prior lines of systemic therapy.
CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; *FGFRalt*, *FGFR* alterations; PD-L1, programmed death-ligand 1.

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



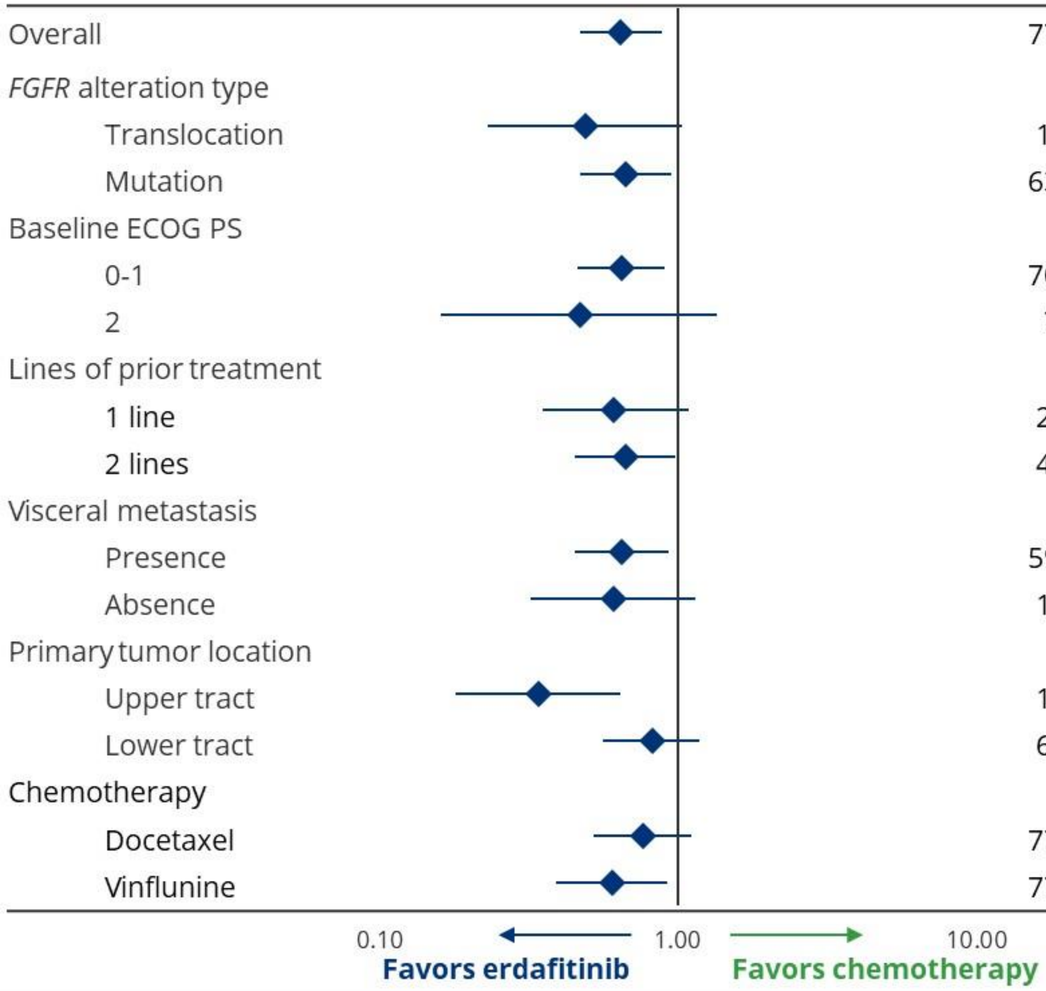

| No. at risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Erdafitinib | 136 | 117 | 97 | 74 | 46 | 35 | 25 | 17 | 15 | 9 | 5 | 3 | 3 | 2 | 2 | 2 | 1 | 0 |
| Chemotherapy | 130 | 87 | 66 | 43 | 30 | 18 | 13 | 9 | 8 | 3 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 |

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

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

# Overall Survival Benefit With Erdafitinib Versus Chemotherapy Was Consistently Observed Across Subgroups

| | Erdafitinib | | Chemotherapy | | |
|---|---|---|---|---|---|
| | n/N[a] | Median | n/N[a] | Median | HR and 95% CI |
| Overall | 77/136 | 12.1 | 78/130 | 7.8 | 0.64 (0.47-0.88) |
| *FGFR* alteration type | | | | | |
| Translocation | 13/25 | 16.4 | 15/19 | 8.0 | 0.49 (0.23-1.03) |
| Mutation | 63/108 | 10.9 | 60/107 | 7.7 | 0.67 (0.47-0.95) |
| Baseline ECOG PS | | | | | |
| 0-1 | 70/125 | 12.2 | 71/119 | 8.7 | 0.65 (0.46-0.90) |
| 2 | 7/11 | 6.1 | 7/11 | 2.8 | 0.47 (0.16-1.35) |
| Lines of prior treatment | | | | | |
| 1 line | 27/45 | 14.0 | 21/33 | 7.8 | 0.61 (0.35-1.09) |
| 2 lines | 49/90 | 11.6 | 57/97 | 7.7 | 0.67 (0.45-0.98) |
| Visceral metastasis | | | | | |
| Presence | 59/103 | 12.2 | 57/101 | 7.7 | 0.65 (0.45-0.93) |
| Absence | 18/33 | 10.6 | 21/29 | 8.8 | 0.61 (0.32-1.14) |
| Primary tumor location | | | | | |
| Upper tract | 16/41 | 23.3 | 27/48 | 7.2 | 0.34 (0.18-0.64) |
| Lower tract | 61/95 | 10.5 | 51/82 | 9.6 | 0.82 (0.56-1.18) |
| Chemotherapy | | | | | |
| Docetaxel | 77/136 | 12.1 | 40/69 | 10.6 | 0.76 (0.52-1.11) |
| Vinflunine | 77/136 | 12.1 | 30/43 | 7.7 | 0.60 (0.39-0.92) |




[a]n=number of events; N=number of patients in subgroup. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

# The Safety Profiles Were Consistent With the Known Profiles of Erdafitinib and Chemotherapy (1/2)

| Patients with AEs, n (%)[a] | Erdafitinib (n=135) | |
|---|---|---|
| | Any grade | Grade 3-4 |
| ≥1 treatment-related AE | **131 (97.0)** | **62 (45.9)** |
| Hyperphosphatemia | **106 (78.5)** | **7 (5.2)** |
| Diarrhea | **74 (54.8)** | **4 (3.0)** |
| Stomatitis | **62 (45.9)** | **11 (8.1)** |
| Dry mouth | **52 (38.5)** | **0** |
| PPE syndrome | **41 (30.4)** | **13 (9.6)** |
| Onycholysis | **31 (23.0)** | **8 (5.9)** |
| **Patients who discontinued study treatment, n (%)** | | |
| Discontinuation due to treatment-related AEs | **11 (8.1%)[b]** | |

- **In the erdafitinib group:**
  - 18 patients (13.3%) had treatment-related serious AEs
  - 1 treatment-related death occurred[c]
  - AEs with erdafitinib were mostly manageable with dose modifications and supportive care
- **In the chemotherapy group:**
  - 27 patients (24.1%) had treatment-related serious AEs
  - 6 treatment-related deaths occurred[d]

| Patients with AEs, n (%)[e] | Chemotherapy (n=112) | |
|---|---|---|
| | Any grade | Grade 3-4 |
| ≥1 treatment-related AE | **97 (86.6)** | **52 (46.4)** |
| Anemia | **31 (27.7)** | **7 (6.3)** |
| Alopecia | **24 (21.4)** | **0** |
| Nausea | **22 (19.6)** | **2 (1.8)** |
| Neutropenia | **21 (18.8)** | **15 (13.4)** |
| Leukopenia | **13 (11.6)** | **9 (8.0)** |
| Febrile neutropenia | **9 (8.0)** | **10 (8.9)** |
| **Patients who discontinued study treatment, n (%)** | | |
| Discontinuation due to treatment-related AEs | **15 (13.4)[f]** | |

[a]AEs by preferred term are listed if events of any grade occurred in ≥30% of patients in the erdafitinib group or if events of grade 3-4 occurred in ≥5% of patients.
[b]Most frequent treatment-related AEs leading to discontinuation of erdafitinib included eye disorders (3 patients) and skin and subcutaneous disorders (3 patients).
[c]Treatment-related AE leading to death was reported as sudden death.
[d]Treatment-related AEs leading to death in the chemotherapy arm included febrile bone marrow aplasia (2 patients), febrile neutropenia (1 patient), septic shock (2 patients), and atypical pneumonia (1 patient).
[e]AEs by preferred term are listed if events of any grade occurred in ≥20% of patients in the chemotherapy group or if events of grade 3-4 occurred in ≥5% of patients.
[f]Most frequent treatment-related AEs leading to discontinuation of chemotherapy included blood and lymphatic system disorders (5 patients) and infections and infestations (3 patients).
AE, adverse event; PPE, palmar-plantar erythrodysesthesia.

# *Take Home Messages*

- Primo studio randomizzato che ha confrontato una terapia target in pazienti molecolarmente selezionati
- Importanza di testare alterazioni di FGFR in una fase precoce della malattia metastatica, in modo da poter offrire una possibilità di terapia target a pazienti selezionati
- La valutazione del profilo di safety può aiutare ad ottimizzare la sequenza terapeutica alla luce dei dati provenienti dagli studi che hanno testato il ruolo degli anticorpi farmaco-coniugati (sacituzumab ed enfortumab)