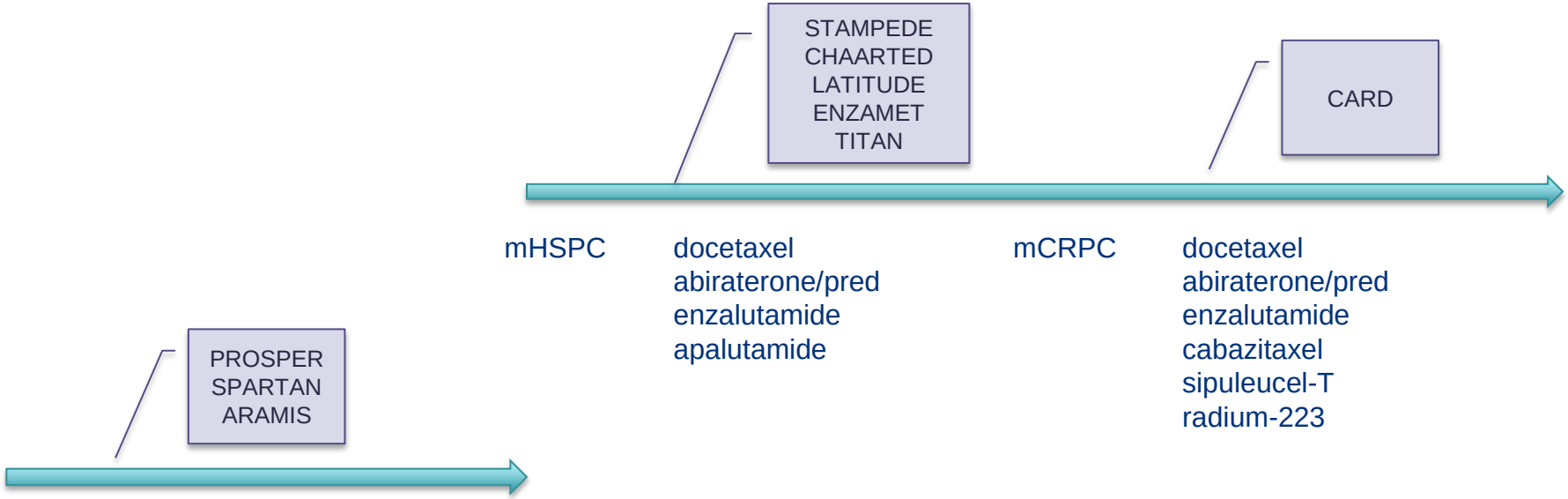

# Updates in Genitourinary Oncology

**Mamta Parikh,MD,MS**

**Advances in Oncology Conferences**

# Prostate Cancer

# 2019 State of the Art in Advanced Prostate Cancer

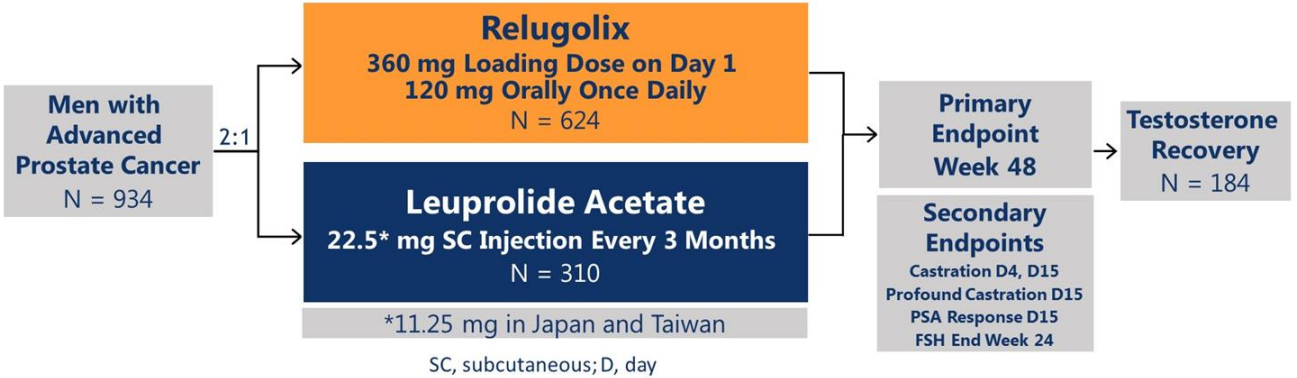


- Relugolix: oral GnRH receptor antagonist

HERO

## Phase 3 HERO Study Design

- A multinational phase 3 randomized, open-label, parallel group study to evaluate the safety and efficacy of relugolix in men with advanced prostate cancer
- **Primary Endpoint**: Sustained castration through 48 weeks (< 50 ng/dL)




SC, subcutaneous; D, day

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Neal Shore, MD, FACS
Carolina Urologic Research Center, SC, USA
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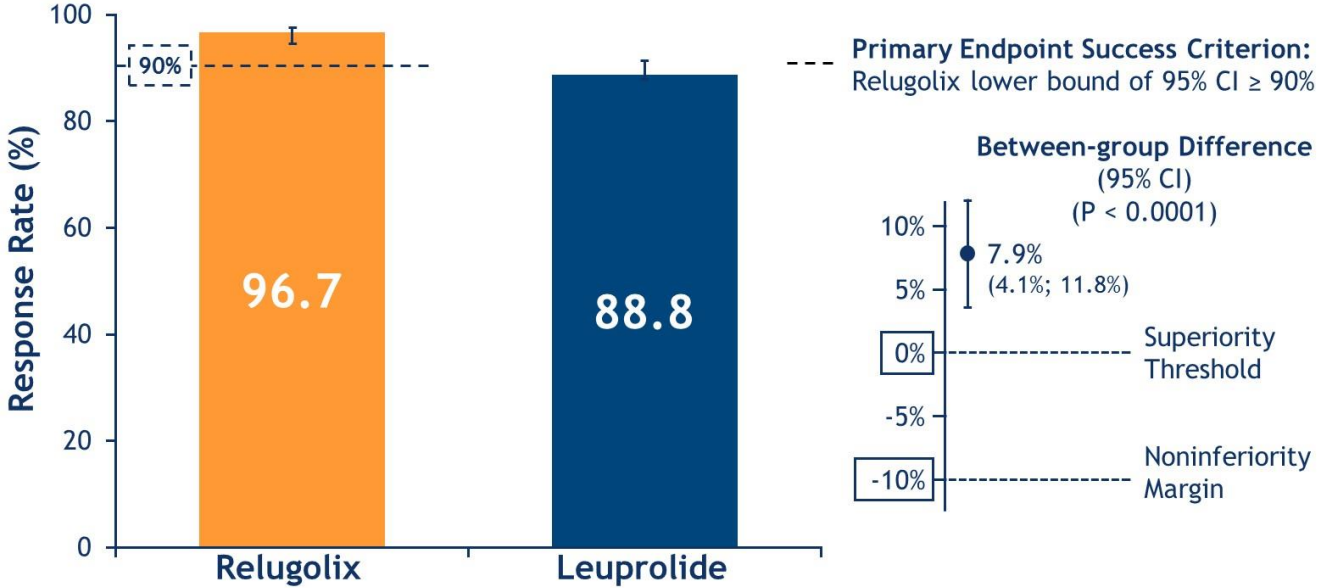
HERO

# Primary Endpoint – Sustained Castration

# Key Secondary Endpoint – Noninferiority to Leuprolide



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# Key Secondary Endpoints

| Secondary Endpoints (alpha-protected) | Relugolix (N = 622) | Leuprolide (N = 308) | P-value |
|---|---|---|---|
| Proportion of patients with **PSA response at Day 15** followed with confirmation at Day 29 | 79.4% | 19.8% | <0.0001 |
| Cumulative probability of **testosterone suppression to <50 ng/dL on Day 15** | 98.71% | 12.05% | <0.0001 |
| Cumulative probability of **profound testosterone suppression to <20 ng/dL on Day 15** | 78.38% | 0.98% | <0.0001 |
| Cumulative probability of **testosterone suppression to <50 ng/dL on Day 4** | 56.04% | 0.00% | <0.0001 |
| Mean of **FSH level at** end of **Week 24 — IU/L** | 1.72 | 5.95 | <0.0001 |

FSH, follicle-stimulating hormone; IU, international unit; PSA, prostate-specific antigen.

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# Cardiovascular Adverse Events

| | Relugolix (N = 622) | Leuprolide (N = 308) |
|---|---|---|
| Adverse Cardiovascular Events | 3.9% | 7.1% |
| Major Adverse Cardiovascular Events (MACE) | 2.9% | 6.2% |
| Ischemic Heart Disease | 2.4% | 1.6% |

| History of MACE | Yes | | No | |
|---|---|---|---|---|
| N (%) | Relugolix 84 (13.5%) | Leuprolide 45 (14.6%) | Relugolix 538 (86.5%) | Leuprolide 263 (85.4%) |
| MACE | 3.6% | 17.8% | 2.8% | 4.2% |
| Odds Ratio Leuprolide vs Relugolix (95% confidence interval) | 5.8 (1.5, 23.3) | | 1.5 (0.7, 3.4) | |

MACE = non-fatal myocardial infarction + non-fatal stroke + all-cause mortality

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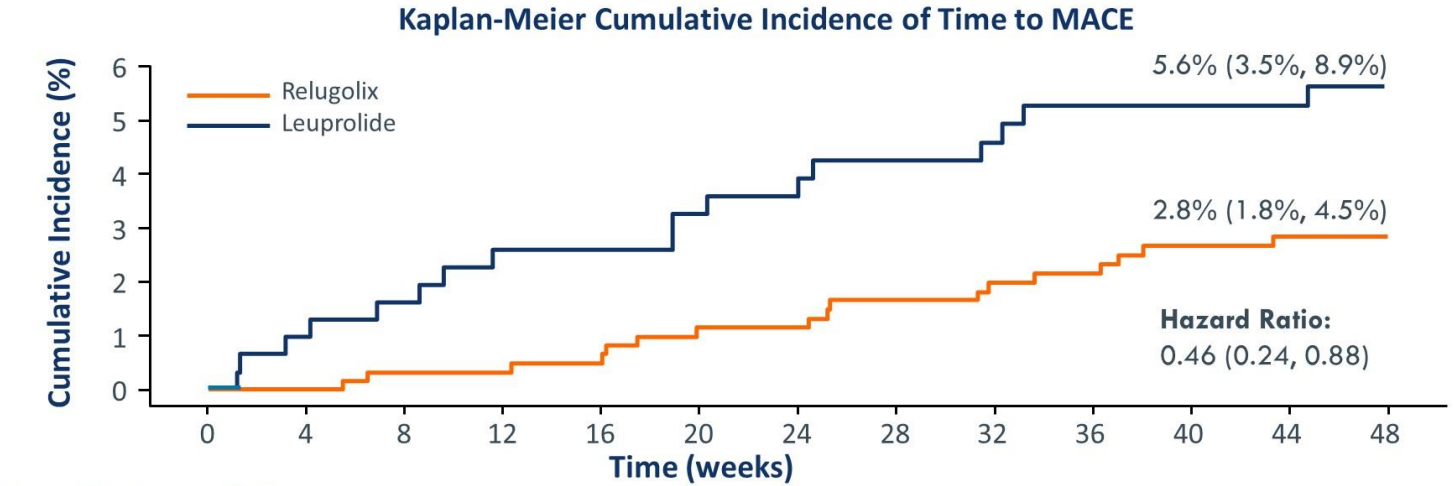
# 54% Reduction in Risk of Major Adverse Cardiovascular Events (MACE)

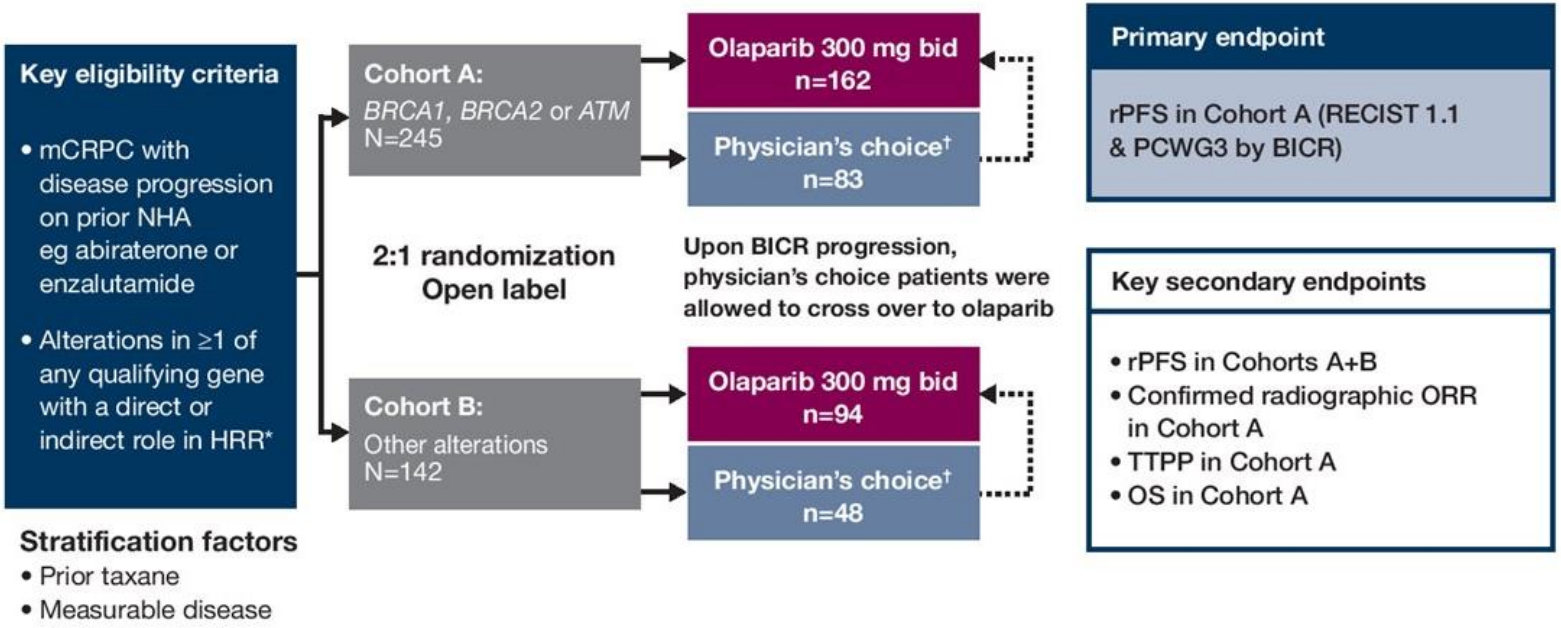



**No. of Patients at Risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relugolix | 622 | 621 | 616 | 610 | 605 | 596 | 595 | 588 | 582 | 575 | 563 | 559 | 538 |
| Leuprolide | 308 | 305 | 303 | 298 | 298 | 293 | 292 | 288 | 281 | 279 | 278 | 269 | 259 |

MACE = non-fatal myocardial infarction + non-fatal stroke + all-cause mortality.

# PROfound Study Design




*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*;
†Either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid]). BICR, blinded independent central review; ORR, objective response rate; OS, overall survival; qd, once daily; TTPP, time to pain progression

| Characteristic | Cohort A | |
|---|---|---|
| | Olaparib (N=162) | Control (N=83) |
| Median age at randomization (range) — yr | 68 (47–86) | 67 (49–86) |
| Age ≥65 yr at randomization — no. (%) | 108 (67) | 60 (72) |
| Metastatic disease at initial diagnosis — no. (%) | 38 (23) | 19 (23) |
| Missing data | 7 (4) | 4 (5) |
| Gleason score ≥8 — no./total no. (%)† | 105/157 (67) | 54/80 (67) |
| Patients with alterations in a single gene — no. (%)‡ | | |
| *BRCA1* | 8 (5) | 5 (6) |
| *BRCA2* | 80 (49) | 47 (57) |
| *ATM* | 60 (37) | 24 (29) |
| *CDK12* | NA | NA |
| Median PSA at baseline (IQR) — μg/liter | 62.2 (21.9–280.4) | 112.9 (34.3–317.1) |
| Measurable disease at baseline — no. (%)§ | 95 (59) | 46 (55) |
| Metastases at baseline — no. (%)§ | | |
| Bone only | 57 (35) | 23 (28) |
| Visceral: lung or liver | 46 (28) | 32 (39) |
| Other | 49 (30) | 23 (28) |
| ECOG performance status — no. (%) | | |

Gene alterations most common in BRCA2 (49%) & ATM (37%)

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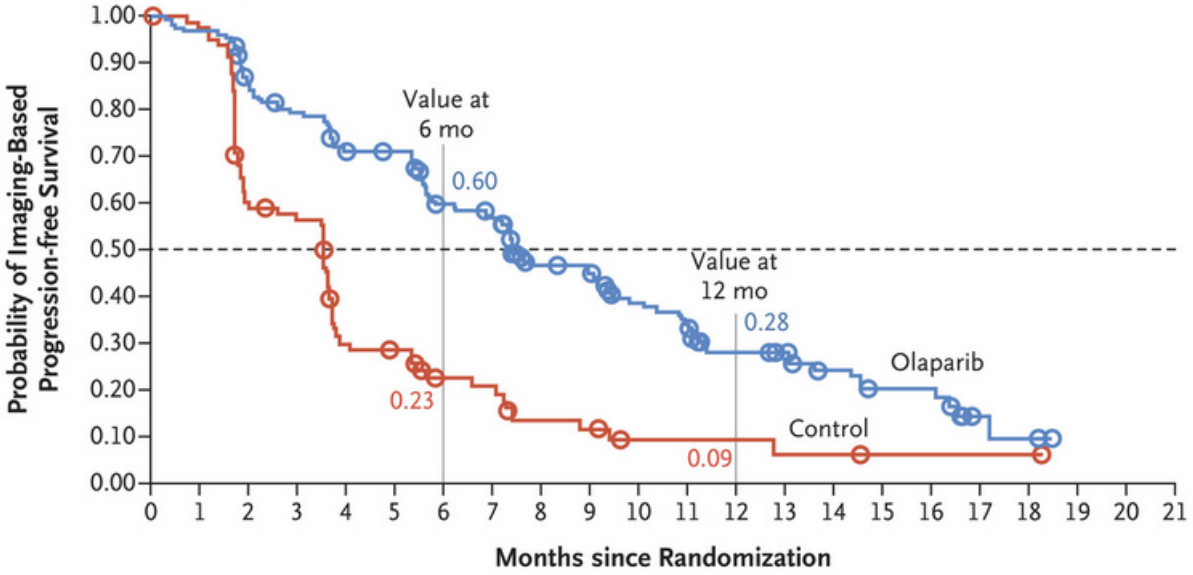
# PROfound Primary Endpoint: rPFS




| | Median |
|---|---|
| | *mo* |
| **Olaparib** | 7.4 |
| **Control** | 3.6 |

Hazard ratio for progression or death, 0.34 (95% CI, 0.25–0.47)
P<0.001

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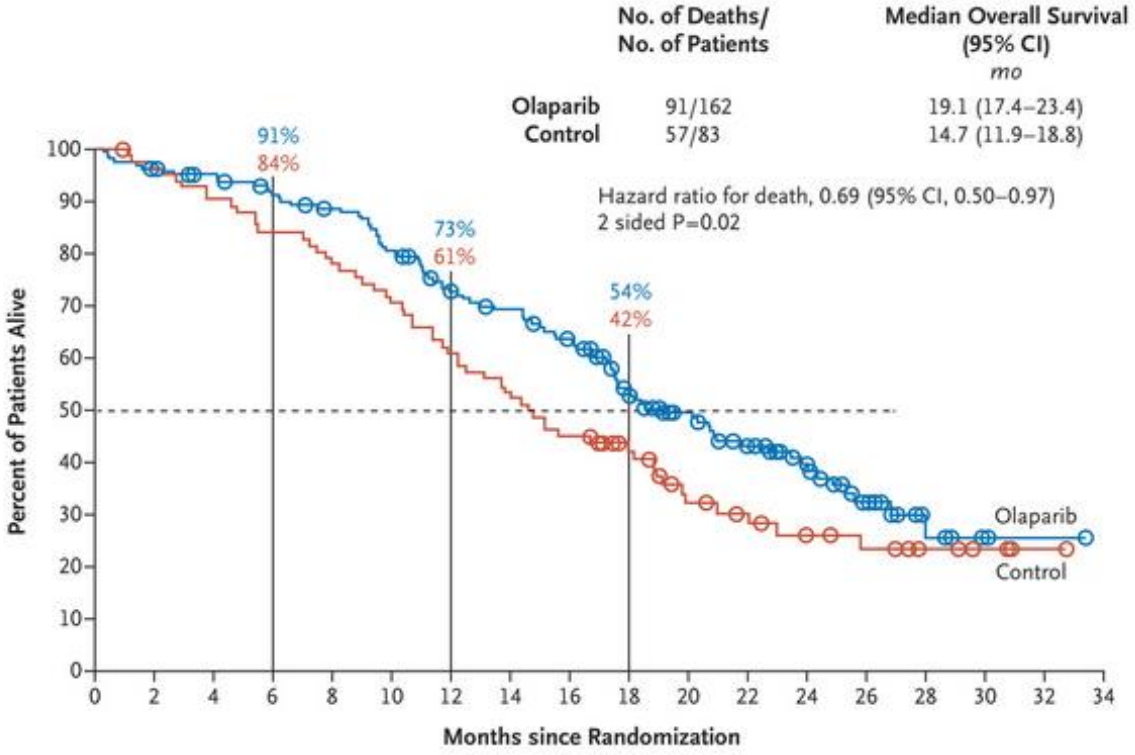
# PROfound Cohort A Overall Survival Results

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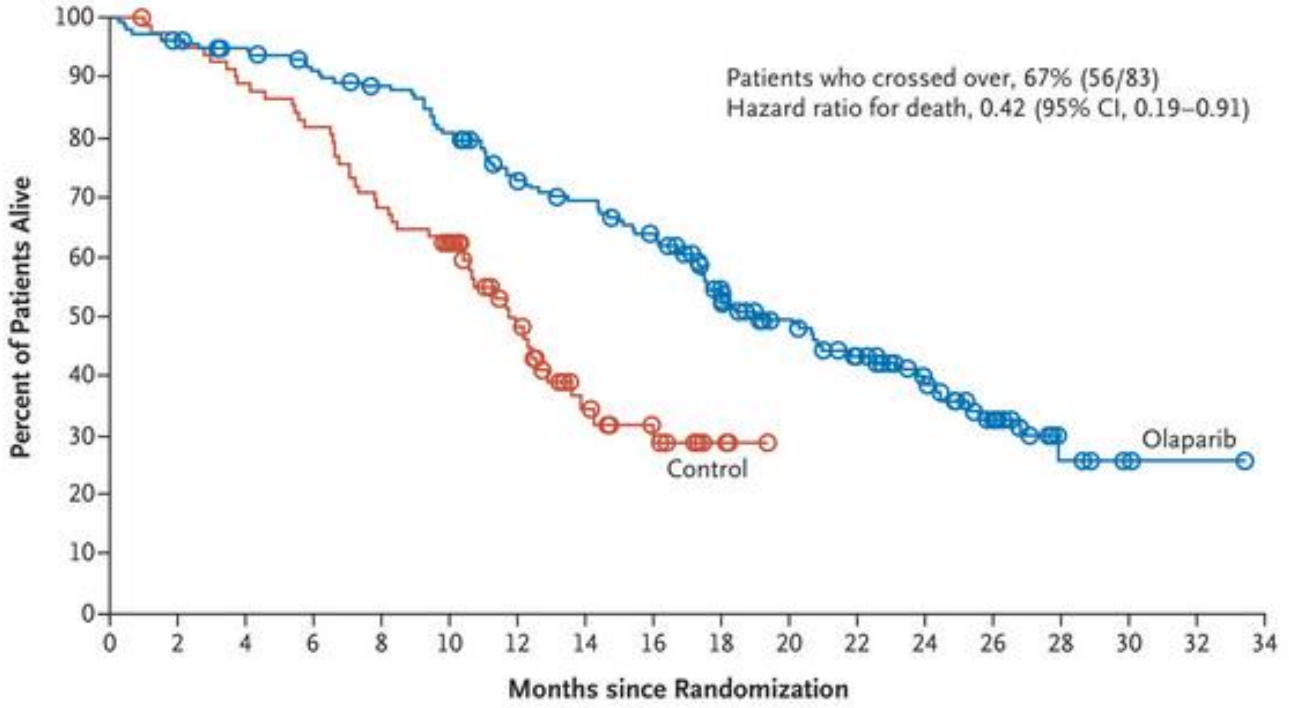
# PROfound Crossover-Adjusted Overall Survival

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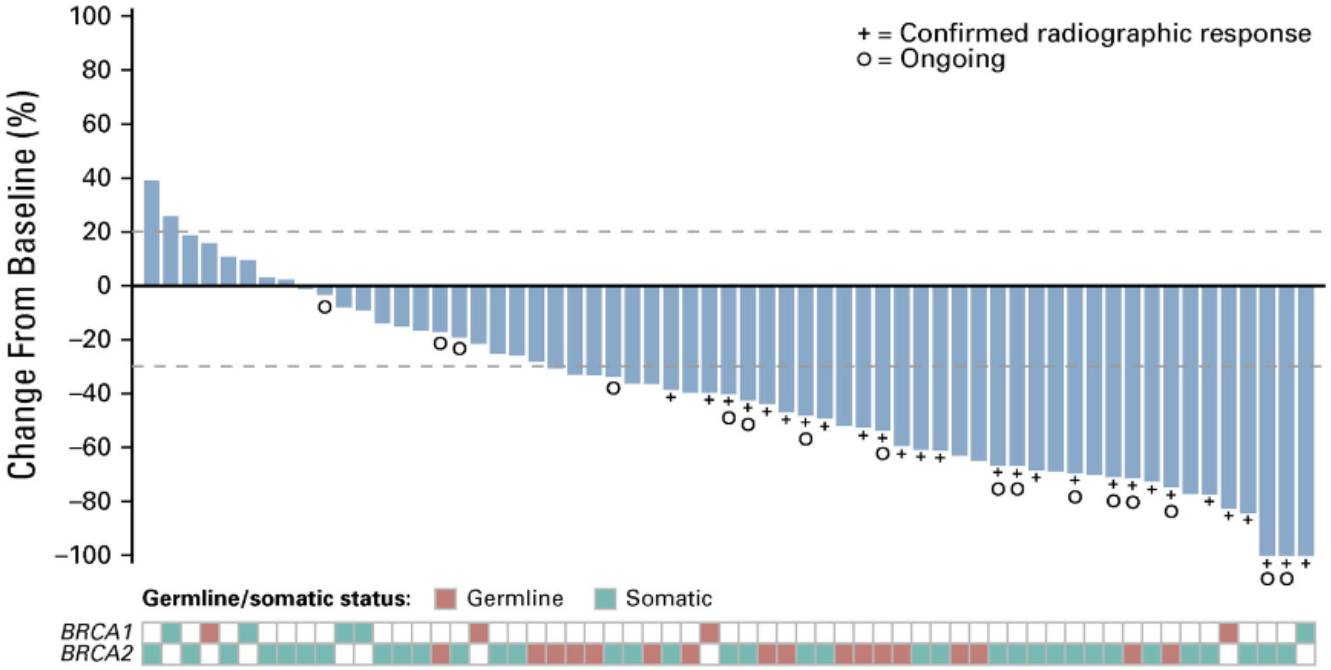
# TRITON2

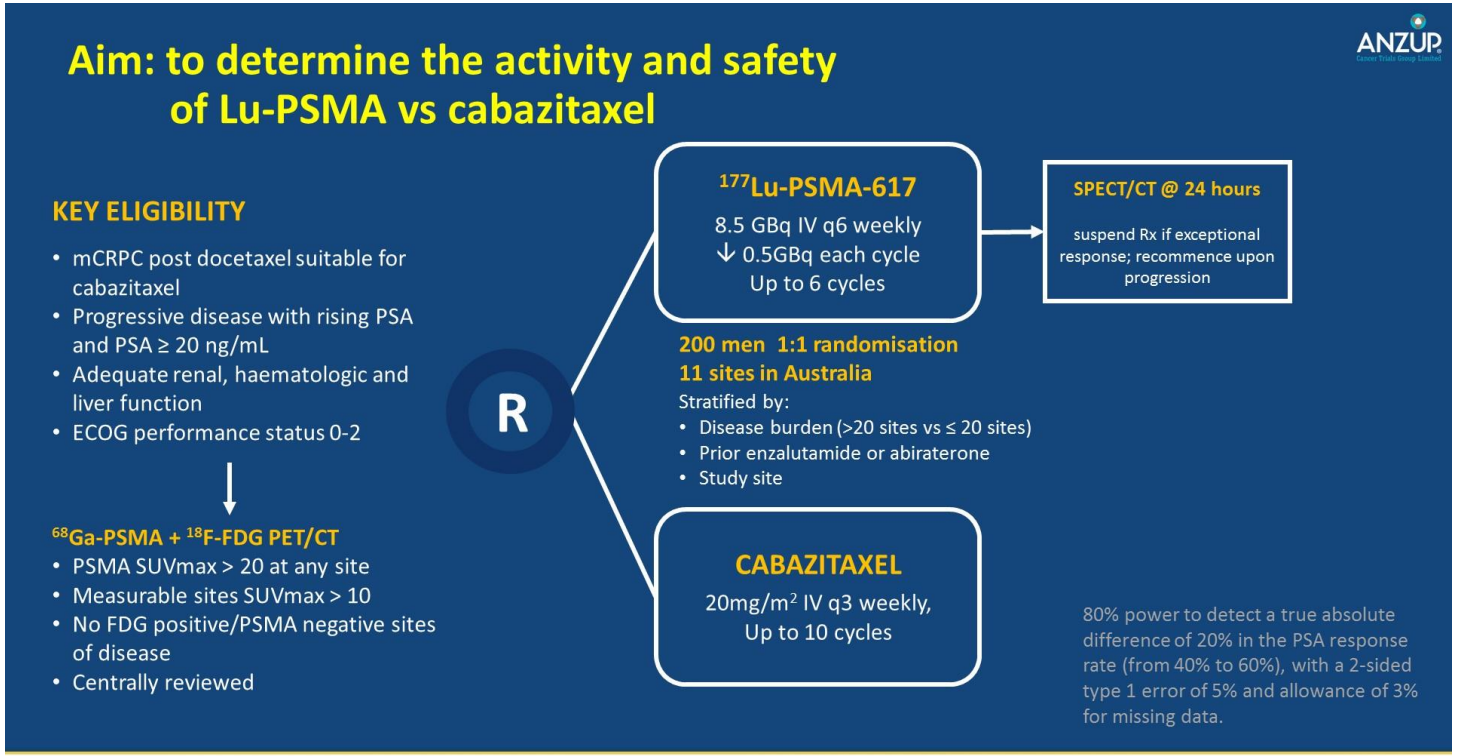
- Phase II open label
- Eligibility:
  - Progression on up to 2 lines of next-generation androgen receptor-directed therapy **AND** one taxane-based chemotherapy for mCRPC
  - Deleterious germline or somatic alteration in BRCA1, BRCA2 or other prespecified DDR genes
- Primary endpoint: Objective Response Rate
- n=115: 102 with BRCA2 alteration, 13 with BRCA1

# TRITON2




Abida *et al* J Clin Oncol 2020

# TheraP Trial Design



# Results: patient characteristics

ANZUP Cancer Trials Group Limited

| | Cabazitaxel (N=101) | Lu-PSMA (n=99) |
|---|---|---|
| Age (Years): Median (IQR) | 72 (67 to 77) | 72 (67 to 77) |
| Prior enzalutamide or abiraterone | 91 | 91 |
| Disease burden (> 20 sites) | 79 | 77 |
| ECOG performance status | | |
| 0 | 44 | 42 |
| 1 | 52 | 53 |
| 2 | 4 | 4 |
| unknown | 1 | |
| PSA: Median (IQR) | 110 (64 to 245) | 94 (44 to 219) |
| ALP: Median (IQR) | 130 (79 to 187) | 111 (83 to 199) |
| Gleason Score at diagnosis | | |
| ≤ 7 | 35 | 25 |
| ≥ 8 | 50 | 53 |
| unknown | 16 | 21 |

- **Updated dataset[1] with cut-off 31 MAR 2020**
- **Median follow-up of 13.3 months (IQR: 9.5 to 17.7) months**





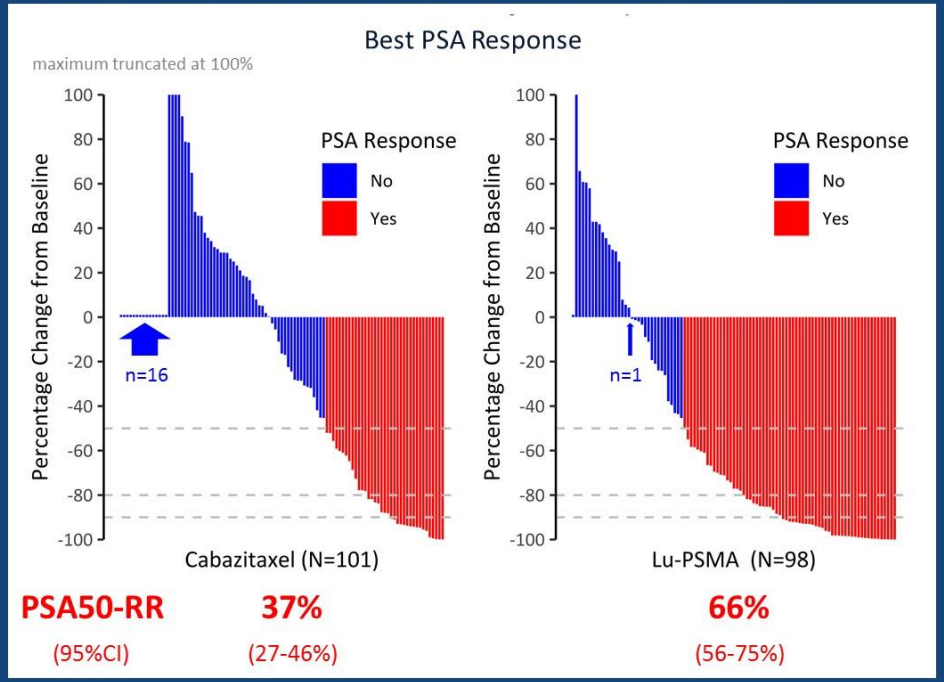




[1]Updated compared to ASCO abstract first analysis cut-off 31 DEC 2019

# Primary endpoint: PSA ≥ 50% response (PSA50-RR)

ANZUP Cancer Trials Group Limited

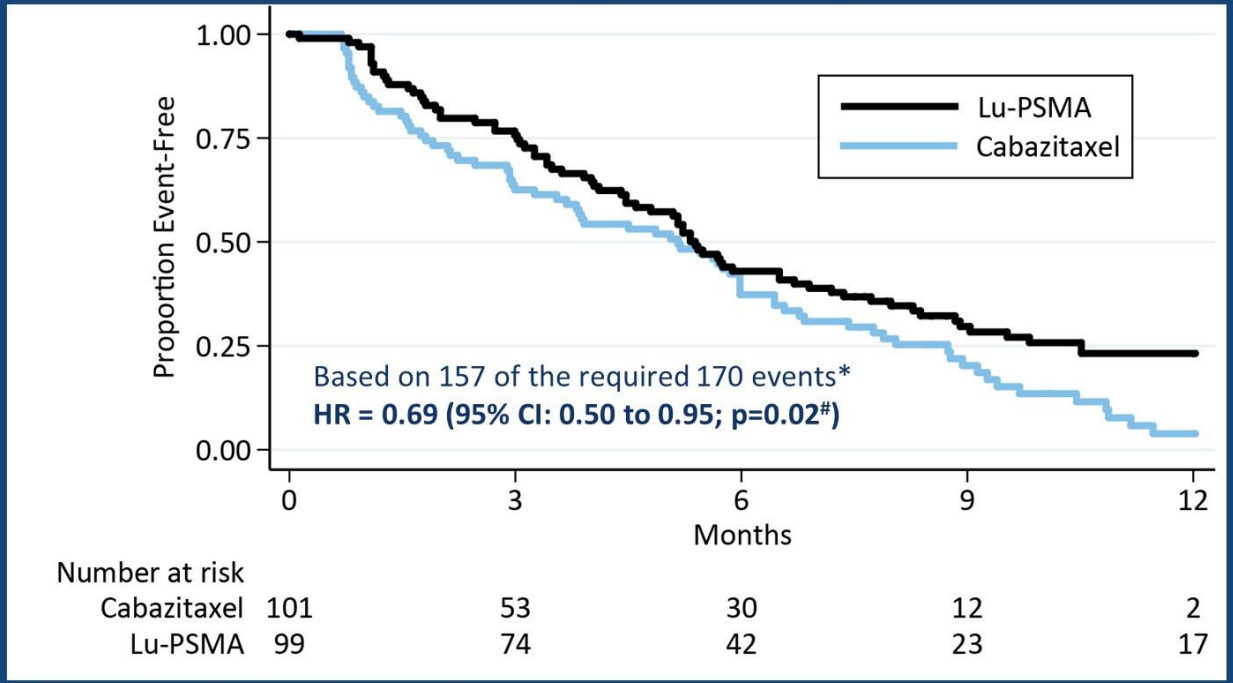



**Lu-PSMA: 29% absolute (95% CI 16%-42%; p<0.0001) greater PSA50-RR compared to cabazitaxel**

For sensitivity analysis per-protocol, the difference was 23% (95% CI 9%-37%; p=0.0016)

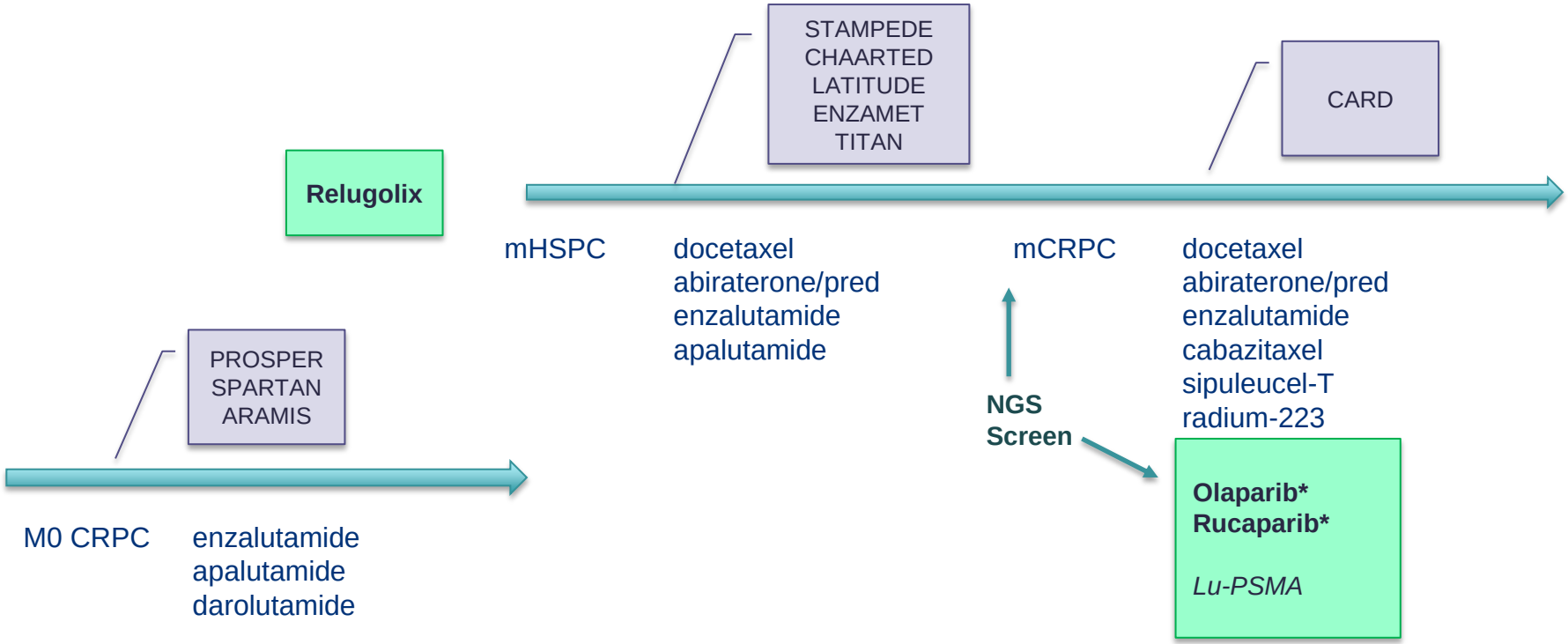
# Secondary endpoint: PSA PFS (preliminary)

ANZUP Cancer Trials Group Limited



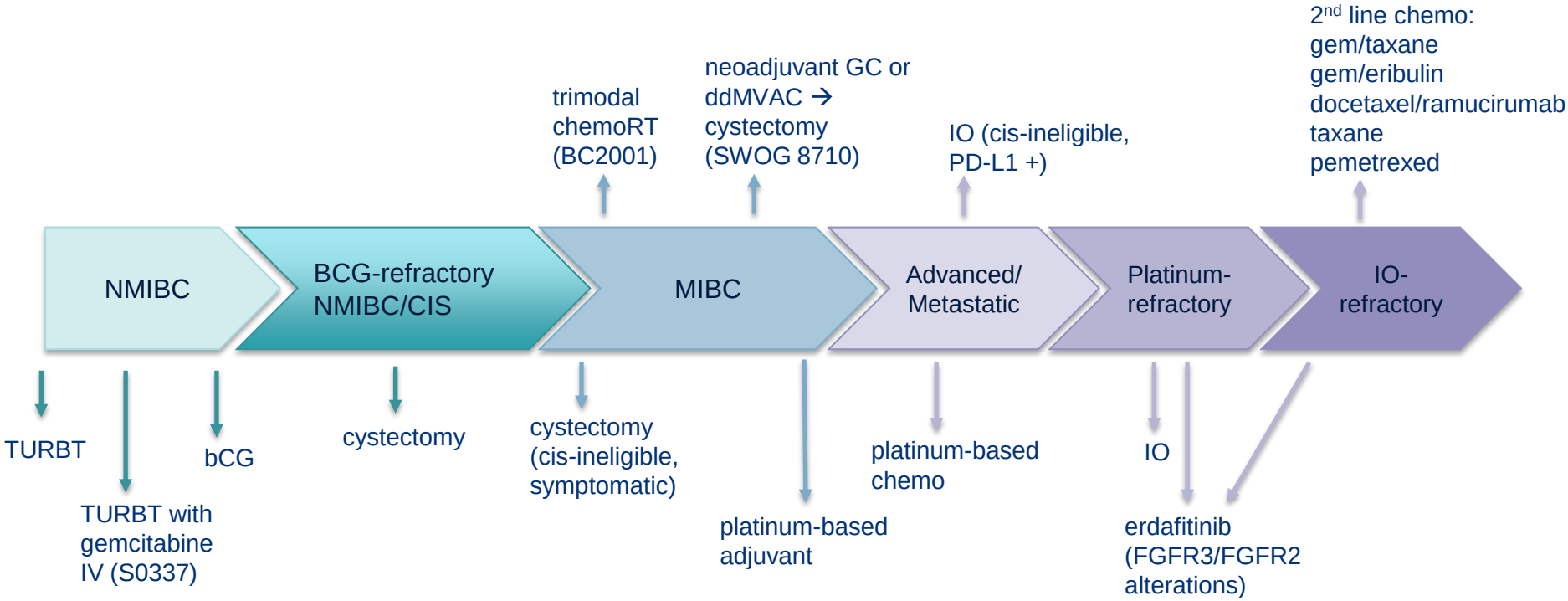

* Primary analysis at 170 events (as per SAP)
# p<0.0027 is required to trigger rejection of null hypothesis prior to planned primary analysis at 170 events (as per SAP)
There have been 71 deaths in total.

# State of the Art in Advanced Prostate Cancer



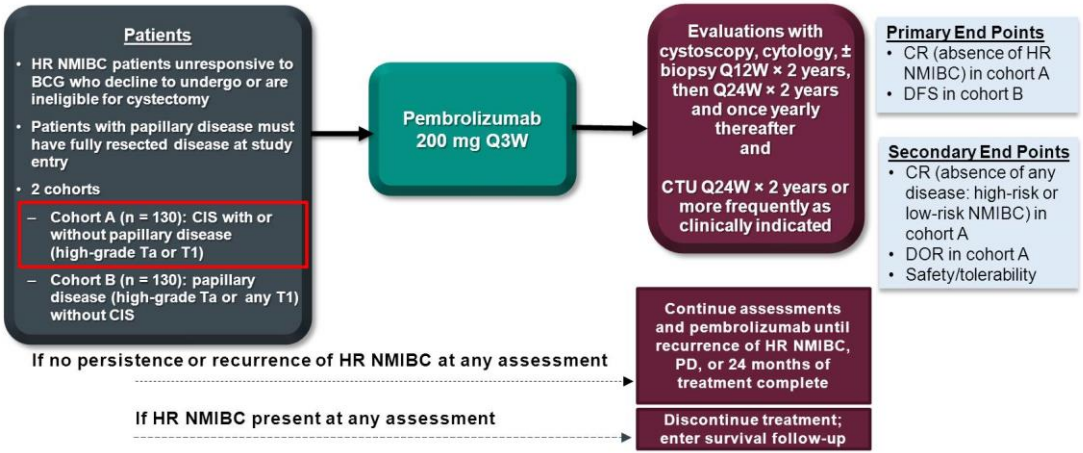
# Bladder Cancer

# Bladder Cancer Treatment



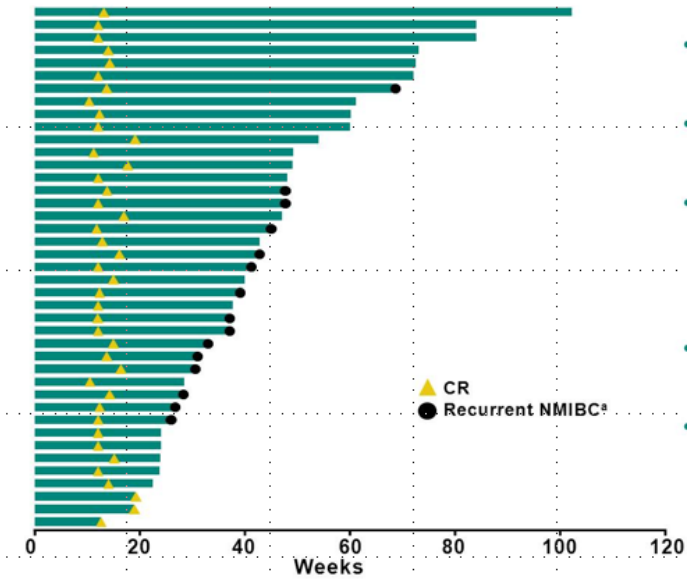
NMIBC | **BCG-refractory NMIBC/CIS** | MIBC | Advanced/ Metastatic | Platinum-refractory | IO-refractory

# KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



# KEYNOTE-057

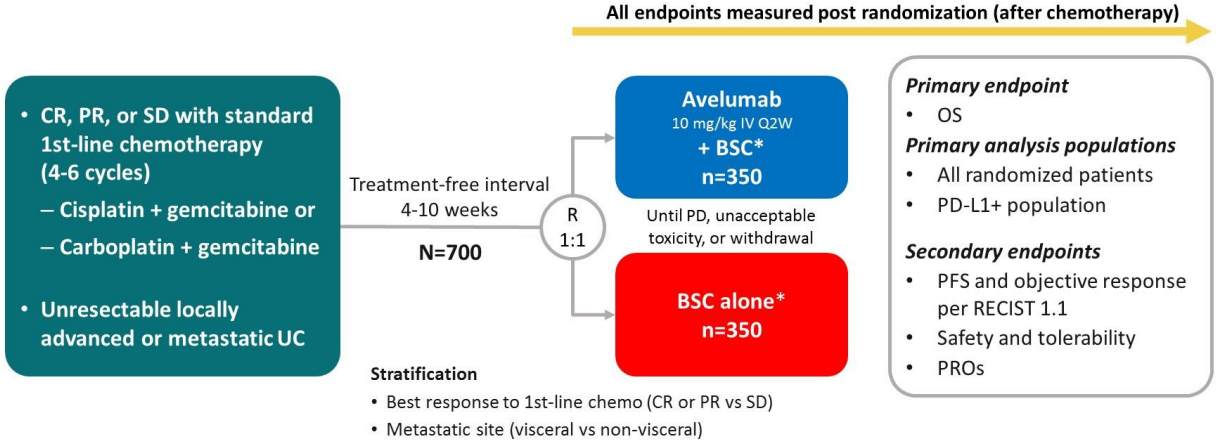
- January 2020: pembrolizumab approved for BCG-unresponsive, high-risk NMIBC with CIS with or without papillary tumors




- n=148, but BCG-unresponsive CIS: n=96
- CR: 41%
- 46% of CRs ≥ 12 months
- median DOR: 16.2 months

NMIBC → BCG-refractory NMIBC/CIS → MIBC → **Advanced/ Metastatic** → Platinum-refractory → IO-refractory

# JAVELIN Bladder 100 study design (NCT02603432)

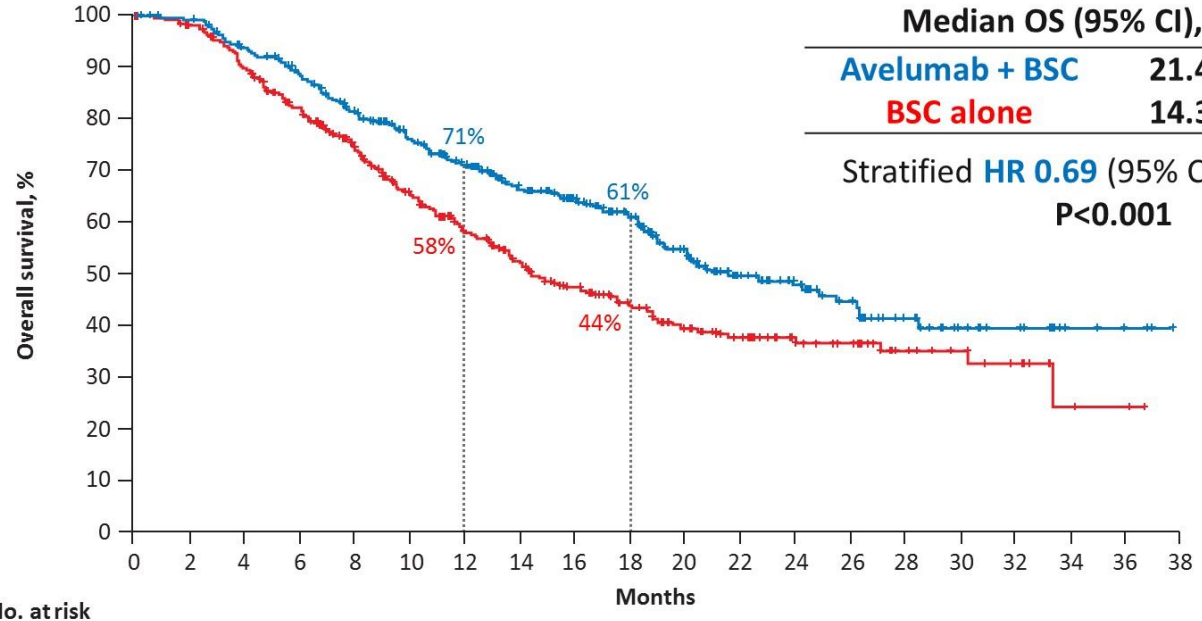



PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

**BSC**, best supportive care; **CR,** complete response; **IV,** intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W,** every 2 weeks; **R**, randomization; **RECIST 1.1,** Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

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

# OS in the overall population

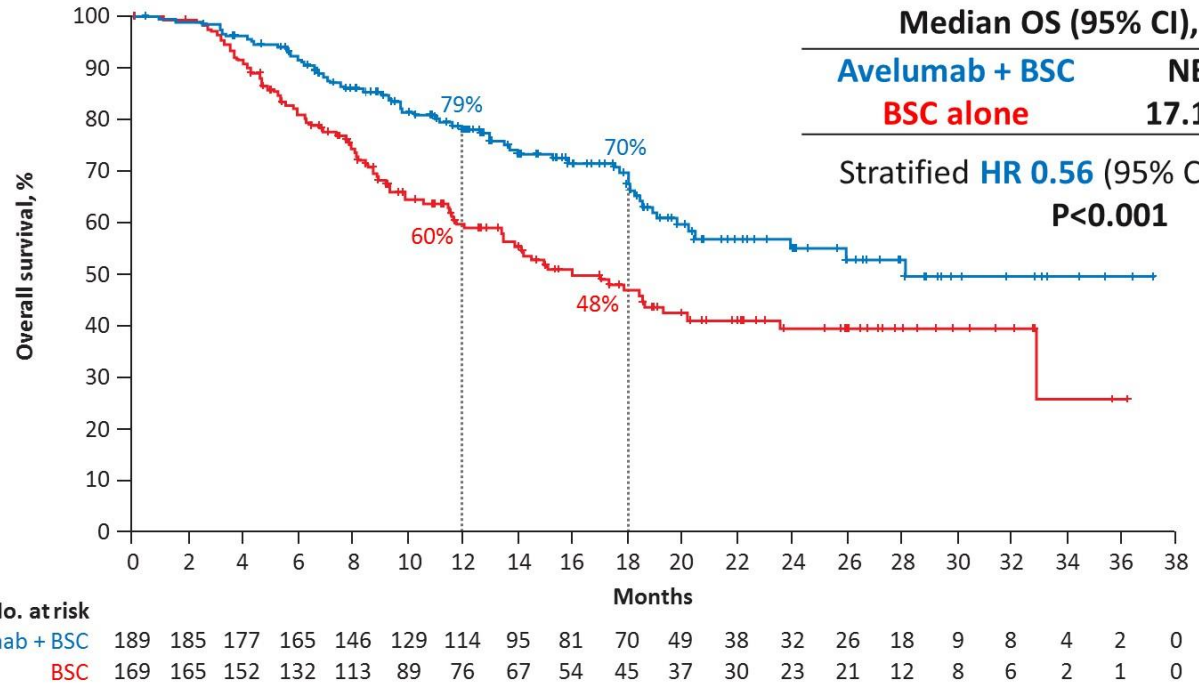



| Median OS (95% CI), months | |
|---|---|
| Avelumab + BSC | **21.4** (18.9, 26.1) |
| BSC alone | **14.3** (12.9, 17.9) |

Stratified **HR 0.69** (95% CI, 0.56, 0.86)
**P<0.001**

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

# OS in the PD-L1+ population



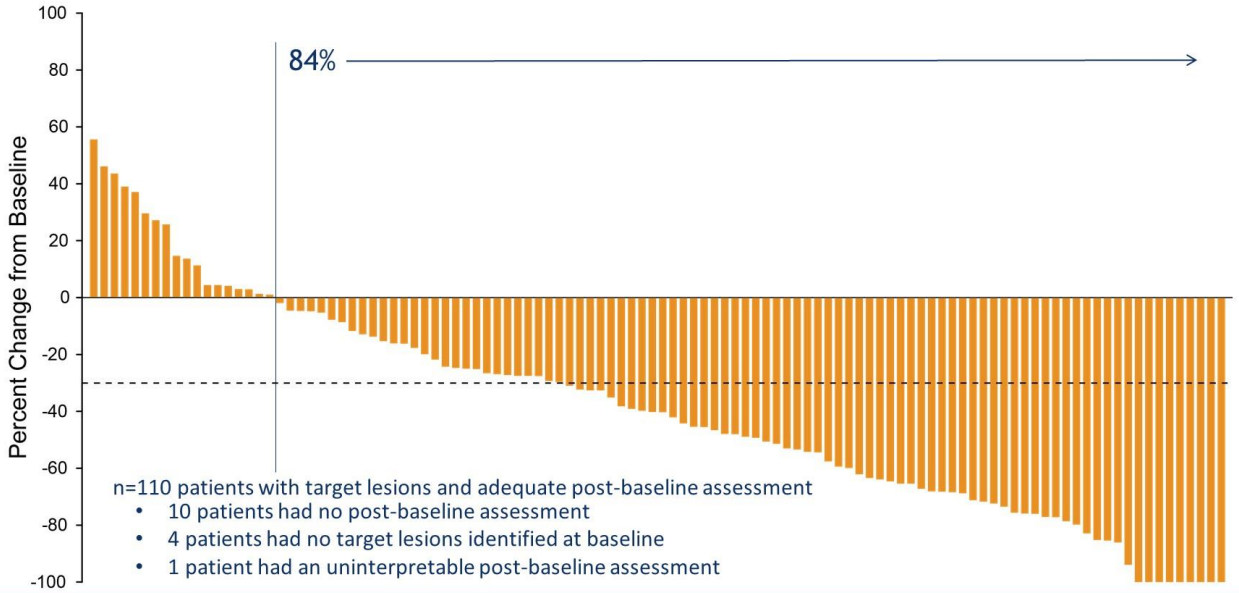

| Median OS (95% CI), months | |
|---|---|
| Avelumab + BSC | **NE** (20.3, NE) |
| BSC alone | **17.1** (13.5, 23.7) |

Stratified **HR 0.56** (95% CI, 0.40, 0.79)
**P<0.001**

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable

NMIBC → BCG-refractory NMIBC/CIS → MIBC → Advanced/ Metastatic → **Platinum-refractory** → **IO-refractory**

## EV-201: Cohort 1 Change in Tumor Measurements per BICR



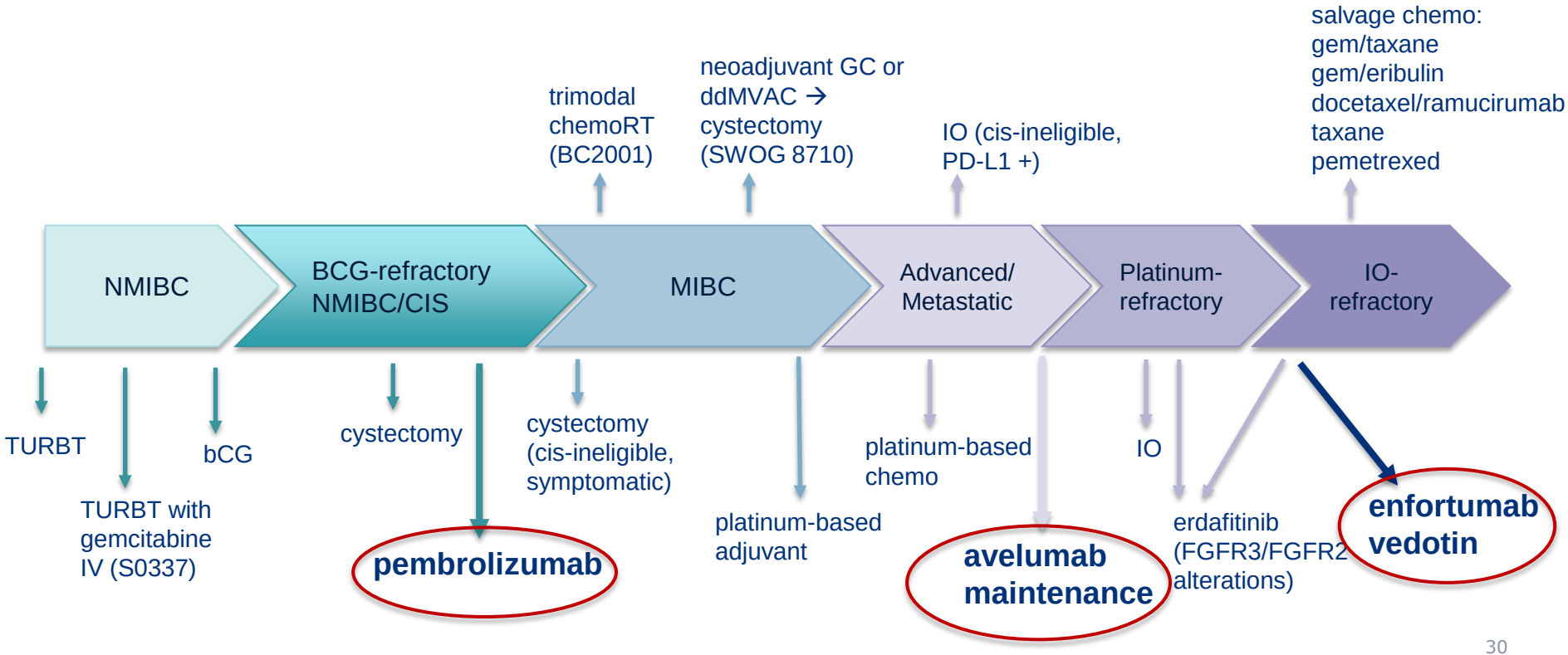

ORR: 44% (35.1-53.2)
CR: 12%
PR: 32%
SD: 28%

**Updated median OS (ESMO 2020): 12.4 months**

# Enfortumab vedotin (Nectin 4 ADC)

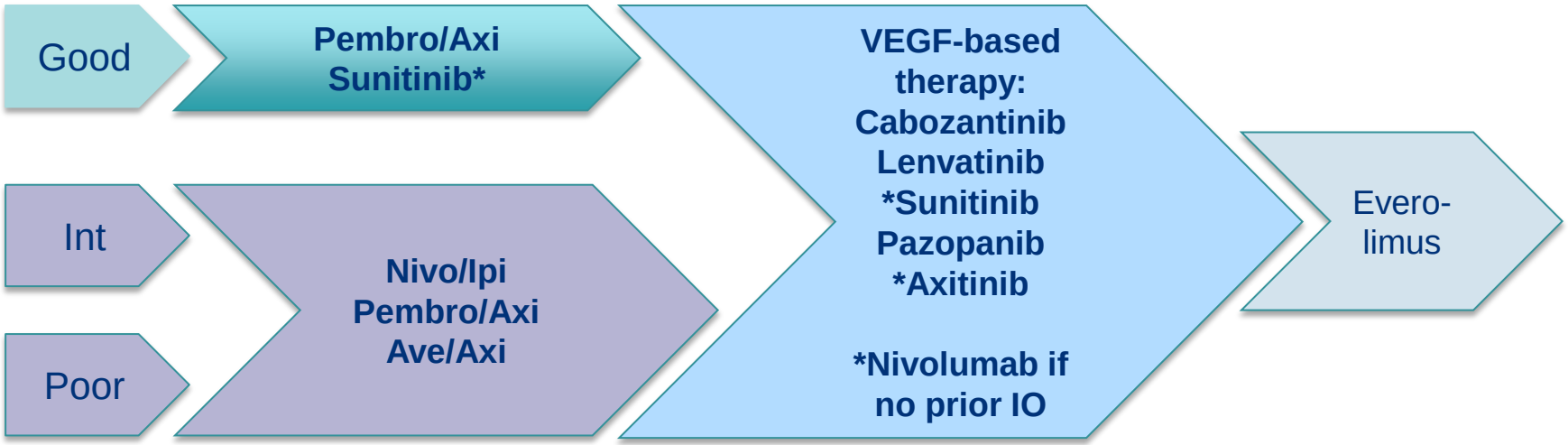
- December 2019 - Accelerated FDA Approval
- EV-301: randomized, Phase III trial of enfortumab vedotin vs chemotherapy (docetaxel, paclitaxel, vinflunine)
  - Stopped early due to positive results at planned interim
  - OS HR= 0.70 (95% CI: 0.56, 0.89; p=0.001)
  - PFS HR= 0.61 (95% CI: 0.50,0.75; p<0.00001)
- EV-201 Cohort 2 (prior IO, platinum-naive): 52% ORR

# Current Bladder Cancer Treatment Paradigm



# Renal Cell Carcinoma

# Treatment of Metastatic RCC

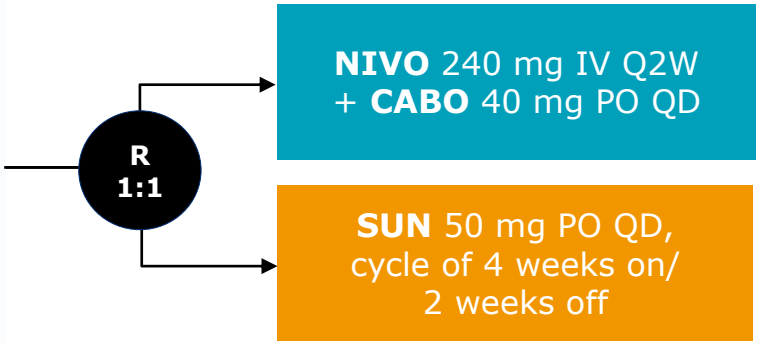


# CheckMate 9ER Study Design

**N = 651**

**Key inclusion criteria**[1,2]

- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group




*Treat until RECIST v1.1–defined progression or unacceptable toxicity*[b]

**Median study follow-up,** 18.1 months (range, 10.6–30.6 months)

**Primary endpoint**: PFS

**Secondary endpoints:** OS, ORR, and safety

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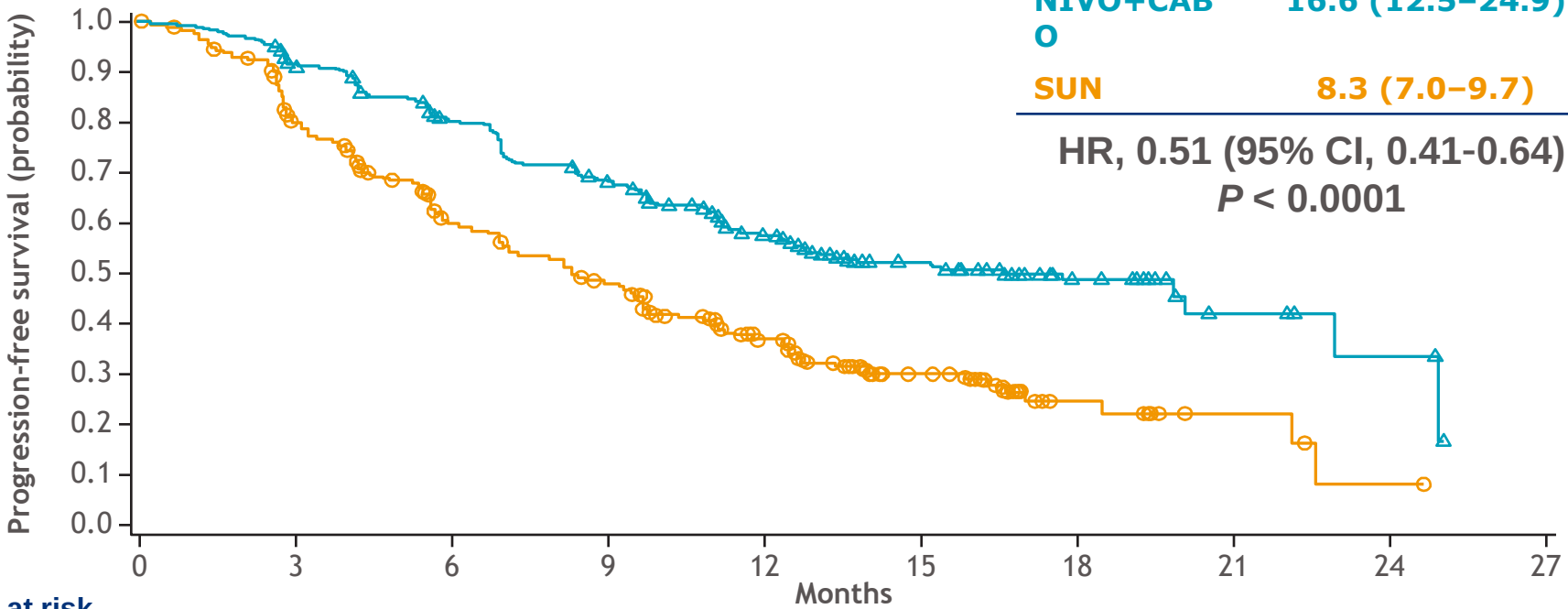
# Progression-free survival per BICR

| Median PFS, months (95% CI) | |
|---|---|
| NIVO+CABO | 16.6 (12.5–24.9) |
| SUN | 8.3 (7.0–9.7) |

HR, 0.51 (95% CI, 0.41-0.64)
*P* < 0.0001

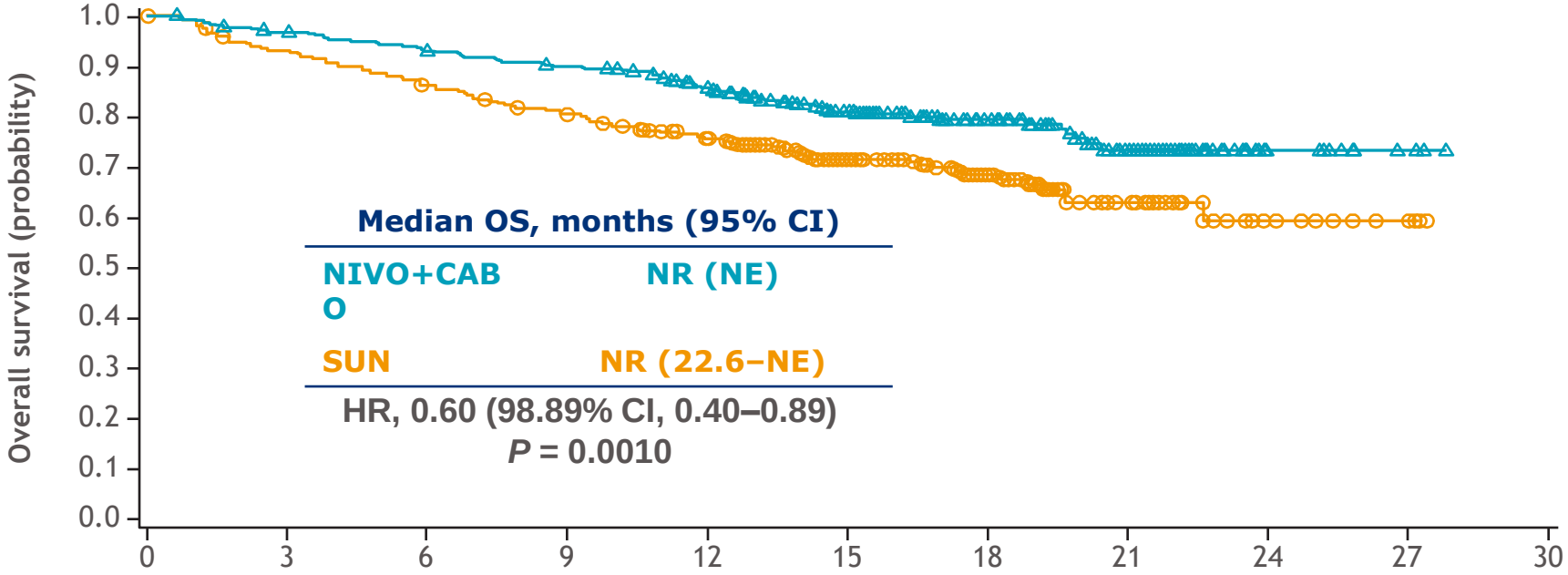



**No. at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| NIVO+CABO | 323 | 279 | 234 | 196 | 144 | 77 | 35 | 11 | 4 | 0 |
| SUN | 328 | 228 | 159 | 122 | 79 | 31 | 10 | 4 | 1 | 0 |

Minimum study follow-up, 10.6 months.

# Overall survival




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO+CABO | 323 | 308 | 295 | 283 | 259 | 184 | 106 | 55 | 11 | 3 | 0 |
| SUN | 328 | 296 | 273 | 253 | 223 | 154 | 83 | 36 | 10 | 3 | 0 |

Minimum study follow-up, 10.6 months.
NE, not estimable; NR, not reached.

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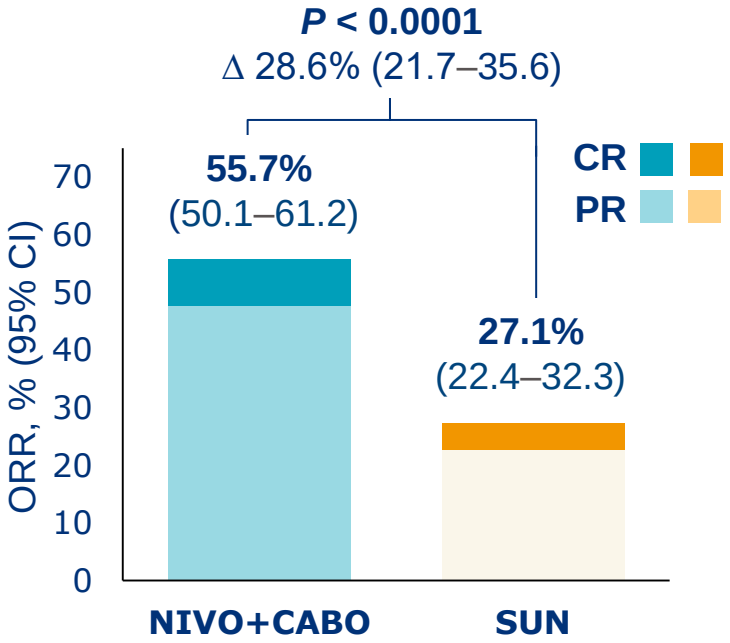
# Objective response and best overall response per BICR



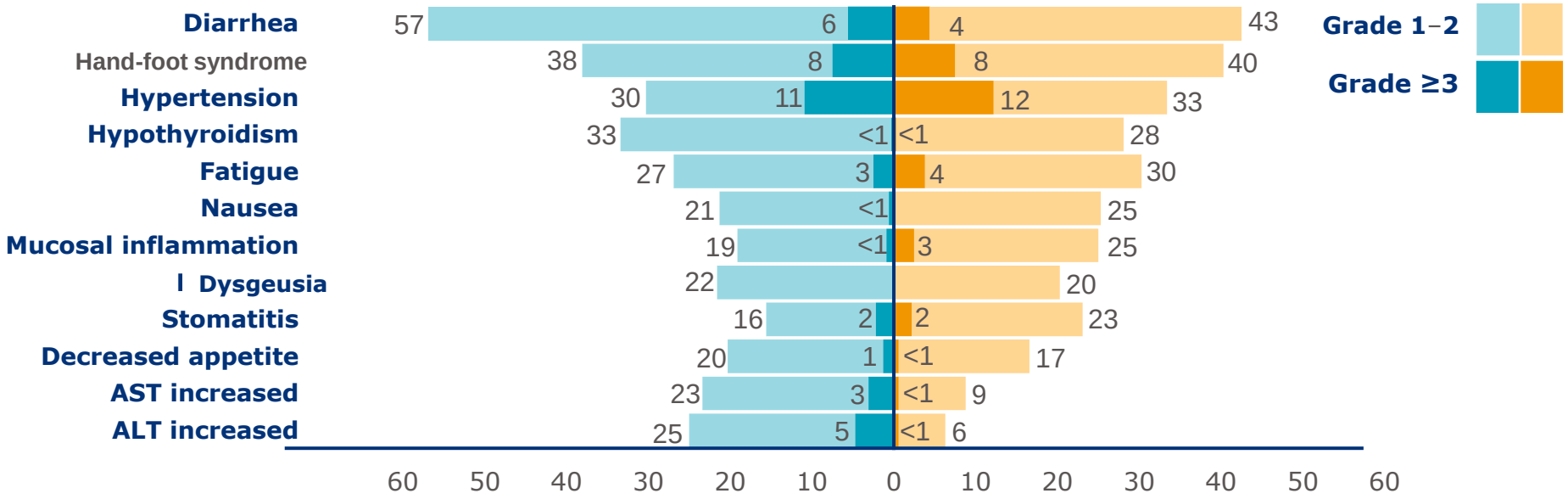

| Outcome, % | NIVO+CABO (n = 323) | SUN (n = 328) |
|---|---|---|
| **Complete response** | 8.0 | 4.6 |
| **Partial response** | 47.7 | 22.6 |
| **Stable disease** | 32.2 | 42.1 |
| **Progressive disease** | 5.6 | 13.7 |
| **Not evaluable/not assessed[a]** | 6.5 | 17.1 |
| **Median time to response (range), months[b]** | 2.8 (1.0–19.4) | 4.2 (1.7–12.3) |
| **Median duration of response (95% CI), months[b]** | 20.2 (17.3–NE) | 11.5 (8.3–18.4) |

- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥ 1% vs < 1%), and bone metastases

**NIVO+CABO, n = 320** **SUN, n = 320**

**Treatment-related AEs occurring in ≥20% of treated patients, %[b]**

| Events, %[a] | Any grade | Grade ≥ 3 | Any grade | Grade ≥ 3 |
|---|---|---|---|---|
| All-cause AEs | 100 | 75 | 99 | 71 |
| Treatment-related AEs | 97 | 61 | 93 | 51 |

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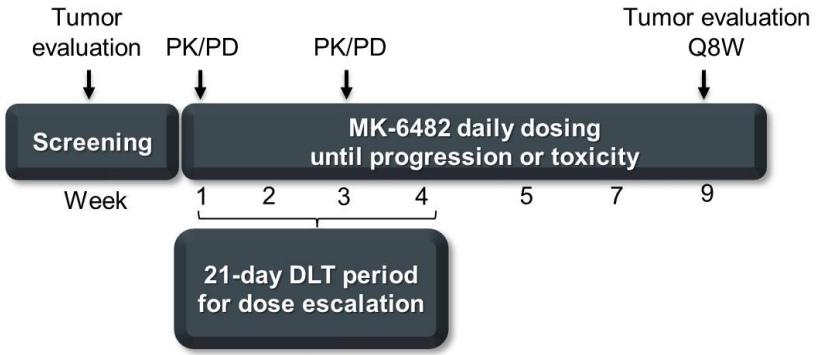
# MK-6482- oral HIF-2α antagonist, Phase I/II study

## Study Design (NCT02974738)




- Dose-escalation cohort for patients with advanced solid tumors
- Dose-expansion cohort for patients with advanced ccRCC who previously received ≥1 therapy
  - Key end points: Safety, ORR, duration of response, PFS

- Dose of 120 mg QD selected for further clinical development from the dose-escalation cohort
- **55 patients with previously treated advanced ccRCC enrolled at 120 mg PO QD in the dose-expansion cohort**
  - 39 (71%) discontinued
    - Most common reason was disease progression: 55%
  - 16 (29%) have treatment ongoing
- Median (95%CI) follow-up:
  - 13.0 (11.0-13.8) months

Data cutoff: May 15, 2019.

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# Baseline Clinical Characteristics

| Characteristics | All Patients N = 55 | IMDC Risk Category | | |
|---|---|---|---|---|
| | | Favorable n = 5 | Intermediate n = 40 | Poor n = 10 |
| Age, median (range), years | 62 (39-75) | 61 (50-71) | 62 (39-75) | 59 (41-75) |
| Sex, n (%) | | | | |
| Female | 11 (20) | 3 (60) | 7 (18) | 1 (10) |
| Male | 44 (80) | 2 (40) | 33 (82) | 9 (90) |
| Prior systemic therapies, median (range), n | 3 (1-9) | 3 (1-5) | 3 (1-6) | 3 (2-9) |
| Prior systemic therapies, n (%) | | | | |
| 1 | 9 (16) | 1 (20) | 8 (20) | 0 (0) |
| 2 | 12 (22) | 1 (20) | 9 (23) | 2 (20) |
| ≥3 | 34 (62) | 3 (60) | 23 (58) | 8 (80) |
| Prior anticancer therapies, n (%) | | | | |
| VEGF/VEGFR | 51 (93) | 5 (100) | 36 (90) | 10 (100) |
| Immune checkpoint inhibitor | 40 (73) | 3 (60) | 29 (73) | 8 (80) |
| Investigational/other | 15 (27) | 2 (40) | 10 (25) | 3 (30) |
| mTOR inhibitor | 12 (22) | 1 (20) | 8 (20) | 3 (30) |
| Cytokine | 7 (13) | 0 (0) | 4 (10) | 3 (30) |

- 37 patients (67%) received anti–PD-1 and anti–VEGF agents

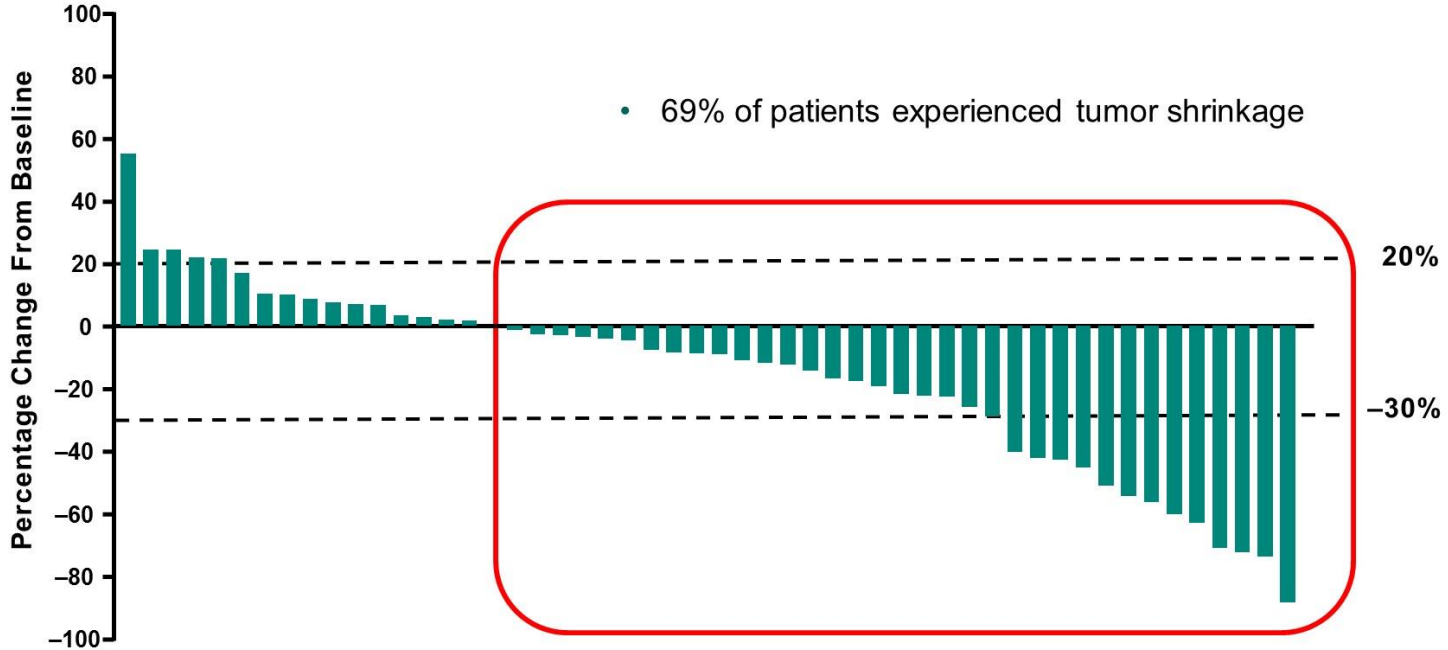
Data cutoff: May 15, 2019.

# Best Confirmed Objective Response by RECIST v1.1 per Investigator Assessment

| Efficacy Parameter, n (%) [95%CI] | All Patients N = 55 | IMDC Risk Category | | |
|---|---|---|---|---|
| | | Favorable n = 5 | Intermediate n = 40 | Poor n = 10 |
| **ORR** | 13 (24) [13-37] | 2 (40) | 10 (25) | 1 (10) |
| PR | 13 (24) | 2 (40) | 10 (25) | 1 (10) |
| **SD** | 31 (56) | 3 (60) | 22 (55) | 6 (60) |
| **Disease control rate (CR + PR + SD)** | 44 (80) | 5 (100) | 32 (80) | 7 (70) |
| **PD** | 9 (16) | 0 (0) | 7 (18) | 2 (20) |
| Nonevaluable | 2 (4) | 0 (0) | 1 (2) | 1 (10) |

Data cutoff: May 15, 2019.

# Maximum Change From Baseline in Target Lesions: All Patients[a]




[a]Includes patients who had a baseline and a postbaseline assessment (n = 52).
Data cutoff: May 15, 2019.

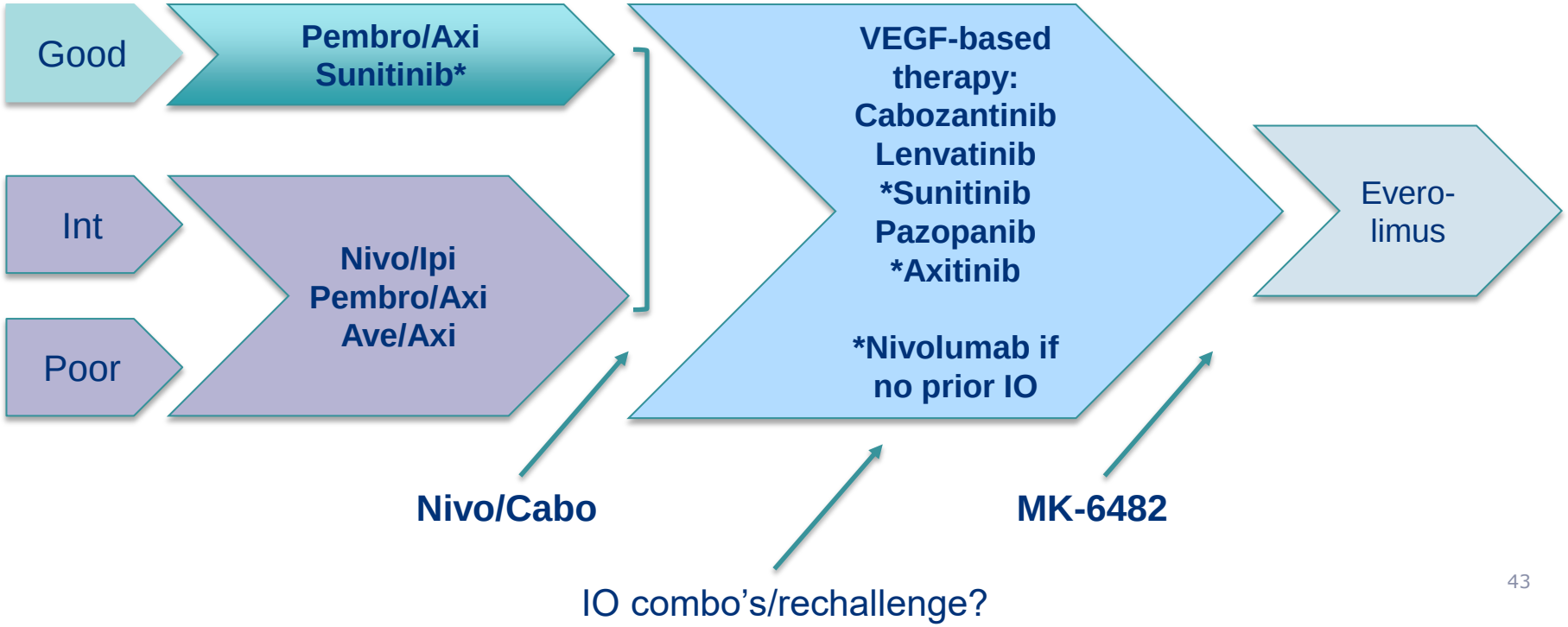
# Adverse Event Summary

| n (%) | N = 55 |
|---|---|
| All AEs | 55 (100) |
| Grade 3-5 AEs | 36 (65) |
| TRAEs | 52 (95) |
| Grade 3-5 TRAEs | 20 (36) |
| Discontinuation because of AEs | 5 (9) |
| Discontinuation because of TRAEs | 2 (4) |
| Death from AEs | 4 (7) |
| Death from TRAEs | 0 (0) |

- 2 patients (4%) experienced a total of four grade 4 AEs
  - Hypercalcemia, sepsis, cardiac arrest, and respiratory failure
- 4 patients (7%) experienced grade 5 AEs secondary to PD
  - Acute kidney injury, disease progression, malignant neoplasm progression, ventricular fibrillation
  - No patient died of a TRAE
- 2 patients (4%) discontinued after the TRAE hypoxia
- 5 patients (9%) required dose reductions to manage TRAEs

Data cutoff: May 15, 2019.

# Potential changes to Treatment of mRCC



# Questions?