



18^{as} Jornadas HITOS
ONCOLÓGICOS: LO
MEJOR
DE 2023

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Actualización en cáncer renal

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Employment: SERMAS

Honoraria for speaker engagements, advisory roles or continuous medical education: Astellas, Astra Zeneca, Janssen, MSD, Bayer, Pfizer, Eisai,

Ipsen, Sanofi, Roche, BMS, Pierre Fabre, Merck

Stock Ownership: None

Research Funding: Astellas, Pfizer

Consultant: Astellas, Roche

1st
line

| FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY | | | |
|---|--|---|--|
| Risk | Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
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More
lines

| SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY) | | | |
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| Immuno-oncology (IO) Therapy History Status | Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
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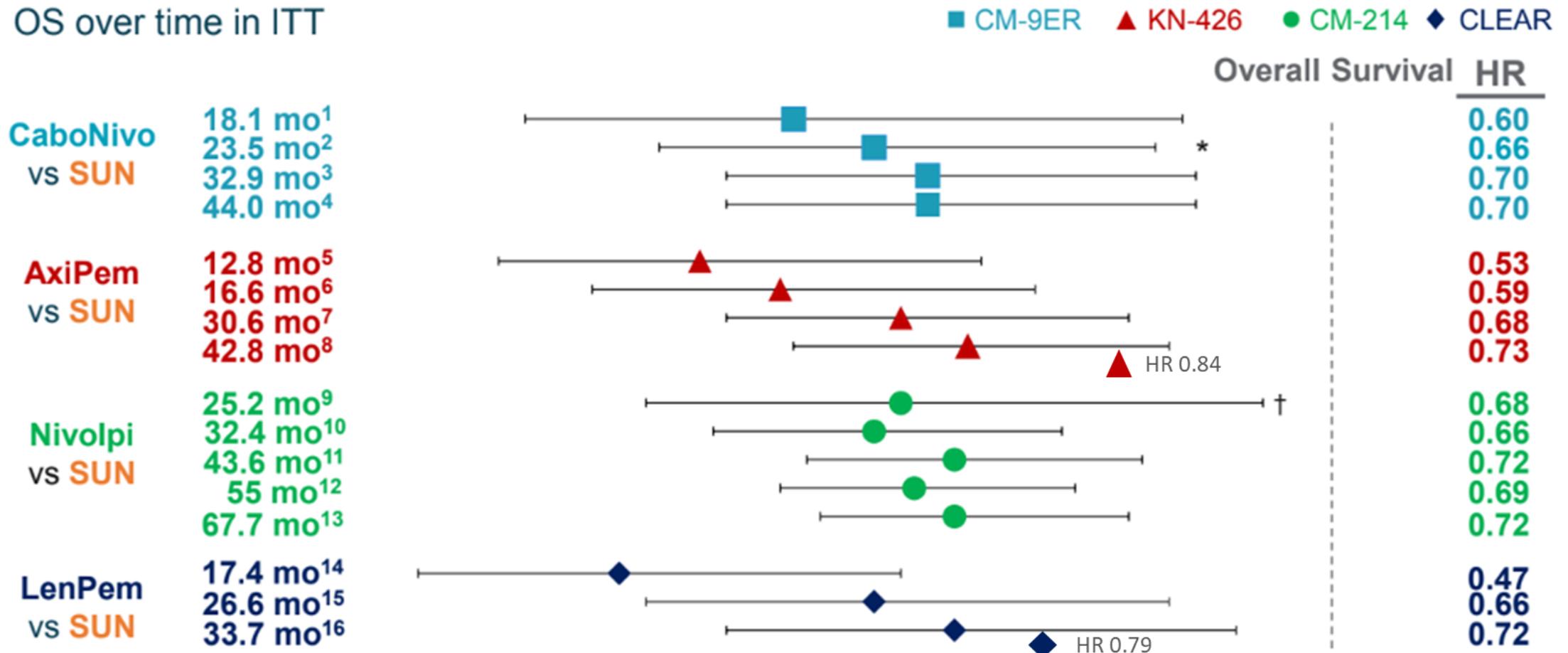
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- Is it possible discontinue treatments? (TIDE-A)
- Management of non-clear cell carcinomas: B61, triplets...

1st
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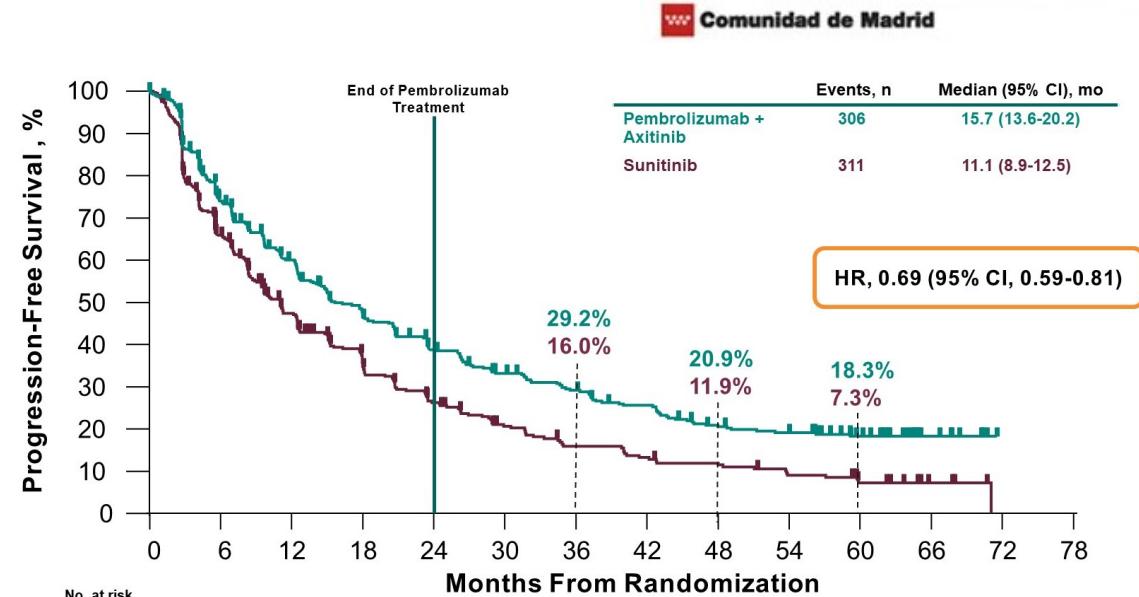
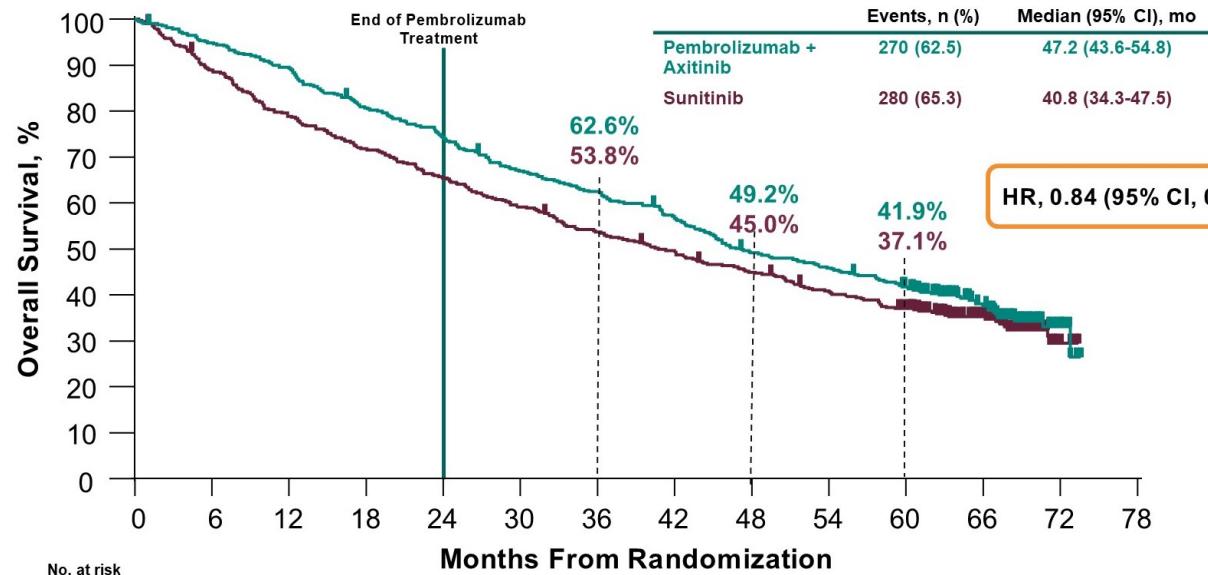
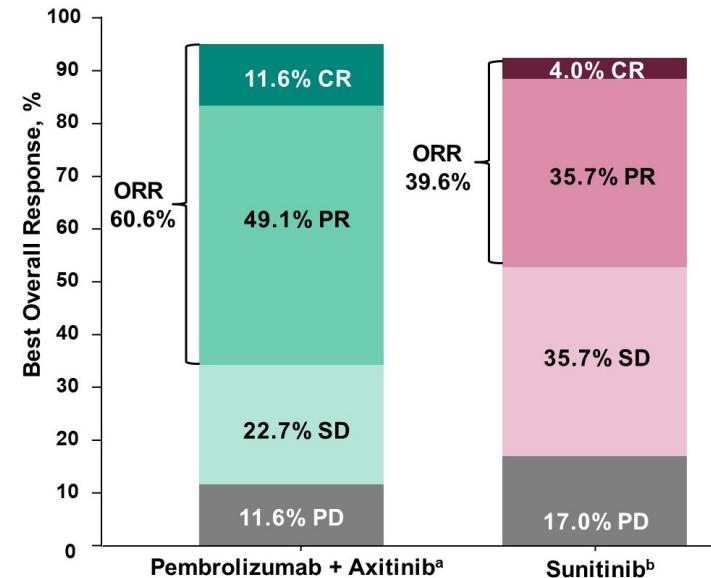
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OS over time in ITT



Keynote-426: results with 67 months FU

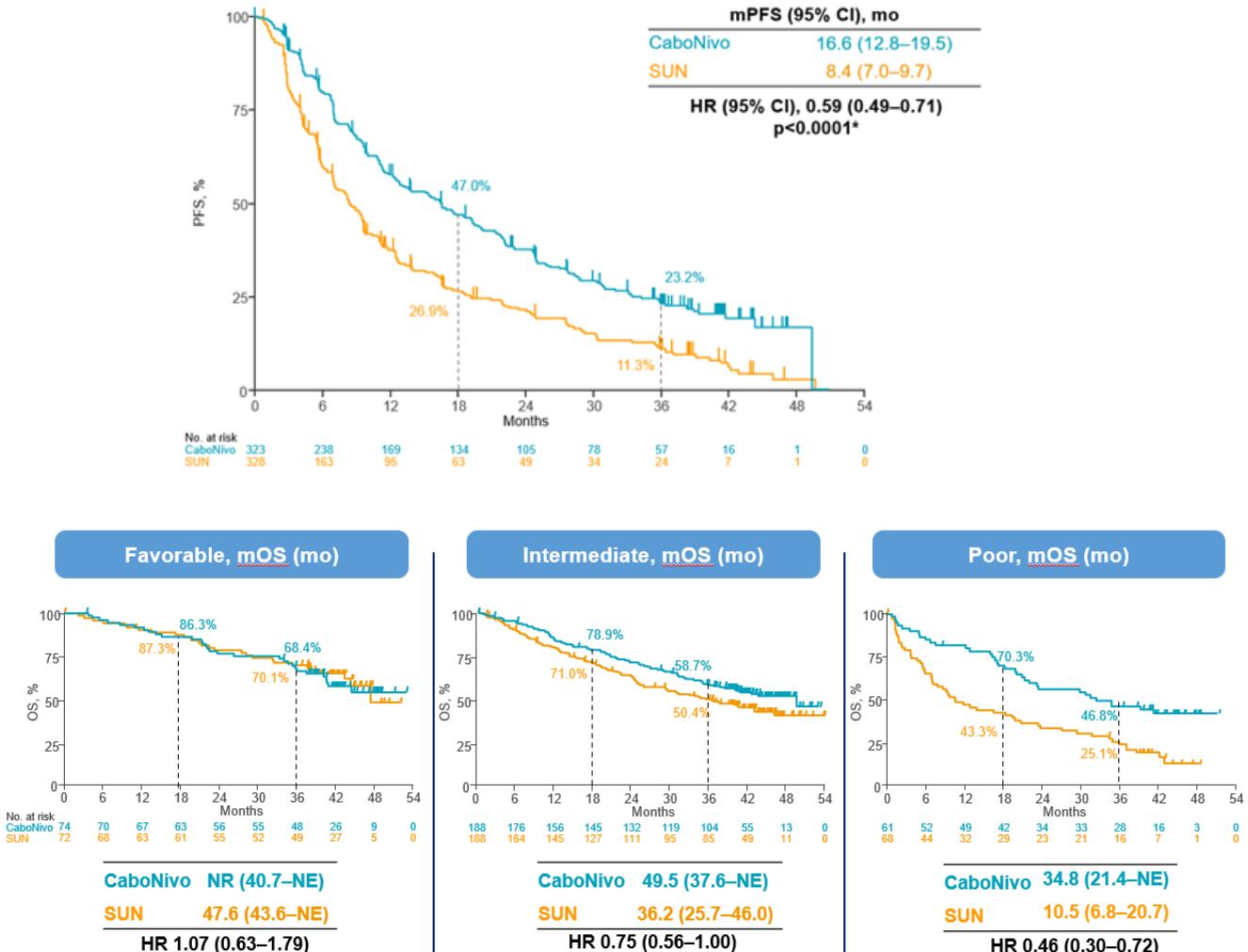
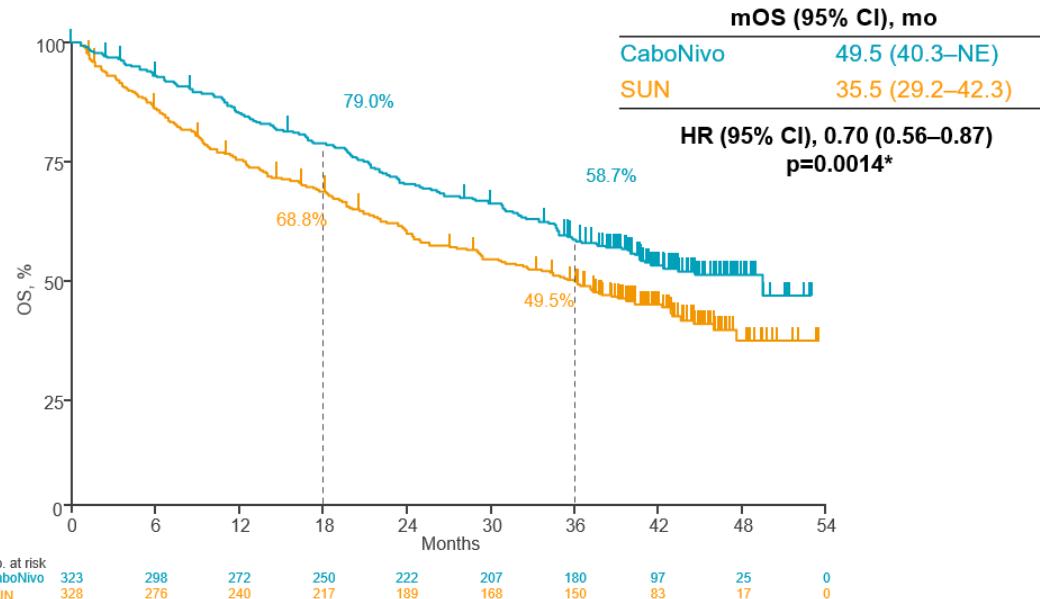


| | Pembrolizumab + Axitinib n = 429 | Sunitinib n = 425 |
|--|-------------------------------------|----------------------|
| Any adverse event | 422 (98.4) | 425 (100) |
| Treatment-related adverse event | 413 (96.3) | 415 (97.6) |
| Grade 3-5 treatment-related adverse event | 291 (67.8) | 270 (63.5) |
| Serious treatment-related adverse event | 126 (29.4) | 69 (16.2) |
| Discontinuation of any drug because of a treatment-related adverse event | 143 (33.3) | 58 (13.6) |
| Death from treatment-related adverse event | 5 (1.2) | 6 (1.4) |

Check-Mate 9ER: results with 44 months FU

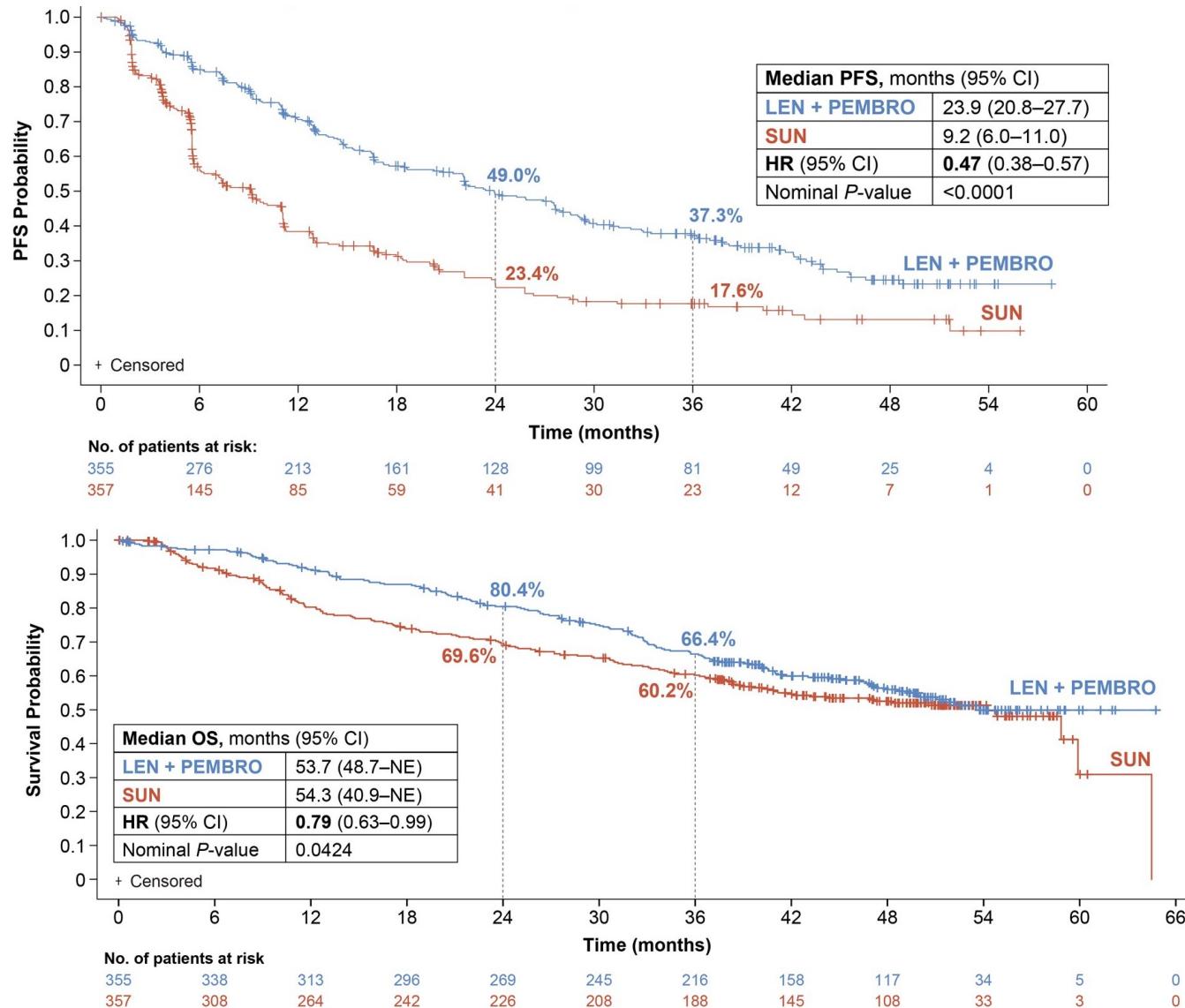
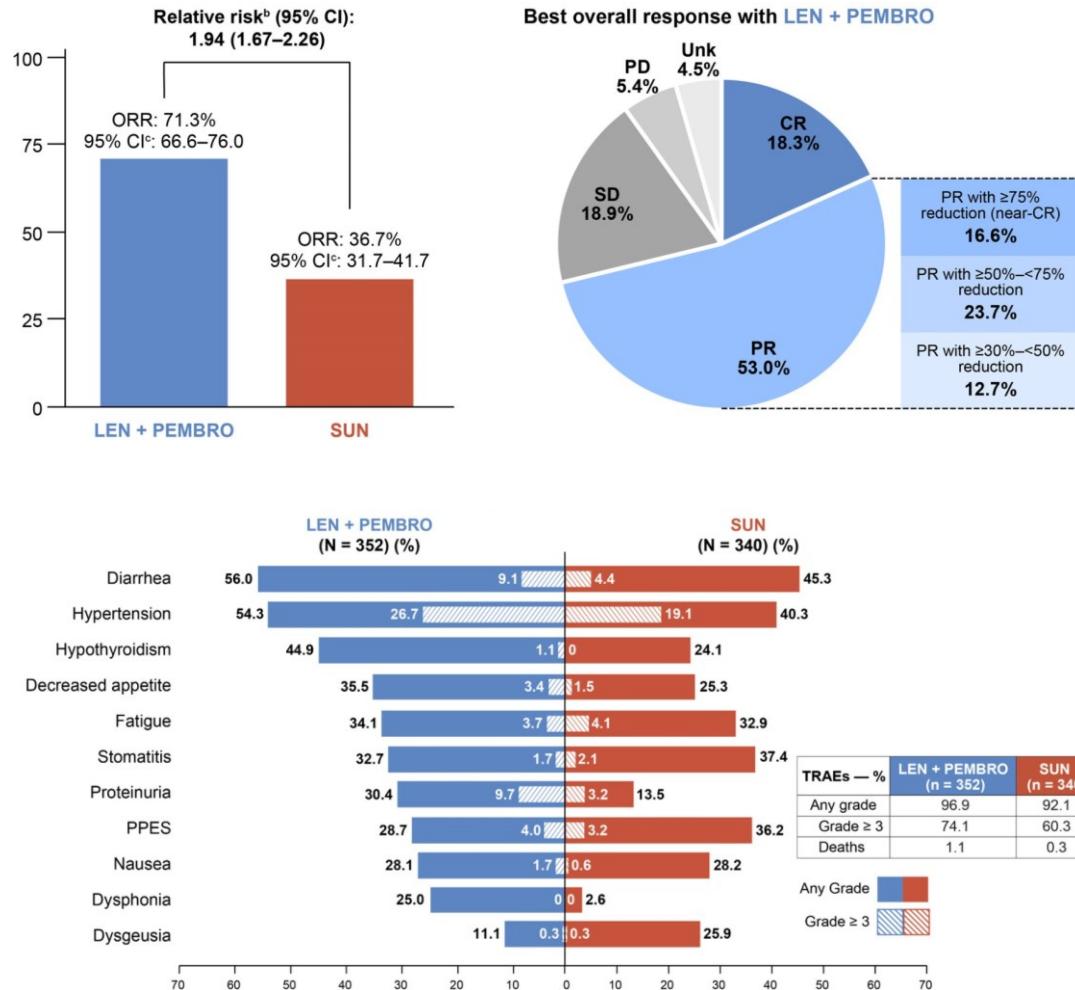
ITT POPULATION

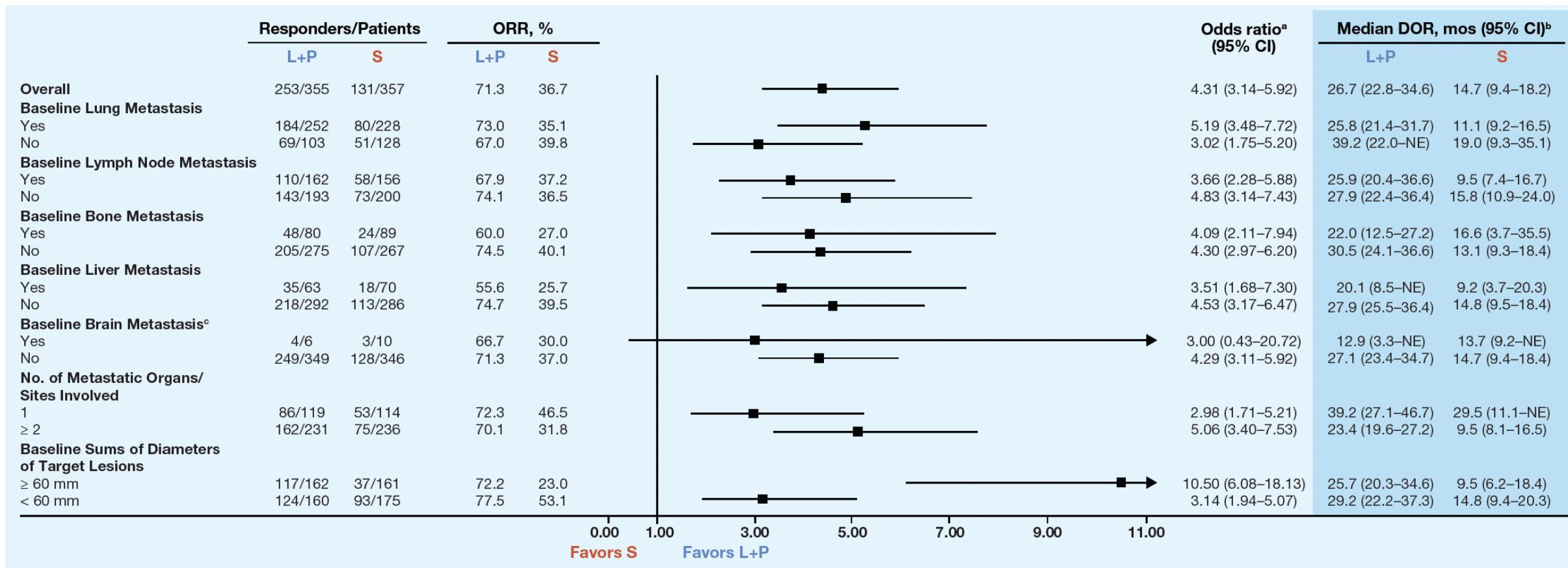
| | CaboNivo (N=323) | SUN (N=328) |
|---|---------------------|------------------|
| ORR (95% CI), % | 56.0 (50.4–61.5) | 28.0 (23.3–33.2) |
| Odds ratio estimate (95% CI) | 3.4 (2.4–4.7) | |
| Complete response, n (%) | 43 (13.3) | 16 (4.9) |
| Partial response, n (%) | 138 (42.7) | 76 (23.2) |
| Stable disease, n (%) | 103 (31.9) | 135 (41.2) |
| Progressive disease, n (%) | 21 (6.5) | 46 (14.0) |
| UTD/not reported, n (%)* | 18 (5.6) | 55 (16.8) |
| Median time to response (range), mo† | 2.8 (1.0–24.4) | 4.3 (1.7–30.4) |
| Median duration of response (95% CI), mo‡ | 22.1 (18.0–26.0) | 16.1 (11.1–19.4) |



Intermediate/Poor mOS (mo): CaboNivo 49.5 (34.9–NE) vs SUN 29.2 (23.7–36.0) [HR (95% CI), 0.65 (0.51–0.83)]*

CLEAR: results with 4 years FU





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- Updates on phase 3 studies (CLEAR, KN-426)

- Is it possible discontinue treatments? (TIDE-A)

- Management of non-clear cell carcinomas: B61, triplets...

TIDE-A Study design:

75 Patients

- Clear cell RCC;
- Measurable disease;
- ECOG 0-1;
- No primary tumor;
- No bulky/symptomatic disease;
- No liver metastases.

36 weeks of

Avelumab 800 mg IV Q2W
Axitinib 5mg PO BID

24 weeks of

CR/PR

Avelumab 800 mg IV Q2W
(axitinib interruption)

PD

Tumor evaluation at W36

SD

Avelumab 800 mg IV Q2W
Axitinib 5mg PO BID

STOP

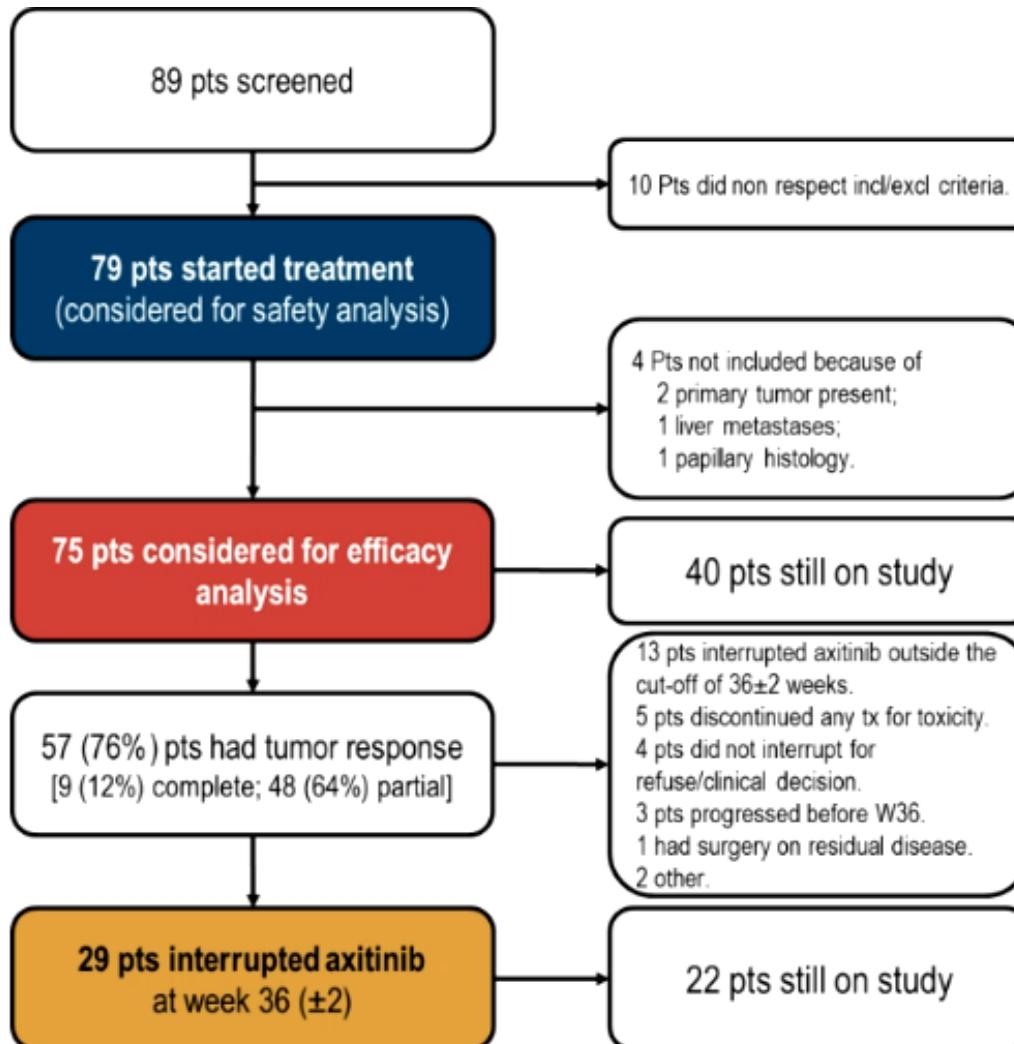
PD



Primary endpoint: The rate of patients free of progression after 8 weeks from axitinib discontinuation (W36±2).

Secondary endpoints: mPFS, mOS, ORR and safety by local evaluation.

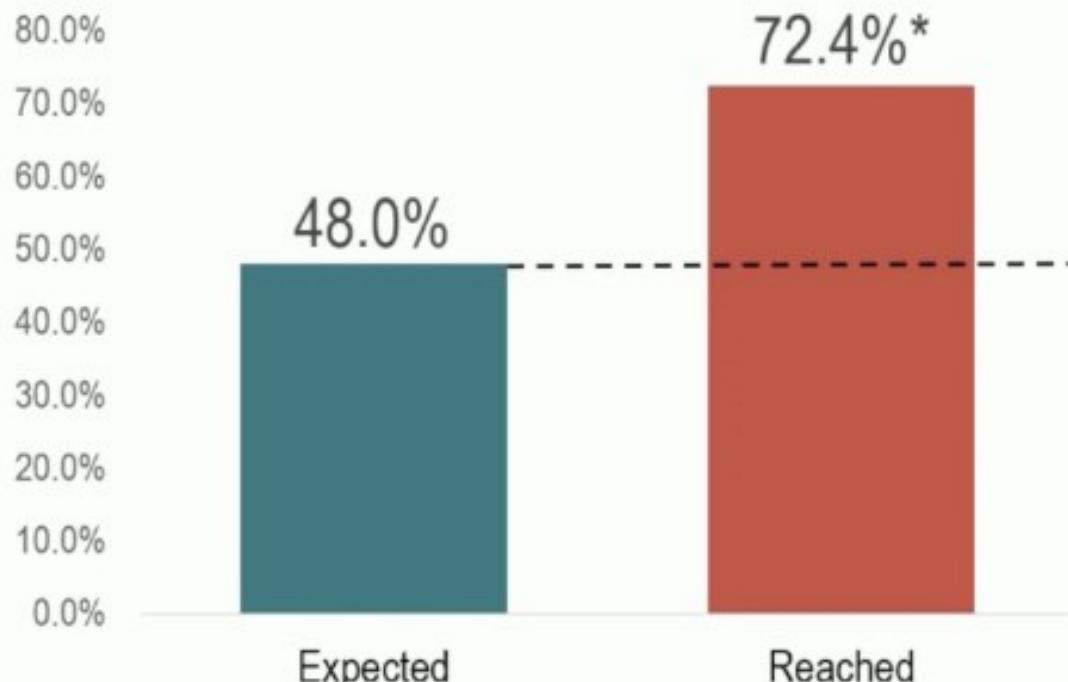
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| Baseline characteristics | Patients N=75 (%) |
|----------------------------|-------------------|
| Median age (min-max) | 64 (42-84) |
| Male sex | 49 (65.3%) |
| Nephrectomy | 75 (100%) |
| Interval from Nx to Tx <1y | 31 (41.3%) |
| Sites of metastases | |
| Lung | 43 (57.3%) |
| Lymph nodes | 31 (41.3%) |
| Pancreas | 16 (21.3%) |
| Bone | 11 (14.7%) |
| Kidney bed | 11 (14.7%) |
| Soft tissue | 11 (14.7%) |
| IMDC prognostic class | |
| Favorable | 30 (40.0%) |
| Intermediate | 43 (57.3%) |
| Poor | 2 (2.7%) |
| ECOG performance status | |
| 0 | 60 (80.0%) |
| 1 | 15 (20.0%) |

Primary endpoint:

Rate of patients free of progression after 8 weeks from axitinib interruption:



Considering the first 22 patients who discontinued axitinib, 14 patients were free from PD at week 8.

The primary endpoint was met.

Patients enrolled (full criteria): 75.

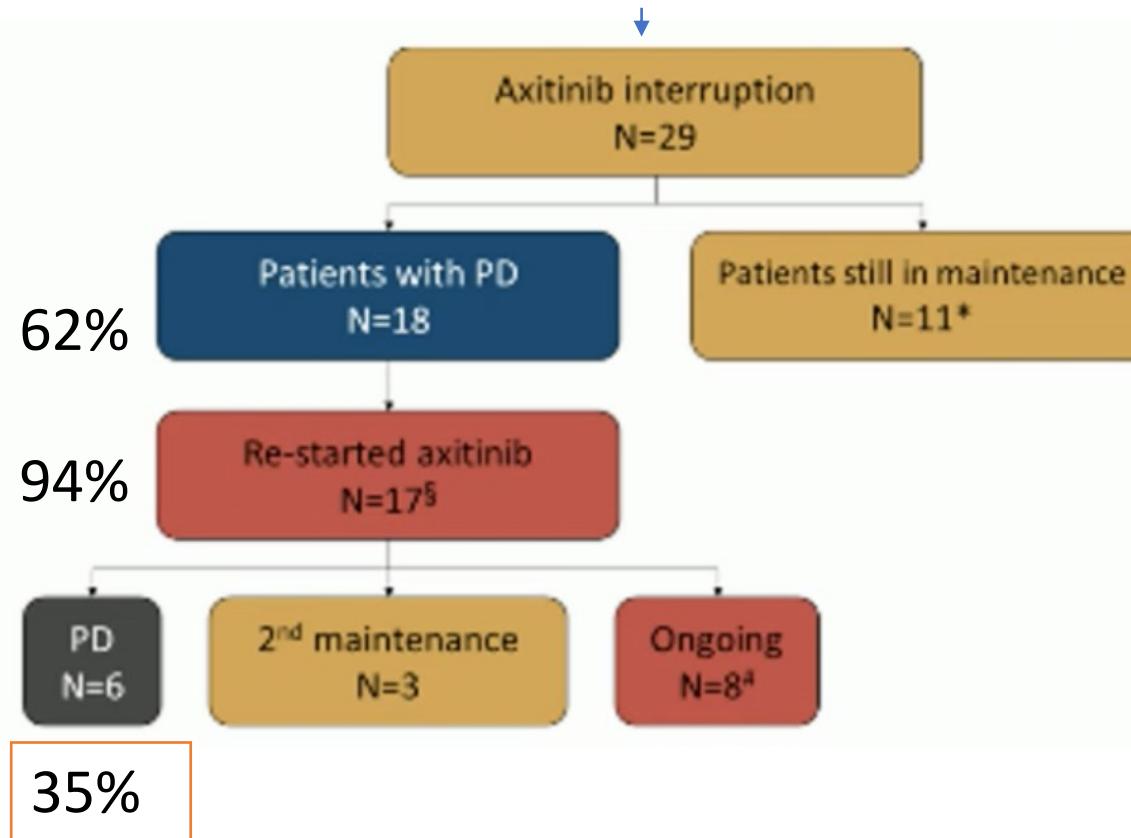
Patients who interrupted axitinib at week 36 (± 2): 29 (38.2%).

Patients with progression within 8 weeks from axitinib discontinuation:

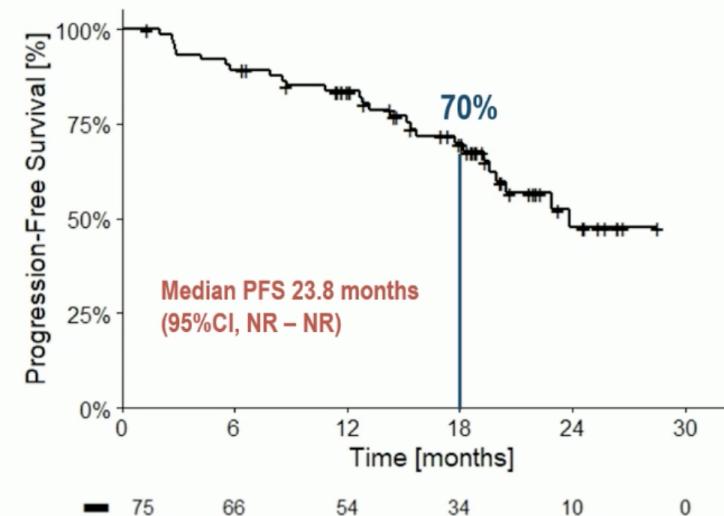
* Evaluated in all 29 patients who interrupted axitinib at week 36.

Comunidad de Madrid

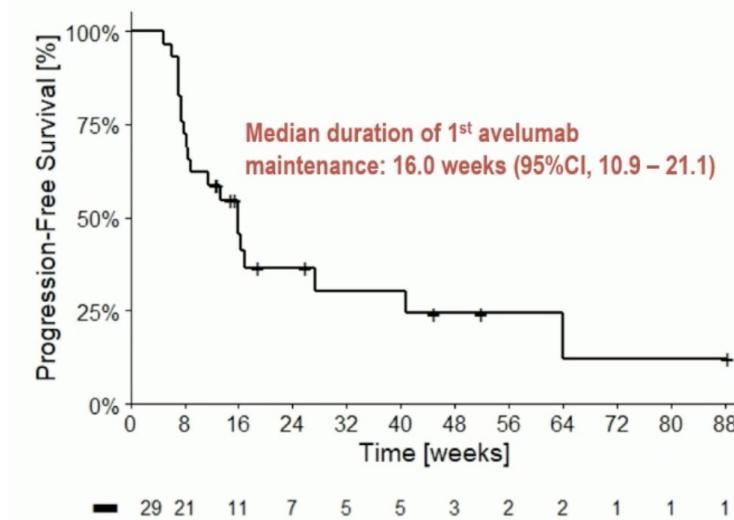
59 patients CR/PR



PFS and OS in the overall population:



Duration of 1st avelumab maintenance

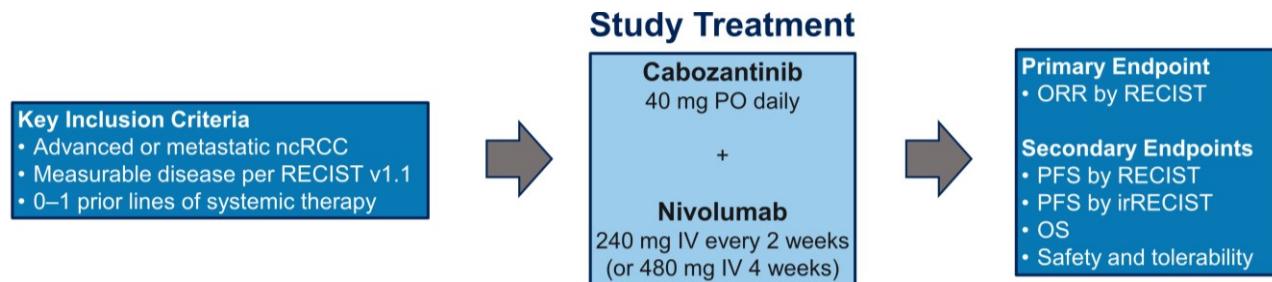


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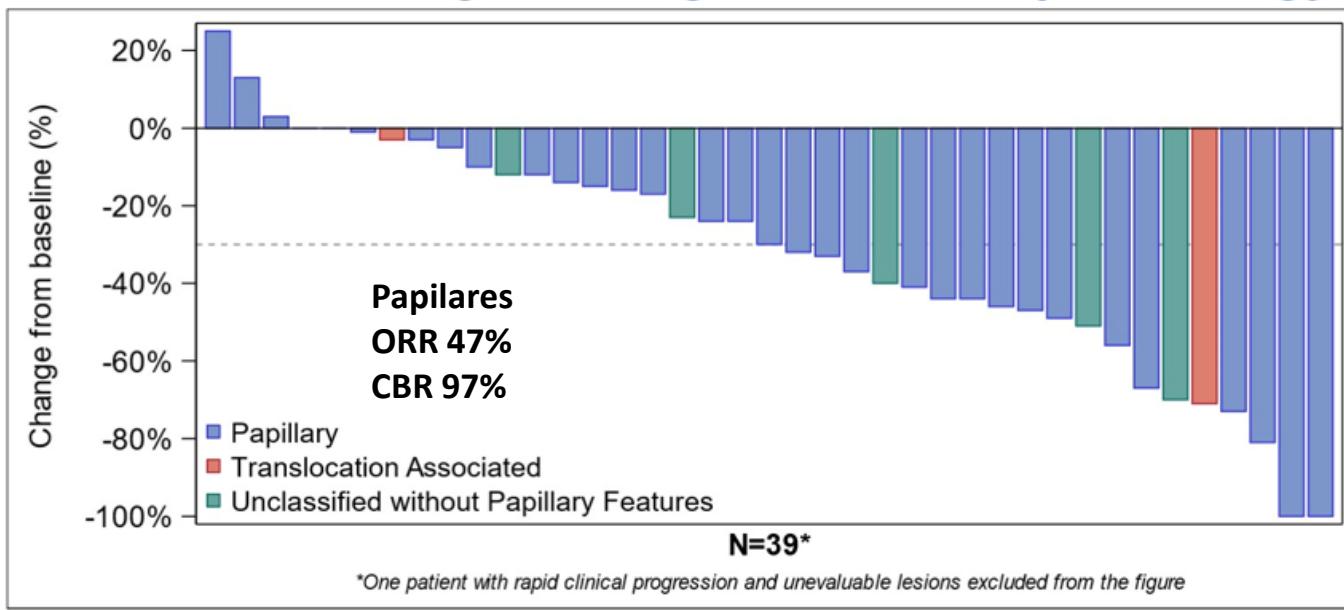
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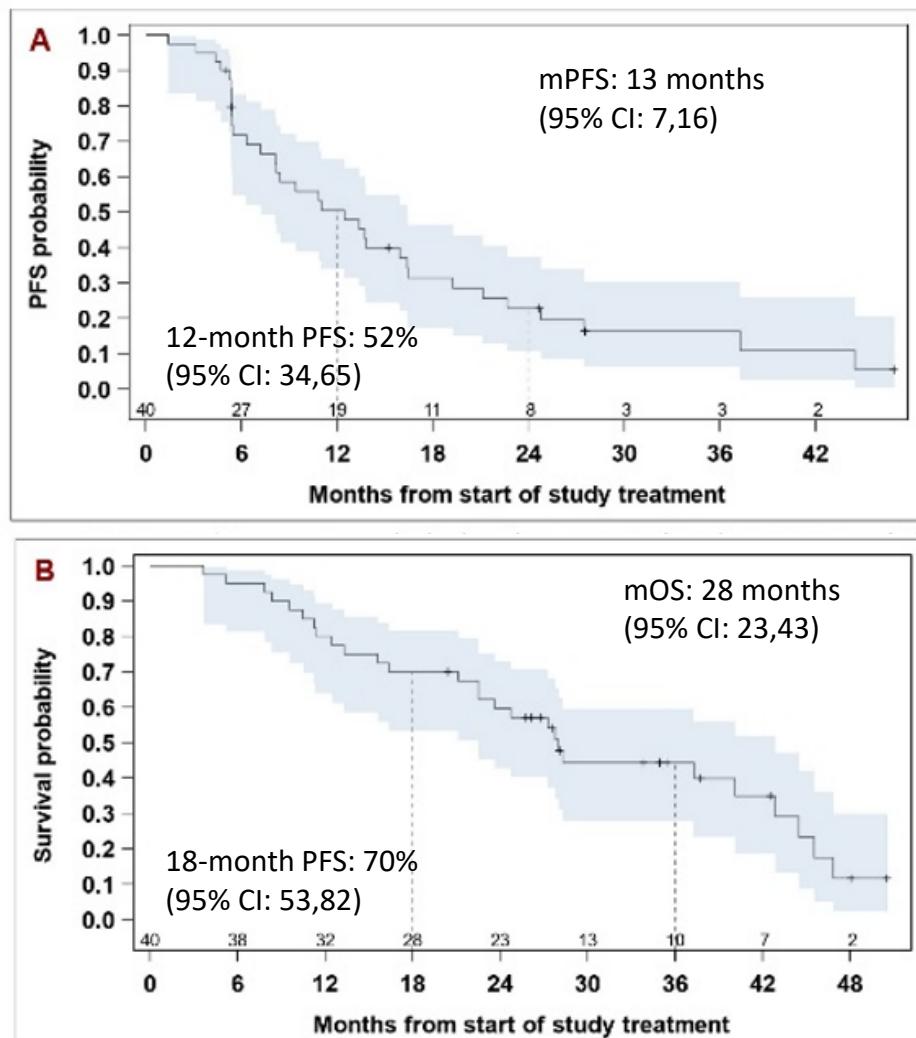
Cabozantinib-Nivolumab nccRCC



Maximum Change in Target Lesions by Histology

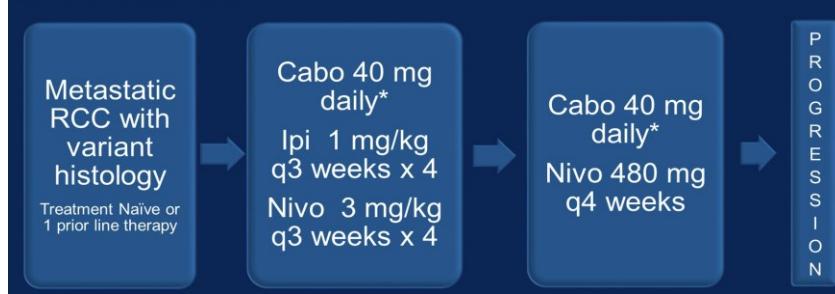


Progression-Free Survival by RECIST and Overall Survival for the 40-patient Cohort

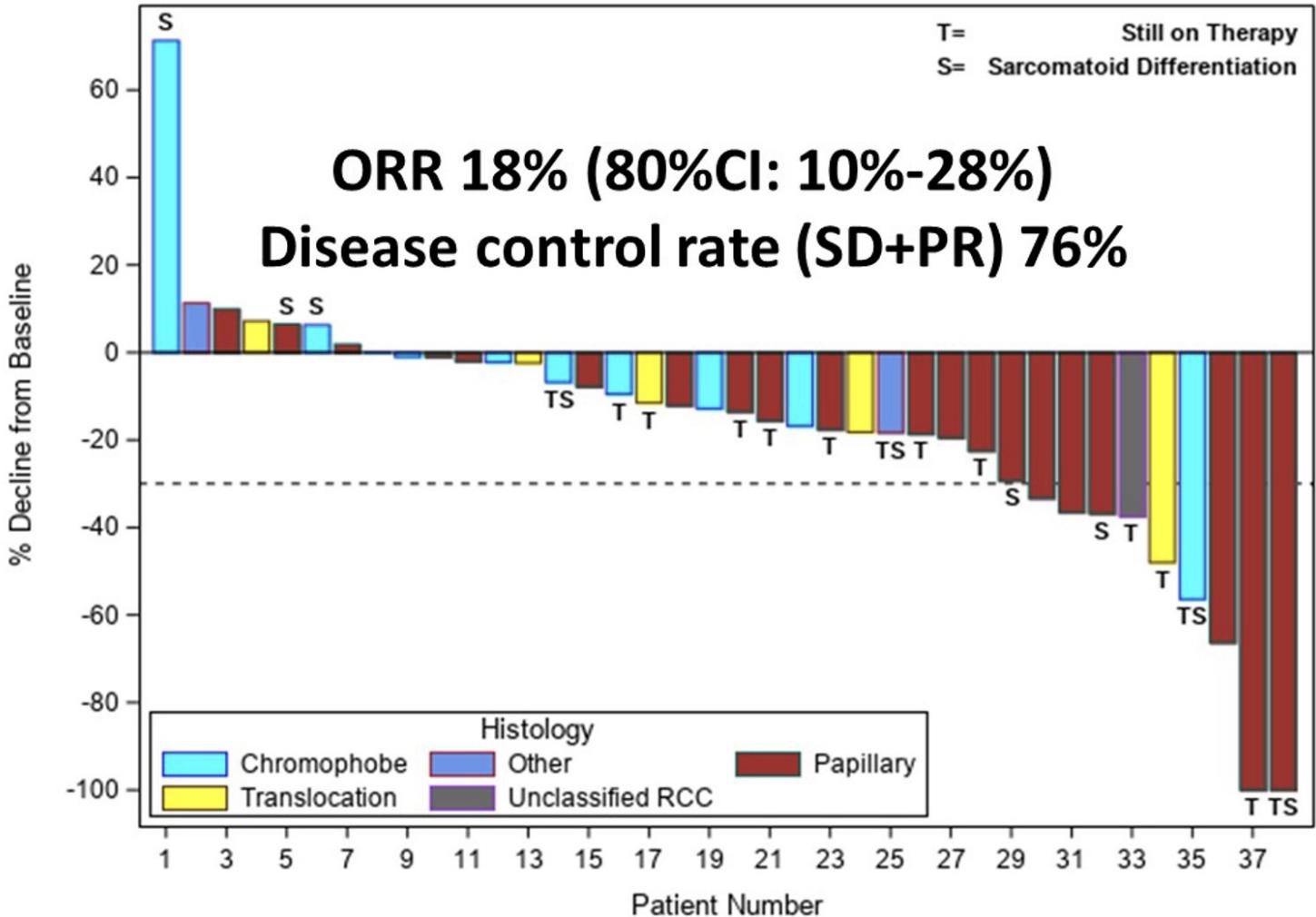


Cabo-Nivolumab-Ipilimumab nccRCC

CaNI Schema

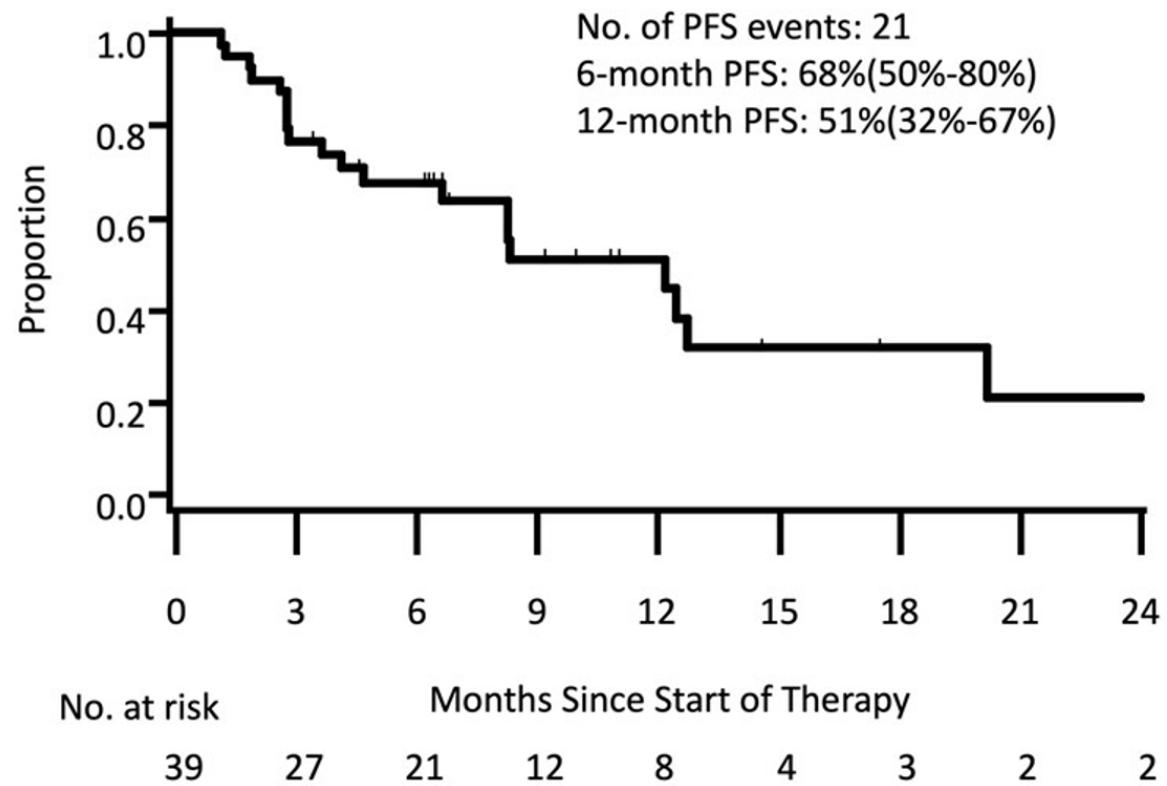


| | Total N | Objective response | | |
|-------------------------|---------|--------------------|----------|---------|
| | | PR | SD | PD |
| Overall | 39 | 7 (18%) | 23 (59%) | 9 (23%) |
| Histology | | | | |
| Papillary | 20 | 5 (25%) | 11 (55%) | 4 (20%) |
| Chromophobe | 11 | 1 (9%) | 5 (45%) | 5 (45%) |
| Translocation | 5 | . | 5 (100%) | . |
| Other | 2 | . | 2 (100%) | . |
| Unclassified RCC | 1 | 1 (100%) | . | . |
| Sarcomatoid Diff | | | | |
| No | 30 | 5 (17%) | 19 (63%) | 6 (20%) |
| Yes | 9 | 2 (22%) | 4 (44%) | 3 (33%) |
| Prior Therapy | | | | |
| No | 34 | 7 (21%) | 20 (59%) | 7 (21%) |
| Yes | 5 | . | 3 (60%) | 2 (40%) |

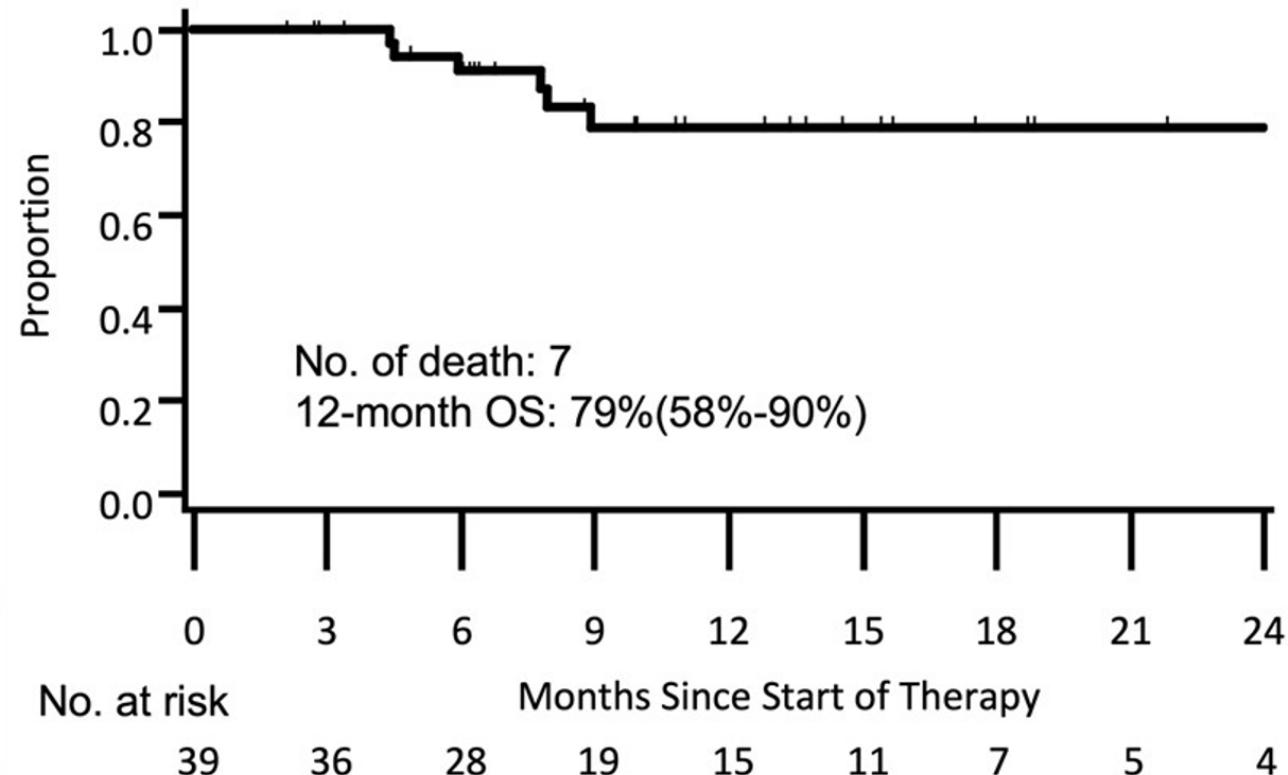


Cabo-Nivolumab-Ipilimumab nccRCC

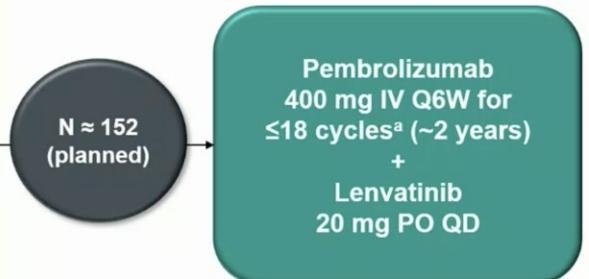
Kaplan Meier estimate of progression free survival



Kaplan Meier estimate of overall survival



Keynote-B61: Len-Pem nccRCC



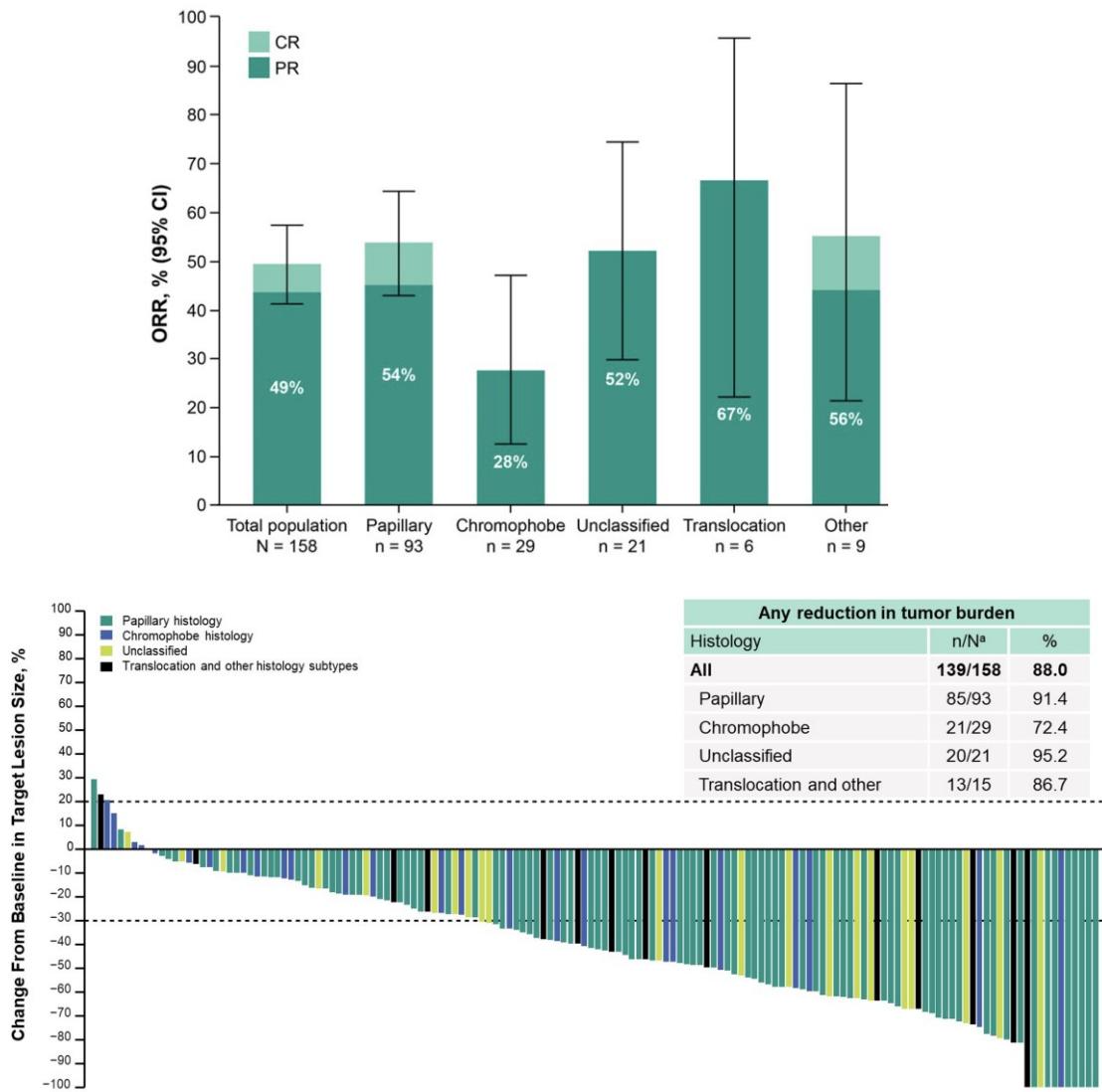
End Points

- Primary: ORR per RECIST v1.1 by BICR
- Secondary: CBR, DCR, DOR, and PFS per RECIST v1.1 by BICR; OS, safety and tolerability

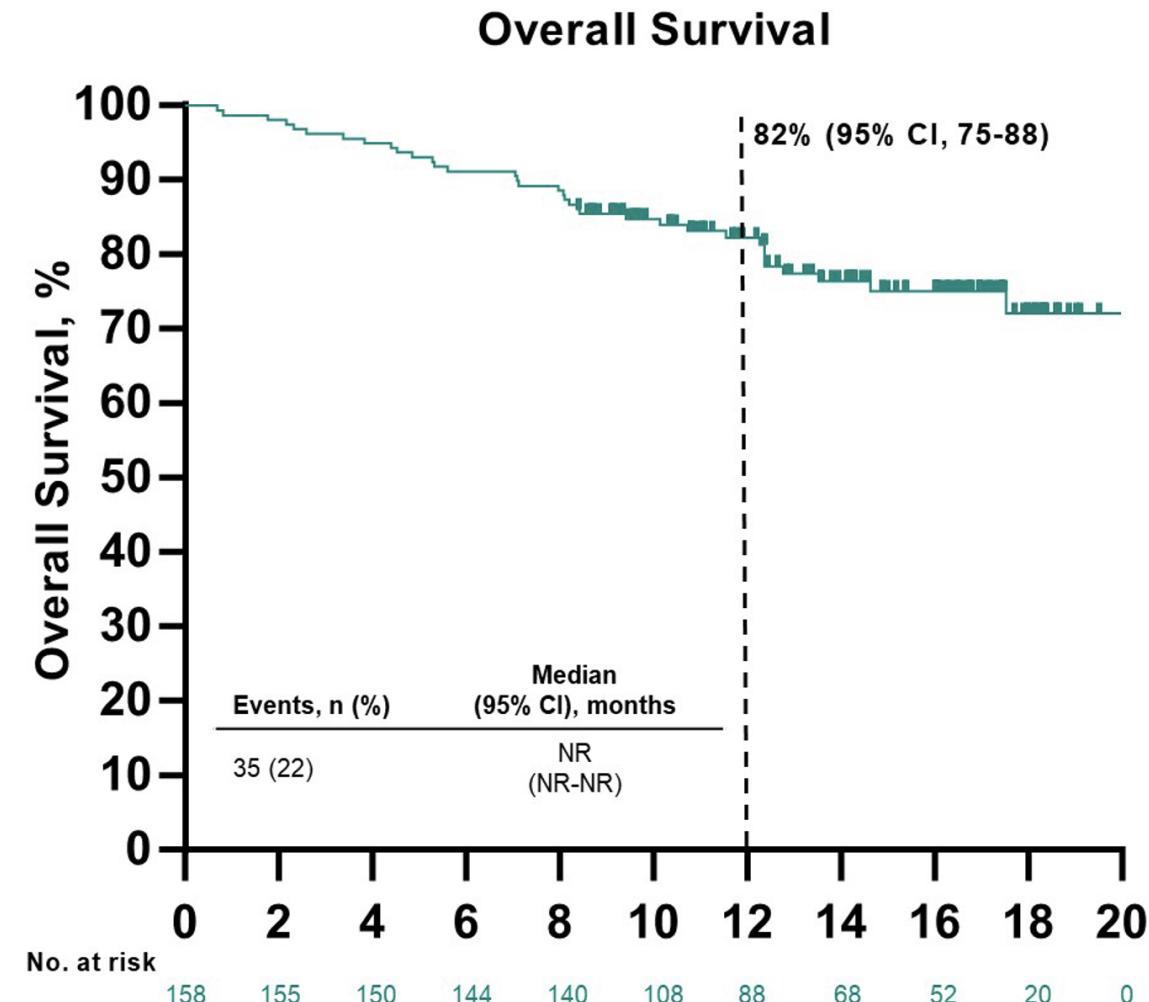
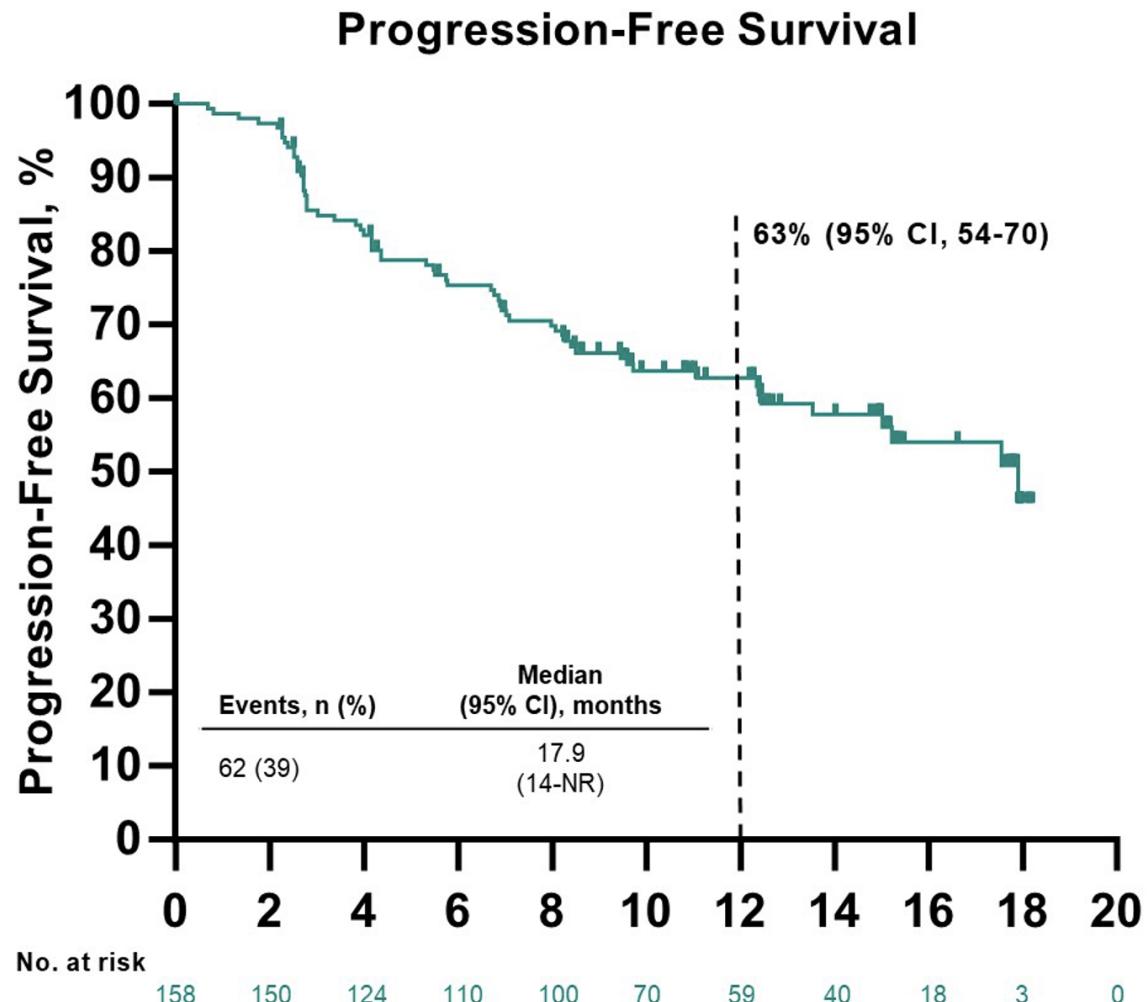
- Tumor Assessments**
- 12 weeks from allocation then Q6W for 54 weeks then Q12W thereafter

| | Efficacy population n = 82 |
|---|---------------------------------------|
| Presence of sarcomatoid features^c | |
| Yes | 10 (12.2) |
| No | 52 (63.4) |
| RCC histology | |
| Papillary | 51 (62.2) |
| Chromophobe | 15 (18.3) |
| Unclassified | 7 (8.5) |
| Translocation | 5 (6.1) |
| Other | 4 (4.9) |
| Liver metastases | 14 (17.1) |
| Bone metastases | 24 (29.3) |

| | Pembrolizumab + lenvatinib N = 158 |
|--|---|
| ORR (CR + PR), % (95% CI) | 49 (41-57) |
| DCR (CR + PR + SD), % (95% CI) | 82 (75-88) |
| CBR (CR, PR, or SD for ≥6 months), % (95% CI) | 72 (64-78) |
| Best response, n (%) | |
| CR | 9 (6) |
| PR | 69 (44) |
| SD | 52 (33) |
| PD | 17 (11) |
| NE ^a | 1 (0.6) |
| NA ^b | 10 (6) |

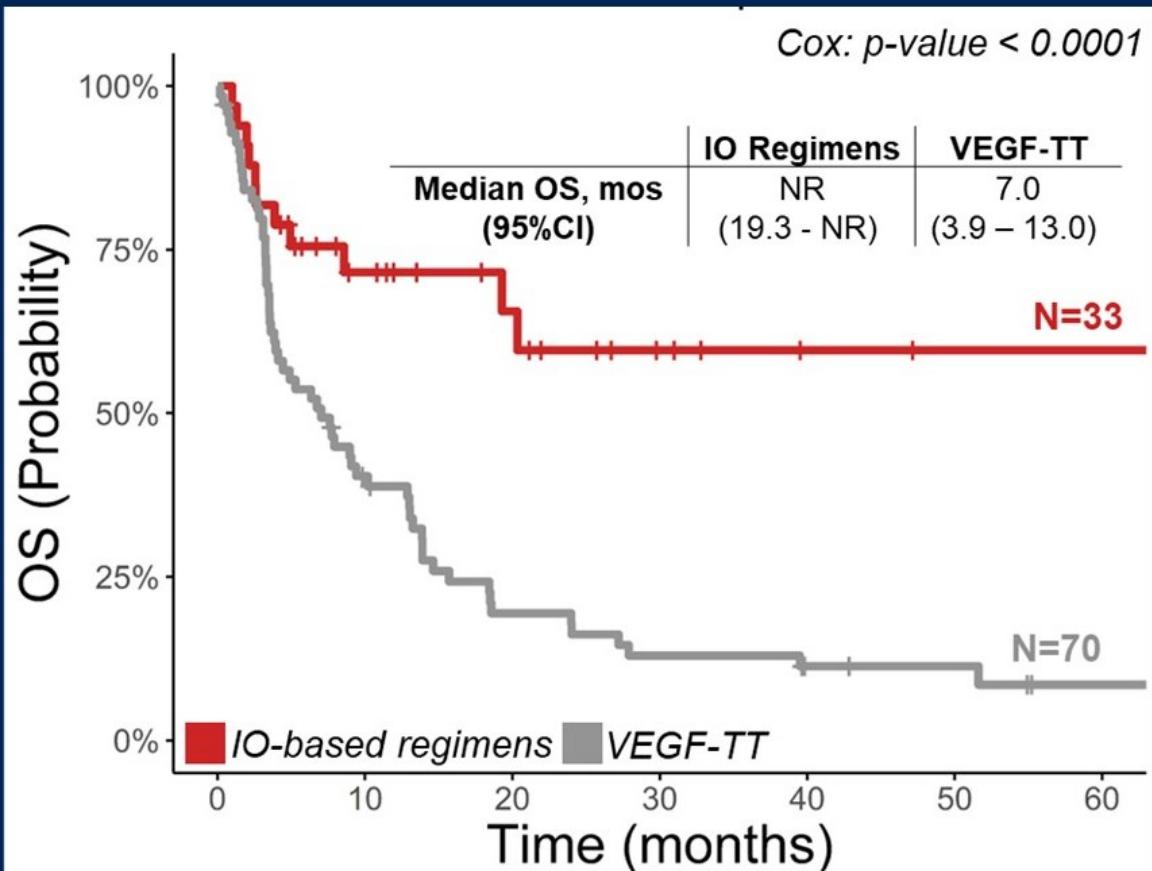


Keynote-B61: Len-Pem nccRCC

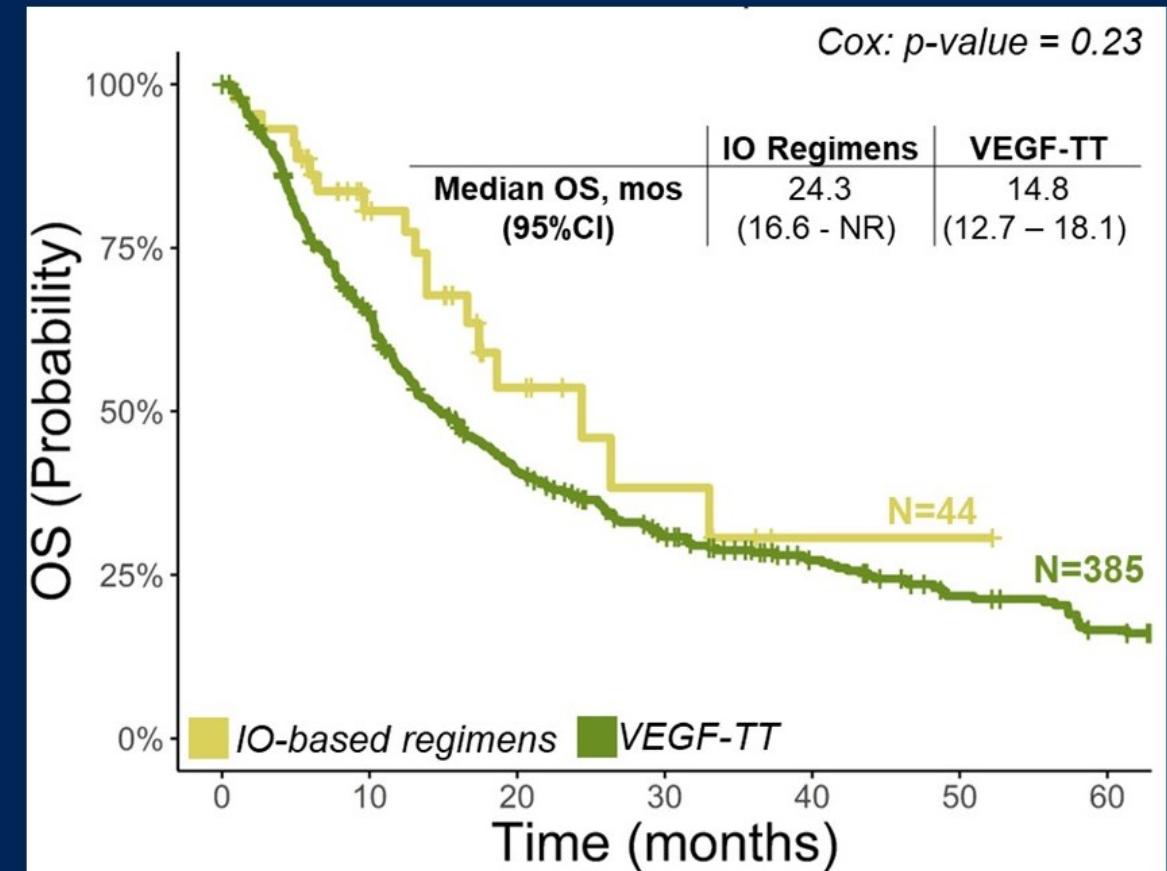


Efficacy of IL IO-based regimens in sarcomatoid nccRCC

S/R nccRCC



Non-S/R nccRCC



More
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Current treatment landscape mRCC

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- Is it possible to maintain IO at PD? (Contact-03)

- Belzutifan: a new kid on the block

More
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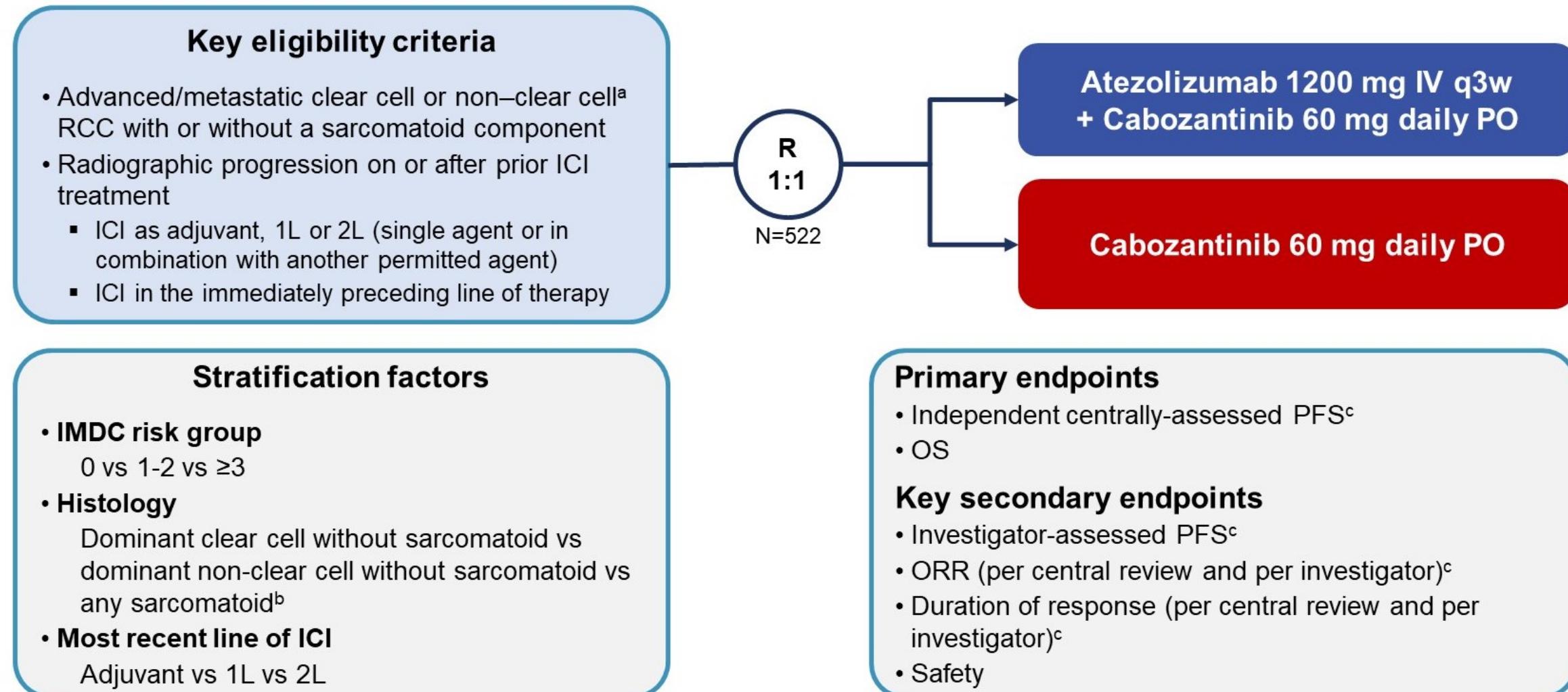
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|---|--|--|---|
| Immuno-oncology (IO) Therapy History Status | Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
| IO Therapy Naïve | <ul style="list-style-type: none"> • None | <ul style="list-style-type: none"> • Axitinib + pembrolizumab^b • Cabozantinib • Cabozantinib + nivolumab^b • Ipilimumab + nivolumab^b • Lenvatinib + everolimus • Lenvatinib + pembrolizumab^b • Nivolumab^b | <ul style="list-style-type: none"> • Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib^f • Belzutifan (category 2B) • Bevacizumab^g (category 2B) • High-dose IL-2 for selected patients^d (category 2B) • Temsirolimus^e (category 2B) • Axitinib + avelumab^b (category 3) |
| Prior IO Therapy | <ul style="list-style-type: none"> • None | <ul style="list-style-type: none"> • Axitinib • Cabozantinib • Lenvatinib + everolimus • Tivozanib^f | <ul style="list-style-type: none"> • Axitinib + pembrolizumab^b • Cabozantinib + nivolumab^b • Everolimus • Ipilimumab + nivolumab^b • Lenvatinib + pembrolizumab^b • Pazopanib • Sunitinib • Belzutifan (category 2B) • Bevacizumab^g (category 2B) • High-dose IL-2 for selected patients^d (category 2B) • Temsirolimus^e (category 2B) • Axitinib + avelumab^b (category 3) |

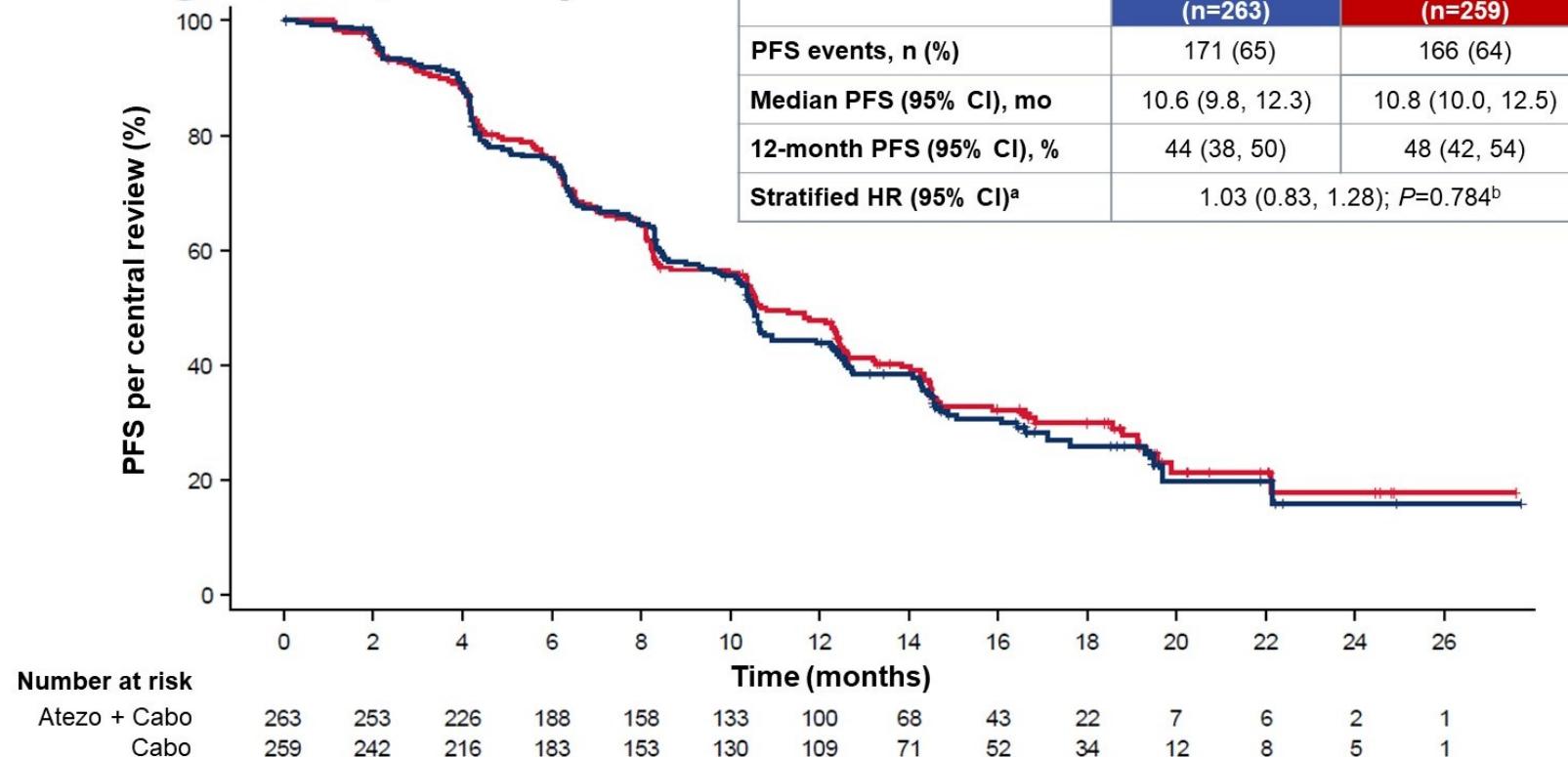
- Is it possible to maintain IO at PD? (Contact-03)

- Belzutifan: a new kid on the block...

CONTACT-03 trial



Primary analysis of centrally reviewed PFS (primary endpoint)



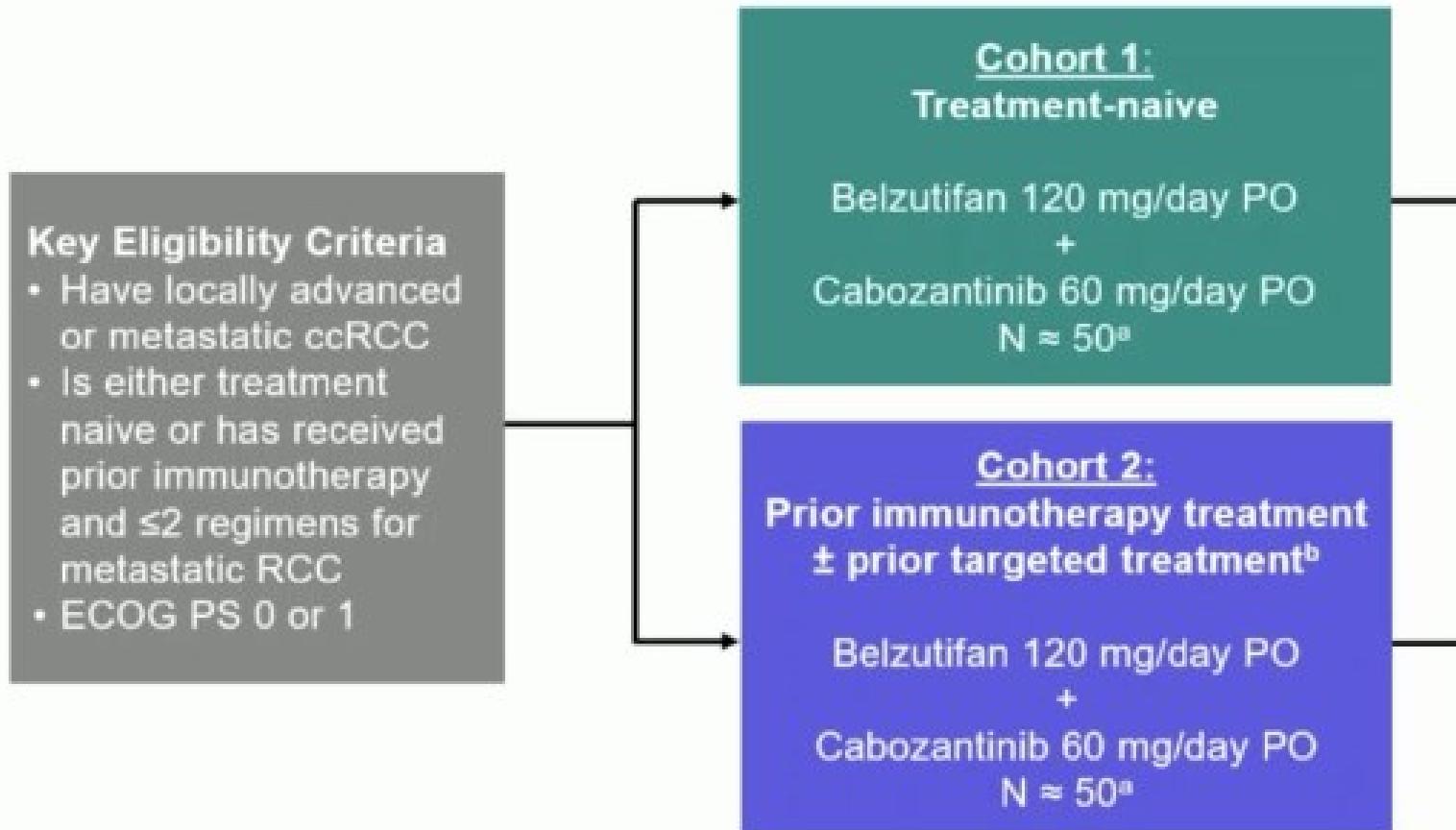
More
lines

Current treatment landscape mRCC

| SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY) | | | |
|---|--|--|---|
| Immuno-oncology (IO) Therapy History Status | Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
| IO Therapy Naïve | <ul style="list-style-type: none"> • None | <ul style="list-style-type: none"> • Axitinib + pembrolizumab^b • Cabozantinib • Cabozantinib + nivolumab^b • Ipilimumab + nivolumab^b • Lenvatinib + everolimus • Lenvatinib + pembrolizumab^b • Nivolumab^b | <ul style="list-style-type: none"> • Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib^f • Belzutifan (category 2B) • Bevacizumab^g (category 2B) • High-dose IL-2 for selected patients^d (category 2B) • Temsirolimus^e (category 2B) • Axitinib + avelumab^b (category 3) |
| Prior IO Therapy | <ul style="list-style-type: none"> • None | <ul style="list-style-type: none"> • Axitinib • Cabozantinib • Lenvatinib + everolimus • Tivozanib^f | <ul style="list-style-type: none"> • Axitinib + pembrolizumab^b • Cabozantinib + nivolumab^b • Everolimus • Ipilimumab + nivolumab^b • Lenvatinib + pembrolizumab^b • Pazopanib • Sunitinib • Belzutifan (category 2B) • Bevacizumab^g (category 2B) • High-dose IL-2 for selected patients^d (category 2B) • Temsirolimus^e (category 2B) • Axitinib + avelumab^b (category 3) |

- Is it possible to maintain IO at PD?

- Belzutifan: a new kid on the block



Tumor Assessments

- Week 9, then Q8W for 12 months and Q12W thereafter

End Points

- Primary: ORR per RECIST v1.1 by investigator
- Secondary: PFS, DOR, and TTR per RECIST v1.1 by investigator, OS, safety/tolerability

| Cohort | ORR |
|--|--------------------|
| Cohort 1 (median follow-up, 14.0 months) | 57% ^{a,3} |
| Cohort 2 (median follow-up, 24.6 months) | 31% ⁴ |

Baseline Characteristics

| | Cohort 1 N = 50 | Cohort 2 N = 52 |
|--|--------------------|--------------------|
| Age, median (range), years | 64.0 (33-89) | 63.0 (43-79) |
| ≥65 years | 23 (46) | 24 (46) |
| Male | 40 (80) | 38 (73) |
| ECOG performance status 0/1, n (%) | 33 (66)/17 (34) | 23 (44)/29 (56) |
| IMDC risk group | | |
| Favorable | 28 (56) | 11 (21) |
| Intermediate/poor | 22 (44) | 41 (79) |
| Prior nephrectomy | 40 (80) | 42 (81) |
| Number of prior lines of anticancer therapy | | |
| 1 | 0 (0) | 29 (56) |
| 2 | 0 (0) | 23 (44) |
| Prior type of anticancer therapy | | |
| Immunotherapy ^a | 0 (0) | 28 (54) |
| Immunotherapy + anti-VEGF/VEGFR therapy ^b | 0 (0) | 24 (46) |

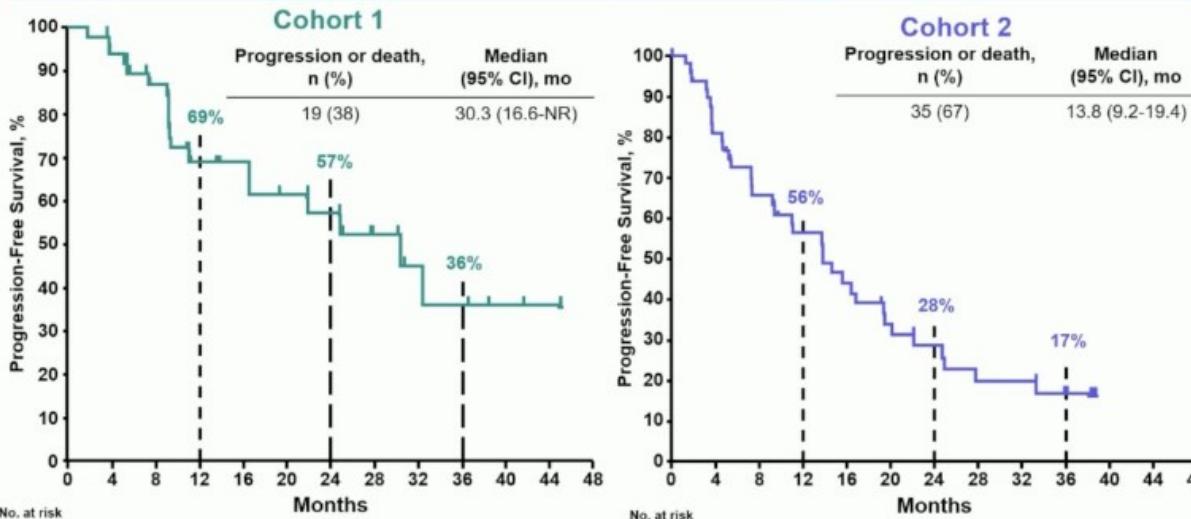
ORR by Investigator in All Patients and by IMDC Risk

| | Cohort 1 | | | Cohort 2 | | |
|----------------------------|-------------------|---------------------|---------------------------------|-------------------|---------------------|---------------------------------|
| | Overall N = 50 | IMDC risk category | | Overall N = 52 | IMDC risk category | |
| | | Favorable n = 28 | Intermediate/ poor n = 22 | | Favorable n = 11 | Intermediate/ poor n = 41 |
| ORR (CR + PR) | 35 (70) | 22 (79) | 13 (59) | 16 (31) | 3 (27) | 13 (32) |
| DCR (CR + PR + SD) | 49 (98) | 28 (100) | 21 (96) | 48 (92) | 11 (100) | 37 (90) |
| Best response | | | | | | |
| CR | 4 (8) | 3 (11) | 1 (5) | 2 (4) | 0 | 2 (5) |
| PR | 31 (62) | 19 (68) | 12 (55) | 14 (27) | 3 (27) | 11 (27) |
| SD | 14 (28) | 6 (21) | 8 (36) | 32 (62) | 8 (73) | 24 (59) |
| PD | 1 (2) | 0 (0) | 1 (5) | 3 (6) | 0 (0) | 3 (7) |
| Not available ^a | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 1 (2) |

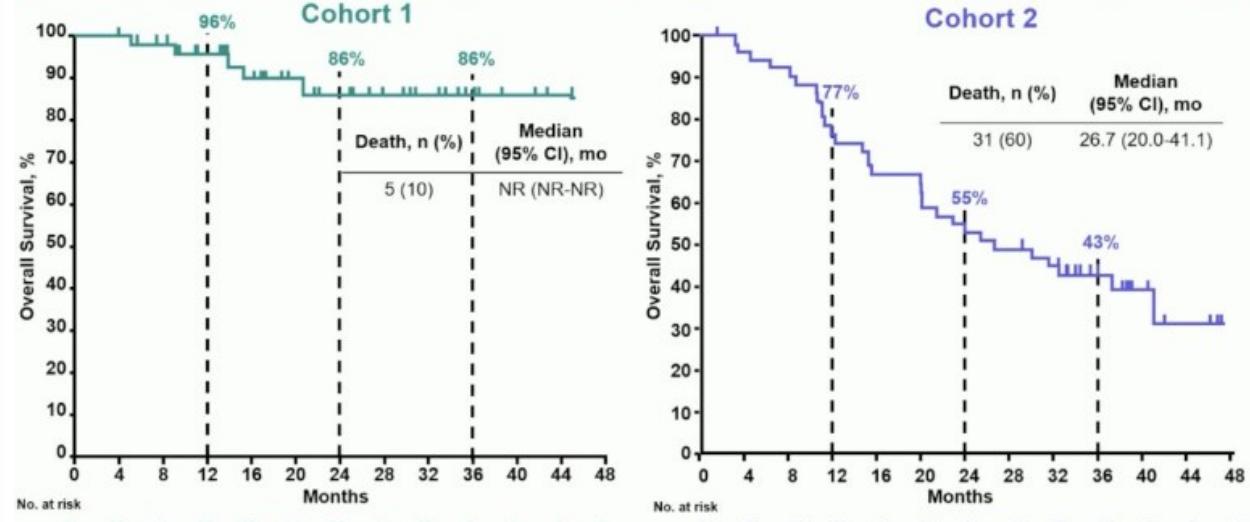
ORR by Prior Anticancer Therapy: Cohort 2

| | Overall N = 52 | Prior anticancer therapy | | Line of prior anticancer therapy | |
|----------------------------|-------------------|--|---|--------------------------------------|---------------------------------------|
| | | Immunotherapy only ^a n = 28 | Immunotherapy/ anti-VEGF therapy ^b n = 24 | 1 line of prior therapy n = 29 | 2 lines of prior therapy n = 23 |
| ORR (CR + PR) | 16 (31) | 9 (32) | 7 (29) | 9 (31) | 7 (30) |
| DCR (CR + PR + SD) | 48 (92) | 26 (93) | 22 (92) | 27 (93) | 21 (91) |
| Best response | | | | | |
| CR | 2 (4) | 1 (4) | 1 (4) | 1 (3) | 1 (4) |
| PR | 14 (27) | 8 (29) | 6 (25) | 8 (28) | 6 (26) |
| SD | 32 (62) | 17 (61) | 15 (63) | 18 (62) | 14 (61) |
| PD | 3 (6) | 1 (4) | 2 (8) | 2 (7) | 1 (4) |
| Not available ^c | 1 (2) | 1 (4) | 0 (0) | 0 (0) | 1 (4) |

Progression-Free Survival by Investigator

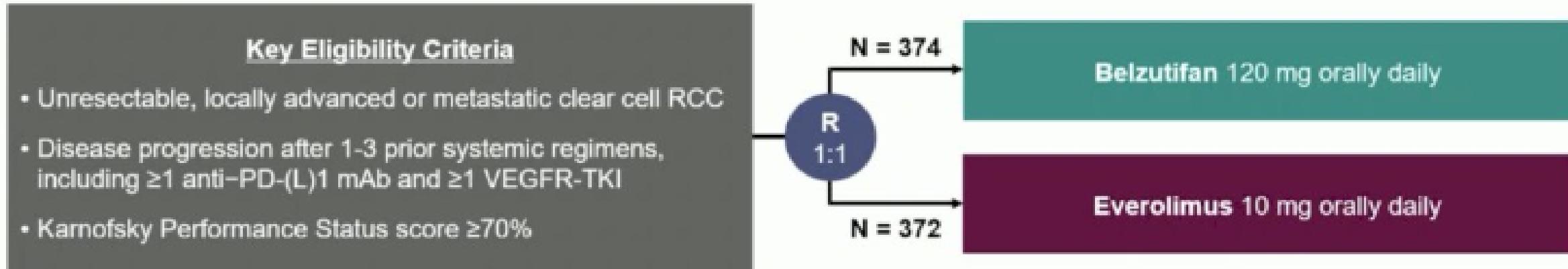


Overall Survival



Summary of Treatment-Related Adverse Events

| | Cohort 1 N = 50 | Cohort 2 N = 52 |
|--|--------------------|--------------------|
| Any-grade treatment-related AE | 50 (100) | 51 (98) |
| Grade ≥ 3 treatment-related AE | 23 (46) | 33 (64) |
| Grade 5 treatment-related AE | 0 (0) | 1 (2) ^a |
| Discontinued any drug because of a treatment-related AE | 7 (14) | 11 (21) |
| Serious treatment-related AE | 7 (14) | 16 (31) |
| Dose reduction because of a treatment-related AE | 38 (76) | 37 (71) |



Stratification Factors

- IMDC prognostic score^a: 0 vs 1-2 vs 3-6
- Prior VEGF/VEGFR-targeted therapies: 1 vs 2-3

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

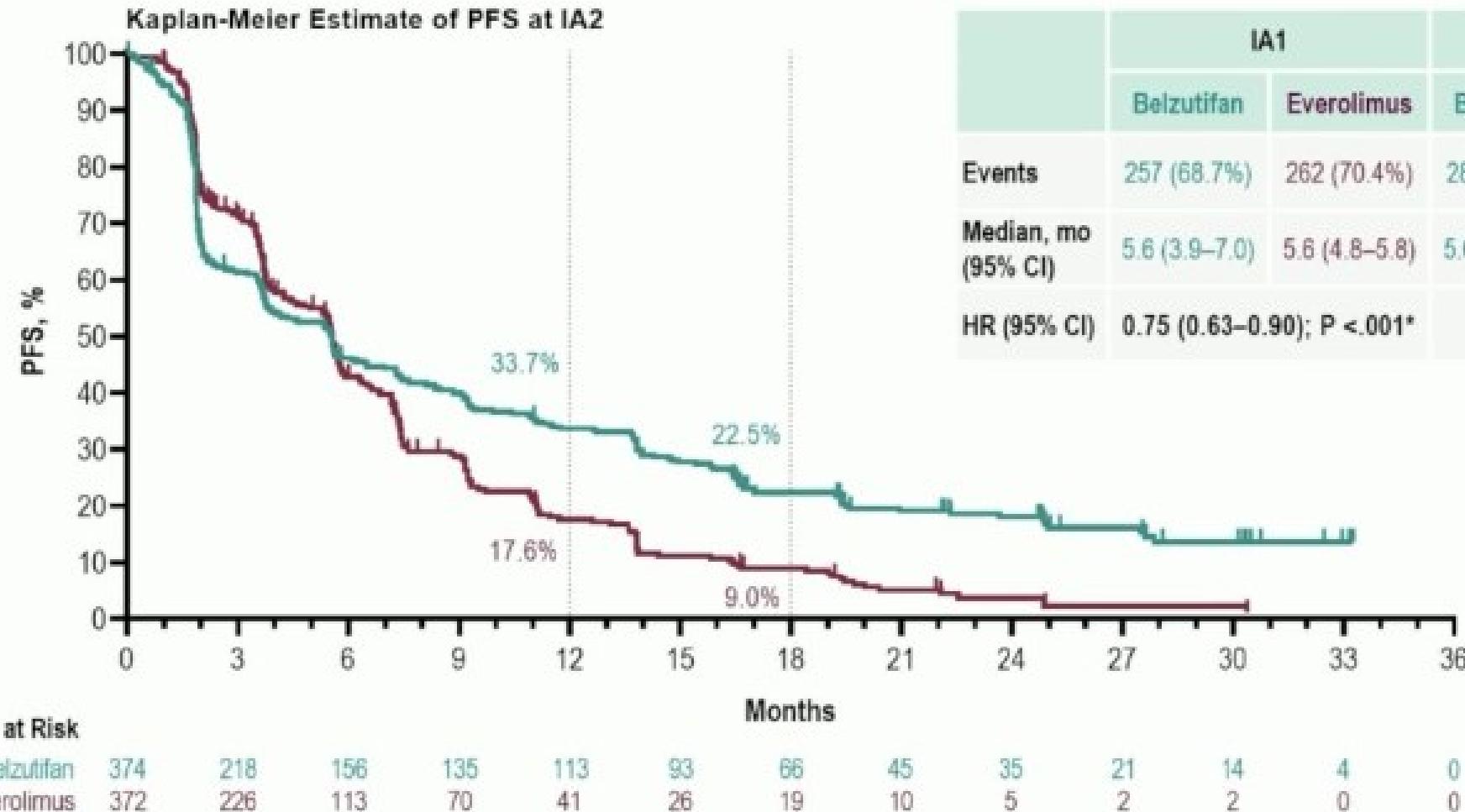
- DOR per RECIST 1.1 by BICR
- Safety
- Time to deterioration in FKSI-DRS and EORTC QLQ-C30 GHS/QoL

| Planned analysis | Planned timing | Planned analysis | Data cutoff date |
|--------------------------|---|--|------------------|
| Interim analysis 1 (IA1) | <ul style="list-style-type: none"> • ~563 PFS events^b, AND • ~7 months after last participant randomized | Interim PFS Interim OS Final ORR | Nov 1, 2022 |
| Interim analysis 2 (IA2) | <ul style="list-style-type: none"> • ~410 OS events, AND • ~17 months after last participant randomized | Interim OS Final PFS | Jun 13, 2023 |
| Final | <ul style="list-style-type: none"> • ~483 OS events, AND • ~27 months after last participant randomized | Final OS | |

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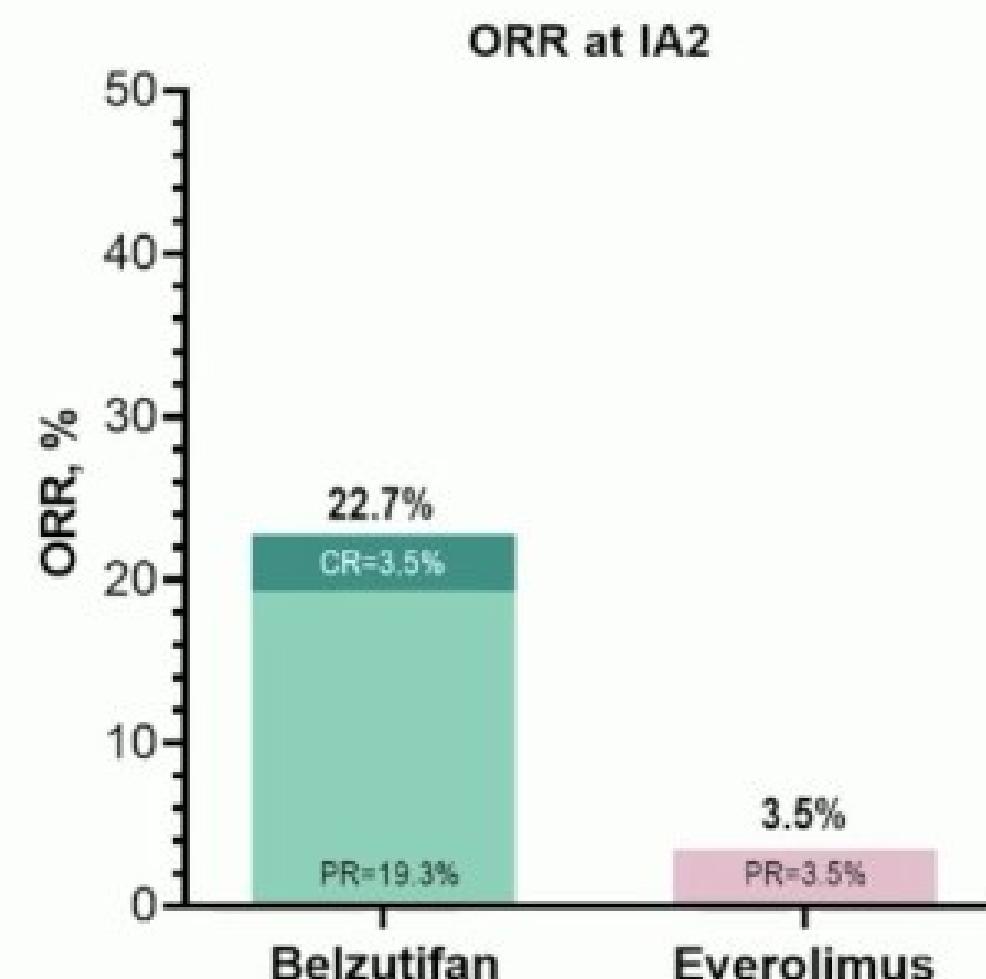
| | Belzutifan (N = 374) | Everolimus (N = 372) |
|---------------------------------------|-----------------------------|-----------------------------|
| Age, median (range), yrs | 62 (22–90) | 63 (33–87) |
| Male | 79.4% | 76.3% |
| KPS score ^a | | |
| 90/100 | 63.6% | 64.5% |
| 70/80 | 36.1% | 35.2% |
| IMDC risk categories | | |
| Favorable | 21.1% | 22.3% |
| Intermediate | 66.6% | 65.6% |
| Poor | 12.3% | 12.1% |
| Sarcomatoid features | | |
| Yes | 11.2% | 8.3% |
| No/Unknown/Missing | 88.8% | 91.7% |
| Prior nephrectomy | 69.8% | 69.6% |
| # Prior VEGF/VEGFR-TKIs | | |
| 1 | 50.0% | 51.1% |
| 2-3 | 50.0% | 48.9% |
| # Prior lines of therapy ^b | | |
| 1 | 12.3% | 14.0% |
| 2 | 42.0% | 44.6% |
| 3 | 45.2% | 40.3% |

Primary Endpoint: PFS per RECIST 1.1 by BICR

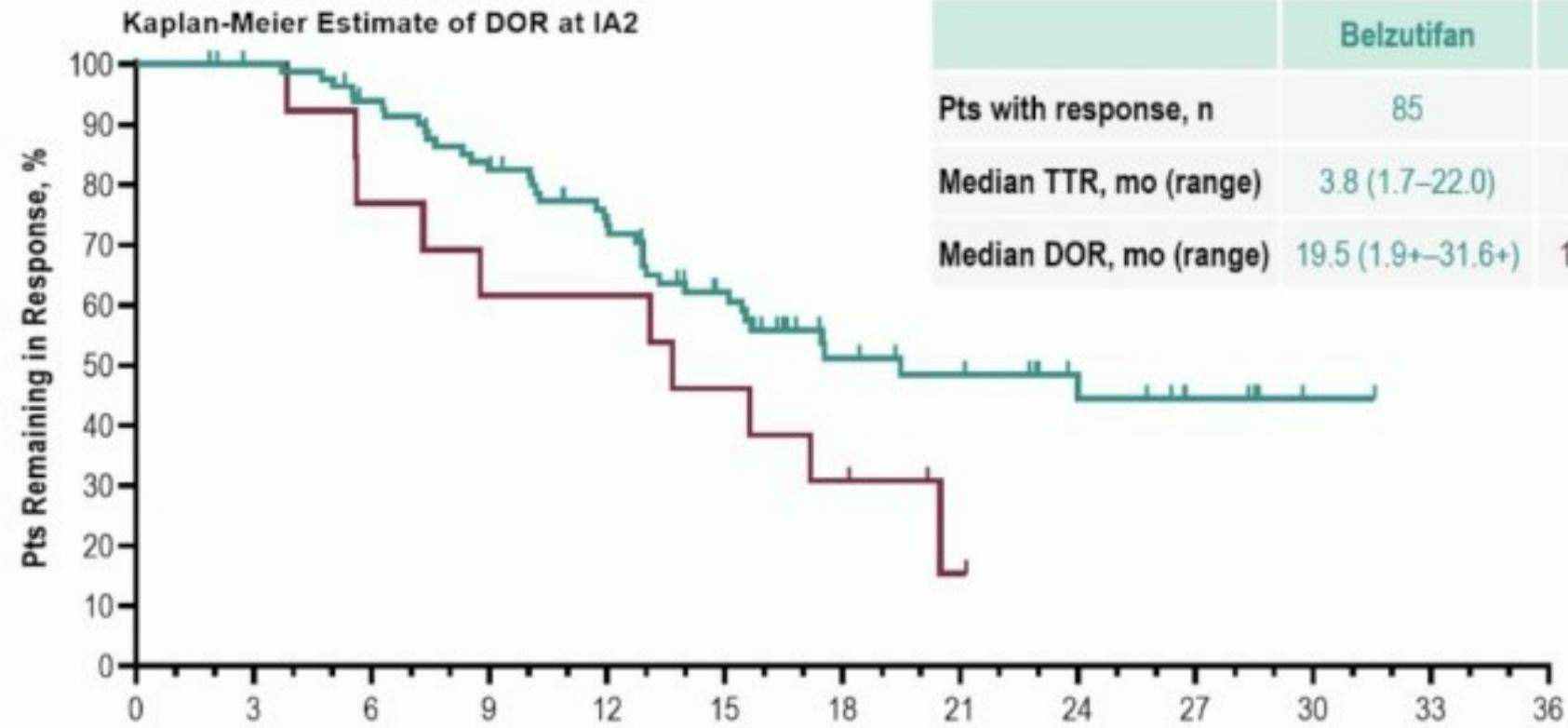


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| | Belzutifan (N = 374) | Everolimus (N = 372) |
|------------------------------------|-------------------------------|-------------------------|
| IA1 | | |
| ORR, % (95% CI) | 21.9% (17.8–26.5) | 3.5% (1.9–5.9) |
| Estimated difference in % (95% CI) | 18.4 (14.0–23.2); P <.000001* | |
| CR | 2.7% | 0 |
| PR | 19.3% | 3.5% |
| SD | 39.3% | 65.9% |
| PD | 33.7% | 21.5% |
| Non-evaluable ^a | 1.3% | 2.2% |
| No assessment ^b | 3.7% | 7.0% |
| IA2 | | |
| ORR, % (95% CI) | 22.7% (18.6–27.3) | 3.5% (1.9–5.9) |
| Estimated difference in % (95% CI) | 19.2 (14.8–24.0) | |



DOR per RECIST 1.1 by BICR

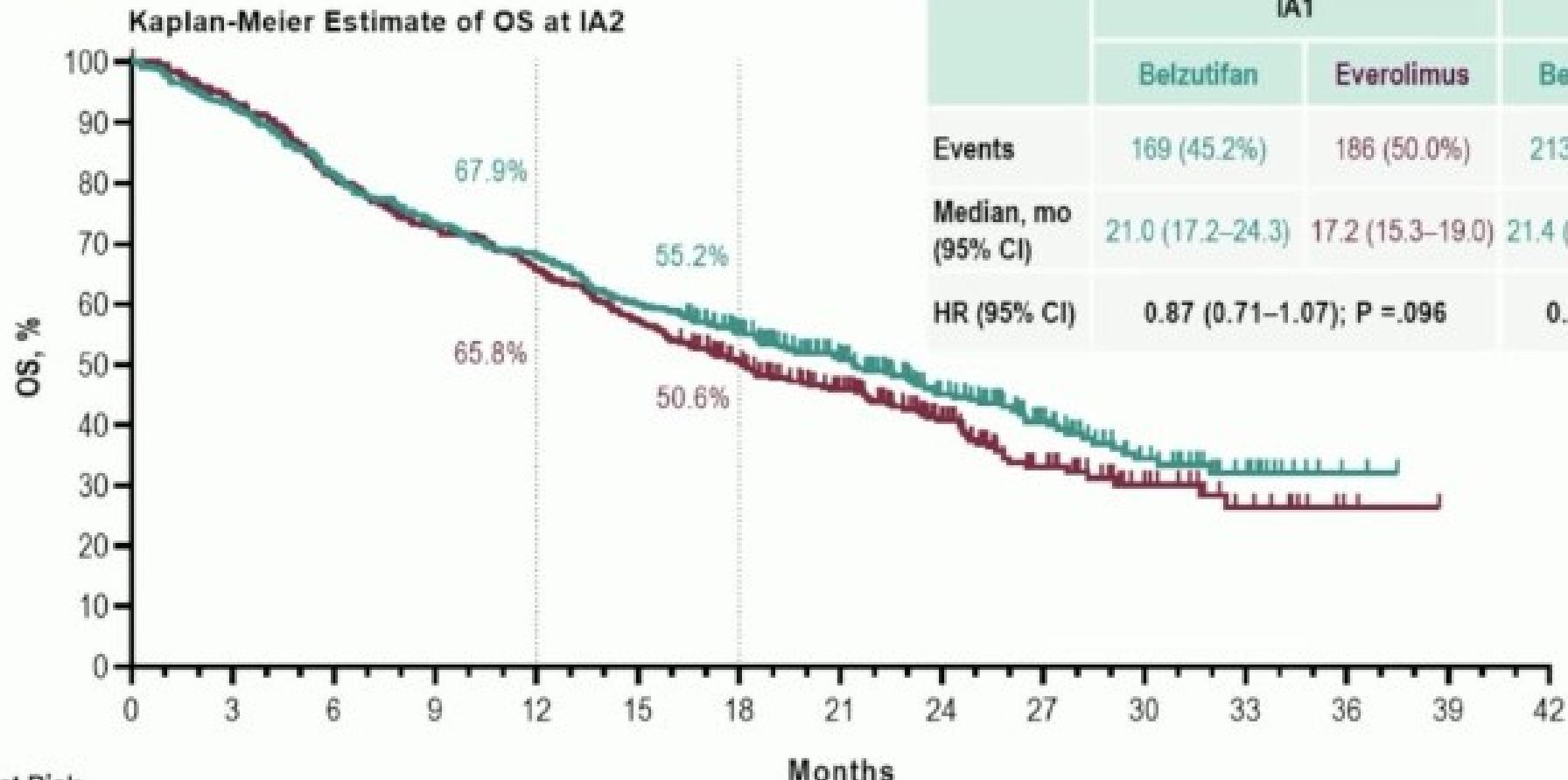


| | Belzutifan | Everolimus |
|------------------------|-------------------|------------------|
| Pts with response, n | 85 | 13 |
| Median TTR, mo (range) | 3.8 (1.7–22.0) | 3.7 (1.8–5.4) |
| Median DOR, mo (range) | 19.5 (1.9+–31.6+) | 13.7 (3.8–21.2+) |

No. at Risk

| | | | | | | | | | | | | | |
|------------|----|----|----|----|----|----|----|----|----|---|---|---|---|
| Belzutifan | 85 | 82 | 75 | 65 | 54 | 40 | 21 | 18 | 12 | 6 | 1 | 0 | 0 |
| Everolimus | 13 | 13 | 10 | 8 | 8 | 6 | 4 | 1 | 0 | 0 | 0 | 0 | 0 |

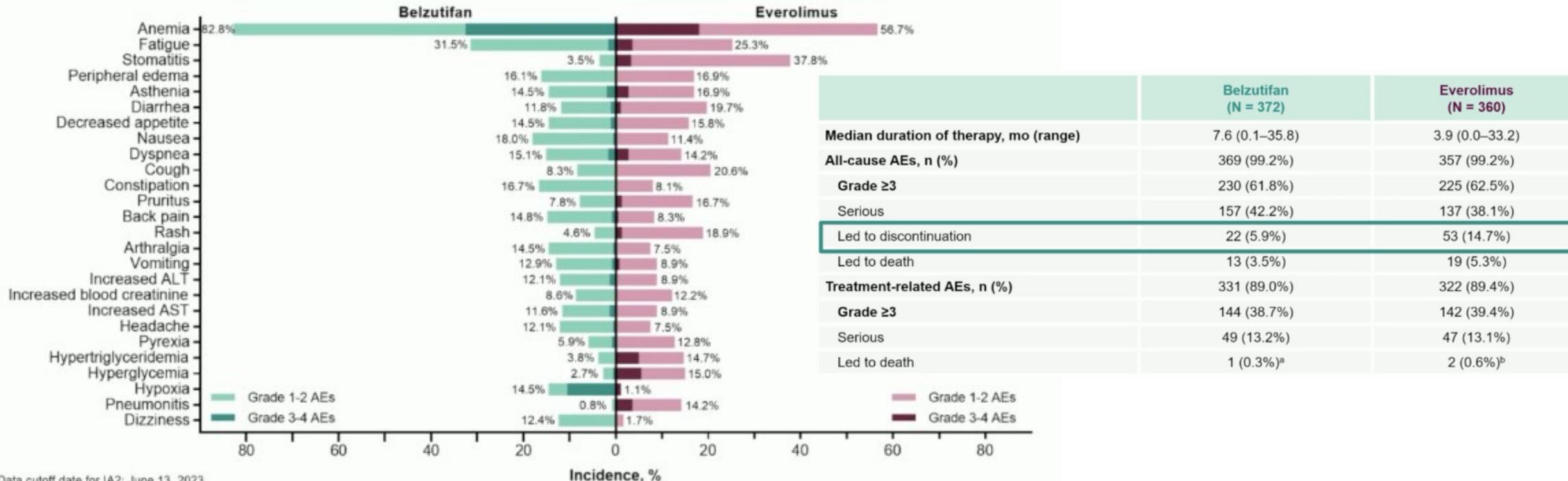
Primary Endpoint: OS



No. at Risk

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 |
|------------|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|
| Belzutifan | 374 | 347 | 305 | 274 | 254 | 224 | 190 | 143 | 95 | 62 | 36 | 16 | 2 | 0 | 0 |
| Everolimus | 372 | 347 | 301 | 270 | 244 | 212 | 170 | 124 | 83 | 43 | 23 | 11 | 2 | 0 | 0 |

All-Cause AEs in ≥10% of Patients in Either Arm



Data cutoff date for IA2: June 13, 2023.

| PROs | CONs |
|--|------------------------|
| RESPONSE RATE: 22,7% (CR 3.5%) vs 3.5% | PD: 33.7 vs 21% |
| DURATION of RESPONSE: 19.5 vs 13.5 m | mPFS: 5.6 vs 5.6 m |
| LONG TERM SURVIVALS 18 m: 22 vs 8% | PENDING OS |
| TOXICITY: Aes G3-4: 61.8 vs 62.5% | SAEs: 42 vs 38% |
| DISCONTINUATION RATE: 5.9 vs 14.7% | COMPARATOR: EVEROLIMUS |



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