# WHICH IMMUNOTHERAPY IS THE STANDARD IN 1ST LINE MRCC TREATMENT:

# IMMUNE DOUBLET

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# DISCLOSURE OF INTEREST

*Employment:* University Hospital Essen

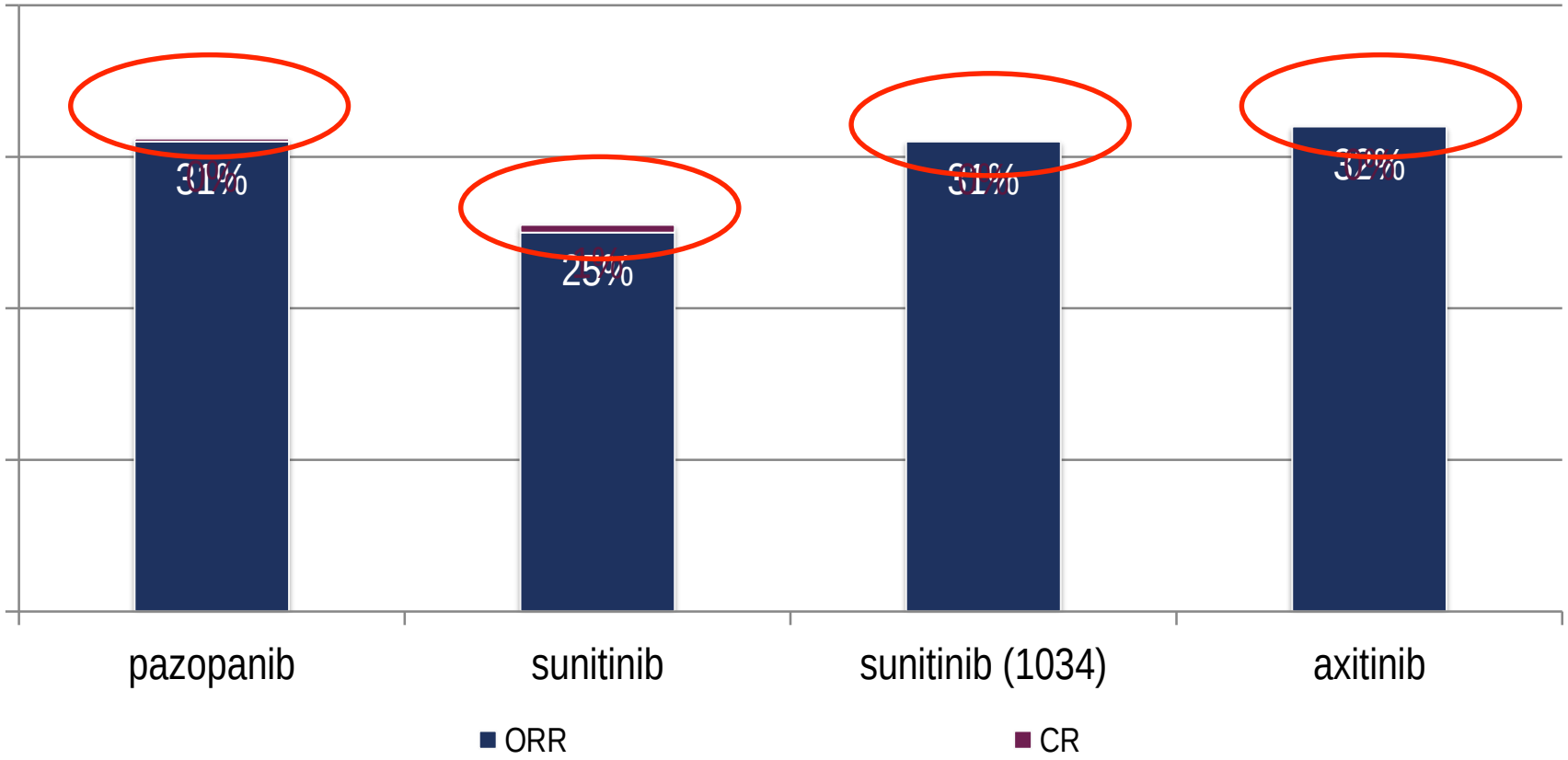
*Honoraria for speaker engagements and advisory roles:* Art tempi, AstraZeneca, Astellas, BMS, Cerulean, COCS, ClinSol, EUSAPharm, EISAI, Ipsen, MedUpdate, Merck Serono, MSD Merck, MedKomAkademie, Novartis, NewConceptOncology, Lilly, Johnson & Johnson, PharmaMar, PeerVoice, Pfizer, Roche, StreamedUp!, ThinkWired!

*Funding:* BMS, Novartis, EISAI, Pfizer, MSD, AstraZeneca, Roche, Ipsen

*Ownership of any stocks and shares:* AstraZeneca, BMS, MSD

# TKI - GREAT FOR PALLIATION, BUT WHERE ARE THE CRS?

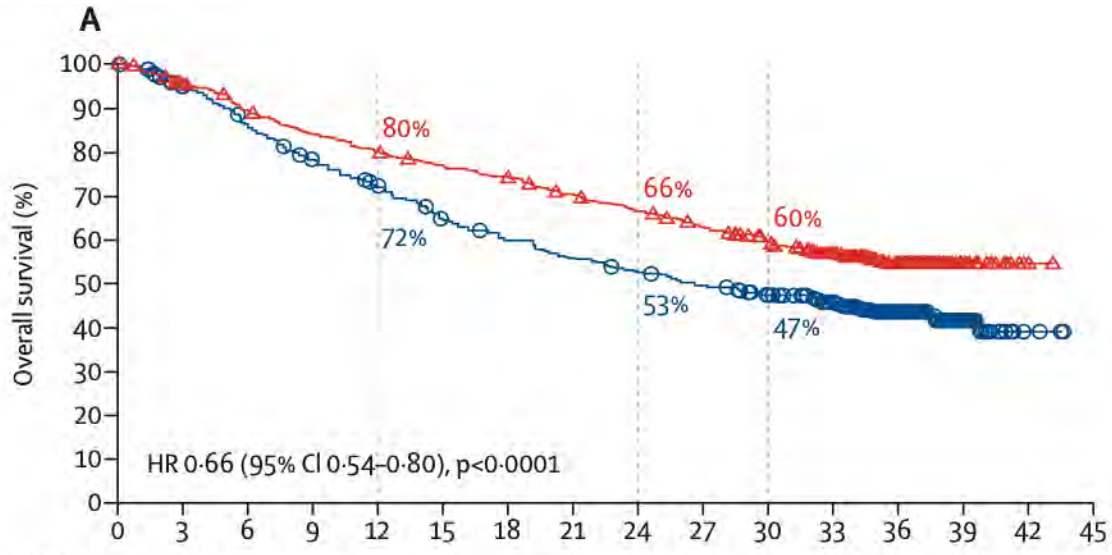
## TKI are devote of significant complete responses




1. Motzer, R. J. et al. N Engl J Med 356, 115–124 (2007). 2. Motzer, R. J. et al. N Engl J Med 369, 722–731 (2013). 3. Hutson, T. E. *et al. Lancet Oncol* **14,** 1287–1294 (2013).

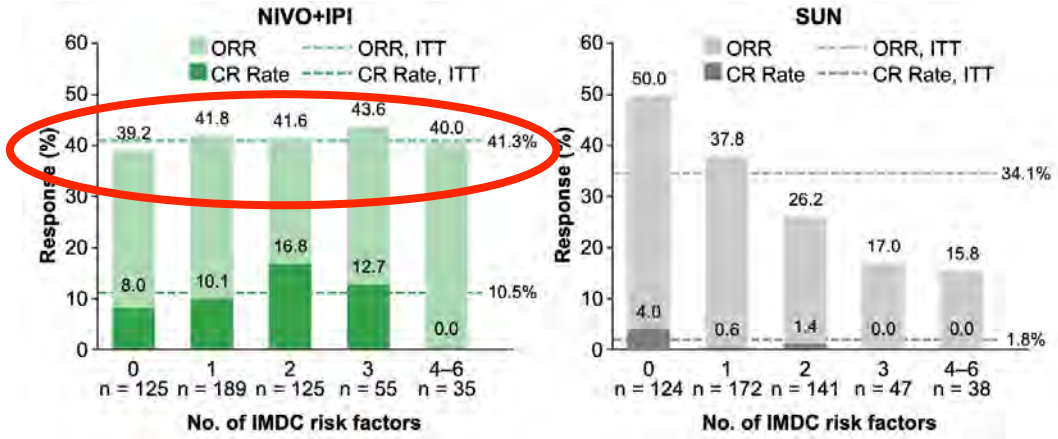
# IPILIMUMAB WITH LONGEST FOLLOW-UP AND BEST CR RATES

## Similar ORR in all risk-groups




| Number at risk (number censored) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab plus ipilimumab | 425 (0) | 399 (7) | 372 (9) | 348 (10) | 332 (10) | 317 (12) | 306 (12) | 287 (15) | 270 (16) | 253 (19) | 233 (26) | 183 (66) | 90 (153) | 34 (209) | 2 (241) | 0 (243) |
| Sunitinib | 422 (0) | 388 (11) | 353 (12) | 318 (15) | 290 (18) | 257 (21) | 236 (22) | 220 (22) | 207 (23) | 194 (24) | 179 (31) | 144 (60) | 75 (123) | 29 (167) | 3 (192) | 0 (195) |

CRs overall: 11%



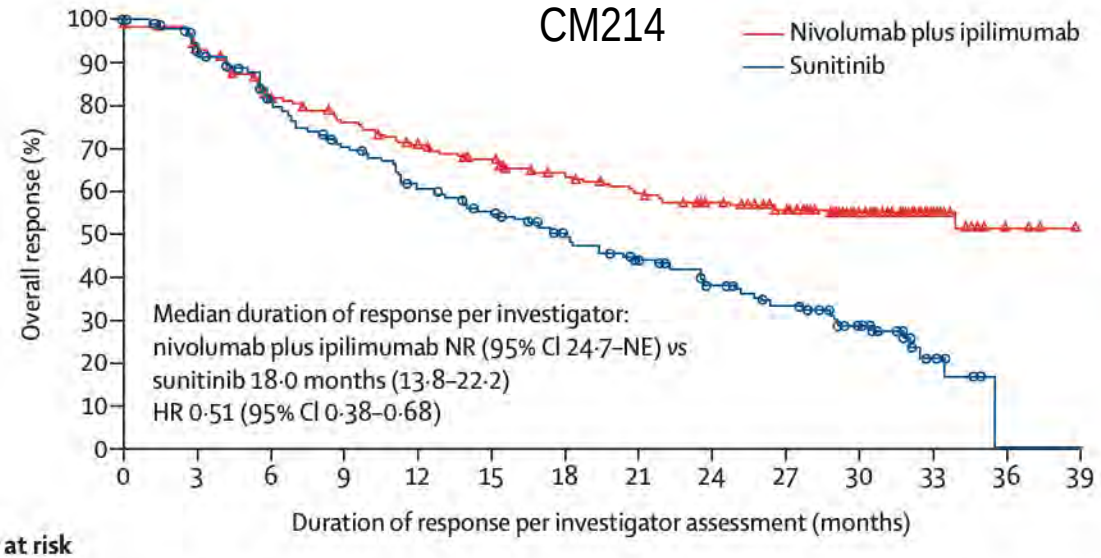

adapted from Escudier et al. ASCO 2019: abstract 4575

Motzer, R. J. *et al. Lancet Oncol* (2019). doi:10.1016/S1470-2045(19)30413-9

# DURATION OF RESPONSE IS OF IMPORTANCE

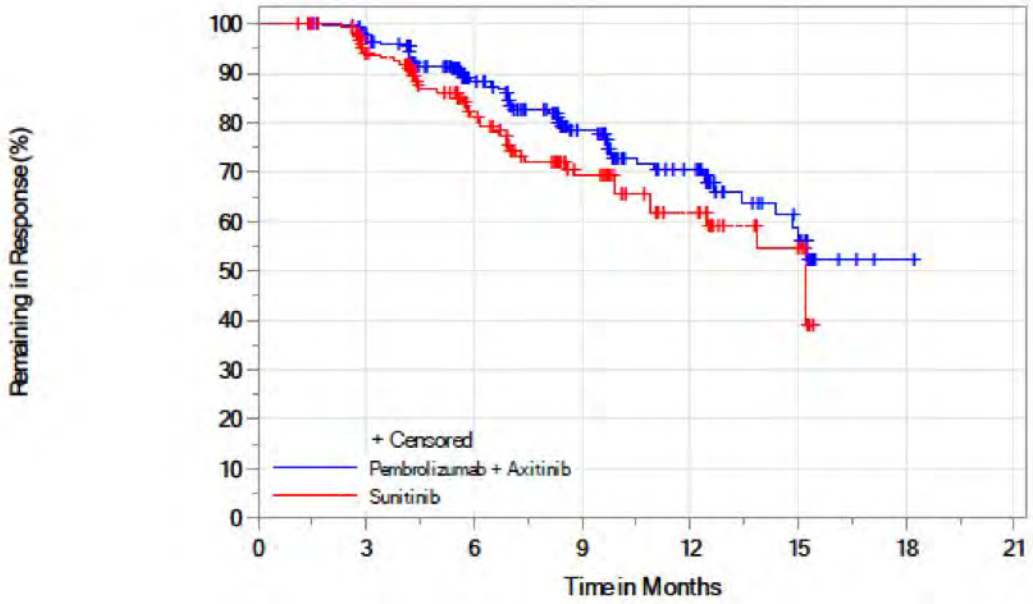
## CM214 has longest FU and compelling outcome

CM214




| Number at risk (number censored) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab plus ipilimumab | 225 (0) | 205 (5) | 175 (10) | 160 (13) | 146 (16) | 136 (19) | 120 (27) | 111 (29) | 102 (34) | 90 (43) | 55 (77) | 20 (112) | 4 (127) | 0 (131) |
| Sunitinib | 186 (0) | 164 (9) | 136 (17) | 116 (19) | 98 (21) | 86 (24) | 72 (30) | 60 (34) | 49 (37) | 40 (40) | 27 (48) | 7 (64) | 0 (69) | 0 (69) |

KN426




| Number of subjects at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pembrolizumab + Axitinib | 256 | 238 | 161 | 94 | 58 | 22 | 1 | 0 |
| Sunitinib | 153 | 130 | 84 | 49 | 26 | 9 | 0 | 0 |

Database Cutoff Date: 24Aug2018.

Motzer, R. J. *et al. Lancet Oncol* (2019). doi:10.1016/S1470-2045(19)30413-9

EPAR Pembrolizumab: EMA/CHMP/455620/2019 25.07.19

# IPILIMUMAB + NIVOLUMAB ACHIEVED HIGHEST CR RATE

| | IM150 (n=103) Atezolizumab * | TITAN (n=108) Nivolumab* | KN427 (N=110) Pembrolizumab * | KN426 (N=861) Pembrolizumab + axitinib | JAVELIN101 (N=886) Avelumab + axitinib | IM151 (N=915) Atezolizumab + Bevacizumab* | CM214 (N=1.096) Ipilimumab + nivolumab |
|---|---|---|---|---|---|---|---|
| ORR, % | 25 | 28.7 | 36.4 | 59.3 | 51.4 | 37.0 | 41.3 |
| CR, % | 11 | 1.9 | 2.7 | 5.8 | 3.4 | 5.0 | 10.5 |
| PR, % | 14 | 26.9 | 33.6 | 53.5 | 48.0 | 31.0 | 30.7 |
| SD, % | - | 24.1 | 31.8 | 24.5 | 29.6 | 39.0 | 30.0 |
| PD, % | - | 32.4 | 30.0 | 10.9 | 11.5 | 18.0 | 22.0 |
| NE, % | - | 14.8 | 1.8 | 3.5 | 5.7 | 7.0 | 6.7 |

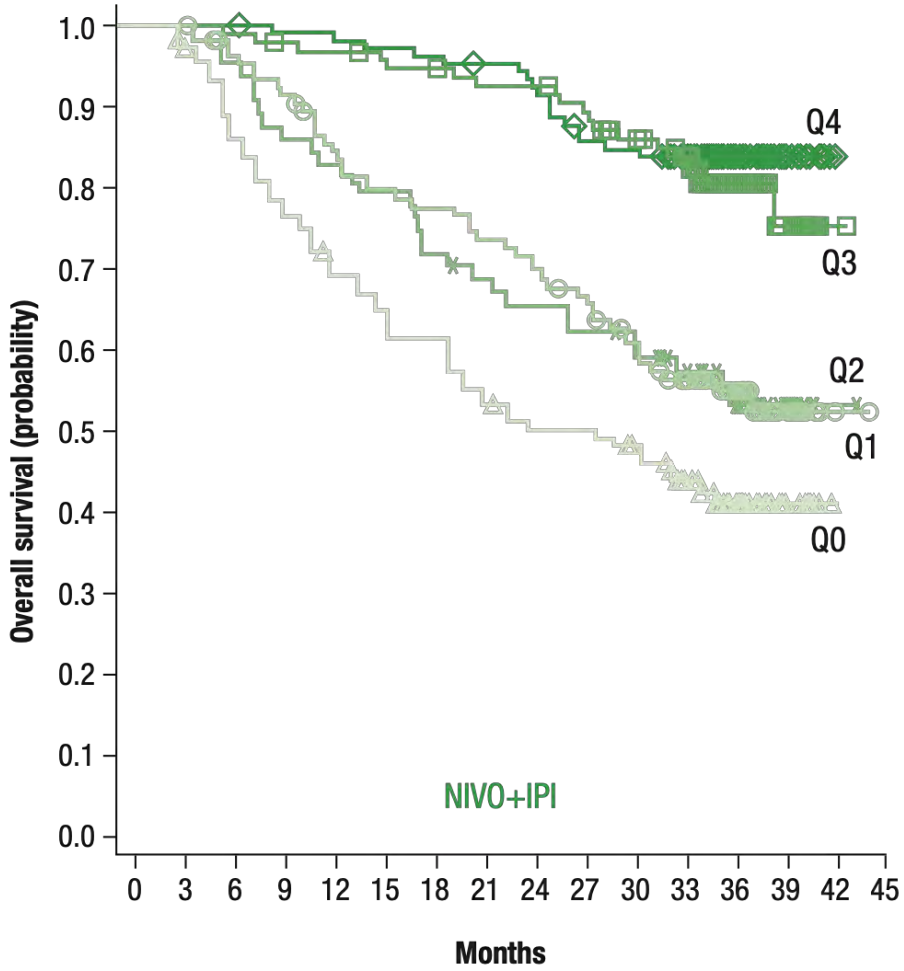
Different follow-up is reported between trials

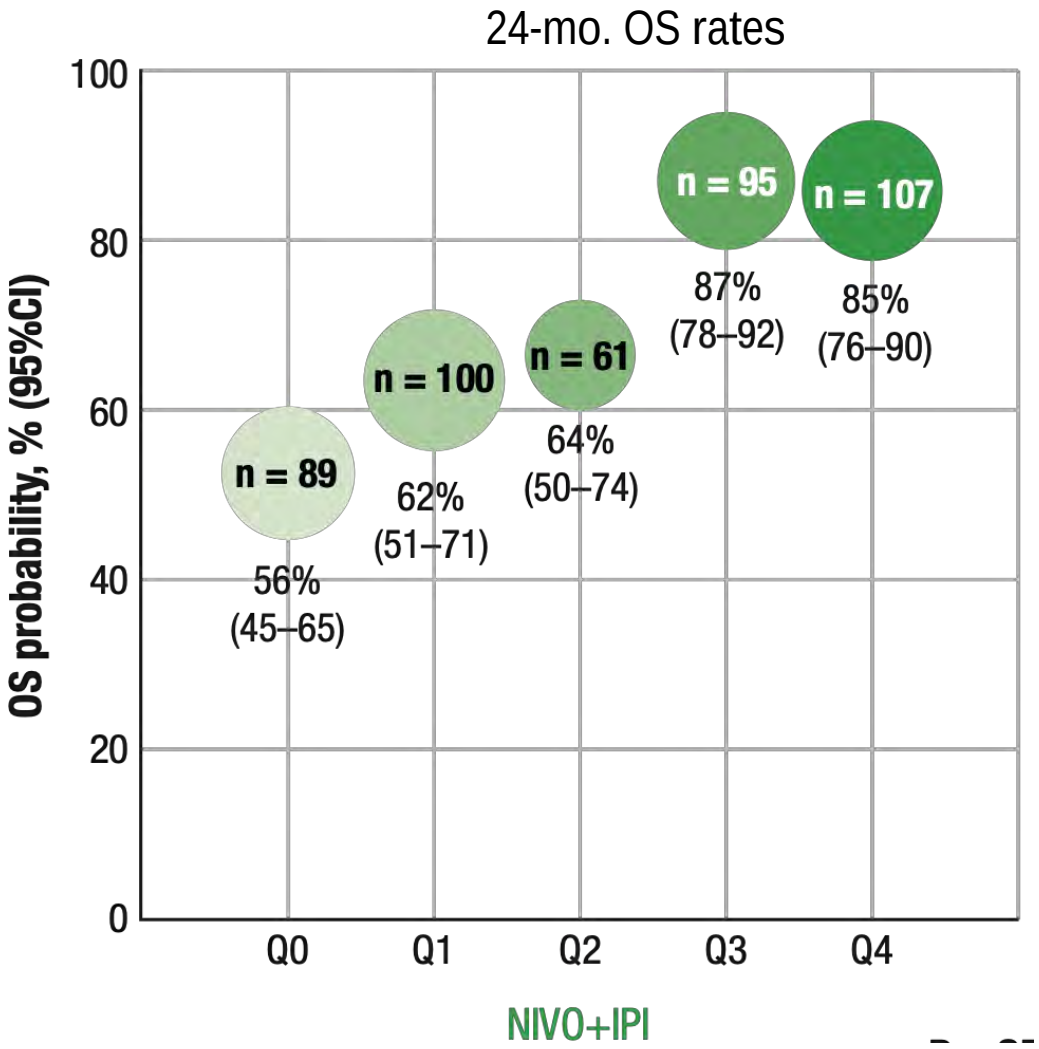
McDermott, D. F. et al. Nat Med 1–14 (2018). doi:10.1038/s41591-018-0053-3. McDermott et al. ASCO 2019; Poster 4570. Rini, B. I. *et al. N Engl J Med* NEJMoa1816714–12 (2019). Motzer et al. ASCO GU 2018: abstract 578. Motzer et al. N Engl J Med NEJMoa1816047 (2019). doi:10.1056/NEJMoa1816047. Rini et al. ESMO 2019: 875P. Grimm et al. ESMO 2019: LBA57

*with a dissease

# A LARGER FRACTION DERIVES BENEFIT FROM IPI-NIVO

## 42% have tumor shrinkage >50%



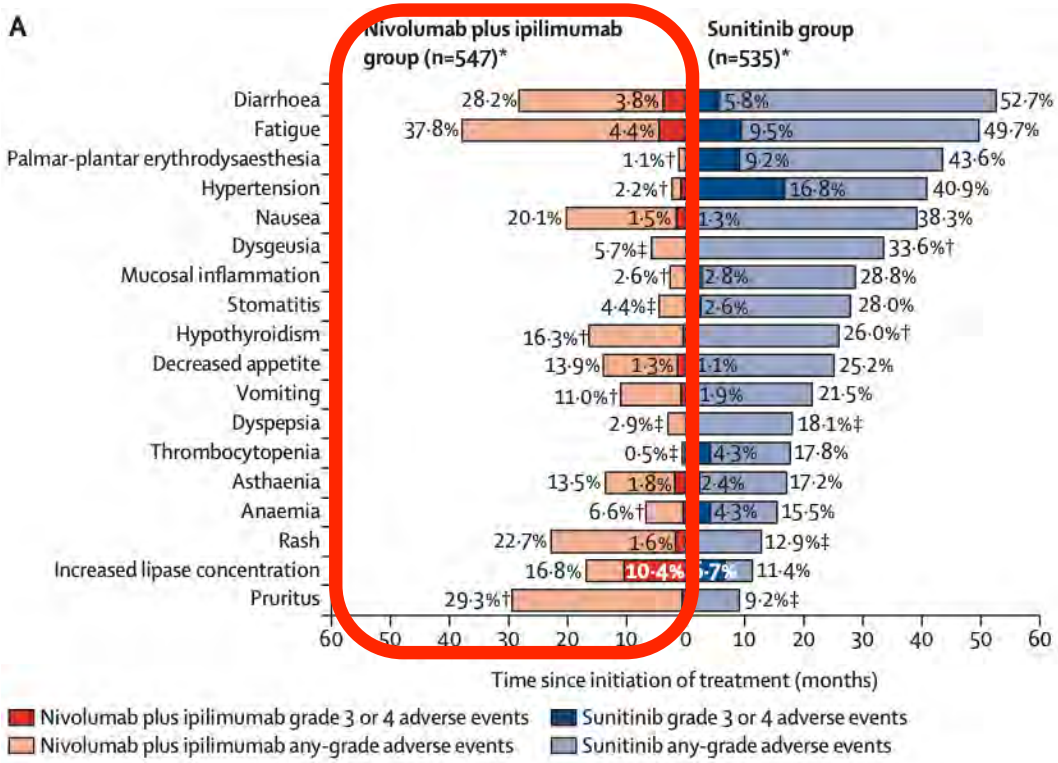

Grünwald ESMO 2019: 950P

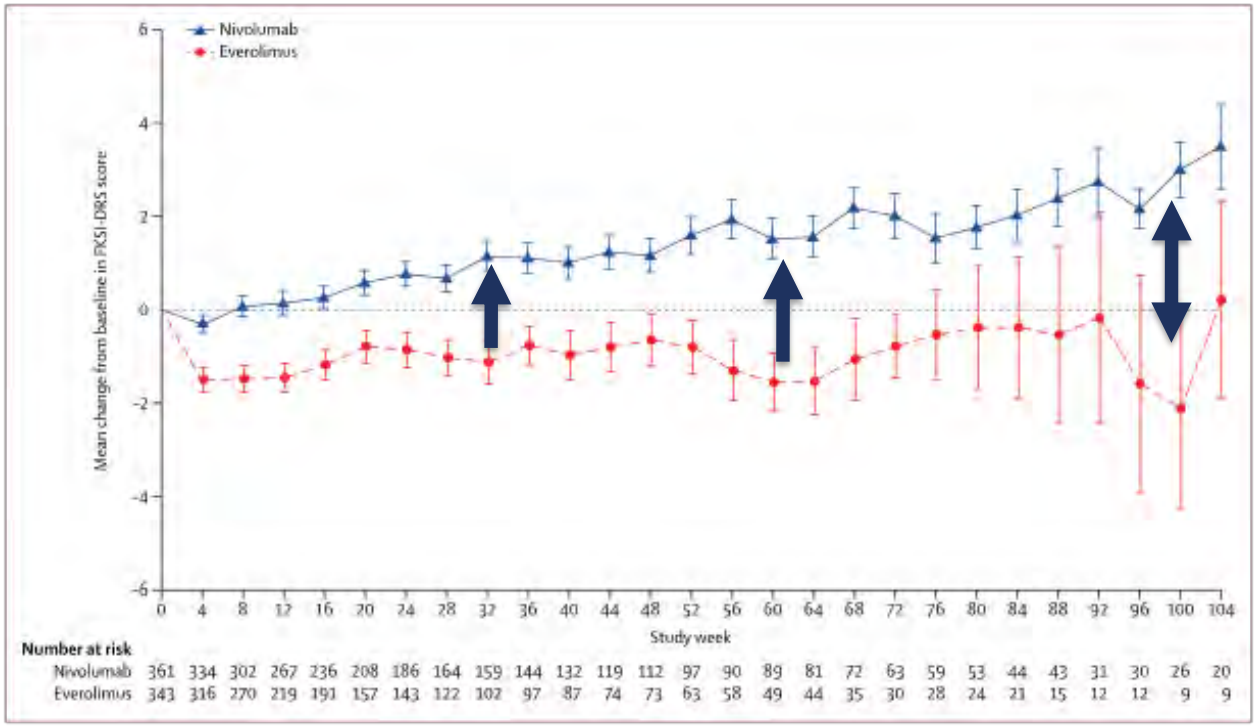
# IPILIMUMAB + NIVOLUMAB HAS BETTER TOLERABILITY

## Less grade ≧ 3 AEs and better HR-QoL than sunitinib

**Grade 3-4 TRAE:**

46,6% 63,9%

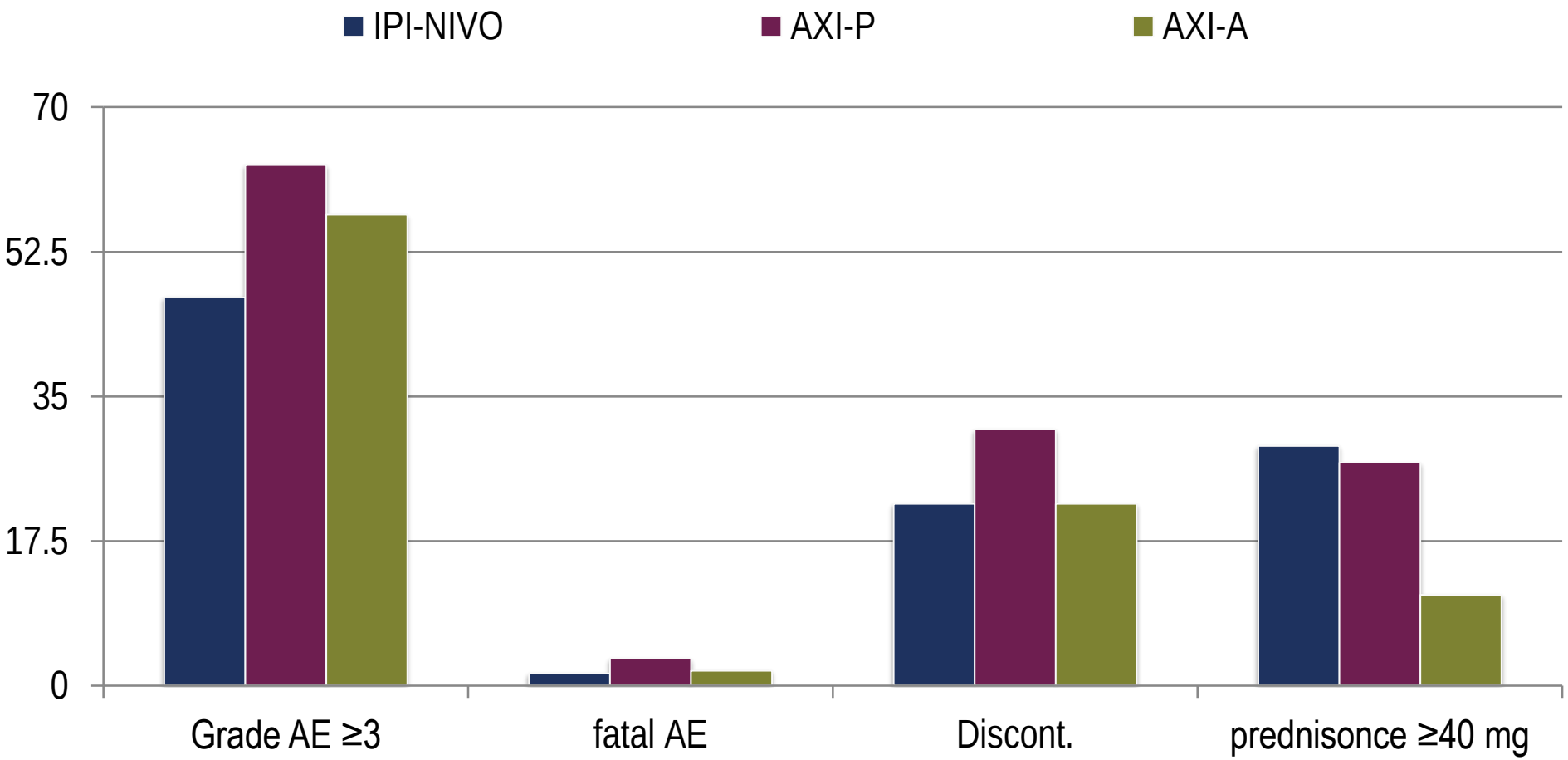



Motzer, R. J. *et al. Lancet Oncol* (2019). doi:10.1016/S1470-2045(19)30413-9

Cella, D., Grünwald, V., Nathan, P., Doan, J., Dastani, H., Taylor, F., et al. (2016). Lancet Oncology, 17(7), 994–1003. http://doi.org/10.1016/S1470-2045(16)30125-5

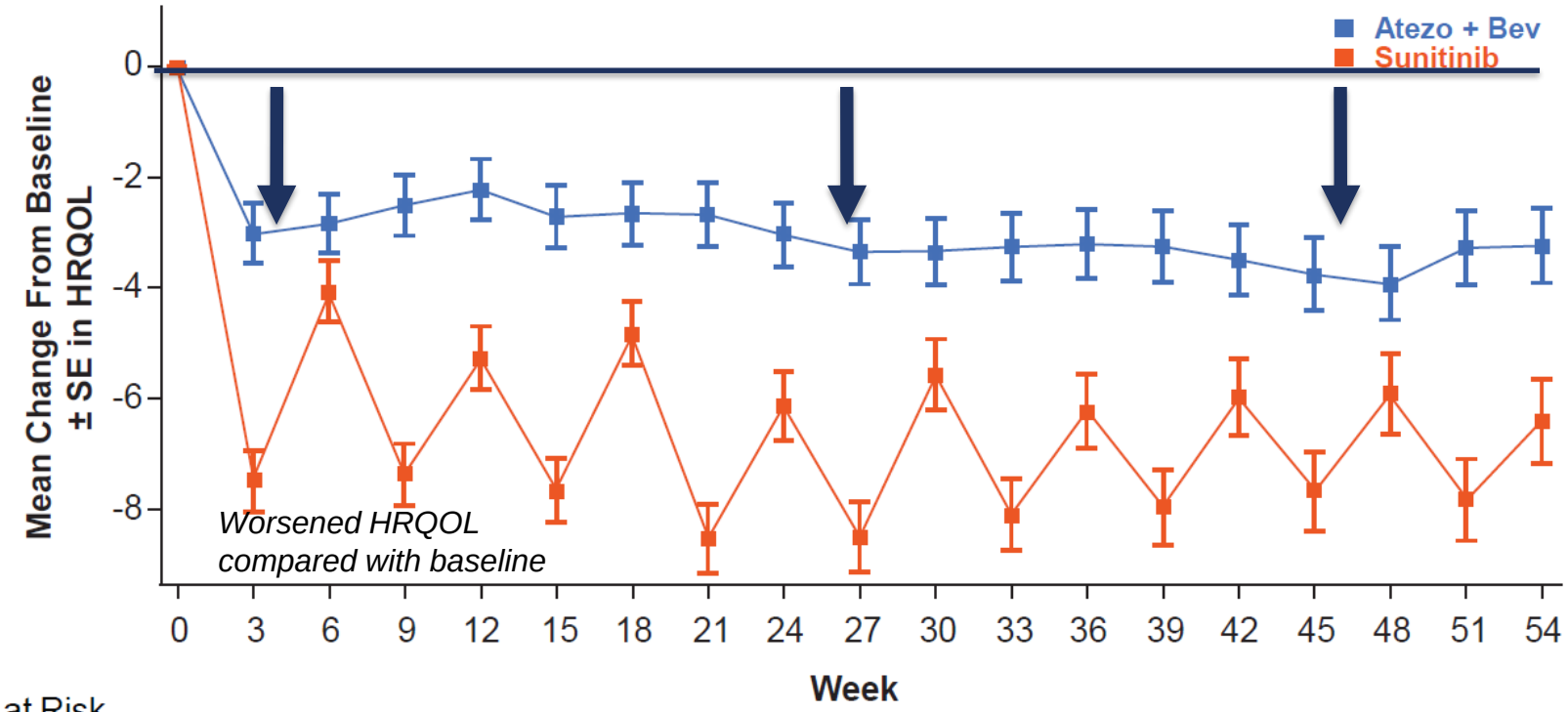
# FAVORABLE TOLERABILITY FOR IPI-NIVO




Motzer et al. Lancer Oncol 2019 http://dx.doi.org/10.1016/S1470-2045(19)30413-9. Motzer et al. N Engl J Med NEJMoa1816047 (2019). doi:10.1056/NEJMoa1816047. Rini, B. I. *et al. N Engl J Med* NEJMoa1816714–12 (2019).

# VEGF INHIBITION IS ASSOCIATED WITH DECREASE IN QOL

## Drop in HR-QoL even with bevacizumab + atezolizumab



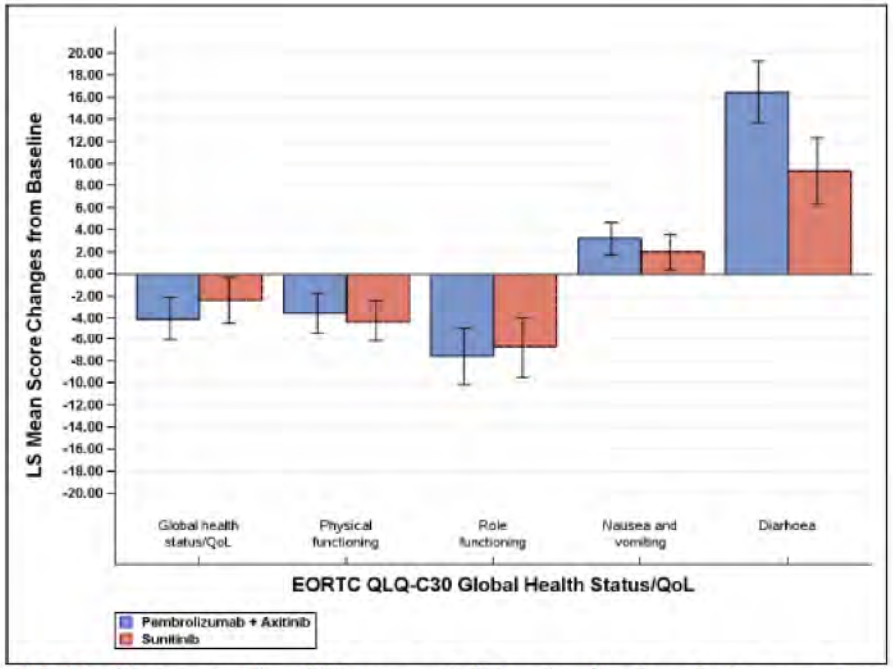

| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Atezo + Bev | 364 | 305 | 297 | 266 | 238 | 223 | 200 | 191 | 185 | 169 |
| Sunitinib | 345 | 276 | 253 | 230 | 210 | 198 | 173 | 161 | 146 | 131 |

Escudier et al. ASCO 2018: 4511

SE, standardized error. Score range, 0-76. Effect size ≥ 0.20 suggests a clinically important difference between arms.
[a] Mean baseline total scores (SD): atezo + bev, 59.8 (9.8) vs sunitinib, 59.5 (9.4). Mean normative FKSI-19 total score for the US general adult population, 59.8.
[b] $P < 0.05$ from repeated-measures model for atezo + bev vs sunitinib at visits until week 72; exception was at week 6.
[c] Average difference in least-squares mean estimates of score changes for atezo + bev vs sunitinib at visits through week 54 was 3.67; mean effect size, 0.42 (range, 0.16, 0.67).
$P < 0.0001$ from linear mixed model of change from baseline to end of treatment; effect size, 0.35. 1. Butt et al. *Cancer.* 2013;119:429-437.

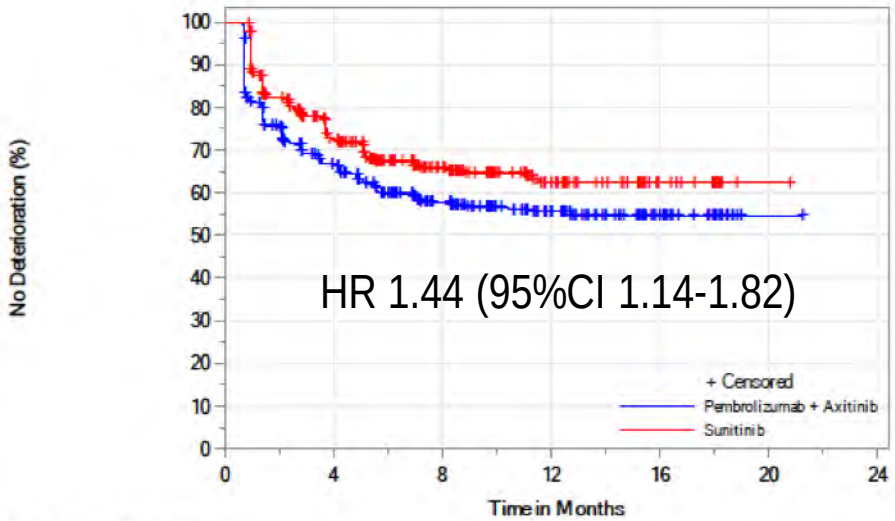
# KN426: WITHOUT HR-QOL-BENEFIT FOR AXITINIB + PEMBROLIZUMAB

EORTC QLQC30




For global health status/quality of life score and all functional scales: a higher score denotes better health related quality of life (HRQOL) or function.
For symptoms scales: a higher score denotes worse symptoms.
Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adplda]

Time to Deterioration (FKSI-DRS)




Number of subjects at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pembrolizumab + Axitinib | 395 | 227 | 144 | 86 | 32 | 1 | 0 |
| Sunitinib | 387 | 226 | 138 | 73 | 26 | 1 | 0 |

Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adpro; adttd]

EPAR Pembrolizumab: EMA/CHMP/455620/2019 25.07.19

# CONCLUSIONS

- IPI-NIVO achieved the highest fraction of CRs
- Durability of CPI-induced responses is better than with TKI
- Quality of response is a key component for improved clinical outcome
- There are no signs of detrimental tolerability for IPI-NIVO
- HR-QoL improved during treatment with IPI-NIVO and is better than with sunitinib
- AXI-PEMBRO has no improvement in HR-QoL
  (in fact: time to deterioration is better with sunitinib)
- AXI-PEMBRO or AVELU have short FU and longevity of outcome data cannot be assessed, yet
- Overall, IPI-NIVO exerts many benefits and should be the preferred 1st line choice