AKERSHUS UNIVERSITETSSYKEHUS

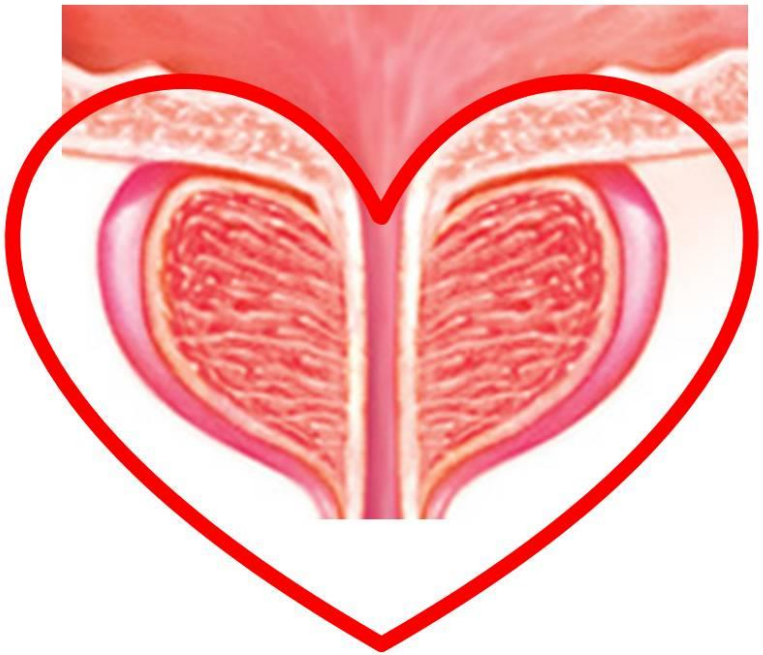
Immunterapi for urologiske krefttyper

Daniel Heinrich
Overlege
Onkologisk avdeling

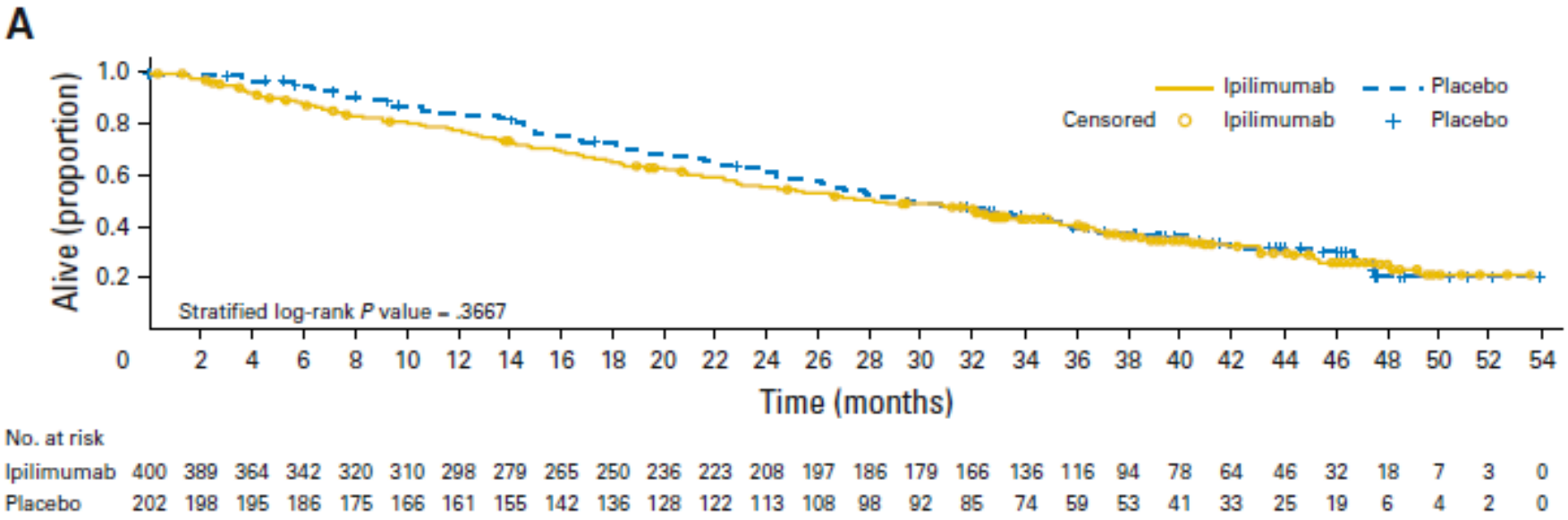
Norsk onkologisk forening
DEN NORSKE LEGEFORENING

IMMUNTERAPI INNEN UROONKOLOGIEN

Prostate: The only “Heart” shaped organ

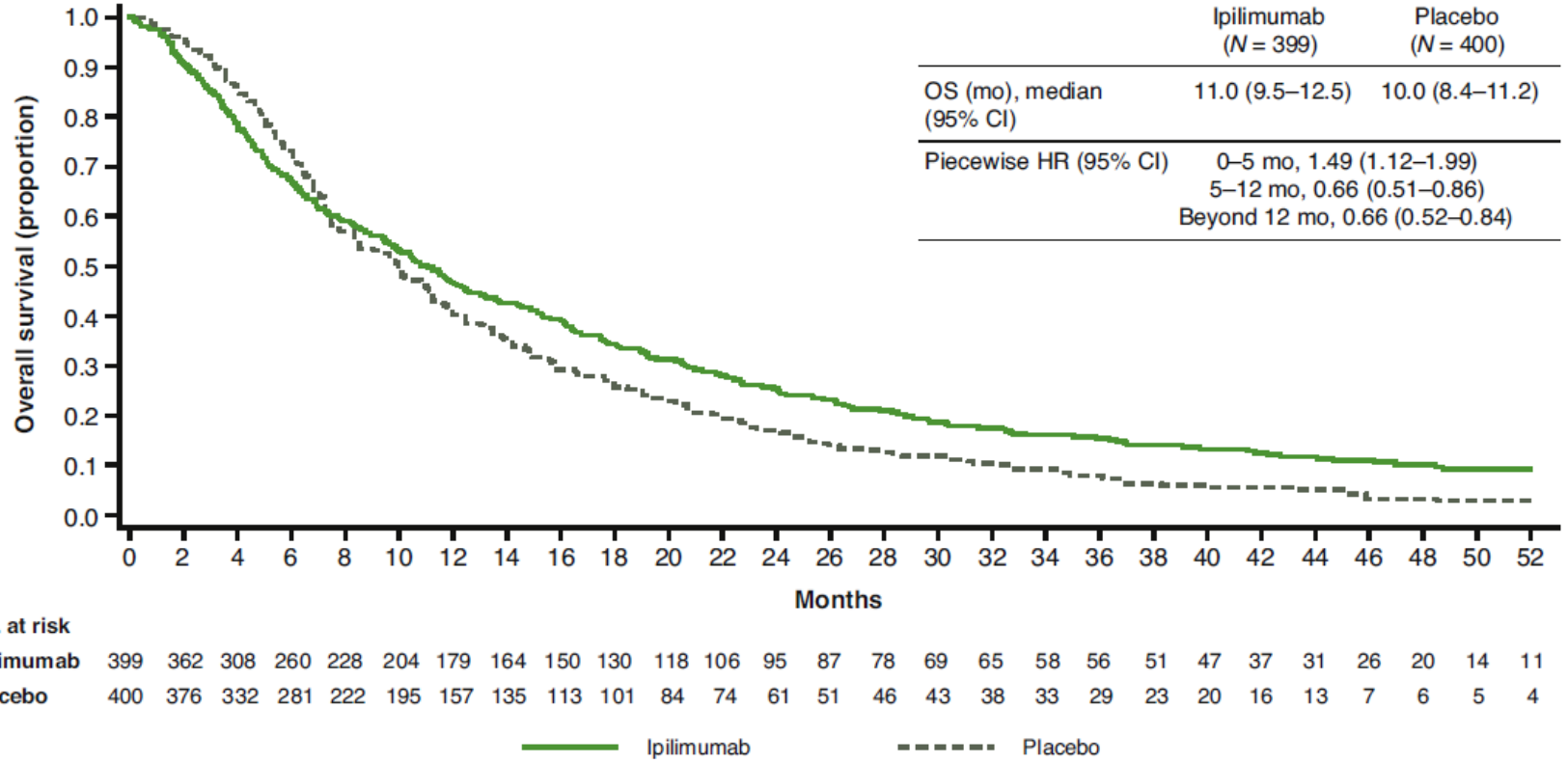


Ipilimumab pre Docetaxel



Beer et al.; J Clin Oncol, 2016

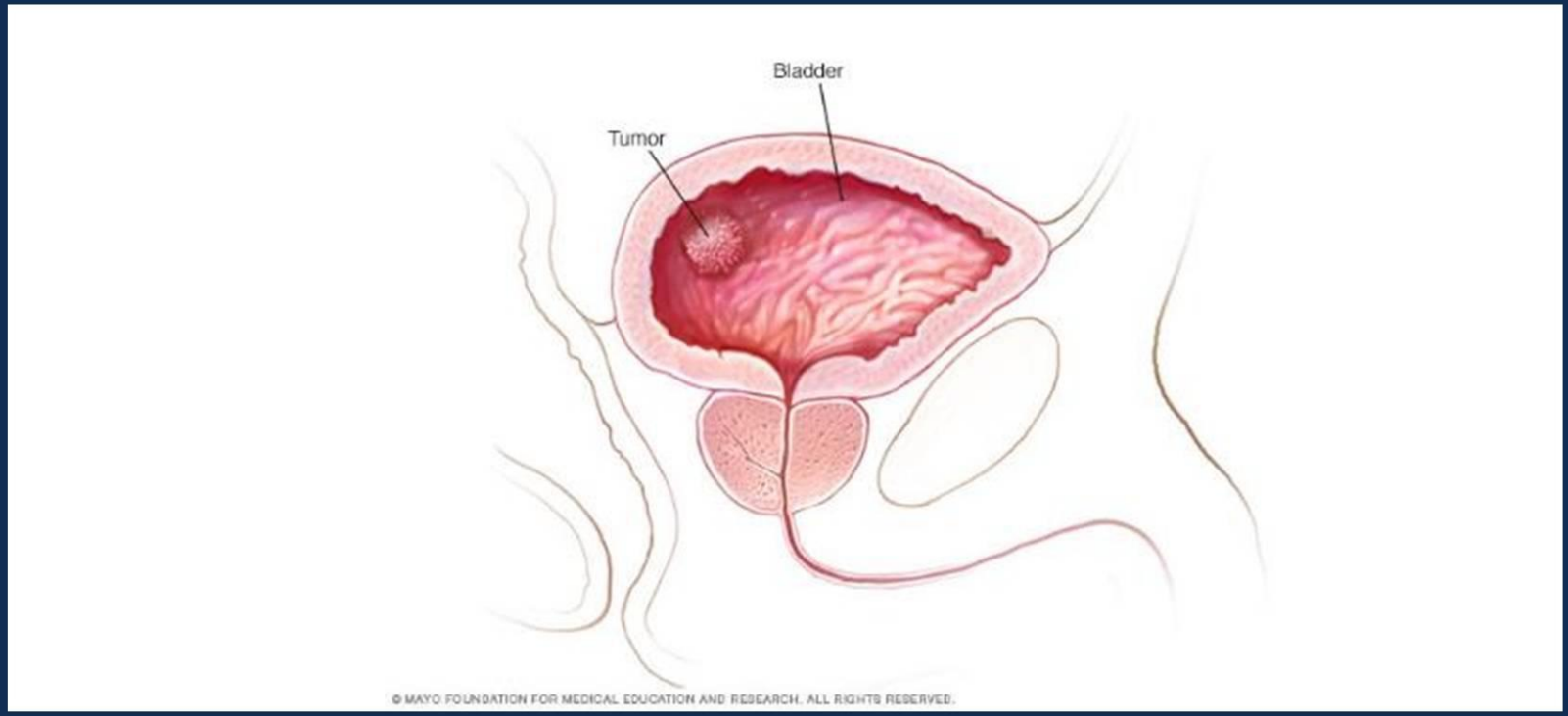
Ipilimumab post Docetaxel



	Ipilimumab (*N* = 399)	Placebo (*N* = 400)
OS (mo), median (95% CI)	11.0 (9.5–12.5)	10.0 (8.4–11.2)
Piecewise HR (95% CI)	0–5 mo, 1.49 (1.12–1.99) 5–12 mo, 0.66 (0.51–0.86) Beyond 12 mo, 0.66 (0.52–0.84)	

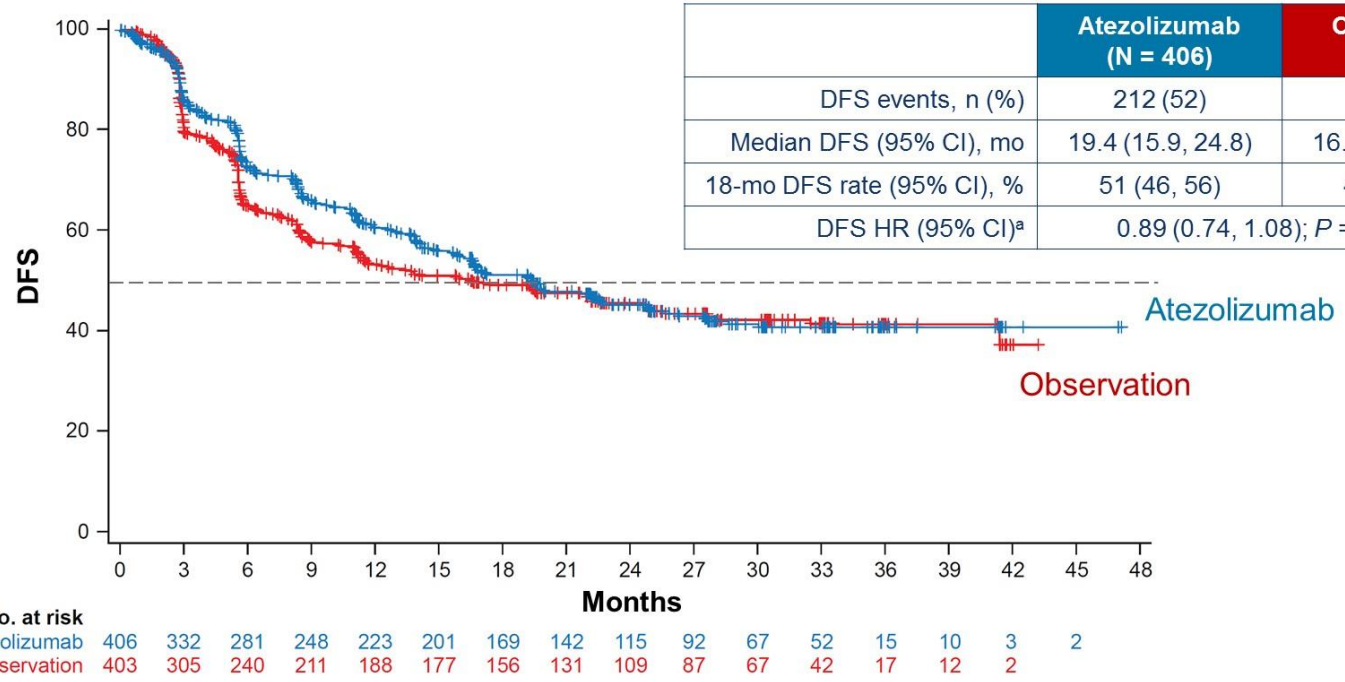
Fizazi et al.; Eur Urol, 2020

Bladder Cancer



Adjuvant immunterapi

DFS in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

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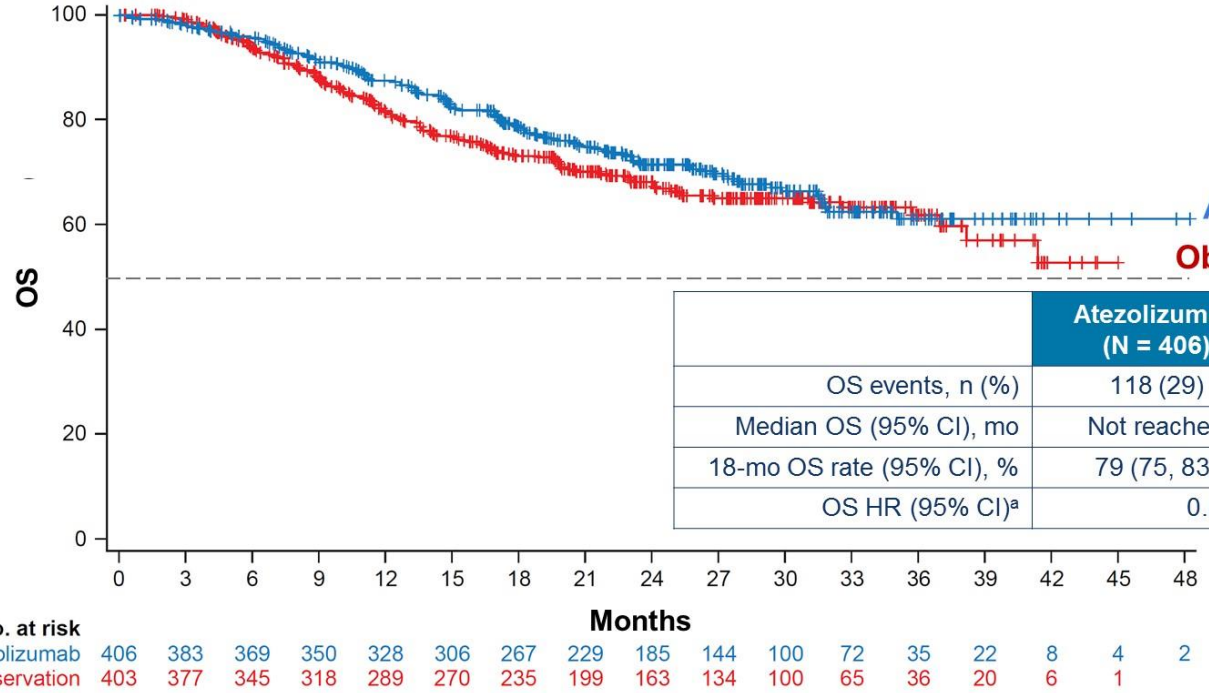
PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000]. https://bit.ly/2SKSAD3

Presented By Maha Hussain at ASCO Virtual 2020

Interim OS Analysis in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). [a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

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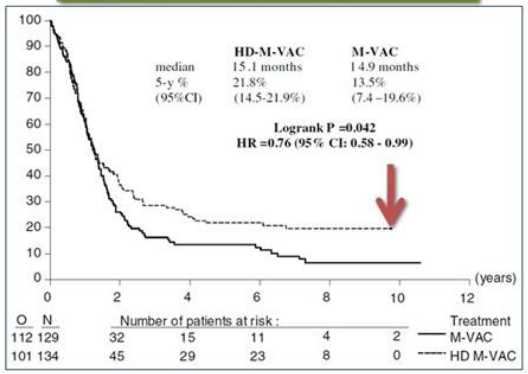
PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000]. https://bit.ly/2SKSAD3

Presented By Maha Hussain at ASCO Virtual 2020

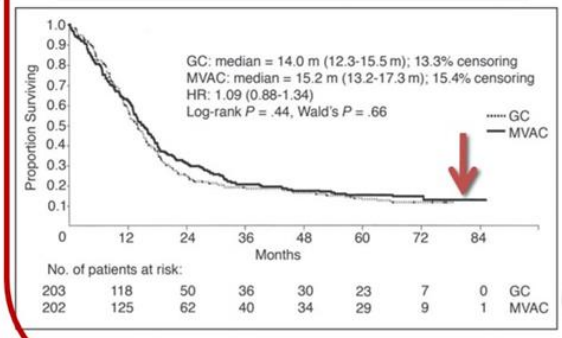
1. linjes kjemoterapi

Cisplatin Eligible

Dose Dense MVAC
ORR 72%
CR 25%
mOS 15.1 mo

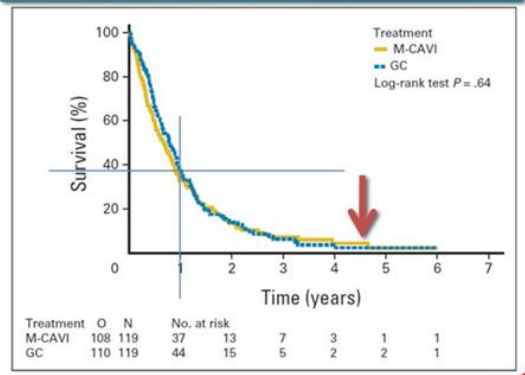


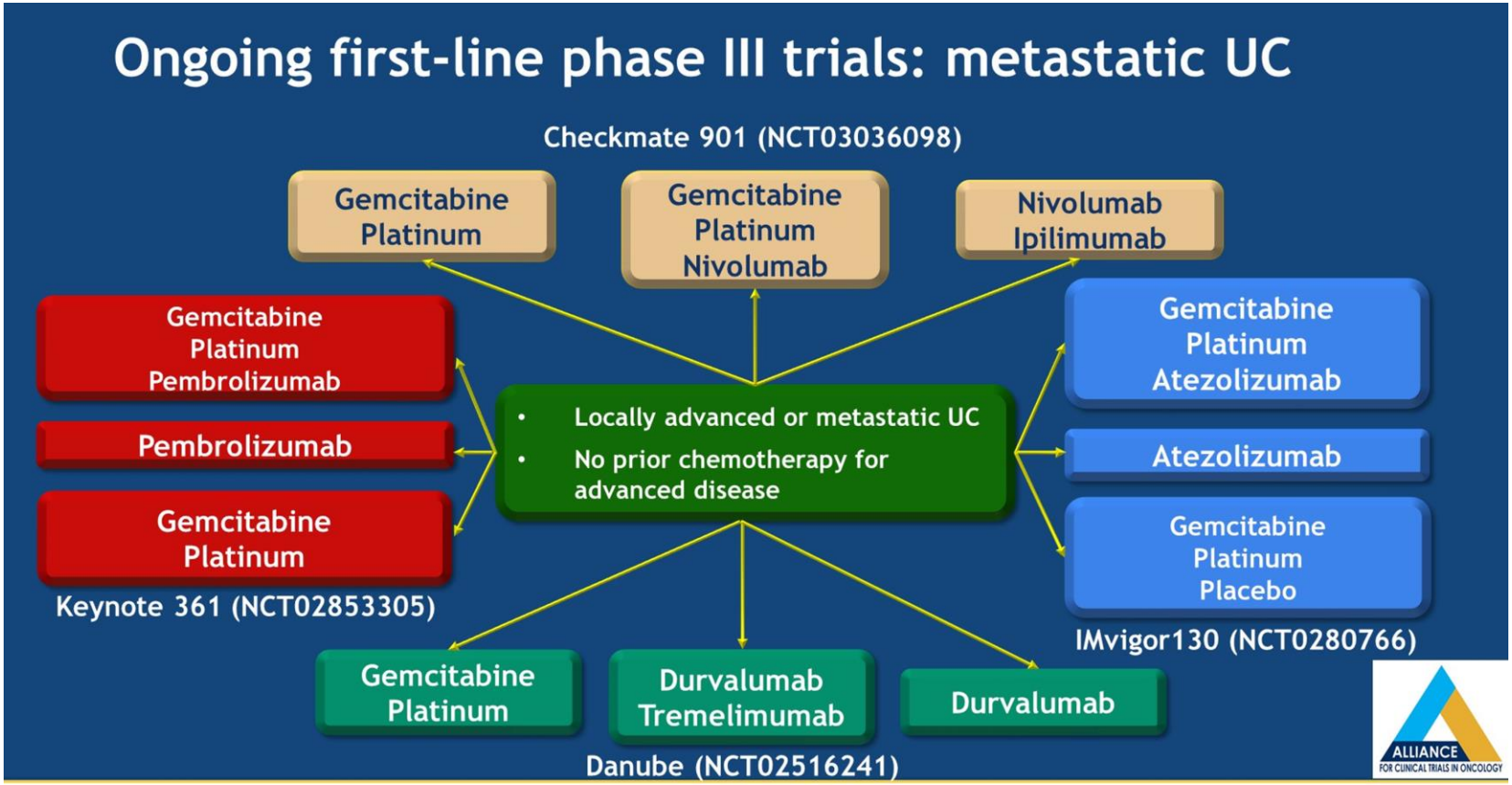
Gemcitabine Cisplatin
ORR 49%
CR 12 %
mOS 14 mo



Cisplatin Ineligible

Gemcitabine Carboplatin
ORR 36%
CR 3%
mOS 9.3 mo




Ongoing first-line phase III trials: metastatic UC
Checkmate 901 (NCT03036098)
Gemcitabine Platinum
Gemcitabine Platinum Nivolumab
Nivolumab Ipilimumab
Gemcitabine Platinum Pembrolizumab
Pembrolizumab
Gemcitabine Platinum
Keynote 361 (NCT02853305)
• Locally advanced or metastatic UC
• No prior chemotherapy for advanced disease
Gemcitabine Platinum Atezolizumab
Atezolizumab
Gemcitabine Platinum Placebo
IMvigor130 (NCT0280766)
Gemcitabine Platinum
Durvalumab Tremelimumab
Durvalumab
Danube (NCT02516241)
ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY
PRESENTED AT: 2019 ASCO ANNUAL MEETING
#ASCO19
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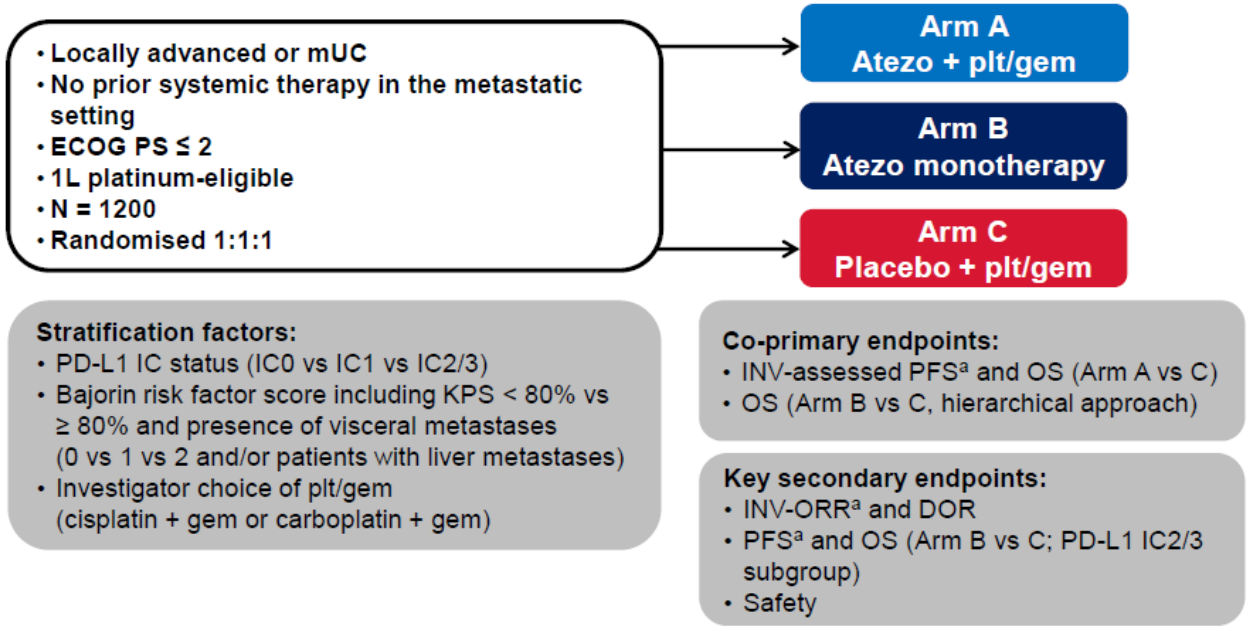
PRESENTED BY: Jonathan E. Rosenberg, MD

IMvigor130 study design

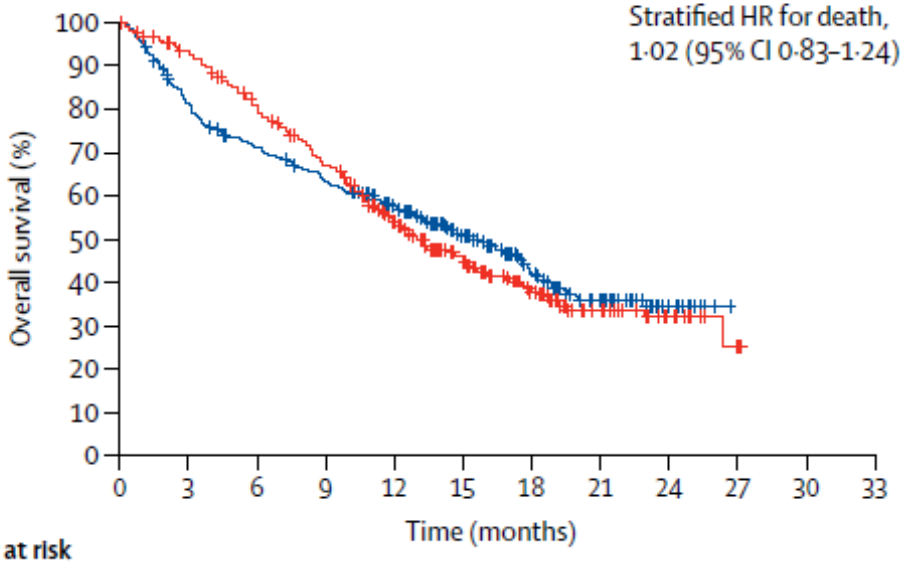


[a] per RECIST 1.1.

IMvigor130—ESMO 2019 (LBA14): presented by Dr Enrique Grande http://bit.ly/2Z1bPbD

Imvigor130 - OS

	Number of events/ number of patients	Median overall survival (95% CI), months
Atezolizumab monotherapy (group B)	191/360	15·7 (13·1–17·8)
Placebo + platinum-based chemotherapy (group C)	198/359	13·1 (11·7–15·1)

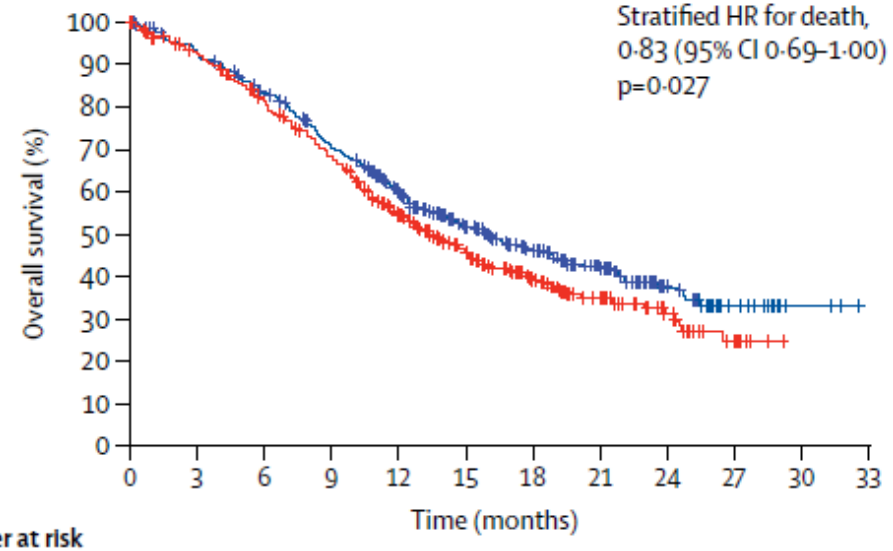


Number at risk (number censored)												
Atezolizumab monotherapy (group B)	360 (0)	285 (10)	245 (14)	216 (16)	173 (41)	120 (75)	72 (107)	42 (128)	16 (153)	NE	NE	NE
Placebo + platinum-based chemotherapy (group C)	359 (0)	322 (13)	274 (19)	224 (24)	158 (48)	103 (79)	62 (107)	35 (128)	15 (147)	3 (158)	NE	NE

Galsky et al.; Lancet 2020

IMvigor130 - OS

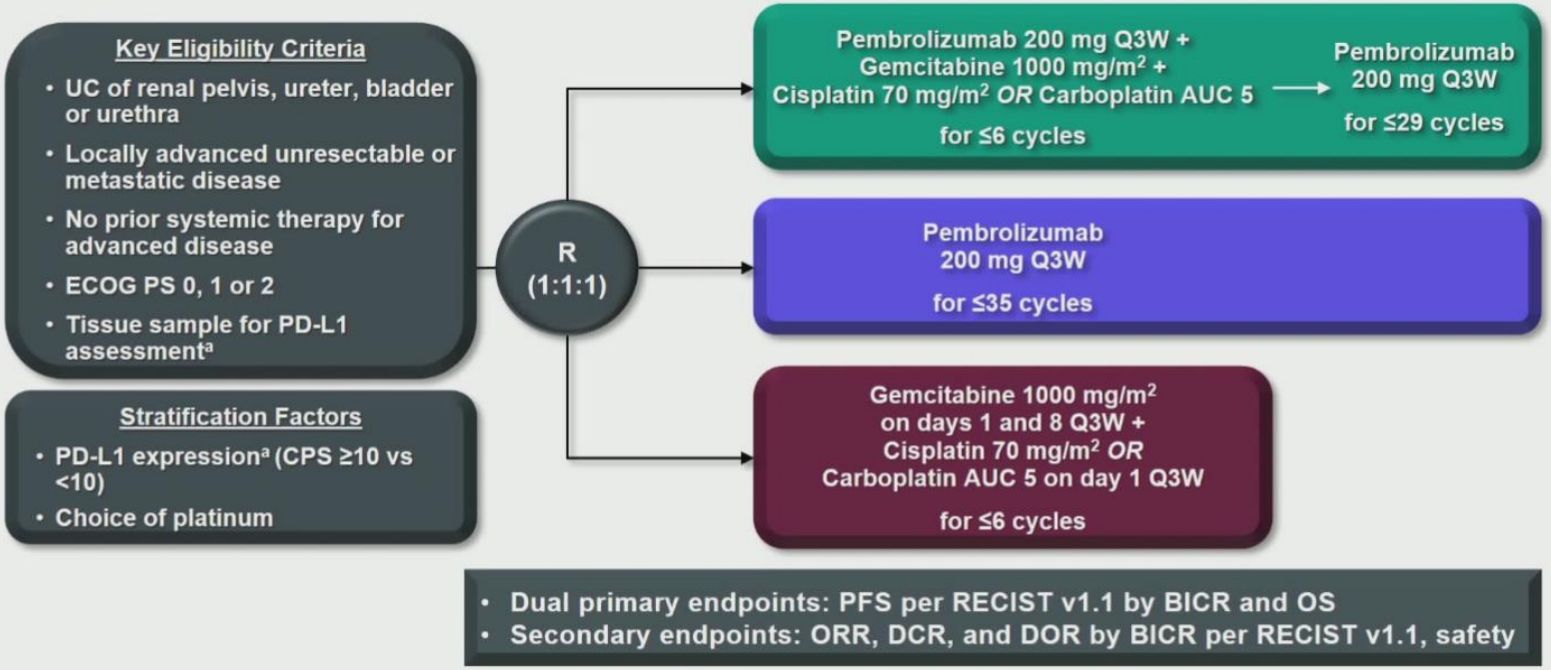
	Number of events/ number of patients	Median overall survival (95% CI), months
Atezolizumab + platinum-based chemotherapy (group A)	235/451	16·0 (13·9–18·9)
Placebo + platinum-based chemotherapy (group C)	228/400	13·4 (12·0–15·2)



Number at risk (number censored)												
Atezolizumab + platinum-based chemotherapy (group A)	451 (0)	408 (11)	360 (17)	301 (23)	229 (51)	163 (88)	117 (118)	72 (154)	36 (184)	16 (200)	3 (213)	NE
Placebo + platinum-based chemotherapy (group C)	400 (0)	359 (13)	308 (19)	255 (24)	182 (48)	123 (79)	79 (108)	49 (131)	25 (151)	8 (164)	NE	NE

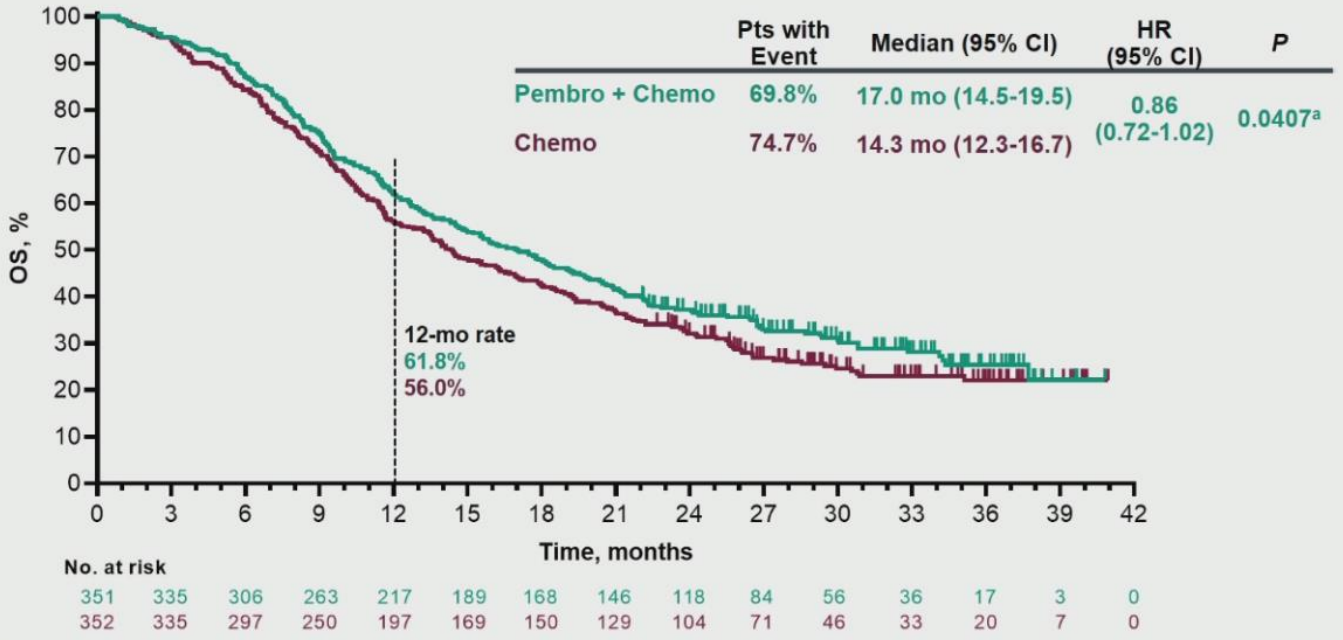
Galsky et al.; Lancet 2020

KEYNOTE-361 Study Design (NCT02853305)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay. CPS (combined positive score) is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.
BICR, blinded independent central review.

OS: Pembro + Chemo vs Chemo, ITT Population

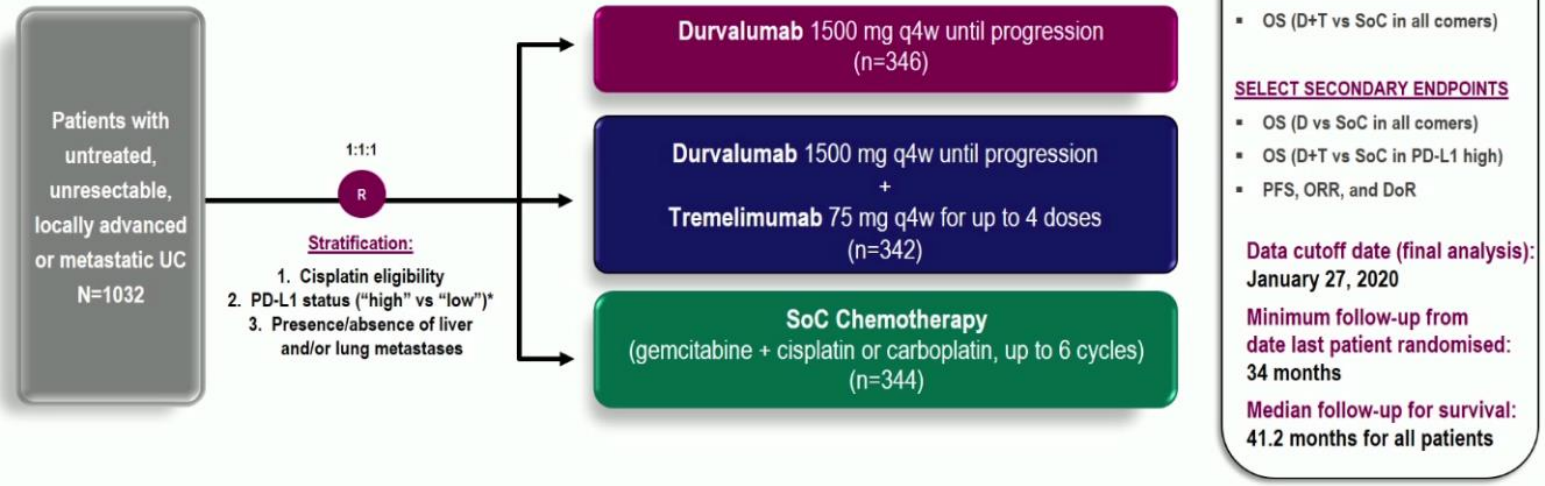


	Pts with Event	Median (95% CI)	HR (95% CI)	*P*
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407[a]
Chemo	74.7%	14.3 mo (12.3-16.7)		

[a]*P*-value boundary of significance at final analysis ≤0.0142. Per the statistical analysis plan, no further formal statistical testing was performed.
Data cutoff date: April 29, 2020.

VIRTUAL 2020 ESMO congress

DANUBE Study Design[1]



*PD-L1 assessed using the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Tucson, AZ)[2]
– High PD-L1 expression[3]: either ≥25% of tumour cells (TCs) with membrane staining or ≥25% of immune cells (ICs) staining for PD-L1 at any intensity

1. Clinicaltrials.gov, NCT02516241. EudraCT number 2015-001633-24.
2. Zajac M, et al. *Arch Pathol Lab Med* 2019;143:722–31.
3. Ventana Medical Systems. VENTANA PD-L1 (SP263) Assay. https://www.accessdata.fda.gov/cdrh_docs/pdf18/p180046c.pdf.

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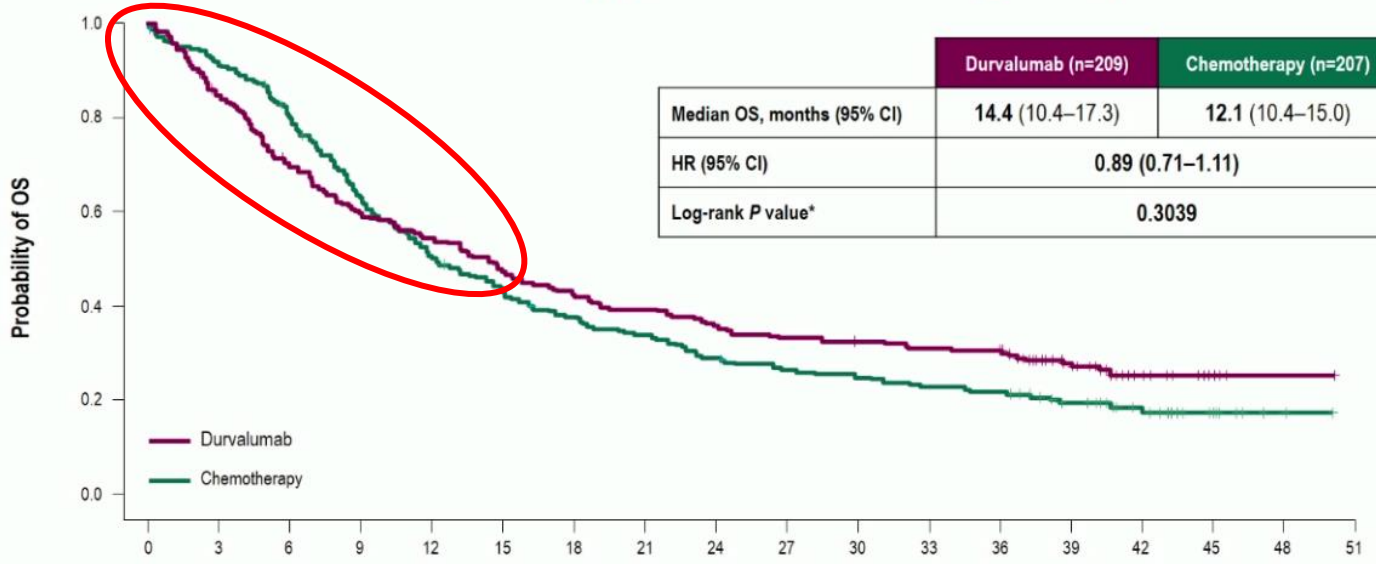
Co-primary Endpoint: OS With Durvalumab vs Chemotherapy in the PD-L1 High Population

	Durvalumab (n=209)	Chemotherapy (n=207)
Median OS, months (95% CI)	**14.4** (10.4–17.3)	**12.1** (10.4–15.0)
HR (95% CI)	**0.89 (0.71–1.11)**	
Log-rank *P* value*	**0.3039**	



Number at risk

Durvalumab	209	176	143	123	112	97	87	81	74	68	66	63	61	39	19	6	1	0
Chemotherapy	207	186	161	126	101	86	74	66	57	51	48	44	42	27	16	8	2	0

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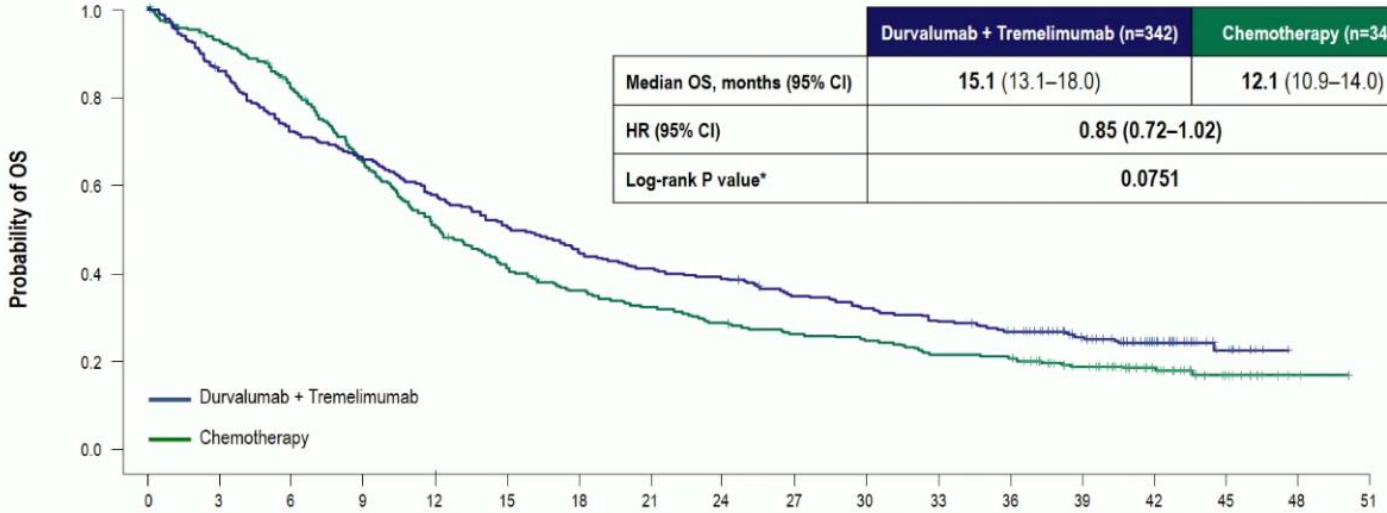
Co-primary Endpoint – OS with Durvalumab + Tremelimumab vs Chemotherapy in the ITT Population

	Durvalumab + Tremelimumab (n=342)	Chemotherapy (n=344)
Median OS, months (95% CI)	**15.1** (13.1–18.0)	**12.1** (10.9–14.0)
HR (95% CI)	**0.85 (0.72–1.02)**	
Log-rank P value*	**0.0751**	



Number at risk

Durvalumab + Tremelimumab	342	292	246	224	197	173	153	140	133	118	108	99	89	61	33	12	0	0
Chemotherapy	344	311	273	216	168	136	119	107	95	86	81	71	68	46	27	11	2	0

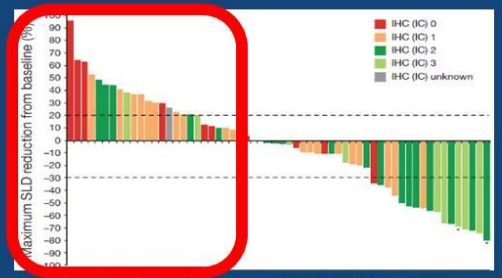
Vi venter fremdeles på CheckMate 901 ….

… som forøvrig fremdeles inkluderer pasienter (bl. a. på Ahus)…

… men ærlig talt…

Initial Second-line Phase I/II Studies with Checkpoint Blockade in Metastatic Urothelial Carcinoma: Summary of ORR

Atezolizumab



Powles T et al., Nature. 2014;515:558-562.

Pembrolizumab

Plimack ER, et al. Lancet Oncol 2017 Feb;18(2):212-220

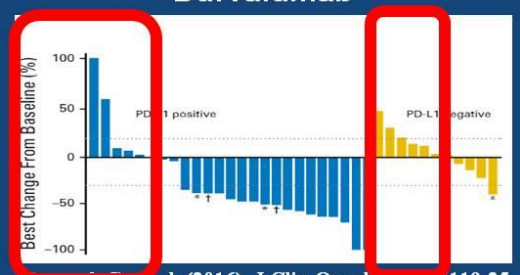
Avelumab

Apolo, AB., et al. (2017) J Clin Oncol 1;35(19):2117-2124

Nivolumab

Sharma, P., et al. (2016). Lancet Oncol 17: 1590-1598

Durvalumab



al. (2016). J Clin Oncol 34(26):3119-25

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

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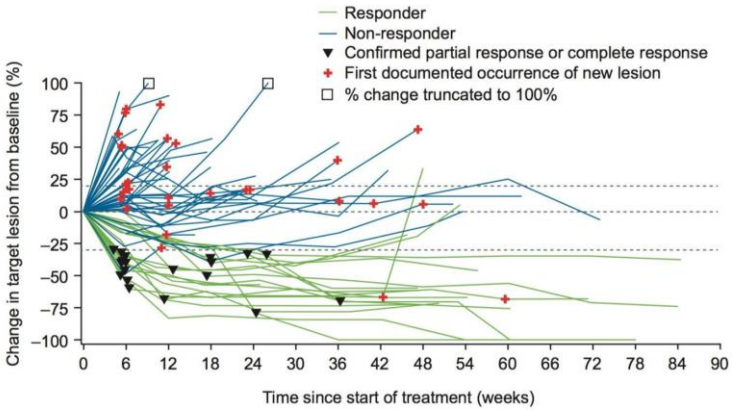
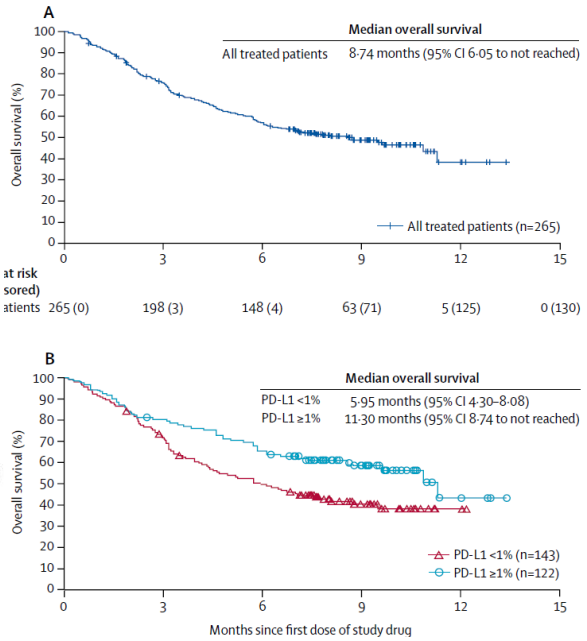
PRESENTED BY: Andrea B. Apolo, MD

PD-1 eller PD-L1 rettede antistoff …
… for behandling av metastatisk UC

- Nivolumab, Atezolizumab, Pembrolizumab (tilfeldig rekkefølge) og snart Durvalumab har alle godkjent indikasjon for metastatisk blærecancer
- Noen er godkjent for 1. linje andre etter kjemoterapi eller for pasienter som ikke er egnet for kjemoterapi

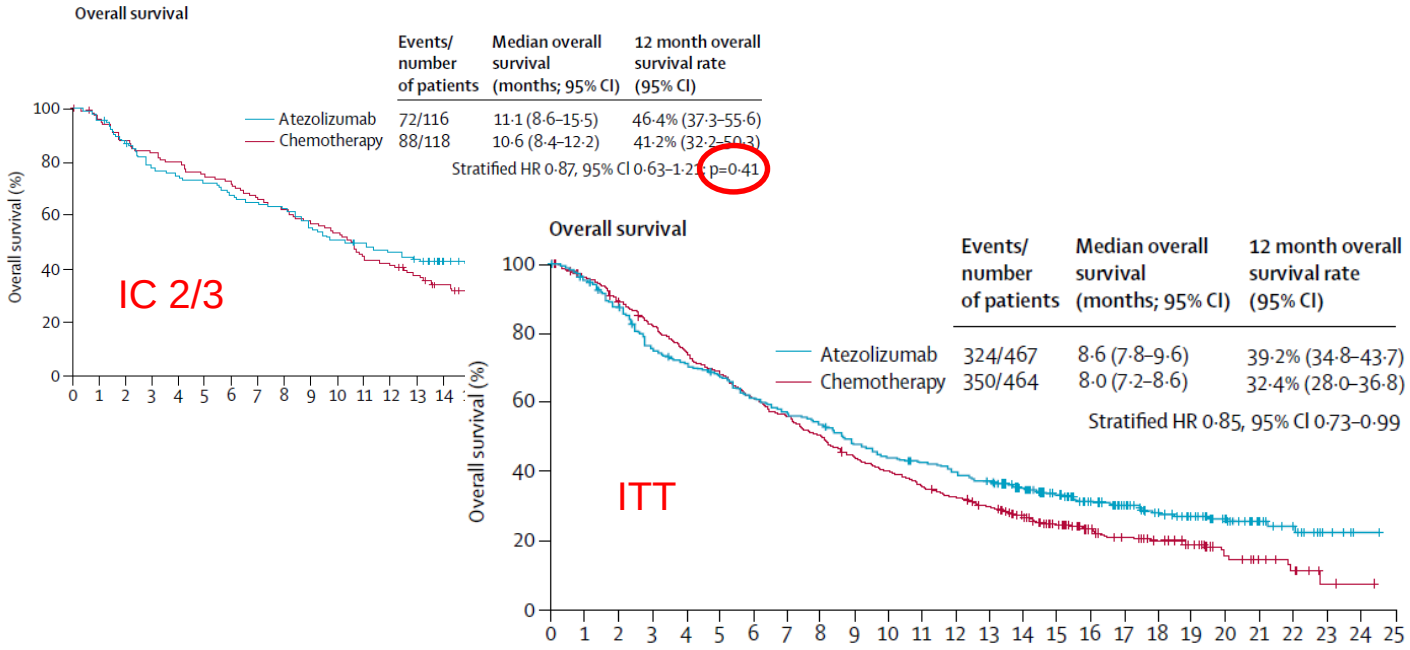




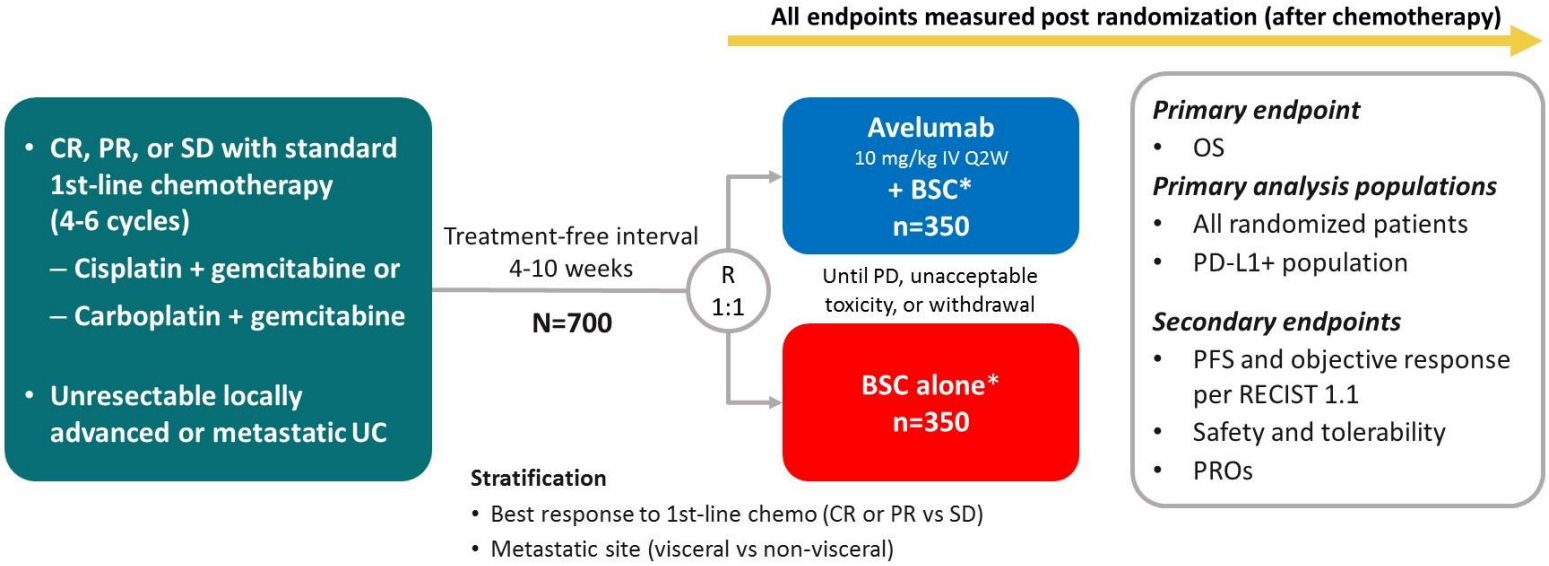
Sharma et al.; Lancet Oncol, 2017

PD-1 eller PD-L1 rettede antistoff …
… for behandling av metastatisk UC

- Responsratene er totalt sett lave (noe bedre i 1. enn i 2. linje)
- Ingen klar sammenheng mellom potensielle prediktive markører og respons på tverrs av medikamentene



JAVELIN Bladder 100 study design (NCT02603432)



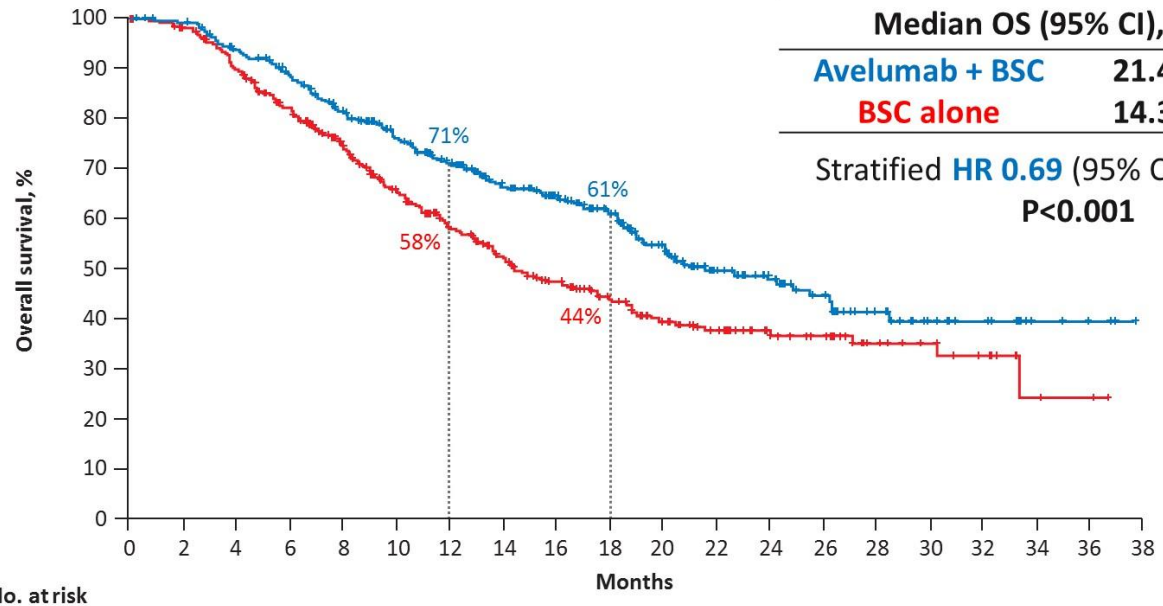
PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

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

Presented By Thomas Powles at ASCO Virtual 2020

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)

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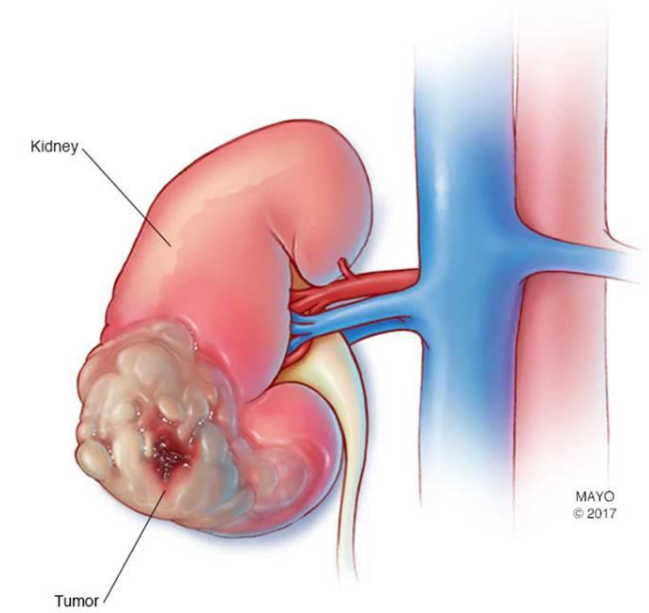
Konklusjoner immunterapi for urotheliale svulster i palliativ setting

- De fleste pasienter bør få én gang i løpet av sin behandlingshistorie
- Første linjes monoterapi er kontraindisert (pasienter dør raskere), første linjes kombinasjonsbehandling byr bare på en liten gevinst for en liten undergruppe
- 2. linjes behandling (for tiden med Atezolizumab som foretrukket preparat) er godkjent av DKNB
- Den desidert største gevinsten gir vedlikeholdsbehandling etter 1. linjes platinbasert kjemoterapi (Avelumab er under vurdering i Nye Metoder)
- Siden det tar tid i praksis i dag: Platinum kombo i 1. linje etterfulgt av umiddelbar "2. linjes" behandling med Atezolizumab … uansett respons

Renal Cancer



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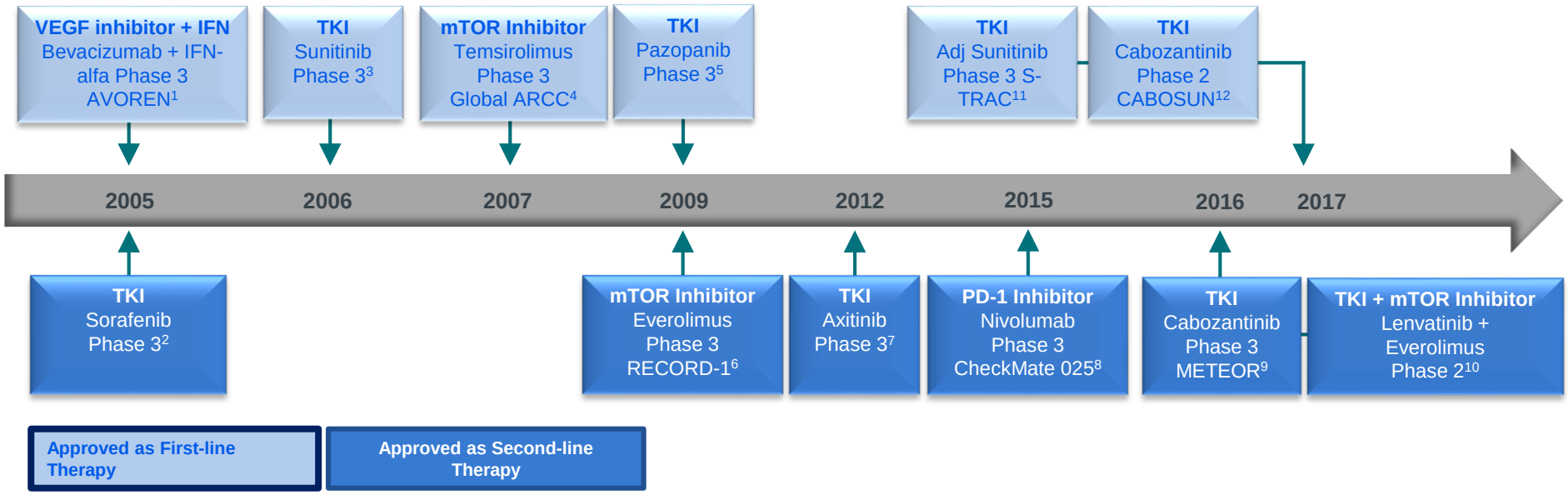
(R)evolusjon av behandlingsmuligheter for mRCC 2005–2018



CheckMate 214

- Treatment-naïve advanced ccRCC
- Measurable disease
- KPS ≥70%
- Tumour tissue available for PD-L1 testing

R*
1:1

NIV 3 mg/kg **+ IPI** 1 mg/kg q3w for 4 doses. then NIV 3 mg/kg q

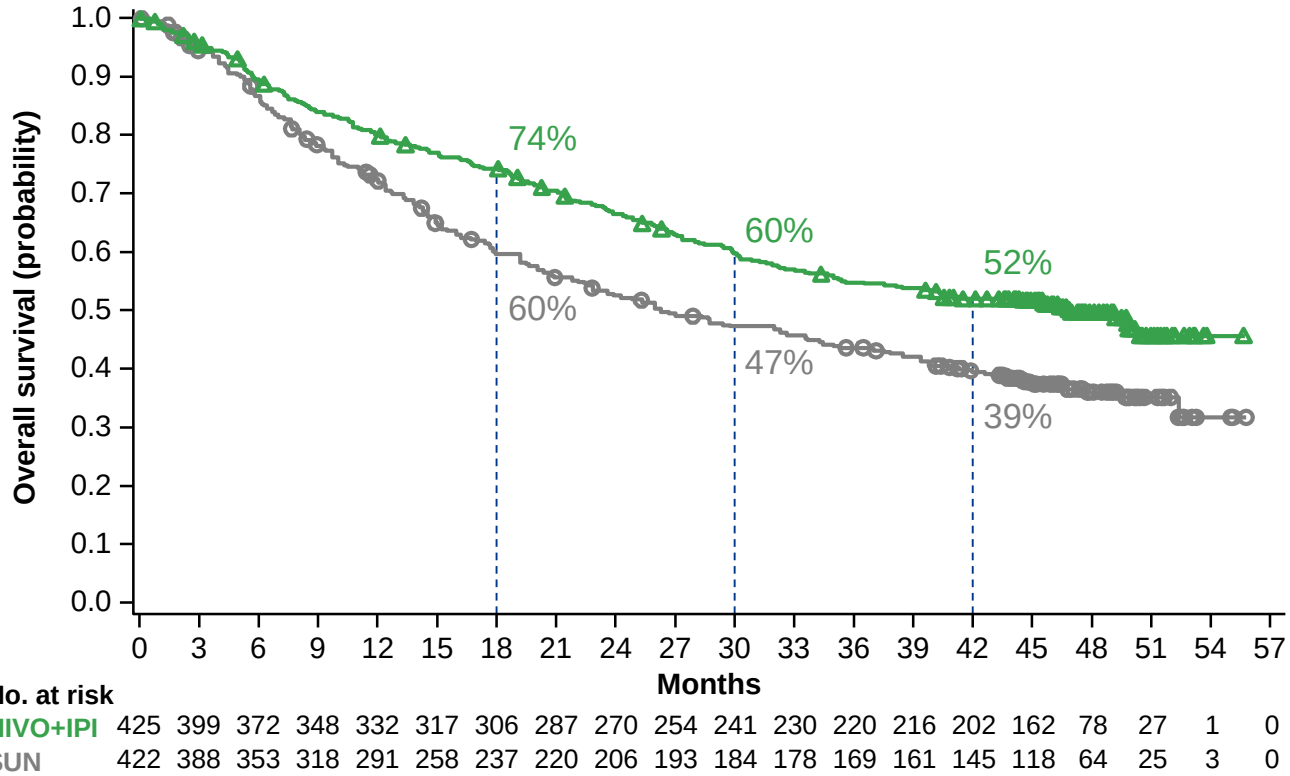
SUN 50 mg qd
(4 wk on, 2 wk off – 6-wk cycles)

Endpoints: OS, PFS
Objective response rate (ORR)

*stratification according to IMDC prognostic score and region

Overall Survival

Primary efficacy population: Intermediate/poor-risk patients



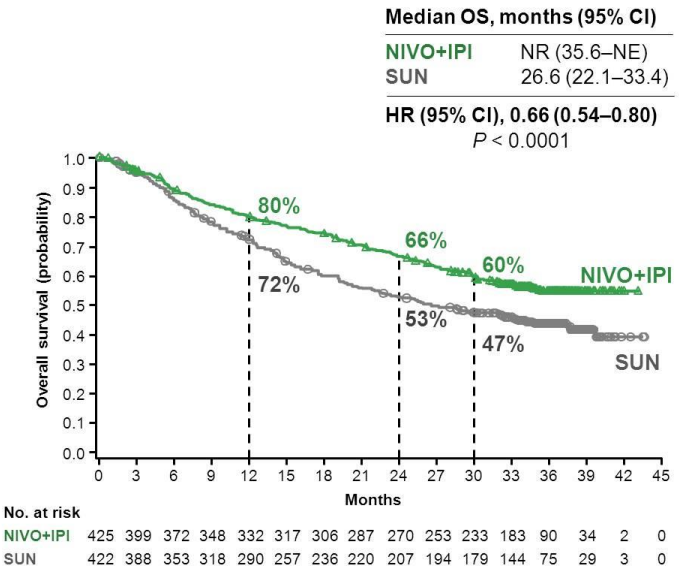
Minimum follow-up	OS	NIVO+IPI N = 425	SUN N = 422
17.5 mo[1]	Median, mo (95% CI)	NR (28.2–NE)	26.0 (22.1–NE)
	HR (99.8% CI)	0.63 (0.44–0.89) *P* < 0.001	
30 mo[2]	Median, mo (95% CI)	NR (35.6–NE)	26.6 (22.1–33.4)
	HR (95% CI)	0.66 (0.54–0.80) *P* < 0.0001	
42 mo	Median, mo (95% CI)	47.0[a] (35.6–NE)	26.6 (22.1–33.5)
	HR (95% CI)	0.66 (0.55–0.80) *P* < 0.0001	

[a]With a minimum follow-up of 42 months, the median OS of 47.0 months in the NIVO+IPI arm could be unstable due to censoring.
NE, not estimable.

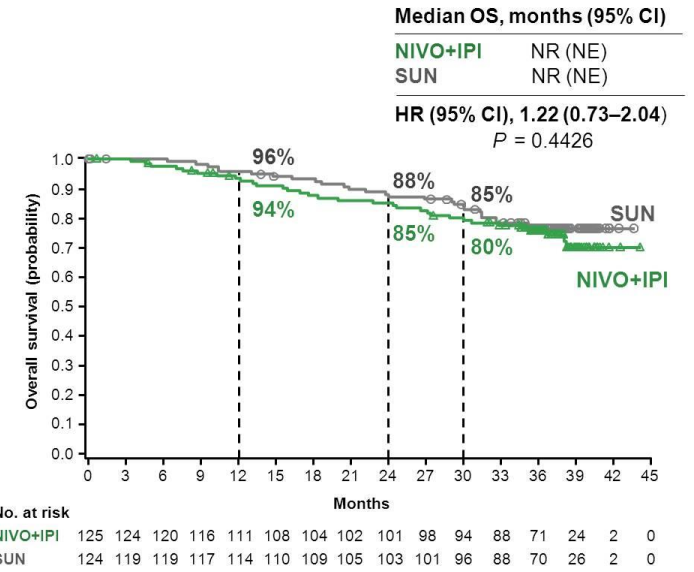
1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277–1290. 2. Motzer RJ, et al. *Lancet Oncol* 2019;20:1370–1385.

Overall Survival: by IMDC Risk

Intermediate/poor risk

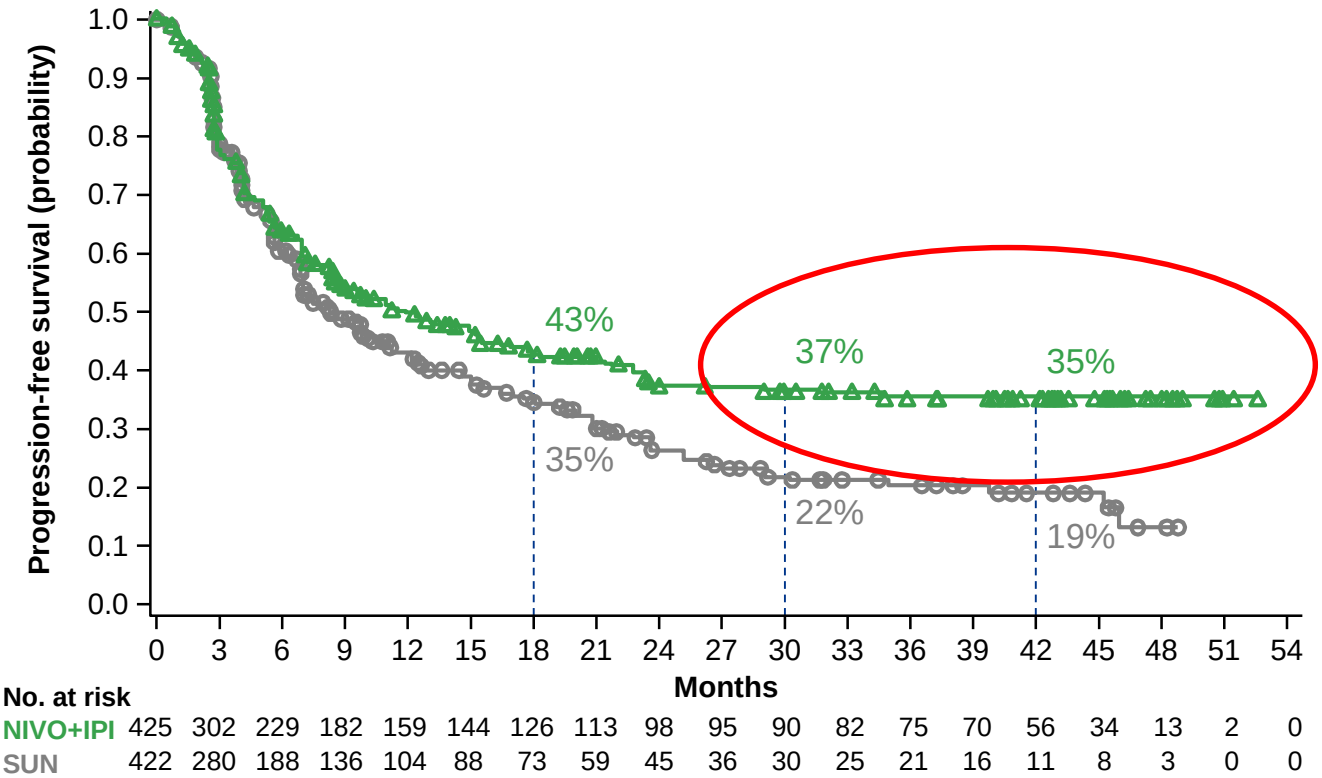


Favorable risk



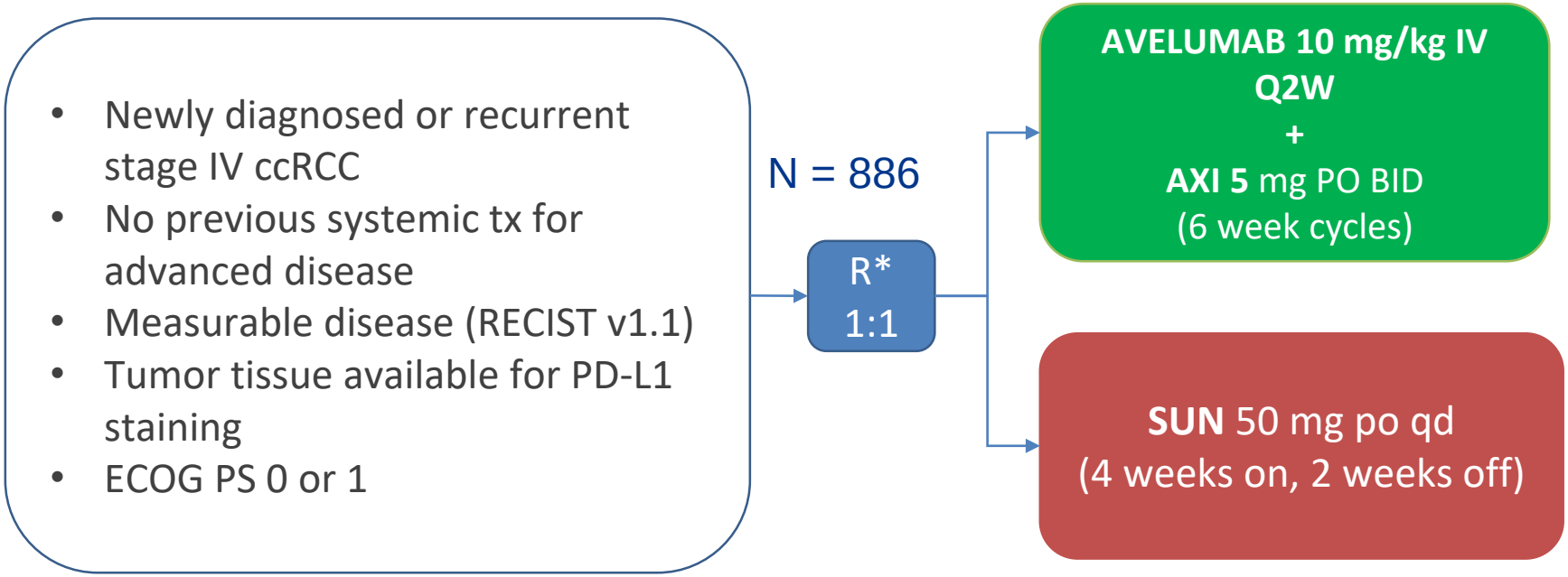
PFS per IRRC

Primary efficacy population: Intermediate/poor-risk patients



Minimum follow-up	PFS	NIVO+IPI N = 425	SUN N = 422
17.5 mo[1]	Median, mo (95% CI)	11.6 (8.7–15.5)	8.4 (7.0–10.8)
	HR (99.1% CI)	0.82 (0.64–1.05) *P* = 0.03	
42 mo	Median, mo (95% CI)	12.0 (8.7–15.5)	8.3 (7.0–11.1)
	HR (95% CI)	0.76 (0.63–0.91) *P* < 0.01	

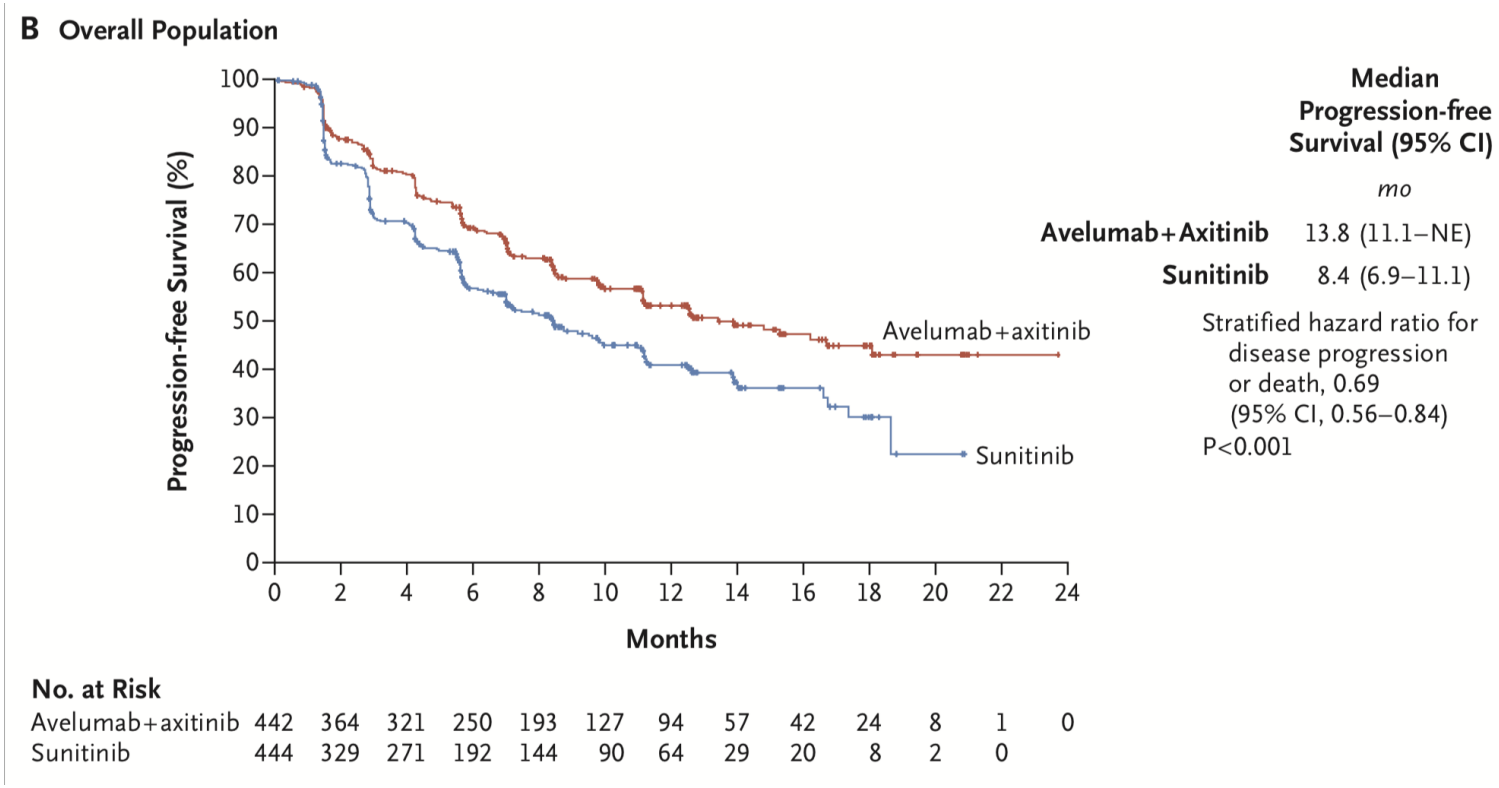
Javelin Renal 101



*stratification according to ECOG and region

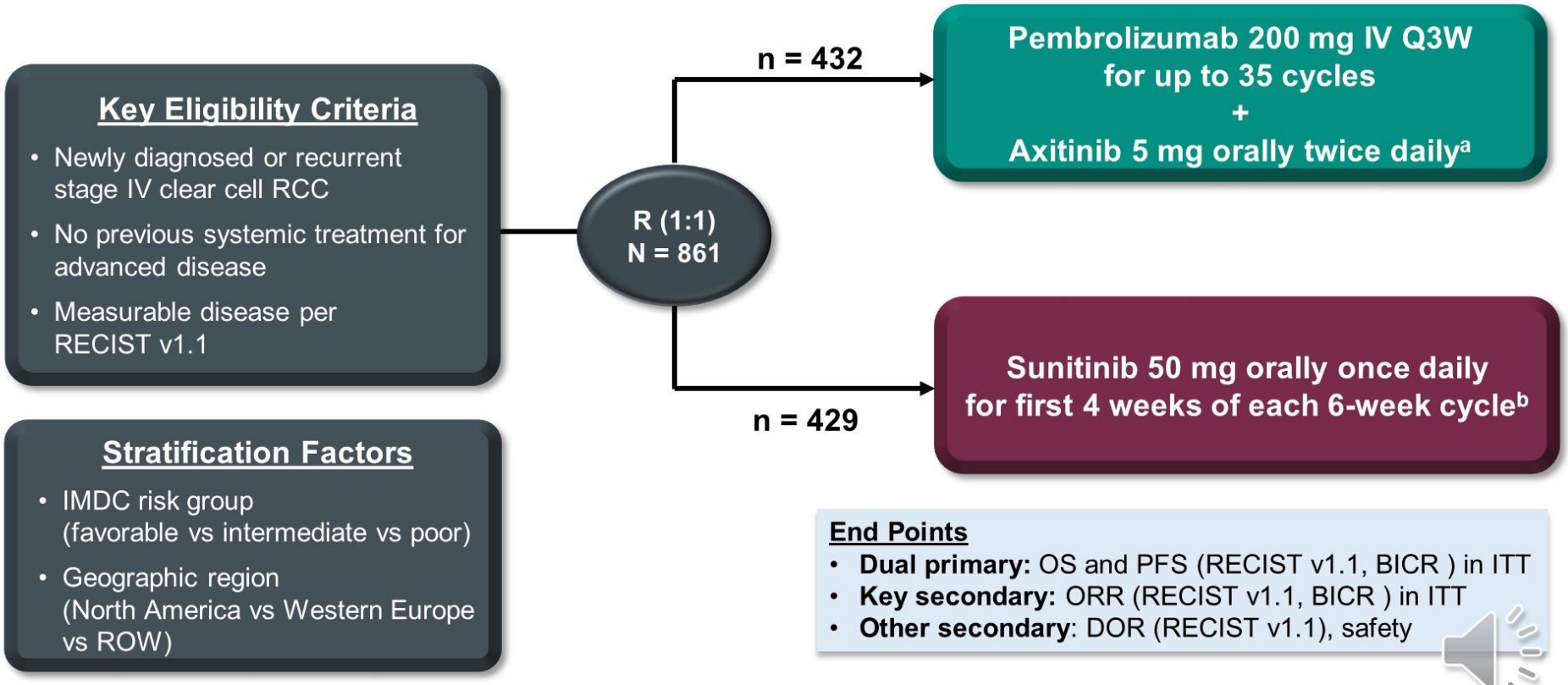
Primary endpoints: To demonstrate the superiority of avelumab + Axi compared with sunitinb for either OS or PFS in patients with PD-L1+ tumors

Progression-free Survival – overall population



Motzer et al., N Engl J Med 2019

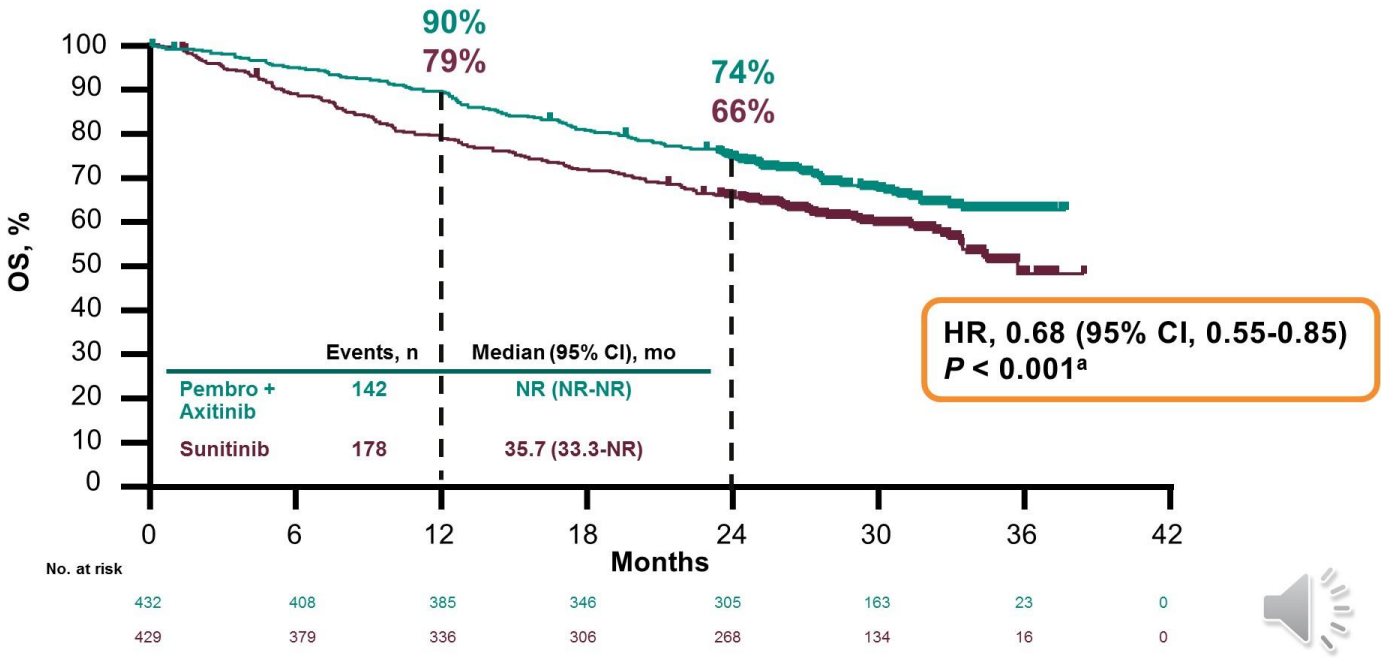
KEYNOTE-426 Study Design



[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 6, 2020.

Presented By Elizabeth Plimack at ASCO Annual Meeting 2020

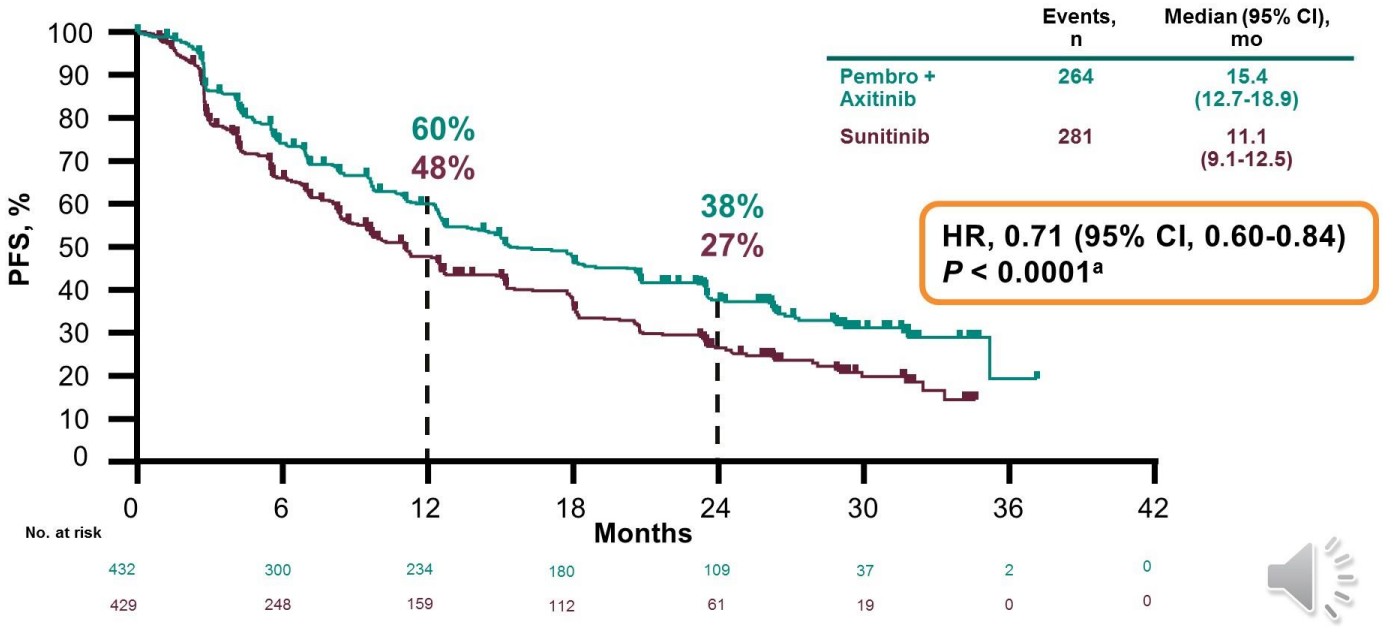
OS in the ITT Population



[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 6, 2020.

Presented By Elizabeth Plimack at ASCO Annual Meeting 2020

PFS in the ITT Population



	Events, n	Median (95% CI), mo
Pembro + Axitinib	264	15.4 (12.7-18.9)
Sunitinib	281	11.1 (9.1-12.5)

HR, 0.71 (95% CI, 0.60-0.84)
***P* < 0.0001[a]**

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to PFS; only nominal *P* values are reported. Data cutoff: January 6, 2020.

Presented By Elizabeth Plimack at ASCO Annual Meeting 2020

CheckMate 9ER: Study design

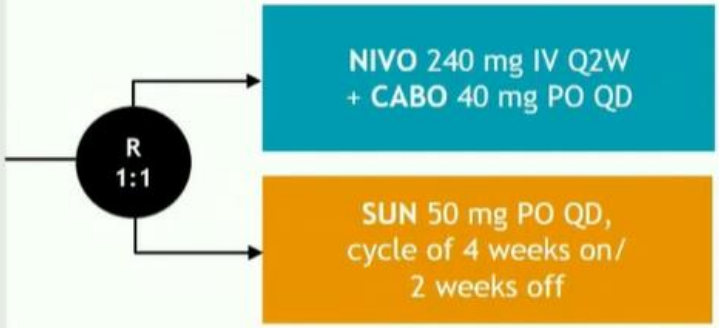
N = 651

Key inclusion criteria[1,2]

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

Stratification factors:

- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region



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

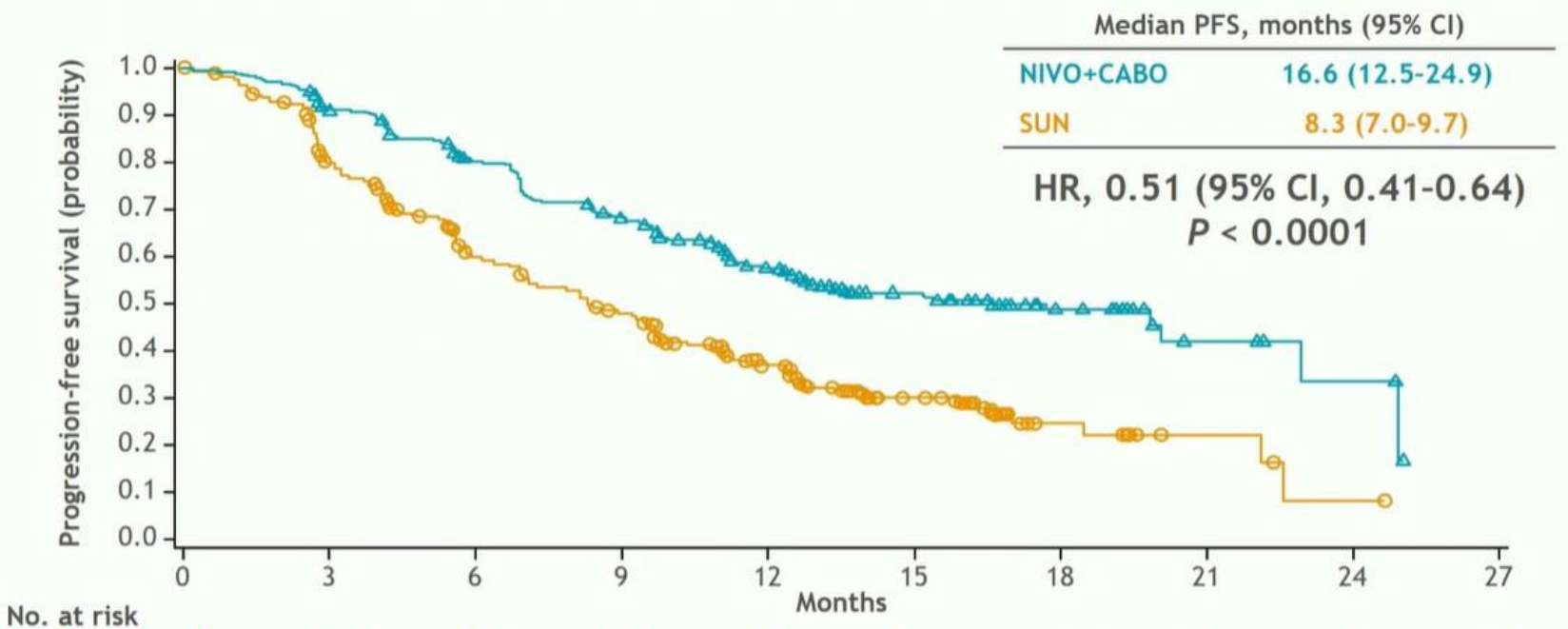
Median study follow-up, 18.1 months (range, 10.6-30.6 months)

Primary endpoint: PFS

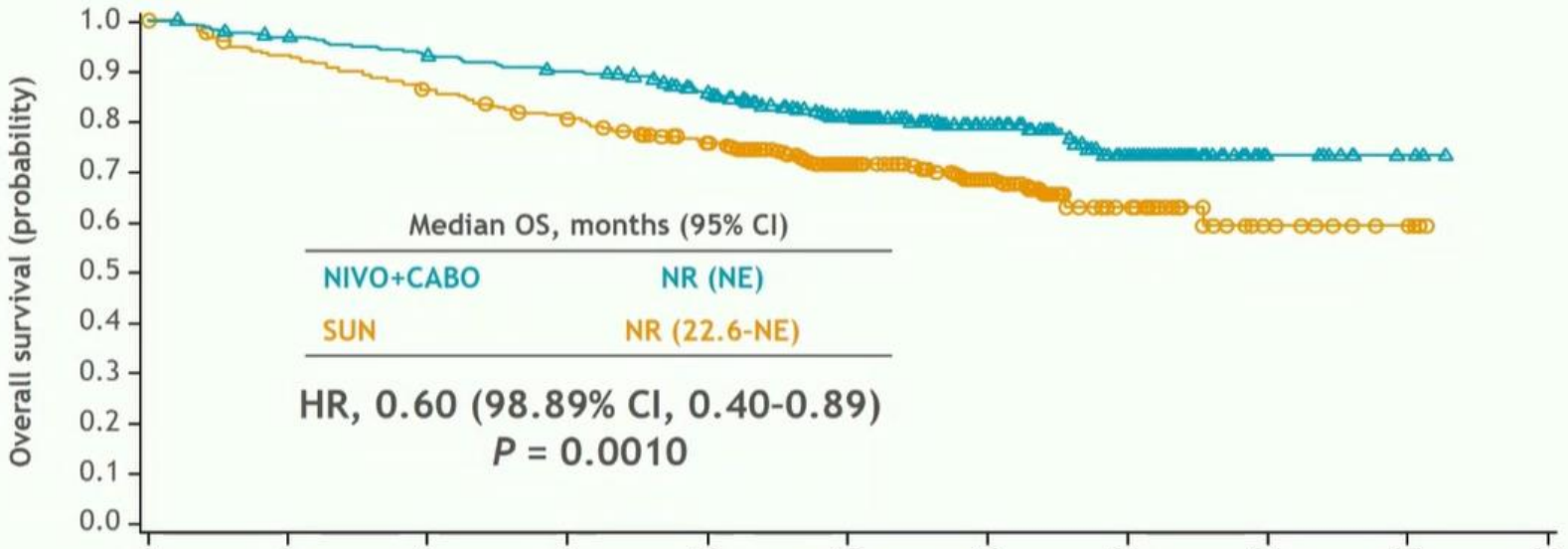
Secondary endpoints: OS, ORR, and safety

CheckMate 9ER

Progression-free survival per BICR



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

KEYTRUDA® (PEMBROLIZUMAB) PLUS LENVIMA® (LENVATINIB) DEMONSTRATED STATISTICALLY SIGNIFICANT IMPROVEMENT IN PROGRESSION-FREE SURVIVAL (PFS), OVERALL SURVIVAL (OS) AND OBJECTIVE RESPONSE RATE (ORR) VERSUS SUNITINIB AS FIRST-LINE TREATMENT FOR PATIENTS WITH ADVANCED RENAL CELL CARCINOMA

LENVIMA Plus Everolimus Also Showed Statistically Significant Improvement in PFS and ORR Endpoints Versus Sunitinib

Results of Investigational Phase 3 KEYNOTE-581/CLEAR Trial (Study 307) to be Presented at Upcoming Medical Meeting

TYPE

Press Release

DATE RELEASED

November 10, 2020

KENILWORTH, N.J., and WOODCLIFF LAKE, N.J., November 10, 2020 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, and Eisai today announced new investigational data demonstrating positive top-line results from the pivotal Phase 3 KEYNOTE-581/CLEAR trial (Study 307). In the trial, the combinations of KEYTRUDA, Merck's anti-PD-1 therapy, plus LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, and LENVIMA plus everolimus were evaluated versus sunitinib for the first-line treatment of patients with advanced renal cell

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ASCO Meeting Library

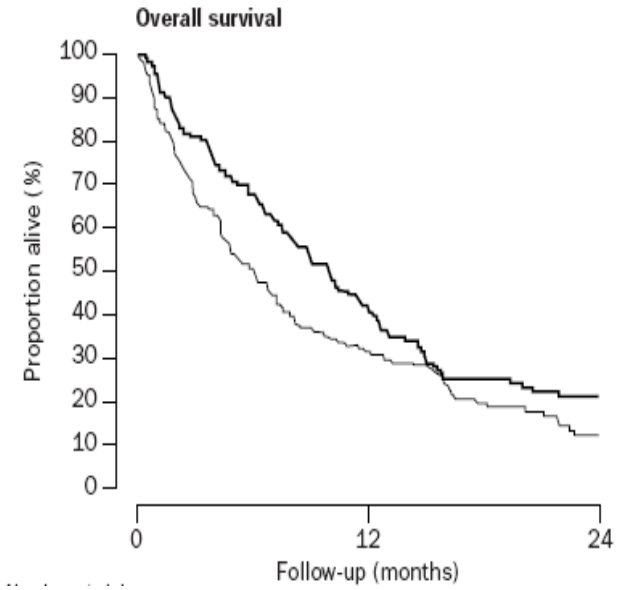
Results:

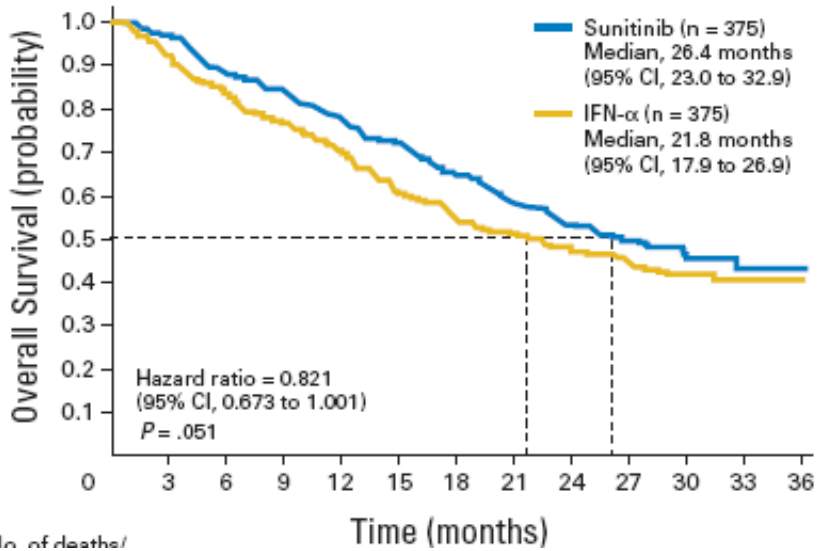
1069 pts were randomized (Table). After a median follow-up of 27 months (data cutoff August 28, 2020), PFS was significantly improved with LEN + PEMBRO (median 24 months [mos]) vs SUN (median 9 mos; HR 0.39, 95% CI 0.32–0.49) and LEN + EVE (median 15 mos) vs SUN (HR 0.65, 95% CI 0.53–0.80). OS was significantly longer with LEN + PEMBRO vs SUN (HR 0.66, 95% CI 0.49–0.88), whereas OS with LEN + EVE vs SUN was not statistically different (HR 1.15, 95% CI 0.88–1.50). ORR was significantly greater with LEN + PEMBRO (ORR 71%; complete response [CR] 16%) vs SUN (ORR 36%; CR 4%; odds ratio 4.35, 95% CI 3.16–5.97) and LEN + EVE (ORR 54%; CR 10%) vs SUN (odds ratio 2.15, 95% CI 1.57–2.93). Grade ≥3 treatment-related adverse events occurred in 72% of pts in the LEN + PEMBRO arm and 73% of pts in the LEN + EVE arm compared with 59% of pts in the SUN arm.

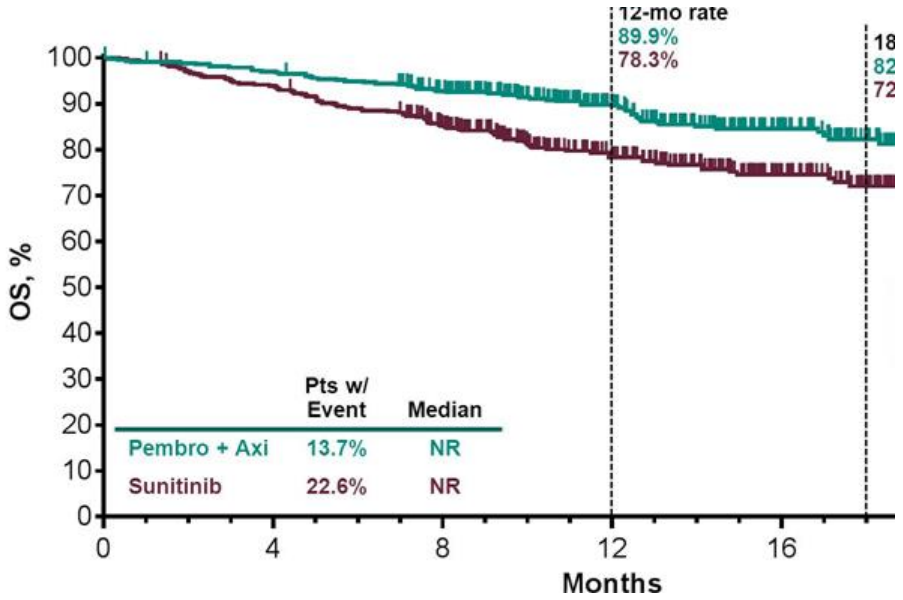
Conclusions:

LEN + PEMBRO demonstrated significant improvements in PFS, OS and ORR vs SUN. LEN + EVE demonstrated significant improvements in PFS and ORR vs SUN. Safety was manageable and consistent with the known single-agent profiles. Clinical trial information: NCT02811861.

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Median PFS, months (95% CI)	24 (21–28)	15 (11–17)	9 (6–11)
PFS HR vs SUN (95% CI); *P*-value	0.39 (0.32–0.49); <0.0001	0.65 (0.53–0.80); <0.0001	-
Median OS, months (95% CI)	NR (34–NE)	NR (NE–NE)	NR (NE–NE)
OS HR vs SUN (95% CI); *P*-value	0.66 (0.49–0.88); 0.0049	1.15 (0.88–1.50); 0.2975	-
24-Month OS rate, % (95% CI)	79 (74–83)	66 (61–71)	70 (65–75)
ORR, % (95% CI)	71 (66–76)	54 (48–59)	36 (31–41)
ORR odds ratio vs SUN (95% CI); Descriptive *P*-value	4.35 (3.16–5.97); <0.0001	2.15 (1.57–2.93); <0.0001	-
Complete response, %	16	10	4
Median duration of response, months (95% CI)	26 (22–28)	17 (15–21)	15 (9–17)


Overall survival
Proportion alive (%)
100
90
80
70
60
50
40
30
20
10
0
0
12
24
Follow-up (months)


Overall Survival (probability)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3
6
9
12
15
18
21
24
27
30
33
36
Time (months)
Sunitinib (n = 375)
Median, 26.4 months
(95% CI, 23.0 to 32.9)
IFN-α (n = 375)
Median, 21.8 months
(95% CI, 17.9 to 26.9)
Hazard ratio = 0.821
(95% CI, 0.673 to 1.001)
P = .051


12-mo rate
89.9%
78.3%
OS, %
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
Months
Pts w/ Event
Median
Pembro + Axi
13.7%
NR
Sunitinib
22.6%
NR

TAKK FOR OPPMERKSOMHETEN!