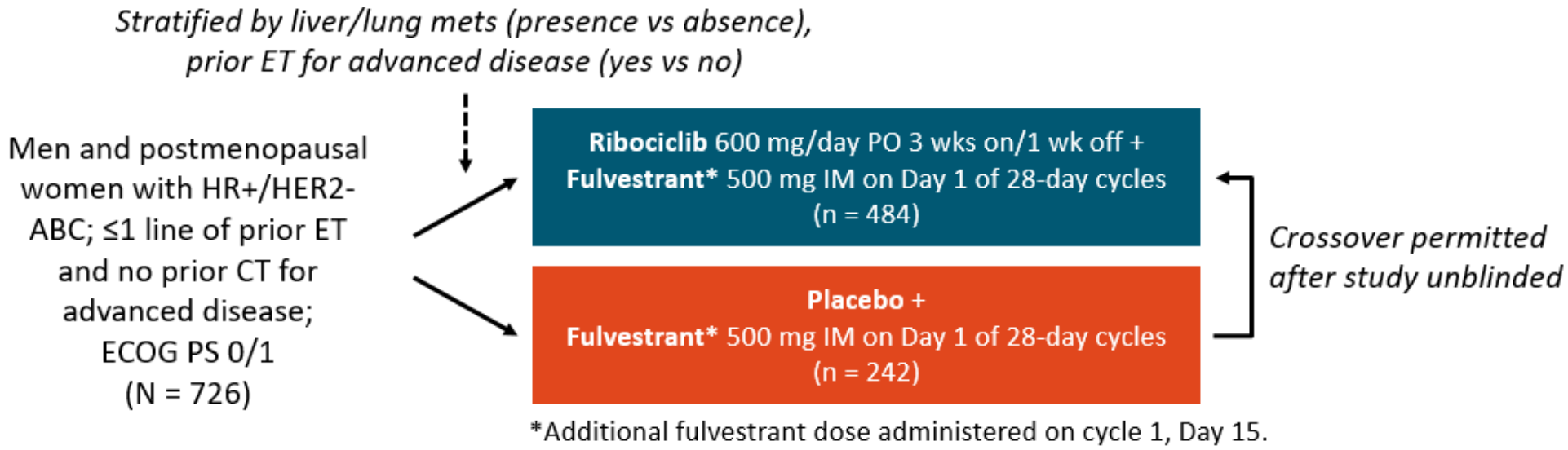
BEST OF ASCO 2021

T. Svoboda

BREAST CANCER UPDATES

MONALEESA-3 Update: Study Design

- International, randomized, double-blind phase III trial
  - Current exploratory analysis conducted with median follow-up of 56.3 mo (data cutoff: October 30, 2020)



- **Primary endpoint:** investigator-assessed PFS
- **Current analysis endpoints:** OS, time to first CT, CT-free survival, PFS2, subsequent antineoplastic treatment, safety

Slamon. Ann Oncol. 2021;[Epub]. Slamon. ASCO 2021. Abstr 1001. Slamon. NEJM. 2020;382:514. Slamon. JCO. 2018;36:2465. NCT02422615.

MONALEESA-3 Update: Time to First CT, CT-Free Survival, PFS2

Median, Mo	Ribociclib + FULV (n = 484)	Placebo + FULV (n = 242)	Hazard Ratio (95% CI)
Time to first CT*	48.1	28.8	0.704 (0.566-0.876)
CT-free survival†	32.3	22.4	0.688 (0.570-0.830)
PFS2‡	37.4	28.1	0.693 (0.570-0.844)

*From randomization to start of first CT after discontinuing study regimen (death censored). †From randomization to start of first CT or death after discontinuing study regimen. ‡From randomization to first physician-reported PD while patient receiving subsequent antineoplastic tx or any-cause death, which occurred first.

- ~20-mo delay in median time to first CT in ribociclib vs placebo arms
- ~10-mo longer median CT-free survival in ribociclib vs placebo arms
- Ribociclib + FULV associated with greater benefit after PD as indicated by longer median PFS2 vs placebo + FULV
  - Benefit consistent across settings but particularly pronounced in first-line setting (hazard ratio: 0.63; 95% CI: 0.47-0.84)

Slamon. Ann Oncol. 2021;[Epub]. Slamon. ASCO 2021. Abstr 1001.

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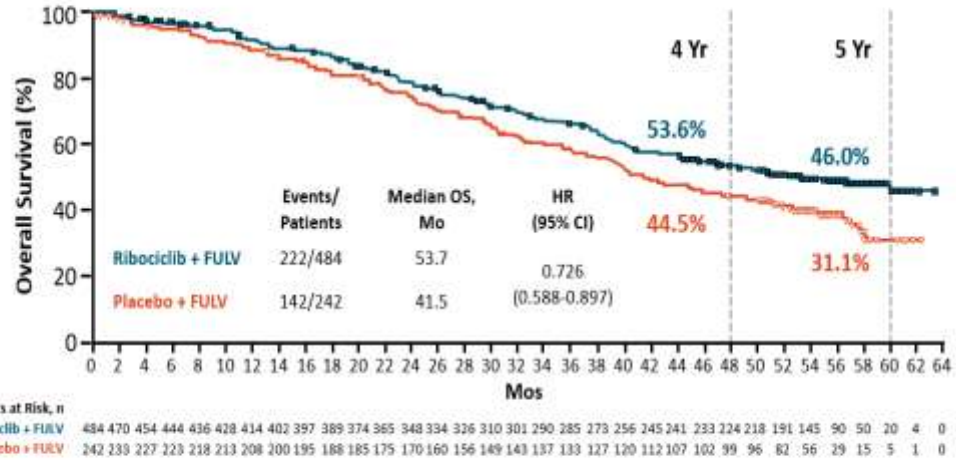
MONALEESA-3 Update: OS in Overall Population



- OS benefit maintained with ribociclib + FULV vs placebo + FULV (>1-yr improvement in median OS for overall population)

Slamon. Ann Oncol. 2021;[Epub].

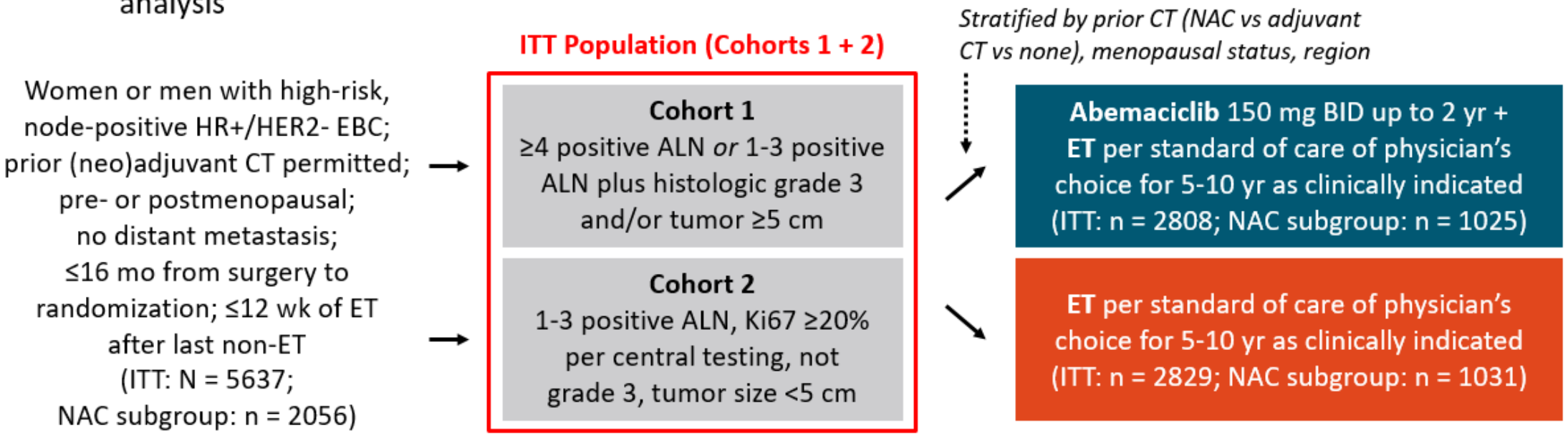
Slide credit: clinicaloptions.com

MONALEESA-3 Update: Conclusions

- In this exploratory analysis update to the phase III MONALEESA-3 trial, OS benefit was maintained with ribociclib + fulvestrant vs placebo + fulvestrant in postmenopausal women with HR+/HER2- ABC
  - Median OS: 53.7 vs 41.5 mo (hazard ratio: 0.73; 95% CI: 0.59-0.90)
  - OS benefit consistent across treatment setting and most subgroups
- Median time to first CT, CT-free survival, and PFS2 all improved with ribociclib + fulvestrant vs placebo + fulvestrant
  - PFS2 benefit observed independent of line of tx
- Comparable patterns of subsequent antineoplastic tx observed between arms except for lower rate of any subsequent CDK4/6 inhibitor with ribociclib vs placebo arms
- Safety data were consistent with earlier MONALEESA-3 analyses and other prior reports

monarchE NAC Subgroup Analysis: Study Design

- International, randomized, open-label phase III trial
  - Prespecified subgroup analysis in those with prior NAC (NAC subgroup) performed at primary outcome analysis



- Primary endpoint: iDFS (primary outcome analysis occurred after 395 iDFS events in ITT population)
- Key secondary endpoints: distant RFS, iDFS in Ki67-high (≥20%) population, OS, safety, PROs, PK

Martin. ASCO 2021. Abstr 517. Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01.

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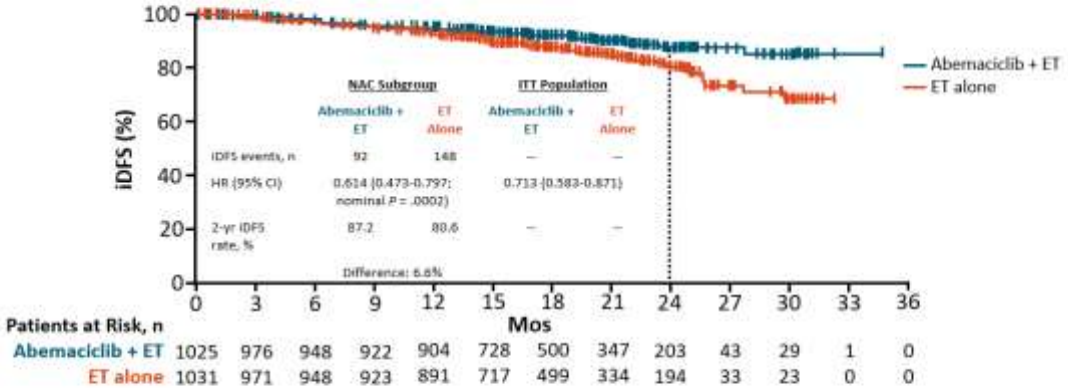
monarchE NAC Subgroup Analysis: iDFS (Primary Endpoint)



- In the NAC subgroup, abemaciclib + ET demonstrated a clinically meaningful 38.6% reduction in risk of an iDFS event vs ET alone
- The 2-yr iDFS rate was higher with abemaciclib + ET vs ET alone in the NAC subgroup (87.2% vs 80.6%; difference: 6.6%)

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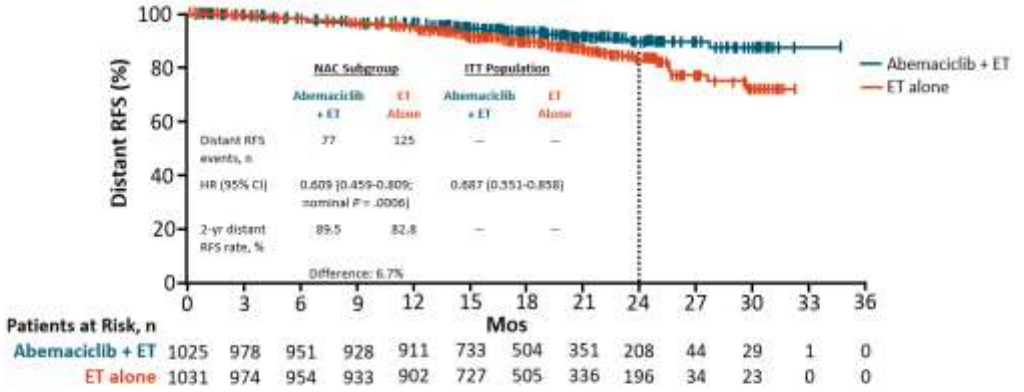
monarchE NAC Subgroup Analysis: Distant RFS



- In the NAC subgroup, abemaciclib + ET demonstrated a clinically meaningful 39.1% reduction in risk of a distant RFS event vs ET alone

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monarchE NAC Subgroup Analysis: iDFS and Distant RFS by Tumor Size at Diagnosis and Surgery

Outcome by Tumor Size		Abemaciclib + ET (n = 1025)		ET Alone (n = 1031)		HR (95% CI)
		Events/Patients, n/N	2-Yr Rate, %	Events/Patients, n/N	2-Yr Rate, %	
iDFS						
Radiologic tumor size at diagnosis	• ≤2 cm	13/194	92.6	30/206	74.3	0.461 (0.240-0.884)
	• >2 cm	71/795	86.9	112/785	81.5	0.618 (0.459-0.832)
Pathologic tumor size at surgery	• 0 cm	2/16	N/A	1/18*	N/A	N/A
	• ≤2 cm	26/405	91.4	46/413	82.2	0.557 (0.344-0.902)
	• >2 cm	59/569	85.0	97/575	79.0	0.608 (0.440-0.841)
Distant RFS						
Radiologic tumor size at diagnosis	• ≤2 cm	9/194	94.8	23/206	78.4	0.414 (0.191-0.895)
	• >2 cm	62/795	88.8	99/785	83.1	0.610 (0.444-0.838)
Pathologic tumor size at surgery	• 0 cm	2/16	N/A	1/18*	N/A	N/A
	• ≤2 cm	19/405	93.7	39/413	84.4	0.482 (0.278-0.834)
	• >2 cm	52/569	87.4	82/575	81.2	0.635 (0.448-0.898)

*No tumor measurement by imaging performed at diagnosis in 1 patient; n = 17 in ET alone arm achieved pCR in breast at surgery.

- Exploratory analyses of outcomes stratified by tumor size, a potential prognostic factor, at diagnosis (before NAC) and at surgery (after NAC)
- Abemaciclib + ET reduced risk of iDFS and DRFS events independent of tumor size at diagnosis or at surgery

Martin. ASCO 2021. Abstr 517.

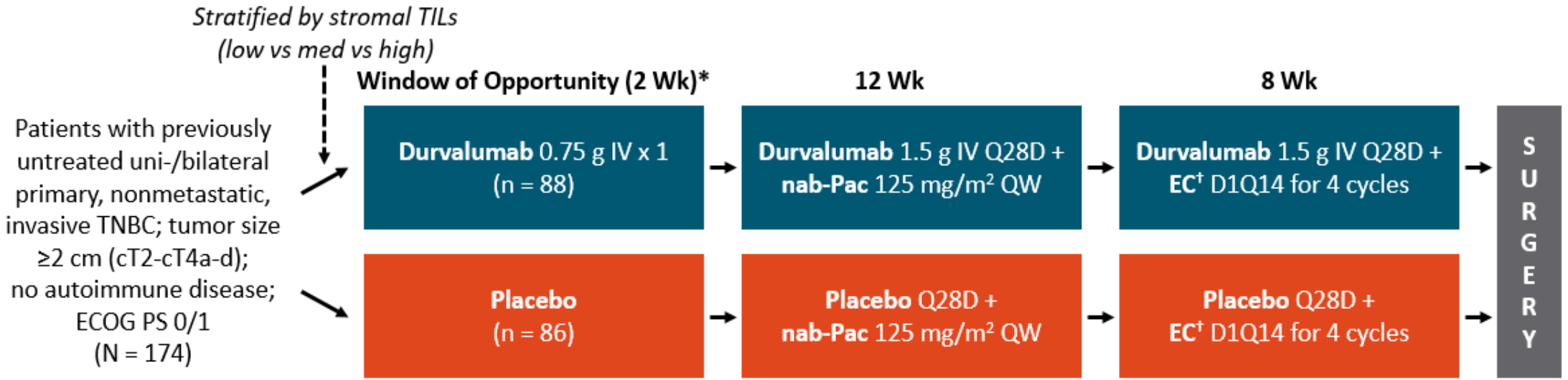
Slide credit: clinicaloptions.com

monarchE NAC Subgroup Analysis: Conclusions

- In this preplanned subgroup analysis of the monarchE trial, abemaciclib + adjuvant ET demonstrated clinically meaningful improvements in iDFS and distant RFS vs ET alone in patients with high-risk HR+/HER2- EBC who received prior NAC[1]
  - Reduction in risk: iDFS, 38.6%; distant RFS, 39.1%
  - Benefits were numerically greater than those observed in ITT population and were maintained independent of tumor size at diagnosis and surgery
- Among those treated with ET alone, the NAC subgroup exhibited a lower 2-yr iDFS rate vs the ITT population consistent with a higher risk of recurrence[1-3]
  - 2-yr iDFS rate comparable to that reported in control arm of phase III PENELOPE-B trial, which compared palbociclib + ET vs placebo + ET in women with high-risk HR+/HER2- EBC after NAC[4]
- Safety profile in this population consistent with prior reports for abemaciclib[1]

GeparNUEVO Survival Analysis: Study Design

- Randomized, double-blind phase II trial
  - Current analysis of long-term outcomes after median follow-up of 43.7 mo (range: 4.9-56.1)



*Window of opportunity closed after n = 117 enrolled due to IDMC concerns about delay in patients starting CT in placebo arm. †Epirubicin 90 mg/m² + cyclophosphamide 600 mg/m².

- **Primary endpoint:**
  pCR (ypT0, ypN0) at surgery
- **Secondary endpoints:**
  invasive DFS, distant DFS, OS

Loibl. ASCO 2021. Abstr 506. Loibl. Ann Oncol. 2019;30:1279. NCT02685059.

Slide credit: clinicaloptions.com

GeparNUEVO Survival Analysis: iDFS

iDFS Outcome	Durvalumab (n = 88)		Placebo (n = 86)	
Events, n	12		22	
3-yr iDFS, %	85.6		77.2	
Stratified HR* (95% CI)	0.48 (0.24-0.97; *P* = .0398)			
By pCR status	**pCR (n = 47)**	**No pCR (n = 40)**	**pCR (n = 38)**	**No pCR (n = 48)**
Events, n	2	9	7	15
3-yr iDFS, %	95.5	76.3	86.1	69.7
Log-rank *P* value	.0071			

- iDFS benefit with durvalumab generally consistent across subgroups
  - Benefit potentially greater in those with PD-L1–positive† disease (*P* = .053 for durvalumab vs placebo)
- HR (95% CI) for pCR vs no pCR: 0.34 (0.16-0.73; log-rank *P* = .004)
- HR (95% CI) for durvalumab vs placebo: pCR, 0.22 (0.05-1.06; log-rank *P* = .038); no pCR, 0.67 (0.29-1.54; log-rank *P* = .346)

Loibl. ASCO 2021. Abstr 506. *Stratified by stromal TILs. †Determined using Ventana SP263 antibody with cutoff of 1%. Slide credit: clinicaloptions.com

GeparNUEVO Survival Analysis: Distant DFS

Distant DFS Outcome	Durvalumab (n = 88)		Placebo (n = 86)	
Events, n	7		20	
3-yr distant DFS, %	91.7		78.4	
Stratified HR* (95% CI)	0.31 (0.13-0.74; *P* = .0078)			
By pCR status	**pCR (n = 47)**	**No pCR (n = 40)**	**pCR (n = 38)**	**No pCR (n = 48)**
Events, n	0	6	6	14
3-yr distant DFS, %	100	84.3	86.1	71.9
Log-rank *P* value	.0012			

- HR (95% CI) for pCR vs no pCR: 0.28 (0.11-0.69; log-rank *P* = .003)
- HR (95% CI) for durvalumab vs placebo:
  - pCR: 0.00 (0.00-; log-rank *P* = .005)†
  - no pCR: 0.48 (0.18-1.25; log-rank *P* = .124)

Loibl. ASCO 2021. Abstr 506. *Stratified by stromal TILs. †No events in durvalumab arm. Slide credit: clinicaloptions.com

GeparNUEVO Survival Analysis: OS

OS Outcome	Durvalumab (n = 88)		Placebo (n = 86)	
Events, n	4		15	
3-yr OS, %	95.2		83.5	
Stratified HR* (95% CI)	0.24 (0.08-0.72; *P* = .0108)			
By pCR status	**pCR (n = 47)**	**No pCR (n = 40)**	**pCR (n = 38)**	**No pCR (n = 48)**
Events, n	0	3	4	11
3-yr OS, %	100	92.0	88.9	78.8
Log-rank *P* value	.0023			

- HR (95% CI) for pCR vs no pCR: 0.27 (0.09-0.81; log-rank *P* = .012)
- HR (95% CI) for durvalumab vs placebo:
  - pCR: 0.00 (0.00-; log-rank *P* = .024)†
  - no pCR: 0.30 (0.08-1.09; log-rank *P* = .053)

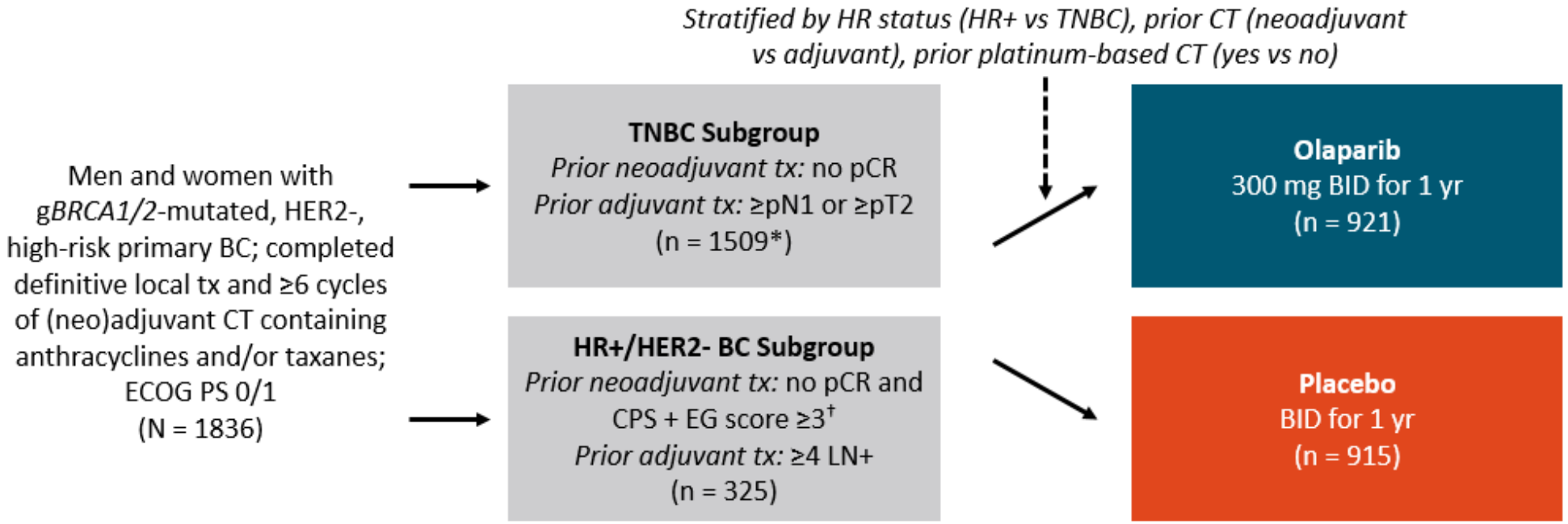
Loibl. ASCO 2021. Abstr 506. *Stratified by stromal TILs. †No events in durvalumab arm. Slide credit: clinicaloptions.com

GeparNUEVO Survival Analysis: Conclusions

- In this analysis of long-term survival outcomes from the phase II GeparNUEVO trial, the addition of durvalumab to neoadjuvant CT significantly prolonged iDFS, distant DFS, and OS vs placebo + neoadjuvant CT in patients with early TNBC
  - 3-yr rates: iDFS, 85.6% vs 77.2% (HR: 0.48; *P* = .0398); distant DFS, 91.7% vs 78.4% (HR: 0.31; *P* = .0078); OS, 95.2% vs 83.5% (HR: 0.24; *P* = .0108)
- In those achieving pCR, survival outcomes improved with addition of durvalumab vs placebo to neoadjuvant CT
- Subgroup analyses of iDFS suggested benefit potentially enriched in PD-L1–positive disease
- Investigators indicate that additional research into relationship between pCR improvement and long-term outcomes with neoadjuvant PD-1/PD-L1 therapy is warranted
- Investigators suggest that further assessment of PD-1/PD-L1 therapies in the adjuvant setting is warranted considering these findings

OlympiA: Study Design

- Prespecified interim analysis of international, randomized, double-blind phase III trial (data cutoff: Mar 27, 2020)



- **Primary endpoint:** iDFS
- **Secondary endpoints:** distant DFS, OS, safety

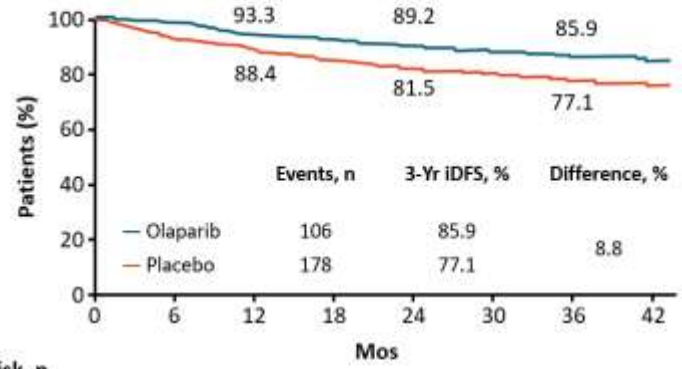
- Prespecified interim analysis of ITT population triggered when 165 invasive disease or death events occurred in first 900 patients enrolled (mature cohort); type I error rate controlled with superiority boundaries per hierarchical multiple-testing procedure

*Excluded n = 2 (both in olaparib arm) due to unconfirmed HER2- status.
†Staging system for BC-specific survival after neoadjuvant tx incorporating pretreatment clinical stage, ER status, nuclear grade, pathologic stage (range: 0-6).

Tutt. NEJM. 2021;[Epub]. NCT02032823.

Slide credit: clinicaloptions.com

OlympiA: iDFS (Primary Endpoint)



	Events, n	3-Yr iDFS, %	Difference, %	Stratified HR for Invasive Disease/Death (99.5% CI)
Olaparib	106	85.9	8.8	0.58 (0.41-0.82; *P* <.001)
Placebo	178	77.1		

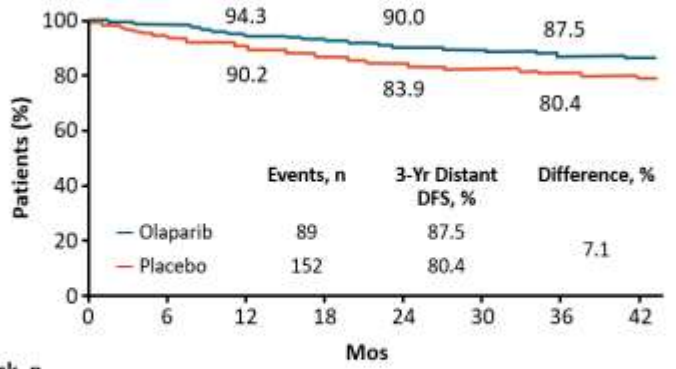
Patients at Risk, n								
Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

- In this prespecified interim analysis, adjuvant olaparib significantly improved iDFS vs placebo (*P* <.001, crossing early-reporting efficacy boundary of *P* <.005)

Tutt. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

OlympiA: Distant DFS



	Events, n	3-Yr Distant DFS, %	Difference, %	Stratified HR for Distant Disease/Death (99.5% CI)
Olaparib	89	87.5	7.1	0.57 (0.39-0.83; *P* <.001)
Placebo	152	80.4		

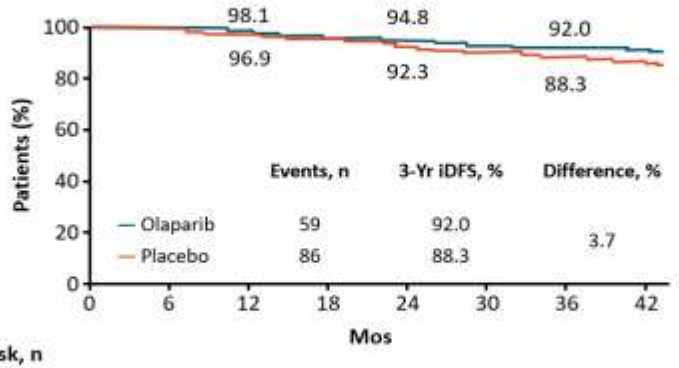
Patients at Risk, n								
Olaparib	921	823	744	612	479	364	279	187
Placebo	915	817	742	594	461	359	263	179

- Adjuvant olaparib significantly improved distant DFS vs placebo (*P* <.001, crossing early-reporting efficacy boundary of *P* <.005)

Tutt. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

OlympiA: Overall Survival



	Events, n	3-Yr iDFS, %	Difference, %	Stratified HR for Death (99% CI)
Olaparib	59	92.0	3.7	0.68 (0.44-1.05; *P* = .02)
Placebo	86	88.3		

Patients at Risk, n								
Olaparib	921	856	801	659	531	400	310	205
Placebo	915	865	801	659	516	397	292	199

- Adjuvant olaparib did not significantly improve OS vs placebo (*P* = .02 did not cross early-reporting efficacy boundary of *P* = .01)
- Main cause of death was BC: olaparib, 55/59 deaths; placebo, 82/86 deaths

Tutt. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

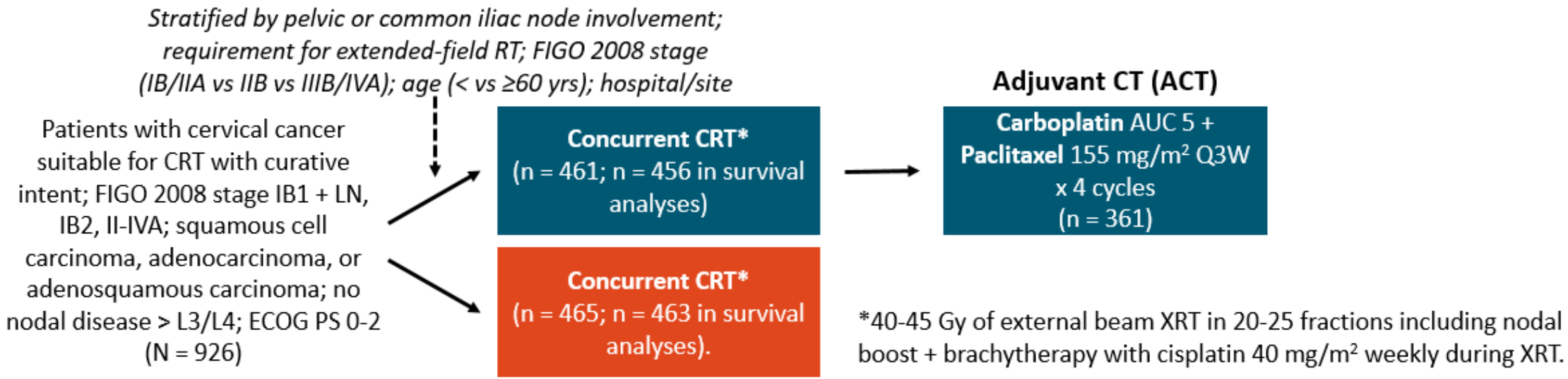
OlympiA: Conclusions

- In this prespecified interim analysis of the phase III OlympiA trial, adjuvant olaparib significantly improved the primary endpoint of iDFS vs placebo in patients with g*BRCA1/2*-mutated, HER2-, high-risk EBC
  - 3-yr iDFS rate: 85.9% vs 77.1%; difference: 8.8% (HR: 0.58; 95% CI: 0.41-0.82; *P* <.001)
  - Distant DFS also significantly improved (HR: 0.57; *P* <.001)
- Despite fewer deaths occurring with olaparib vs placebo, OS was not significantly improved in this analysis (HR: 0.68; *P* = .02 not crossing early-reporting efficacy boundary of *P* = .01)
  - Blinded follow-up continuing
- Safety profile of olaparib consistent with prior reports, did not affect global health quality
- Investigators concluded that positive results from this trial support use of g*BRCA1/2* sequencing to select optimal systemic therapy for patients with EBC

GYN CANCER UPDATES

OUTBACK: Study Design

- International, randomized phase III trial (median follow-up: 5 yr)



- **Primary endpoint:** OS
  - Study protocol amended in 2016 to increase sample size from N = 780 to 900 due to nonadherence with adjuvant CT and lower event rate than anticipated (80% power and 2-sided $\alpha = 0.05$ to detect 8% absolute improvement in OS at 5 yr [72% to 80%])
- **Secondary endpoints:** PFS, patterns of disease recurrence, radiation protocol compliance, PROs, safety

Mileshkin. ASCO 2021. Abstr LBA3. NCT01414608.

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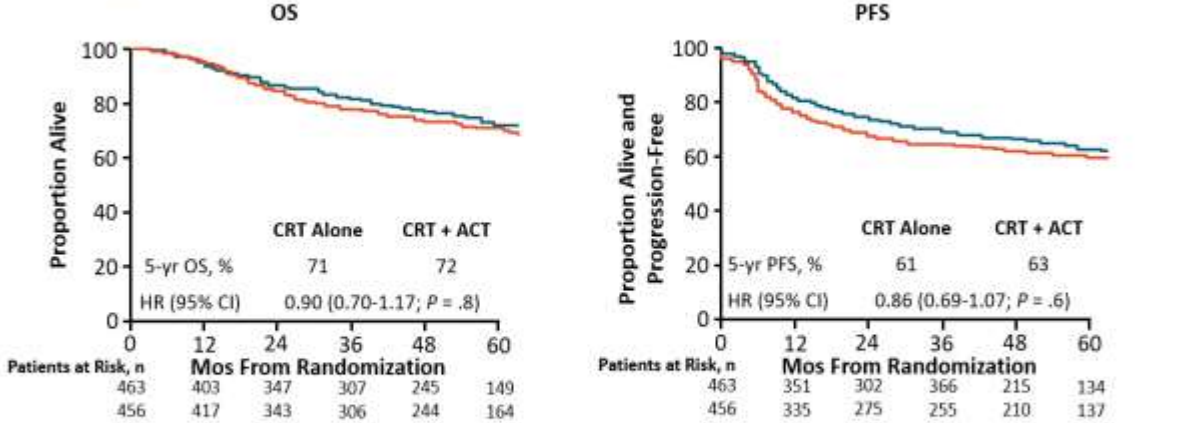
OUTBACK: OS and PFS



- No significant improvement in 5-yr rates for OS or PFS with CRT + ACT vs CRT alone
- Sensitivity analyses found no significant differences in OS or PFS in CRT + ACT arm for those who did vs did not complete CRT
- Treatment effects consistent across subgroups except for those aged < vs ≥60 yr, where younger patients had greater OS and PFS benefit with CRT + ACT (interaction $P = .01$ and .03, respectively)

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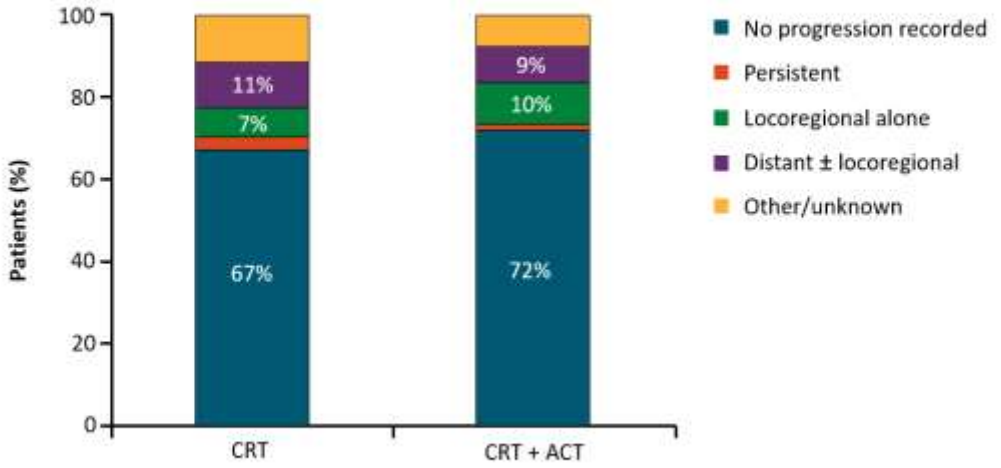
OUTBACK: Disease Recurrence



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OUTBACK: Conclusions

- In this analysis of the phase III OUTBACK trial, the addition of adjuvant carboplatin/paclitaxel following concurrent CRT did not improve OS or PFS vs CRT alone in patients with locally advanced cervical cancer
- Investigators indicate that results do not support addition of adjuvant carboplatin/paclitaxel after CRT with weekly cisplatin in this setting
  - Recommend further research into identifying other adjuvant therapies with greater potential efficacy and tolerability after standard CRT
- Investigators conclude that pelvic CRT with concurrent weekly cisplatin remains the standard of care

Niraparib in *BRCA*m Ovarian Cancer: PFS

Outcome	Niraparib n/N	Niraparib Median PFS, mo	Placebo n/N	Placebo Median PFS, mo	HR for PFS (95% CI)
PRIMA (1L Maintenance)					
*BRCA*m	49/152	22.1	40/71	10.9	0.40 (0.27-0.62)
▪ *BRCA1*	40/105	19.6	26/43	8.4	0.39 (0.23-0.66)
▪ *BRCA2*	9/47	NE	14/28	13.6	0.35 (0.15-0.84)
NOVA (2L Maintenance)					
*gBRCA*m	59/138	21.0	44/65	5.5	0.27 (0.17-0.41)
▪ *BRCA1*	41/84	12.9	27/43	5.8	0.39 (0.23-0.66)
▪ *BRCA2*	16/50	NE	13/18	5.4	0.12 (0.05-0.33)
NORA (2L Maintenance)					
*gBRCA*m	24/65	NE	28/35	5.5	0.22 (0.12-0.39)

Gonzalez Martin. ASCO 2021. Abstr 5518.

Slide credit: clinicaloptions.com

Niraparib in *BRCA*m Ovarian Cancer: Investigator Conclusions

- In patients with *BRCA*m ovarian cancer, niraparib maintenance following platinum-based CT in first-line or recurrent disease settings was associated with significant PFS benefit
  - Median PFS in PRIMA: 22.1 mo with niraparib vs 10.9 mo with placebo
  - Median PFS in NOVA: 21.0 mo with niraparib vs 5.5 mo with placebo
  - Median PFS in NORA: NE with niraparib vs 5.5 mo with placebo
- The safety profile of niraparib was consistent with previous data
  - Thrombocytopenia, anemia, and neutropenia were most common TEAEs

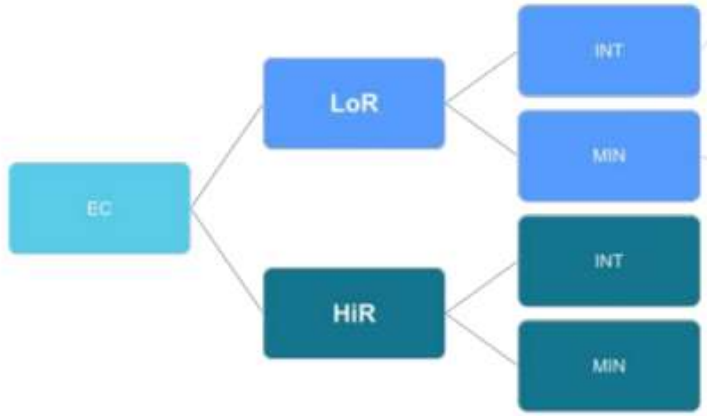
Gonzalez Martin. ASCO 2021. Abstr 5518.

Slide credit: clinicaloptions.com

Surveillance in Endometrial Cancer

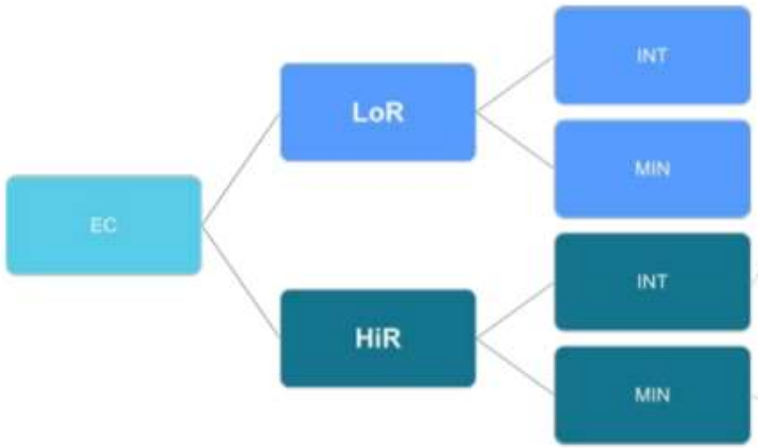
The objective was to compare intensive (NT) versus minimalist (MIN) follow up over 5 years on OS

1847 eligible for analysis
1111 low risk
736 HIR



	Months since randomization														
PROCEDURES	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
Clinical Examination	X	X		X	X	X		X	X	X	X	X	X	X	X
Pap Smear					X				X		X		X		X
CT chest, abdomen, pelvis					X				X						

	Months since randomization														
PROCEDURES	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
Clinical Examination	X		X		X		X		X	X	X	X	X	X	X



	Months since randomization																
PROCEDURES	0	4	6	8	12	16	18	20	24	28	30	32	36	42	48	54	60
Clinical Examination	X	X		X	X	X		X	X	X		X	X	X	X	X	X
Ca125		X		X	X	X		X	X	X		X	X	X	X	X	X
Abdomen & TV US		X		X		X		X		X		X		X		X	
Pap Smear					X				X				X		X		X
CT chest, abdomen, pelvis					X				X				X		X		X

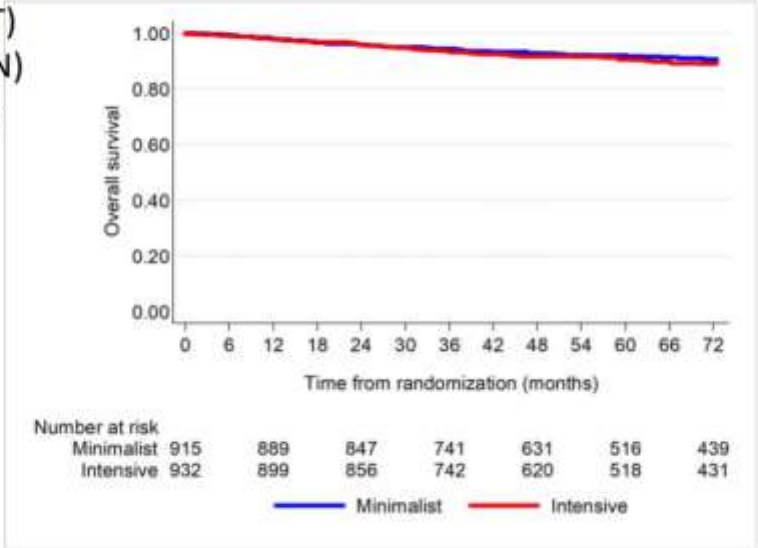
	Months since randomization																
PROCEDURES	0	4	6	8	12	16	18	20	24	28	30	32	36	42	48	54	60
Clinical Examination	X	X		X	X	X		X	X		X		X	X	X	X	X
CT chest, abdomen, pelvis					X				X								

Zola et al. TOTEM trial ASCO 2021;Abstract 5506.

Surveillance in Endometrial Cancer: OS

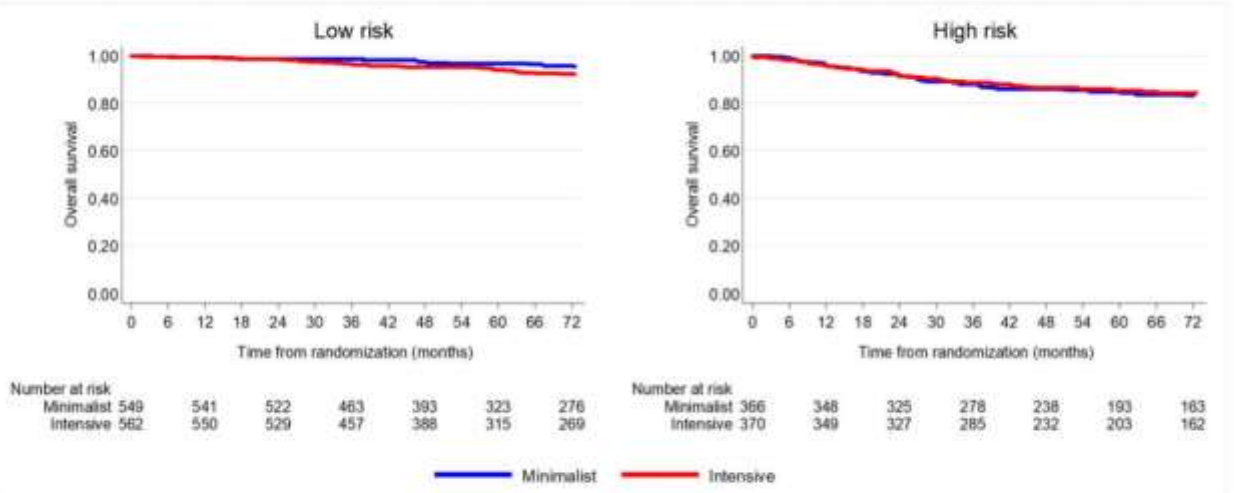
The objective was to compare intensive (NT) versus minimalist (MIN) follow up over 5 years on OS

1847 eligible for analysis
1111 low risk
736 HIR



Zola et al. TOTEM trial ASCO 2021;Abstract 5506.

Surveillance in Endometrial Cancer: OS

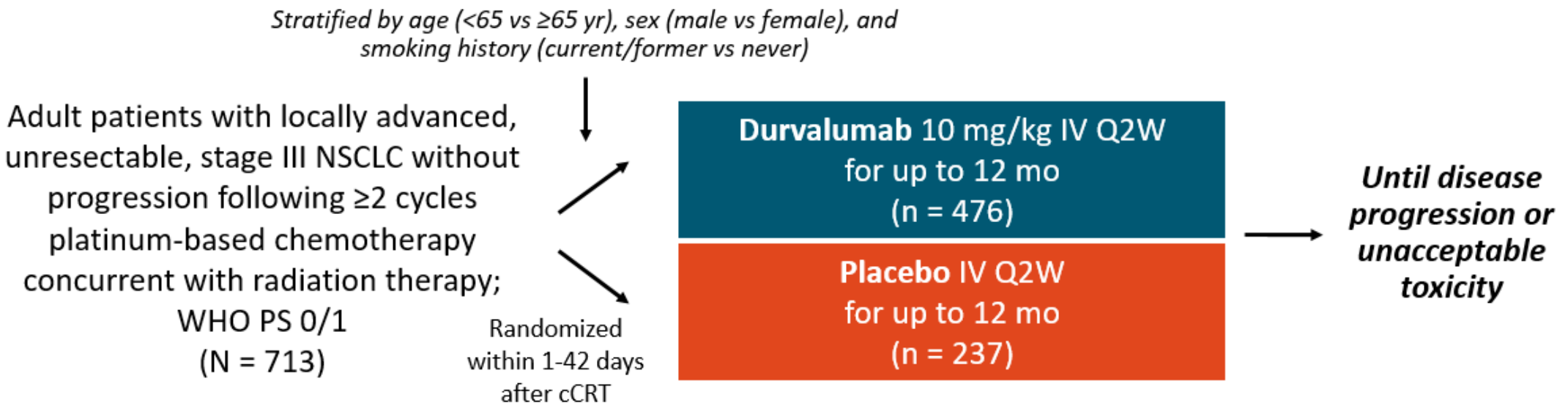


Zola et al. TOTEM trial ASCO 2021;Abstract 5506.

LUNG CANCER UPDATES

PACIFIC 5-Yr Update: Study Design

- Randomized, double-blind, placebo-controlled phase III trial



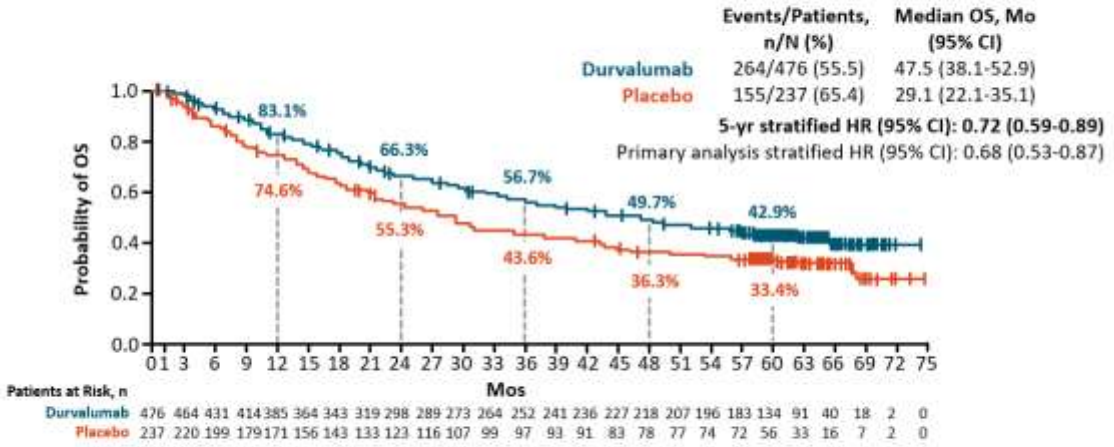
Patients enrolled regardless of PD-L1 status. If available, pre-cCRT tumor tissue archived for PD-L1 testing.

- Primary endpoints: PFS by BICR per RECIST v1.1, OS
- Secondary endpoints: ORR, DoR, TTDM, safety, PROs

Spigel. ASCO 2021. Abstr 8511.

Slide credit: clinicaloptions.com

PACIFIC 5-Yr Update: OS (ITT)

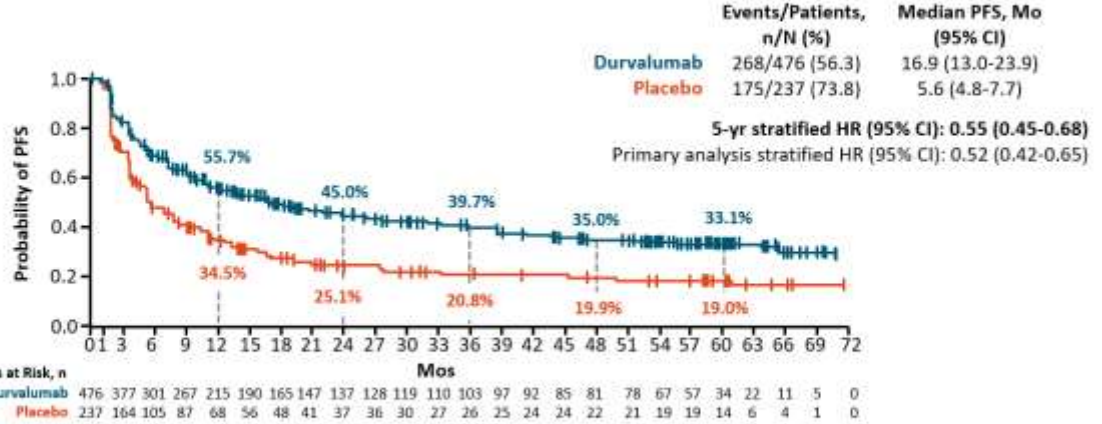


- 120 additional OS events reported since time of primary analysis (data cutoff: March 22, 2018); updated results, including across patient subgroups, consistent with those from primary analysis

Spigel. ASCO 2021. Abstr 8511.

Slide credit: clinicaloptions.com

PACIFIC 5-Yr Update: PFS (ITT)



- 72 additional PFS events reported since time of primary analysis (data cutoff: February 13, 2017); updated results, including across patient subgroups, consistent with those from primary analysis

Spigel. ASCO 2021. Abstr 8511.

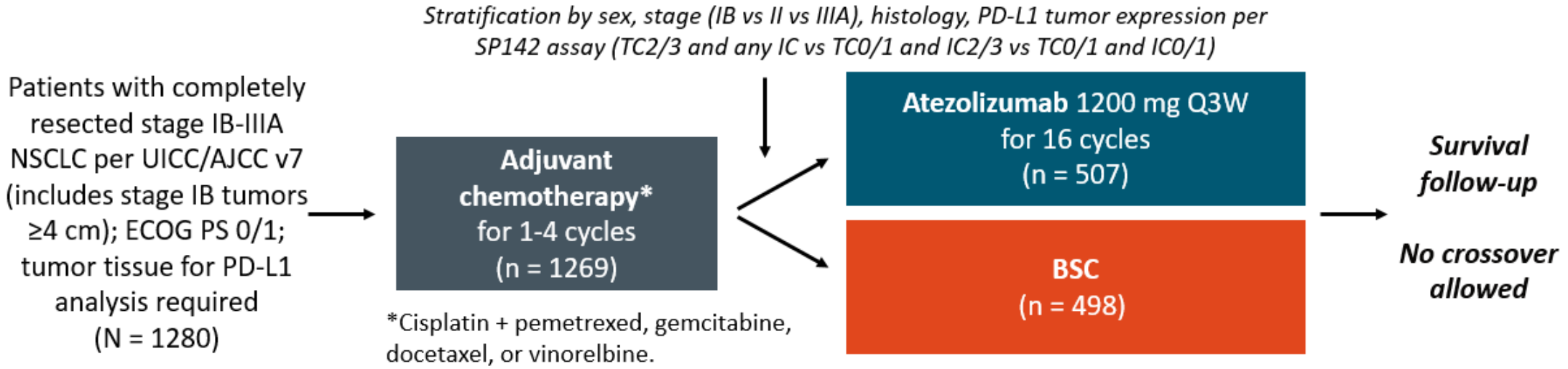
Slide credit: clinicaloptions.com

PACIFIC 5-Yr Update: Conclusions

- Updated 5-year results from phase III PACIFIC trial demonstrate robust and sustained OS benefit and durable PFS benefit with consolidation durvalumab following cCRT in unresectable stage III NSCLC across patient subgroups[1]
  - 5-yr OS: 42.9% (vs 33.4% with placebo)
  - 5-yr PFS: 33.1% (vs 19.0% with placebo)
- Durvalumab currently being investigated with several regimens in unresectable stage III NSCLC to extend clinical benefit to additional patients[2]
  - In combination with CRT
  - With different CRT regimens (eg, sequential) than those evaluated in PACIFIC
  - After CRT in combination with other agents

IMpower010: Study Design

- Randomized, open-label phase III trial (data cutoff for interim analysis: January 21, 2021)

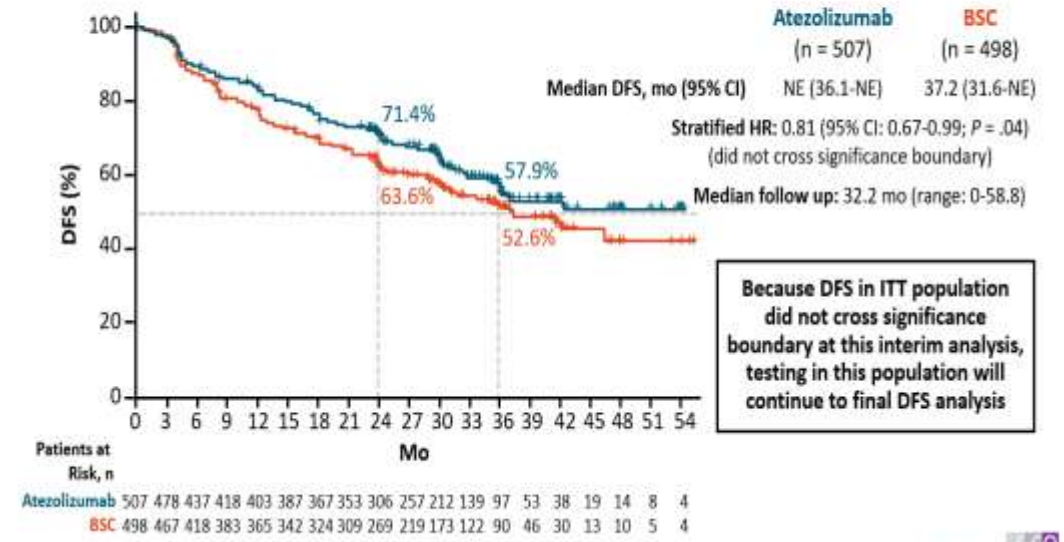


- Primary endpoint: hierarchical evaluation of investigator-assessed DFS in 3 populations
  - Stage II-IIIA with PD-L1 TC ≥1% (by PD-L1 SP264 IHC assay) → all randomized stage II-IIIA → ITT population (stage IB-IIIA)
- Key secondary endpoints: OS (ITT); DFS in stage II-IIIA with PD-L1 TC ≥50 (by PD-L1 SP264 IHC assay); 3-yr and 5-yr DFS in all 3 populations; safety

Wakelee. ASCO 2021. Abstr 8500.

Slide credit: clinicaloptions.com

IMpower010: DFS in ITT Population (Stage IB-IIIA NSCLC; Primary Endpoint)



Because DFS in ITT population did not cross significance boundary at this interim analysis, testing in this population will continue to final DFS analysis

Wakelee. ASCO 2021. Abstr 8500. Reproduced with permission.

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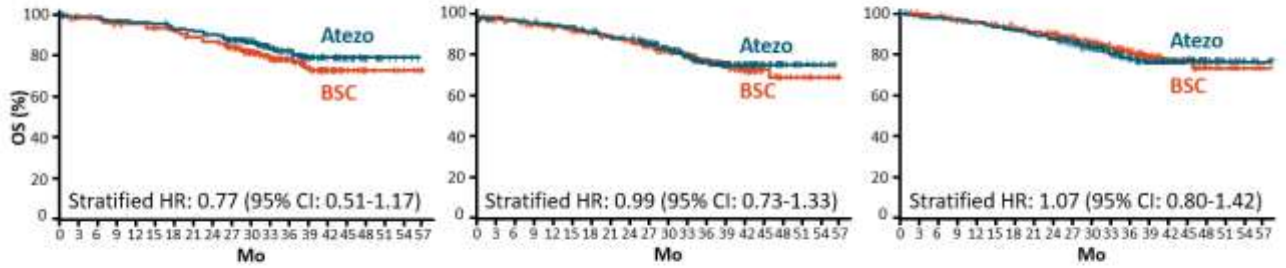
IMpower010: Early OS



- OS data immature at pre-planned interim DFS analysis, not formally tested

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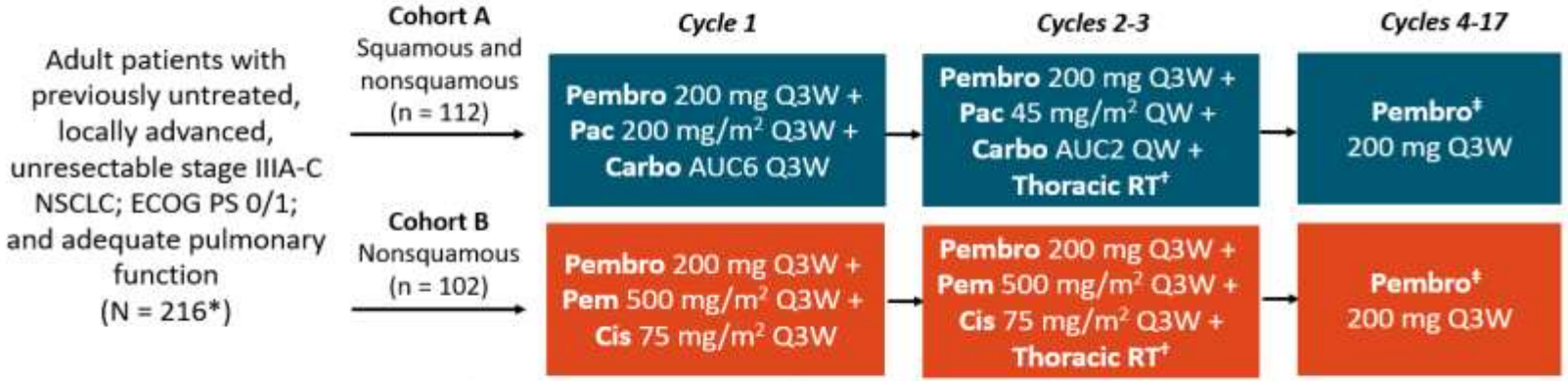
IMpower010: Conclusions

- In a preplanned interim analysis of the phase III IMpower010 trial, adjuvant atezolizumab achieved a significant DFS benefit in the following patients with resected early-stage NSCLC after adjuvant chemotherapy:
  - Stage II-IIIA NSCLC and PD-L1 TC ≥1% (HR: 0.66; 95% CI: 0.50-0.88)
  - All randomized patients with stage II-IIIA (HR: 0.79; 95% CI: 0.64-0.96)
- OS data were immature and not formally tested
- DFS in the ITT population, which includes stage IB disease, did not cross the significance boundary
  - Follow-up for DFS and OS will continue in the ITT population
- No unexpected safety signals emerged with use of adjuvant atezolizumab
- Investigators conclude that atezolizumab may be considered a practice-changing adjuvant treatment option for patients with stage II-IIIA NSCLC and PD-L1 TC ≥1%

KEYNOTE-799: Study Design

- Nonrandomized, open-label phase II trial



*n = 2 did not receive treatment. †60 Gy in 30 daily 2-Gy fractions. ‡Until completion of cycle 17, PD, unacceptable AEs, or study withdrawal.

- Primary endpoints: ORR per RECIST 1.1 by BICR, grade ≥3 pneumonitis
- Secondary endpoints: PFS per RECIST 1.1 by BICR, OS, safety

Jabbour. ASCO 2021. Abstr 8512.

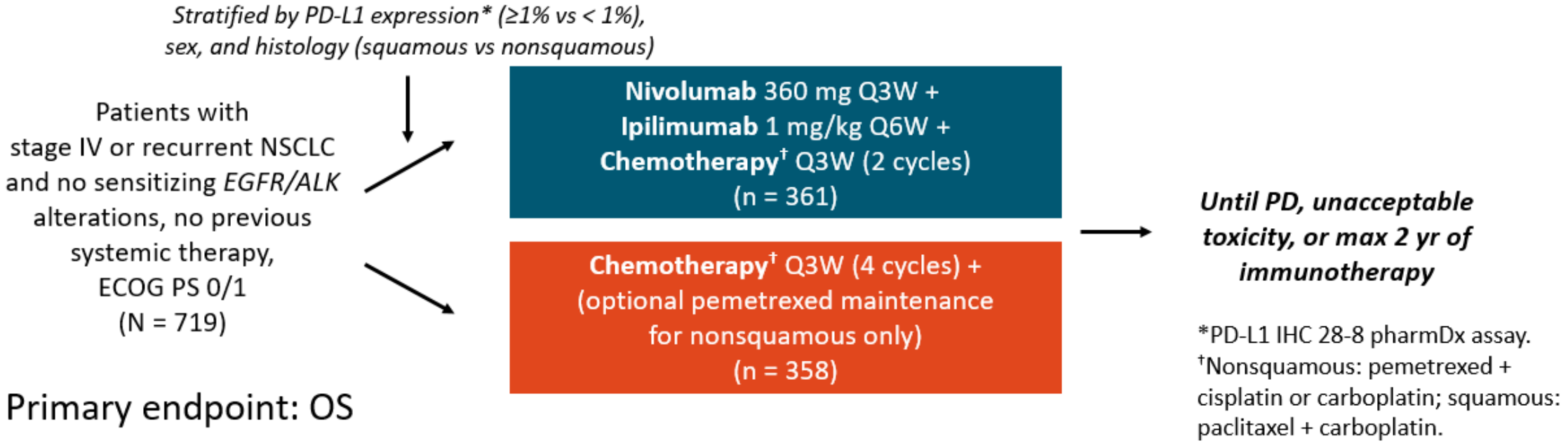
Slide credit: clinicaloptions.com

KEYNOTE-799: Conclusions

- In this ongoing phase II trial, pembrolizumab + concurrent CRT followed by pembrolizumab consolidation conferred robust antitumor activity in patients with previously untreated, locally advanced stage III NSCLC
  - ORR ~70% regardless of tumor histology and PD-L1 TPS; >75% of responding patients achieved DoR ≥12 mo; 12-mo PFS >65%, and 12-mo OS >80%
- Toxicity deemed manageable, with incidence of grade ≥3 pneumonitis ≤8%
  - Consistent with prior studies of anti–PD-(L)1 mAb therapy + concurrent CRT for stage III NSCLC
- Investigators conclude that pembrolizumab + concurrent CRT represents a promising therapeutic approach for previously untreated, locally advanced stage III NSCLC
- Phase III KEYLYNK-012 trial: pembrolizumab + concurrent CRT followed by pembrolizumab ± olaparib vs concurrent CRT followed by durvalumab (current SoC) for stage III NSCLC

CheckMate 9LA 2-Yr Update: Study Design

- Randomized, open-label, phase III study (data cutoff: February 18, 2021; minimum/maximum follow up for OS: 24.4 mo/30.7 mo)



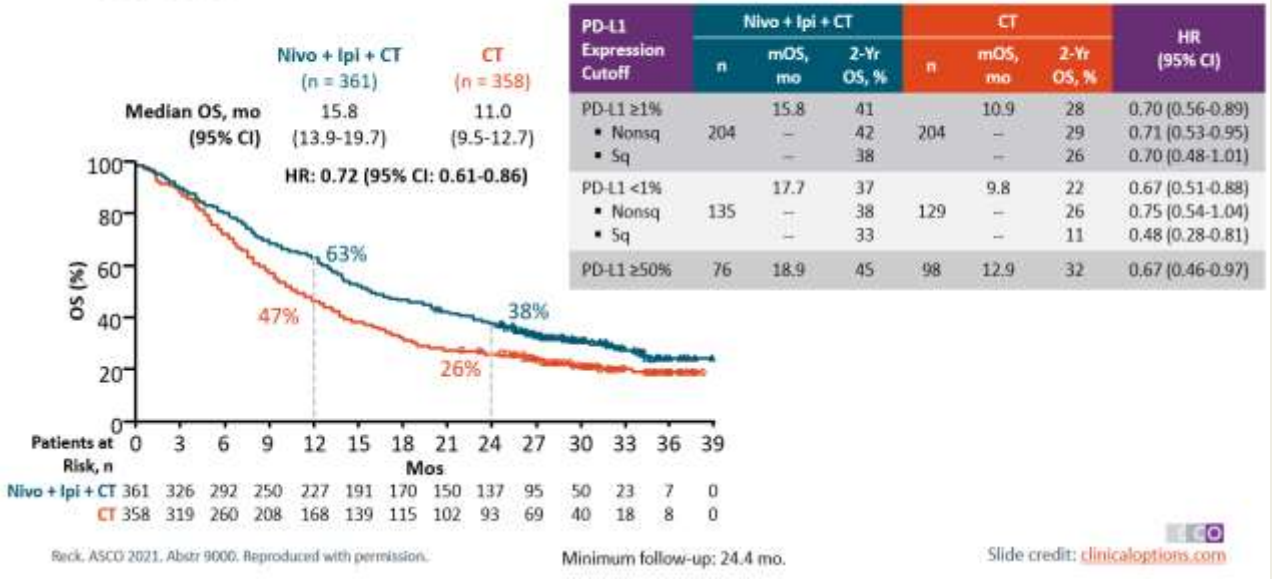
*PD-L1 IHC 28-8 pharmDx assay.
†Nonsquamous: pemetrexed + cisplatin or carboplatin; squamous: paclitaxel + carboplatin.

- Primary endpoint: OS
- Secondary endpoints: PFS (BICR), ORR (BICR), efficacy by tumor PD-L1 expression
- Exploratory endpoint: safety

Reck. ASCO 2021. Abstr 9000.

Slide credit: clinicaloptions.com

CheckMate 9LA 2-Yr Update: OS in All Randomized Patients



PD-L1 Expression Cutoff	Nivo + Ipi + CT n	Nivo + Ipi + CT mOS, mo	Nivo + Ipi + CT 2-Yr OS, %	CT n	CT mOS, mo	CT 2-Yr OS, %	HR (95% CI)
PD-L1 ≥1%		15.8	41		10.9	28	0.70 (0.56-0.89)
• Nonsq	204	--	42	204	--	29	0.71 (0.53-0.95)
• Sq		--	38		--	26	0.70 (0.48-1.01)
PD-L1 <1%		17.7	37		9.8	22	0.67 (0.51-0.88)
• Nonsq	135	--	38	129	--	26	0.75 (0.54-1.04)
• Sq		--	33		--	11	0.48 (0.28-0.81)
PD-L1 ≥50%	76	18.9	45	98	12.9	32	0.67 (0.46-0.97)

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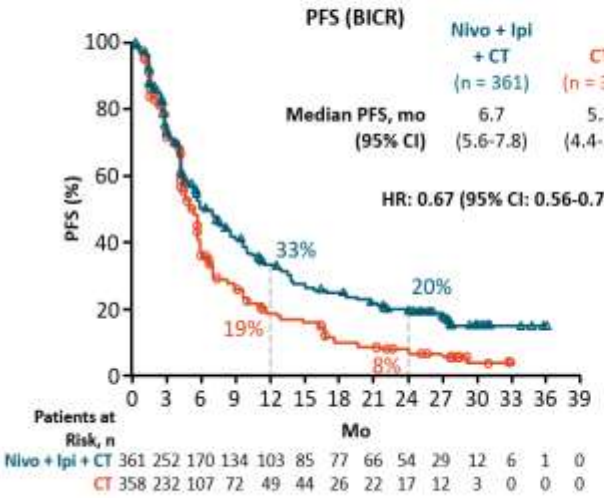
Minimum follow-up: 24.4 mo.

Slide credit: clinicaloptions.com

CheckMate 9LA 2-Yr Update: PFS



PD-L1 Expression Cutoff	Nivo + Ipi + CT n	Nivo + Ipi + CT mPFS, Mo	CT n	CT mPFS, Mo	HR (95% CI)
PD-L1 ≥1%	204	7.0	204	5.0	0.67 (0.53-0.84)
PD-L1 <1%	135	5.8	129	4.9	0.68 (0.51-0.89)
PD-L1 ≥50%	76	7.5	98	4.5	0.59 (0.41-0.84)

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Minimum follow-up: 23.3 mo.

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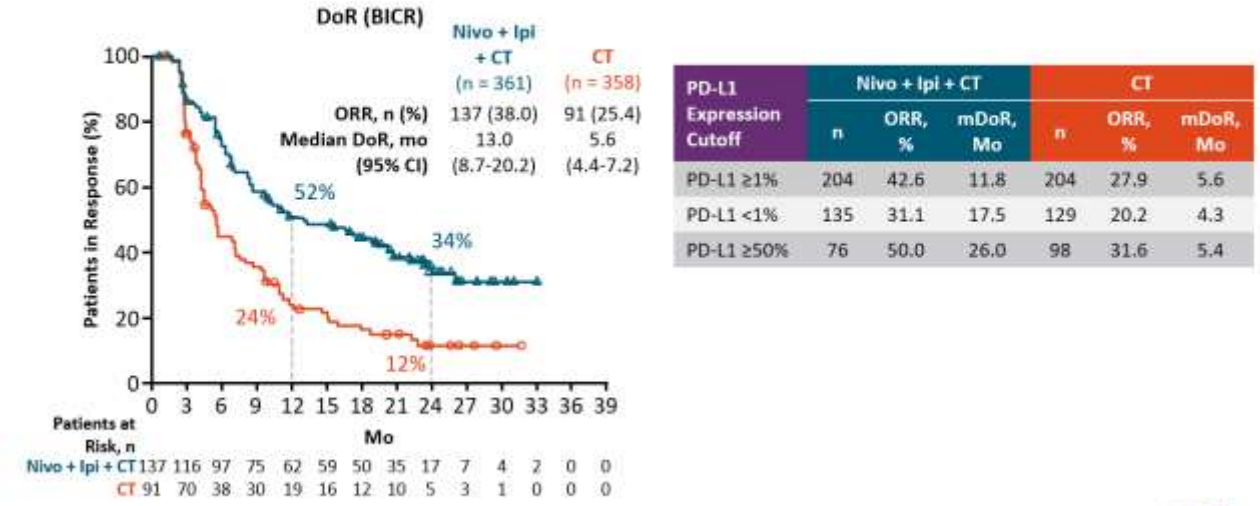
CheckMate 9LA 2-Yr Update: Duration of Response



PD-L1 Expression Cutoff	Nivo + Ipi + CT n	Nivo + Ipi + CT ORR, %	Nivo + Ipi + CT mDoR, Mo	CT n	CT ORR, %	CT mDoR, Mo
PD-L1 ≥1%	204	42.6	11.8	204	27.9	5.6
PD-L1 <1%	135	31.1	17.5	129	20.2	4.3
PD-L1 ≥50%	76	50.0	26.0	98	31.6	5.4

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Minimum follow-up: 23.3 mo.

Slide credit: clinicaloptions.com

CheckMate 9LA 2-Yr Update: Conclusions

- In an update of CheckMate 9LA with longer follow-up, first-line nivolumab + ipilimumab + CT continued to demonstrate durable OS, PFS, and DoR benefits vs CT in patients with advanced NSCLC
  - 2-yr OS: 38% vs 26%, respectively
  - Results consistent across subgroups examined, including PD-L1 expression level, histology, and CNS metastases
- Safety profile consistent with previous reports, with most grade 3/4 TRAEs with the combination occurring during the 2 cycles of CT
- Discontinuation of nivolumab + ipilimumab + CT because of TRAEs did not negatively affect long-term outcomes in a post hoc analysis
  - 56% of those who discontinued due to TRAE maintained responses ≥1 yr
- Investigators concluded that nivolumab + ipilimumab + CT is an effective first-line treatment option for patients with advanced NSCLC

- Prostate Cancer
  - ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer likely a new standard of care
  - Bone protecting agents significantly reduce SRE when 2nd-generation AR-antagonists/Radium-223 combined
  - Up-front Multimodal therapy in advanced HSPC improves PFS. Impacts on OS unknown.

PROSTATE CANCER UPDATES

Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC

Eligible patients

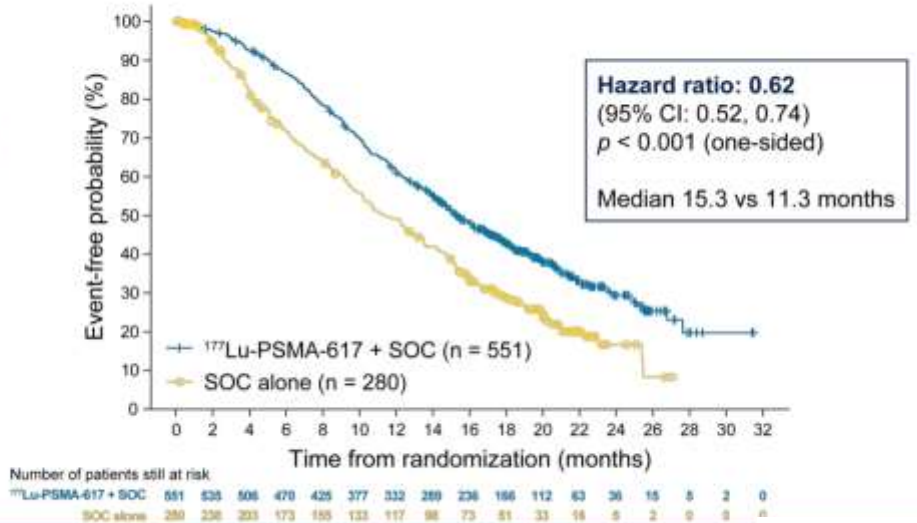
- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

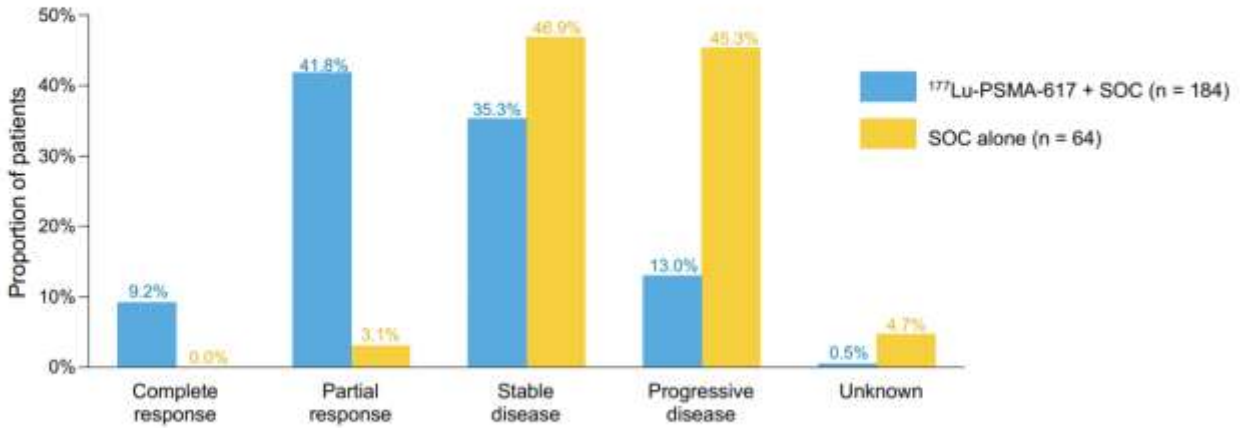
Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients
(N = 831)



Secondary endpoint: RECIST v1.1 responses favored the ^{177}Lu-PSMA-617 arm in patients with measurable disease



EORTC GUCG 1333 (PEACE-3) original design

EORTC Genito-Urinary Cancers Group
The future of cancer therapy

Study population

- **Patients with bone-predominant mCRPC (≥2 bone metastases)**
- Asymptomatic or mildly symptomatic
- WHO PS of 0 or 1
- No prior treatment with, cyp17 inhibitors, enzalutamide, Ra233, other radionucleotides, hemibody radiotherapy
- No known brain or visceral metastases

Target Accrual N=560

1:1 Randomisation,

Enzalutamide 160 mg qd
Radium-223
55 kBq/kg IV every 4 weeks for 6 cycles

Stratification factors

- Country
- Baseline pain (BPI worst pain 0-1 vs 2-3)
- Prior docetaxel (yes vs no)
- Use of bone health agents*

Enzalutamide 160 mg qd

Primary endpoint

- rPFS

Secondary endpoints

- OS
- DSS
- SSE
- Time to initiation of next systemic anti-neoplastic therapy
- PFS2
- Brief Pain Inventory (BPI),
- (EQ-5D-5L)

Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; Initiation during study was prohibited to prevent confounding effects.

Bone fractures and cumulative incidence - safety population

Time point	Without BPA		With BPA	
	Enza+Rad (N=35)	Enza (N=32)	Enza+Rad (N=87)	Enza (N=97)
	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
9 months	25.7 (12.6-41.0)	9.4 (2.3-22.5)	2.7 (0.5-8.5)	1.3 (0.1-6.1)
12 months	**37.1 (21.3-53.0)**	**15.6 (5.6-30.3)**	**2.7 (0.5-8.5)**	**2.6 (0.5-8.3)**
15 months	42.9 (26.1-58.6)	21.9 (9.5-37.5)	4.3 (1.1-10.9)	2.6 (0.5-8.3)
18 months	**45.9 (28.6-61.6)**	**21.9 (9.5-37.5)**	**4.3 (1.1-10.9)**	**2.6 (0.5-8.3)**
21 months	52.0 (33.8-67.5)	21.9 (9.5-37.5)	4.3 (1.1-10.9)	2.6 (0.5-8.3)

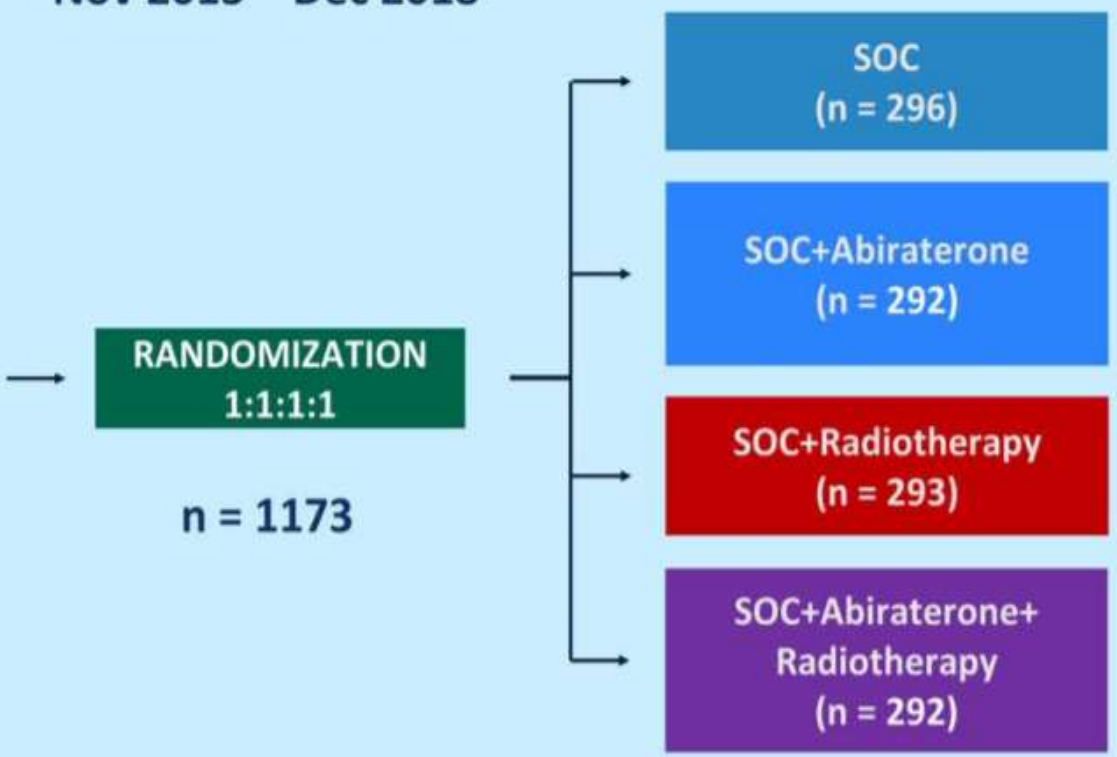
Design of PEACE-1

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

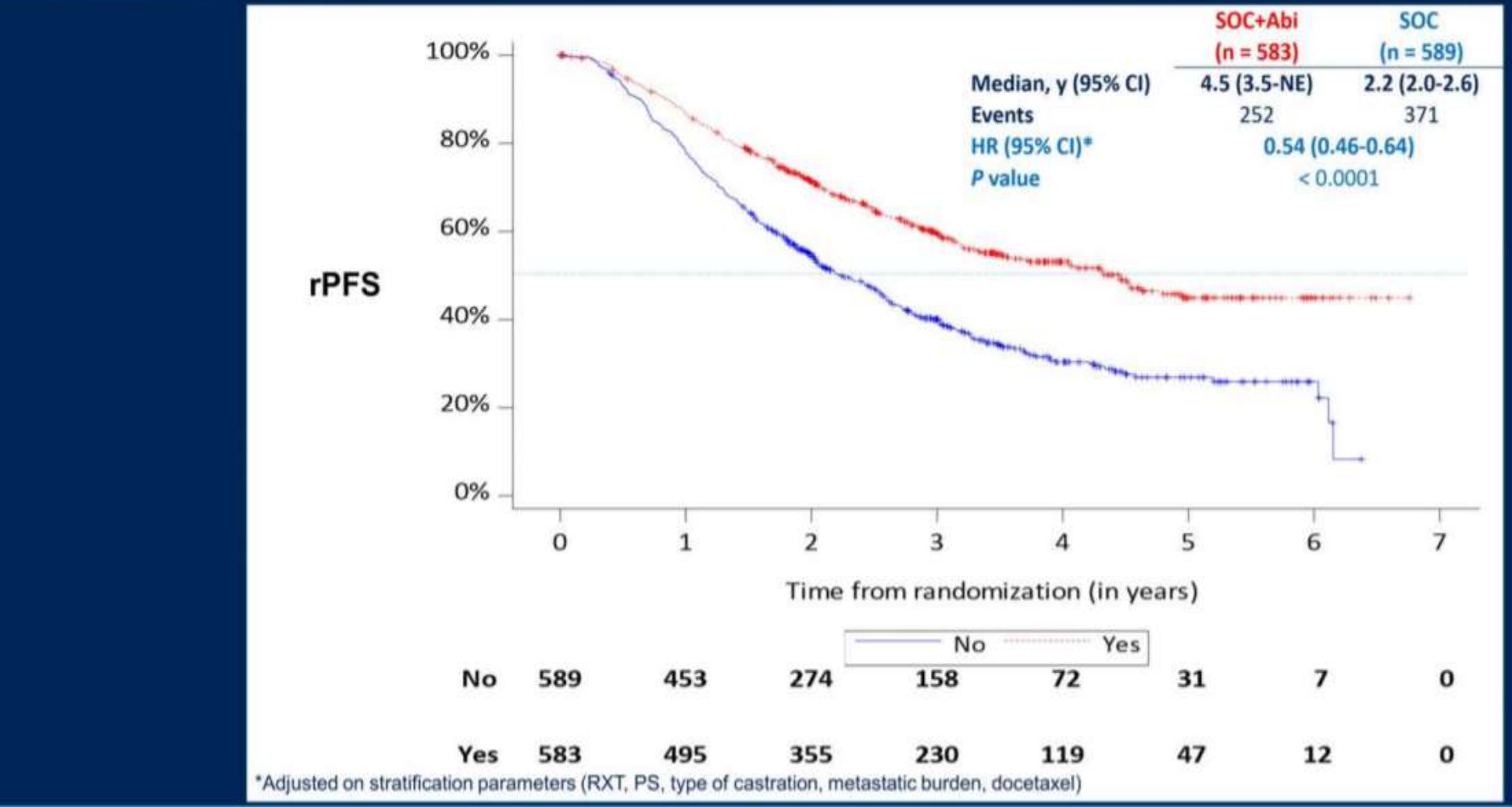
Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

Radiographic Progression-Free Survival (rPFS)
Overall population: SOC=ADT+/- Docetaxel (+/- RXT)



- Bladder Cancer
  - Bladder Preservation therapy in MIBC gaining new ground, leveraging combination strategies with chemotherapy and chemoradiation.
  - Responses (especially CRs) to immunotherapy in first-line metastatic urothelial cancer are durable and lead to long-term survival

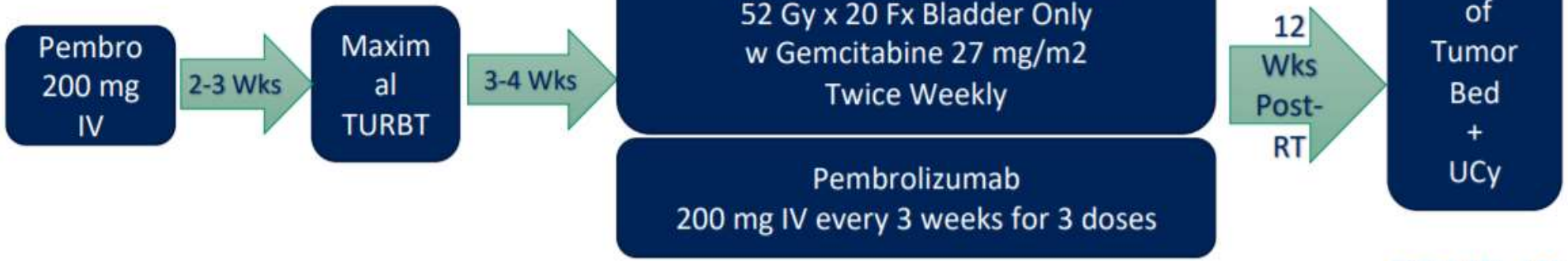
BLADDER CANCER UPDATES

TREATMENT SCHEMA

NYU Langone Health

KEY ELIGIBILITY CRITERIA

- UC Histology Mixed Allowed
- cT2-T4aN0M0
- ECOG PS 0 or 1
- RC ineligible/ refusing
- No Perioperative ChemoTx



Assessment of Response

CT/MR AP w Contrast

5 Years Disease Surveillance on Study beginning post-RT

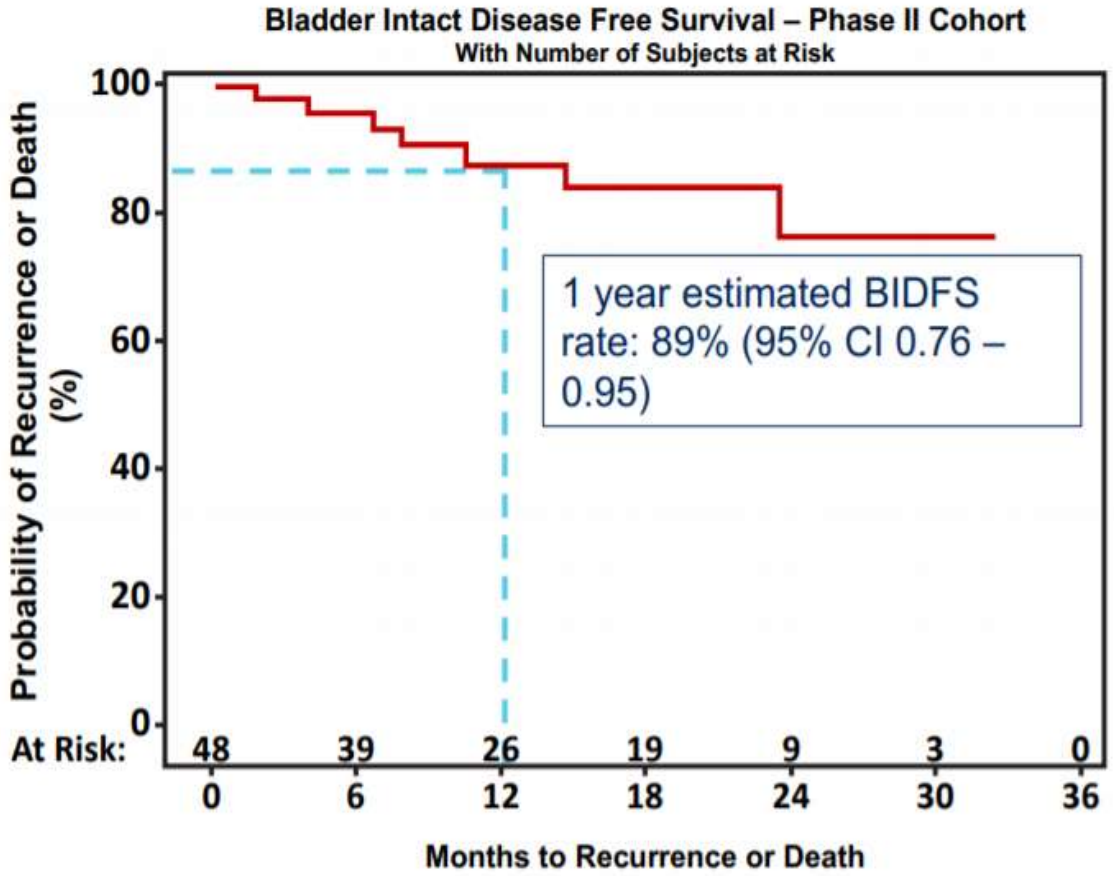
Imaging:

CT/MR AP Q3 months for 18 months, Q6 months for 18 months, Q12 months for 24 months.

Cystoscopy/Cytology

Q3 months for 12 months, Q4 months for 12 months, Q6 months for 3 years

Bladder-Intact Disease-Free Survival
All Patients (N=54)



Median Follow up All Patients: 15.5 months (1.6 months – 56.5 months)

HCRN GU16-257

cT2-4aN0M0

Gemcitabine + Cisplatin + Nivolumab X 4 cycles

Clinical Restaging

Cysto + biopsies
Urine cytology
MRI

Clinical CR

No cystectomy → **Nivo x 4 mos**

* Treatment based on patient choice

Cystectomy

No Clinical CR → **Cystectomy**

- Determine the clinical CR rate
- Determine the ability of clinical CR to predict "benefit"

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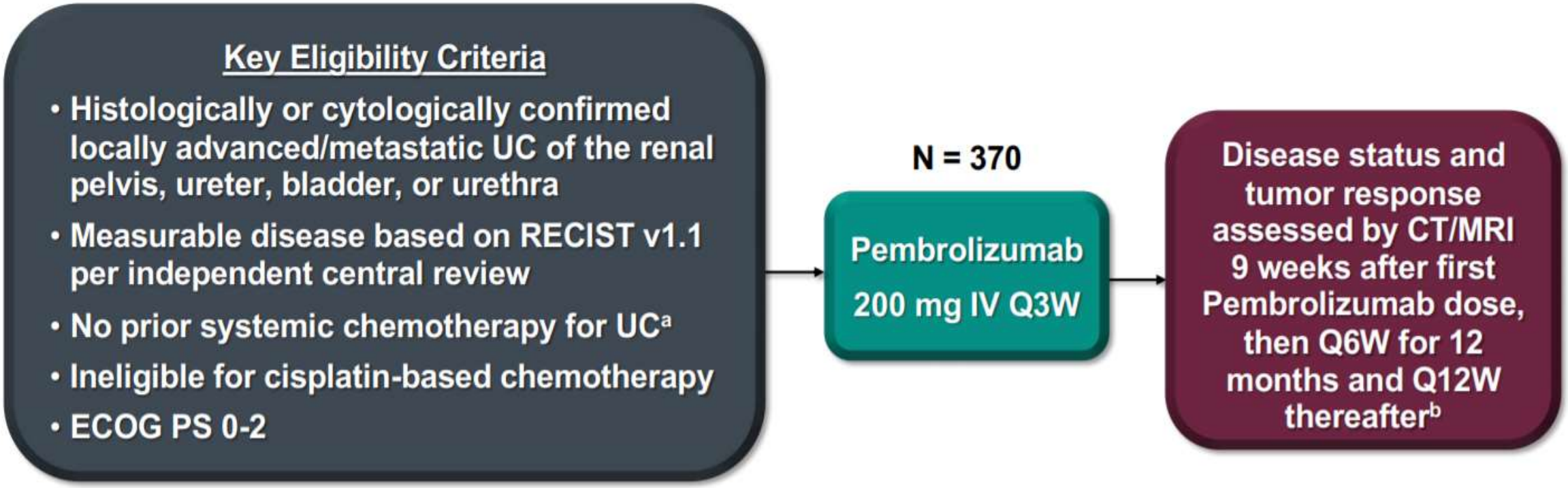
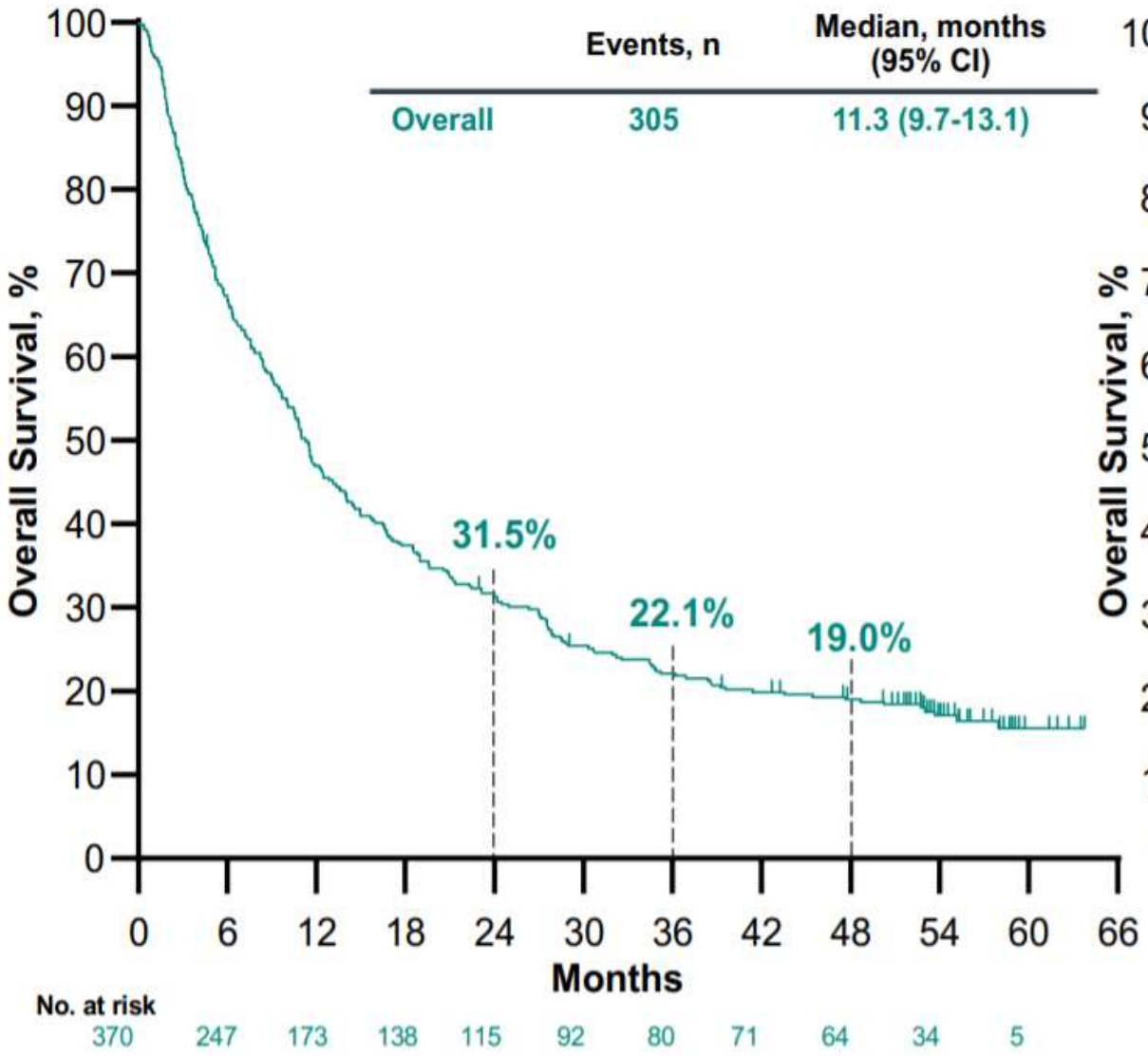
KEYNOTE-052 Study Design

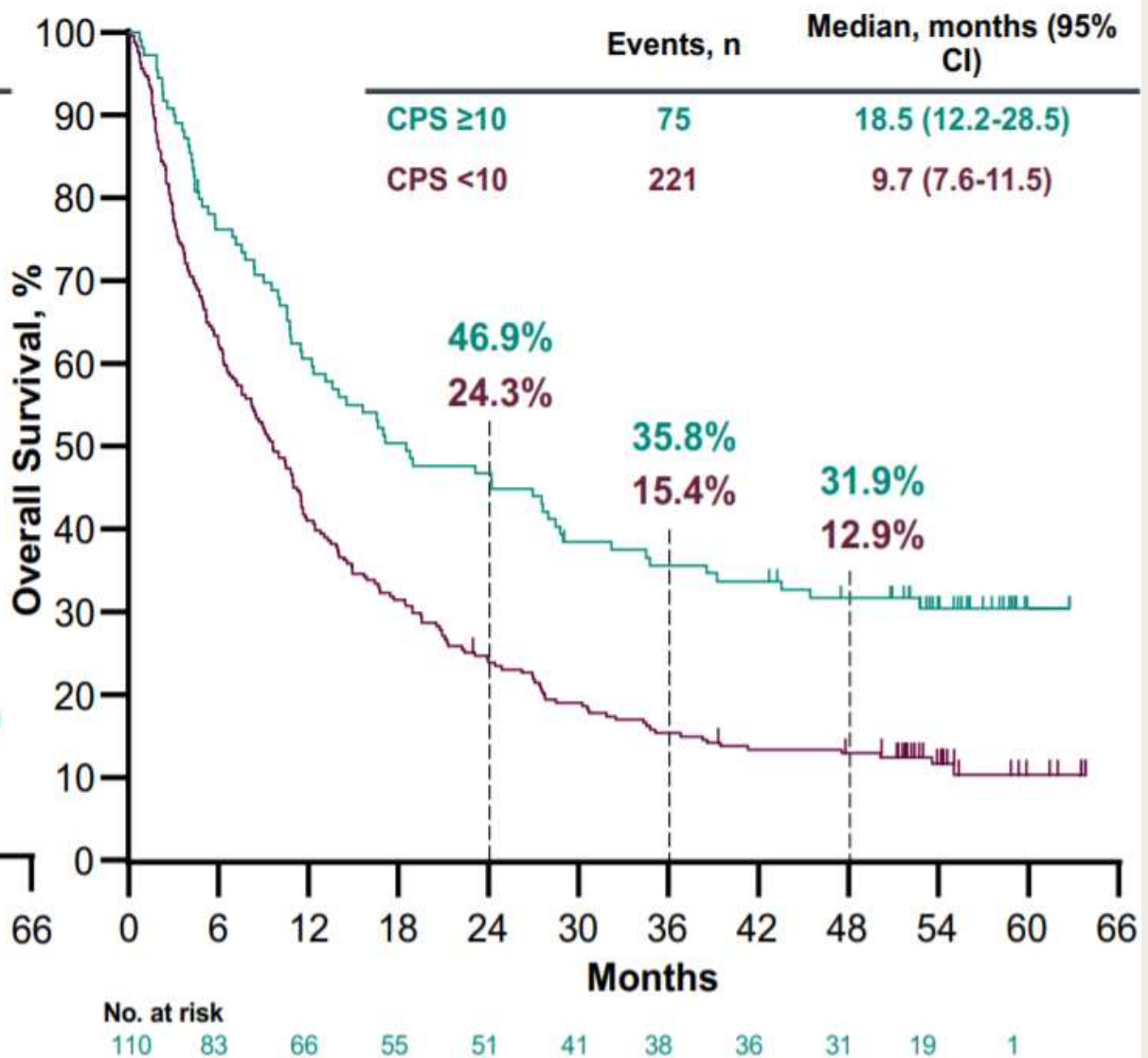


- Primary end point: confirmed ORR per RECIST v1.1 by independent radiology review
- Secondary end points: PFS and DOR per RECIST v1.1 by independent radiology review, OS, safety
- End points analyzed for the overall population, patients with PD-L1 CPS ≥10 and CPS <10[c]

[a]Patients who received adjuvant/neoadjuvant platinum-based chemotherapy before/after radical cystectomy and experienced recurrence >12 months after completion were eligible to participate. [b]Until disease progression, start of new anticancer treatment, withdrawal of consent, or death. [c]CPS defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Kaplan-Meier Estimates of OS





Data cutoff: September 26, 2020.

- Renal Cell Carcinoma
  - Adjuvant Pembrolizumab improves DFS and trend towards OS benefit in high-risk RCC after surgery and could be a new standard of care
  - Subgroup analyses of CM—ER highlights the unique activity of cabozanitib/nivolumab in high-risk clinical subgroups over sunitinib (liver, bone and extensive disease).
  - Long-term follow up confirms benefit of 1st-line axitinib/pembrolizumab over sunitinib but PFS durability likely not the same as Ipi/nivo.

RENAL CELL CARCINOMA UPDATES

CheckMate 9ER: Study design

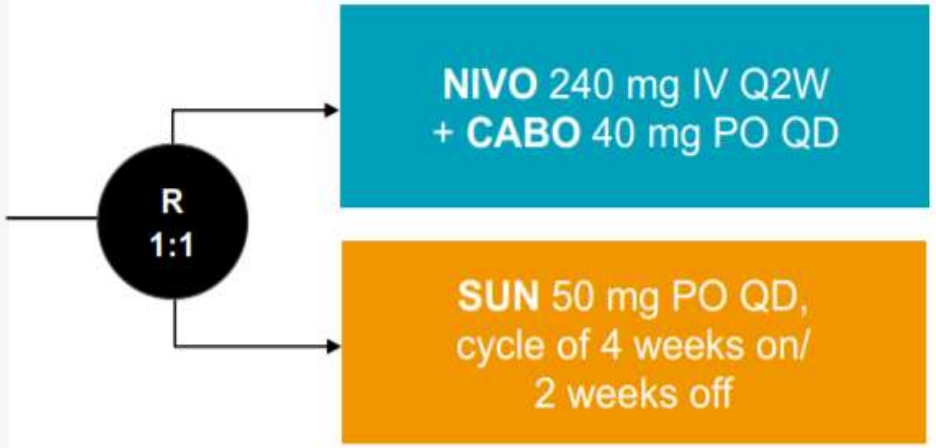
Stratification factors:

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

N = 651

Key inclusion criteria[1,2]

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



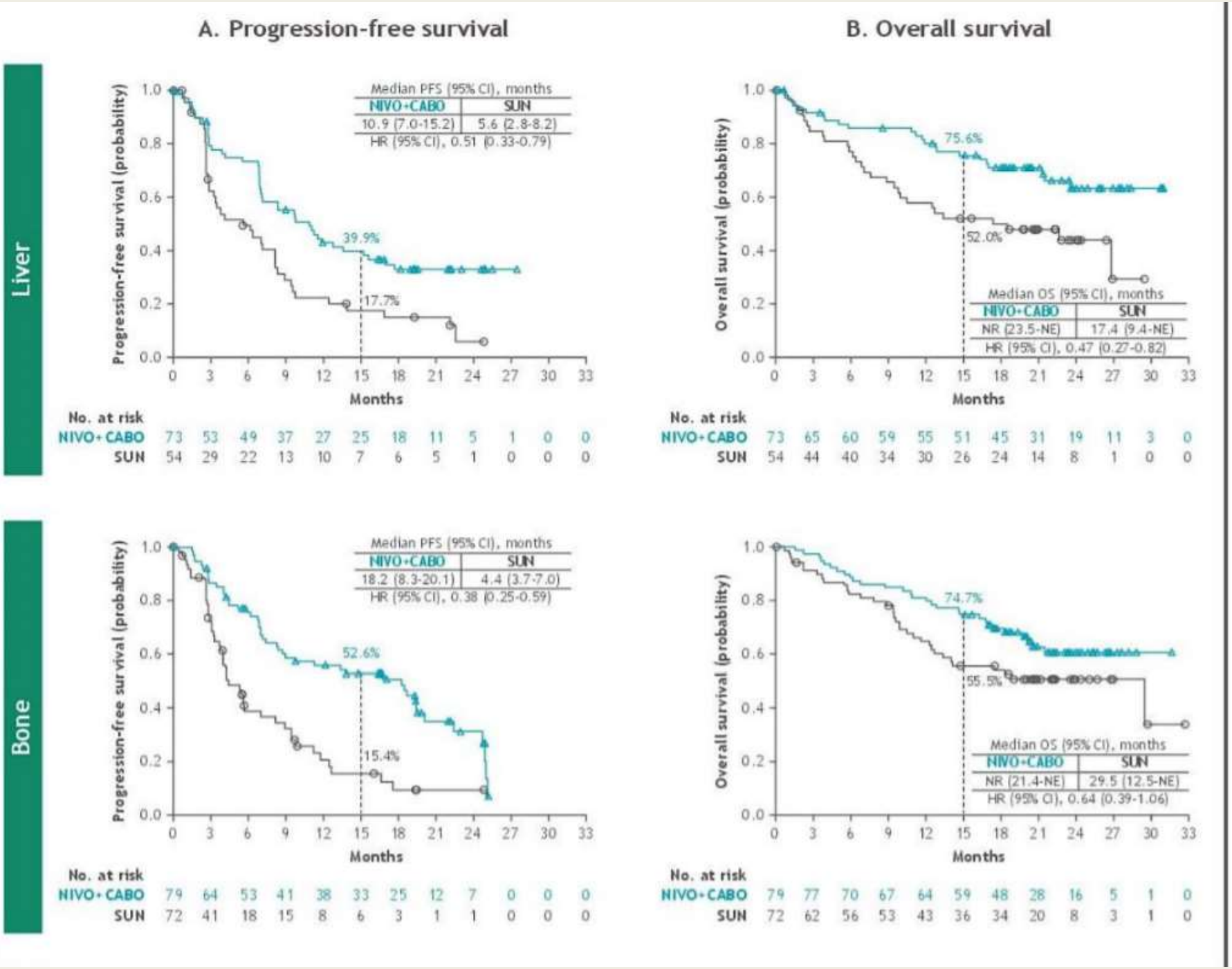
Treat until RECIST v1.1–defined progression or unacceptable toxicity[b]

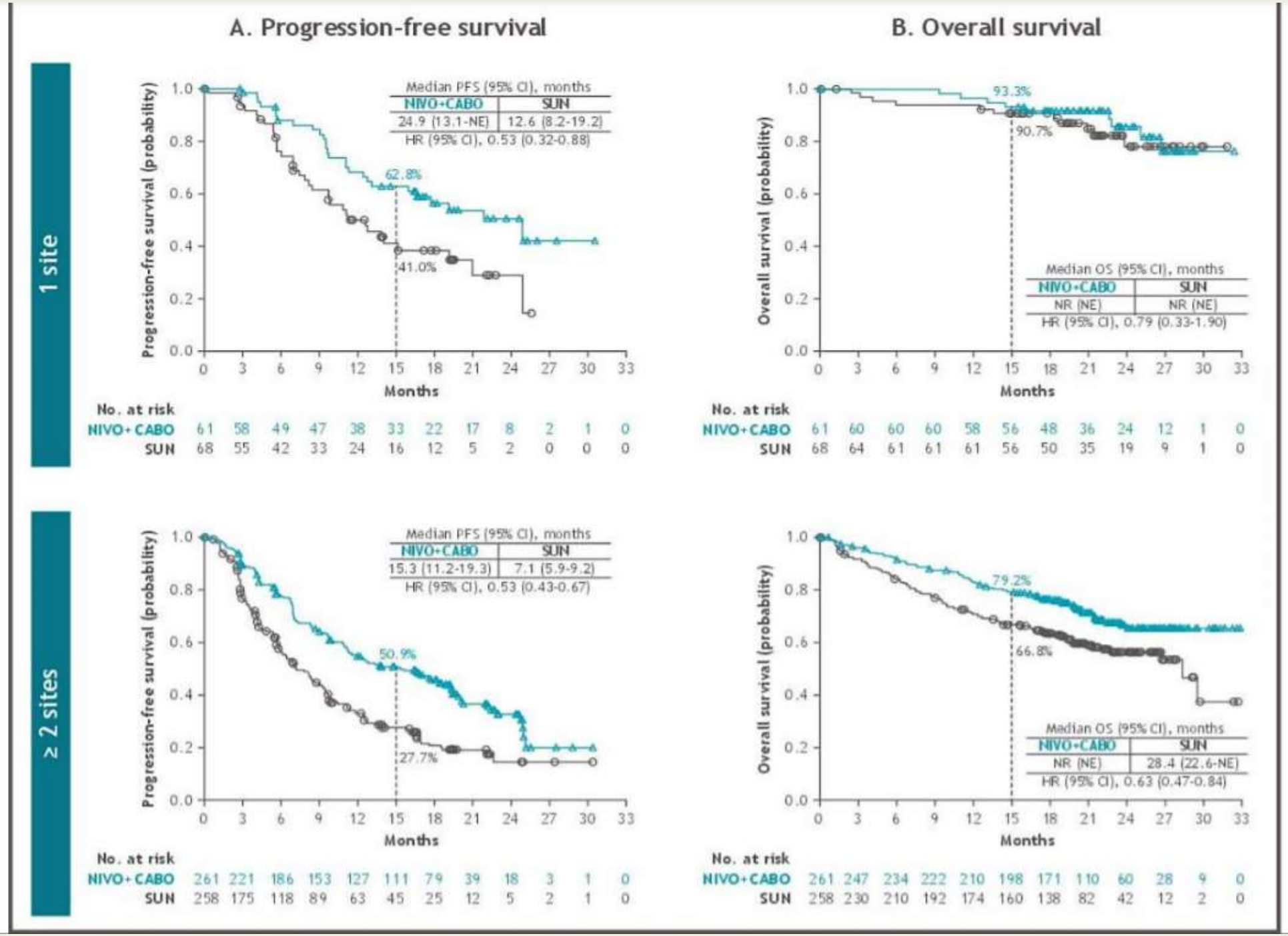
Median study follow-up, 18.1 months (range, 10.6–30.6 months)

Primary endpoint: PFS

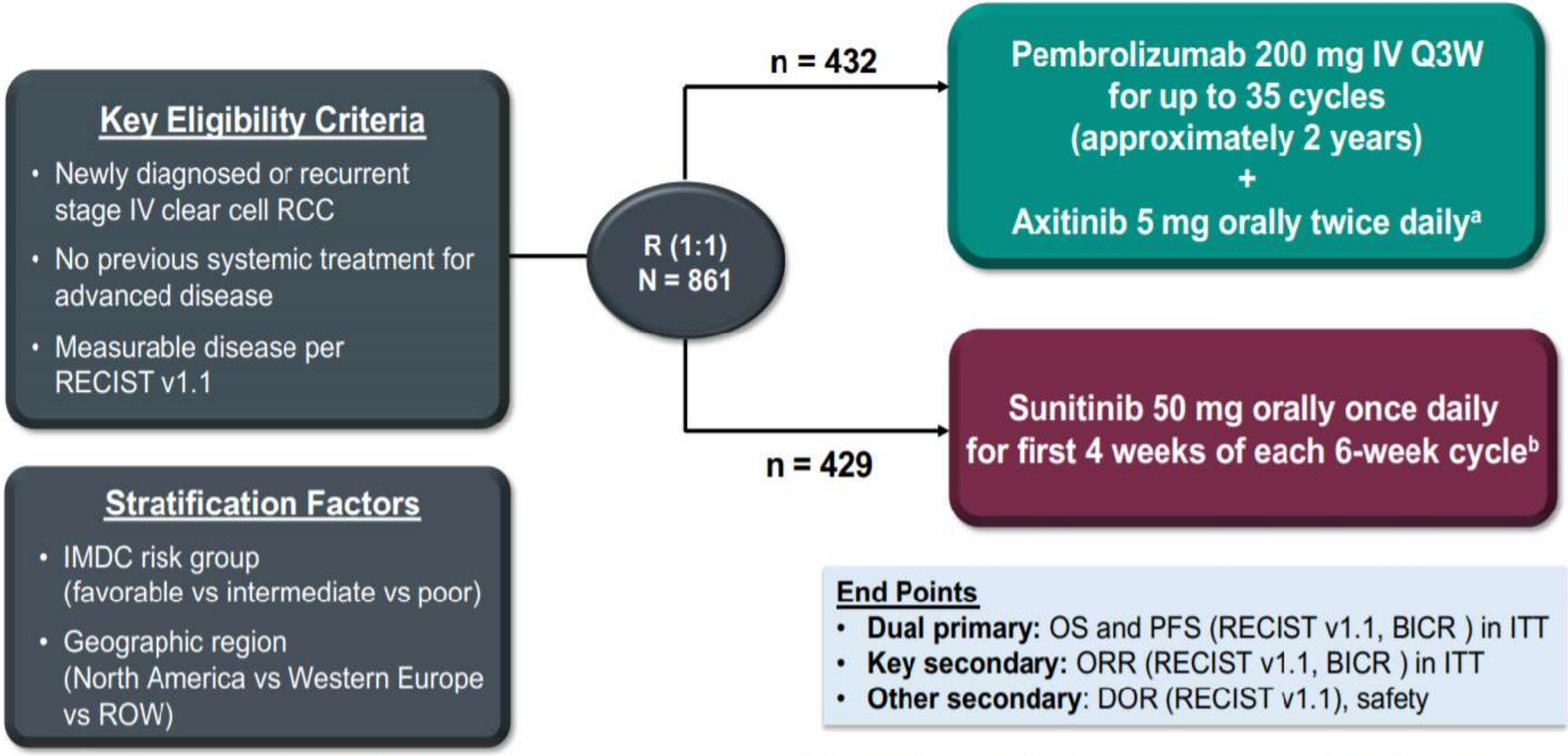
Secondary endpoints: OS, ORR, and safety

[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.
[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
1. Clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri TK et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.


A. Progression-free survival
B. Overall survival
Liver
Progression-free survival (probability)
Median PFS (95% CI), months
NIVO+CABO | SUN
10.9 (7.0-15.2) | 5.6 (2.8-8.2)
HR (95% CI), 0.51 (0.33-0.79)
39.9%
17.7%
Months
No. at risk
NIVO+CABO 73 53 49 37 27 25 18 11 5 1 0 0
SUN 54 29 22 13 10 7 6 5 1 0 0 0
Overall survival (probability)
75.6%
52.0%
Median OS (95% CI), months
NIVO+CABO | SUN
NR (23.5-NE) | 17.4 (9.4-NE)
HR (95% CI), 0.47 (0.27-0.82)
No. at risk
NIVO+CABO 73 65 60 59 55 51 45 31 19 11 3 0
SUN 54 44 40 34 30 26 24 14 8 1 0 0
Bone
Progression-free survival (probability)
Median PFS (95% CI), months
NIVO+CABO | SUN
18.2 (8.3-20.1) | 4.4 (3.7-7.0)
HR (95% CI), 0.38 (0.25-0.59)
52.6%
15.4%
Months
No. at risk
NIVO+CABO 79 64 53 41 38 33 25 12 7 0 0 0
SUN 72 41 18 15 8 6 3 1 1 0 0 0
Overall survival (probability)
74.7%
55.5%
Median OS (95% CI), months
NIVO+CABO | SUN
NR (21.4-NE) | 29.5 (12.5-NE)
HR (95% CI), 0.64 (0.39-1.06)
No. at risk
NIVO+CABO 79 77 70 67 64 59 48 28 16 5 1 0
SUN 72 62 56 53 43 36 34 20 8 3 1 0

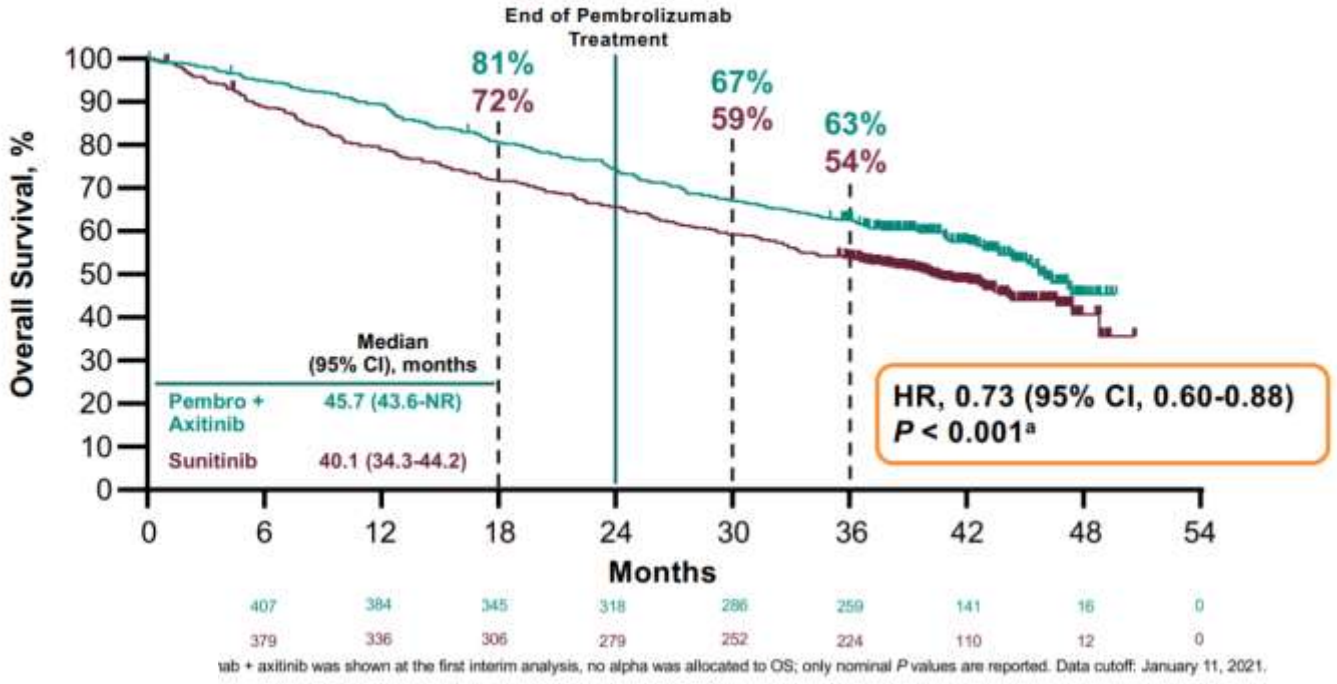

A. Progression-free survival
B. Overall survival
1 site
≥ 2 sites
Progression-free survival (probability)
Overall survival (probability)
Months
Median PFS (95% CI), months
NIVO+CABO
SUN
24.9 (13.1-NE)
12.6 (8.2-19.2)
HR (95% CI), 0.53 (0.32-0.88)
62.8%
41.0%
93.3%
90.7%
Median OS (95% CI), months
NR (NE)
NR (NE)
HR (95% CI), 0.79 (0.33-1.90)
15.3 (11.2-19.3)
7.1 (5.9-9.2)
HR (95% CI), 0.53 (0.43-0.67)
50.9%
27.7%
79.2%
66.8%
28.4 (22.6-NE)
HR (95% CI), 0.63 (0.47-0.84)
No. at risk
NIVO+CABO 61 58 49 47 38 33 22 17 8 2 1 0
SUN 68 55 42 33 24 16 12 5 2 0 0 0
NIVO+CABO 61 60 60 60 58 56 48 36 24 12 1 0
SUN 68 64 61 61 61 56 50 35 19 9 1 0
NIVO+CABO 261 221 186 153 127 111 79 39 18 3 1 0
SUN 258 175 118 89 63 45 25 12 5 2 1 0
NIVO+CABO 261 247 234 222 210 198 171 110 60 28 9 0
SUN 258 230 210 192 174 160 138 82 42 12 2 0

KEYNOTE-426 Study Design



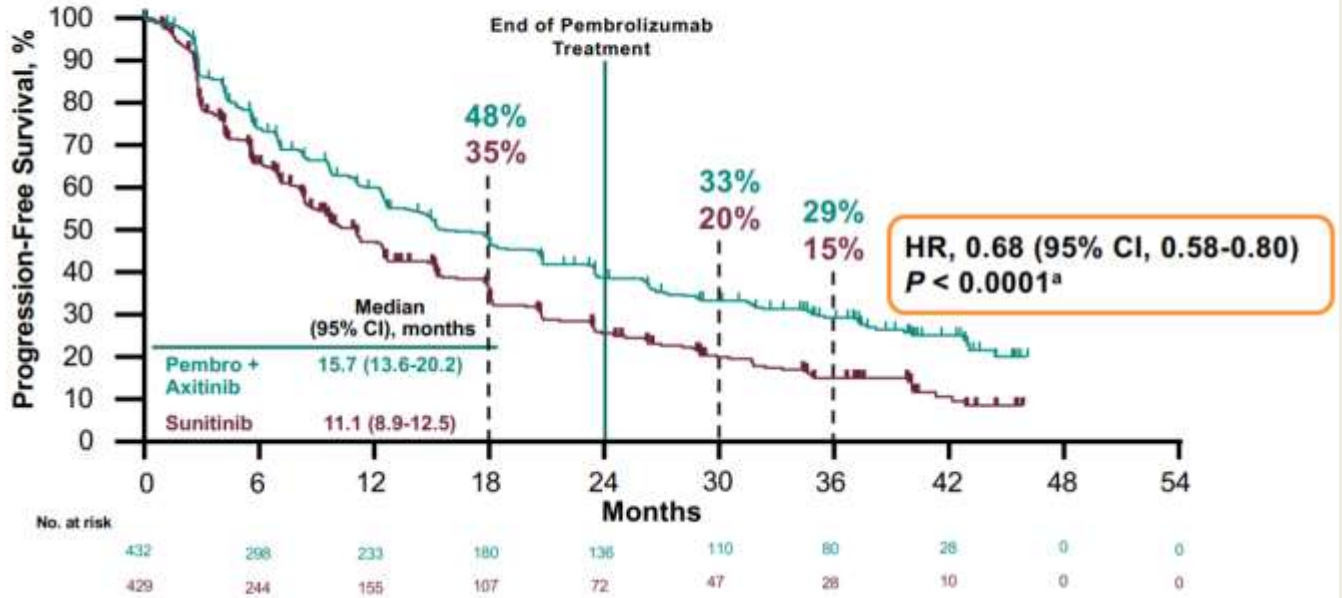
[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 11, 2021.

OS in the ITT Population



ab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

PFS in the ITT Population



aBecause 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 11, 2021.