Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Immunotherapy as Part of Standard of Care in Head and Neck Cancer

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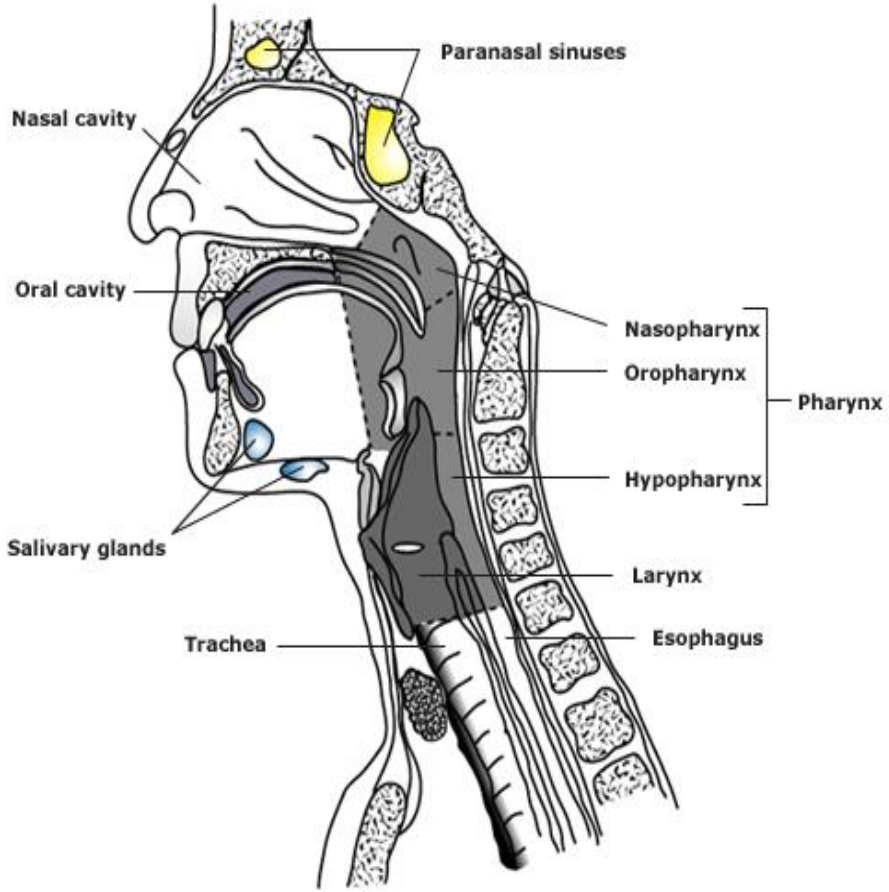
Disclosures

- Clinical Research Grants (IITs): Merck & Co., BMS, AstraZeneca, Tesaro/GSK, Janssen, IsoRay
- Advisory Board for Head and Neck: Merck & Co.
- Consulting: Rakuten, Shattuck Labs, Caris Life Sciences
- Executive Steering Committee for Cavrotolimod: Exicure
- Caris Life Sciences, HNC POA Chair
- I will be discussing non-FDA approved indications during my presentation.

Head and Neck Cancer

- 550,000 new cases worldwide each year; >90% are squamous cell carcinomas (SCC)
- Etiologic factors: Tobacco and EtOH use, and Human Papilloma Virus (HPV)
- Successful treatment requires a multidisciplinary approach including surgery, chemotherapy and radiation
- Despite aggressive therapy, HPV negative patients have a 50-70% 1 yr DFS
- Historically poor OS for recurrent/metastatic (R/M) HNSCC of 10-15%



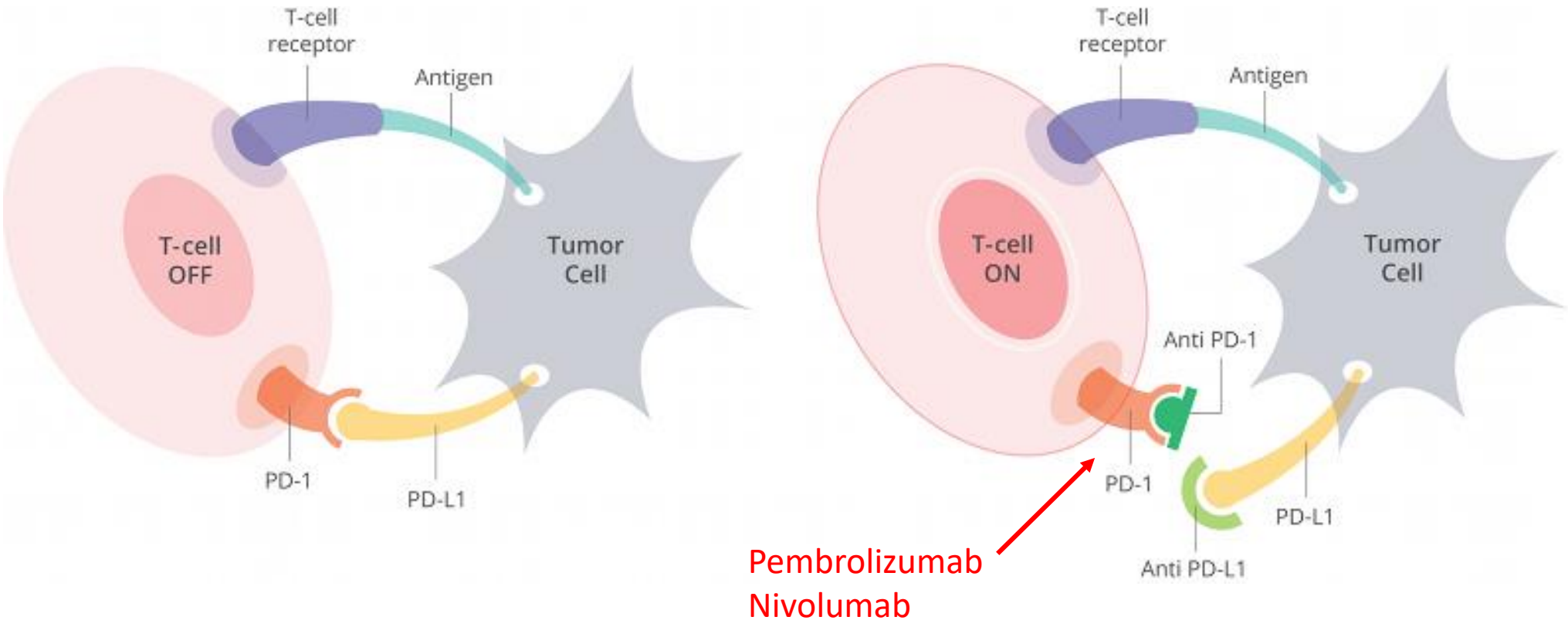
R/M HNSCC Therapeutic Options

- Single agent options after failure of first line therapy historically had response rates of 3-13%
- Single agents include cetuximab, taxanes and methotrexate
- HNSCC patients often have impaired immune functions and high levels of mutations (HPV neg)
- Tumors with high T cell infiltration have superior survival outcomes

Can immune dysfunction be reversed?

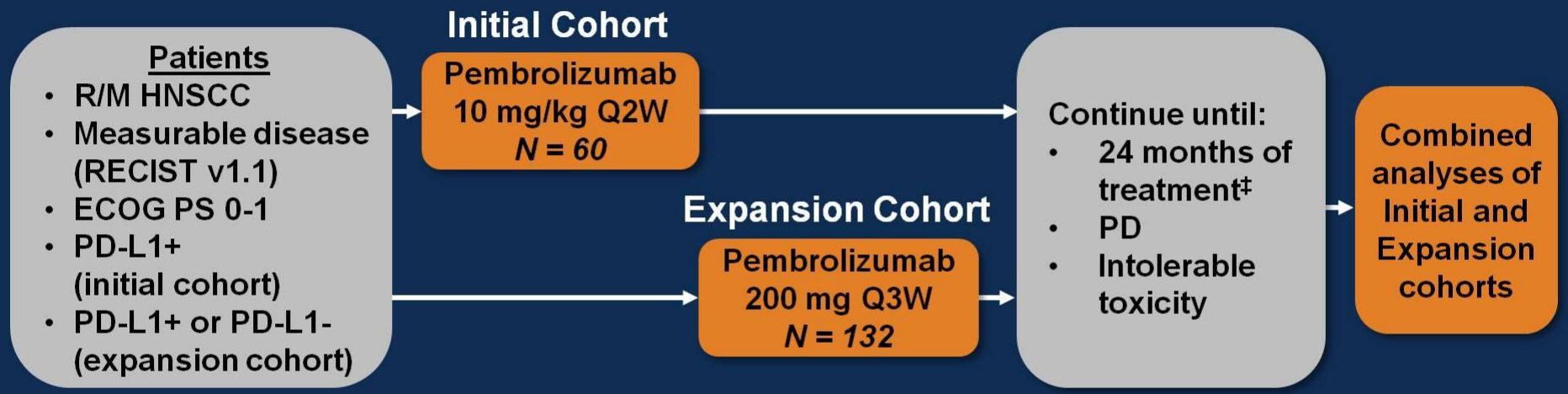
Denaro et al, Oncology 2014, Patel et al., Clin Med Insights Ear Nose Throat, 2012

PD-1 Inhibitors



Smart Patients. Cancer immunotherapy: PD-1 and beyond. www.smartpatients.com/targets/PD-1.

HNSCC Cohorts of Nonrandomized, Phase 1b, Multi-cohort KEYNOTE-012 Trial†



Response assessment: Every 8 weeks

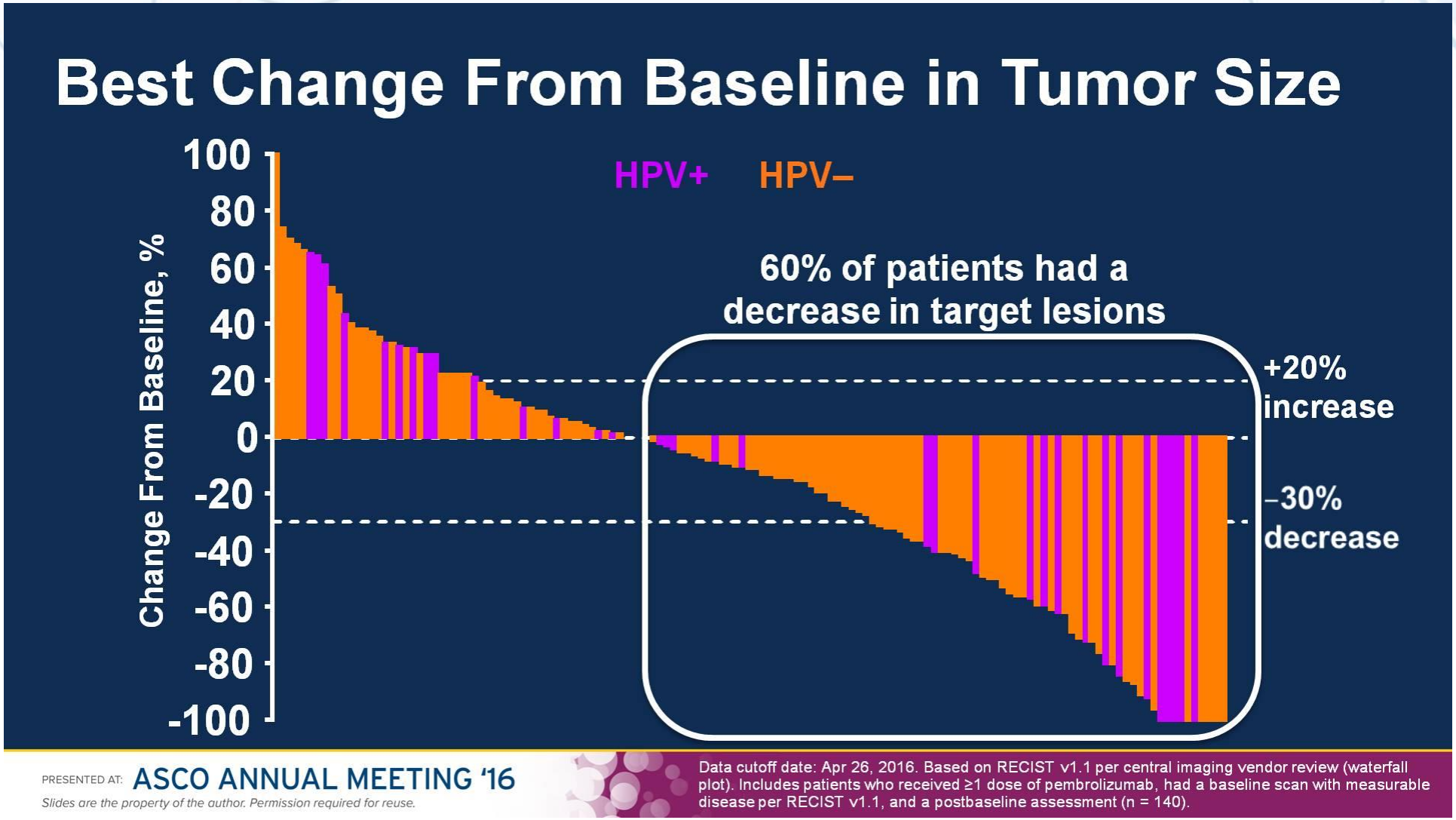
Primary end points: ORR (RECIST v1.1, central imaging vendor), safety

Secondary end points: ORR (investigator), PFS, OS, response duration, ORR in HPV+ patients§

PRESENTED AT: ASCO ANNUAL MEETING '16

†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§Initial cohort only.

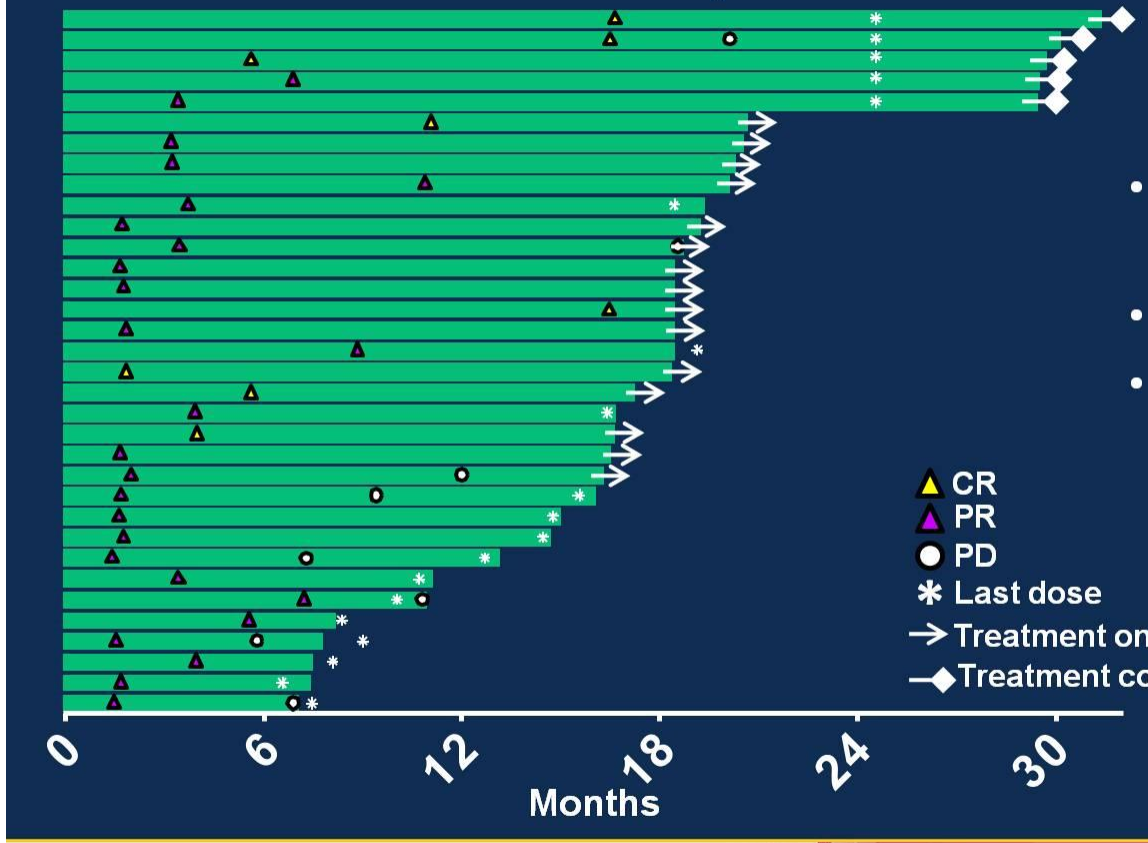
Presented By Ranee Mehra at 2016 ASCO Annual Meeting



ORR of 18%

Presented By Ranee Mehra at 2016 ASCO Annual Meeting

Duration of Response in Responders



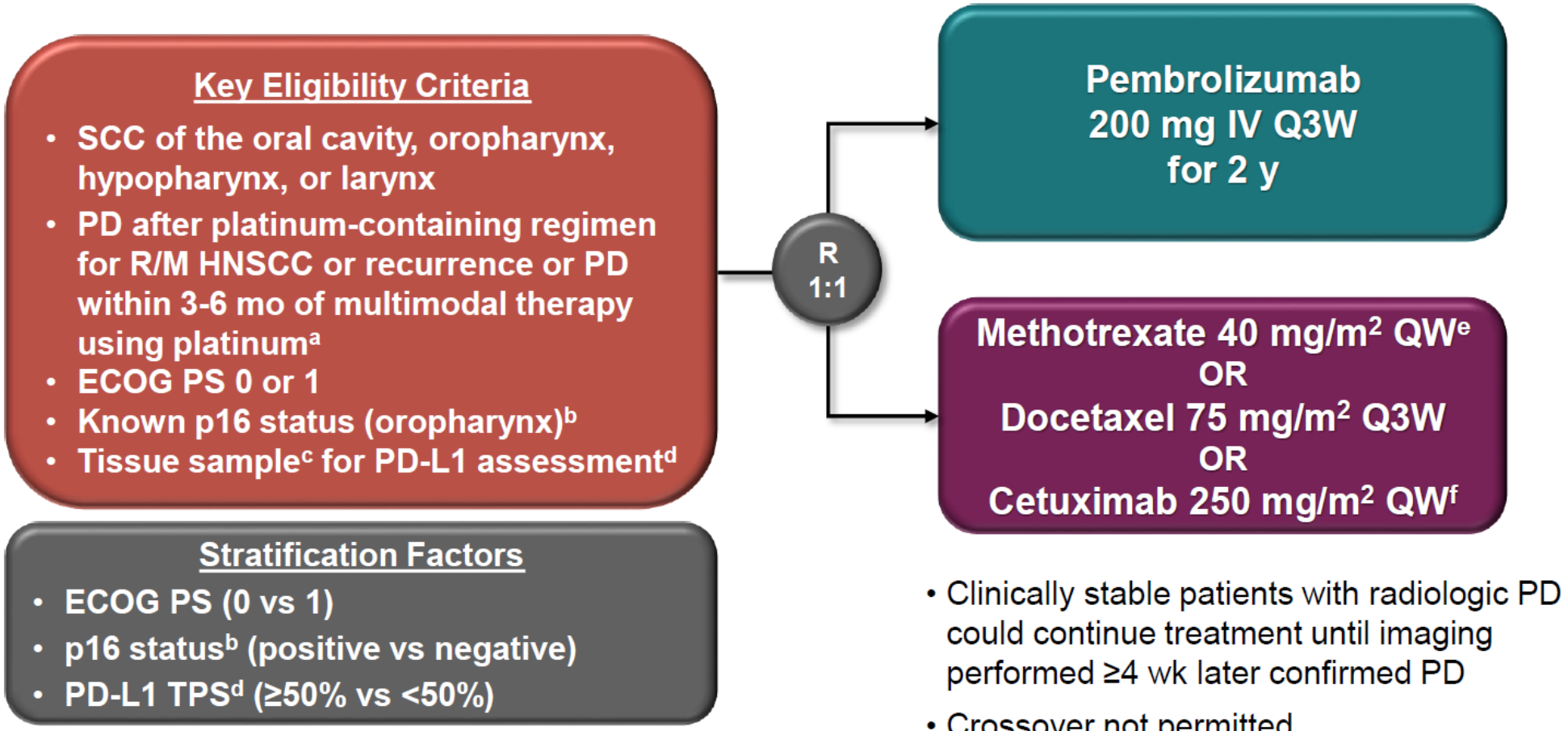
- Median time to response
  - 2 months (range, 2–17)
- 24% of responders had CR
- 65% (22/34) of responders remain in response

PRESENTED AT: ASCO ANNUAL MEETING '16

Data cutoff date: Apr 26, 2016.
Based on RECIST v1.1 per central imaging vendor review (swimlane plot).
Only confirmed responses shown.

Presented By Ranee Mehra at 2016 ASCO Annual Meeting

Phase 3 KEYNOTE-040 Study (NCT02252042)



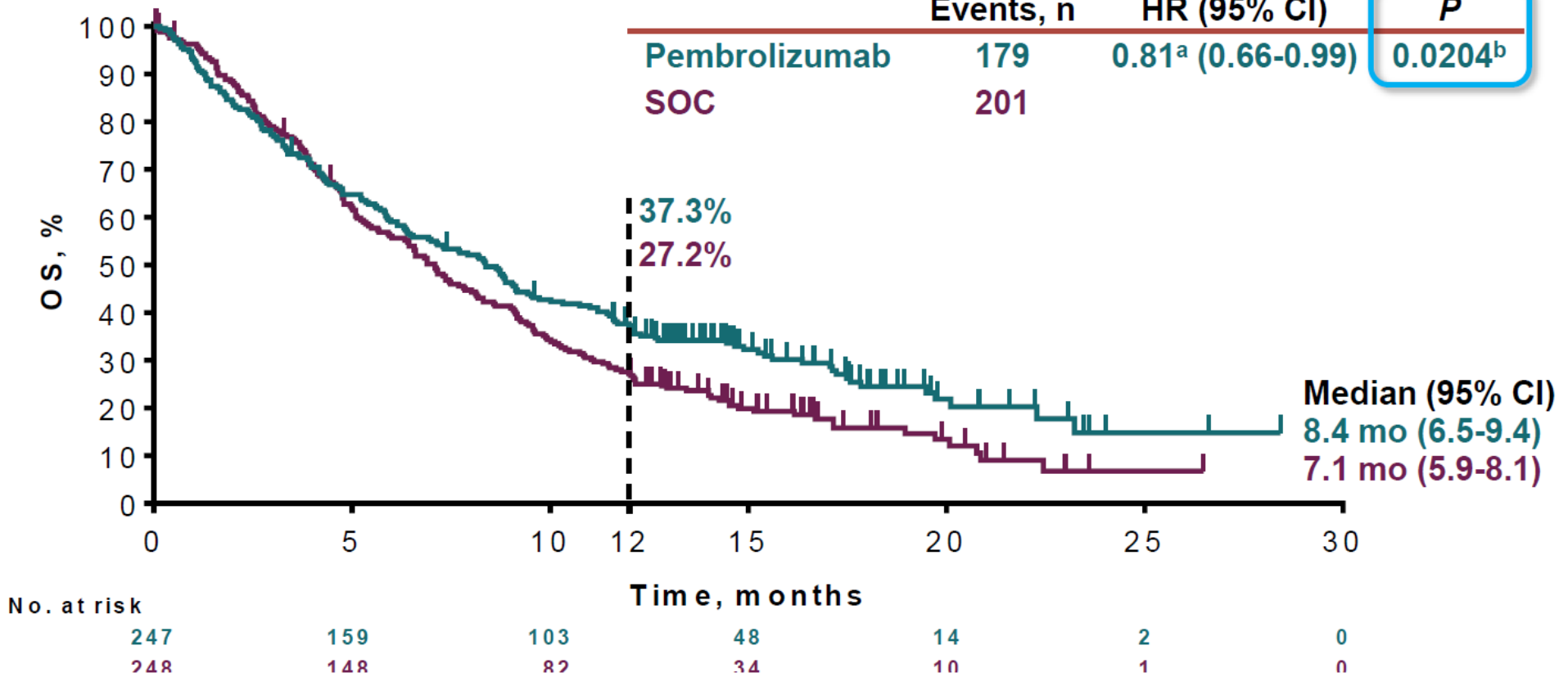
- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%.
[c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[e]Could be increased to 60 mg/m² QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m².

Presented By Ezra Cohen at 2017 ESMO Congress

Overall Survival in ITT Population

	Events, n	HR (95% CI)	*P*
Pembrolizumab	179	0.81[a] (0.66-0.99)	0.0204[b]
SOC	201		



[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI, 0.67-1.01), *P* = 0.0316. After the initial report, updated survival data were obtained for 4 patients. [b]One-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

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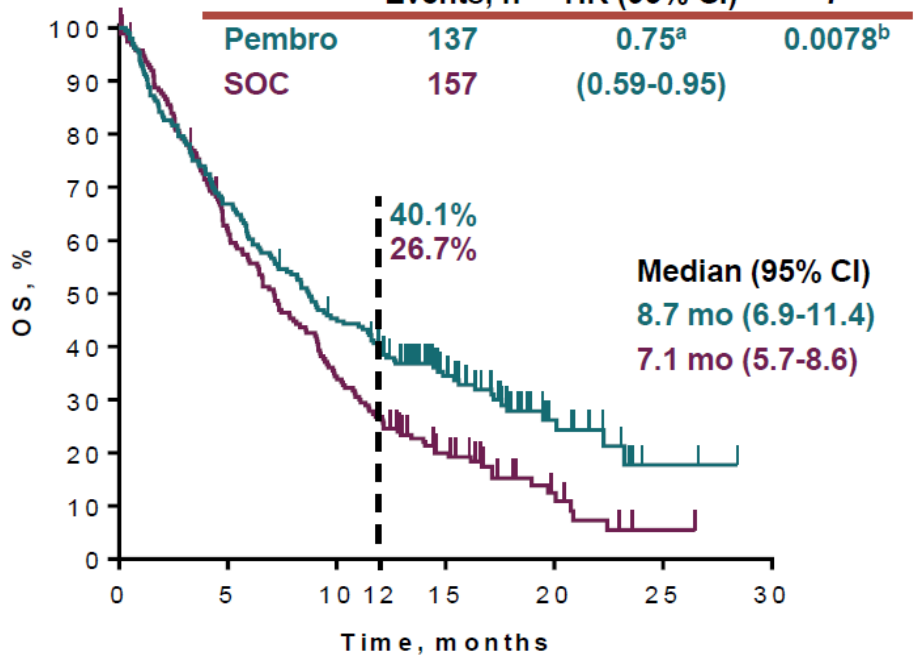
Overall Survival by PD-L1 Expression

PD-L1 CPS ≥1

	Events, n	HR (95% CI)	*P*
Pembro	137	0.75[a]	0.0078[b]
SOC	157	(0.59-0.95)	

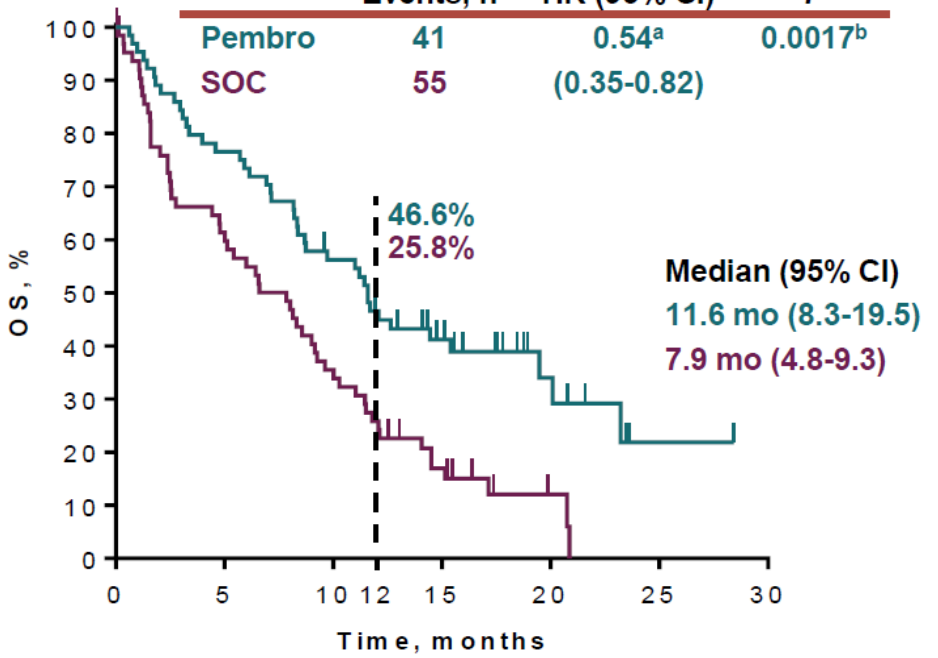


No. at risk

	196	131	87	43	14	2	0
	191	113	63	28	8	1	0

PD-L1 TPS ≥50%

	Events, n	HR (95% CI)	*P*
Pembro	41	0.54[a]	0.0017[b]
SOC	55	(0.35-0.82)	



No. at risk

	64	49	35	19	7	1	0
	65	38	22	9	2	0	0

[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors.
[b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors.
Data cutoff date: May 15, 2017.

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Presented By Ezra Cohen at 2017 ESMO Congress

Best Overall Response
(RECIST v1.1, Blinded Independent Radiology Review)

	ITT		CPS ≥1		TPS ≥50%	
Best Response, (%)	Pembro N = 247	SOC N = 248	Pembro n = 196	SOC n = 191	Pembro n = 64	SOC n = 65
CR	4 (1.6)	1 (0.4)	4 (2.0)	1 (0.5)	3 (4.7)	1 (1.5)
PR	32 (13.0)	24 (9.7)	30 (15.3)	18 (9.4)	14 (21.9)	5 (7.7)
SD	56 (22.7)	65 (26.2)	46 (23.5)	53 (27.7)	15 (23.4)	15 (23.1)
PD	108 (43.7)	97 (39.1)	77 (39.3)	72 (37.7)	22 (34.4)	23 (35.4)
NonCR/nonPD[a]	2 (0.8)	1 (0.4)	2 (1.0)	0	1 (1.6)	0
Not evaluable or assessable[b]	45 (18.2)	60 (24.2)	37 (18.9)	47 (24.6)	9 (14.1)	21 (32.3)

[a]Patients without measurable disease at baseline per RECIST v1.1 by independent radiology review who did not experience CR or PD.
[b]Not evaluable: patients who had ≥1 postbaseline tumor assessment, none of which were evaluable (n = 9); not assessable: patients who had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy (n = 96).
Data cutoff date: May 15, 2017.

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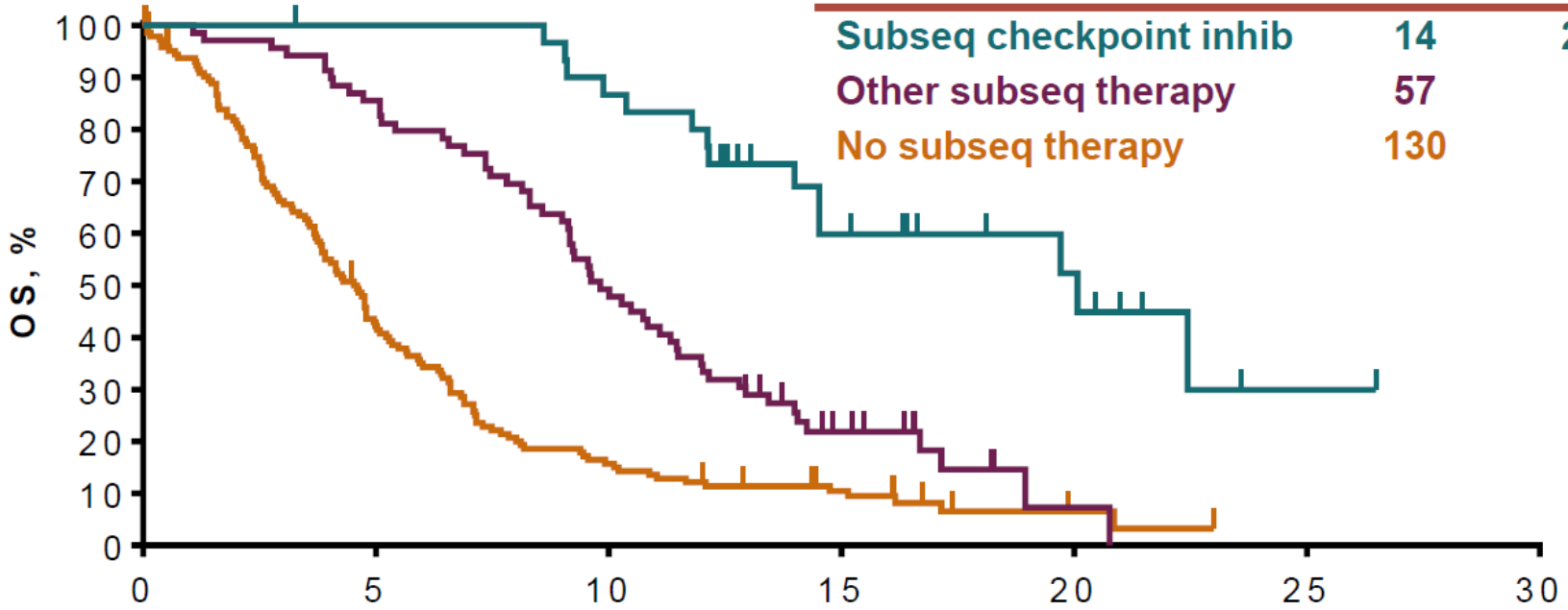
Overall Survival: Effect of Subsequent Immune Checkpoint Inhibitors in the SOC Arm

	Events, n	Median (95% CI), mo
Subseq checkpoint inhib	14	20.1 (14.5-NE)
Other subseq therapy	57	9.8 (9.1-11.5)
No subseq therapy	130	4.6 (3.8-5.0)



No. at risk

31	30	26	13	7	1	0
69	59	34	10	1	0	0
148	59	22	11	2	0	0

Data cutoff date: May 15, 2017.

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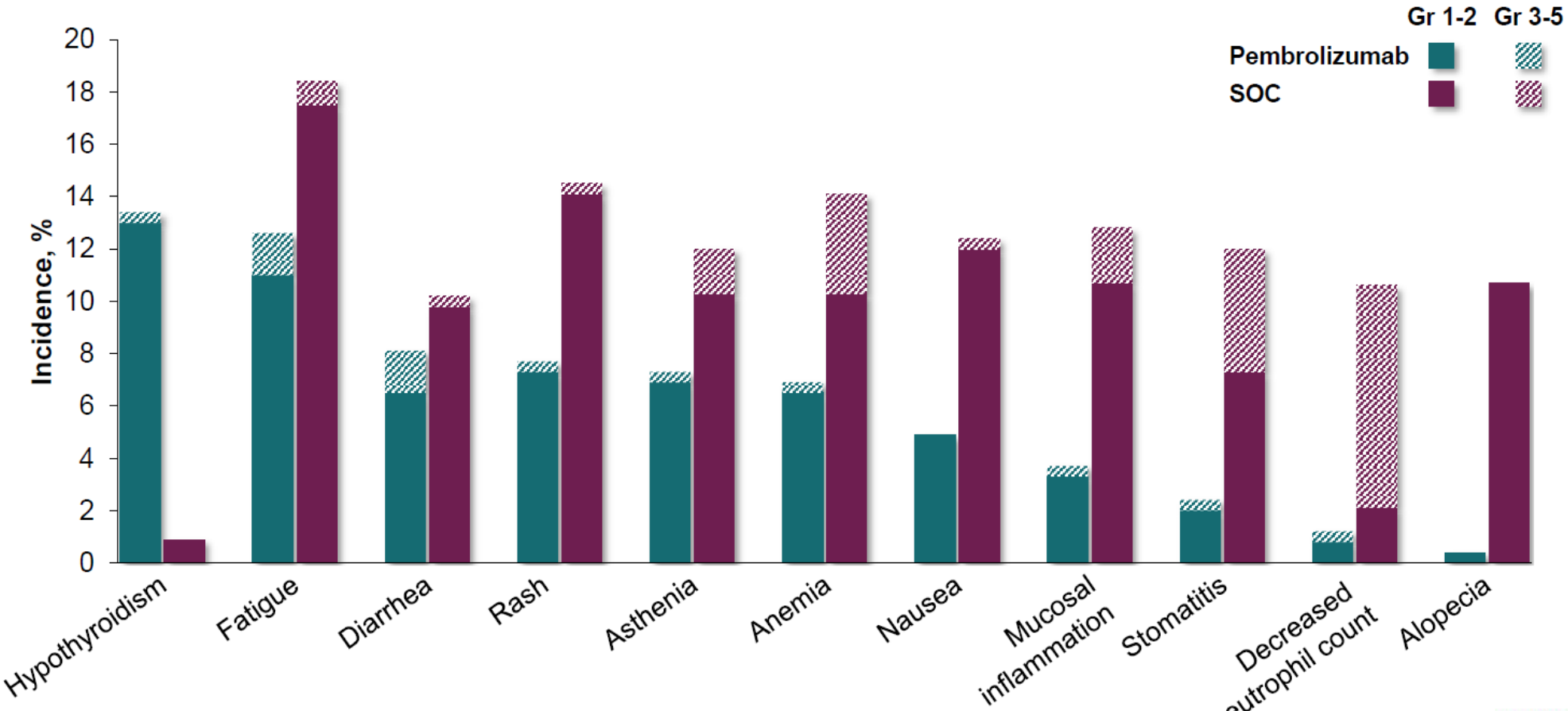
Treatment-Related AEs With Incidence ≥10%



Relationship to treatment was determined by the investigator.
Data cutoff date: May 15, 2017.

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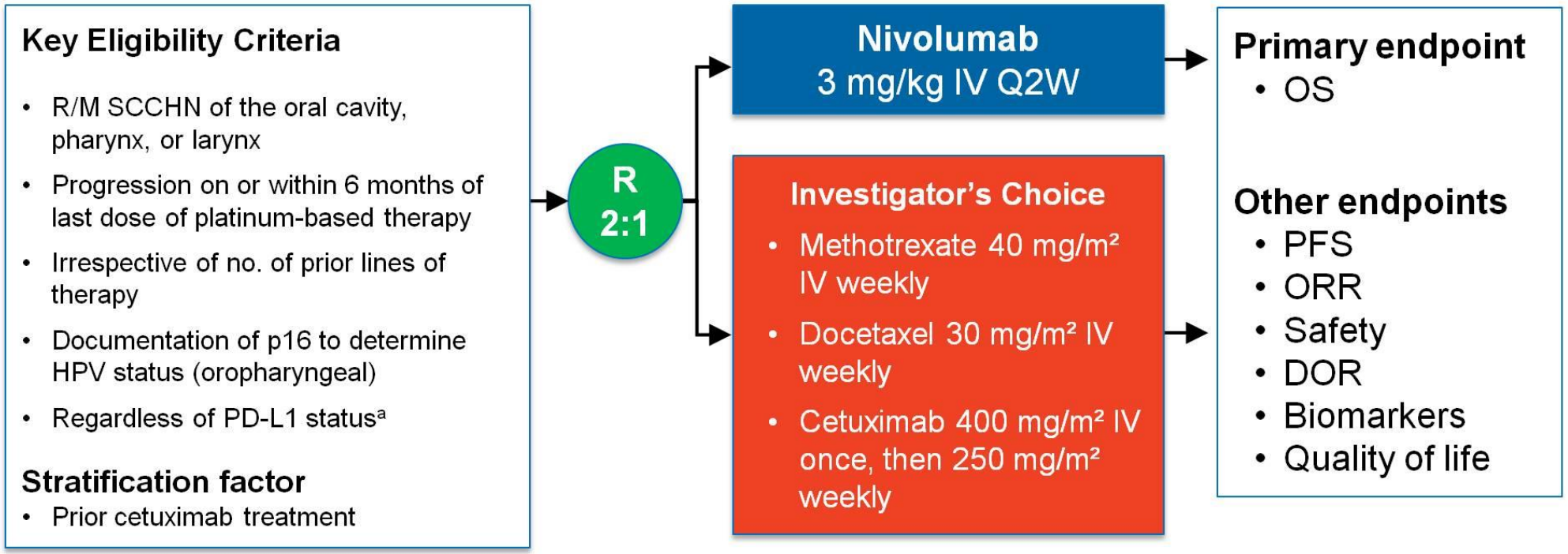
Phase 3 CheckMate 141 Study Design
Nivolumab in R/M SCCHN After Platinum Therapy

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN



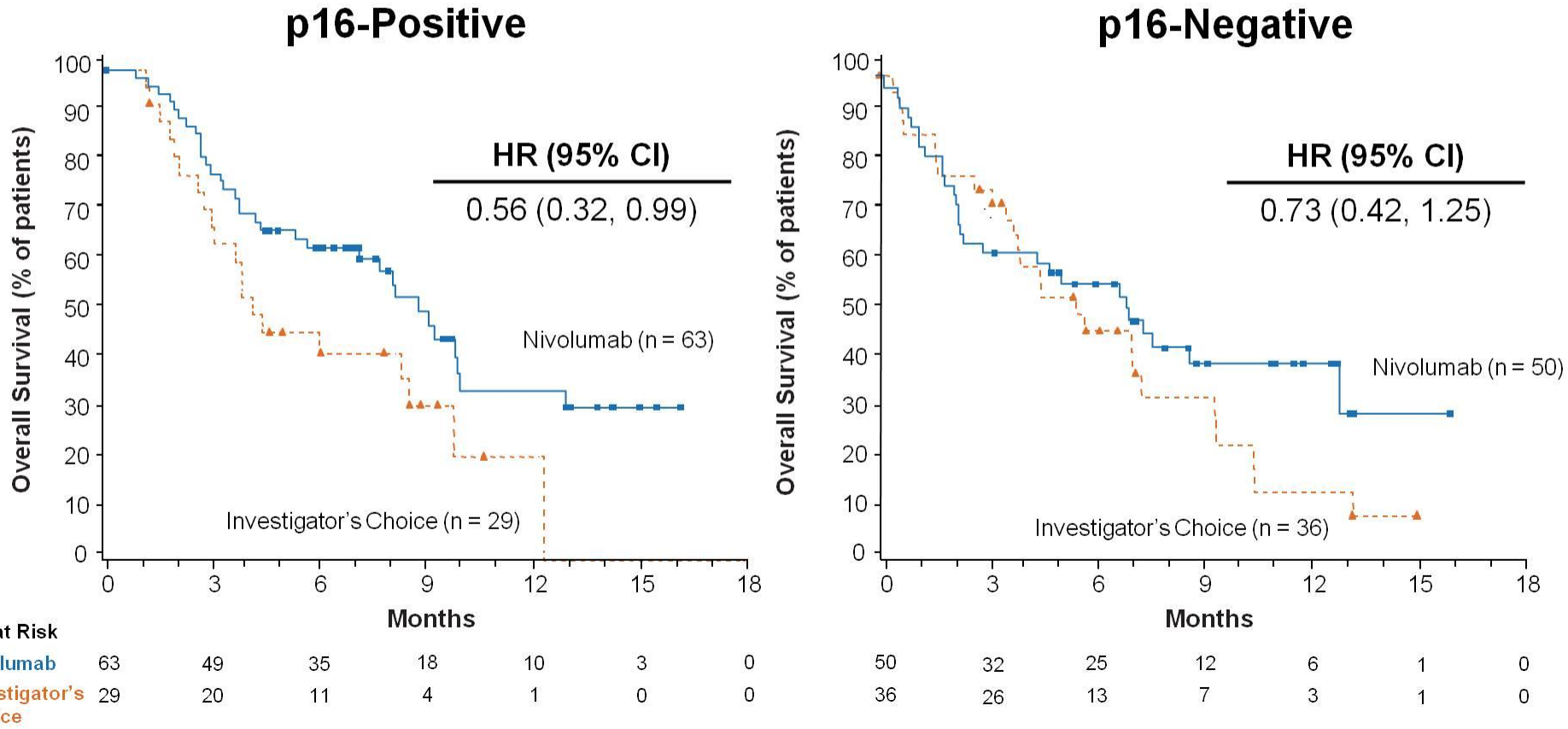
[a]Tissue required for testing

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

Presented By Robert Ferris at 2016 ASCO Annual Meeting

Overall Survival by p16 Status

Nivolumab in R/M SCCHN After Platinum Therapy



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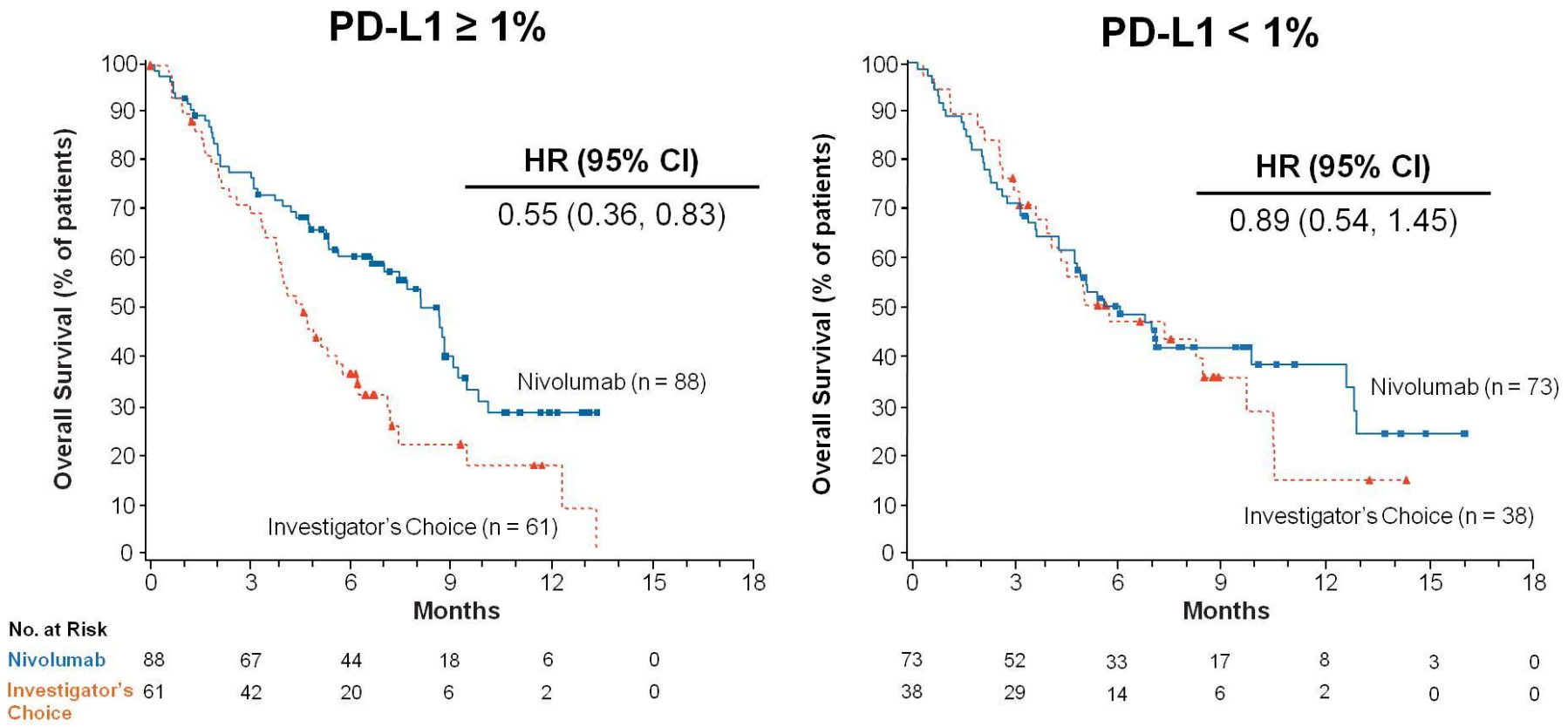
Presented By Robert Ferris at 2016 ASCO Annual Meeting

Overall Survival by Tumor PD-L1 Expression at 1%

Nivolumab in R/M SCCHN After Platinum Therapy



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PD-1 inhibitors in R/M HNSCC

- Pembrolizumab approved for HNSCC patients whose disease progressed during or after platinum containing chemotherapy
- Nivolumab approved following progression on platinum-based therapy

- What about first line treatment in R/M HNSCC?

Metastatic/Recurrent HNSCC First Line

- Prior to 2019, first line standard of care treatment for unresectable disease included chemotherapy/cetuximab combinations

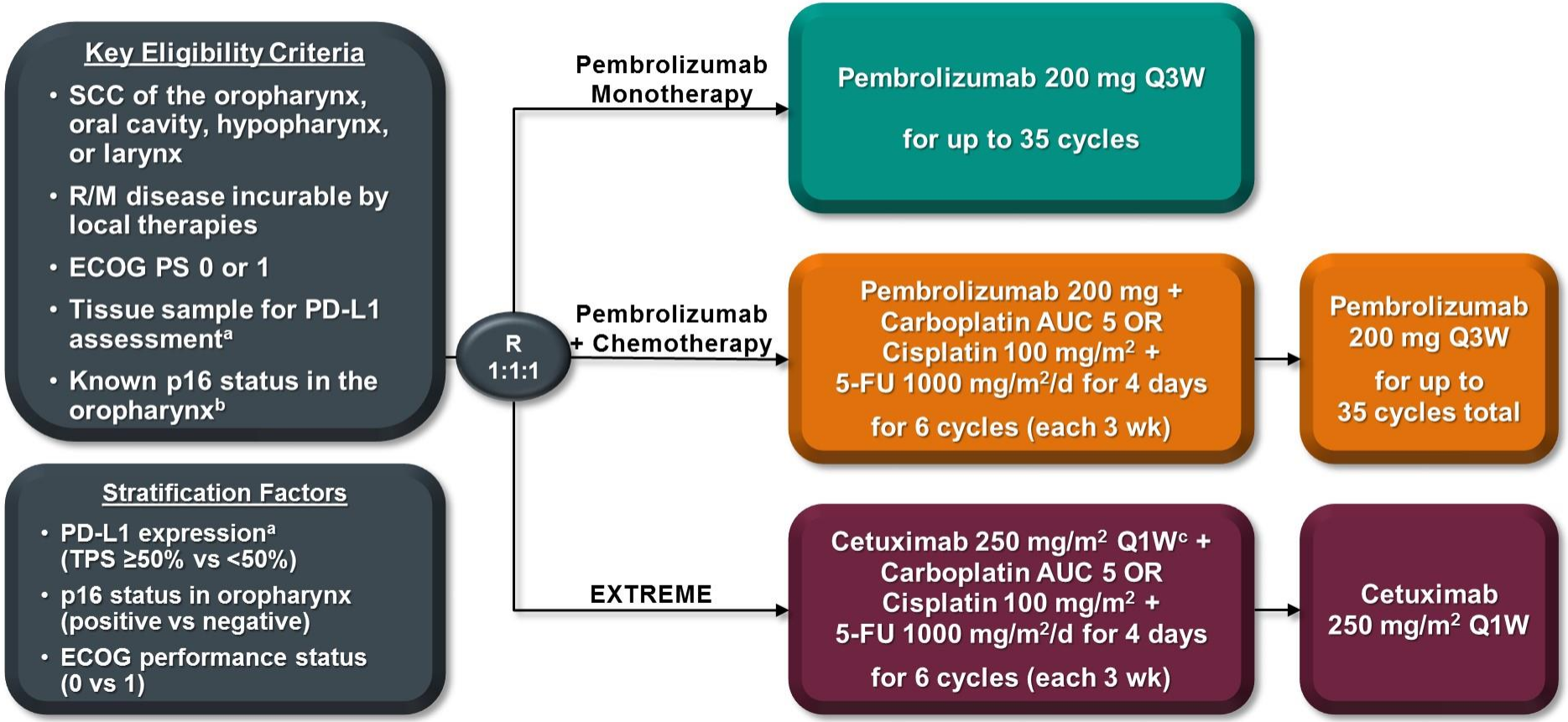
Table 2. Responses to Treatment and Survival.*

Variable	Cetuximab plus Platinum–Fluorouracil (N=222)	Platinum–Fluorouracil Alone (N=220)	Hazard Ratio or Odds Ratio (95% CI)	P Value
Survival — mo†				
Overall	10.1 (8.6–11.2)	7.4 (6.4–8.3)	Hazard ratio, 0.80 (0.64–0.99)	0.04‡
Progression-free	5.6 (5.0–6.0)	3.3 (2.9–4.3)	Hazard ratio, 0.54 (0.43–0.67)	<0.001‡
Best response to therapy — %				
Overall	36 (29–42)	20 (15–25)	Odds ratio, 2.33 (1.50–3.60)	<0.001§
Disease control¶	81 (75–86)	60.0 (53–67)	Odds ratio, 2.88 (1.87–4.44)	<0.001§
Time to treatment failure — mo†	4.8 (4.0–5.6)	3.0 (2.8–3.4)	Hazard ratio, 0.59 (0.48–0.73)	<0.001‡
Duration of response — mo‖	5.6 (4.7–6.0)	4.7 (3.6–5.9)	Hazard ratio, 0.76 (0.50–1.17)	0.21‡

*82% Grade 3 or 4 Adverse Events

Vermorken et al, NEJM 2008

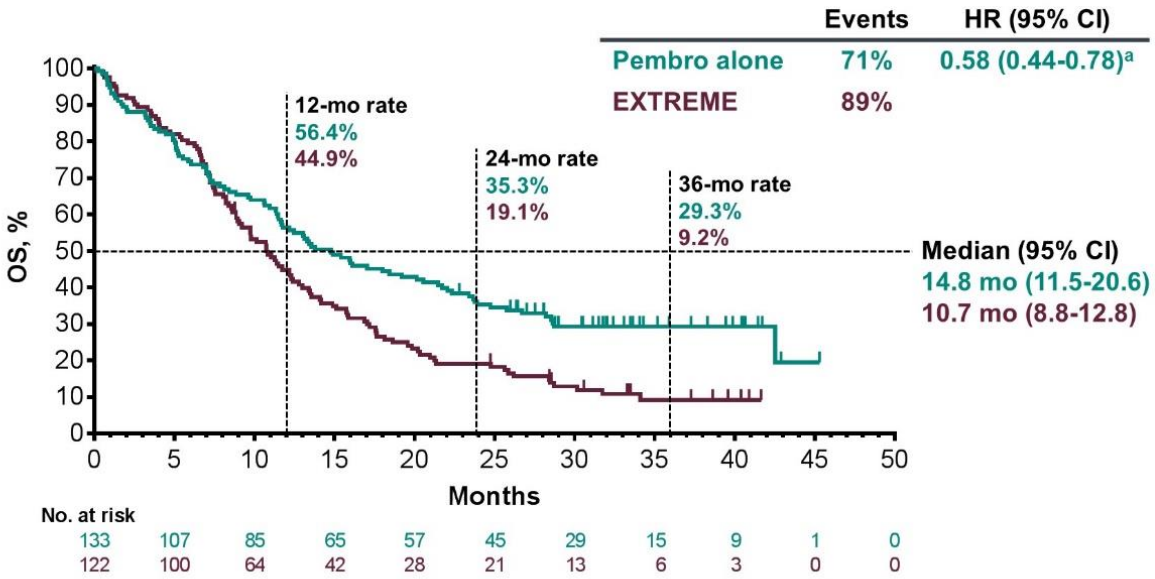
KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

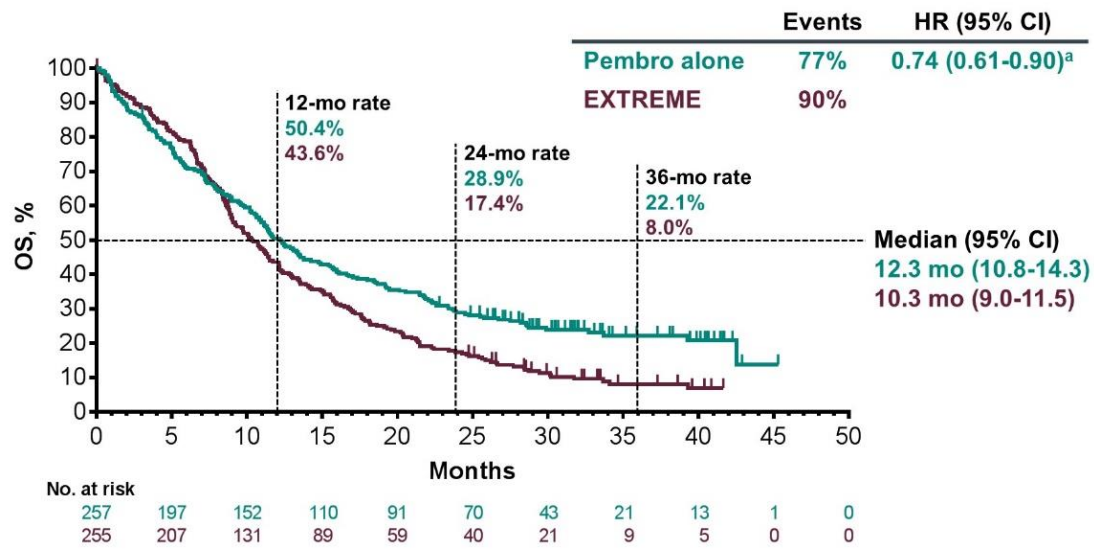
OS, Pembrolizumab vs Extreme

OS, P vs E, CPS ≥20 Population



aAt IA2 (data cutoff date: Jun 13, 2018): HR 0.61 (95% CI 0.45–0.83).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, CPS ≥1 Population



aAt IA2 (data cutoff date: Jun 13, 2018): HR 0.78 (95% CI 0.64–0.96).
FA (data cutoff date: Feb 25, 2019).

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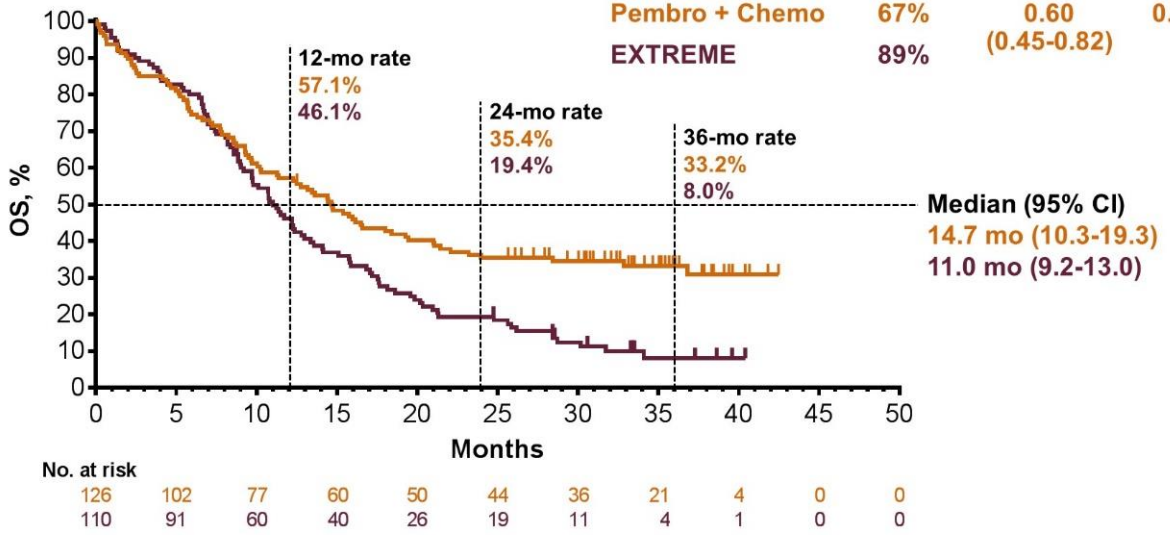
OS, Pembro+ Chemo vs Extreme

OS, P+C vs E, CPS ≥20 Population

	Events	HR (95% CI)	*P*
Pembro + Chemo	67%	0.60 (0.45-0.82)	0.0004[a]
EXTREME	89%		

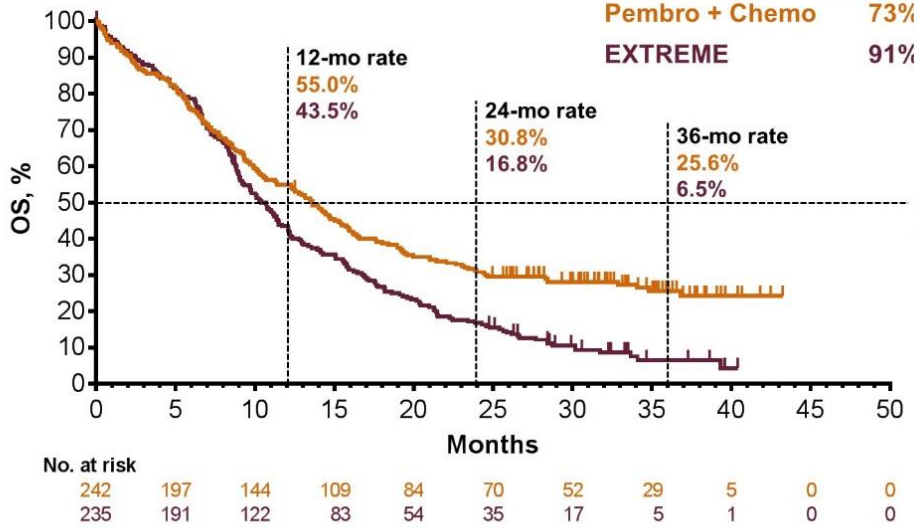


Median (95% CI)
14.7 mo (10.3-19.3)
11.0 mo (9.2-13.0)

[a]Statistically significant at the superiority threshold of $P = 0.0023$.
FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, CPS ≥1 Population

	Events	HR (95% CI)	*P*
Pembro + Chemo	73%	0.65 (0.53-0.80)	<0.0001[a]
EXTREME	91%		



Median (95% CI)
13.6 mo (10.7-15.5)
10.4 mo (9.1-11.7)

[a]Statistically significant at the superiority threshold of $P = 0.0026$.
FA (data cutoff date: Feb 25, 2019).

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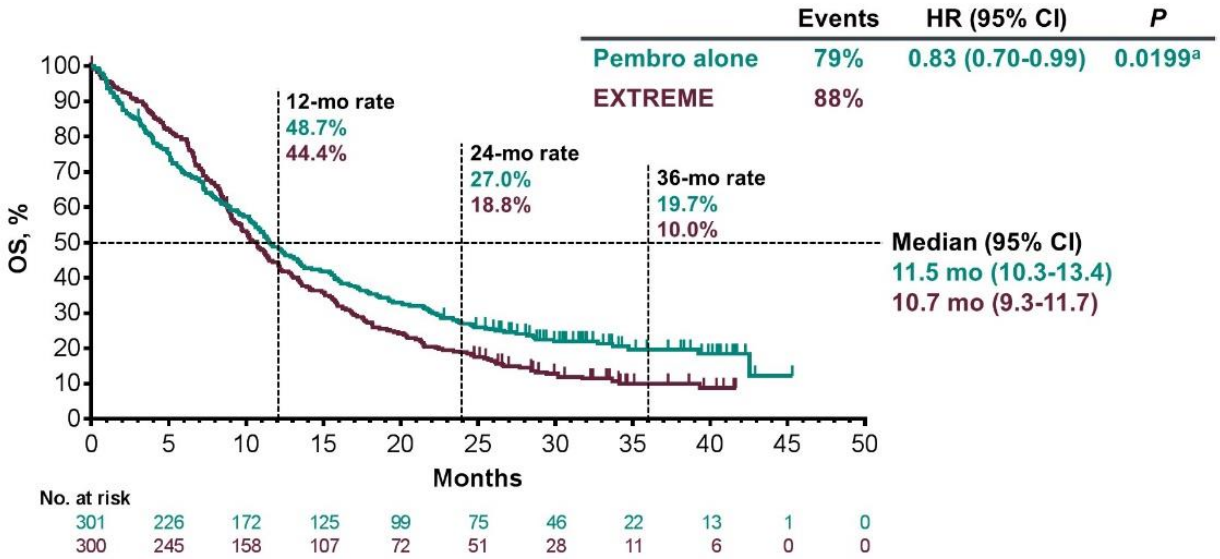
Presented By Danny Rischin at 2019 ASCO Annual Meeting

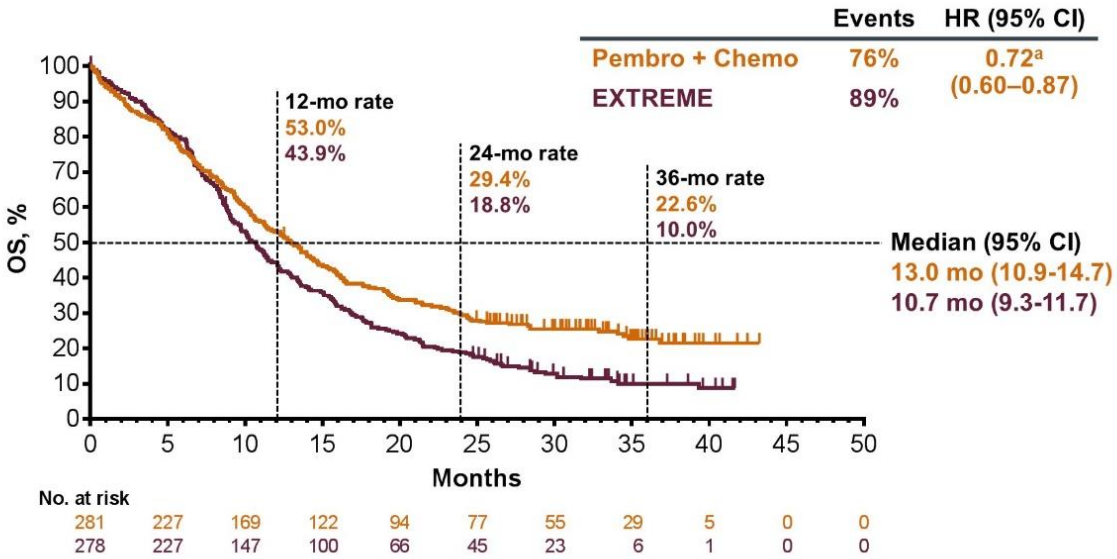
Overall Survival Total Population

OS, P vs E, Total Population



aNot statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, Total Population



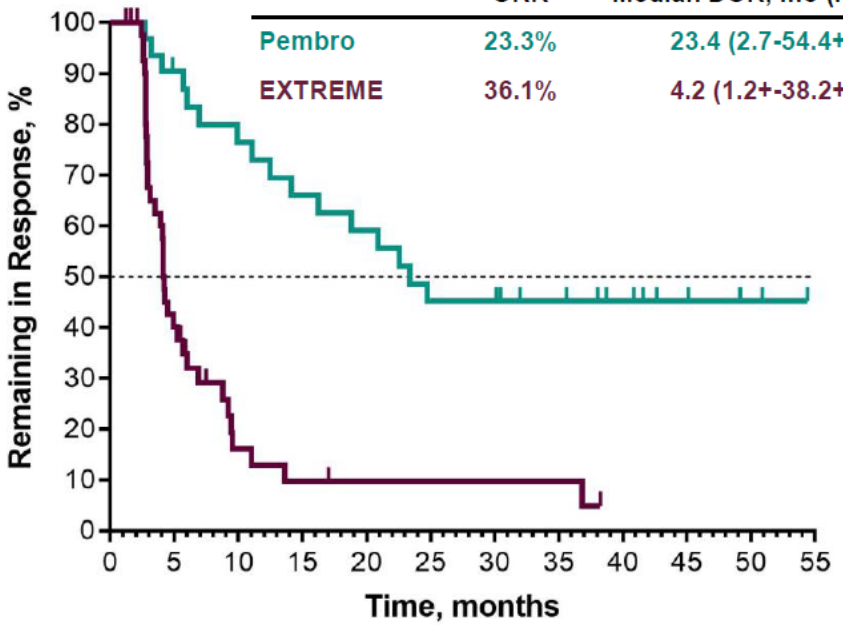
aAt IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

Presented By Danny Rischin at 2019 ASCO Annual Meeting

DOR: Pembrolizumab vs EXTREME

PD-L1 CPS ≥20

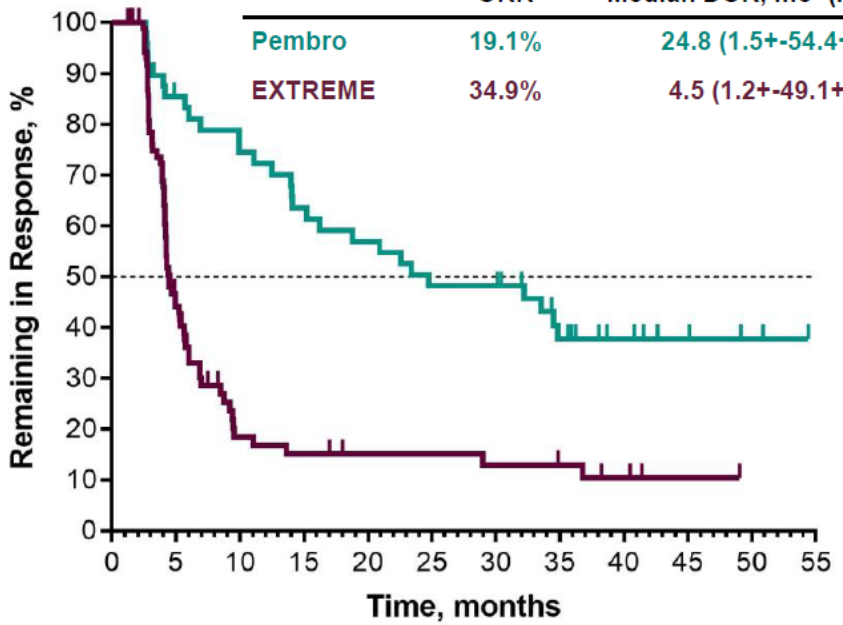
	ORR	Median DOR, mo (range
Pembro	23.3%	23.4 (2.7-54.4+)
EXTREME	36.1%	4.2 (1.2+-38.2+)



No. at Risk												
Pembro	31	26	22	19	17	13	13	10	7	4	2	0
EXTREME	44	16	5	3	2	2	2	2	0	0	0	0

PD-L1 CPS ≥1

	ORR	Median DOR, mo (range)
Pembro	19.1%	24.8 (1.5+-54.4+)
EXTREME	34.9%	4.5 (1.2+-49.1+)



No. at Risk												
Pembro	49	39	34	29	26	22	22	14	8	5	2	0
EXTREME	89	34	11	9	7	7	6	5	3	1	0	0

ORR, overall response rate.
Data cutoff: February 18, 2020.

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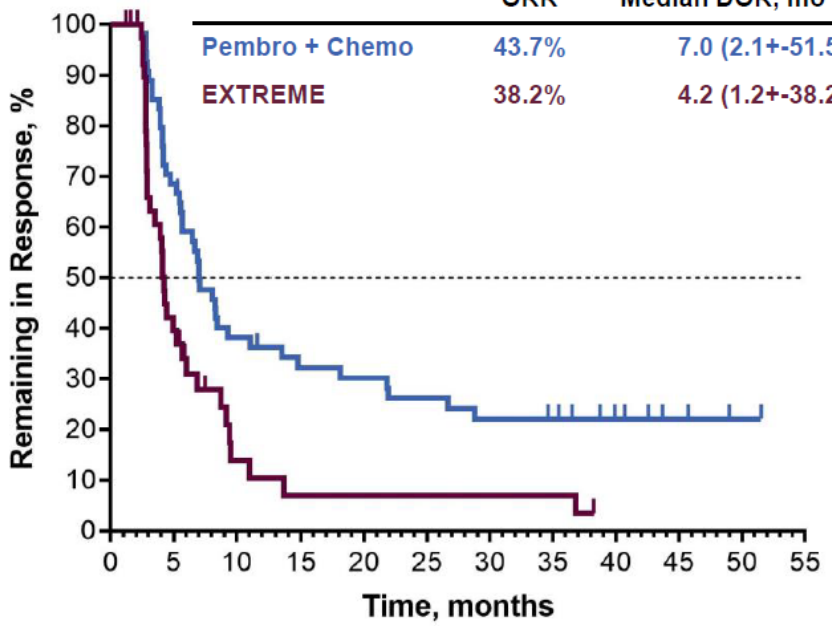
DOR: Pembrolizumab + Chemo vs EXTREME

PD-L1 CPS ≥20

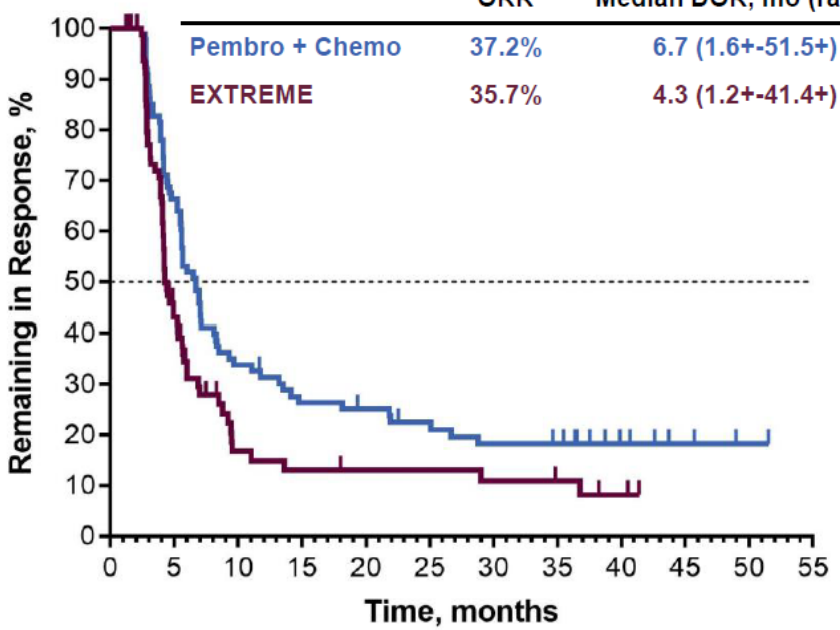
	ORR	Median DOR, mo (range)
Pembro + Chemo	43.7%	7.0 (2.1+-51.5+)
EXTREME	38.2%	4.2 (1.2+-38.2+)



No. at Risk												
Pembro + Chemo	55	37	20	16	15	13	11	10	6	3	1	0
EXTREME	42	15	4	2	2	2	2	2	0	0	0	0

PD-L1 CPS ≥1

	ORR	Median DOR, mo (range)
Pembro + Chemo	37.2%	6.7 (1.6+-51.5+)
EXTREME	35.7%	4.3 (1.2+-41.4+)



No. at Risk												
Pembro + Chemo	90	56	28	21	19	16	13	12	6	3	1	0
EXTREME	84	31	9	7	6	6	5	4	2	0	0	0

Data cutoff: February 18, 2020.

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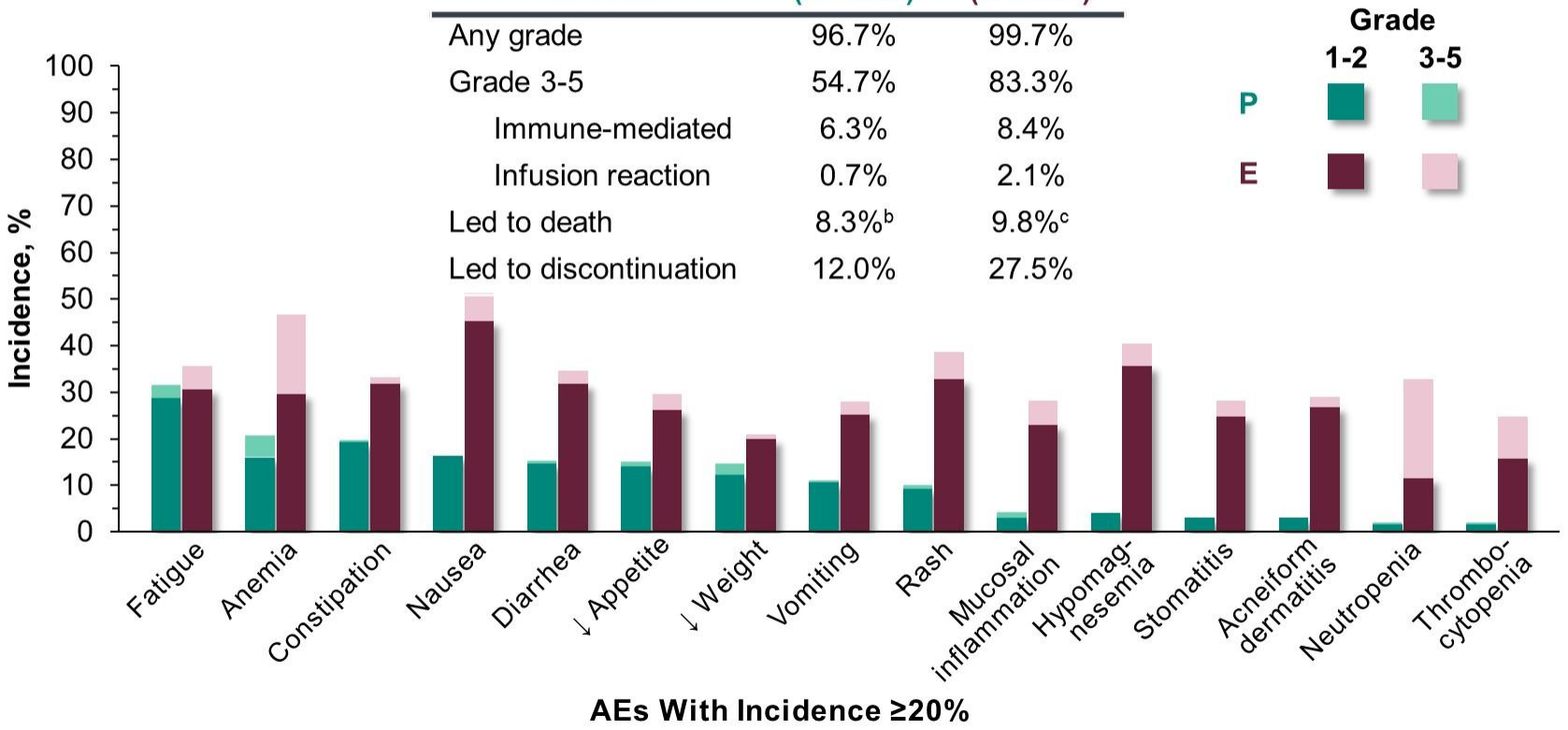
All-Cause AEs,[a] P vs E, Total Population

All AEs	P (n = 300)	E (n = 287)
Any grade	96.7%	99.7%
Grade 3-5	54.7%	83.3%
Immune-mediated	6.3%	8.4%
Infusion reaction	0.7%	2.1%
Led to death	8.3%[b]	9.8%[c]
Led to discontinuation	12.0%	27.5%



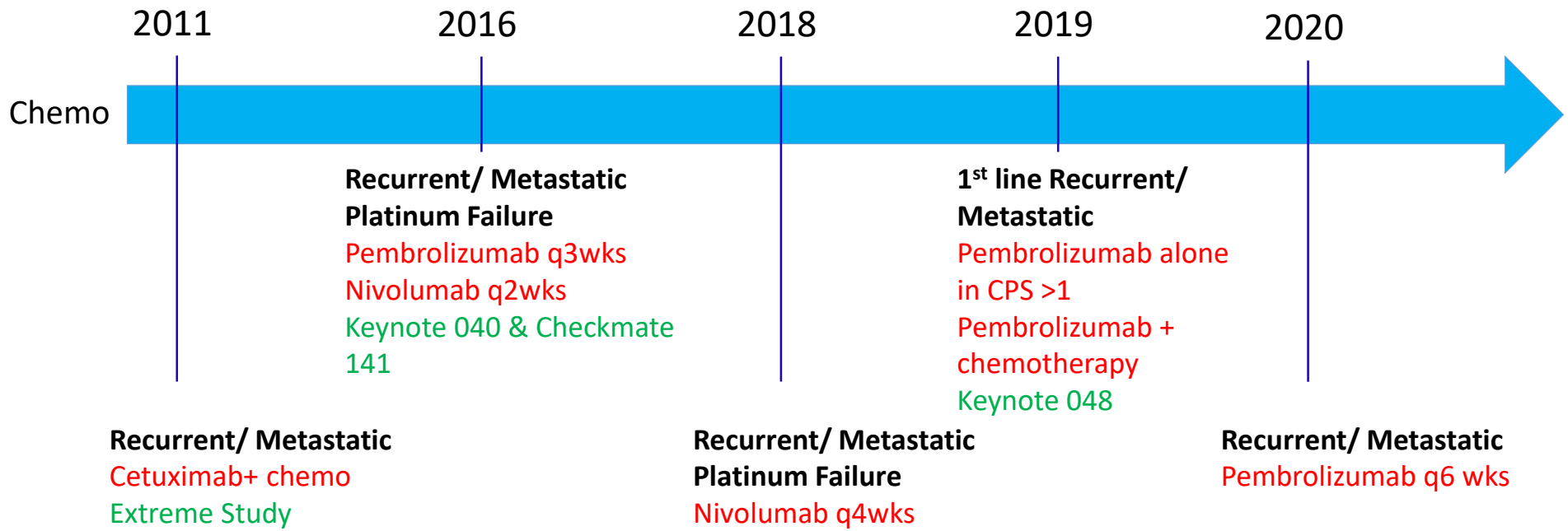
[a]Data for treatment-related AEs were presented at ESMO 2018. [b]Events were considered treatment related in 1.0%. [c]Events were considered treatment related in 2.8%. FA (data cutoff date: Feb 25, 2019).

Presented By Danny Rischin at 2019 ASCO Annual Meeting

Pembrolizumab as First Line in R/M HNSCC

- Favorable safety profile for pembrolizumab alone and comparable between extreme regimen and pembro + chemo
- Longer duration of response for pembro as well as pembro + chemo
- FDA approval in first line unresectable recurrent or metastatic HNSCC:
  - Pembrolizumab monotherapy in those with PD-L1 CPS ≥ 1
  - Pembrolizumab + platinum + 5FU regardless of PD-L1 score

Timeline of FDA Approvals



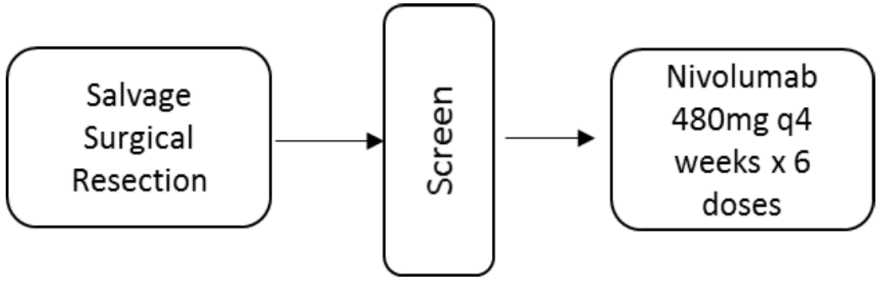
Taxanes and Immunotherapy

- Early evidence of success of taxanes after immunotherapy failure
  - Retrospective study demonstrated OS of 5.8 mo post platinum failure vs 10 mo post nivolumab (Moloney et al., ASCO 2020)
- Taxane substitution for 5FU in chemo+pembro 1st line treatment
  - Ongoing trials but based on TPEx demonstrating similar efficacy with less toxicity to Extreme regimen, many advocate for substitution to taxane as standard of care

Salvage Surgery and Immunotherapy

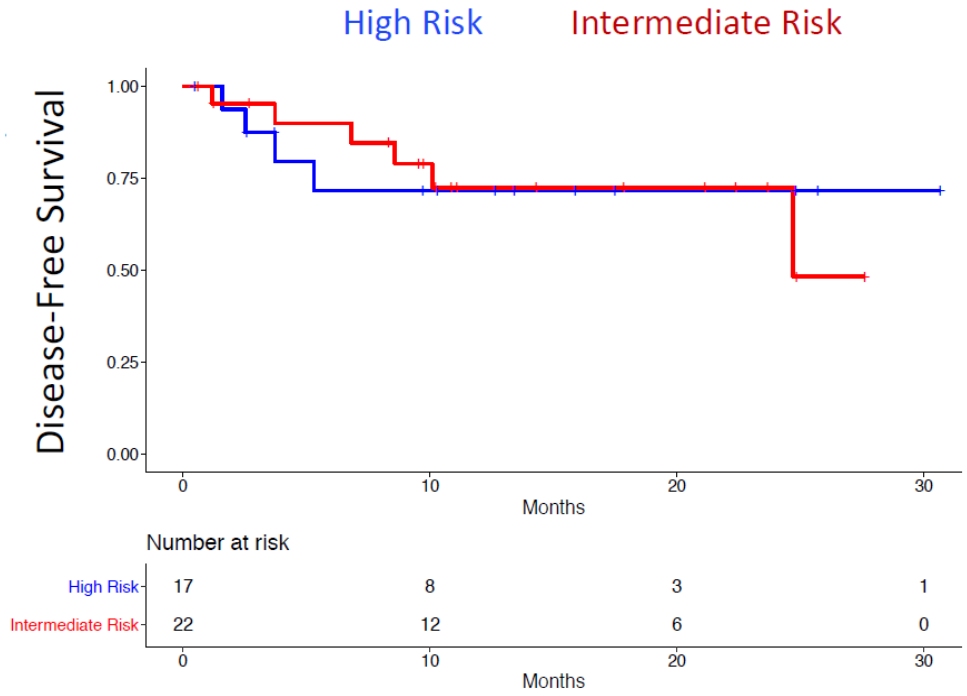
- <40% long term survival for HNSCC patients undergoing salvage resection
- Early evidence for nivolumab as adjuvant therapy in recurrent surgical salvage setting

Trial Design



Primary End Point: DFS at 2 years

Secondary End Points: Safety, tolerability, & OS



Presented By Jen Leddon at 2021 ASCO Annual Meeting

Conclusions

- Pembrolizumab monotherapy is approved as first line therapy for HNSCC patients with PD-L1 CPS ≥ 1
- Pembrolizumab + Platinum and 5FU is approved first line for all HNSCC patients
- Nivolumab and pembrolizumab monotherapy are approved for R/M patients after platinum failure
- Taxanes may be substituted for 5FU and may be good options after immunotherapy failure although trials ongoing (NCT04489888, NCT04831320)
- PD-1 inhibitors may prolong survival in the salvage setting but randomized trials are ongoing (EA3191)

- Any Questions?