Immune Checkpoint Therapy in Lung Cancer

Rasna Gupta

DISCLOSURES

- **Relationships with financial sponsors:**
  - **Speakers Bureau/Honoraria:** AstraZeneca, Novartis
  - **Other:** Purdue Pharma Clinical Trial, AD Board

- **Potential for conflict(s) of interest:**
  - No speakers present any conflicts with sponsoring organization
  - No products discussed in this program present a conflict

Objectives

- Review the recent data of immune checkpoint inhibitors in stage 3 and 4 non-small cell lung cancer.
- Review management of toxicities.

Stage III NSCLC

- **22-30% of patients have stage III disease at diagnosis**
- **Concurrent chemoradiation is the standard of care for unresectable stage III disease**
- **Median PFS with concurrent chemoradiation is 8-10 months**
- **There have been no major advances in the treatment of stage III disease beyond chemoradiation**

Meza, PLOS 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

Scott J. Antonia, M.D., Ph.D., Augusto Villegas, M.D., Davey Daniel, M.D., David Vicente, M.D., Shuji Murakami, M.D., Rina Hui, Ph.D., Takashi Yokoi, M.D., Ph.D., Alberto Chiappori, M.D., Ki H. Lee, M.D., Ph.D., Maike de Wit, M.D., Ph.D., Byoung C. Cho, M.D., Ph.D., Maryam Bourhaba, M.D., Xavier Quantin, M.D., Ph.D., Takaaki Tokito, M.D., Ph.D., Tarek Mekhail, M.D., David Planchard, M.D., Ph.D., Young-Chul Kim, M.D., Ph.D., Christos S. Karapetis, M.D., Sandrine Hiret, M.D., Gyula Ostoros, M.D., et al., for the PACIFIC Investigators*

November 2017

Pacific

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

Co-primary endpoints

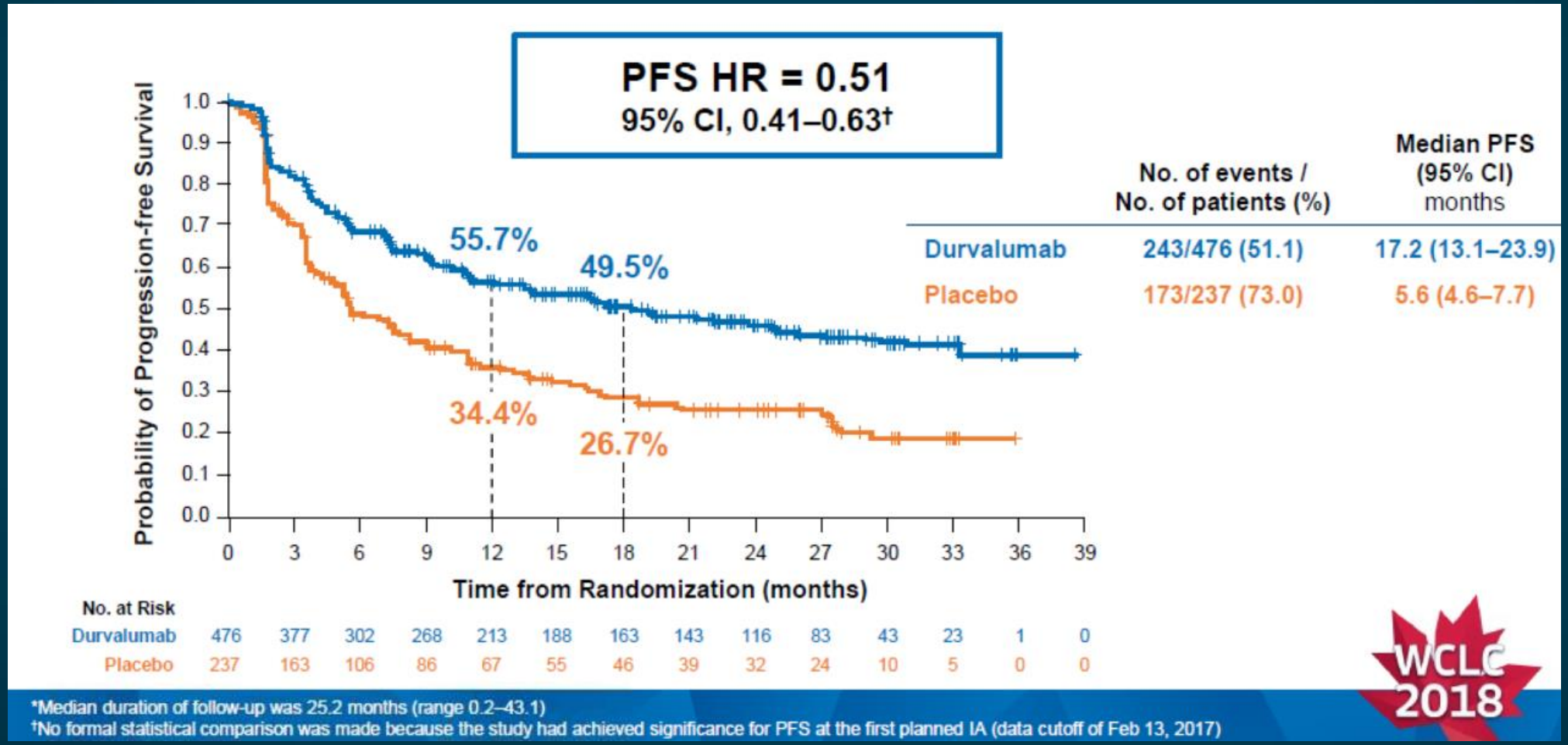
- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

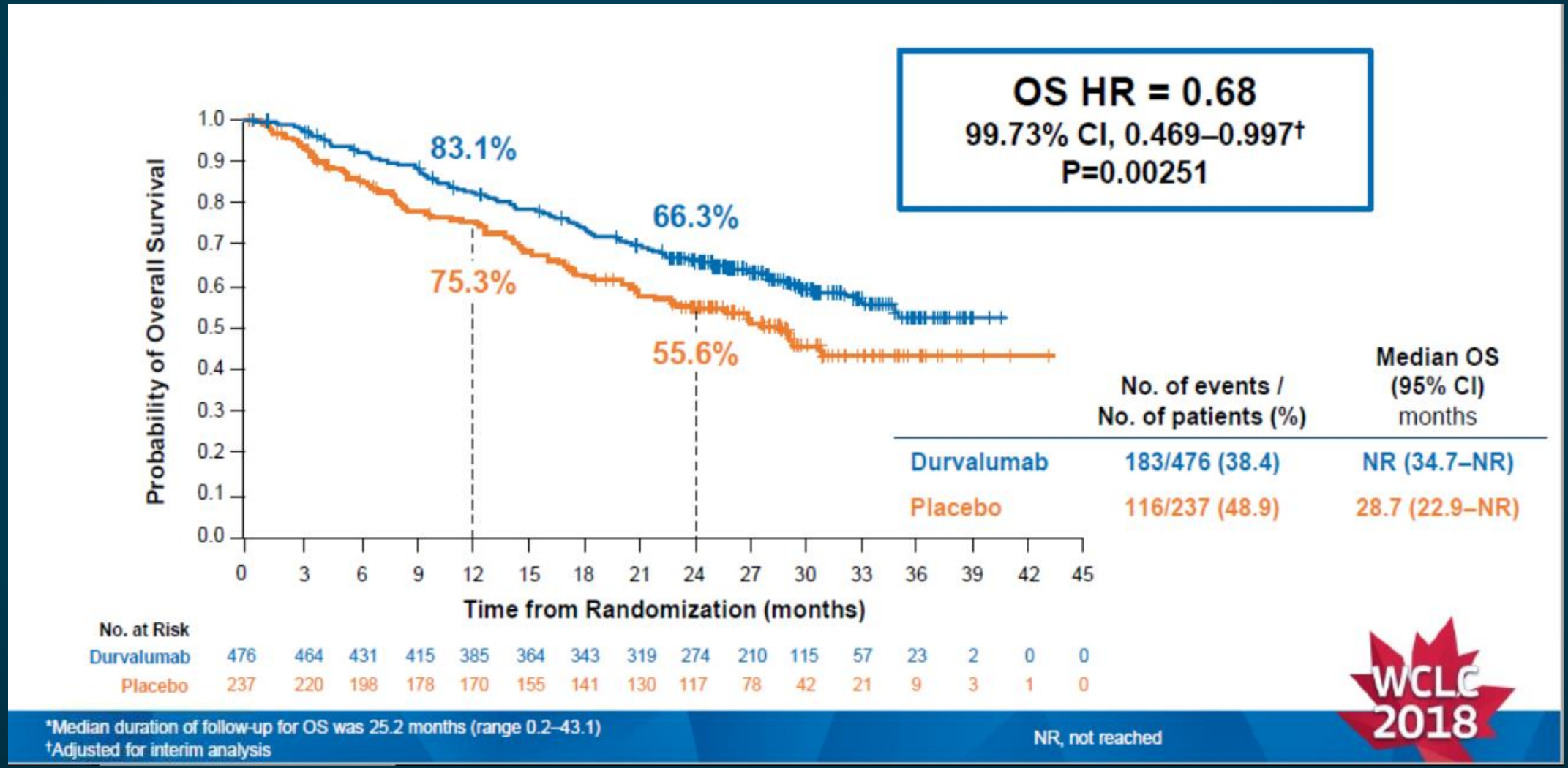
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

Paz-Ares, ESMO 2017

Pacific: PFS


PFS HR = 0.51
95% CI, 0.41–0.63†
Probability of Progression-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
55.7%
49.5%
34.4%
26.7%
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Time from Randomization (months)
No. at Risk
Durvalumab 476 377 302 268 213 188 163 143 116 83 43 23 1 0
Placebo 237 163 106 86 67 55 46 39 32 24 10 5 0 0
No. of events / No. of patients (%)
Median PFS (95% CI) months
Durvalumab 243/476 (51.1) 17.2 (13.1–23.9)
Placebo 173/237 (73.0) 5.6 (4.6–7.7)
*Median duration of follow-up was 25.2 months (range 0.2–43.1)
†No formal statistical comparison was made because the study had achieved significance for PFS at the first planned IA (data cutoff of Feb 13, 2017)
WCLC 2018

Overall survival



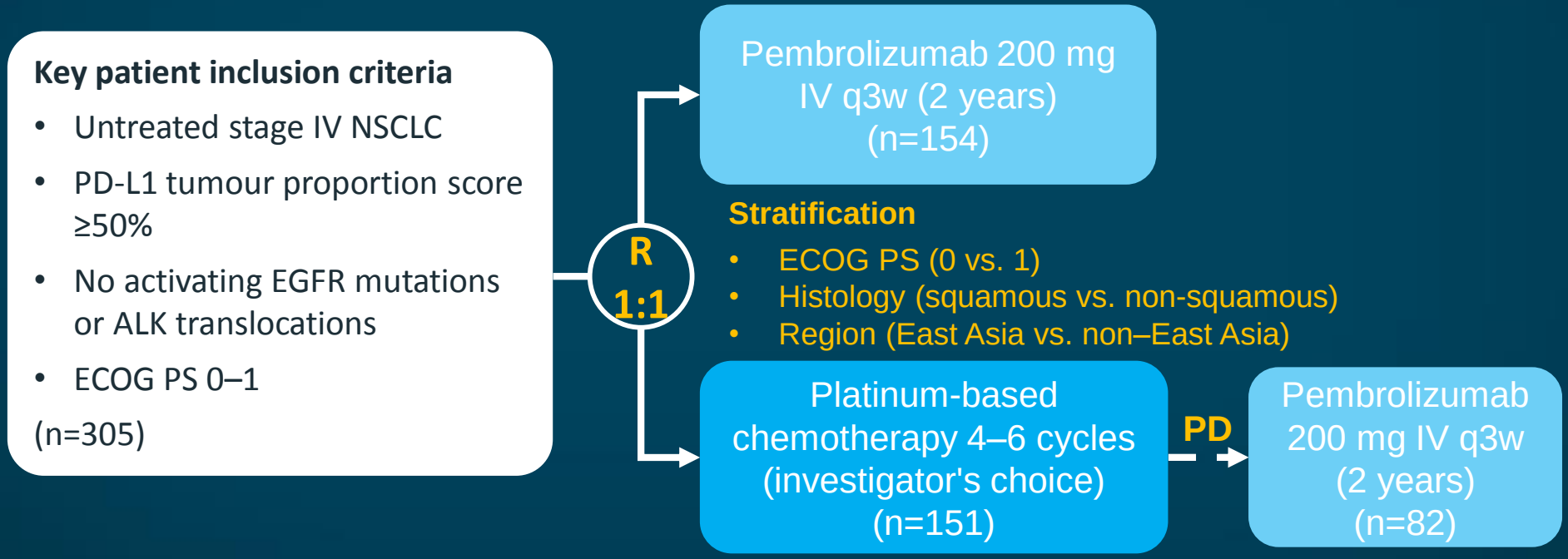
Reck M, et al. IMpower150 PFS analysis.

Stage 4

Immunotherapy as First line treatment

KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy for Advanced NSCLC With PD-L1 TPS ≥50%

- **Study objective**
  - To compare the efficacy and safety of 1L pembrolizumab with platinum-based chemotherapy for patients with advanced NSCLC



Primary endpoint

- PFS

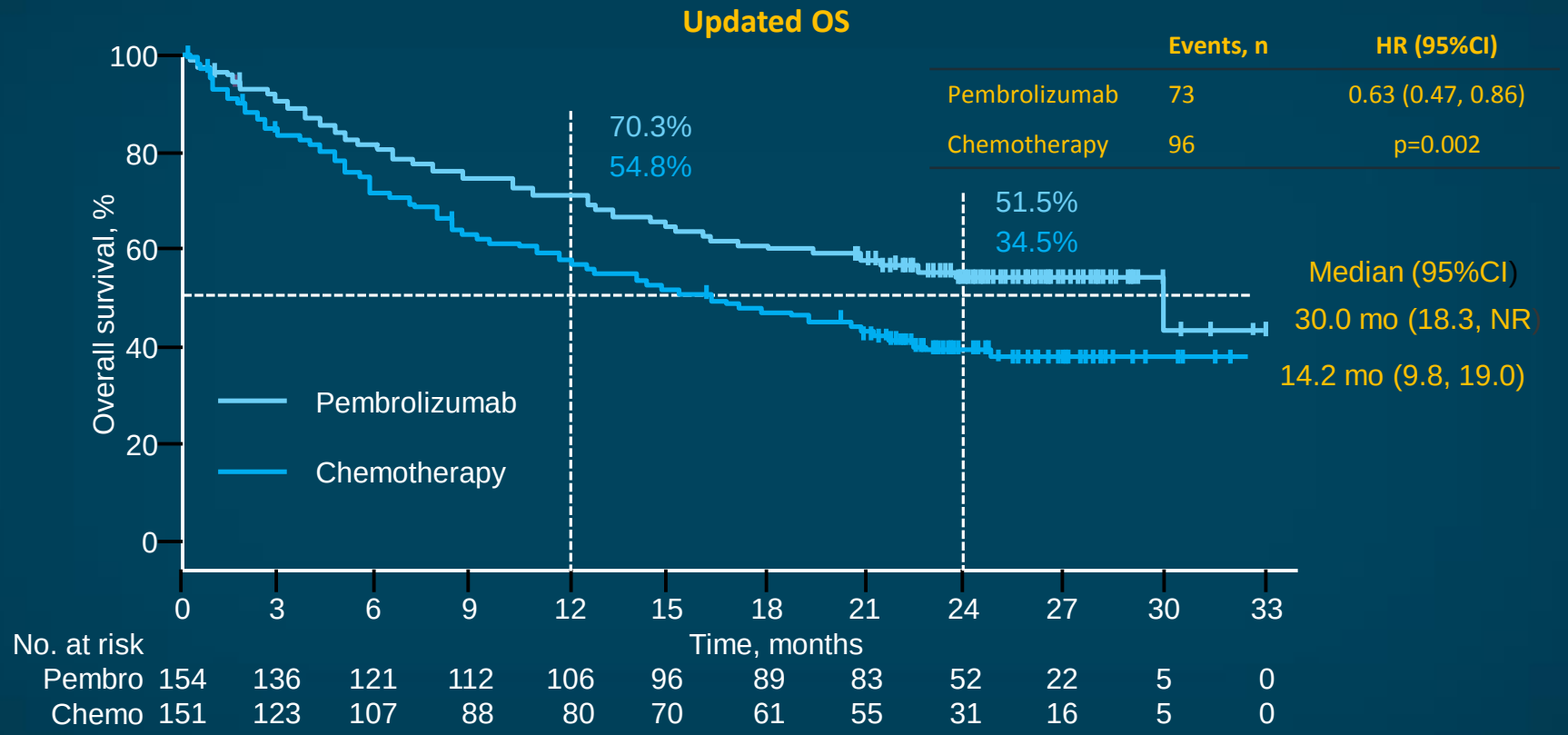
Secondary endpoints

- OS, ORR, DoR, safety

Brahmer JR et al. J Thorac Oncol 2017;12(suppl):Abstr OA 17.06

KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy for Advanced NSCLC With PD-L1 TPS ≥50%

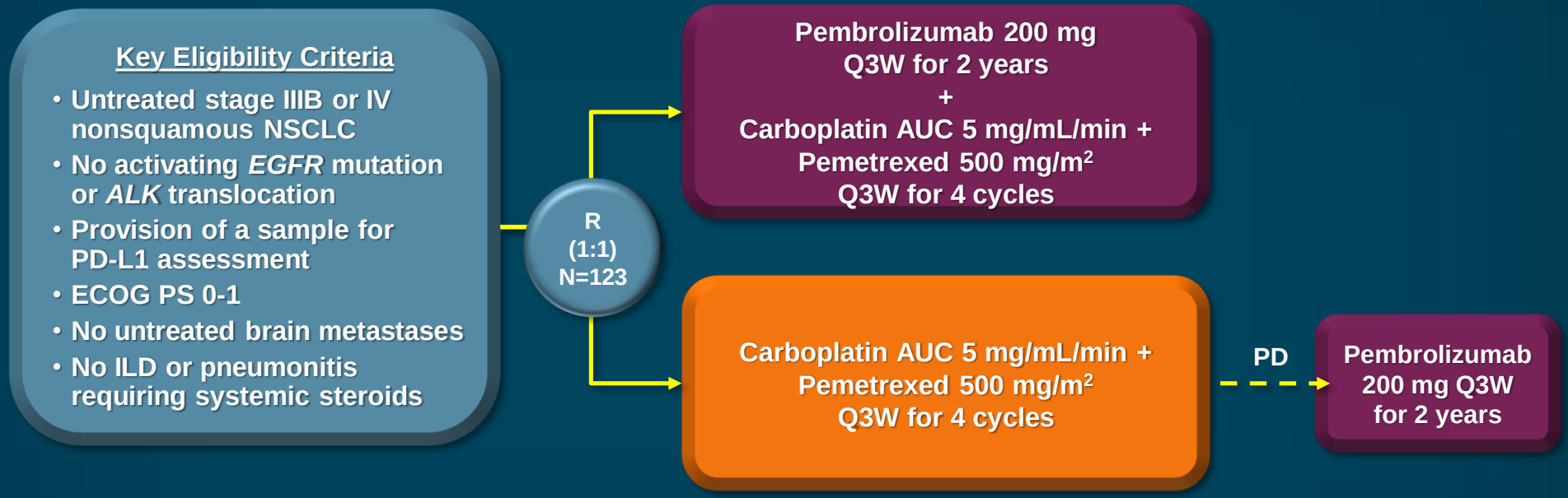
- **Key results**



- **Conclusion**
  - Pembrolizumab continues to show an OS benefit as 1L therapy compared with platinum-based chemotherapy for advanced NSCLC with PD-L1 TPS ≥50%

Brahmer JR et al. J Thorac Oncol 2017;12(suppl):Abstr OA 17.06

KEYNOTE-021:
Pem/Carbo +/- Pembrolizumab



End Points

Primary: ORR (RECIST v1.1 per blinded, independent central review)

Key secondary: PFS

Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

Langer et al, Lancet Oncology, 2016

Updated Results from Keynote-021 Cohort G: PFS and OS

	Progression-free survival				Overall survival			
Treatment	Events, n/N	Median, mos.	HR	P-value	Events, n/N	Median, mos.	HR	P-value
Pembro + PC	26/60	19.0 (8.5-NR)	0.54	0.007[a]	20/60	NR (22.8-NR)	0.59	0.03[a]
PC alone	40/63	8.9 (6.2-11.8)			31/63	20.9 (14.9-NR)		
Median follow-up: 18.7 months								

[a]*P* value is descriptive (one-sided $P < 0.025$).

Data cut-off: May 31, 2017.

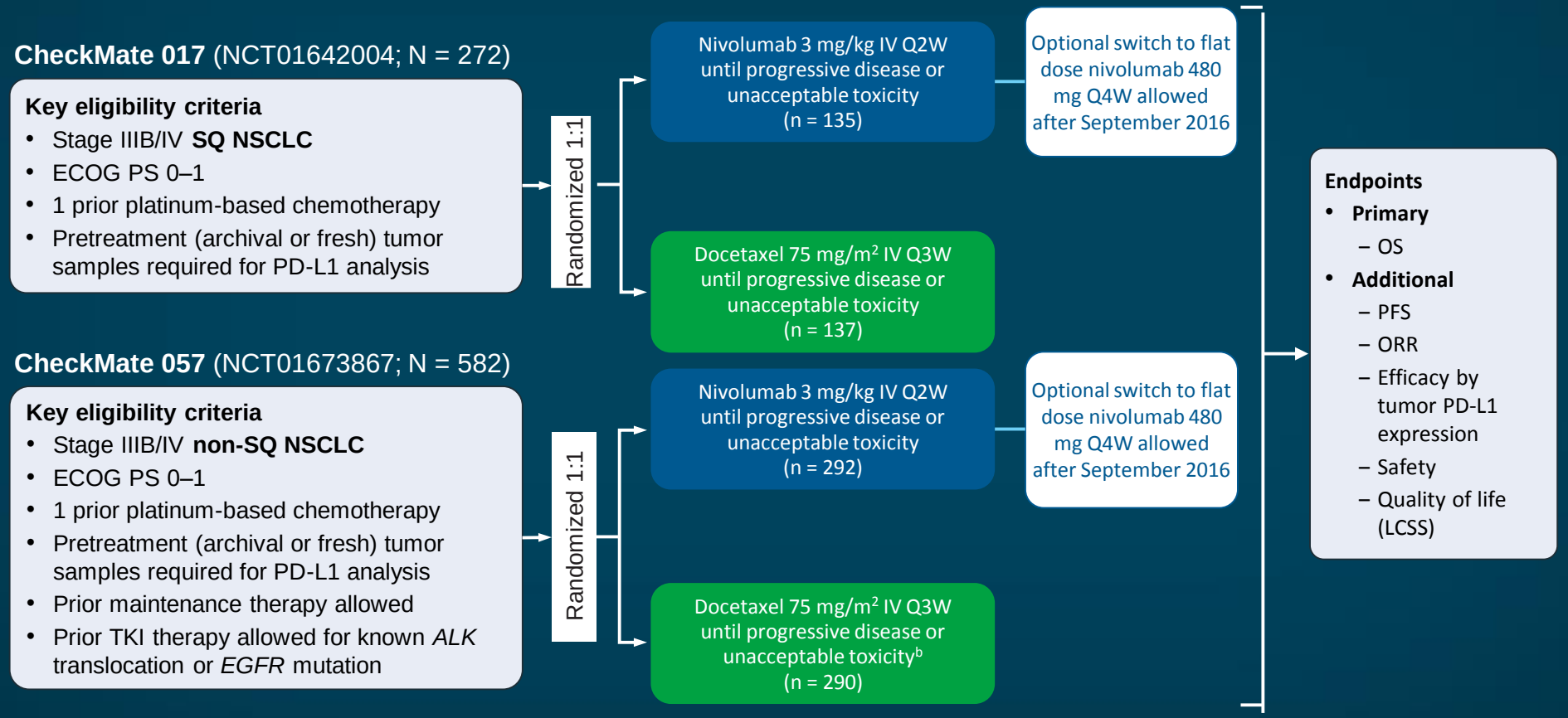
Borghaei et al, ESMO 9-17; Langer WCLC 10-17.

Stage 4

Immunotherapy as Second line treatment.

Methods

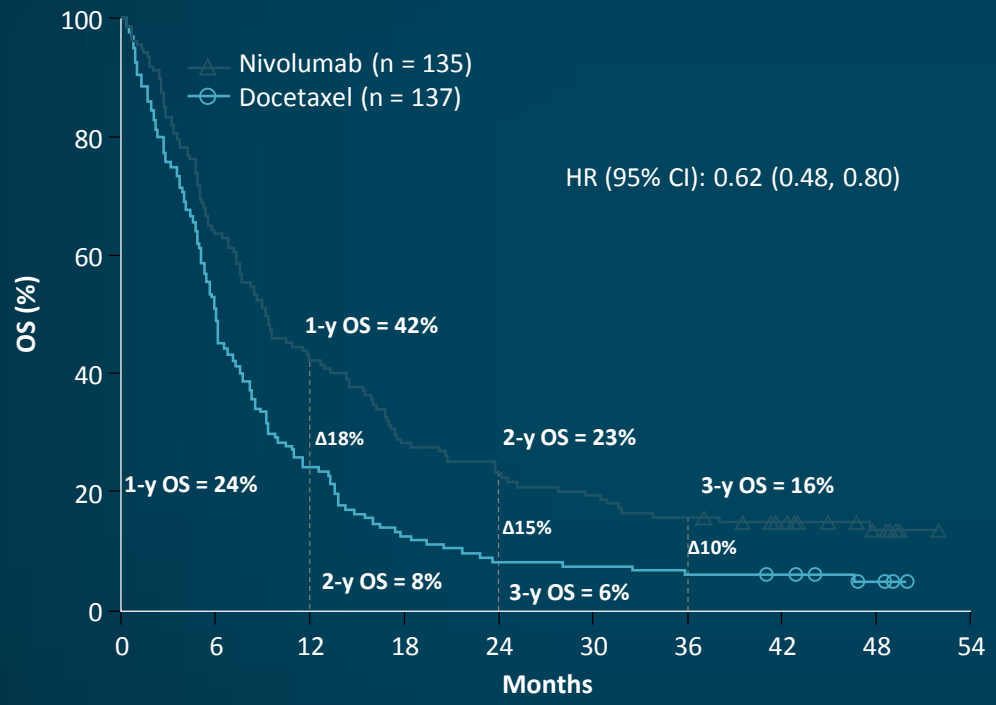
CheckMate 017 and 057 study designs



Results

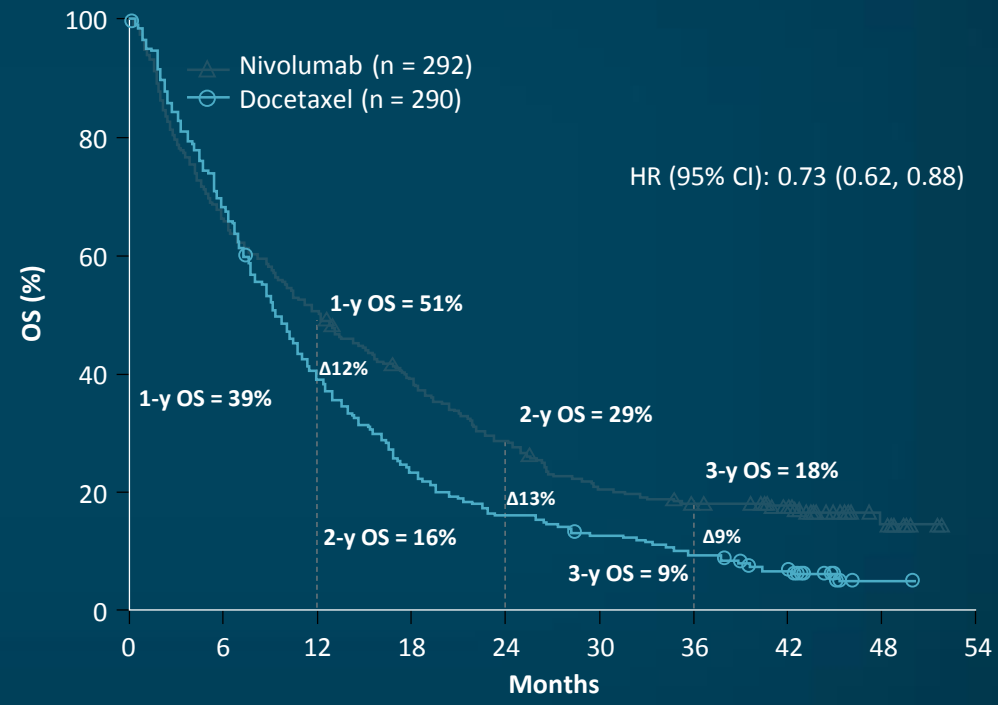
OS (3 years' minimum follow-up)

CheckMate 017 (SQ NSCLC)



No. of patients at risk										
Nivolumab	135	86	57	38	31	26	21	16	8	0
Docetaxel	137	69	33	17	11	10	8	7	3	0

CheckMate 057 (non-SQ NSCLC)



No. of patients at risk										
Nivolumab	292	194	148	112	82	58	49	39	7	0
Docetaxel	290	195	112	67	46	35	26	16	1	0

CI = confidence interval; HR = hazard ratio

Common toxicities

Immune-Mediated Toxicities

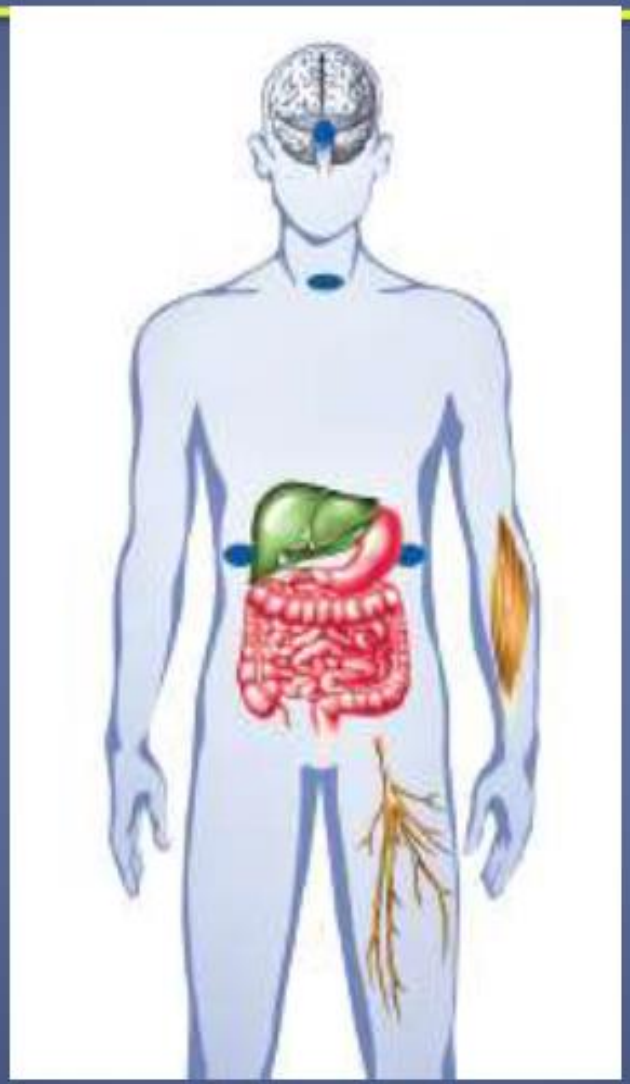
- Can occur immediately, 1-3 months after initiation, late or after discontinuation
- Occasional (5% to 20%)
  - Fatigue, headache, arthralgia, fevers, chills, lethargy
  - Rash: maculopapular, pruritus (topical treatments)
  - Diarrhea/colitis (initiate steroids early, taper slowly)
  - Hepatitis, liver/pancreatic enzyme abnormalities
  - Infusion reactions
  - Endocrinopathies: thyroid, adrenal, hypophysitis

- Rare (< 5%)
  - Pneumonitis (low grade reversible with steroids and discontinuation)
  - Anemia/thrombocytopenia

Weber JS, et al. J Clin Oncol. 2012;30:2691
Weber JS, et al. J Clin Oncol. 2015;33:2092

Select immune-related adverse reactions

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Enterocolitis
- Dermatitis



- Pneumonitis
- Hepatitis
- Pancreatitis
- Motor & sensory neuropathies
- Arthritis

Lipson, ASCO 2014

Toxicity Management

- Check TFTs, CBCs, LFTs and metabolic panels regularly and every 6-12 wks for 6 mos post treatment in all pts receiving immune checkpoint inhibitors
  - ACTH, cortisol should also be checked in pts with fatigue and nonspecific symptoms, plus testosterone in men
- Frequency of follow-up testing should be adjusted to individual response and AEs that occur
- Corticosteroids are usually effective to reverse immune-related AEs associated with these agents

Weber JS, et al. J Clin Oncol. 2015;33:2092

General Principles of Immune-Related Toxicity Management

- Management generally based on severity of symptoms
  - Grade 1: supportive care; ± withhold drug
  - Grade 2: withhold drug, consider redose if toxicity resolves to grade ≤ 1; low-dose corticosteroids (prednisone 0.5 mg/kg/day or equivalent) if symptoms do not resolve within 1 wk
  - Grade 3/4: discontinue drug; high-dose corticosteroids (prednisone 1-2 mg/kg/day or equivalent) slow taper (≥ 1 mo) once toxicity resolves to grade ≤ 1

Specifics

- Pneumonitis: Rule out infectious causes
  - Consider infliximab if steroids not rapidly reversing symptoms or taper challenging
- Colitis: Rule out infectious causes, consider endoscopy
  - Consider infliximab if steroids not rapidly reversing symptoms or taper challenging
- Dermatitis: Consult dermatology
- Endocrinopathy: Hormone replacement as needed
- Hypophysitis: prednisone 1-2 mg/kg/d and taper over >4 wk before resuming immunotherapy
- High dose steroids: oral prednisone 1 mg/kg/d if symptoms persist > 5-7 d; infliximab 5 mg/kg Q2W

Adapted from: Kumar -*Front Pharmacol*. 2017; 8:49

Summary

- Checkpoint inhibition toxicity can mimic many issues and can occur at any time
- Be vigilant and do not be afraid of steroids
- Re-challenge with extreme caution
- Checkpoint inhibitors okay in elderly, chronic hepatitis, organ dysfunction
- Okay in some with autoimmune disease (caution)
- Extreme caution in organ transplant (but not absolute contraindication).

Thanks