Activity and Tolerability of Immunotherapy in Special NSCLC Populations: Elderly and PS 2

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2017 Winter Lung Meeting

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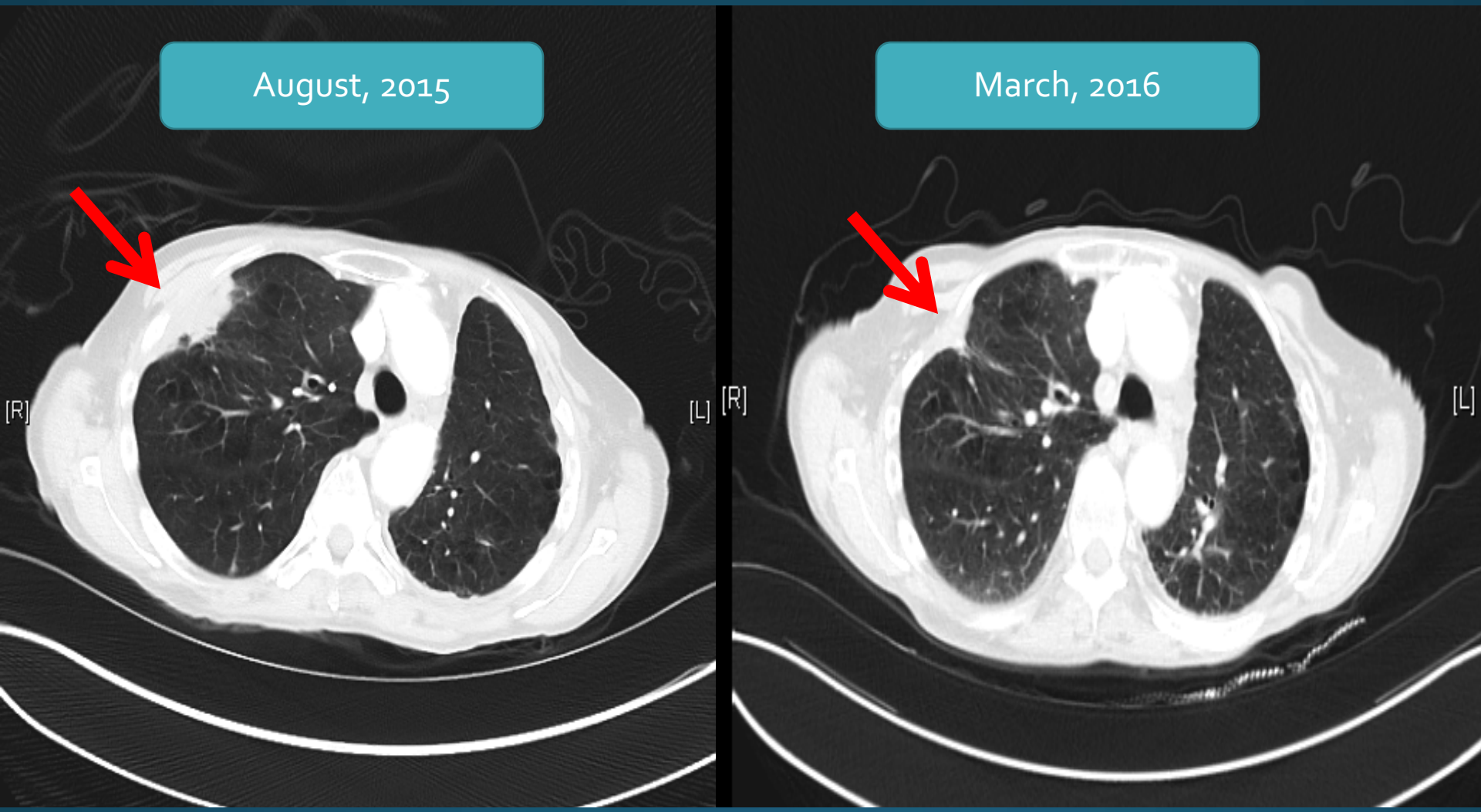
Elderly Pt with Advanced NSCLC on I/O Tx

- 75 yo WF with Hx NSCLC s/p LLLobectomy and subsequent dev't of RUL mass and additional pulmonary nodules, treated initially with Pem/Carbo/Bev, with initial response
- Subsequent PD in RUL, LLL and liver. Dev't of R upper chest pain
- Started on Nivolumab 8/15 with marked PR, but c/b massive 4+ "weeping" peripheral edema, plunge in Alb from 3.5 to 2.1 (01/16),
- EF 60%; Creat 1.0 g/dl; US/Dopplers (-) for DVT. No e/o NS….

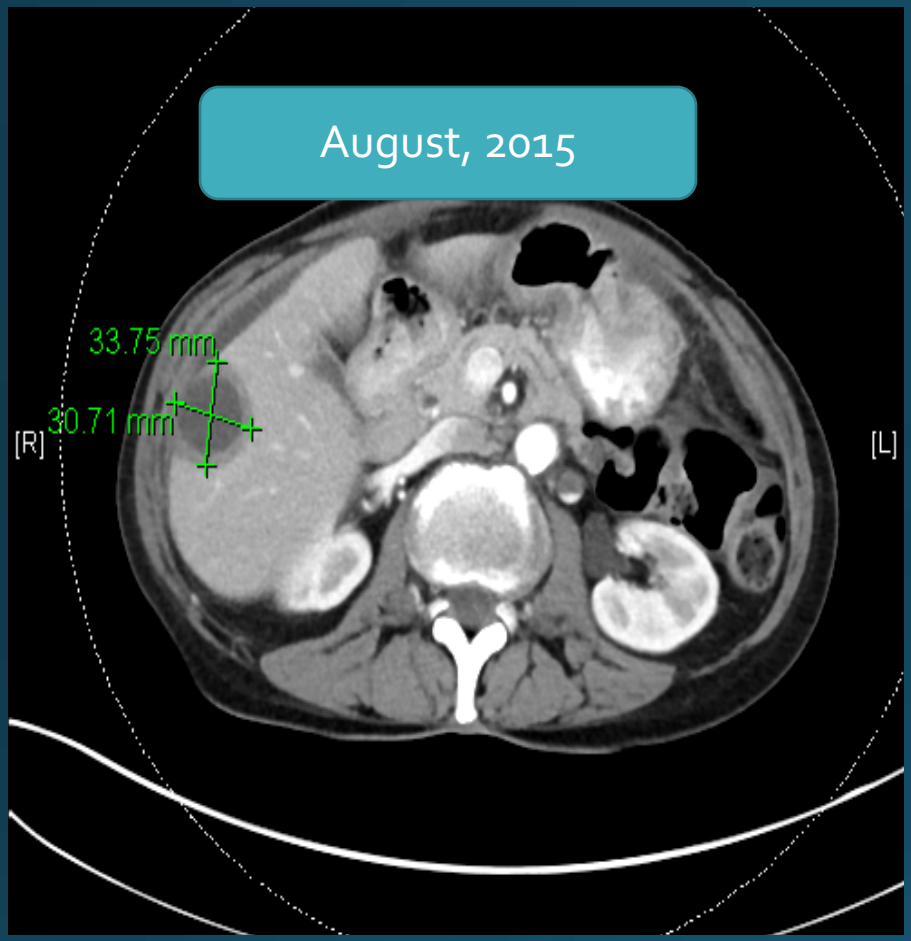
Further course

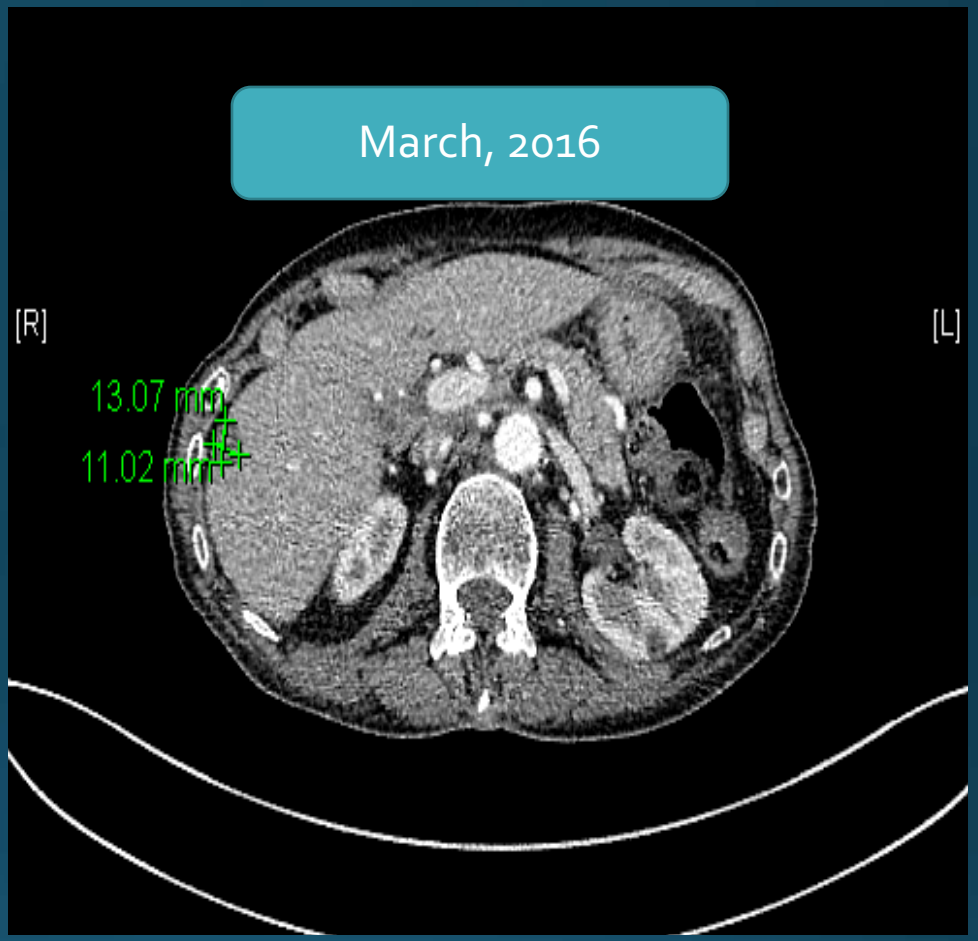
- Pt treated with steroids.
- Nivo withheld.
- After six weeks, edema resolved with Alb back to WNL.
- Pt on steroid taper
- Now what?

1. Resume Nivo, Continue Steroids
2. Repeat CT, then Decide
3. Switch to Docetaxel
4. Refer to Hospice



75 yo WF with Hx NSCLC to liver s/p LLLobectomy and subsequent dev't of RUL mass and additional pulmonary nodules, treated initially with Pem/Carbo/Bev, with subsequent PD in RUL and liver. Started on Nivolumab 8/15 with marked PR, but c/b + peripheral edema, plunge in Alb from 3.5 to 2.1 (01/16), treated with steroids. Nivo withheld. After six weeks, edema resolved with Alb back to WNL. Sustained PR off Tx





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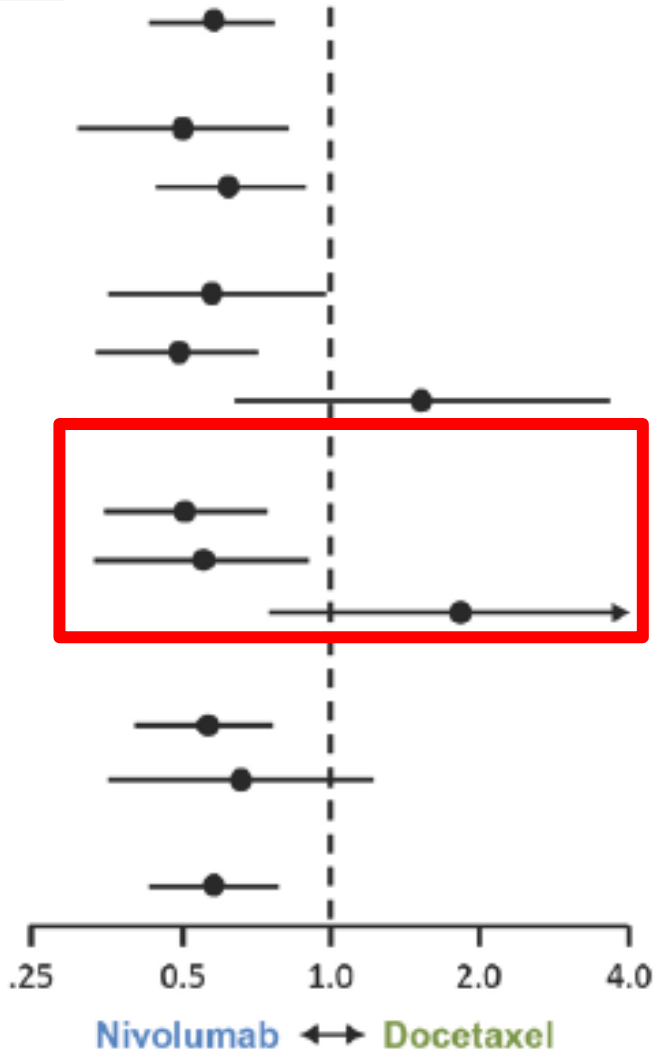
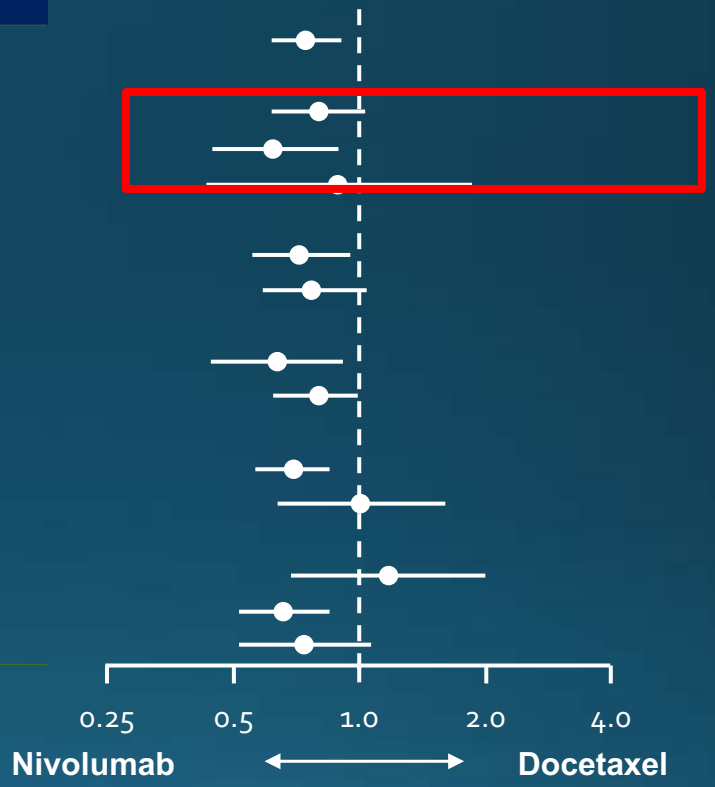
CheckMate-017: Treatment Effect on OS in Predefined Subgroups

	N	Unstratified HR (95% CI)
Overall	**272**	**0.59 (0.44, 0.78)**
Prior paclitaxel vs other prior treatment		
Prior paclitaxel	92	0.51 (0.31, 0.83)
Another agent	180	0.63 (0.45, 0.90)
Region		
US/Canada	86	0.59 (0.36, 0.98)
Europe	155	0.50 (0.34, 0.72)
Rest of world	31	1.53 (0.65, 3.62)
Age		
<65 years	152	0.52 (0.35, 0.75)
≥65 and <75 years	91	0.56 (0.34, 0.91)
≥75 years	29	1.85 (0.76, 4.51)
Gender		
Male	208	0.57 (0.41, 0.78)
Female	64	0.67 (0.36, 1.25)
Race		
White	252	0.59 (0.44, 0.79)



CheckMate-057: Treatment Effect on OS in Predefined Subgroups

	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)
***EGFR* Mutation Status**		
Positive	82	1.18 (0.69, 2.00)
Not Detected	340	0.66 (0.51, 0.86)
Not Reported	160	0.74 (0.51, 1.06)



All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

KEYNOTE-010: Treatment Effect on OS in Predefined Subgroups

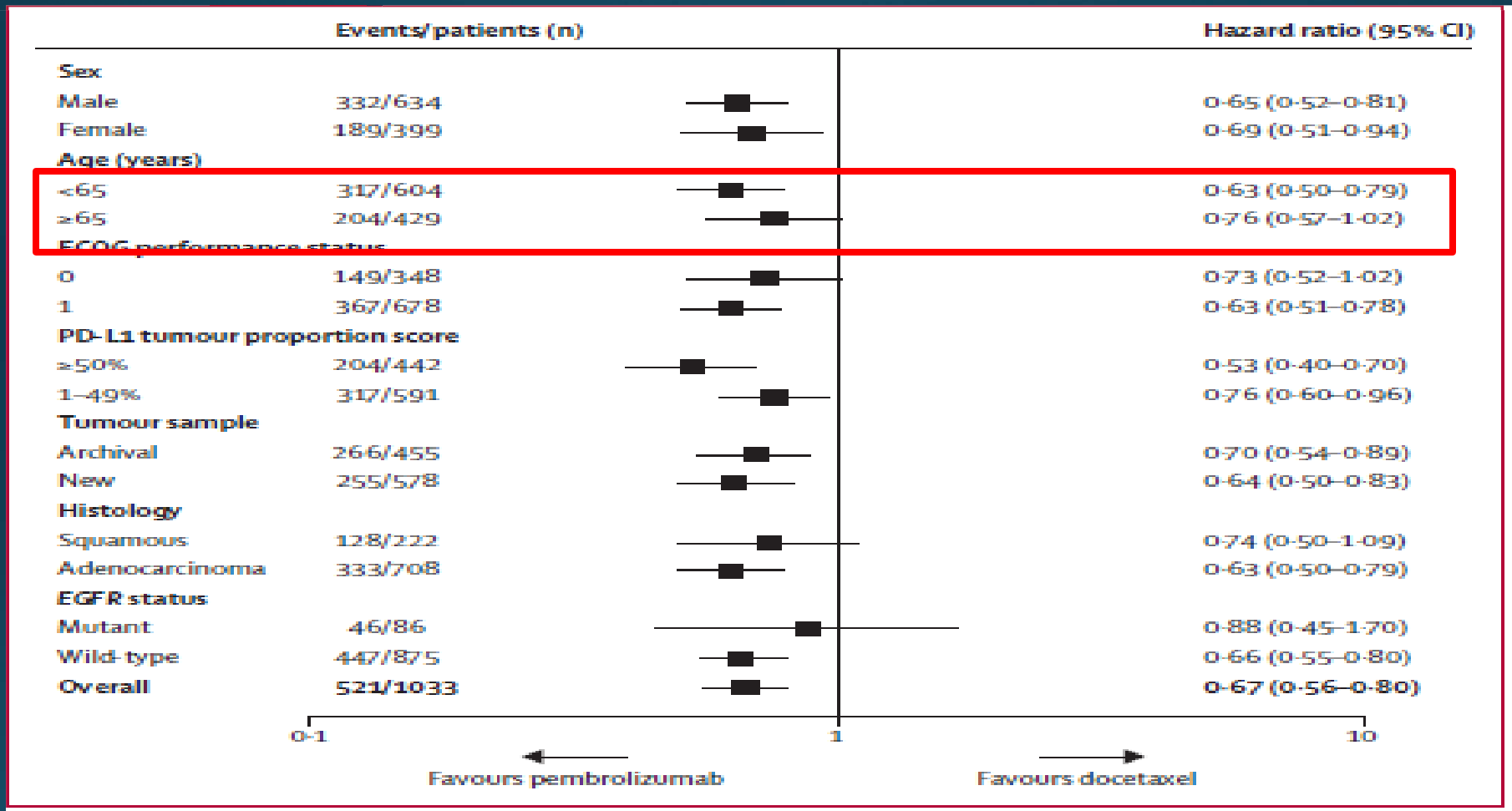
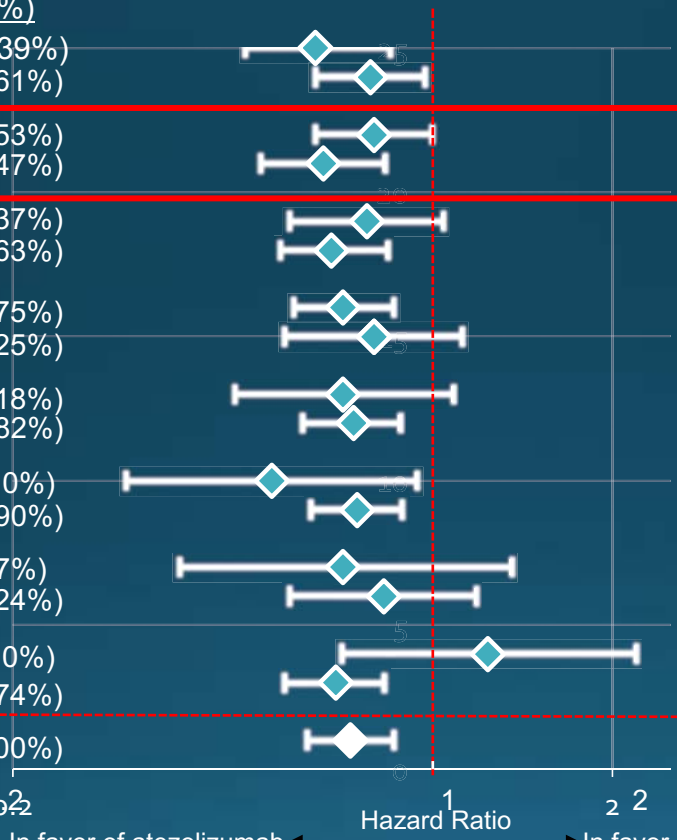


Figure 3: Subgroup analysis of overall survival

Herbst RS et al. Lancet 2016;387(10027):1540-50.

ATEZOLIZUMAB VERSUS DOCETAXEL: OS IN SELECTED SUBGROUPS

Subgroup	n (%)	HR[a]	Median OS, mo: Atezolizumab n = 425	Median OS, mo: Docetaxel n = 425
Female	330 (39%)	**0.64**	16.2	11.2
Male	520 (61%)	**0.79**	12.6	9.2
< 65 years	453 (53%)	**0.80**	13.2	10.5
≥ 65 years	397 (47%)	**0.66**	14.1	9.2
ECOG PS 0	315 (37%)	**0.78**	17.6	15.2
ECOG PS 1	535 (63%)	**0.68**	10.6	7.6
1 prior therapy	640 (75%)	**0.71**	12.8	9.1
2 prior therapies	210 (25%)	**0.80**	15.2	12.0
Never smokers	156 (18%)	**0.71**	16.3	12.6
Current/previous smokers	694 (82%)	**0.74**	13.2	9.3
CNS mets	85 (10%)	**0.54**	20.1	11.9
No CNS mets	765 (90%)	**0.75**	13.0	9.4
KRAS mutant	59 (7%)	**0.71**	17.2	10.5
KRAS wildtype	203 (24%)	**0.83**	13.8	11.3
EGFR mutant	85 (10%)	**1.24**	10.5	16.2
EGFR wildtype	628 (74%)	**0.69**	15.3	9.5
ITT	850 (100%)	**0.73**	13.8	9.6



[a]Stratified HR for ITT. Unstratified HR for subgroups.
OS, overall survival.

Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

Toxicity of I/Os in the Elderly

P346

ESMO (2015)

Nivolumab Safety Profile: Summary of Findings From Trials in Patients With Advanced Squamous Non-Small Cell Lung Cancer (NSCLC)

Scott Gettinger,[1] Leora Horn,[2] Suresh Ramalingam,[3] David Spigel,[4]
Luis Paz-Ares,[5] Paul Paik,[6] Martin Reck,[7] Karen Reckamp,[8]
Julien Mazières,[9] Thomas Stinchcombe,[10] Mark Lynch,[11] Julie Brahmer[12]

Patients from CheckMate 017 and CheckMate 063 who received at least one dose of nivolumab 3 mg/kg IV Q2W until disease progression, unacceptable toxicity, or other reasons were included in this analysis

Email: scott.gettinger@yale.edu

Results: Subgroup analyses of treatment-related AEs

Subgroup category	n	Nivolumab (N = 248) Treatment-related AEs[a]	
		Any grade, %	Grade 3-4, %
Age			
<65 years	134	67.9	11.2
≥65 to <75 years	87	66.7	13.8
≥75 years	27	52.0	7.4
Region			
US/Canada	108	70.4	17.6
Europe	126	61.9	7.9
Rest of world	14	64.3	0
ECOG performance status			
0	53	60.4	13.2
1	195	67.2	11.3
Prior radiotherapy			
Yes	155	71.0	12.3
No	93	57.0	10.8
Smoking status			
Current/former	226	66.4	11.1
Never smoker	18	61.1	22.2
Number of prior systemic therapies			
1	114	65.8	7.9
2	58	55.2	12.1
3	52	78.8	23.1
>3	24	62.5	4.2
Prior TKI therapy			
Yes	39	66.7	12.8
No	209	65.6	11.5

FDA subset analysis of the safety of nivolumab in elderly patients with advanced cancers.

ASCO 2016

Harpreet Singh, Geoffrey Kim, Virginia Ellen Maher, Julia A. Beaver, Lee H. Pai-Scherf, Sanjeeve Balasubramaniam, Marc Robert Theoret, Gideon Michael Blumenthal, Richard Pazdur; U.S. Food and Drug Administration, Silver Spring, MD

ASCO 2016

non-small lung cancer (CA209057 and CA209017)

advanced renal cell cancer (CA209025)

melanoma (CA209066)

Adverse events by age in patients treated with nivolumab.

	Patients < 65 yrs (N=616) n%	Patients ≥ 65 yrs (N=414) n%	Patients ≥ 70 yrs (N=212) n%
Grade 1-2 Adverse Events	584 (94.8)	394 (95.2)	202 (95.3)
Grade 3-5 Adverse Events	360 (58.4)	259 (62.6)	152 (71.7)
Serious Adverse Events	313	242	123
All Adverse Events leading to Discontinuation	89 (14.4)	71 (17.1	42 (19.8)
AEs Requiring Treatment with Immune Modulating Medication	256 (41.5)	196 (47.3)	110 (51.9)
Select irAE's where immune modulating medication was initiated			
Diarrhea/colitis	15 (2.4)	17 (4.1)	11 (5.2)
Pneumonitis	23 (3.7)	8 (1.9)	5 (2.4)
Hepatitis	8 (1.3)	3 (0.7)	1 (0.5)
Nephritis and renal dysfunction	6 (1.0)	8 (1.9)	7 (3.3)
Rash	47 (7.6)	34 (8.2)	22 (10.4)

Baseline Characteristics

Baseline Characteristic	n=122
Median age (range), yr	65 (38-85)
Male, no. (%)	74 (61)
Tumor histology, no. (%)*	
Squamous	47 (39)
Non-squamous	73 (60)
ECOG PS, no. (%)†	
0-1	117 (96)
2	2 (2)
Number of prior therapies, no. (%)‡	
1-2	49 (40)
≥3	**67 (55)**
Nature of prior therapy, no. (%)	
Platinum-based chemotherapy	115 (94)
Tyrosine-kinase inhibitor	41 (34)
Radiotherapy	40 (33)

*Unknown: 2 (2%). †Not reported: 3 (2%). ‡Not reported: 6 (5%).

Brahmer J R et al. *N Engl J Med*. 2012;366:2455-2465.

Italian Cohort of Nivolumab Expanded Access Program: Preliminary Data From a Real-World Population

Lucio Crinò,[1] Paolo Bidoli,[2] Angelo Delmonte,[3] Francesco Grossi,[4] Filippo de Marinis,[5] Francesca Sperandi,[6] Francovito Piantedosi,[7] Milena Vitali,[8] Hector Soto Parra,[9] Simone Scagnoli,[10] Gabriele Minuti,[11] Luana Calabrò,[12] Marcello Tiseo,[13] Daniele Turci,[14] Silvia Quadrini,[15] Paola Antonelli,[16] Anna Manzo,[17] Irene Prediletto,[18] Diana Giannarelli,[19] Domenico Galetta[20]

Table 1. Baseline patient characteristics

Characteristic	N = 371
Gender, n (%)	
Male	298 (80)
Female	73 (20)
Median age, years (range)	68 (31–91)
Patients ≥75 years, n (%)	70 (19)
Smoking status, n (%)	
Smoker	83 (22)
Ex-smoker	225 (61)
Never smoker	38 (10)
Unknown	25 (7)
ECOG PS, n (%)	
0	134 (36)
1	215 (58)
2	22 (6)
Metastasis site, n (%)	
Brain	37 (10)
Liver	64 (17)
Bone	120 (32)
Number of prior therapies, n (%)	
1	162 (44)
2	120 (32)
3	68 (18)
≥4	21 (6)

Crinò L et al, ASCO 2016

Phase II Trial of Pembrolizumab in NSCLC PS2 Pts

- NCT02733159
- Based at U. of Alabama – Birmingham
- Targets 60 pts for accrual
- Primary Endpoints: Toxicity; RR%
- Secondary Endpoints: ORR; HRQoL; TTP, PFS, OS
- Slated to start 4/16, but not yet recruiting

Automimmunity and I/Os

Core Exclusion Criteria:

- Untreated symptomatic brain or leptomeningeal metastatic disease.
- Medical or psychiatric conditions comprising informed consent.
- Any medical condition which in the opinion of the investigator would compromise the ability of the patient to participate in the trial or which would jeopardise compliance with the protocol.
- Radiotherapy within 4 weeks of trial entry.
- Active autoimmune disease that has required systemic treatment in past 2 years
- Chronic usage of steroids or other immunosuppressant medication.
- Previous history of pneumonitis.
- Any evidence of clinical autoimmunity.

Additional Questions: Checkpoint Inhibitors in AID

1. Does immunosuppression blunt immunotherapy's favorable effect? **No, most likely; multiple reports of pts on steroids with sustained responses**

2. What are risks of immunosuppression?

3. Can these drugs be given to patients with autoimmune disease?

Response in Patients Who Received or Did not Receive Systemic Immunosuppression

	NIVO monotherapy with IM N = 139	NIVO monotherapy without IM N = 437
ORR, n (%), [95% CI]	40 (28.8) [21.4–37.1]	141 (32.3) [27.9–36.9]
BOR, n (%)		
CR	7 (5.0)	22 (5.0)
PR	33 (23.7)	119 (27.2)
SD	31 (22.3)	102 (23.3)
PD	63 (45.3)	173 (39.6)
Not evaluable	5 (3.6)	21 (4.8)
Median duration of response, mo (95% CI)	NR (9.3–NR)	22.0 (22.0–NR)
Median time to response, mo (range)	2.1 (1.2–8.8)	2.1 (1.4–9.2)

- ORR was 28.8% in pts who had received an IM and was 32.3% in pts who had not received immunosuppression
- Time to response was similar in both subgroups (median of 2.1 months), and median duration of response was 22 months in those who did not receive an IM and had not been reached in pts who received systemic IMs

Pts evaluable for response had a baseline tumor assessment and a confirmatory scan at least 4 weeks after the first documented response. BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease

Weber et al. ASCO 2015

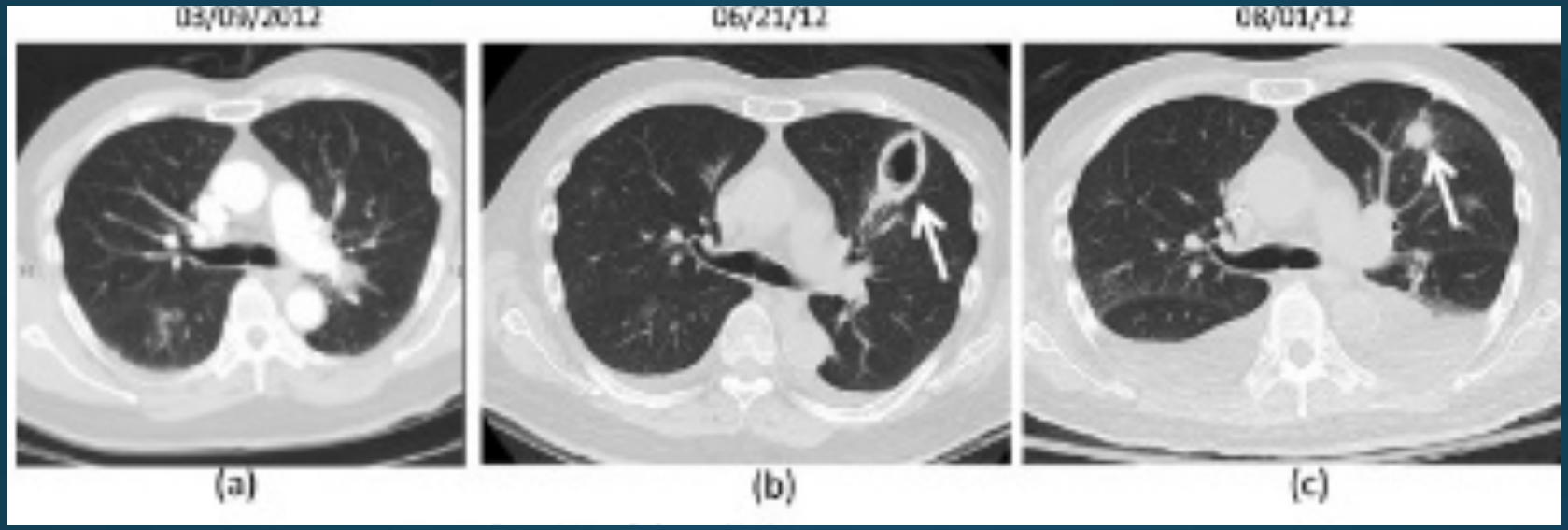
Additional Questions: Checkpoint Inhibitors in AID

1. Does immunosuppression blunt immunotherapy's favorable effect? **No, most likely; multiple reports of pts on steroids with sustained responses**

2. What are risks of immunosuppression? **Unclear since such pts were excluded from initial trials; but allograft failure has been seen in those started on I/Os**

3. Can these drugs be given to patients with autoimmune disease?

Possibility of Opportunistic Infection



- Ipilimumab diarrhea treated with prednisone and infliximab, subsequent *Aspergillus fumigatus* infection treated with voriconazole

- Consider prophylaxis for PCP (Bactrim, atovaquone) in patients on 20mg of prednisone for at least 4 weeks (Category 2B from NCCN)

Kyi and Postow *JITC* 2014

Additional Questions: Checkpoint Inhibitors in AID

1. Does immunosuppression blunt immunotherapy's favorable effect? **No, most likely; multiple reports of pts on steroids with sustained responses**

2. What are risks of immunosuppression? **Unclear since such pts were excluded from initial trials; but allograft failure has been seen in those started on I/Os**

3. Can these drugs be given to patients with autoimmune disease? **Tough to say since such pts were excluded from clinical trials; PI recommends against treating such pts**

Safety in Patients with Existing Autoimmune Diseases?

1. Knowledge is limited since patients with autoimmunity not included in clinical trials

2. Anecdotal observations suggest it may be safe

3. Risk/benefit discussion with patients

Kyi and Postow *JITC* 2014
Johnson ASCO 2015

Conclusions: I/Os in Special Populations with NSCLC

- Activity of PD1 inhibitors preserved in elderly pts, with minimal, if any, increase in toxicity
- Paucity of data in PS 2 pts and those with autoimmune disease