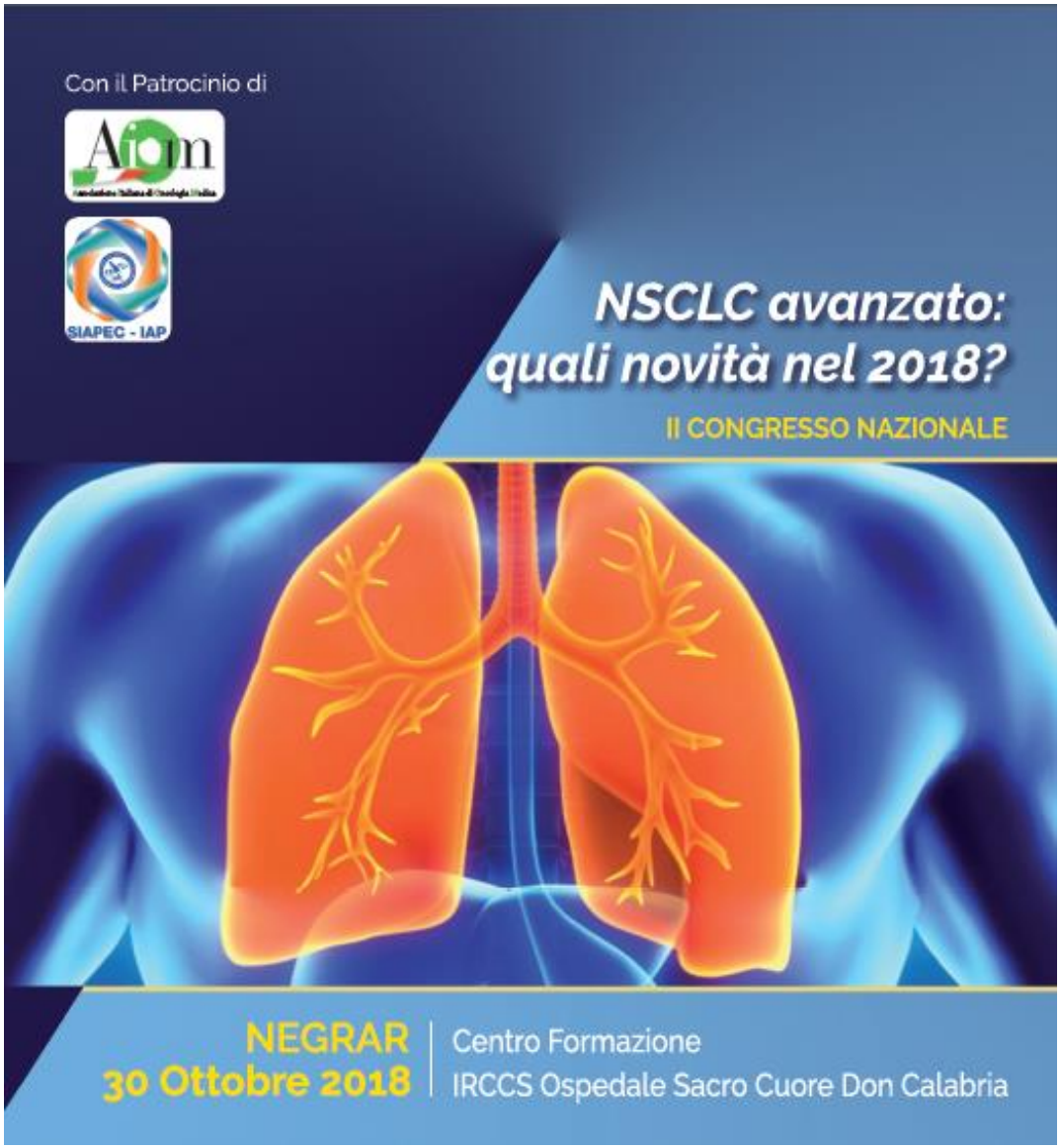


II sessione

Immunoterapia oltre la prima linea

Alessandro Tuzi
ASST Sette Laghi, Varese

AGENDA

- **Immunotherapy post-chemo (“true 2/3L”)**
- **Immunotherapy in *oncogene addicted* NSCLC (yes/no? when?)**
- **Immunotherapy beyond progression (“false 2/3L”)**
- **Conclusions**

AGENDA

- **Immunotherapy post-chemo ("true 2/3L")**
- **Immunotherapy in *oncogene addicted* NSCLC (yes/no? when?)**
- **Immunotherapy beyond progression ("false 2/3L")**
- **Conclusions**

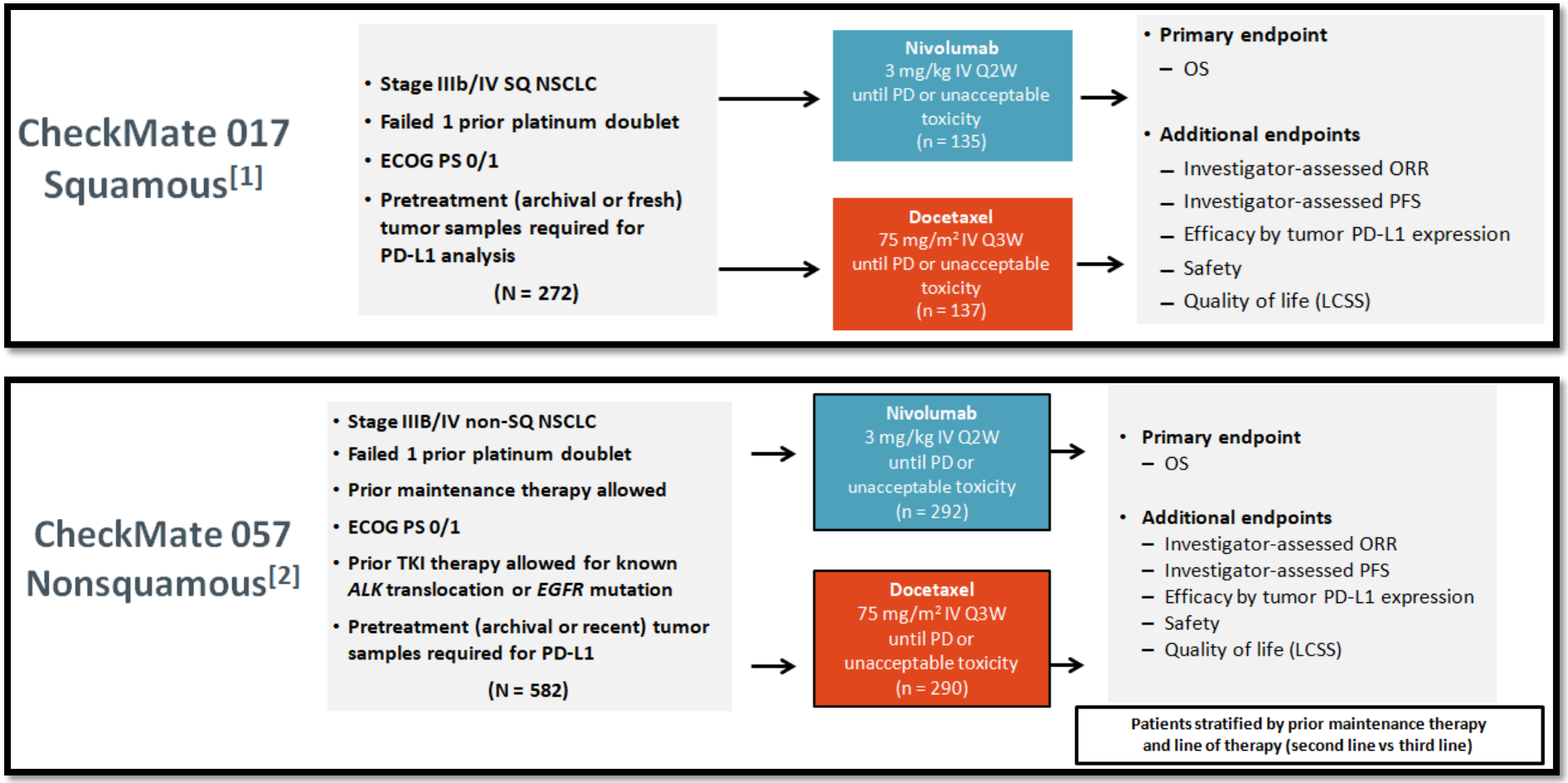
Overview of Immunotherapy as Second-line or Subsequent Therapy for Advanced NSCLC

Compound	Trial	ORR, %	PFS, Mos (Range)	OS, Mos (Range)
Nivolumab	CheckMate 017[1]	20.0	3.5 (2.1-4.9)	9.2 (7.3-13.3)
	CheckMate 057[2]	19.2	2.3 (2.2-3.3)	12.2 (9.7-15.0)
Pembrolizumab	KEYNOTE 010*[3]	18	3.9 (3.1-4.1) 4.0 (2.7-4.3)	10.4 (9.4-11.9) 12.7 (10.0-17.3)
Atezolizumab	OAK[4]	14.0	2.8 (2.6-3.0)	13.8 (11.8-15.7)
Avelumab	JAVELIN[5]	12.0	11.6 wks (8.4-13.7) wks	8.4 (7.3-10.6)
Durvalumab	ATLANTIC†‡[6]	7.5 (3.1-14.9) 16.4 (10.8-23.5) 30.9 (20.2-43.3)	1.9 (1.8-1.9) 3.3 (1.9-3.7) 2.4 (1.8-5.5)	9.3 (5.9-10.8) 10.9 (8.6-13.6) NR (5.9-NC)

*2 and 10 mg/kg at PD-L1 TPS ≥ 1%. †PD-L1 < 25%, ≥ 25%, and ≥ 90%. ‡EGFR/ALK wild-type patients.

1. Brahmer J, et al. N Engl J Med. 2015;373:123-135. 2. Borghaei H, et al. N Engl J Med. 2015;373:1627-1639. 3. Herbst RS, et al. Lancet. 2016;387:1540-1550. 4. Rittmeyer A, et al. Lancet. 2017;389:255-265. 5. Gulley JL, et al. Lancet Oncol. 2017;18:599-610. 6. Garassino MC, et al. Lancet Oncol. 2018;19:521-536.

Nivolumab vs Docetaxel in Previously Treated Advanced NSCLC

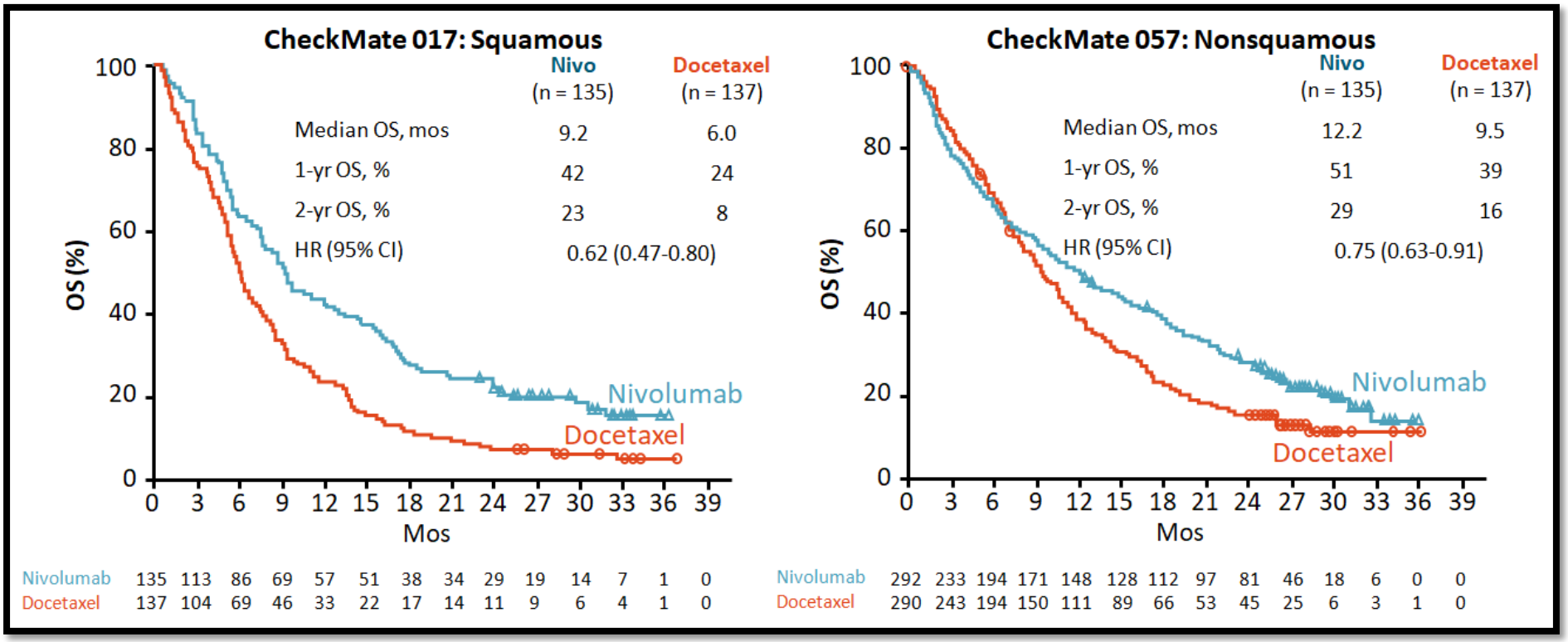


The protocols of both studies were amended in September 2016, when minimum follow-up was approximately 2.5 years, allowing patients to ***switch to nivolumab 480 mg Q4W*** *starting 2 weeks after their last 3-mg/kg Q2W dose. After completion of the primary analyses, patients in the docetaxel arms who ended treatment at any time during the studies were allowed to* ***cross over*** *to nivolumab.*

1. Brahmer J, et al. N Engl J Med. 2015;373:123-135.

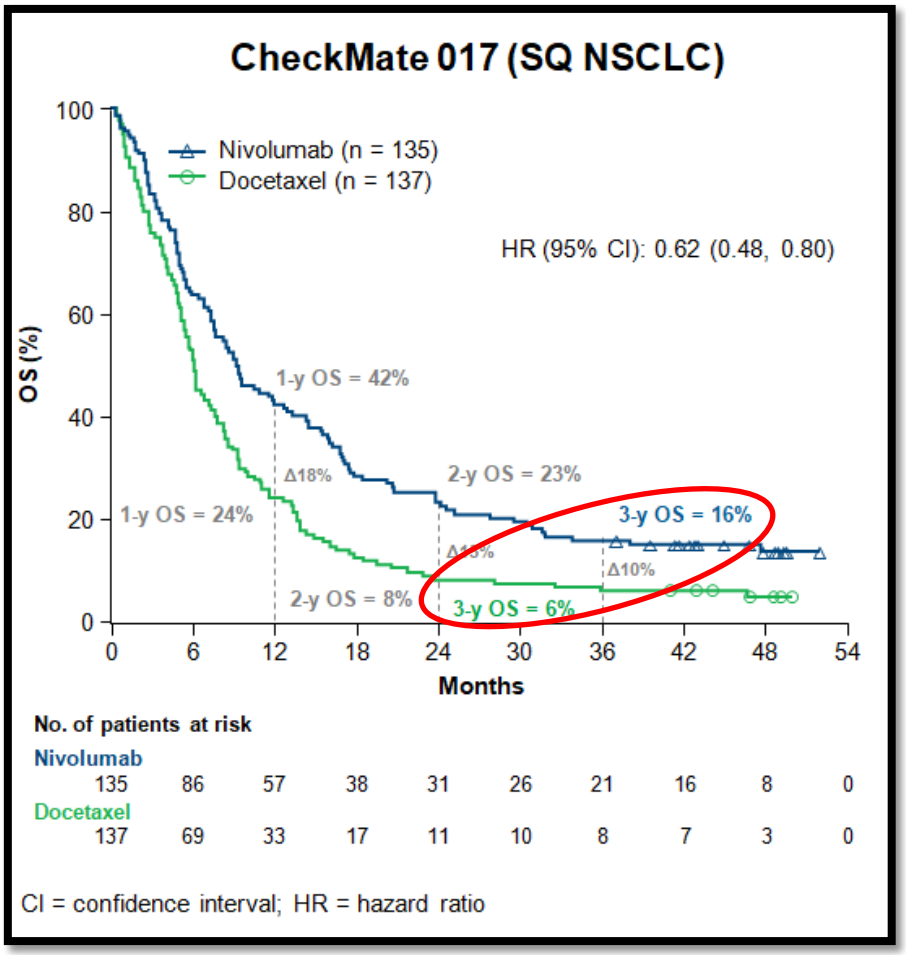
2. Borghaei H, et al. N Engl J Med. 2015;373:1627-1639.

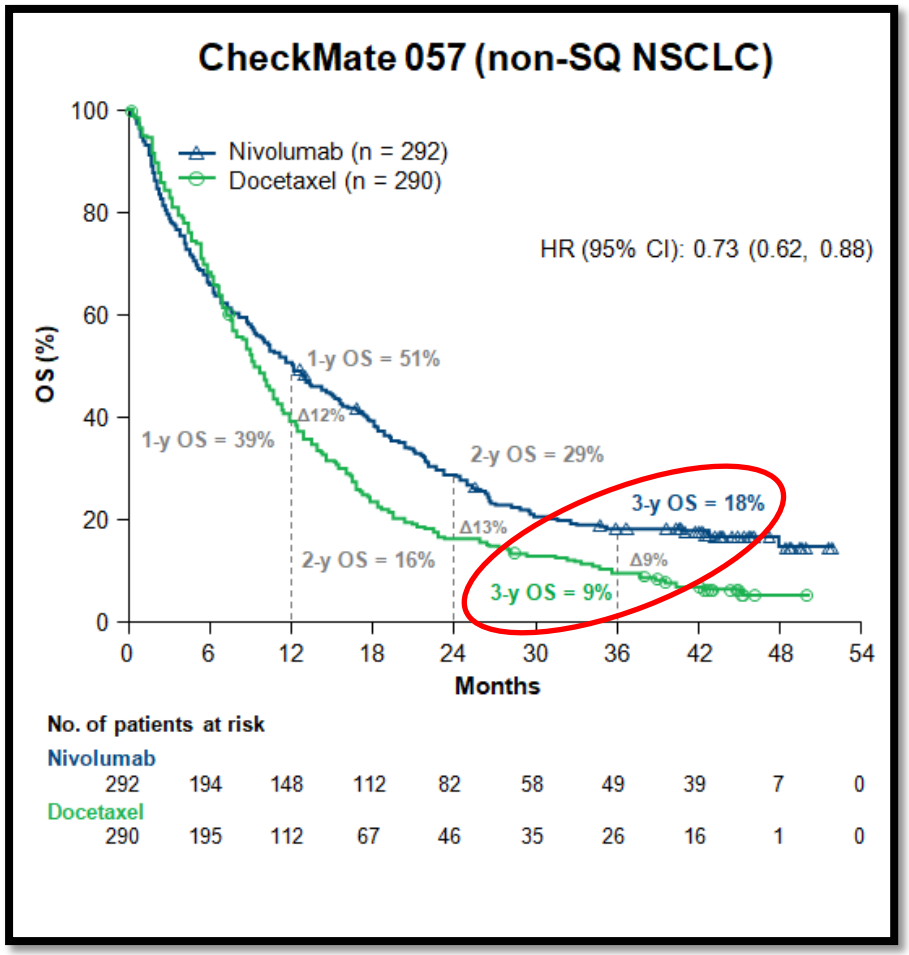
CheckMate 017 and 057
OS With a Minimum 2-Yr Follow-up



Horn L, et al. J Clin Oncol. 2017;35:3924-3933.

Three-Year Follow-up From CheckMate 017/057: OS





Felip et al. ESMO 2017 – 1301PD

CheckMate 017: OS by PD-L1 Expression

Median OS by PD-L1 Expression Level,* Mos	Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P* Value
≥ 1%	9.3	7.2	0.69 (0.45-1.05)	.56
< 1%	8.7	5.9	0.58 (0.37-0.92)	
≥ 5%	10.0	6.4	0.53 (0.31-0.89)	.47
< 5%	8.5	6.1	0.70 (0.47-1.02)	
≥ 10%	11.0	7.1	0.50 (0.28-0.89)	.41
< 10%	8.2	6.1	0.70 (0.48-1.01)	
Not quantifiable			0.39 (0.19-0.82)	

OS benefit seen with nivolumab vs docetaxel independent of PD-L1 expression; similar trend in PFS, ORR.

Spigel DR, et al. ASCO 2015. Abstract 8009.

CheckMate 057: OS by PD-L1 Expression

Median OS by PD-L1 Expression Level, mos	Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P* Value
≥ 1%	17.2	9.0	0.59 (0.43-0.82)	.0646
< 1%	10.4	10.1	0.90 (0.66-1.24)	
≥ 5%	18.2	8.1	0.43 (0.30-0.63)	.0004
< 5%	9.7	10.1	1.01 (0.77-1.34)	
≥ 10%	19.4	8.0	0.40 (0.26-0.59)	.0002
< 10%	9.9	10.3	1.00 (0.76-1.31)	

Similar interaction results based on baseline PD-L1 expression observed for PFS and ORR.

Paz-Ares L, et al. ASCO 2015. Abstract LBA109.

Three-Year Follow-up From CheckMate 017/057: SAFETY

	Pooled nivolumab (N = 418)	
	Any grade	Grade 3–4
TRAEs, %		
Any AE	67.7	10.5
AE leading to discontinuation	6.0	4.1
Most frequent TRAEs,*%		
Fatigue	17.0	1.0
Nausea	11.0	0.5
Decreased appetite	11.0	0.2
Asthenia	10.5	0.2
Diarrhea	8.9	1.0
Rash	8.1	0.5
Pruritus	6.9	0.2
Hypothyroidism	6.0	0
Arthralgia	5.7	0.2
Vomiting	5.0	0

There were no grade 5 TRAEs; *Reported in ≥5% of patients

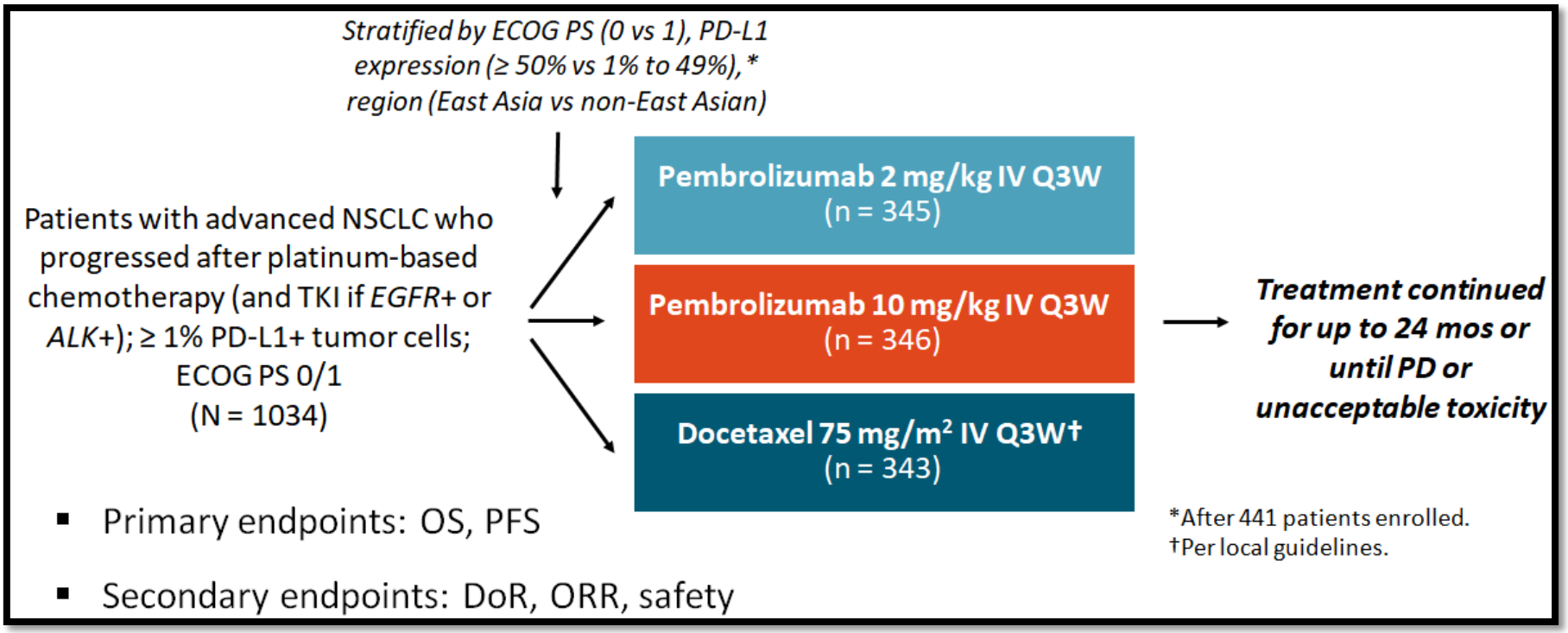
Felip et al. ESMO 2017 – 1301PD

Three-Year Follow-up From CheckMate 017/057: treatment-related select AEs

	Pooled nivolumab (N = 418)	
	Any grade	Grade 3–4
Overall, %	**37.1**	**4.8**
Skin	16.3	1.0
Gastrointestinal	9.1	1.2
Endocrine	8.6	0
Hepatic	5.7	1.0
Pulmonary	4.5	1.4
Renal	2.6	0.2
Hypersensitivity/infusion reaction	2.4	0

Felip et al. ESMO 2017 – 1301PD

KEYNOTE-010
Pembrolizumab vs Docetaxel in Advanced PD-L1–Positive NSCLC

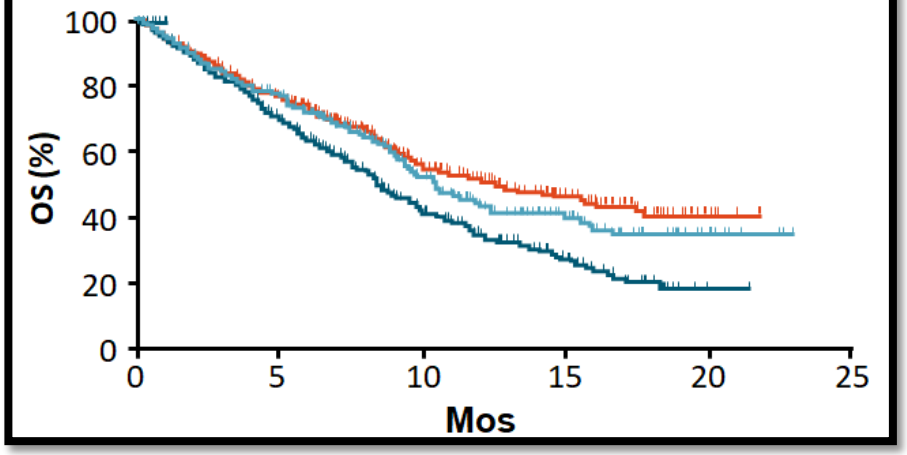


Herbst RS, et al. Lancet. 2016;387:1540-1550.

KEYNOTE-010
OS in Patients With PD-L1 TPS ≥ 1% and TPS ≥ 50%

Patients With PD-L1 TPS ≥ 1%

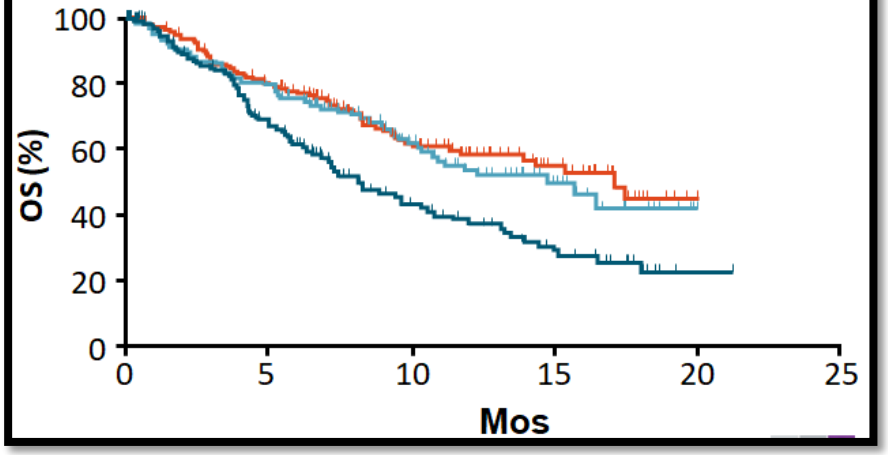
	ORR, %	mOS, Mos	1-Yr OS, %	HR (95% CI)
Pembrolizumab 2 mg/kg (n = 344)	18	10.4	43.2	0.71 (0.58-0.88)
Pembrolizumab 10 mg/kg (n = 346)	18	12.7	52.3	0.61 (0.49-0.75)
Docetaxel (n = 343)	9	8.5	34.6	



Median follow-up 13.1 months

Patients With PD-L1 TPS ≥ 50%

	ORR, %	mOS, Mos	HR (95% CI)
Pembrolizumab 2 mg/kg (n = 139)	30	14.9	0.54 (0.38-0.77)
Pembrolizumab 10 mg/kg (n = 151)	29	17.3	0.50 (0.36-0.70)
Docetaxel (n = 152)	8	8.2	

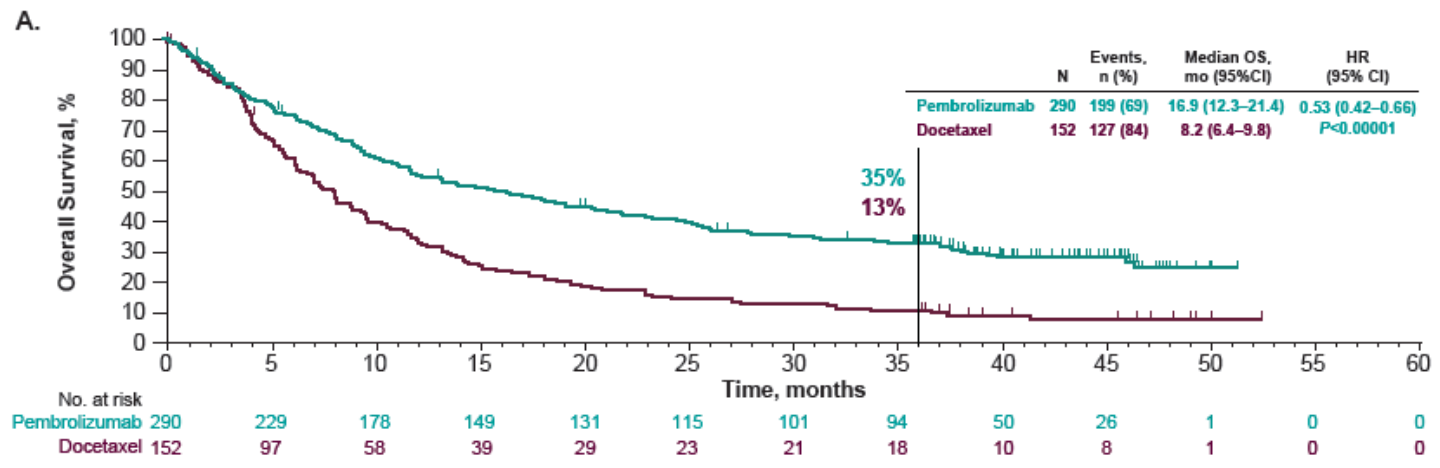


Herbst RS, et al. Lancet. 2016;387:1540-1550.

KEYNOTE-010
Long term survival (follow-up 42.6 months)

Efficacy in the PD-L1 TPS ≥50% and ≥1% Populations

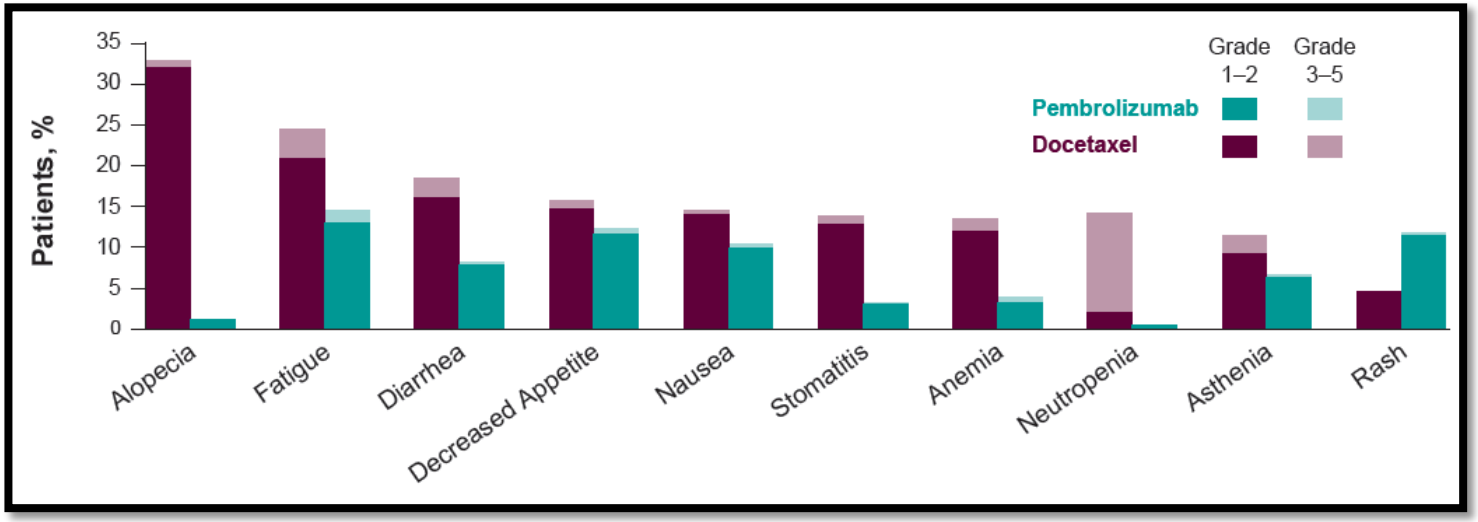
Figure 2. Kaplan-Meier Estimates of OS. (A) PD-L1 TPS ≥50% Population. (B) PD-L1 TPS ≥1% Population.

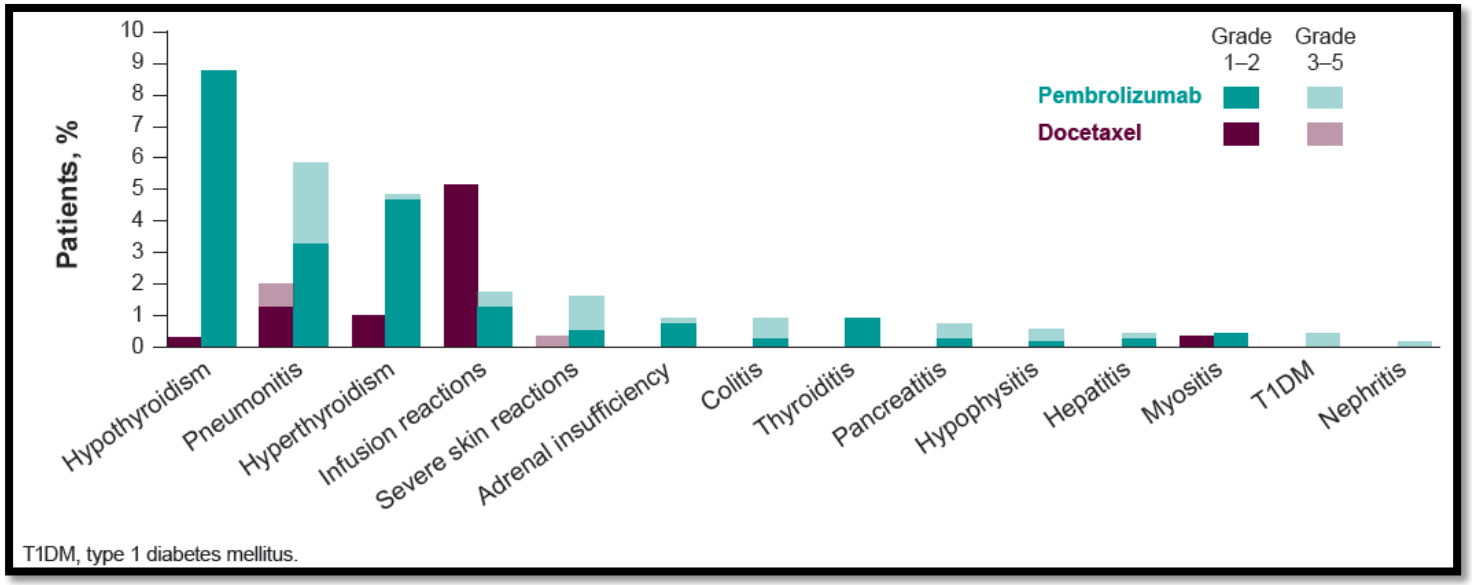


Herbst RS, ESMO 2018

KEYNOTE-010
Safety

Treatment-Related AEs With Incidence ≥10% in Any Group in the Overall Study Population



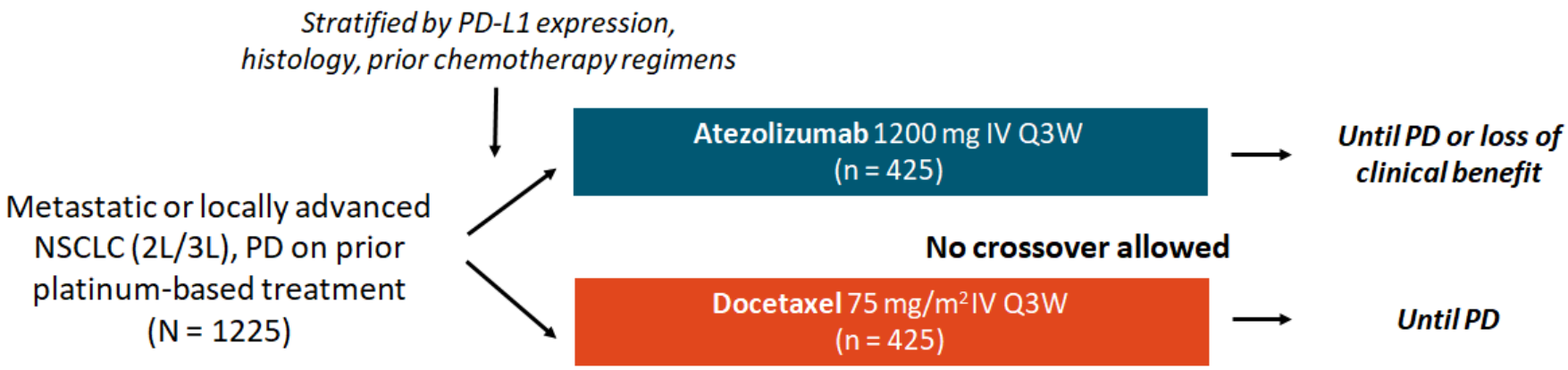


Immune-Mediated AEs and Infusion Reactions in the Overall Study Population

Herbst RS, ESMO 2018

OAK
Atezolizumab vs Docetaxel in Progressive Advanced NSCLC

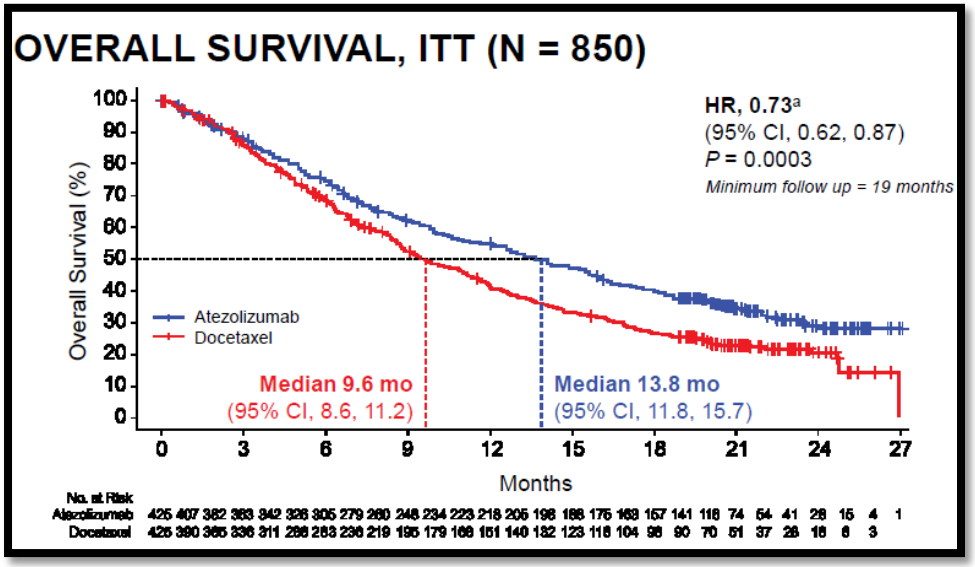
- Multicenter, randomized, open-label phase III trial

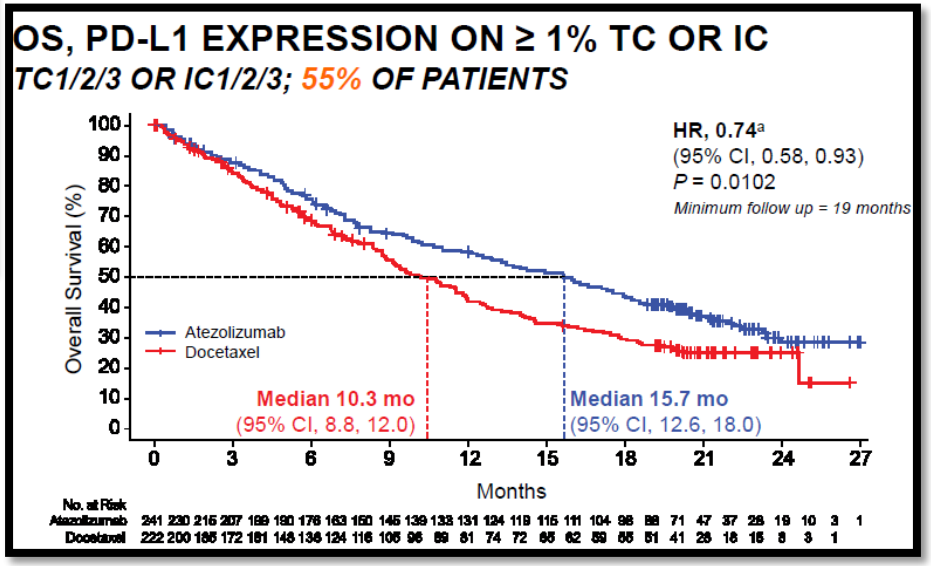


- Primary endpoints (first 850 patients enrolled): OS in ITT population; OS in patients with ≥ 1% PD-L1 expression
- Secondary endpoints: ORR, PFS, DoR, safety

Rittmeyer A, et al. Lancet. 2017;389:255-265.

OAK
Overall Survival

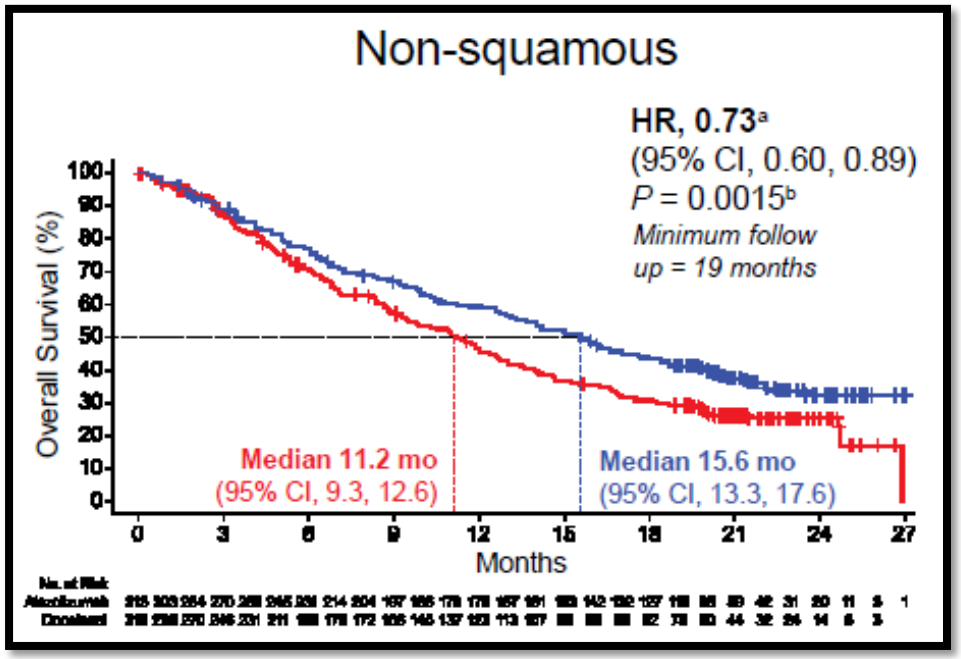


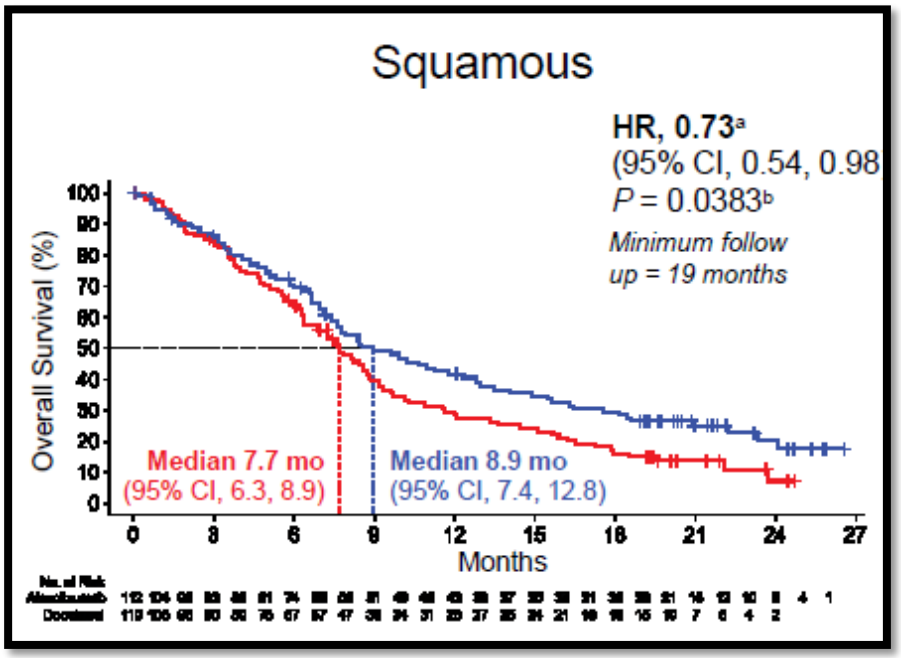


Rittmeyer A, et al. Lancet. 2017;389:255-265.

Barlesi F et al, Annals of Oncology (2016) 27 (6): 1-36. 10.1093 ADAPTED for ESMO PRESENTATION

OAK
Overall Survival by histology



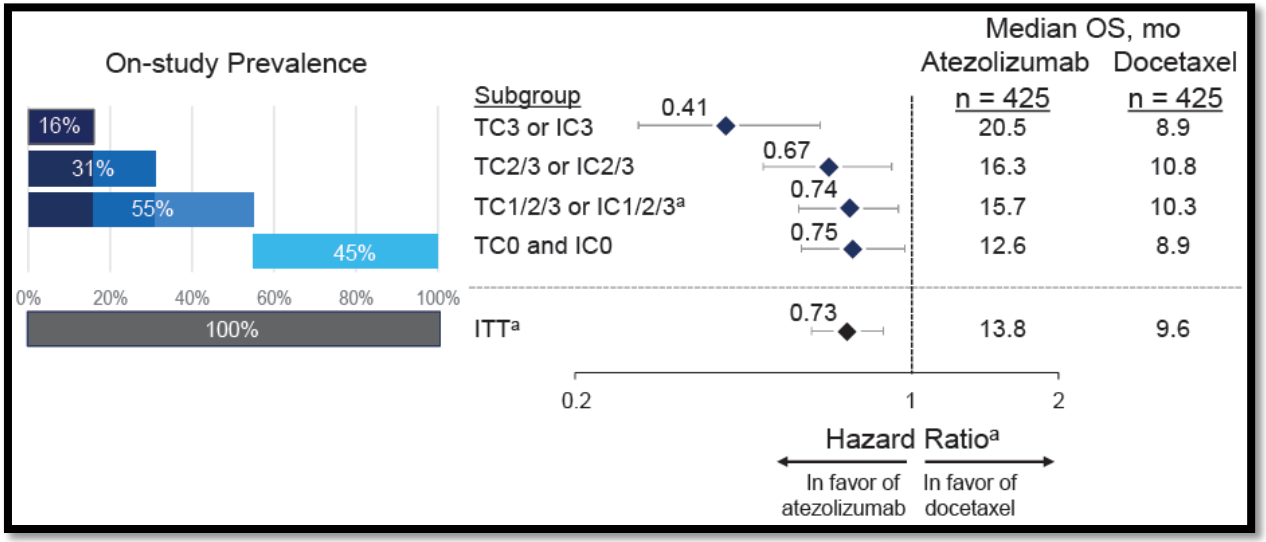


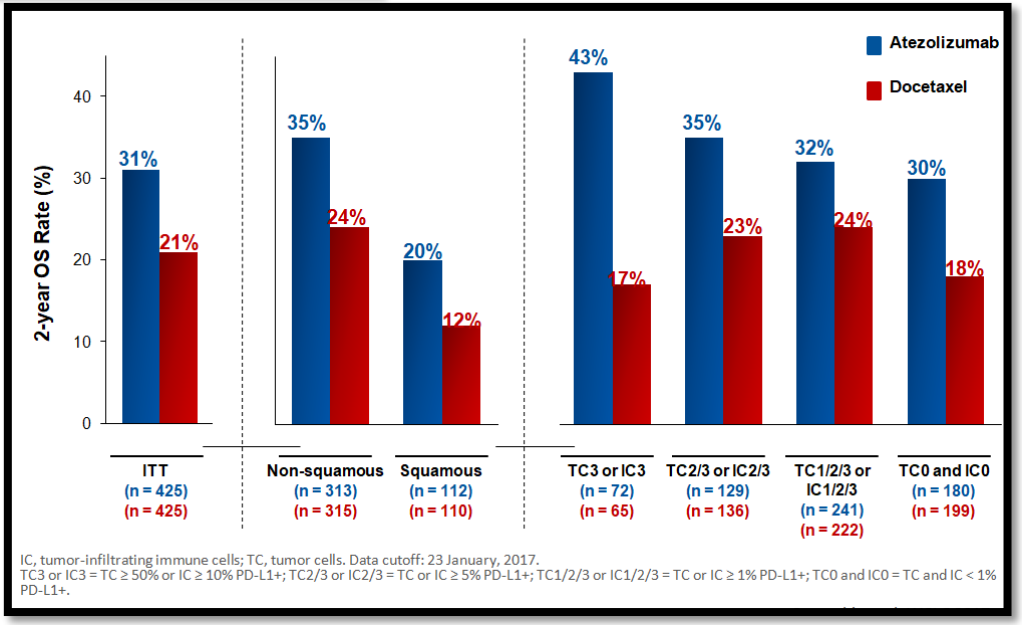
[a]Unstratified HRs.
[b]*P* values for descriptive purpose only.
Histology information from eCRF.
OS, overall survival.

Rittmeyer A, et al. Lancet. 2017;389:255-265.

Barlesi F et al, Annals of Oncology (2016) 27 (6): 1-36. 10.1093 ADAPTED for ESMO PRESENTATION

OAK:
Long-term survival benefit by histology and PD-L1 expression subgroups





IC, tumor-infiltrating immune cells; TC, tumor cells. Data cutoff: 23 January, 2017.
TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+.

Barlesi F et al, Annals of Oncology (2016) 27 (6): 1-36. 10.1093

Satouchi, et al. WCLC 2017

OAK
Safety summary and Treatment-Related AEs

	Atezolizumab n = 609	Docetaxel n = 578
Median treatment duration	3.4 mo[a]	2.1 mo
Patients treated ≥ 12 months	20.5%	2.4%
All Grade AEs, any cause	94%	96%
Treatment-related AEs	64%	86%
Grade 3–4 AEs, any cause	37%	54%
Treatment-related Grade 3–4 AEs	15%	43%
Grade 5 AEs, any cause	2%	2%
Treatment-related Grade 5 AEs	0%	0.2%[b]
AEs leading to treatment withdrawal	8%	19%
AEs leading to dose modification, delay or interruption	25%	36%

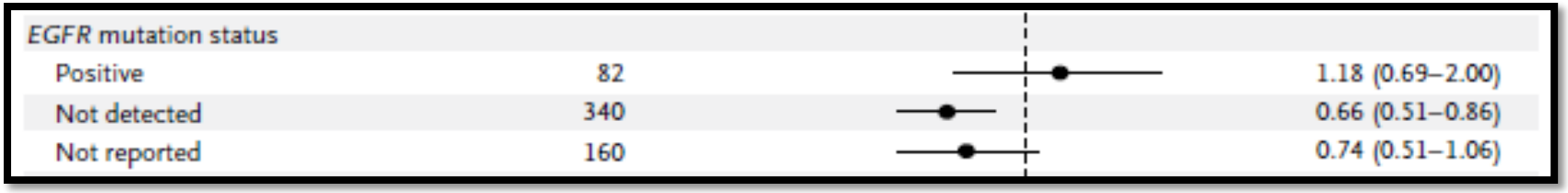
	Atezolizumab n = 609	
Selected immune-mediated AEs	All Grade	Grade 3–4
Pneumonitis	1.0%	0.7%
Hepatitis	0.3%	0.3%
Colitis	0.3%	0%

Barlesi F et al, Annals of Oncology (2016) 27 (6): 1-36. 10.1093 ADAPTED for ESMO PRESENTATION

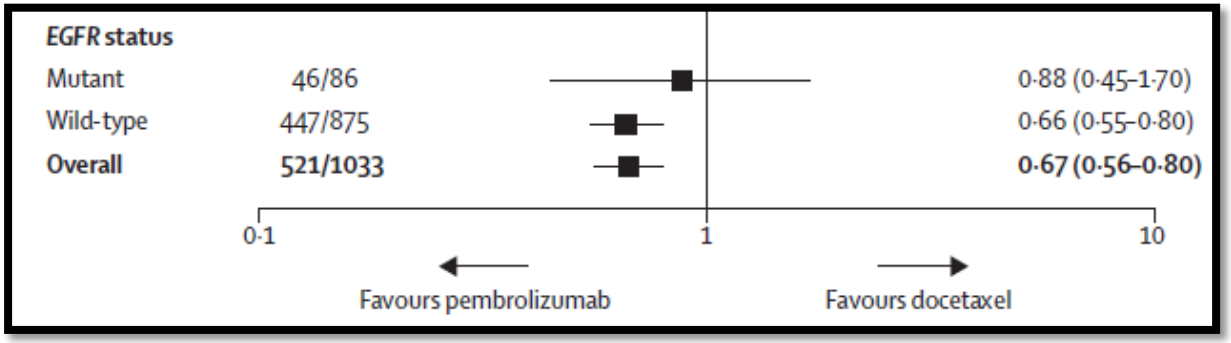
AGENDA

- Immunotherapy post-chemo ("true 2/3L")
- **Immunotherapy in *oncogene addicted* NSCLC (yes/no? when?)**
- Immunotherapy beyond progression ("false 2/3L")
- Conclusions

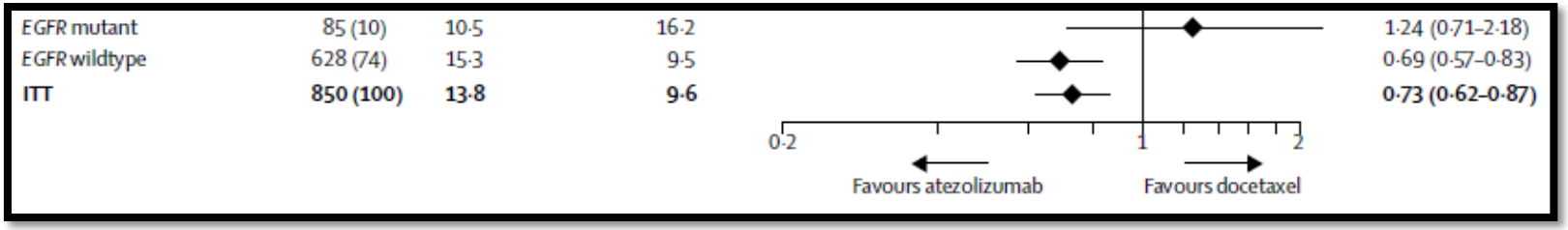
Immunotherapy in *oncogene addicted* Adv NSCLC



NIVO - CM 057, Borghaei et al. NEJM 2015

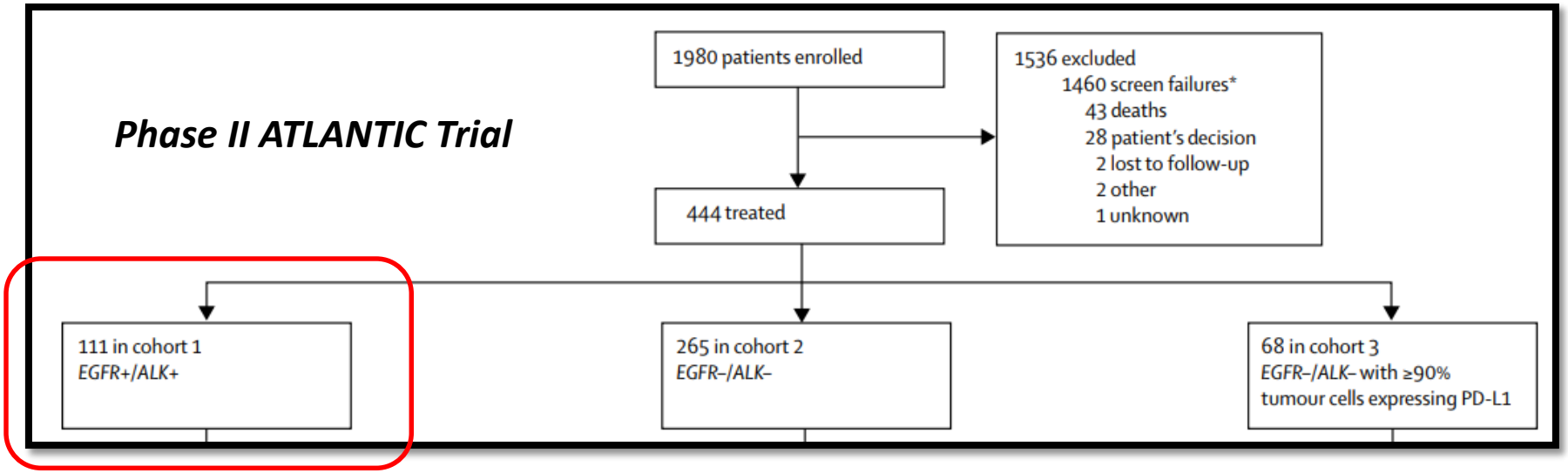


PEMBRO – KN 010, Herbst et al. Lancet 2016



ATEZO – OAK, Rittmeyer et al. Lancet 2017

Immunotherapy in *oncogene addicted* Adv NSCLC

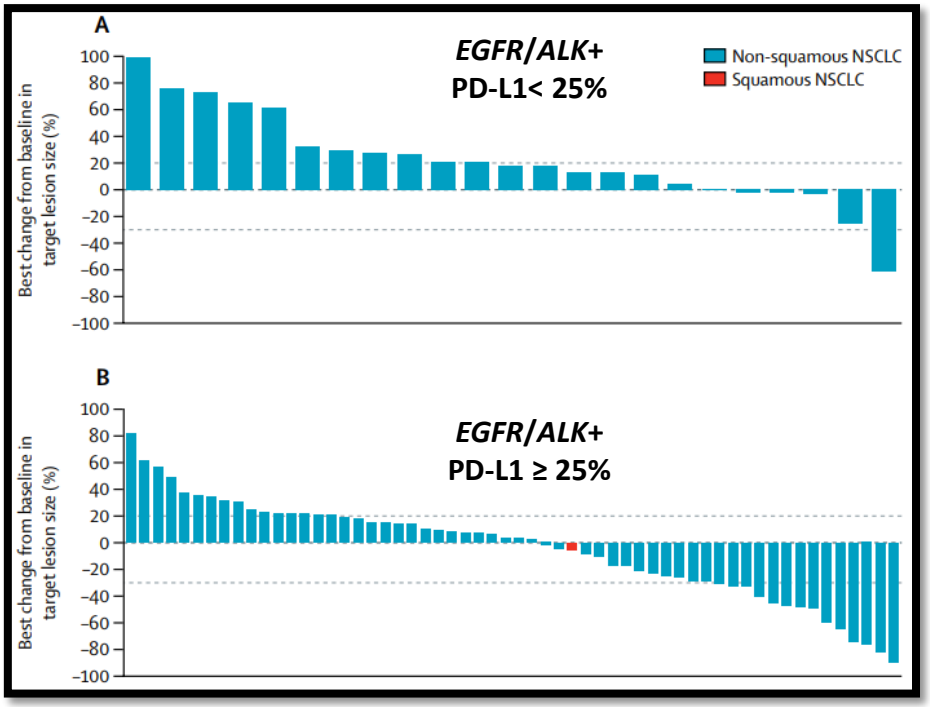


Durvalumab → NSCLC with disease progression following at least two previous systemic regimens, including platinum-based chemotherapy (and tyrosine kinase inhibitor therapy if indicated).

Primary efficacy endpoint: proportion of patients who achieved an objective response.

Garassino MC, et al. Lancet Oncol. 2018;19:521-536.

Immunotherapy in *oncogene addicted* Adv NSCLC



	EGFR+/ALK+ (n = 111)	
	PD-L1 < 25%	PD-L1 ≥ 25%
Evaluable patients, n	28	74
Confirmed ORR, n (%)	1 (3.6)	9 (12.2)
Confirmed DCR at 6 mos, n (%)	2 (7.1)	15 (20.3)
CR, n (%)	0	0
PR, n (%)	1 (4)	9 (12)
SD, n (%)	5 (18)	23 (31)

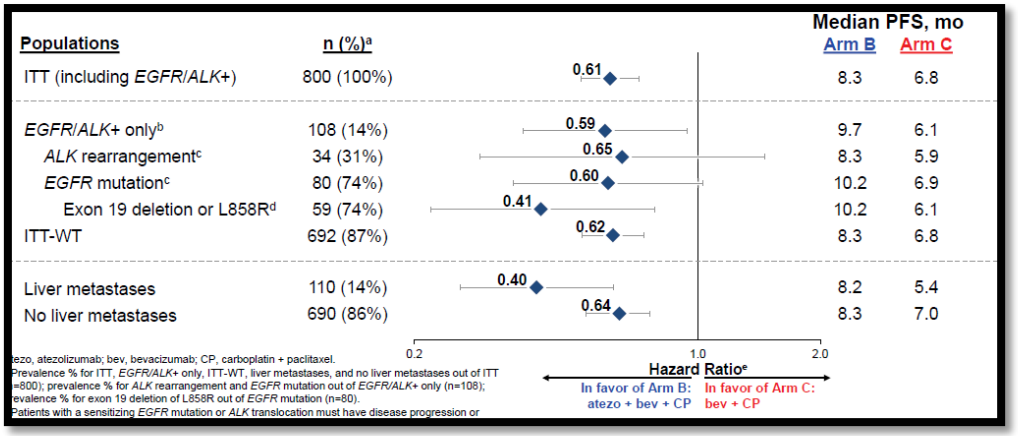
- ORR 12% seen in *EGFR*/*ALK*+ patients with PD-L1 ≥ 25%, but only 4% in those with PD-L1 < 25%
- Among the EGFR+ responders (n = 10), 6 were current/former smokers and 8 had PD-L1 ≥ 90%
- Typically, 26% of *EGFR*+ NSCLC patients have PD-L1 ≥ 25% and 15% have PD-L1 ≥ 90%
- No responses seen in patients with *ALK*+ and PD-L1 ≥ 25% (n = 16)

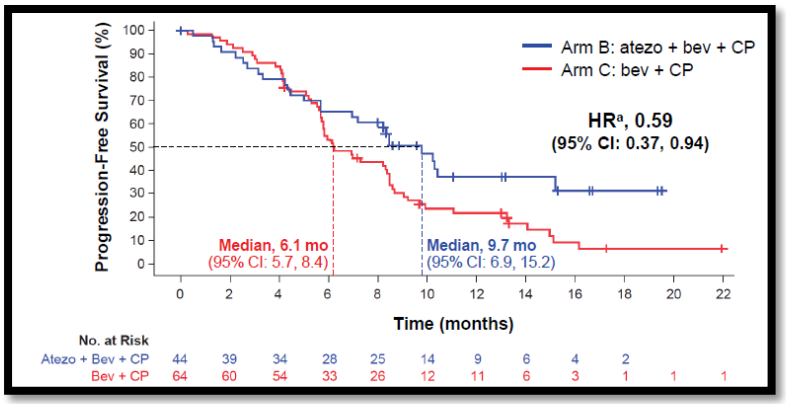
Garassino MC, et al. Lancet Oncol. 2018;19:521-536.

Immunotherapy in *oncogene addicted* Adv NSCLC

- **Upcoming studies**
  - NCT02864251 (CM-722): nivolumab + chemotherapy or nivolumab + ipilimumab vs chemotherapy in *EGFR* mutation–positive NSCLC after TKI
  - KEYNOTE-789: chemotherapy ± pembrolizumab in *EGFR* mutation–positive NSCLC after TKI

- **Unanswered questions**
  - How should *EGFR* mutation–positive patients with PD-L1 expression of 100% be treated?
  - What is the best timing of immunotherapy and TKI in these patients?
  - Is there a role for immunotherapy + chemotherapy after progression on TKI?
  - Is there a role for immunotherapy/TKI combinations?
  - Is there a role for immunotherapy in BRAF or KRAS +ve?
  - What is the role of bevacizumab in the responses seen in IMpower150?





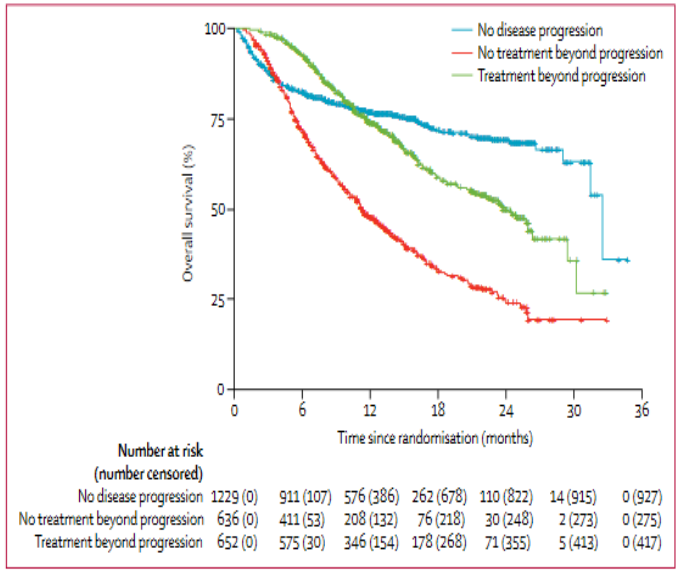
Kowanetz M, et al. AACR 2018. Abstract CT076.

AGENDA

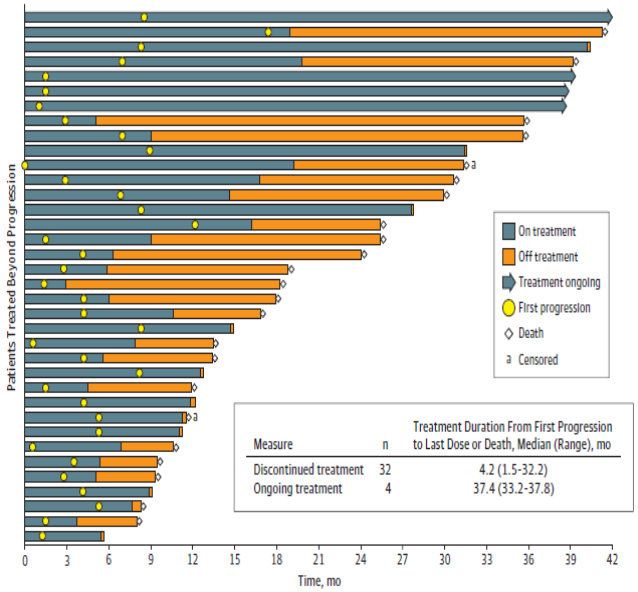
- Immunotherapy post-chemo ("true 2/3L")
- Immunotherapy in *oncogene addicted* NSCLC (yes/no? when?)
- **Immunotherapy beyond progression ("false 2/3L")**
- Conclusions

Immunotherapy beyond progression ("false-2L")

OS in Pooled Melanoma Meta-analysis[1]



Treatment Beyond Progression in RCC[2]

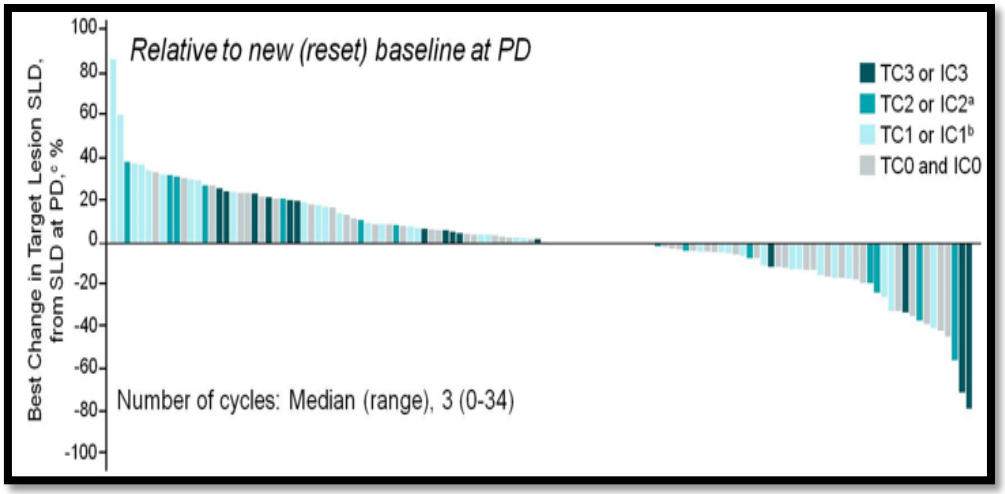


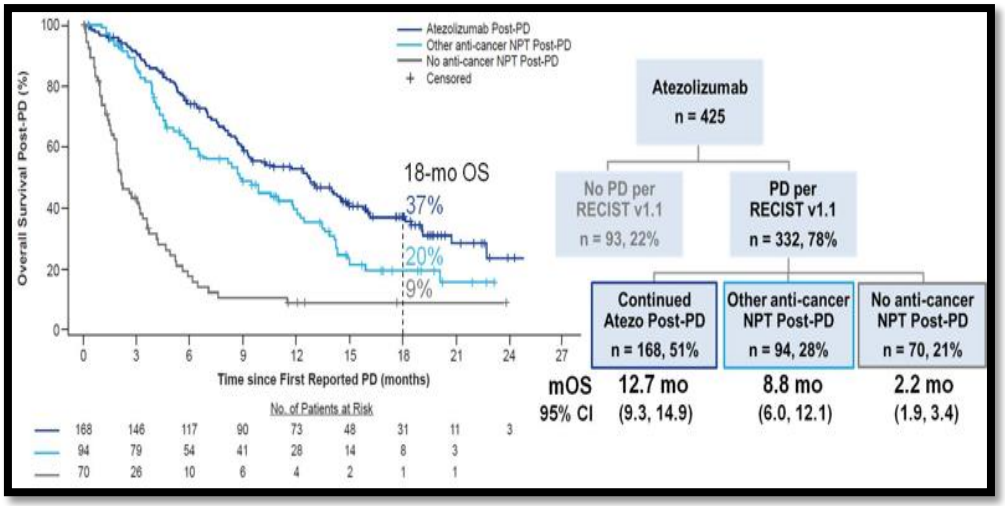
Evidence in other settings suggests immunotherapy may have a survival benefit extending beyond response

- Pooled melanoma meta-analysis: 51% were treated beyond progression, of which 14% had a subsequent PR from disease measurement at time of progression (4% of all patients treated); adverse event profile similar when treating beyond progression
- Subset of a phase II RCC study: 23% were treated beyond progression, of which 69% had subsequent tumor reduction or stabilization

1. Beaver JA, et al. Lancet Oncol. 2018;19:229-239.
2. George S, et al. JAMA Oncol. 2016;2:1179-1186.

Immunotherapy beyond progression: OAK



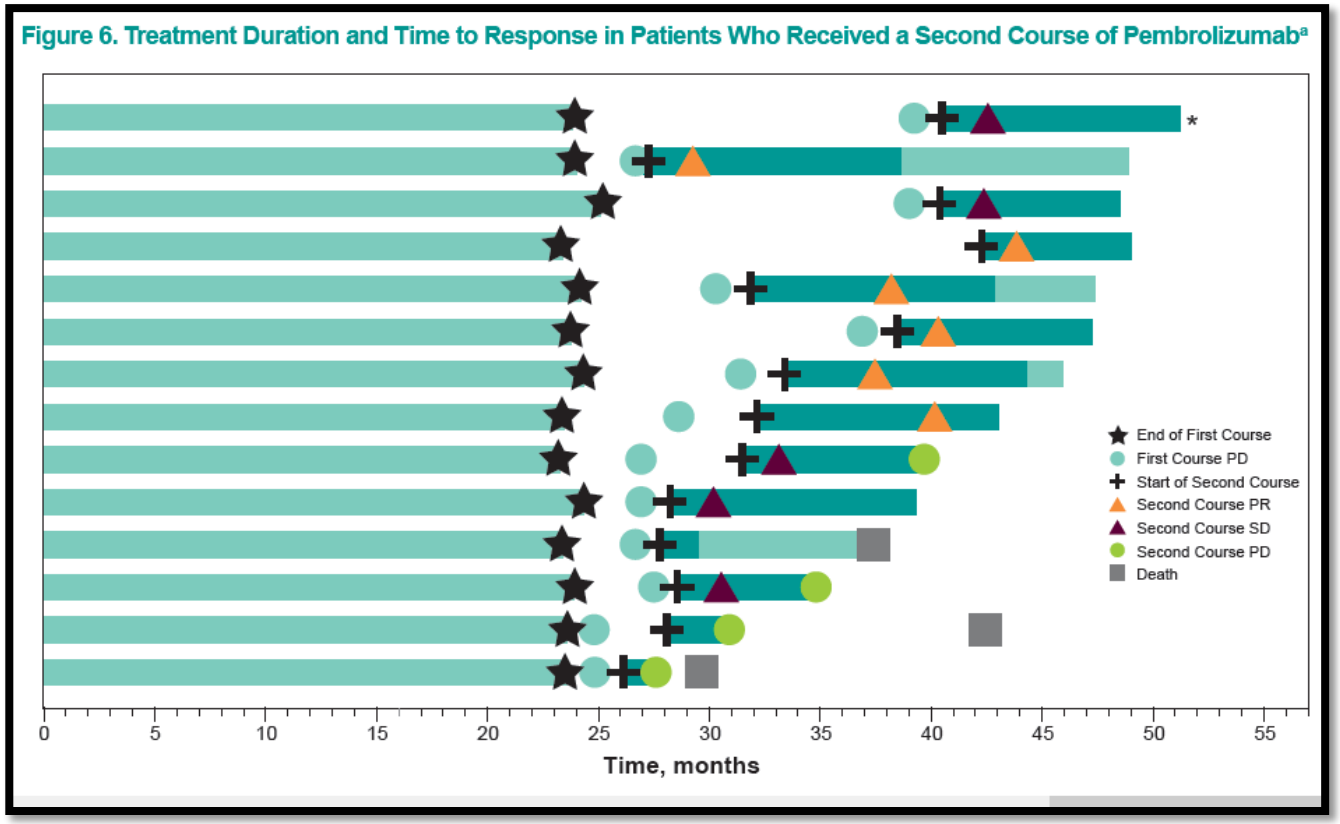


- 40% of pts who progressed on atezo continued beyond progression
  - 7% (12/168) had subsequent PR;
  - 49% (83/168) had SD
- Clinical characteristics similar at baseline and upon progression between those who continued atezo or who switched to new treatments.
- No increased safety risk in those treated beyond progression.

BIAS → Recist Criteria inadequate? (Pseudoprogression?)

Gandara DR, et al. ASCO 2017. Abstract 9001.

Immunotherapy “second course”: KEYNOTE 010



KEYNOTE 010:
14 patients who had progressive disease after stopping pembrolizumab were able to receive a second course of pembrolizumab treatment

Of the 14 patients who received second course pembrolizumab, 6 (43%) had a partial response and 5 (36%) had stable disease per RECIST Criteria.

Herbst RS, ESMO 2018

AGENDA

- Immunotherapy post-chemo ("true 2/3L")
- Immunotherapy in *oncogene addicted* NSCLC (yes/no? when?)
- Immunotherapy beyond progression ("false 2/3L")
- **Conclusions**

Conclusions

Immunotherapy post-chemo ("true 2/3L")

- Use of a PD-1 or PD-L1 antibody in pts with advanced NSCLC after progression on platinum doublet chemotherapy, regardless of histology or level of PD-L1 expression, is associated with better OS and less toxicity compared with single-agent docetaxel.
- Higher levels of PD-L1 expression are associated with higher response rates and better survival in all reported randomized studies.

Immunotherapy in *oncogene addicted* NSCLC

- Role of PD-L1 expression and response to immuno-oncology treatment needs to be defined
- Other treatments should be considered before choosing an IO agent in the second-line setting
- Some EGFR+/ALK+ pts may benefit from IO + chemo combinations, in contrast to the lack of benefit seen with single-agent immunotherapy in this population
- Not enough information is currently available to support the use of combination treatment with 2 immuno-oncology agents or an immuno-oncology agent plus chemotherapy
- Randomized studies are needed to explore regimens, timing, and patient characteristics for possible benefit in this patient subset

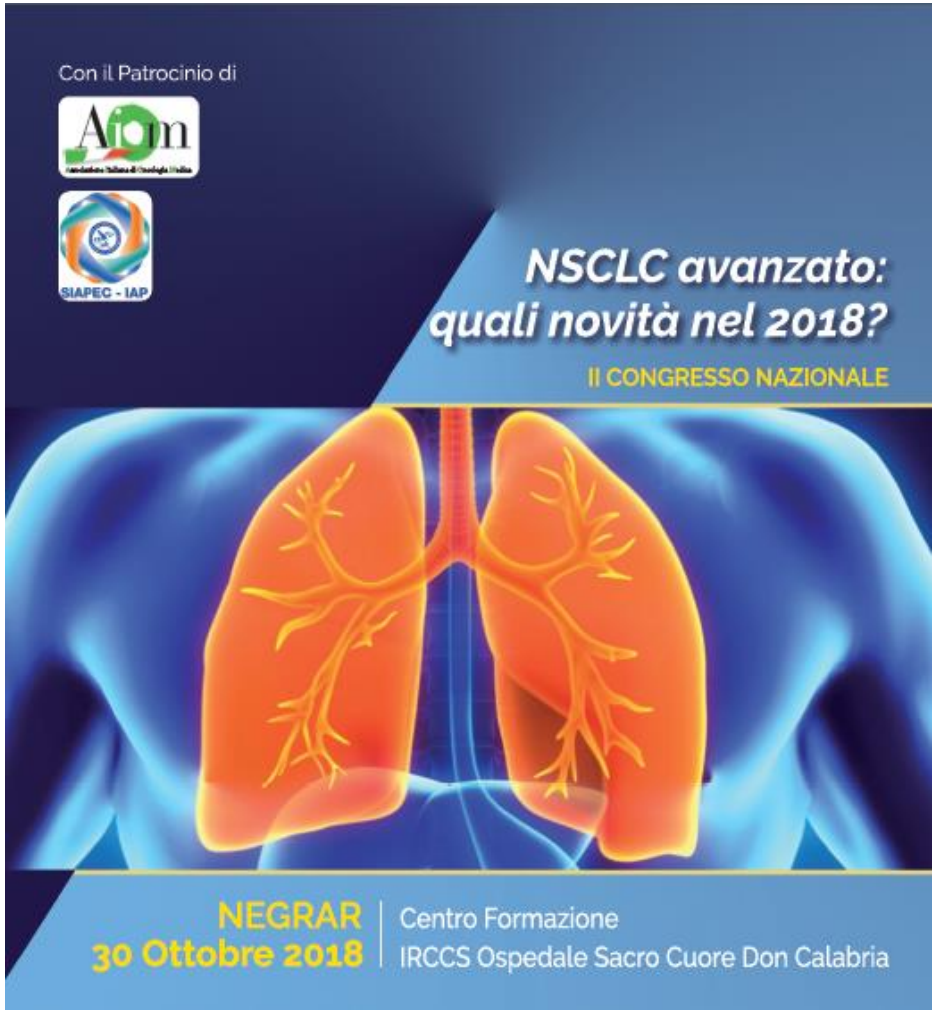
Conclusions

Immunotherapy beyond PD ("false 2/3L")

- We await outcomes of the ongoing trials of treatment after progression on first-line immunotherapy monotherapy or combinations; currently, there is no way to identify patients who will benefit from treatment beyond progression.
- The clinical benefit is crucial to choose whether or not to continue with immunotherapy.
- Role of iRECIST in new trials

Other considerations

- Second-line immunotherapy will become less relevant as more patients receive first-line immunotherapy as single agent or in combinations
- Immunotherapy always and for all patients? → Doce (+/- antiangiogenesis drugs) remains a choice in some situations (eg Adenoca/PDL1<1%/fast PD; autoimmue diseases)



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