Discussion 1 in Proferred papers Thoracic Cancers

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Disclosure

- Thank to the presenters for timely delivery of their slides on the ESMO platform

- Institutional grant: Astra-Zeneca
- Consultant: Astra-Zeneca, MSD, Novartis, Boehringer
- Speaker function: Eli-Lilly, Novartis, Boehringer

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Content

- **Abstract 417O – L. Horn et al. – Checkmate 057**
  - **Phase 3 RCT in relapsed non-squamous NSCLC**
    - **Subgroup analyses and Patient-Reported Outcomes (PROs)**

This article was published on September 27, 2015, at NEJM.org.

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

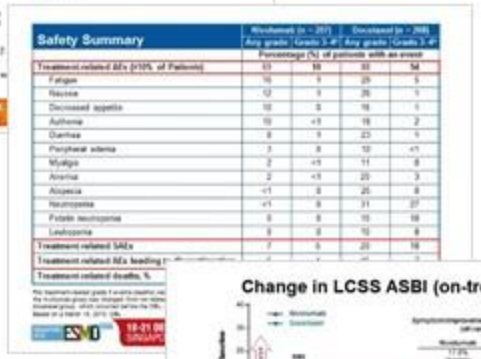
H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

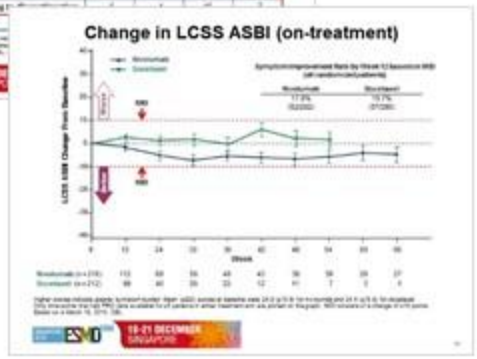
- **Abstract 418O – N. Rizvi et al.**
  - **Phase 1b study in (mostly) pretreated NSCLC (90% non-squamous)**
  - **Durvalumab (MEDI4736) + Tremelimumab**

417O – Checkmate 057 subgroup analysis

- Superior OS vs. docetaxel (HR 0.72)
- Safety profile of nivolumab favorable vs. docetaxel
- Symptom improvement by week 12 similar
  - But curves split later on
- Objective responses across subgroups
  - Magnitude of benefit greater among patients whose tumors express PD-L1

➢ Immunotherapy is becoming a reality in the second-line therapy of NSCLC





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417O – Checkmate 057 subgroup analysis

		Nivolumab		Docetaxel	
		n	ORR,[a] %	n	ORR,[a] %
Overall		292	19	290	12
Age categorization (yrs)	<65 ≥65	184 108	17 22	155 135	13 12
Gender	Male Female	151 141	21 17	168 122	12 13
Baseline ECOG PS[b]	0 1	84 208	24 17	95 194	15 11
CNS metastases	Yes No	34 258	18 19	34 256	6 13
Prior use of maintenance therapy	Yes No	122 170	17 21	111 179	14 11
Time from completion of most recent regimen to randomization	<3 mos ≥3 mos	181 111	18 21	183 107	11 15
Smoking status	Current/Former smoker Never smoked	231 58	22 9	227 60	11 15
EGFR mutation status	Positive Not detected Not reported	44 168 80	11 18 25	38 172 80	16 9 18

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417O – Checkmate 057 subgroup analysis

Benefits documented in PS 0-1 patients

		Nivolumab		Docetaxel	
				n	ORR,[a] %
Overall				290	12
Age categorization (yrs)		184	17	155	13
		108	22	135	12
Gender	Male	151	21	168	12
	Female	141	17	122	13
Baseline ECOG PS[b]	0	84	24	95	15
	1	208	17	194	11
CNS metastases	Yes	34	18	34	6
	No	258	19	256	13
Prior use of maintenance therapy	Yes	122	17	111	14
	No	170	21	179	11
Time from completion of most recent regimen to randomization	<3 mos	181	18	183	11
	≥3 mos	111	21	107	15
Smoking status	Current/Former smoker	231	22	227	11
	Never smoked	58	9	60	15
EGFR mutation status	Positive	44	11	38	16
	Not detected	168	18	172	9
	Not reported	80	25	80	18

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417O – Checkmate 057 subgroup analysis

Benefits documented in PS 0-1 patients

Benefits in patients with CNS metastases

		Nivolumab		Docetaxel	
		n	ORR,[a] %	n	ORR,[a] %
Overall				290	12
Age categorization (yrs)					
Gender	Male				
	Female	141	17	122	13
Baseline ECOG PS[b]	0	84	24	95	15
	1	208	17	194	11
CNS metastases	Yes	34	18	34	6
	No	258	19	256	13
Prior use of maintenance therapy	Yes	122	17	111	14
	No	170	21	179	11
Time from completion of most recent regimen to randomization	<3 mos	181	18	183	11
	≥3 mos	111	21	107	15
Smoking status	Current/Former smoker	231	22	227	11
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417O – Checkmate 057 subgroup analysis

		Nivolumab		Docetaxel	
				n	ORR,[a] %
Overall				290	12
Age categorization (yrs)					
Gender	Female	141	17	122	13
Baseline ECOG PS[b]	1	84 208	24 17	95 194	15 11
CNS metastases	Yes No	34 258	18 19	34 256	6 13
Prior use		122 70	17 21	111 179	14 11
Time fro regimen		81 61	18 21	183 107	11 15
Smoking status	Never smoked	231 58	22 9	227 60	11 15
EGFR mutation status	Positive Not detected Not reported	44 168 80	11 18 25	38 172 80	16 9 18

Benefits documented in PS 0-1 patients

Benefits in patients with CNS metastases

Less benefits in never-smokers or patients with druggable oncogene driver

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Pembrolizumab ph1 [KEYNOTE 001]
> response rates

	PD-L1 ≥50%		PD-L1 1-49%		PD-L1 <1%		Total[a]	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	n	ORR, % (95% CI)	N	ORR, % (95% CI)
Overall	144	38.2 (30.2-46.7)	185	11.9 (7.6-17.4)	80	10.0 (4.4-18.8)	550	20.2 (16.9-23.8)
Never-smoker	29	31.0 (15.3-50.8)	55	5.5 (1.1-15.1)	20	0.0 (0.0-16.8)	135	10.4 (5.8-16.8)

	PD-L1 ≥50%		PD-L1 1-49%		PD-L1 <1%		Total[a]	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	n	ORR, % (95% CI)	N	ORR, % (95% CI)
Overall	144	38.2 (30.2-46.7)	185	11.9 (7.6-17.4)	80	10.0 (4.4-18.8)	550	20.2 (16.9-23.8)
EGFR mutant	20	20.0 (5.7-43.7)	23	8.7 (1.1-28.0)	14	0.0 (0.0-23.2)	77	7.8 (2.9-16.2)

Hellman et al, WCLC 2015

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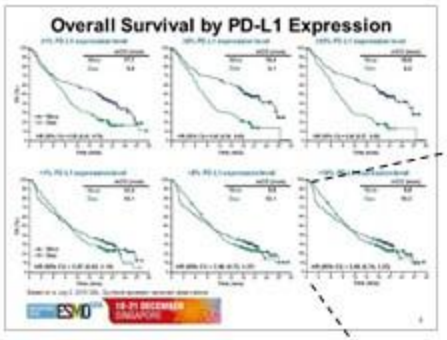
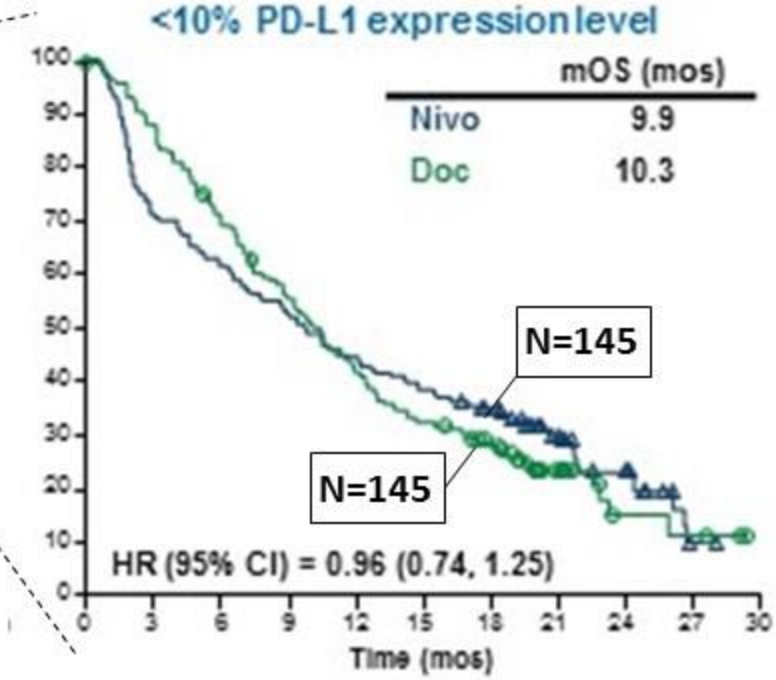
417O – Checkmate 057 subgroup analysis





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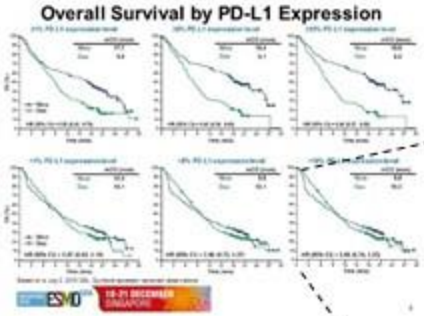
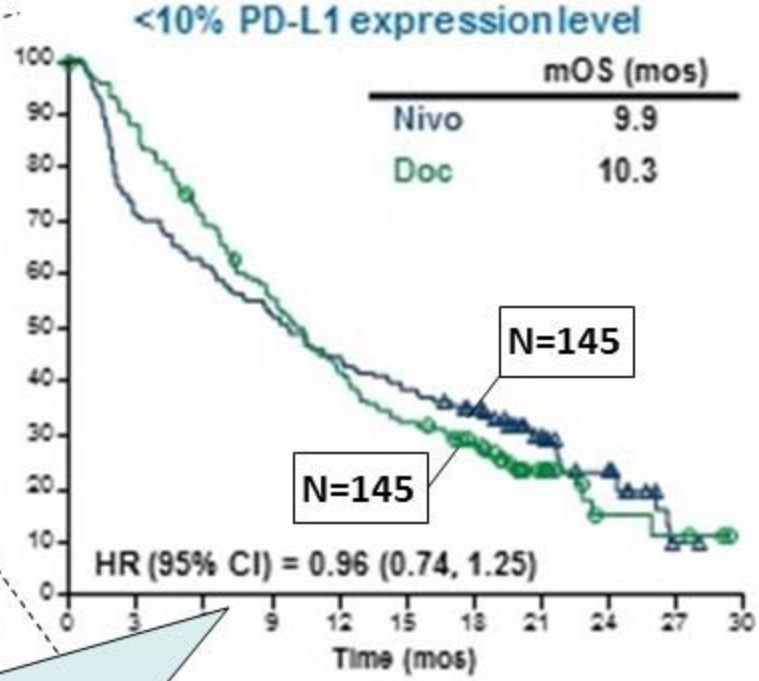
417O – Checkmate 057 subgroup analysis





- In 290 patients, OS is the same with nivolumab and docetaxel
- Nivolumab has less toxicity
- What about “financial toxicity”?

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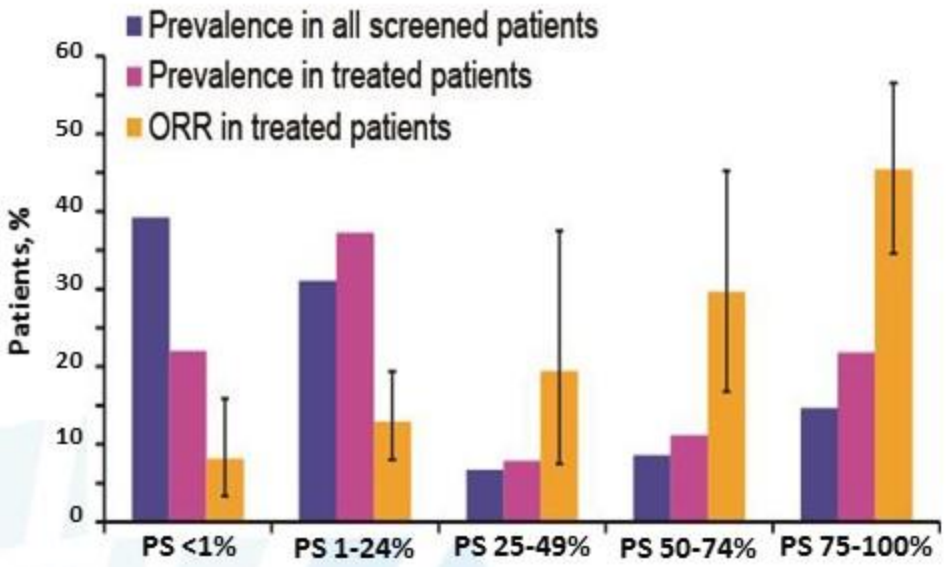
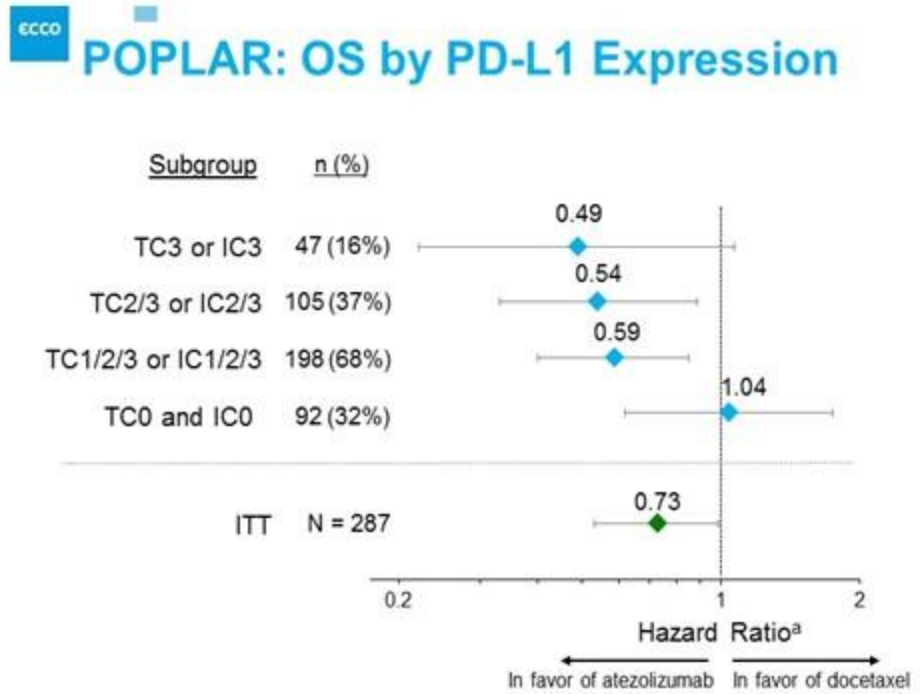
Biomarker PD-L1

> Pembrolizumab ph1 and Atezolimzumab ph2R studies



<1%	1-24%	25-49%	50-74%	75-100%



IHC 0 (TC <1%)	IHC 1 (TC 1-4%)	IHC 2 (TC 5-49%)	IHC 3 (TC≥50%)

Garon et al, N Engl J Med 372:2018-2028, 2015 Suppl Material
Vansteenkiste et al, ESMO 2015

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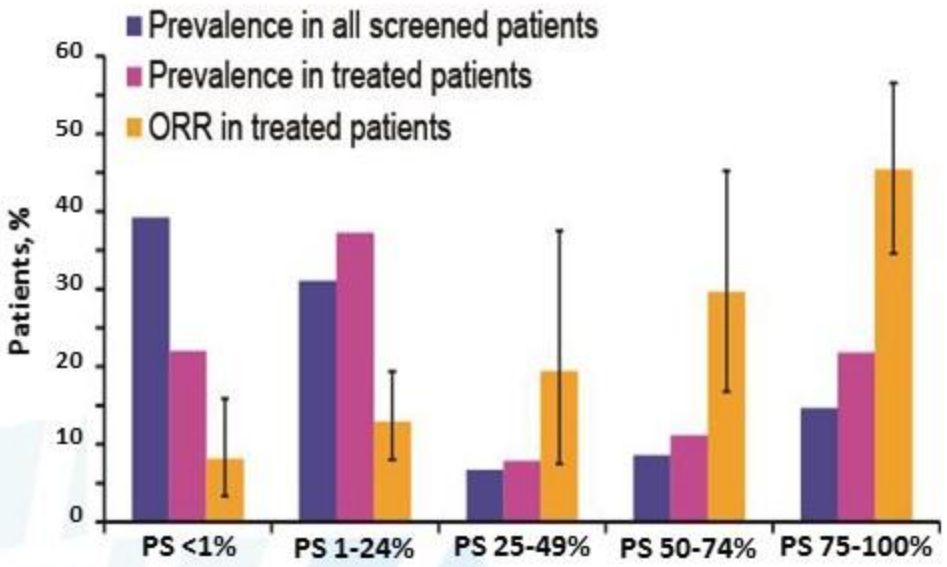
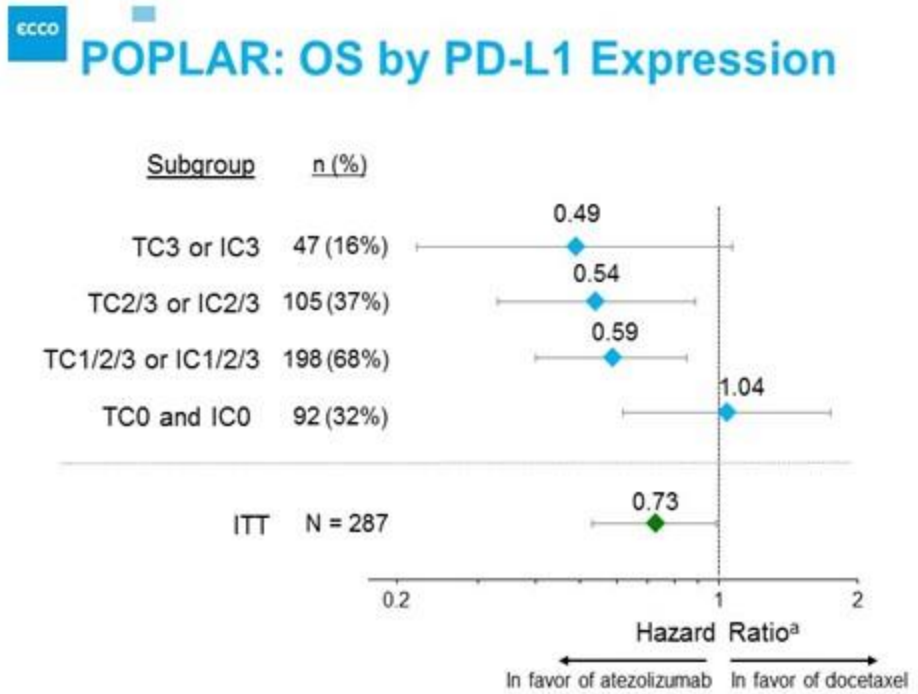
Biomarker PD-L1

> Pembrolizumab ph1 and Atezolimzumab ph2R studies





<1%	1-24%	25-49%	50-74%	75-100%

IHC 0 (TC <1%)	IHC 1 (TC 1-4%)	IHC 2 (TC 5-49%)	IHC 3 (TC≥50%)

- **These are "whole spectrum" information data**
- **What about PD-L1 between 10% and 100% for nivolumab?**

Garon et al, N Engl J Med 372:2018-2028, 2015 Suppl Material
Vansteenkiste et al, ESMO 2015

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NSCLC relapse therapy
> recent studies

Squamous

- **Nivolumab vs Doc:**
  9.2 vs 6.0 months; HR 0.62 (0-48-0.81)
- **Pemetrexed vs Doc**
  6.2 vs 7.4 months; HR 1.56 (0.8-2.26)
- **Doc-Ramucirumab vs Doc**
  9.5 vs 8.2 months; HR 0.88 (0·69–1.13)
- **Doc-Nintedanib vs Doc**
  8.6 vs 8.7 months; HR 1.01 (0.85-1.21)
- **Afatinib vs Erlotinib**
  7.9 vs 6.8 months; HR 0.81 (0.69-0-95)

Brahmer et al, N Engl J Med 2015
Scagliotti al, Clin Lung Cancer 2010
Garon et al, Lancet Oncol 2014
Reck et al, Lancet Oncology 2014
Soria et al, Lancet Oncol 2015

Non-squamous

- **Nivolumab vs Doc:**
  12.2 vs 9.4 months; HR 0.73 (0-59-0.89)
- **Pemetrexed vs Doc**
  9.3 vs 8.0 months; HR 0.78 (0.61-1.00)
- **Doc-Ramucirumab vs Doc**
  11.1 *vs* 9.7 months; HR 0.83 (0.71–0.97)
- **Doc-Nintedanib vs Doc**
  12.6 vs 10.3 months, HR 0.83 (0.70-0.99)

Borghaei et al, N Engl J Med 2015
Scaglotti Clin Lung Cancer 2010
Garon, Lancet Oncol 2014
Reck, Lancet Oncology 2014

Slide adapted from Stahel et al, ESMO 2015

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417O – Checkmate 057 subgroup analysis
> my conclusion

- **Overall, in relapsing nonsq NSCLC, nivolumab compared to docetaxel**
  - **Provides a clinically relevant survival benefit**
  - **Has a better safety profile (but special toxicities need special care)**
  - **Stable or improved PROs are clinically relevant**
- **Subgroups**
  - **Response rates are lower compared to docetaxel in never-smokers and in EGFR driven NSCLC (in line with other anti-PD1/PDL1 datasets)**
  - **PD-L1 acts as a biomarker, not perfect and with need for further refinement and validation (in line with most other anti-PD1/PDL1 datasets)**
  - **Whole spectrum knowledge on the PD-L1 biomarker in Checkmate 057 is of interest in the light of several options for relapsing nonsq NSCLC**

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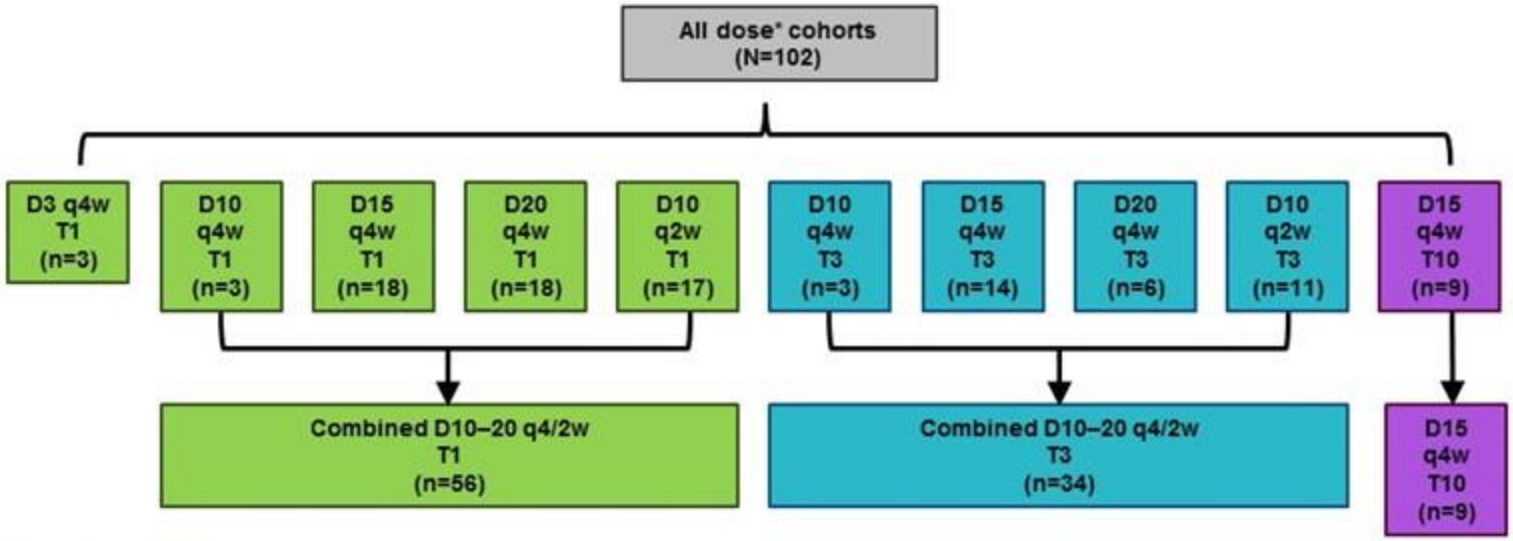
418O – Phase 1b Durvalumab-Tremelimumab



- **Several comparisons in one trial**
  - **Durvalumab: 10mg q4w, 15mg/kg q4w, 20mg/kg q4w, 10mg/kg q2w**
  - **Tremelimub: 1 mg/kg, 3 mg/kg, and 10 mg/kg, all q4w**

- **Median follow-up 18.8 weeks**

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418O – Phase 1b Durvalumab-Tremelimumab

Safety summary

Event, n (%)	D10–20 q4/2w + T1* (n=56)	D10–20 q4/2w + T3 (n=34)	D15 q4w + T10 (n=9)	All cohorts (N=102)
Related AE	41 (73)	32 (94)	8 (89)	82 (80)
Related Grade 3/4 AE	17 (30)	19 (56)	7 (78)	43 (42)
Related death†	2 (4)	1 (3)	0	3 (3)
Related SAE	12 (21)	18 (53)	7 (78)	37 (36)
Related AE leading to discontinuation	9 (16)	15 (44)	5 (56)	29 (28)

- **All cohorts**
  - 42% related grade 3/4 toxicity
  - 3% related death
  - 28% AEs leading to discontinuation
- **Tremelimumab 1mg/kg cohorts**
  - 30% related grade 3/4 toxicity
  - 4% related death
  - 16% AEs leading to discontinuation

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418O – Phase 1b Durvalumab-Tremelimumab

ORR (confirmed + unconfirmed response) by PD-L1 status

PD-L1 status	D10–20 q4/2w T1		All cohorts*		D10 q2w monotherapy†	
	n/N	95% CI	n/N	95% CI	n/N	95% CI
All patients	11/39 (28%)	15–45	21/84 (25%)	16–36	32/200 (16%)	11–22
PD-L1⁺						
≥25%	3/9 (33%)	8–70	7/20 (35%)	15–59	23/84 (27%)	18–38
PD-L1⁻						
<25%	6/23 (26%)	10–48	11/49 (22%)	12–37	5/92 (5%)	2–12
0%	6/12 (50%)	21–79	9/27 (33%)	17–54	1/33 (3%)	0–16
All 2L patients	7/16 (44%)	20–70	15/32 (47%)	29–65	10/54 (19%)	9–31
PD-L1⁺						
≥25%	2/3 (67%)	9 – 99	6/8 (75%)	35–97	8/25 (32%)	15–54
PD-L1⁻						
<25%	4/11 (36%)	11–69	7/18 (39%)	17–64	0/19 (0%)	0–18
0%	4/5 (80%)	28–100	6/8 (75%)	35–97	0/5 (0%)	0–52

Data cut-off: June 1, 2015. Investigator-reported ORR based on RECIST 1.1.
*Eleven of the 84 patients had EGFR or ALK mutations; none of these patients had a response. †Rizvi et al, ASCO 2015 abstract 8032; patients with 12 week follow-up. Response evaluable population includes those with measurable disease at baseline + ≥1 follow-up scan including discontinuations due to disease progression or death without any follow-up scan; all patients were dosed ≥16 weeks prior to data cut-off.
2L, receiving D+T in second line. CI, confidence interval; D, durvalumab; q#w, every # weeks; PD-L1, programmed cell death ligand-1; q#w, every # weeks; T, tremelimumab.

418O – Phase 1b Durvalumab-Tremelimumab

- **Anti PD1/PDL1 strategies established in 2nd line NSCLC**

- **Further development**
  - **1st line setting (versus chemotherapy)**

  - **Combination settings of anti PD1/PDL1 with**
    - **Chemotherapy (little tox overlap)**
    - **TKI (some tox overlap: diarrhea, pneumonitis)**
    - **Vaccines (little tox expected)**
    - **Anti-CTLA4 (inherent tox overlap, including the financial toxicity)**

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418O – Phase 1b Durvalumab-Tremelimumab

- Anti PD1/PDL1 strategies established in 2nd line NSCLC

- Further development
  - 1st line setting (versus chemotherapy)

  - Combination settings of anti PD1/PDL1 with
    - Chemotherapy (little tox overlap)
    - TKI (some tox overlap: diarrhea, pneumonitis)
    - Vaccines (little tox expected)
    - Anti-CTLA4 (inherent tox overlap, including the financial toxicity)

- Is the gain in efficacy in balance with the increased toxicity?

Recent checkpoint inhibitor studies

	Nivo NSQ CHECKM 057 (n=287 imm)	Atezolizumab POPLAR (n=142 imm)	Pembrolizumab KEYNOTE 001 (n=495)	Durvalumab Study 1108 (n=200)
Non-squam	100%	66%	83%	55%
Therapy line	2nd	2nd/3rd	81% pretreated	88% pretreated
Never-smoker	20%	19%	26%	17%

Rizvi et al, ASCO 2015

Garon et al, N Engl J Med 372:2018-2028, 2015

Vansteenkiste et al, ESMO 2015

Spigel et al, ASCO 2015 *and* Brahmer et al, N Engl J Med 373:123-135, 2015

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Recent checkpoint inhibitor studies

	Nivo NSQ CHECKM 057 (n=287 imm)	Atezolizumab POPLAR (n=142 imm)	Pembrolizumab KEYNOTE 001 (n=495)	Durvalumab Study 1108 (n=200)	Nivo+Ipi CHECKM 012 (n=148)	Durva+Treme phase 1 (n=102)
Non-squam	100%	66%	83%	55%	82%	90%
Therapy line	2nd	2nd/3rd	81% pretreated	88% pretreated	1st	94% pretreated
Never-smoker	20%	19%	26%	17%	20%	17%

418O

Rizvi et al, WCLC 2015

Rizvi et al, ASCO 2015

Garon et al, N Engl J Med 372:2018-2028, 2015

Vansteenkiste et al, ESMO 2015

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Recent checkpoint inhibitor studies

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Non-squam	100%		66%		83%		55%		82%	90%
Therapy line	2nd		2nd/3rd		81% pretreated				1st	94% pretreated
Never-smoker	20%		19%		26%		17%		20%	17%
Toxicity	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**		
Total patients with a TR-AE	69%	10%	67%	12%	71%	9.5%	50%	8%		

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Recent checkpoint inhibitor studies

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Non-squam	100%		66%		83%		55%		82%		90%	
Therapy line	2nd		2nd/3rd		81% pretreated				1st		94% pretreated	
Never-smoker	20%		19%		26%		17%		20%		17%	
Toxicity	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Total patients with a TR-AE	69%	10%	67%	12%	71%	9.5%	50%	8%			80%	42%
Anti- CTLA4 low (1mg/kg)									69-77%	19-35%	73%	30%
Anti-CTLA4 high (3mg/kg)											94%	56%

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Non-squam	**100%**		**66%**		**83%**		**55%**		**82%**		**90%**	
Therapy line	**2nd**		**2nd/3rd**		**81% pretreated**				**1st**		**94% pretreated**	
Never-smoker	**20%**		**19%**		**26%**		**17%**		**20%**		**17%**	
Toxicity	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Total patients with a TR-AE	69%	10%	67%	12%	71%	9.5%	50%	8%			80%	42%
Anti- CTLA4 low (1mg/kg)									69-77%	19-35%	73%	30%
Anti-CTLA4 high (3mg/kg)											94%	56%
Activity	**ORR**	**mDur**	**ORR**	**mDur**	**ORR**	**mDur**	**ORR**	**mDur**				
Overall	**19%**	**17.2m**	**15%**	**14.3m**	**18%**	**10.4m**	**16%**	**NR**				
PD-L1 pos	*31%*	*16.0m*	*29%*	*NR*	*44%*	*23.3m*	*23%*	*NR*				
PD-L1 neg	*9%*	*18.3m*	*13%*	*NR*	*9%*	*7.2m*	*5%*	*NR*				
Anti-CTLA4 low												
PD-L1 pos												
PD-L1 neg												

Recent checkpoint inhibitor studies

	Nivo NSQ CHECKM 057 (n=287)		Atezolizumab POPLAR (n=142)		Pembrolizumab KEYNOTE 001 (n=495)		Durvalumab Study 1108 (n=200)		Nivo+Ipi CHECKM 012 (n=148)		Durva+Treme phase 1 (n=102)	
Non-squam	**100%**		**66%**		**83%**		**55%**		**82%**		**90%**	
Therapy line	**2nd**		**2nd/3rd**		**81% pretreated**				**1st**		**94% pretreated**	
Never-smoker	**20%**		**19%**		**26%**		**17%**		**20%**		**17%**	
Toxicity	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Total patients with a TR-AE	69%	10%	67%	12%	71%	9.5%	50%	8%			80%	42%
Anti- CTLA4 low (1mg/kg)									69-77%	19-35%	73%	30%
Anti-CTLA4 high (3mg/kg)											94%	56%
Activity	**ORR**	**mDur**	**ORR**	**mDur**	**ORR**	**mDur**	**ORR**	**mDur**	**ORR**	**mDur**	**ORR**	**mDur**
Overall	**19%**	**17.2m**	**15%**	**14.3m**	**18%**	**10.4m**	**16%**	**NR**				
PD-L1 pos	*31%*	*16.0m*	*29%*	*NR*	*44%*	*23.3m*	*23%*	*NR*				
PD-L1 neg	*9%*	*18.3m*	*13%*	*NR*	*9%*	*7.2m*	*5%*	*NR*				
Anti-CTLA4 low									**13-39%**	**NR**	**28%**	**NR**
PD-L1 pos									*8-48%*	*NR*	*33%*	*NR*
PD-L1 neg									*0-22%*	*NR*	*26%*	*NR*

Recent checkpoint inhibitor studies

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Toxicity	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
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Anti-CTLA4 low									13-39%	NR	28%	NR
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PD-L1 neg									*0-22%*	*NR*	*26%*	*NR*

418O – Phase 1b Durvalumab-Tremelimumab
> my conclusion

- **Combination: interesting and rational concept**
- **Toxicity**
  - **Study confirms that standard dose anti-PD1/PDL1 and anti CTLA4 is hardly feasible in NSCLC**
  - **At lower level anti-CTLA4, grade 3/4 toxicity around 30% with around 15% of the patients discontinued**
- **Efficacy**
  - **Higher with combination, seems mostly by PD-L1 negative groups**
  - **Long-term value still to be established, as studies are to recent to know**
- **Choice of phase 3 dose D20 and T1 q4w is well taken, and clinically welcome**

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Thank you for your kind attention

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