APPLICAZIONI CLINICHE

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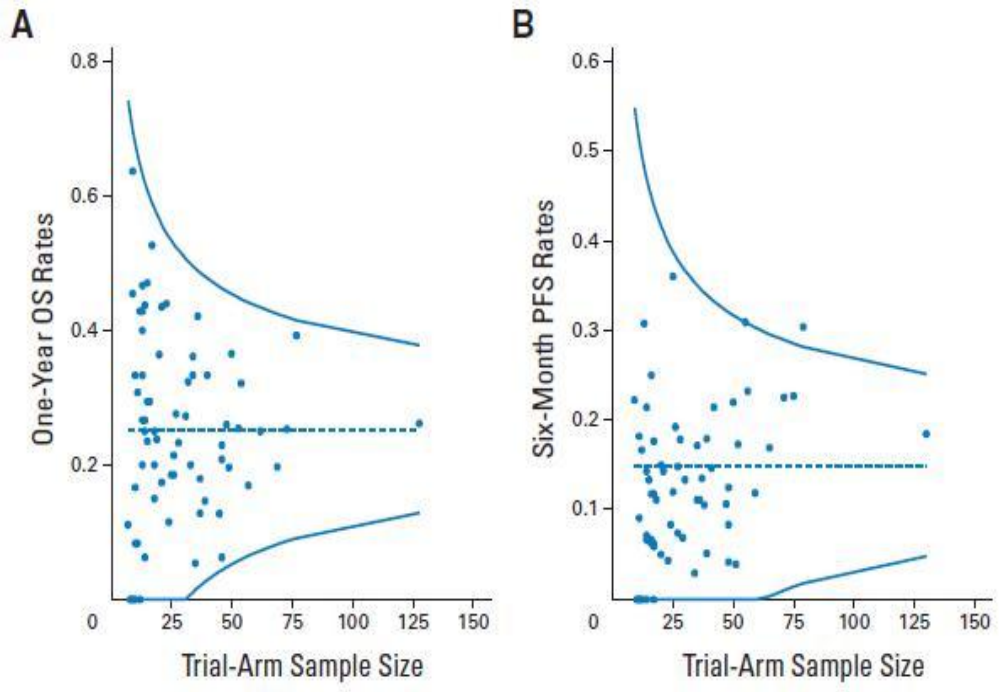
Negrar, 11 novembre 2015

AGENDA

- Anti PD-1 in melanoma (as a model)
  - Single agent
  - Combination immunotherapy
- Anti PD-1 in NSCLC
- Anti PD-1 in renal cell
- Anti PD-L1 (atezolizumab)

Meta-Analysis of Phase II Trials in Metastatic Stage IV Melanoma to Determine Progression-Free and Overall Survival Benchmarks for Future Phase II Trials



Median survival time
6.2 months

Alive at 1 year
25.5%

Median PFS
1.7 months

Progression free at 6 months
14.5%

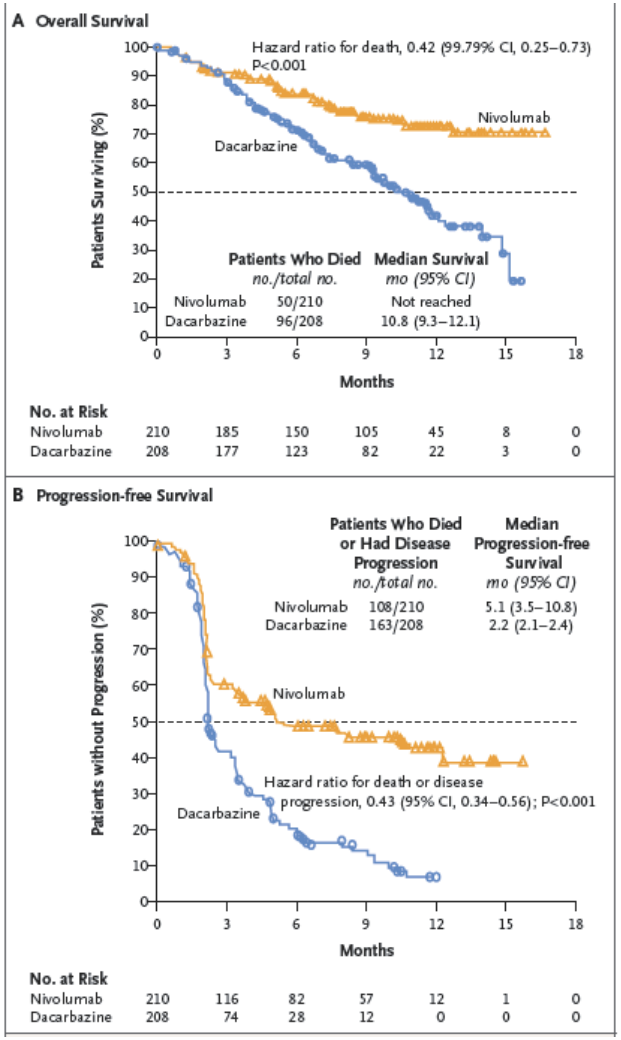
Korn E. et al. J Clin. Oncol. 2008

NIVOLUMAB, first line, BRAF WT

- **Checkmate 066 trial**
  - First line, randomised phase III trial
- Nivolumab 3 mg/Kg q14 vs dacarbazine 1000 mg/sqm q21
  - Double blind
- N=418, BRAF not mut
- Primary endpoint:
  - OS

Robert et al, NEJM 2014

NIVOLUMAB, first line, BRAF WT

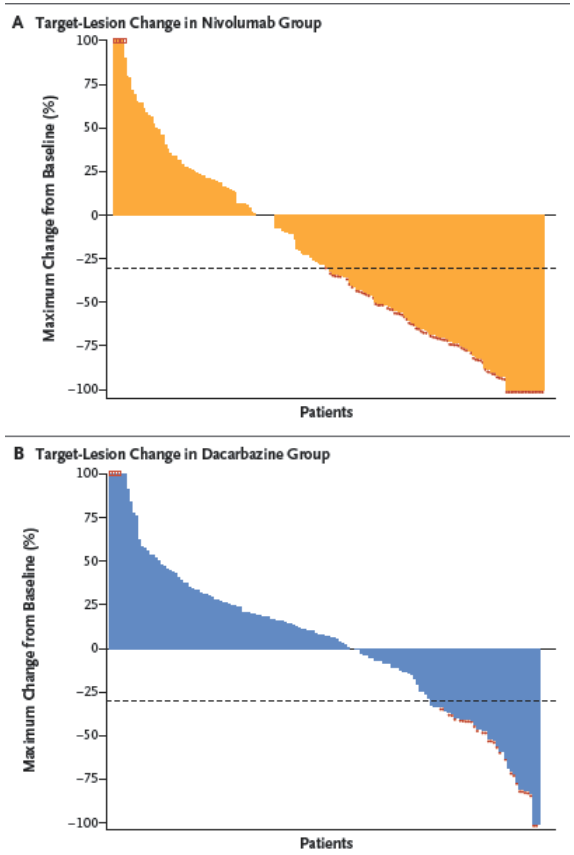


- OS
  - NR vs 10.8 m
    - HR=0.42, 95% CI 0.25-0.73
- PFS
  - 5.1 vs 2.2 m
    - HR=0.43, 95%CI 0.34-0.56

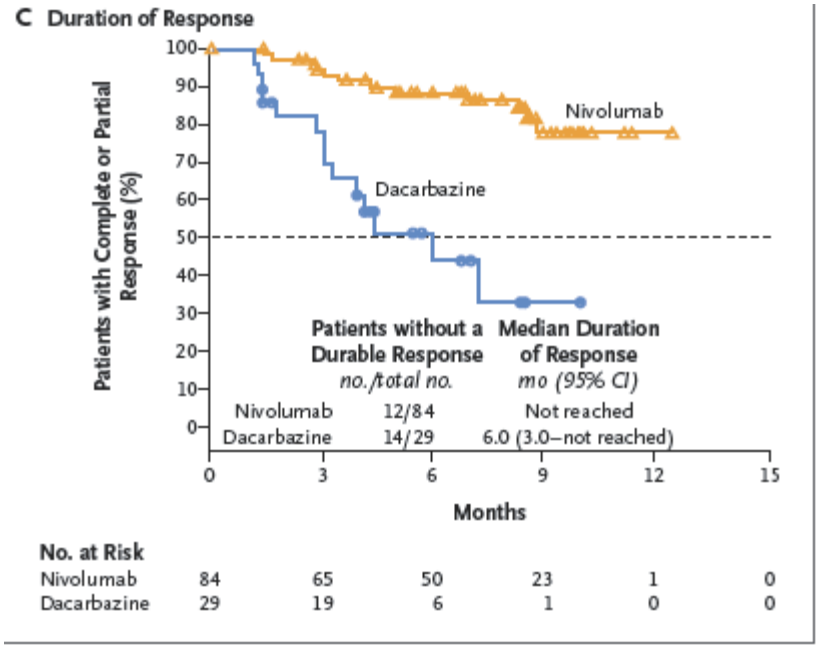
Robert et al, NEJM 2014

NIVOLUMAB, first line, BRAF WT

RR = 40 vs 14%



Duration of response



Robert et al, NEJM 2014

NIVOLUMAB, first line, BRAF WT

- Subgroup analysis PD-L1 expression
  - 35% PD-L1 pos (>5%)
  - Benefit in OS either in PD-L1 pos and neg
    - HR=0.30 vs HR=0.48
  - Higher RR in PD-L1
    - 52.7 vs 33.1%

Robert et al, NEJM 2014

NIVOLUMAB, safety

Table 3. Adverse Events.*

Event	Nivolumab (N=206)		Dacarbazine (N=205)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients with event (%)			
Any adverse event	192 (93.2)	70 (34.0)	194 (94.6)	78 (38.0)
Treatment-related adverse event†	153 (74.3)	24 (11.7)	155 (75.6)	36 (17.6)
Fatigue	41 (19.9)	0	30 (14.6)	2 (1.0)
Pruritus	35 (17.0)	1 (0.5)	11 (5.4)	0
Nausea	34 (16.5)	0	85 (41.5)	0
Diarrhea	33 (16.0)	2 (1.0)	32 (15.6)	1 (0.5)
Rash	31 (15.0)	1 (0.5)	6 (2.9)	0
Vitiligo	22 (10.7)	0	1 (0.5)	0
Constipation	22 (10.7)	0	25 (12.2)	0
Asthenia	21 (10.2)	0	25 (12.2)	1 (0.5)
Vomiting	13 (6.3)	1 (0.5)	43 (21.0)	1 (0.5)
Neutropenia	0	0	23 (11.2)	9 (4.4)
Thrombocytopenia	0	0	21 (10.2)	10 (4.9)
Adverse event leading to discontinuation of treatment	14 (6.8)	12 (5.8)	24 (11.7)	19 (9.3)
Serious adverse event				
Any event	64 (31.1)	43 (20.9)	78 (38.0)	54 (26.3)
Treatment-related event	19 (9.2)	12 (5.8)	18 (8.8)	12 (5.9)

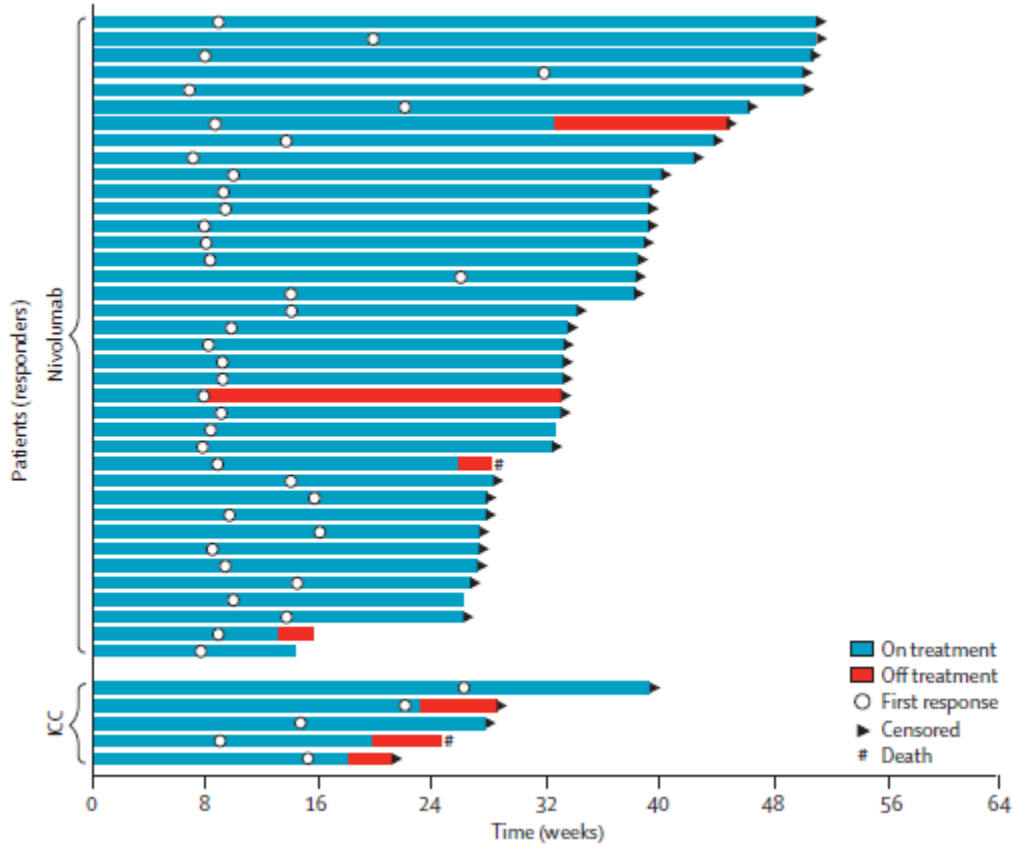
Robert et al, NEJM 2014

NIVOLUMAB, ipi pretreated

- **Checkmate 037 trial**
  - Open label, phase III
- Nivolumab 3 mg/Kg q14 vs CT
  - after ipilimumab (and BRAF inhibitor)
    - 272 vs 133 pts
- Primary endpoint
  - RR

Weber et al, Lancet Oncol 2015

NIVOLUMAB, ipi pretreated



RR

- 31.7 vs 10.8%

Duration of response

- NR vs 3.5 m

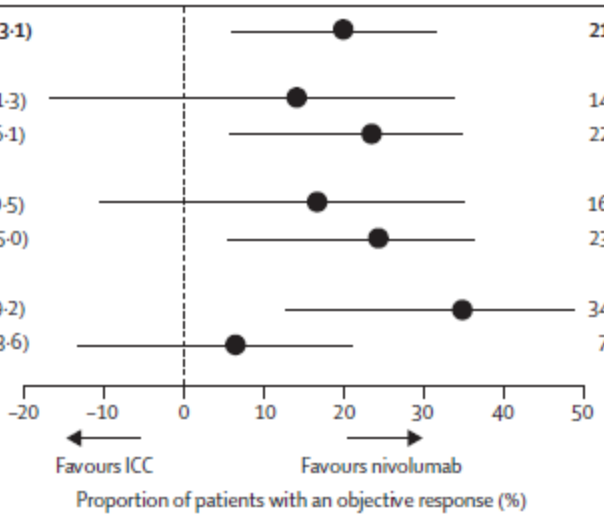
Time to response

- 2.1 vs 3.5 m

Weber et al, Lancet Oncol 2015

NIVOLUMAB, ipi pretreated

	n	Objective response % (95% CI)		Proportion of patients with an objective response % (95% CI)
		Nivolumab	ICC	
Overall	**167**	**31·7 (23·5 to 40·8)**	**10·6 (3·5 to 23·1)**	**21·0 (6·8 to 31·7)**
***BRAF* status**				
Mutant	37	23·1 (9·0 to 43·6)	9·1 (0·2 to 41·3)	14·0 (–17·1 to 34·4)
Wild-type	130	34·0 (24·6 to 44·5)	11·1 (3·1 to 26·1)	22·9 (6·2 to 35·0)
Previous ipilimumab benefit				
Yes	55	30·0 (16·6 to 46·5)	13·3 (1·7 to 40·5)	16·7 (–10·6 to 34·8)
No	112	32·5 (22·4 to 43·9)	9·4 (2·0 to 25·0)	23·1 (5·6 to 35·6)
PD-L1 status				
Positive	77	43·6 (30·3 to 57·7)	9·1 (1·1 to 29·2)	34·5 (12·2 to 49·2)
Negative	87	20·3 (11·3 to32·2)	13·0 (2·8 to 33·6)	7·3 (–13·4 to 21·5)



Weber et al, Lancet Oncol 2015

PEMBROLIZUMAB, first line

- **Keynote 006**
  - Pembrolizumab vs ipilimumab in first-line advanced melanoma
- Phase III trial
  - Pembro 10 mg/Kg q14, Pembro 10 mg/Kg q21, Ipi 3 mg/Kg q21
- N=834 pts advanced melanoma
  - *Not selected for BRAF status*
- Primary endpoint
  - OS and PFS

Robert et al, NEJM 2015

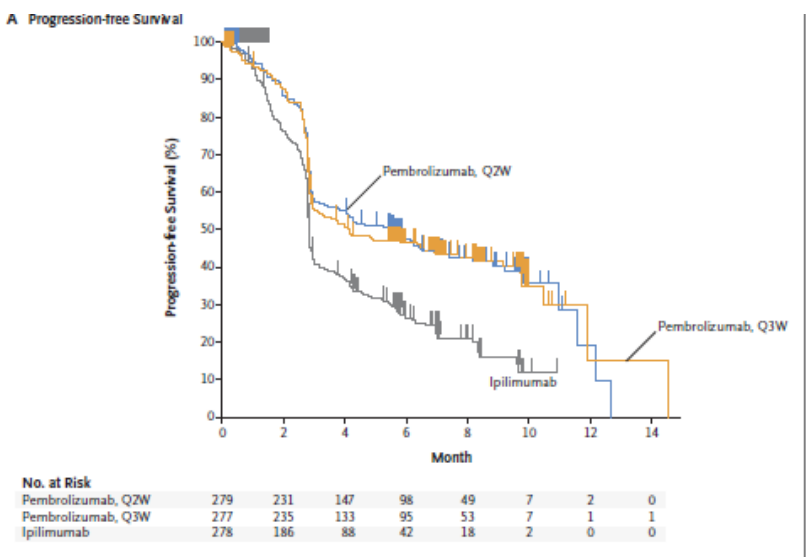
PEMBROLIZUMAB, first line

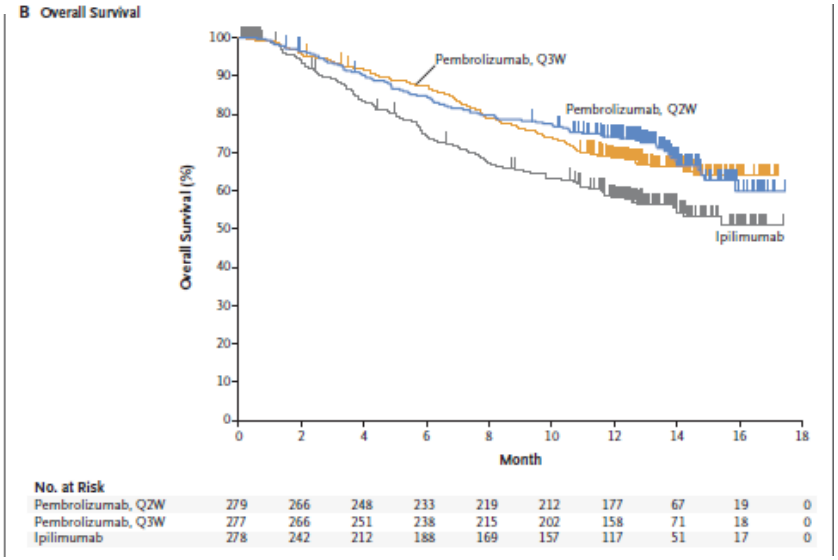
PFS: 5.5 vs 4.1 vs 2.1 m

HR=0.58, p<0.001

OS: 74 vs 68 vs 58% at 12m

OR=0.69, p=0.003





Benefit in PDL-1 pos and neg

Robert C et al, NEJM 2015

PEMBROLIZUMAB, safety

Table 2. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Every 2 Wk (N=278)		Pembrolizumab Every 3 Wk (N=277)		Ipilimumab (N=256)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)					
Related to treatment*						
Any	221 (79.5)	37 (13.3)	202 (72.9)	28 (10.1)	187 (73.0)	51 (19.9)
Occurring in ≥10% of patients in any study group						
Fatigue	58 (20.9)	0	53 (19.1)	1 (0.4)	39 (15.2)	3 (1.2)
Diarrhea	47 (16.9)	7 (2.5)	40 (14.4)	3 (1.1)	58 (22.7)	8 (3.1)
Rash	41 (14.7)	0	37 (13.4)	0	37 (14.5)	2 (0.8)
Pruritus	40 (14.4)	0	39 (14.1)	0	65 (25.4)	1 (0.4)
Asthenia	32 (11.5)	1 (0.4)	31 (11.2)	0	16 (6.3)	2 (0.8)
Nausea	28 (10.1)	0	31 (11.2)	1 (0.4)	22 (8.6)	1 (0.4)
Arthralgia	26 (9.4)	0	32 (11.6)	1 (0.4)	13 (5.1)	2 (0.8)
Vitiligo	25 (9.0)	0	31 (11.2)	0	4 (1.6)	0
Adverse event of special interest†						
Hypothyroidism	28 (10.1)	1 (0.4)	24 (8.7)	0	5 (2.0)	0
Hyperthyroidism	18 (6.5)	0	9 (3.2)	0	6 (2.3)	1 (0.4)
Colitis	5 (1.8)	4 (1.4)	10 (3.6)	7 (2.5)	21 (8.2)	18 (7.0)
Hepatitis	3 (1.1)	3 (1.1)	5 (1.8)	5 (1.8)	3 (1.2)	1 (0.4)
Hypophysitis	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)	6 (2.3)	4 (1.6)
Pneumonitis	1 (0.4)	0	5 (1.8)	1 (0.4)	1 (0.4)	1 (0.4)
Type 1 diabetes mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0
Uveitis	1 (0.4)	0	3 (1.1)	0	0	0
Myositis	0	0	2 (0.7)	0	1 (0.4)	0
Nephritis	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)

Robert C et al, NEJM 2015

NIVOLUMAB + IPILIMUMAB

- Randomised first line phase II trial, double blind
  - Nivolumab 1 mg/kg + Ipilimumab 3 mg/Kg q21 x 4
  - Ipilimumab 3 mg/Kg q21 x4
- 142 pts (109 BRAF wt and 33 BRAF mut)
- Primary endpoint
  - RR in BRAF wild-type cohort

Postow et al NEJM 2015

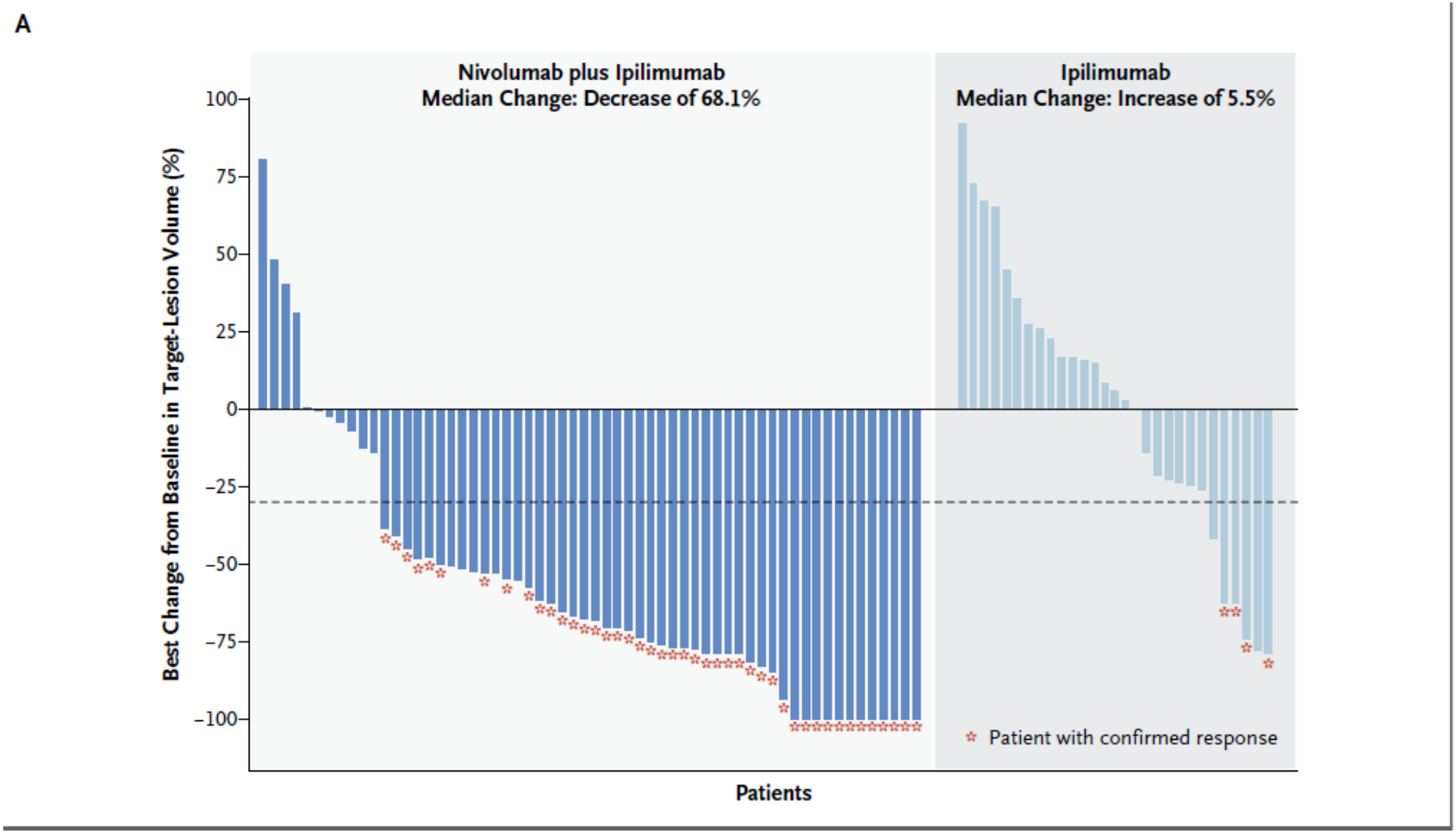
NIVOLUMAB+IPILIMUMAB

Table 2. Response to Treatment.

Variable	Patients with *BRAF* Wild-Type Tumors		Patients with *BRAF* V600 Mutation–Positive Tumors	
	Nivolumab plus Ipilimumab (N=72)	Ipilimumab (N=37)	Nivolumab plus Ipilimumab (N=23)	Ipilimumab (N=10)
Best overall response — no. (%)*				
Complete response	16 (22)	0	5 (22)	0
Partial response	28 (39)	4 (11)	7 (30)	1 (10)
Stable disease	9 (12)	13 (35)	3 (13)	1 (10)
Progressive disease	10 (14)	15 (41)	5 (22)	7 (70)
Could not be determined	9 (12)	5 (14)	3 (13)	1 (10)
Patients with objective response — no. (% [95% CI])†	44 (61 [49–72])	4 (11 [3–25])	12 (52 [31–73])	1 (10 [0–45])

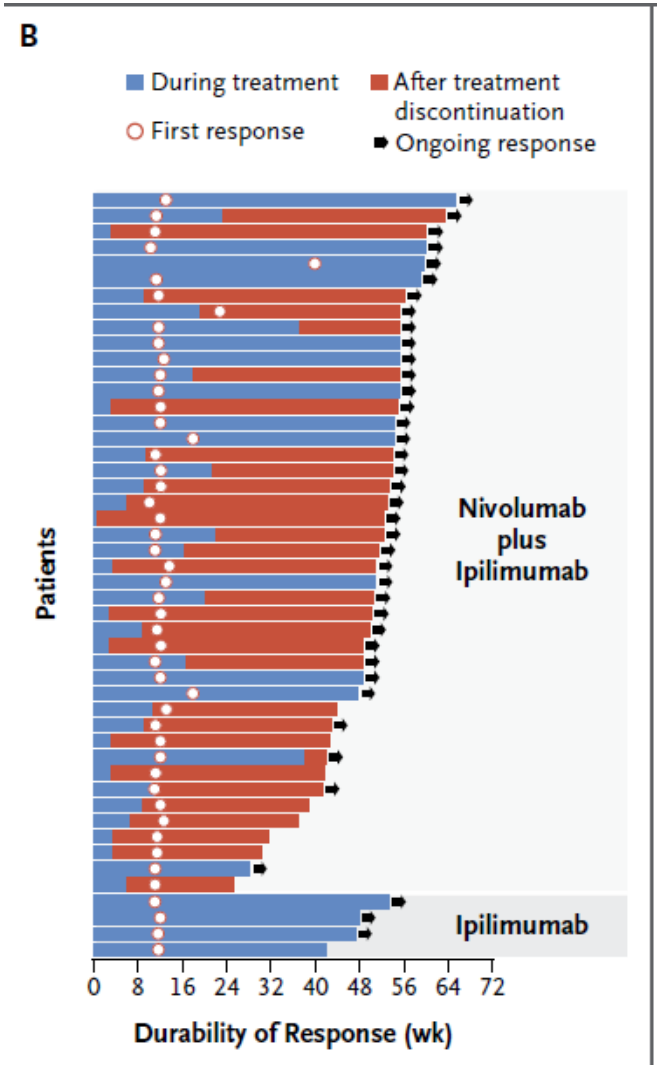
Postow et al NEJM 2015

NIVOLUMAB+IPILIMUMAB



Postow et al NEJM 2015

NIVOLUMAB+IPILIMUMAB



Postow et al NEJM 2015

NIVOLUMAB + IPILIMUMAB vs IPILIMUMAB

- Nivolumab+ipilimumab vs ipilimumab vs nivolumab
  - **Phase III, checkmate 067 trial**
  - First-line, advanced melanoma

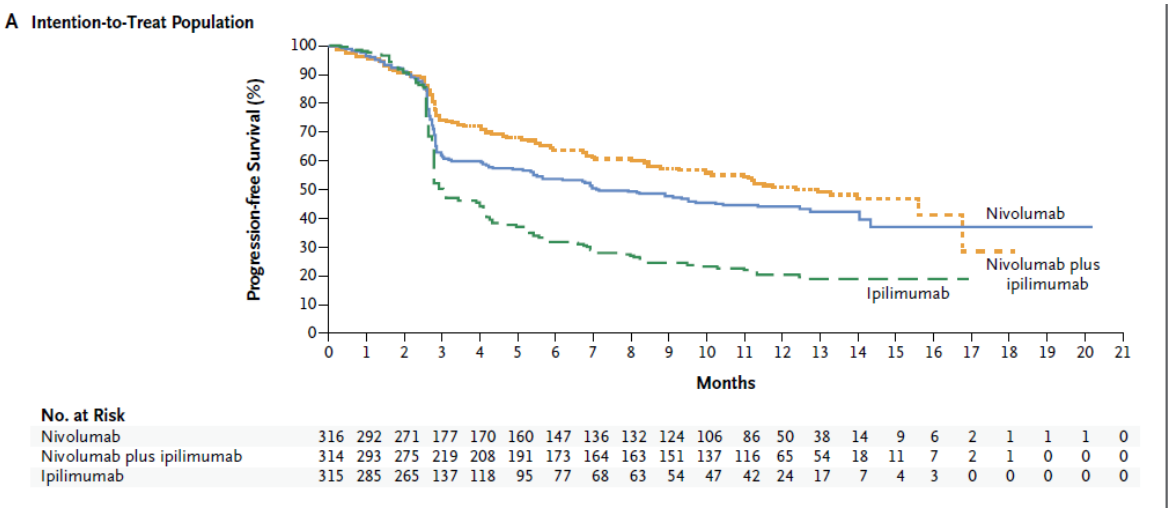
- 1296 pts
  - Stratification: PD-L1, BRAF, stage (M1a/b vs M1c)

- Primary endpoint
  - PFS
  - OS

Larkin et al, NEJM 2015

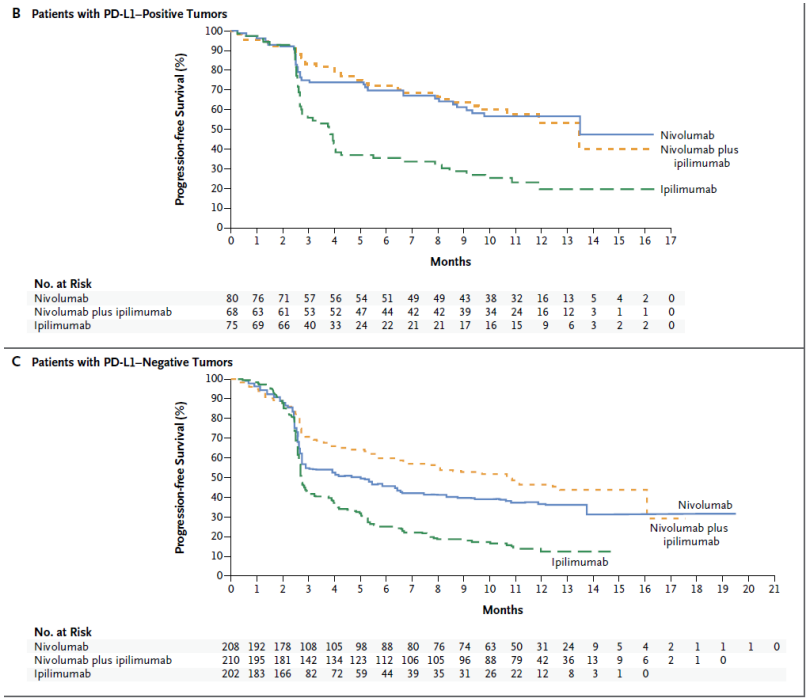
NIVOLUMAB + IPILIMUMAB vs IPILIMUMAB

- PFS
  - Ipi+Nivo: 11.5 m
  - Nivo: 6.9m
  - Ipi: 2.9m
    - HR for N+I vs I: 0.42 (99.5%CI 0.31-0.57)
    - HR for N vs I: 0.57 (99.5%CI 0.43-0.76)



Larkin et al, NEJM 2015

NIVOLUMAB + IPILIMUMAB vs IPILIMUMAB



- PFS according to
  - PDL-1 status
    - Higher benefit of combo in PD-L1 neg
      - Comparable PFS and RR with nivolumab vs combo in PD-L1 pos
  - BRAF status
    - Similar efficacy of combo in BRAF mut or wt

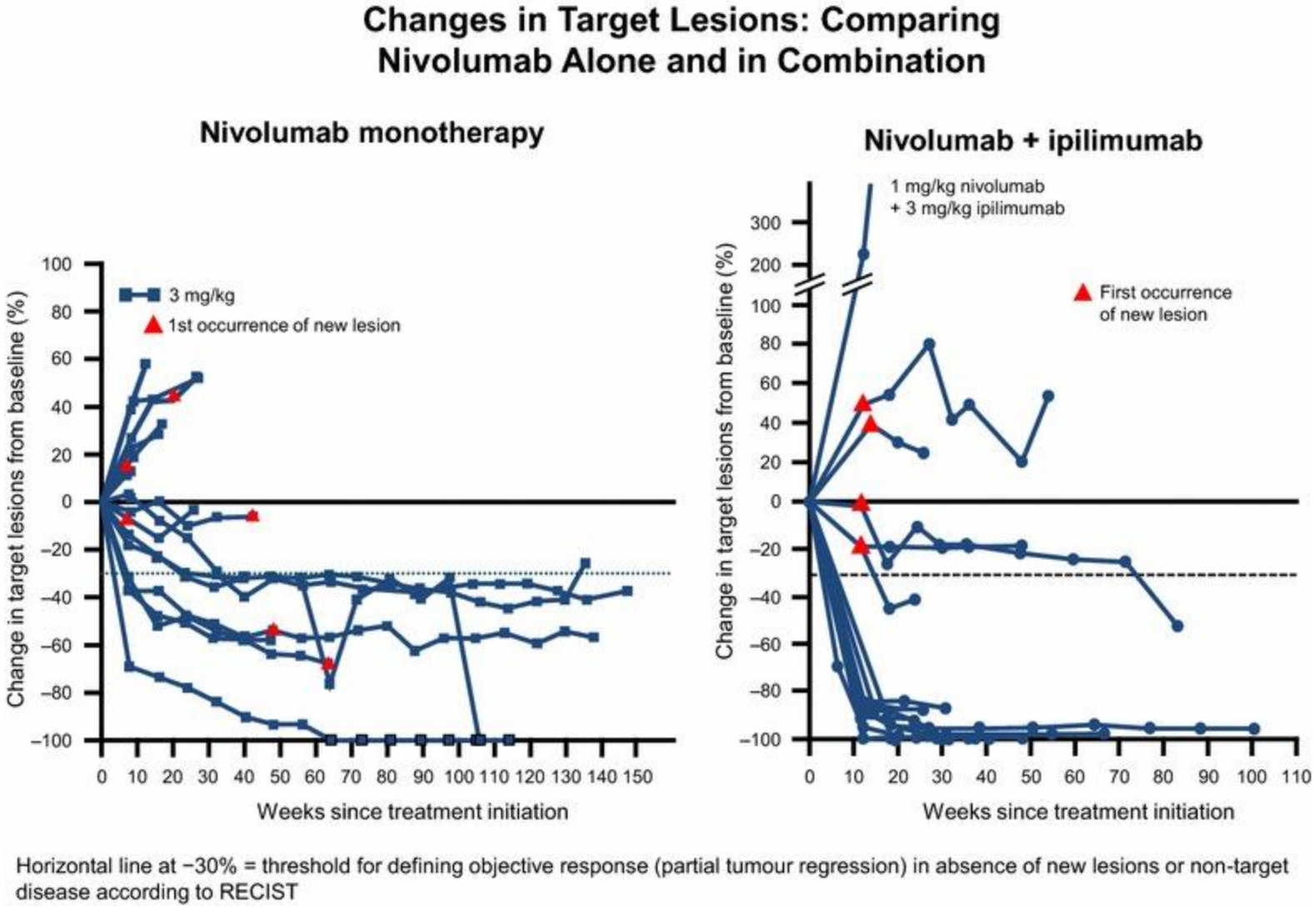
Larkin et al, NEJM 2015

NIVOLUMAB + IPILIMUMAB

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

Larkin et al, NEJM 2015



Ascierto et al, J Transl Med 2015

SECOND LINE NSCLC

- Erlotinib
  - mOS: 6.7 m

- Docetaxel = pemetrexed
  - mOS: 8.3 vs 7.9 m

Hanna et al, JCO 2004

- Docetaxel + nindetanib vs docetaxel
  - Benefit in mOS only in adeno: 12.6 vs 10.3 m

Reck M et al, Lancet Oncol 2014

- Docetaxel + ramucirumab vs docetaxel
  - mOS: 10.5 vs 9.1m

Garon EB et al, Lancet 2014

NIVOLUMAB IN SQUAMOUS NSCLC

- **Checkmate 017 trial**
  - Phase III, second line
  - Nivolumab 3 mg/Kg q14 vs docetaxel 75 mg/sqm q21
  - 272 pts

- **Primary endpoint**
  - OS

Brahmer et al, NEJM 2015

NIVOLUMAB IN SQUAMOUS NSCLC

- **OS**
  - Median 9.2 vs 6 m
    - HR=0.59 (05% CI 0,44-0,79)
    - Alive at 1 year: 42 vs 24%

Early separation

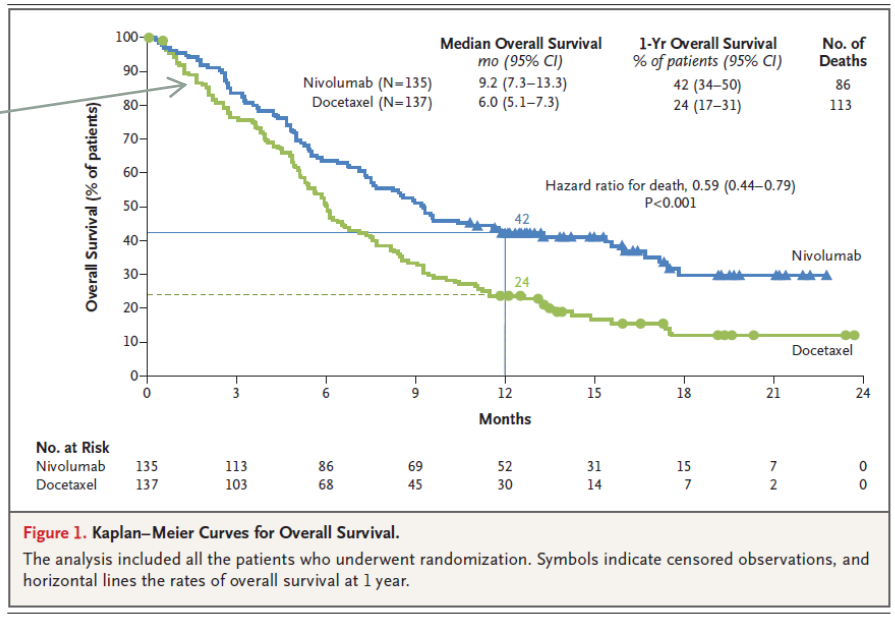
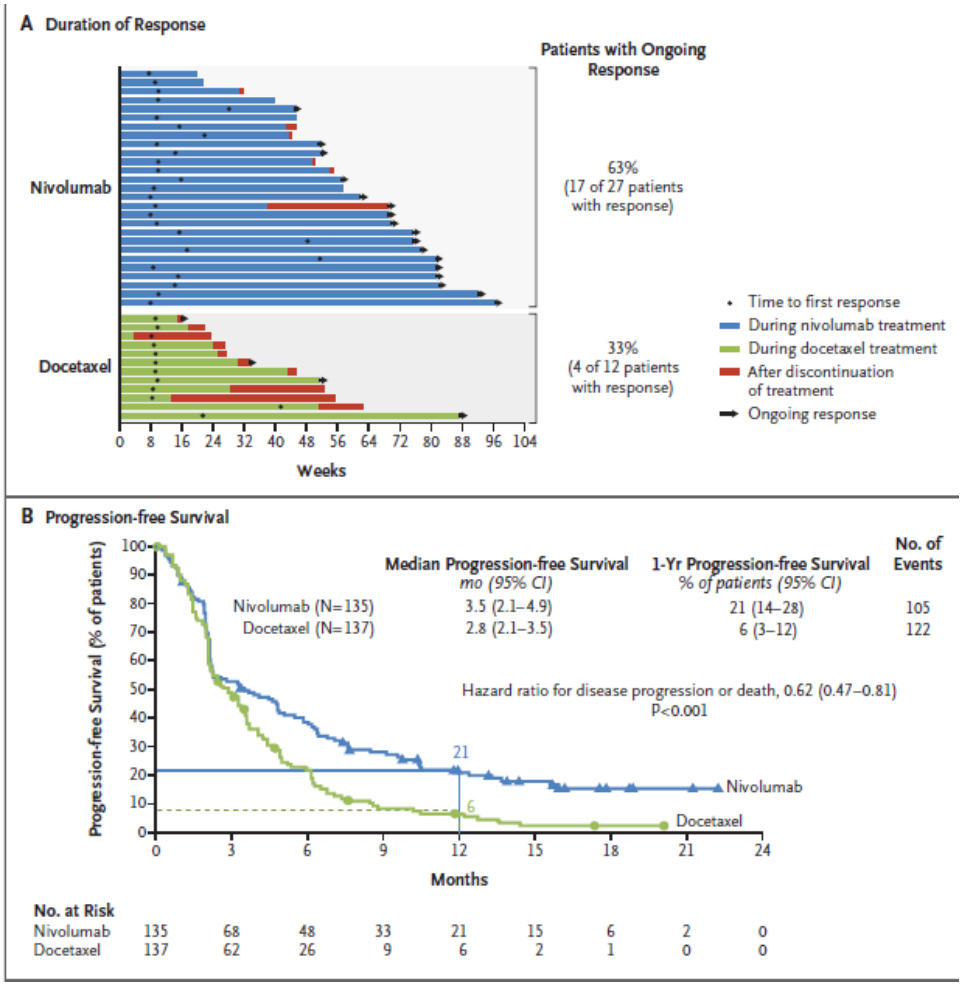


Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Brahmer et al, NEJM 2015

NIVOLUMAB IN SQUAMOUS NSCLC

- **RR**
  - 27% vs 12%
- **Duration of response**
  - NR vs 8.4 m
- **PFS**
  - HR=0.62
- *No difference in PD-L1+/-*



Brahmer et al, NEJM 2015

NIVOLUMAB IN SQUAMOUS NSCLC

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

* Safety analyses included all the patients who received at least one dose of study drug. No treatment-related deaths occurred in patients treated with nivolumab. Treatment-related deaths were reported in three patients treated with docetaxel (one death each from interstitial lung disease, pulmonary hemorrhage, and sepsis).

Brahmer et al, NEJM 2015

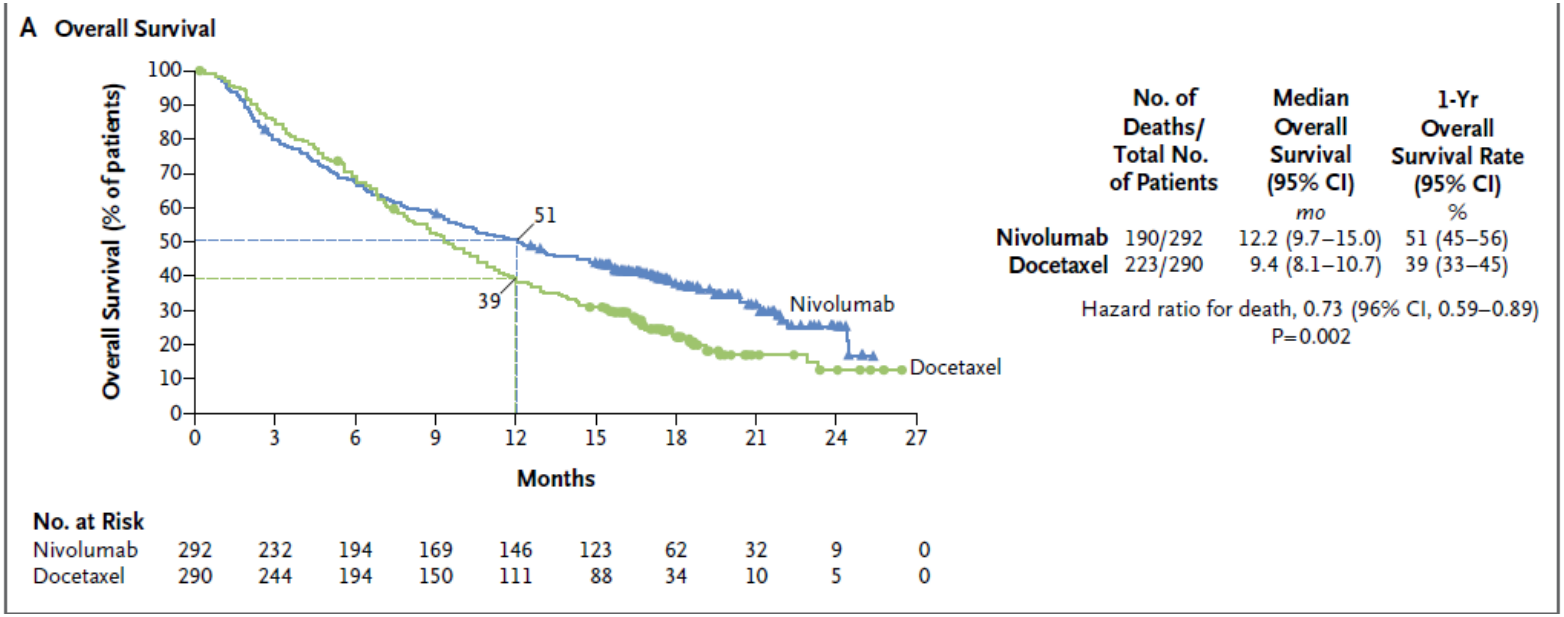
NIVOLUMAB IN NON-SQUAMOUS NSCLC

- **Checkmate 057 trial**
  - Phase III, second line
  - Nivolumab 3 mg/Kg q14 vs docetaxel 75 mg/sqm q21
  - 582 pts
- **Primary endpoint**
  - OS
- **Characteristics**
  - EGFR mut=15%
  - Current or former smokers=79%

Borghaei et al, NEJM 2015

NIVOLUMAB IN NON-SQUAMOUS NSCLC

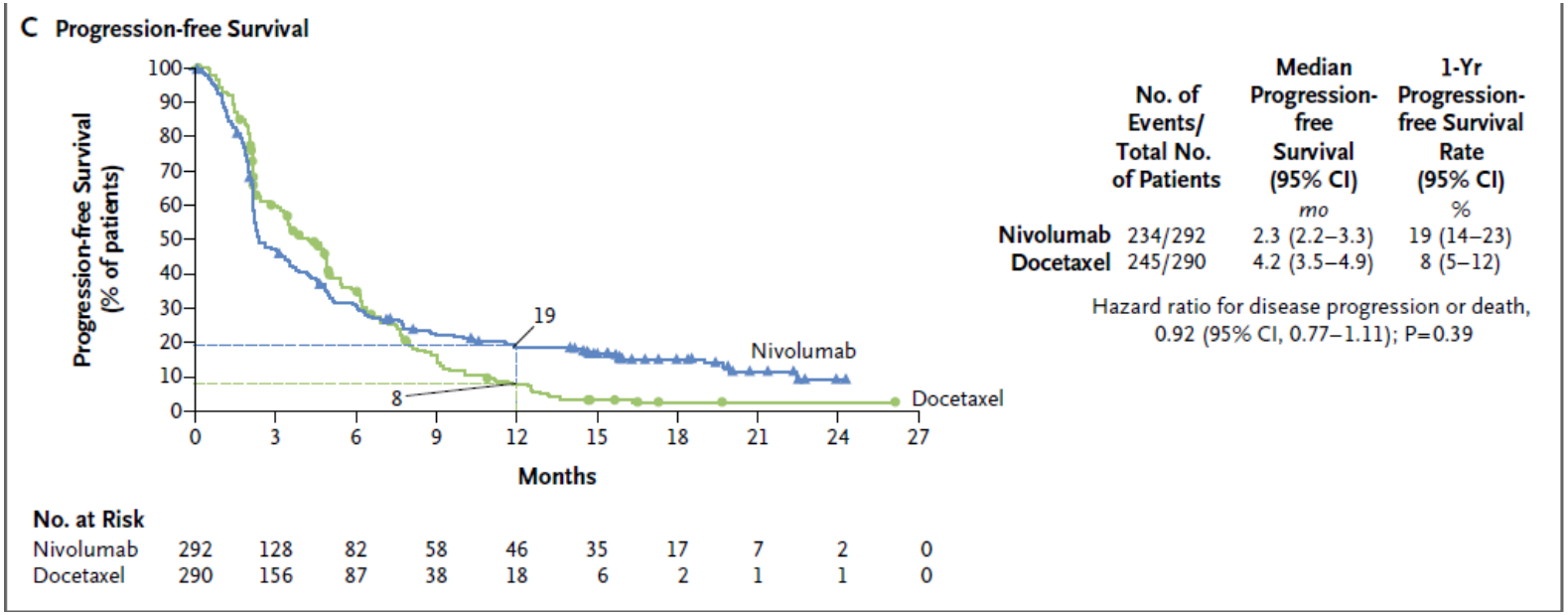
- **OS**
  - Median 12.2 vs 9.4 m
  - HR=0.73 (05% CI 0.59-0.89)
  - Alive at 1 year: 51 vs 39 %



Borghaei et al, NEJM 2015

NIVOLUMAB IN NON-SQUAMOUS NSCLC

- PFS !!!!



	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate (95% CI)
		mo	%
Nivolumab	234/292	2.3 (2.2–3.3)	19 (14–23)
Docetaxel	245/290	4.2 (3.5–4.9)	8 (5–12)

Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39

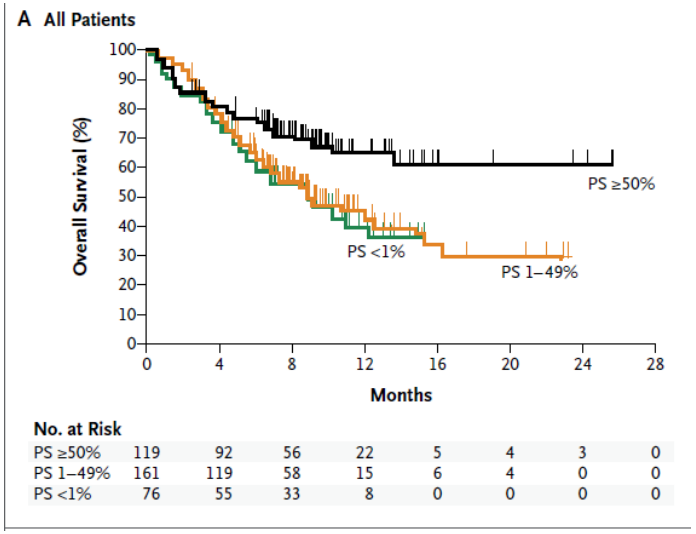
Most benefit in smokers, EGRF not mutated!

Borghaei et al, NEJM 2015

PEMBROLIZUMAB IN NSCLC

- **Large international phase I trial, expansion cohorts**
  - 492 pts with advanced NSCLC
  - Pembro 10 mg/Kg q2w or q3w

- **Median OS**
  - 12m (95% CI 9.3-14.7m)
    - Pretreated: 9.3 m
    - Naive: 16 m
  - Greatest benefit in PD-L1+ > 50%



Garon et al, NEJM 2015

SECOND LINE RCC

- Axitinib vs sorafenib
  - mPFS: 6.8 vs 4.7 m
  - No benefit in OS
  - Safety: diarrhea, hypertension, fatigue, nausea, decreased appetite, dysphonia, and palmar-plantar erythrodysesthesia

Rini BI et al, Lancet 2011

- Everolimus vs placebo
  - mPFS: 4.9 vs 1.9m

Motzer RJ, et al. Cancer 2010

NIVOLUMAB IN RENAL CC

- **Checkmate 025 trial**
  - Phase III, everolimus vs nivolumab
  - Previously treated with antiangiogenics
- 821 pts with advanced RCC
  - MSKCC favourable group 36%, poor 15%
- Primary endopoint
  - OS

Motzer, NEJM 2015

NIVOLUMAB IN RENAL CC

- **OS**
  - Median: 25 vs 19.6 m
  - HR=0.73 (95% CI 0.57-0.93)

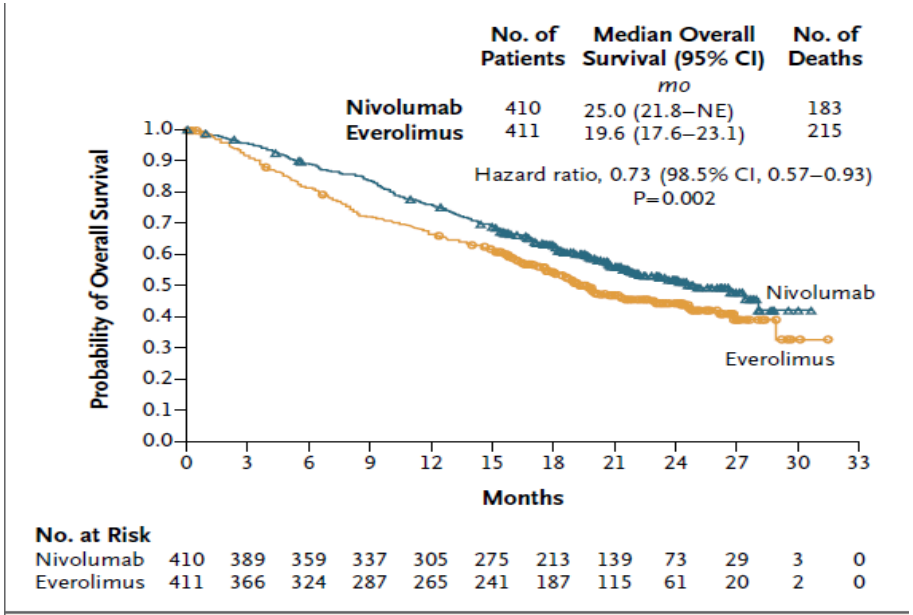
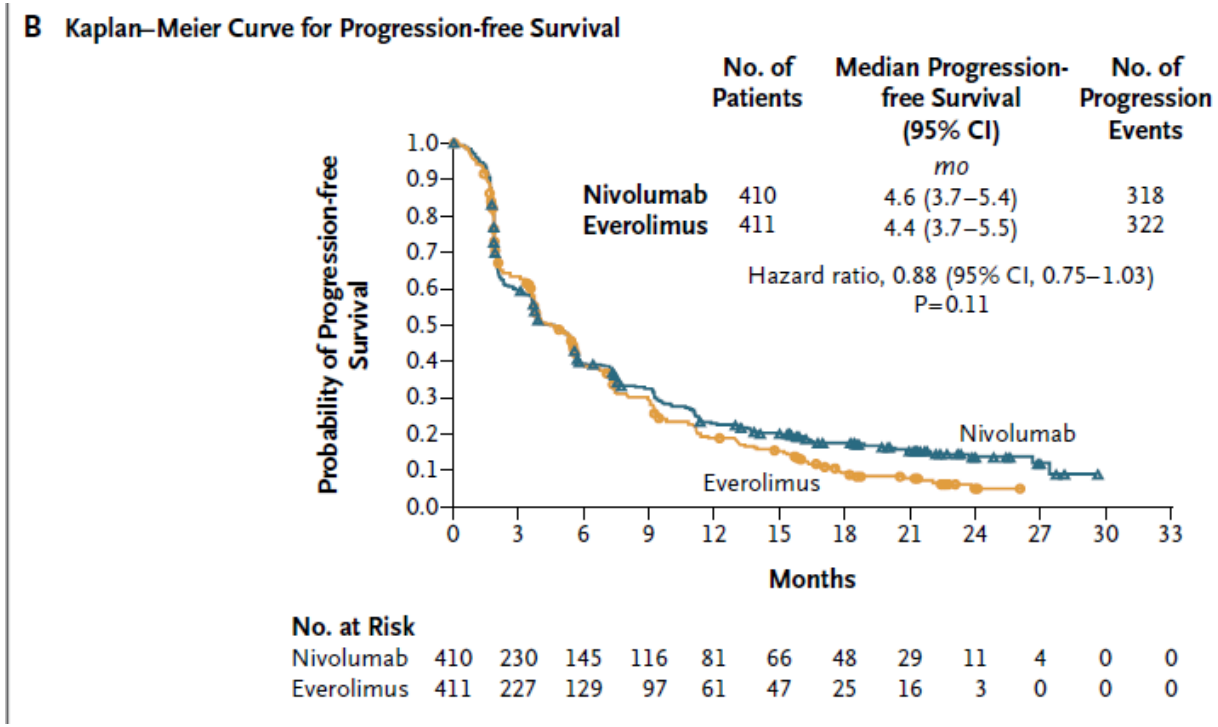


Figure 1. Kaplan–Meier Curve for Overall Survival.
CI denotes confidence interval, and NE not estimable.

Motzer, NEJM 2015

NIVOLUMAB IN RENAL CC

- PFS: no difference, late benefit
- RR: 25 vs 5%
- No effect of PD-L1 expression



Motzer, NEJM 2015

ANTI PD-L1

- **Atezolizumab**
  - Promising results in
    - Metastatic urothelial cancer
      - IMvigor trial
        - 316 pts with metastatic urthelial cancer progressing after Platinum-based CT
          - RR= 15%, 27% in IC2/3 PD-L1 expression
            - 92% of responses still ongoing after 24 weeks

Rosenberg et al, ESMO 2015

    - Advanced NSCLC
      - POPLAR, phase III trial: docetaxel vs atezolizumab
        - median OS: 12.6 vs 9.7m, HR=0.73

Vansteenkiste et al, ESMO 2015

      - BIRCH phase II trial
        - RR= 24-27% in PD-L1+

Besse et al, ESMO 2015

CONCLUSIONS

- **Exciting results of anti PD-1 in melanoma, NSCLC, RCC**
  - Caution with PFS, benefit could be late
  - Probably no differences in PD-L1+ vs –
  - Generally well tolerated
  - Antigenic heterogeneity could play a role
    - E.g. squamous NSCLC, Colorectal cancer
  - Nivolumab (L648 Squamous NSCLC, EAP in adeno), pembrolizumab (EAP melanoma)

- **Promising results of anti PD-L1**

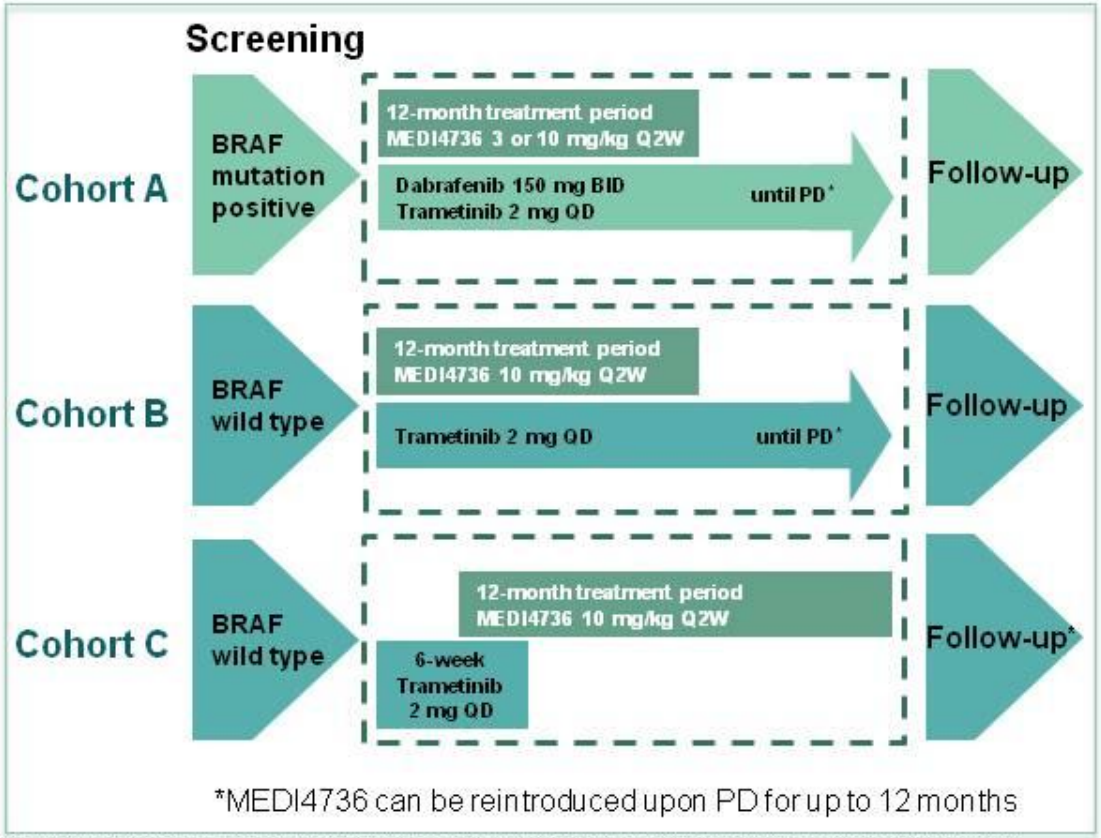
- **Combination therapies**
  - Anti CTLA4 + anti PD1 in melanoma
    - FDA approval of combo Ipilimumab+nivolumab in melanoma
    - Waiting for OS results in phase III
  - Anti PD-L1 + MEK + BRAF inhibitors in melanoma

Ribas et al, ASCO 2015

GRAZIE PER L'ATTENZIONE!

ANTI PD-L1 + BRAFi + MEKi Phase I

Study design and population



- **Key inclusion criteria**
  - Stage IIIC/IV melanoma
  - BRAF mutation status
    - Cohort A: confirmed $BRAF^{V600E/K}$ mutation positive
    - Cohort B and C: confirmed $BRAF^{V600E/K}$ mutation negative
  - ECOG PS 0–1
  - Adequate organ and marrow function
  - Prior immunotherapy permitted:
    - anti-CTLA-4
    - anti-PD-1/anti-PD-L1
  - Measurable disease required

- **Key exclusion criteria**
  - Active or prior autoimmune disease
  - Prior BRAF or MEK inhibitor therapy
  - Prior severe or persistent irAE

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; irAE, immune-related adverse event; PD, progressive disease; Q2W, every 2 weeks; QD, once daily; SD, stable disease

Clinical activity to date

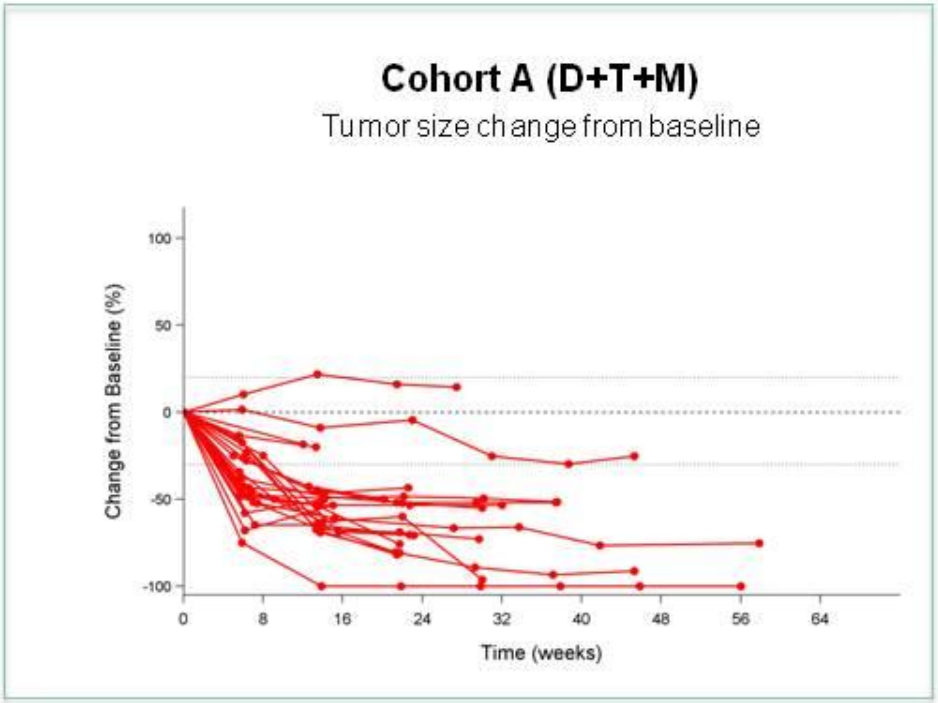
- Response evaluable population includes all patients dosed ≥16 weeks prior to the cut-off date with measurable disease at baseline and ≥1 f/u scan (or discontinuation due to death or PD prior to 1st scan)

	Cohort A (n=26)	Cohort B (n=19)	Cohort C* (n=15)
Clinical activity	**D + T + M**	**T + M**	**T → M (sequential)**
ORR, n (%)	18 (69)	4 (21)	2[a] (13)
DCR (CR + PR + SD), n (%)	26 (100)	15 (79)	12 (80)
SD ≥12 weeks, n (%)[b]	4 (15)	10 (53)	6 (40)
Ongoing responders, n/N (%)	16/18 (89%)	4/4 (100%)	1/2 (50%)
Range of duration of ongoing response, wks[c]	7.7+–50.6+	7.9+–24.7+	7.0+

- Median duration of response has not yet been reached for Cohorts A and B
- *Shorter follow up in Cohort C, with 5 additional patients ongoing with best response of unconfirmed PR

D, dabrafenib; DCR, disease control rate; M, MEDI4736; ORR, overall response rate; T, trametinib.
[a]Responses based on the principles of immune-related RECIST; the two patients in Cohort C had unconventional confirmed PRs; [b]includes subjects with unconfirmed PR or SD as the best overall response; [c]duration of response is calculated for subjects with confirmed responses.
Data cut-off: 7 May 2015

Tumor size change and time to response: Cohort A



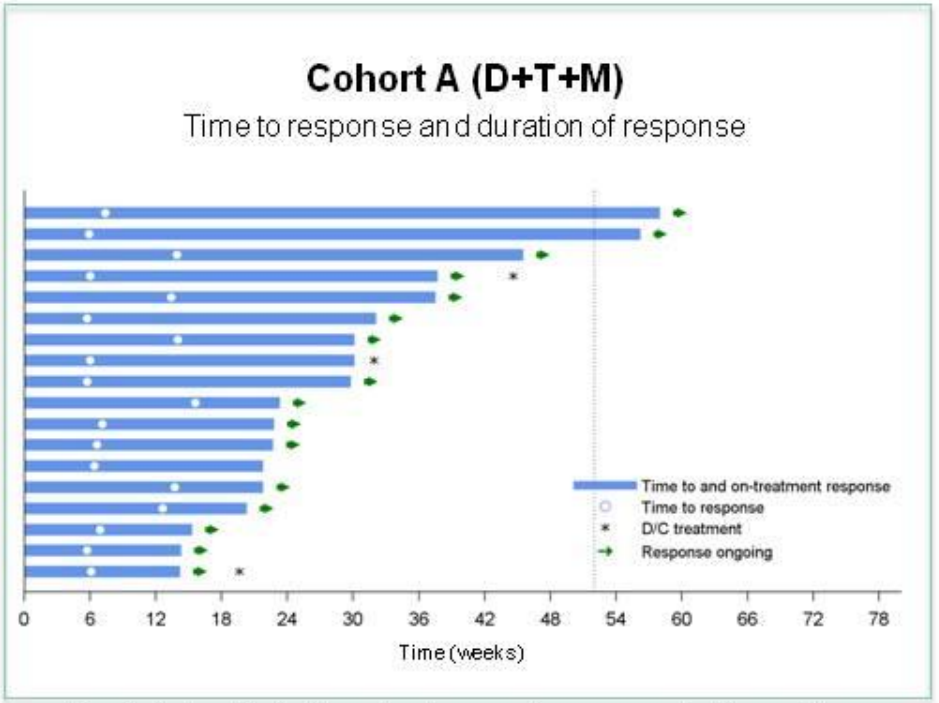


Figure includes subjects with confirmed response in response evaluable population;
D/C treatment=Discontinuation of the regimen

As-treated population. Data cut-off: 7 May 2015

NOVEL STRATEGIES

- Novel immune checkpoints
  - LAG3
  - CD160
  - VISTA
  - CD244
  - BTLA
  - TIM3

CONCLUSIONS

- **Anti PD1**
  - Active and effective in advanced melanoma
    - BRAF WT and mutant
    - PD-L1 + and –
      - Probably highest activity in PD-L1 +
        - Deserves further investigation as a predictive factor
  - Safe
    - Could be combined with anti-CTLA-4 even if higher toxicity
  - Rapid onset of response
    - irRC could capture delayed benefit
- **Anti PD-L1**
  - Promising, waiting for more data
    - Combination with BRAF/MEK inhibitors