EMA - CDDF JOINT MEETING
CHALLENGES FOR THE APPROVAL OF ANTI-CANCER IMMUNOTHERAPEUTIC DRUGS
4th-5th February 2016
London, United Kingdom

Differences between the use of immunotherapy in the adjuvant as opposed to advanced setting

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Outline

- Ongoing studies
  - Melanoma
  - NSCLC
- Dose, length of treatment
- Design
- Endpoint
- Safety
- Biomarker
- Combination
- Regulatory challenges

Outline

- **Ongoing studies**
  - **Melanoma**
  - **NSCLC**
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Melanoma

ONGOING ADJUVANT STUDIES

Study	Experimental arm	Control arm	Main inclusion criteria	Primary endpoint	Design	Pts
NCT02437279	Post-surgery infusion for 12 weeks with the combination of ipilimumab 3 mg/kg q21 + nivolumab 1 mg/kg q21	6 weeks upfront surgery and 6 weeks post-surgery infusion of ipilimumab 3 mg/kg q21 + nivolumab 1 mg/kg q21	Stage III melanoma with palpable disease, naïve for CTLA-4/PD-1/PD-L1	• The alteration in magnitude of the neo-antigen specific T cell response in the time interval pre- to post-adjuvant therapy in peripheral blood • Safety	Two-arm Phase 1b feasibility	20
NCT02362594 MK-3475-054/KEYNOTE-054	Pembrolizumab 200 mg on Day 1 q21 for up to 1 year	Matched placebo	Completely resected Stage III melanoma	RFS • All comers • PD-L1-positive subgroup	Phase III	900
NCT02388906	Nivolumab q14	Ipilimumab	Completely removed melanoma by surgery performed within 12 weeks of randomization Stage IIIb/C or Stage IV before complete resection	RFS	Phase III	800

www.clinicaltrials.gov

NSCLC

ONGOING ADJUVANT STUDIES

Study	Experimental arm	Control arm	Main inclusion criteria	Primary endpoint	Design	Pts
NCT02504372 PEARLS	**Pembrolizumab** 200 mg iv q21 for 1 y	Matched placebo	•Resected IB–IIIA NSCLC +/- Adjuvant chemotherapy	DFS • All comers • PD-L1-positive subgroup	Phase III	1380
NCT02273375 BR31	**Durvalumab** 10mg/kg q14 for 6 mo. then 20mg/kg q28 for 6 mo	Matched placebo	•Resected IB–IIIA NSCLC PDL1+ +/- Adjuvant chemotherapy	DFS	Phase III	1100
NCT02595944 **ANVIL**	**Nivolumab** q14 for 1 year	Matched placebo	•Resected IB–IIIA NSCLC +/- Adjuvant chemotherapy	DFS, OS	Phase III	714
NCT02486718	**Atezolizumab** (MPDL3280A) 1200 mg will be administered intravenously (IV) q21 for 16 cycles	Matched placebo	•Resected IB–IIIA NSCLC +/- Adjuvant chemotherapy	DFS	Phase III	845

www.clinicaltrials.gov

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Phase I

Compound	n Ph I	DLT	MTD/RP2D	Selected dose	Registered
Ipilimumab	4	NA	Not defined	3 mg/kg for 4 doses	3 mg/kg for 4 doses
Tremelimumab	2	4 late-onset at 10 mg/kg in 1 study	MTD not defined RP2D 10 mg/kg q4w	10 mg/kg q4w	NA
Nivolumab	2	NA	Not defined	3 mg/kg q2w	3 mg/kg q2w
Pembrolizumab	3	NA	Not defined	200 mg q3w	2 mg/kg q2w
Durvalumab	1	NA	Not defined	10 mg/kg q2w	NA
Atezolizumab	2	NA	Not defined	120mg q3w	NA
Pidilizumab	1	NA	Not defined	-	NA
BMS-936559	1	NA	Not defined	-	NA

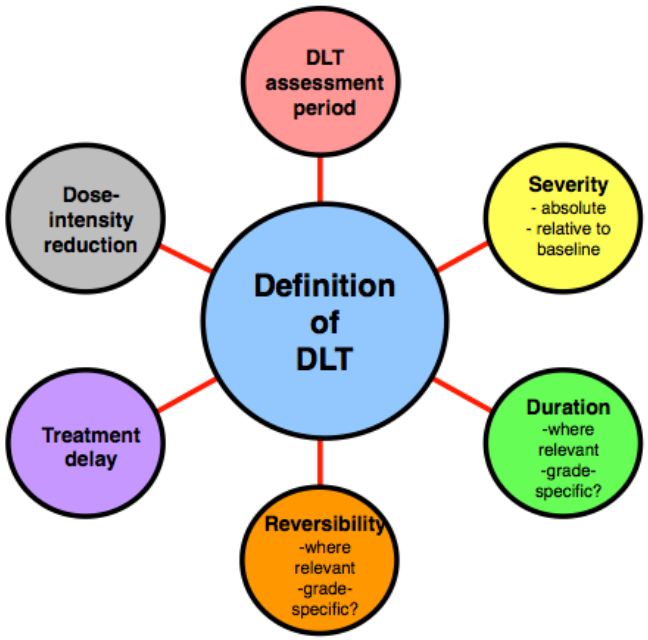
Postel-Vinay S, Ann Oncol 2015

Open questions

Many questions remain about the **optimal dose** and **schedule.**

Dose

- In multiple studies **doses > 1 mg/kg do not increase efficacy**.
    - 173 pts with melanoma randomly assigned to pembrolizumab 10 mg/kg or 2 mg/kg administered every 3 weeks. Efficacy and safety in both treatment arms were the same.
- Ongoing phase III studies will continue to clarify whether there is a **dose-response relationship** with PD-1 agents.



Schedule

- FDA: ipilimumab is delivered every 3 weeks for 4 total treatments (induction).
- In the registrational study, pts with SD or a response with acceptable toxicity after induction but who subsequently progressed were offered a reinduction of 4 doses of ipilimumab (q21): among the 31 pts treated, 19% achieved a subsequent CR or PR with no new types of toxicities.
- **All compounds are administered on a continuous schedule, yet it remains unclear if it is necessary.**

Adjuvant ipilimumab

Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial

Alexander M M Eggermont, Vanna Chiarion-Sileni, Jean-Jacques Grob, Reinhard Dummer, Jedd D Wolchok, Henrik Schmidt, Omid Hamid, Caroline Robert, Paolo A Ascierto, Jon M Richards, Céleste Lebbé, Virginia Ferraresi, Michael Smylie, Jeffrey S Weber, Michele Maio, Cyril Konto, Axel Hoos, Veerle de Pril, Ravichandra Karra Gurunath, Gaetan de Schaetzen, Stefan Suciu, Alessandro Testori

- The dose of 10 mg/kg was chosen based on data from a random ph 2 trial that compared various doses of ipilimumab in pts with advanced melanoma (small but statistically significant higher ORR 11.1% *v* 4.2%).

- The ongoing intergroup trial ECOG 1609 (NCT 01274338) in the USA comparing high-dose interferon treatment with 1 year of treatment with ipilimumab at either 10 mg/kg or 3 mg/kg might provide additional insight and is less toxic than high-dose interferon.

Eggermont AMM, Lancet Oncol 2015; 16: 522–30

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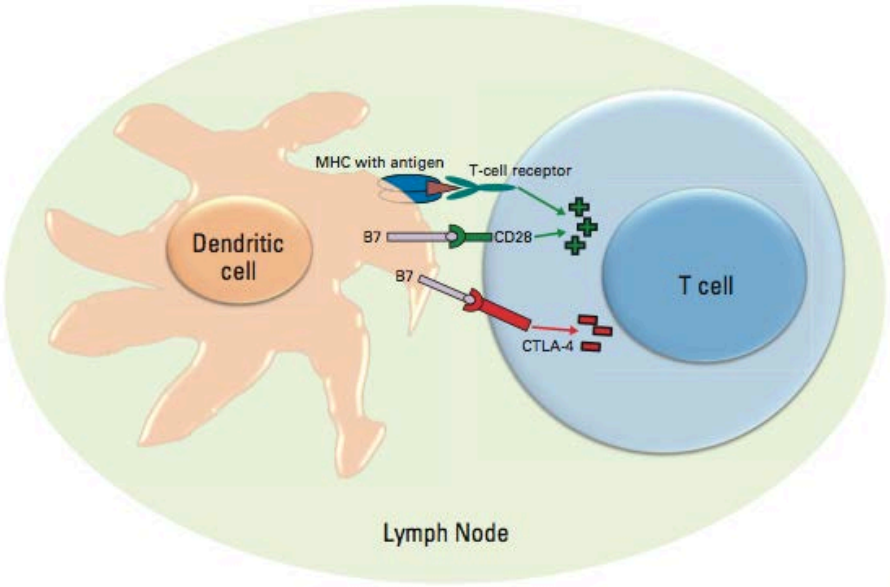
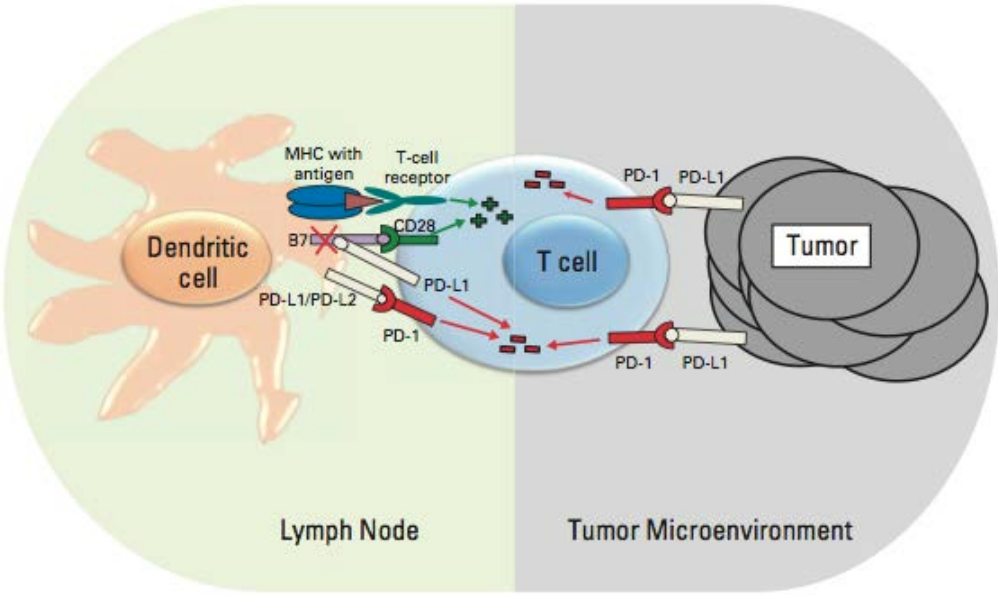
From biology to design



CTLA-4

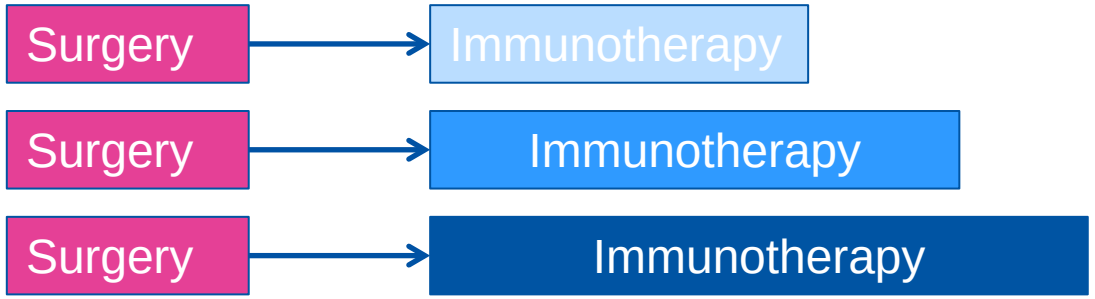
PD-1



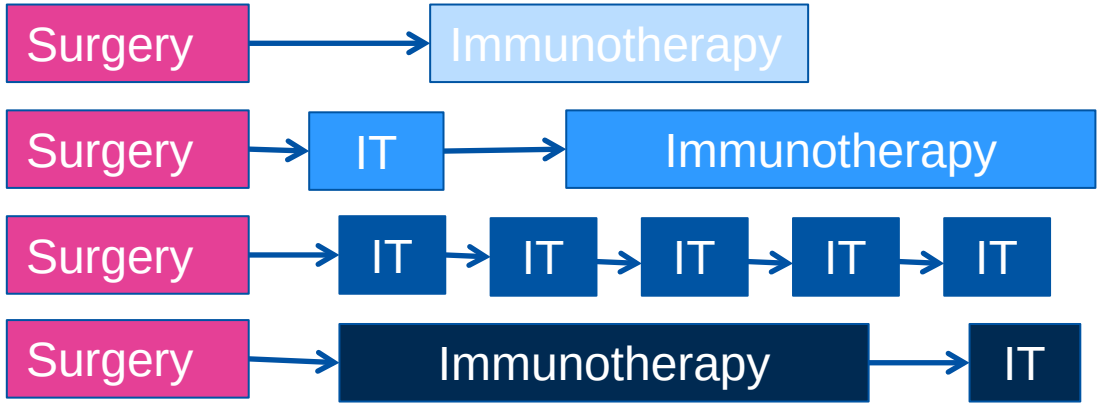
Postow MA, J Clin Oncol 2015

Design

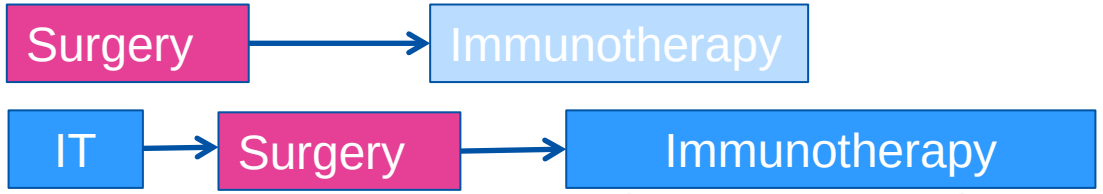
- **Length**
  - 6 months?
  - 1 year?
  - 2 years?



- **Continous? Intermittent?**



- **Sequence?**



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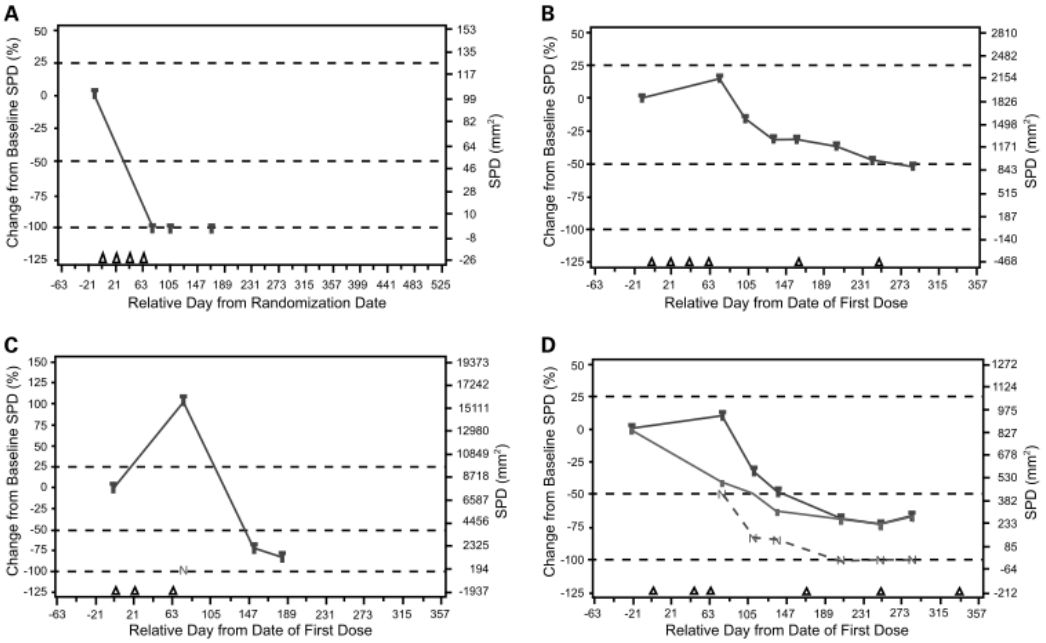
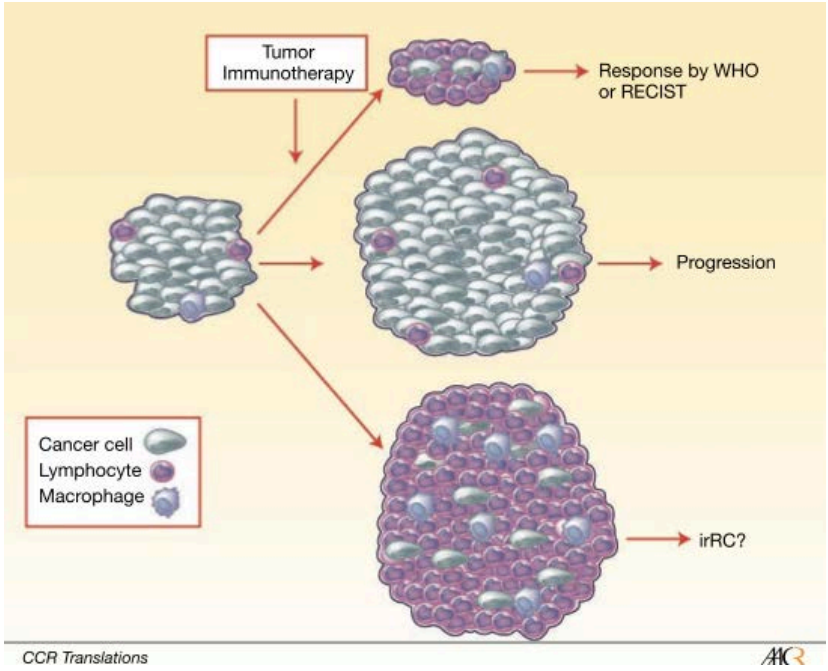
Endpoint





In multicenter clinical trials is important to use an endpoint which is **objectively and uniformly assessed** across the participating

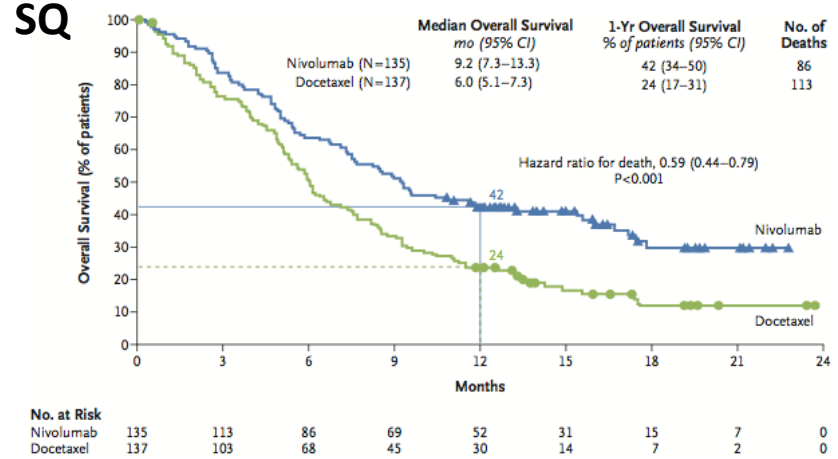
Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

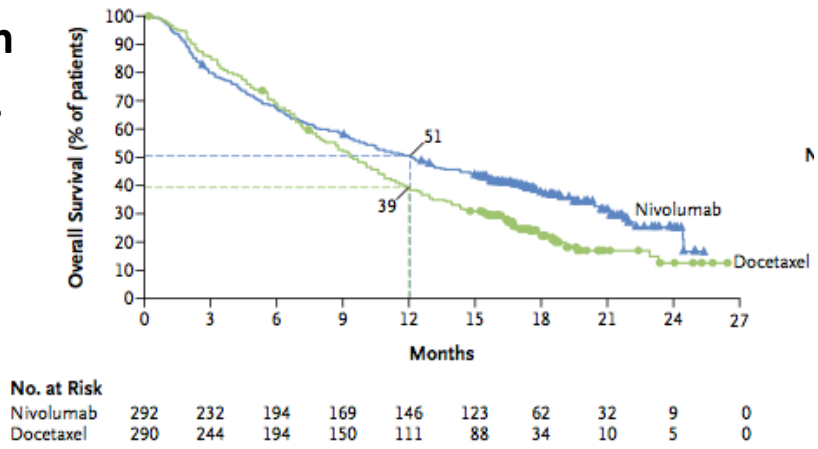
Wolchock JD, Clin Cancer Res 2009;15(23):7412-20
Ribas A, Clin Cancer Res 2009;15(23):7116–8

Endpoint

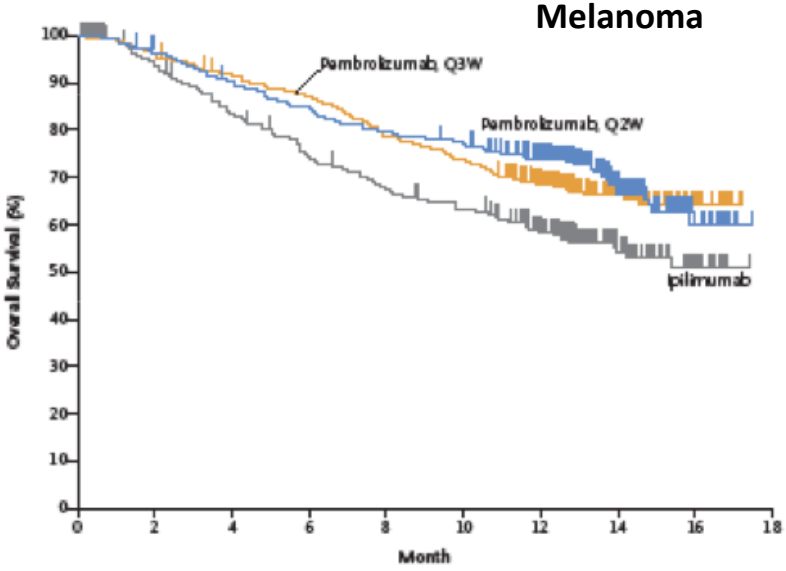
SQ



Non SQ



Melanoma



Study	OS	PFS
Robert C, Lancet Oncol 2015;16:375-85	HR 0.63 (74.1% vs 68.4%)	HR 0.58 (5.5 vs 4.1)
Brahmer J, N Engl J Med 2015;373:123-35	HR 0.59 (9.2 vs 6.0)	HR 0.62 (3.5 vs 2.8)
Borghaei H, N Engl J Med 2015;373:1627-39	HR 0.73 (12.2 vs 9.4)	HR 0.92 (2.3 vs 4.2)

Endpoint

CHECKMATE-066

- EORTC QLQ-C30 + EQ-5D at baseline and at cycles Q6W.
- Adjusted completion rates at baseline
  - EQ-5D: 69.5% vs 64.9%
  - EORTC QLQ-C30: 70.0% vs 64.9%
- **QoL analysis was not feasible after wk 13 due to a high attrition rate in the control arm.**
- NIVO does not impair QoL and may enhance it compared with BL in treatment-naïve pts with advanced MEL.

Long GV, J Clin Oncol 33, 2015 (suppl; abstr 9027)

Figure 4. Time to first decline of EORTC QLQ-C30 global health status/QoL score by study arm[a]

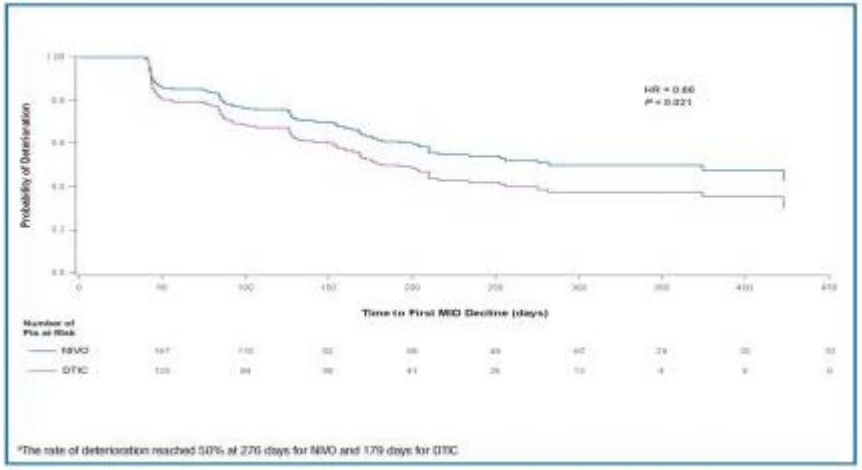
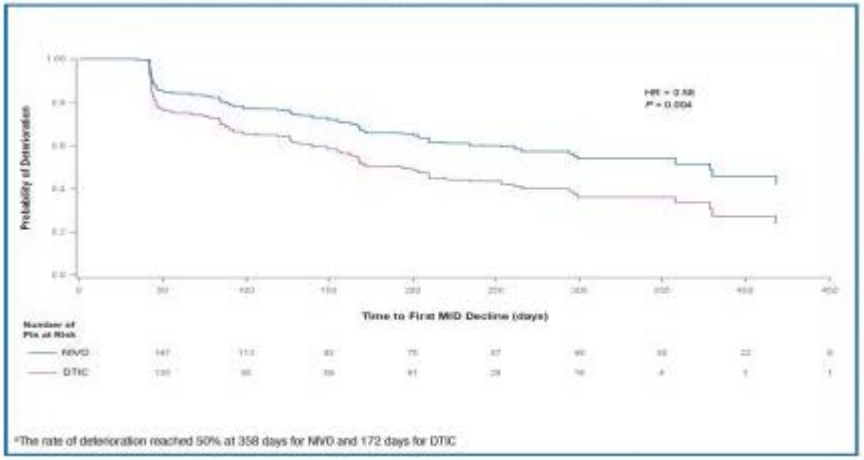
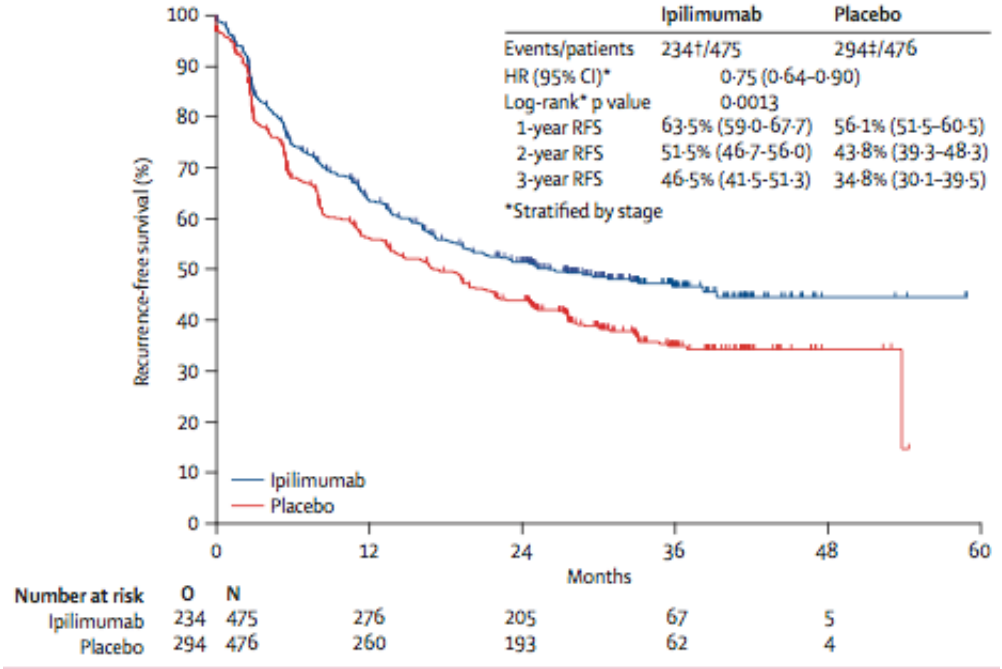


Figure 5. Time to first decline of EORTC QLQ-C30 physical functioning score by study arm[a]



Endpoint



	Ipilimumab	Placebo
Events/patients	234†/475	294‡/476
HR (95% CI)*	0·75 (0·64–0·90)	
Log-rank* p value	0·0013	
1-year RFS	63·5% (59·0–67·7)	56·1% (51·5–60·5)
2-year RFS	51·5% (46·7–56·0)	43·8% (39·3–48·3)
3-year RFS	46·5% (41·5–51·3)	34·8% (30·1–39·5)

*Stratified by stage

Eggermont AMM, Lancet Oncol 2015; 16: 522–30

- Recurrence or metastatic lesions were histologically confirmed whenever possible.
- The first date when recurrence was observed irrespective of the method of assessment.
- An independent review committee assessed disease status and date of recurrence.

- Pts received either ipilimumab 10 mg/kg or placebo every 3 weeks for 4 doses, then every 3 months up to a max of 3 years, or until disease recurrence, unacceptable toxicity, major protocol violation, or treatment refusal.
- Maintenance was added based on the theoretical principles of continued re-stimulation of the immune system.

- The unmet need for an improved adjuvant treatment for melanoma is shown by the HR for recurrence or death of 0·83–0·85 with high-dose or low-dose interferon compared with observation only.
- **950 pts were planned to be randomly assigned.**

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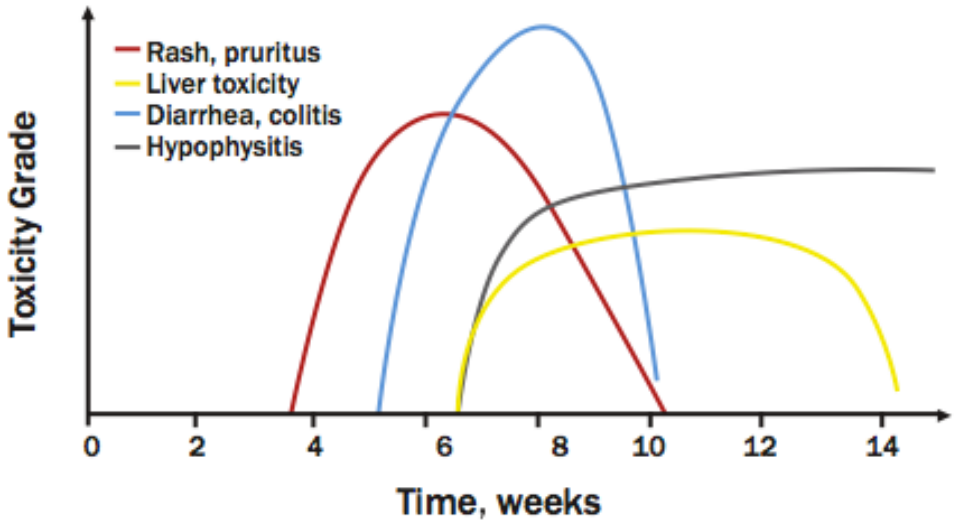
Compliance/safety

SAFETY

- The most common grade 3–4 immune-related AEs are **GI, hepatic, dermatological and endocrine**.
- **The median time to onset ranged from 4·3 weeks to 13·1 weeks**.
- **40% of pts discontinued treatment** by the end of the initial dosing period—ie, before maintenance therapy.
- Higher frequency than observed in a pooled analysis of studies with 10 mg/kg in pts with advanced melanoma.
- Most manifestations resolved within 4–6 weeks but for endocrinopathies the median **time to resolution** was 31 weeks, 44% of pts remaining on hormone replacement therapies.
- **Effective management** is complex and requires proactive monitoring, early intervention, and aggressive immuno- suppressive management and meticulous instruction of patients.

COMPLIANCE

- At least **one maintenance dose** was received by 42% of pts in the ipilimumab and 70% of pts in the placebo group.
- **29% of pts in the ipilimumab group received at least seven doses** (about 1 year of treatment) compared with 57% in the placebo group.
- 52% discontinued ipilimumab because of an AE being 49% drug-related;. 4% of pts receiving placebo discontinued treatment because of an AE.



	Ipilimumab group (n=471)				Placebo group (n=474)			
	Grade 1–2	Grade 3	Grade 4	Grade 5†	Grade 1–2	Grade 3	Grade 4	Grade 5†
All adverse events, regardless of cause								
Any event	205 (44%)	215 (46%)	39 (8%)	6 (1%)	307 (65%)	103 (22%)	15 (3%)	6 (1%)
Dermatological								
Pruritus	192 (41%)	11 (2%)	0 (0%)	0 (0%)	70 (15%)	0 (0%)	0 (0%)	0 (0%)
Rash	179 (38%)	6 (1%)	0 (0%)	0 (0%)	80 (17%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal disorders								
Diarrhoea	185 (39%)	46 (10%)	0 (0%)	0 (0%)	134 (28%)	9 (2%)	0 (0%)	0 (0%)
Nausea	115 (24%)	1 (<1%)	0 (0%)	0 (0%)	83 (18%)	0 (0%)	0 (0%)	0 (0%)
Colitis	39 (8%)	32 (7%)	4 (<1%)	0 (0%)	5 (1%)	1 (<1%)	0 (0%)	0 (0%)
Abdominal pain	64 (14%)	2 (<1%)	0 (0%)	0 (0%)	44 (9%)	1 (<1%)	0 (0%)	0 (0%)
Vomiting	57 (12%)	2 (<1%)	0 (0%)	0 (0%)	27 (6%)	1 (<1%)	0 (0%)	0 (0%)
Colitis, ulcerative	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
Hepatic								
Alanine aminotransferase increased	77 (16%)	19 (4%)	6 (1%)	0 (0%)	26 (5%)	0 (0%)	0 (0%)	0 (0%)
Aspartate aminotransferase increased	58 (12%)	18 (4%)	2 (<1%)	0 (0%)	24 (5%)	0 (0%)	0 (0%)	0 (0%)
Endocrine disorders								
Hypophysitis	63 (13%)	22 (5%)	3 (<1%)	0 (0%)	3 (<1%)	0 (0%)	0 (0%)	0 (0%)
Other								
Fatigue	179 (38%)	9 (2%)	1 (<1%)	0 (0%)	136 (29%)	6 (1%)	1 (<1%)	0 (0%)
Headache	148 (31%)	4 (<1%)	0 (0%)	0 (0%)	85 (18%)	1 (<1%)	0 (0%)	0 (0%)
Weight loss	145 (31%)	2 (<1%)	0 (0%)	0 (0%)	34 (7%)	2 (<1%)	0 (0%)	0 (0%)
Pyrexia	77 (16%)	5 (1%)	0 (0%)	0 (0%)	21 (4%)	1 (<1%)	0 (0%)	0 (0%)
Weight increased	68 (14%)	1 (<1%)	0 (0%)	0 (0%)	109 (23%)	1 (<1%)	0 (0%)	0 (0%)
Cough	68 (14%)	0 (0%)	0 (0%)	0 (0%)	48 (10%)	0 (0%)	0 (0%)	0 (0%)
Decreased appetite	64 (14%)	1 (<1%)	0 (0%)	0 (0%)	15 (3%)	1 (<1%)	0 (0%)	0 (0%)
Immune-related adverse events								
Any immune-related adverse event	226 (48%)	172 (37%)	26 (6%)	2 (<1%)	171 (36%)	11 (2%)	1 (<1%)	0 (0%)
Dermatological	277 (59%)	21 (4%)	0 (0%)	0 (0%)	99 (21%)	0 (0%)	0 (0%)	0 (0%)
Pruritus	176 (37%)	11 (2%)	0 (0%)	0 (0%)	51 (11%)	0 (0%)	0 (0%)	0 (0%)
Rash	156 (33%)	6 (1%)	0 (0%)	0 (0%)	52 (11%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal	142 (30%)	70 (15%)	5 (1%)	1 (<1%)	80 (17%)	3 (<1%)	1 (<1%)	0 (0%)
Diarrhoea	150 (32%)	45 (10%)	0 (0%)	0 (0%)	77 (16%)	2 (<1%)	0 (0%)	0 (0%)
Colitis	39 (8%)	32 (7%)	4 (<1%)	0 (0%)	5 (1%)	1 (<1%)	0 (0%)	0 (0%)
Colitis, ulcerative	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
Endocrine	137 (29%)	37 (8%)	3 (<1%)	0 (0%)	31 (7%)	0 (0%)	0 (0%)	0 (0%)
Hypophysitis	62 (13%)	22 (5%)	2 (<1%)	0 (0%)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)
Hypothyroidism	41 (9%)	1 (<1%)	0 (0%)	0 (0%)	4 (<1%)	0 (0%)	0 (0%)	0 (0%)
Hepatic	68 (14%)	37 (8%)	13 (3%)	0 (0%)	20 (4%)	1 (<1%)	0 (0%)	0 (0%)
Liver function test increase	68 (14%)	18 (4%)	7 (1%)	0 (0%)	19 (4%)	0 (0%)	0 (0%)	0 (0%)
Neurologic	12 (3%)	5 (1%)	4 (<1%)	0 (0%)	9 (2%)	0 (0%)	0 (0%)	0 (0%)
Other	73 (15.5)	35 (7%)	2 (<1%)	1 (<1%)	13 (3%)	8 (2%)	0 (0%)	0 (0%)
Multiorgan failure	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Eggermont AMM, Lancet Oncol 2015; 16: 522–30

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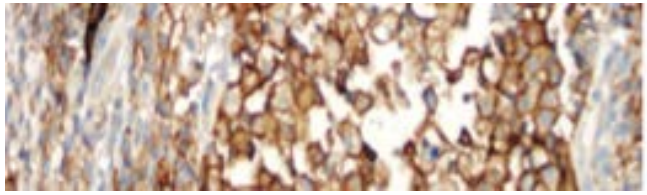
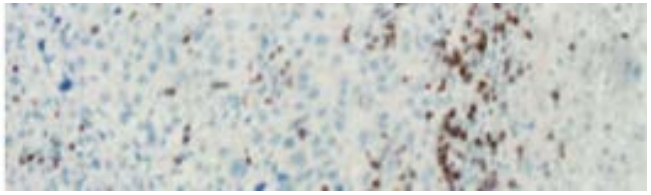
Biomarker



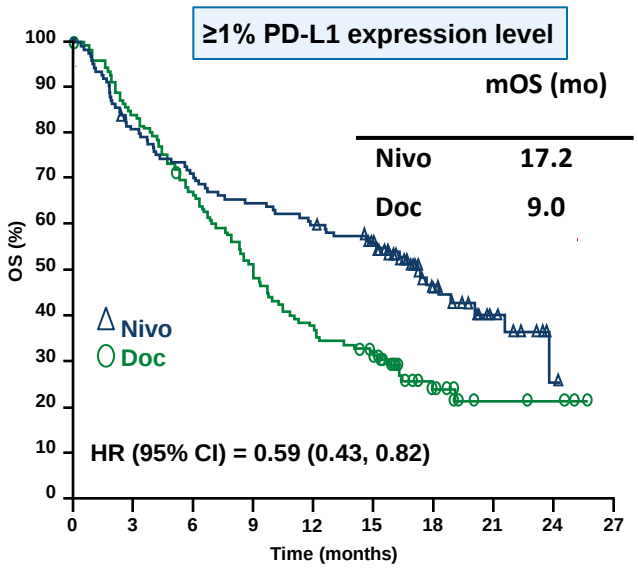


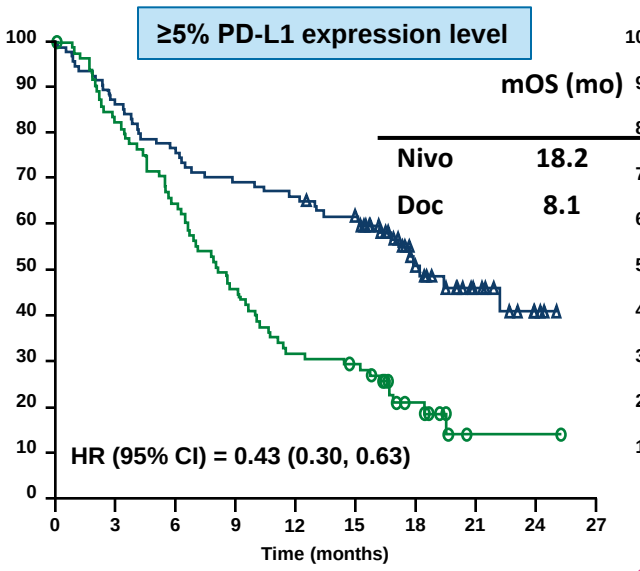
1 biomarker
4 testing Ab assays
Heterogeneity of assessment

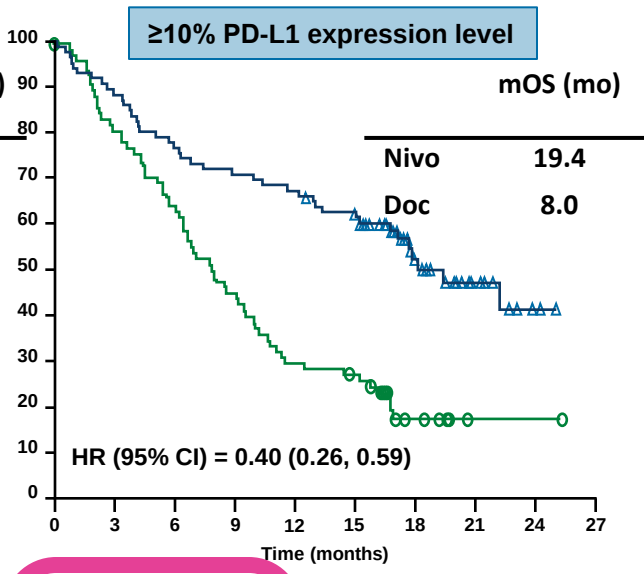
Novel immune monitoring assays for biomarker discovery and personalized cancer immunotherapy

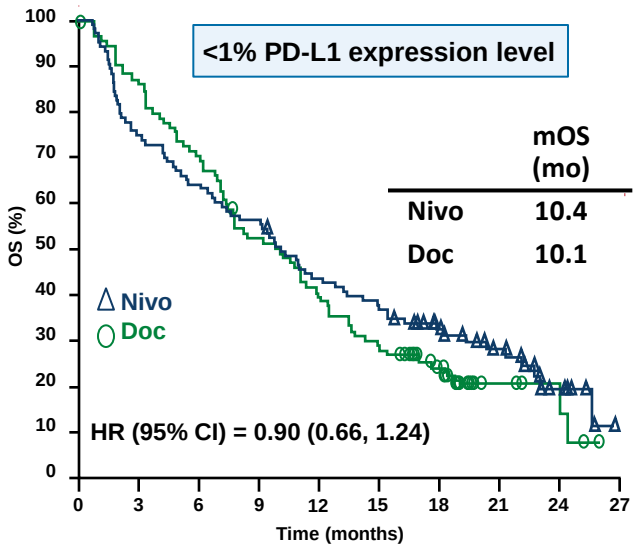
Monitoring strategy	Immunologically-unresponsive tumor	Immunologically-responsive tumor
Whole exome sequencing	Low mutational burden	High mutational burden
Gene signature/patterns	↓ activation signature	↑ activation signature
Epigenetic modification	↑ Treg/CD3 ratio ↓ CD3 cells	↓ Treg/CD3 ratio ↑ CD3 cells
Protein microarray	Poor general antibody response	Robust general antibody response
B/ T-cell receptor repertoire	Low CD3 count Low clonality	High CD3 count High clonality
Flow/Mass cytometry	↓ effector cells ↓ Teff/Treg ratio	↑ effector cells ↑ Teff/Treg ratio
Multicolor IHC	↓ effector cells, ↑ suppressor cells low PD-L1 on tumor and tumor infiltrating immune cells	↑ effector cells ↓ suppressor cells high PD-L1 on tumor and tumor infiltrating immune cell
Therapeutic strategy	Vaccination , ablation, radiotherapy, chemotherapy, oncolytic therapy, adaptive cellular therapy first	Immune checkpoint blockade therapies and other immunotherapies first
Legend	Blood vessel, Lymph node, Live tumor, Dying tumor, Naive T-cell, Memory T-cell, Immature dendritic cell, Mature dendritic cell	

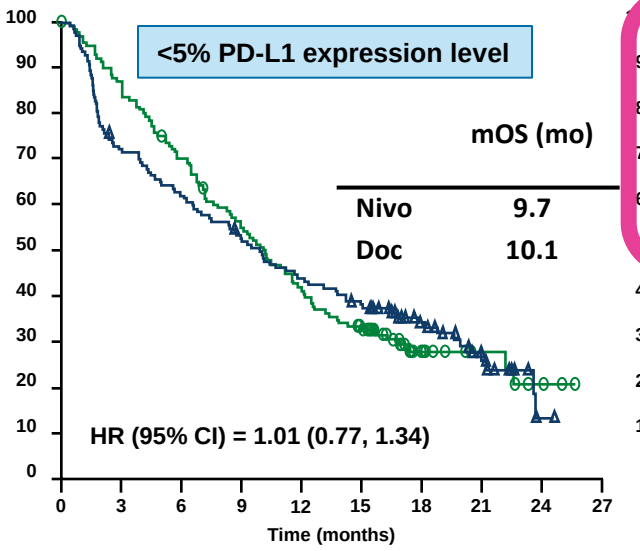
OS by PD-L1 Expression (Non-squamous)

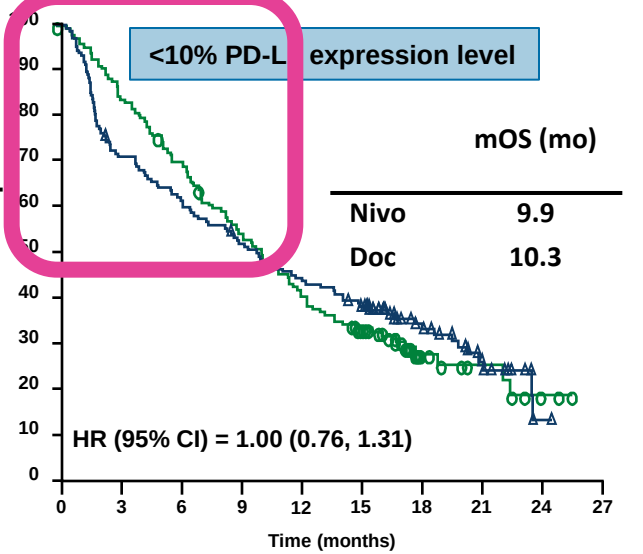












Symbols represent censored observations.

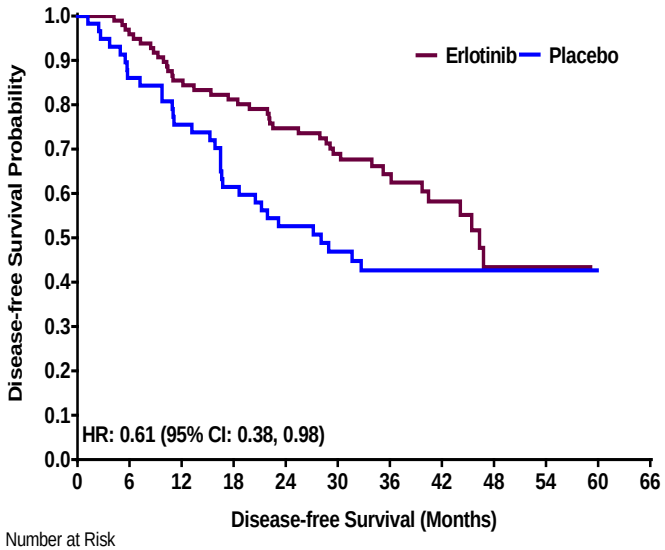
EORTC

CheckMate 057

(53% pts PD-L1≥1%)

The future of cancer therapy

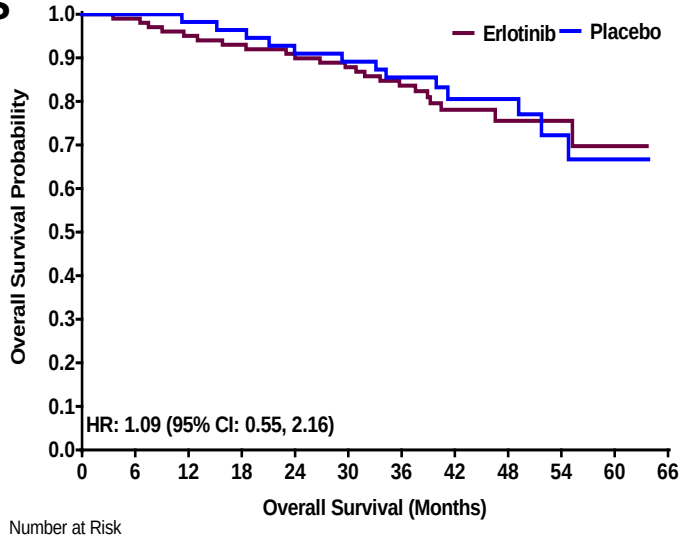
DFS



Number at Risk

Placebo	59	49	43	35	30	23	15	12	10	5	0	0
Erlotinib	102	94	80	76	68	56	35	22	10	3	0	0

OS

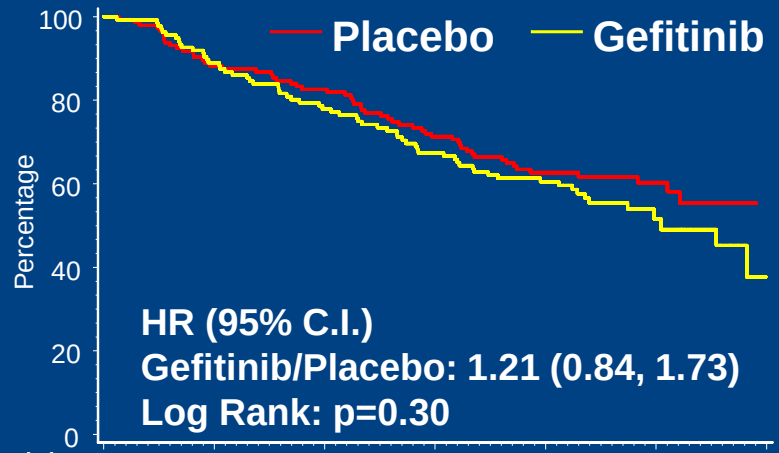


Number at Risk

Placebo	59	57	56	53	51	50	41	30	24	14	5	0
Erlotinib	102	100	94	91	88	86	75	43	26	15	7	0

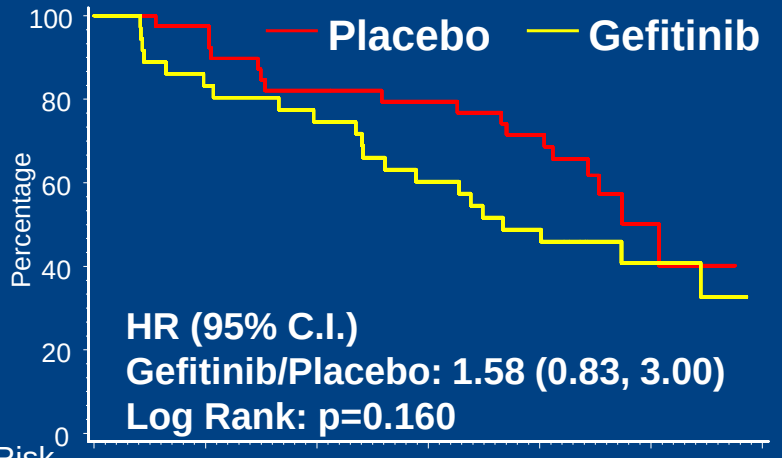
BR19

Wild type EGFR



# at Risk							
Placebo	145	126	118	101	77	34	2
Gefitinib	136	121	105	89	74	21	2

Sensitizing EGFR mutation



# at Risk							
Placebo	40	38	32	30	26	6	1
Gefitinib	36	29	26	21	17	7	0

Outline

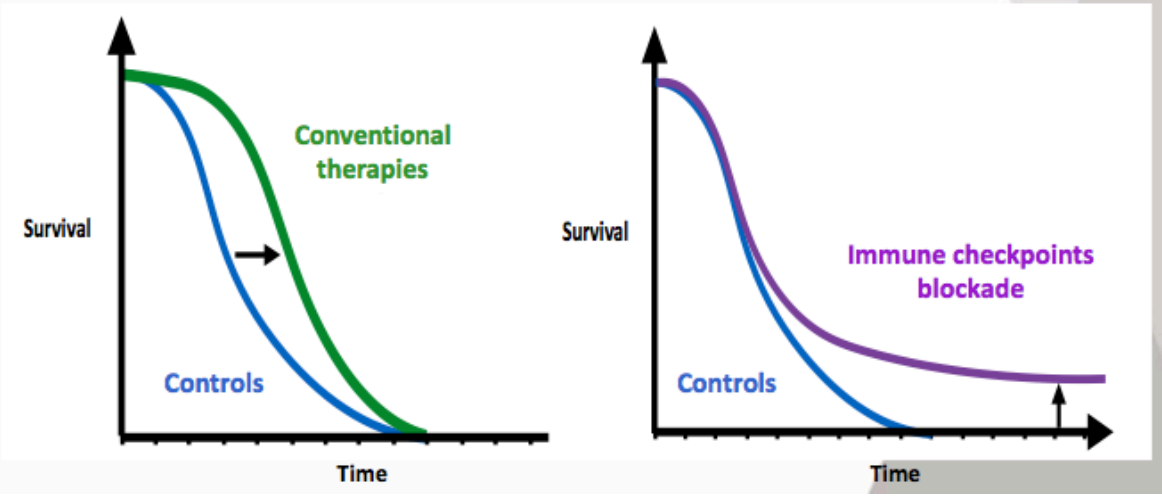
- Ongoing studies
  - Melanoma
  - NSCLC
- Dose, length of treatment
- Design
- Endpoint
- Safety
- Biomarker
- **Combination**
- Regulatory challenges

Combination

- Dose?
- Sequence?
- Sequential design?
- Endpoint?
- Safety?

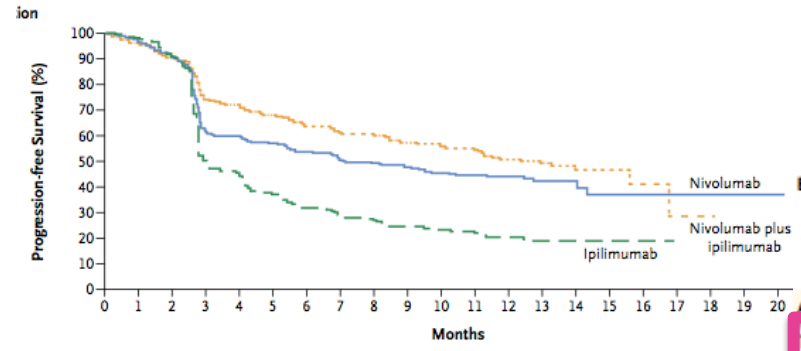
Rationale for Combination

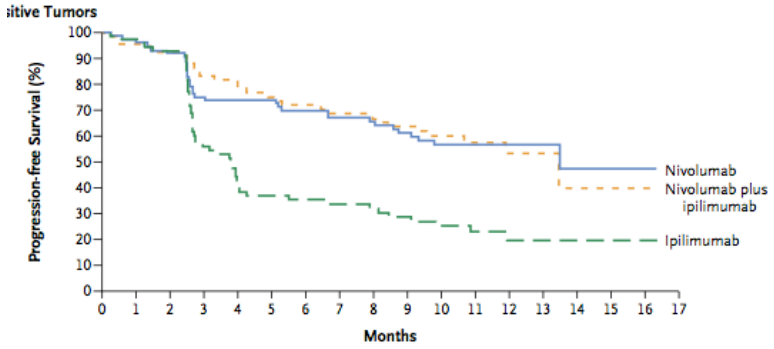
Combine TKI rapid and high response rate with immune checkpoints prolonged disease control

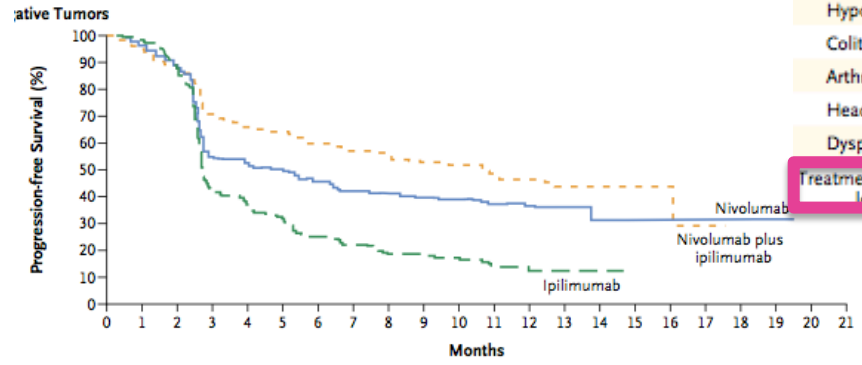


On courtesy of B Besse

Combination







Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

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 J, N Engl J Med 2015;373:23-34.

Outline

- Ongoing studies
  - Melanoma
  - NSCLC
- Dose, length of treatment
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- Combination
- **Regulatory challenges**

Regulatory challenges

Specificity of immunotherapy	Related regulatory challenge
Length of response	Lack of biomarkers for early assessment of efficacy
Heterogeneity of response (e.g. about 80 % of melanoma patients get little or no benefit from ipilimumab)	Lack of predictive biomarkers
Conventional clinical response criteria are insufficient	Lack of validated endpoints
Specific & unique side effects, possibly late effects (e.g. auto-immune reactions)	Lack of effective safety monitoring and management guidelines
Spectacular response ("breakthrough")	Justification of randomization, lack of external benchmarks & related methodology
Costs	Affordability and willingness of HTA to reimburse

Courtesy of A Negrouk

Thank you for the attention

Acknowledgments

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