ISTITUTO NAZIONALE TUMORI
RCCS – Fondazione Pascale

How do we Sequence or Combine Immunotherapies with Targeted Therapies: European Perspective

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Disclosures

- **Employment or Leadership Position:** None
- **Consultant/Advisory Role:** Bristol-Meyers Squibb, Merck Sharp & Dohme, Roche-Genentech, Ventana, Novartis, Amgen, Array
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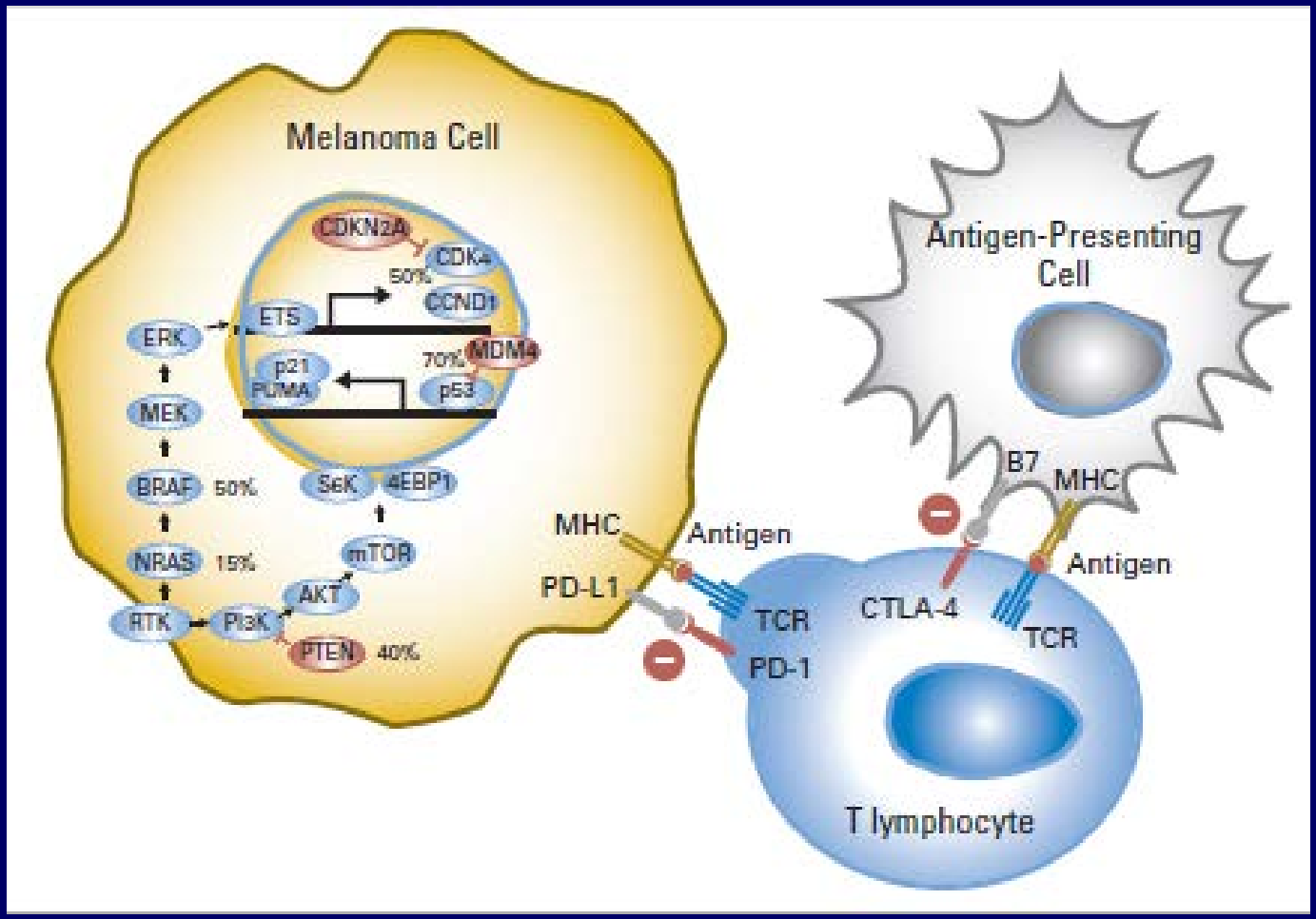
- **Other Remuneration:** None

How do we Sequence or Combine Immunotherapies with Targeted Therapies ?

The answer to this question is in a perspective, randomized,

clinical trial

Targeting Oncogenic Drivers and the Immune System in Melanoma



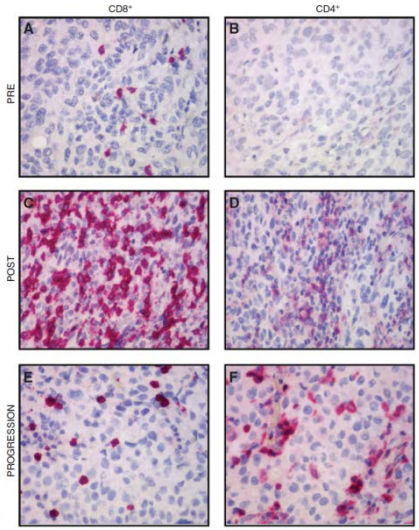
McArthur & Ribas, J Clin Oncol, 2013.

Summary of Published Data of Immunotherapy in Combination with Targeted Agents

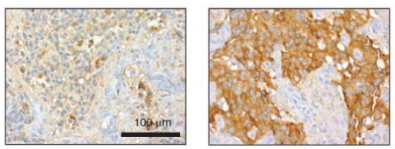
- The combination of ipilimumab with targeted agents could in theory result in synergistic effects

Jang, S, Atkins M. Lancet Oncol 2013;14:e60–9
Ribas A, et al. N Engl J Med 2013;368:1365–6

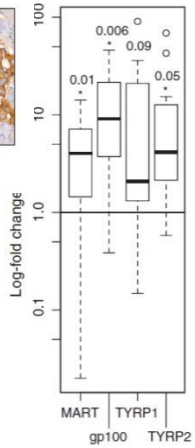
Effect of BRAF inhibitors on the immune system

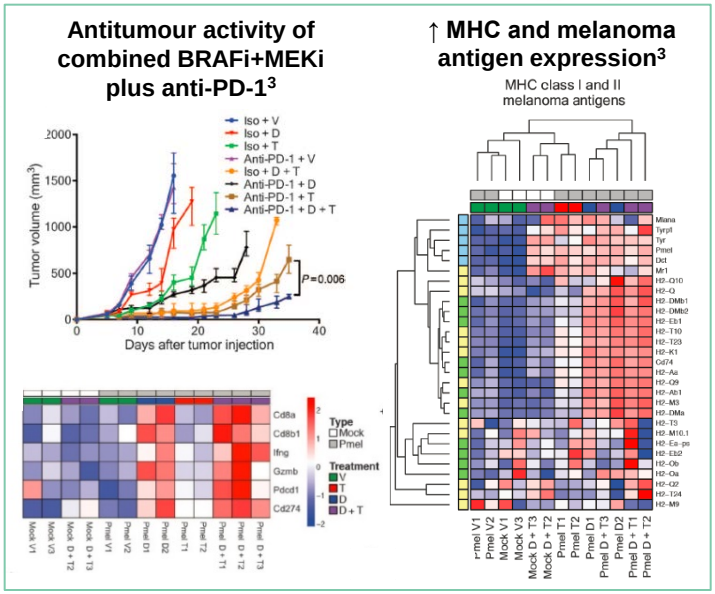


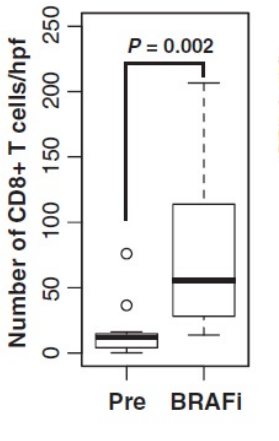
CD4+ and CD8+ increase in responder lesion and decrease in lesions which progressed

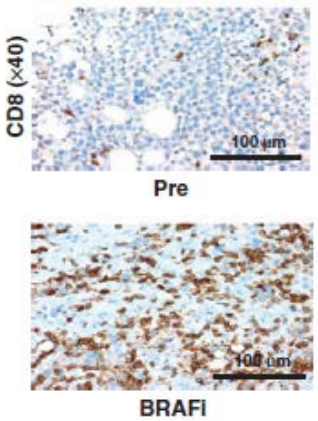


BRAF inhibition is associated with increased melanoma antigen expression in tumours of patients with metastatic melanoma





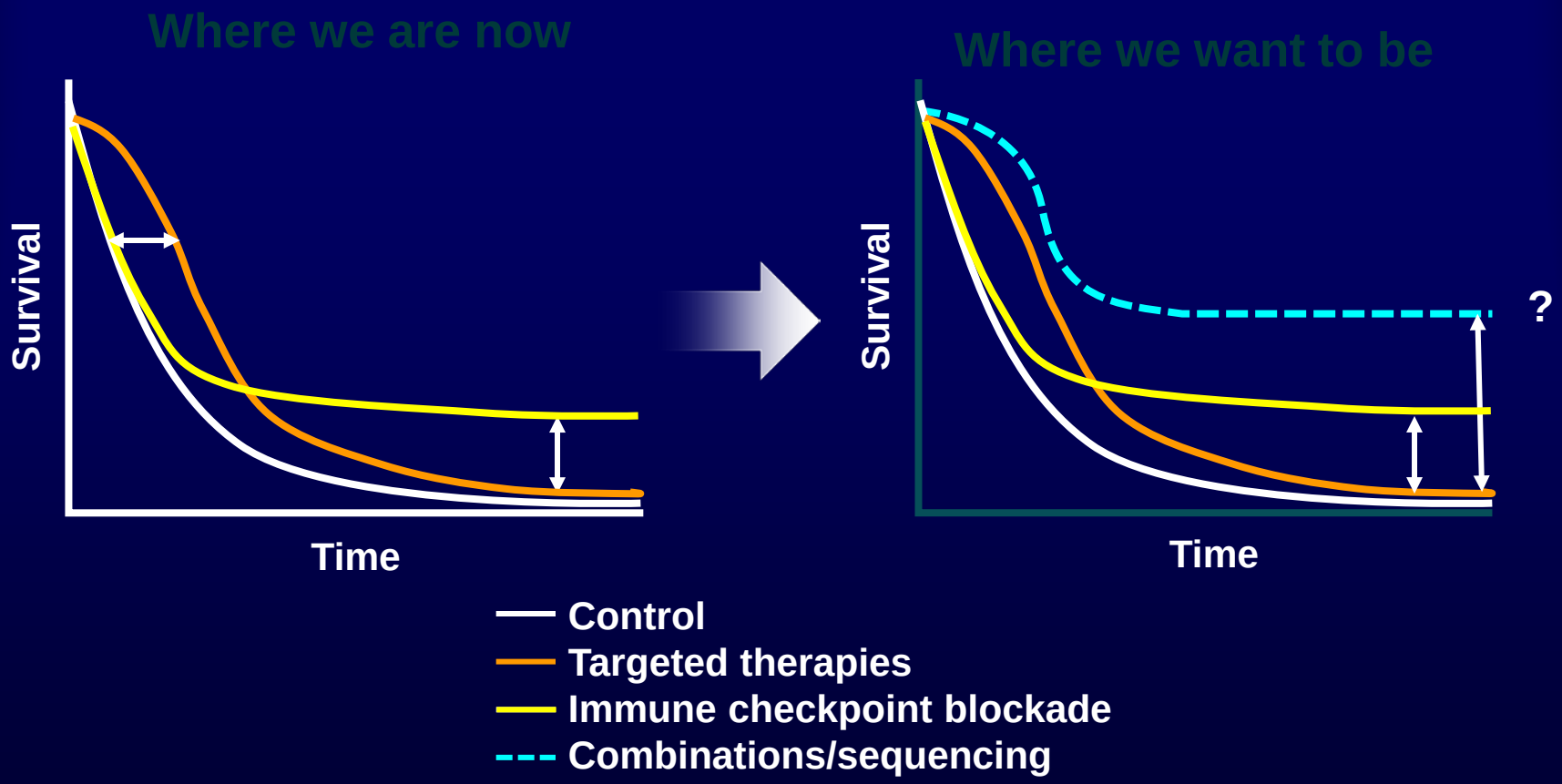




BRAF inhibition is associated with increased CD8+ T-cell infiltrate in tumours of patients with metastatic melanoma

Wilmott JS, *et al*. Clin Cancer Res 2011;18:1386–94, Reprinted from Clinical Cancer Research 2012, with permission from AACR
Frederick DT, *et al*. Clin Cancer Res 2013;19:1225–31, Reprinted from Clinical Cancer Research 2013, with permission from AACR
3. From Hu-Lieskovan S *et al*. Sci Transl Med 2015;7:279ra41., Reprinted with permission from AAAS

Hypothetical effect of targeting distinct and potentially complementary immune evasion pathways: advanced melanoma



Hypothetical slide illustrating a scientific concept, and is beyond data available to date
These charts are not intended to predict what may actually be observed in clinical studies

1. Adapted from Ribas A, presented at WCM, 2013; 2. Ribas A, et al. Clin Cancer Res 2012;18:336–341
3. Drake CG. Ann Oncol 2012;23(suppl 8):viii41–viii46

Summary of Published Data of Immunotherapy in Combination with Targeted Agents

- The combination of ipilimumab with targeted agents could in theory result in synergistic effects
- Concurrent administration of vemurafenib and ipilimumab may not be feasible
  - Increased incidence of hepatotoxicity observed in a phase 1 safety study
  - Toxicity may preclude adequate dosing

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Hepatotoxicity with Combination of Vemurafenib and Ipilimumab

TO THE EDITOR: There has been great interest in testing combination therapy with the BRAF inhibitor vemurafenib and the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)–blocking antibody ipilimumab, currently the only two agents approved for the treatment of advanced melanoma on the basis of improved overall survival.[1] Vemurafenib and ipilimumab have different mechanisms of action, and preclinical studies have suggested that BRAF inhibitors may enhance immune-cell function and antigen presentation.[2-5] The only clinically significant overlapping toxic effects for these agents are in skin and liver, which rarely limit their use in patients. Therefore, ample rationale exists to investigate combined therapy with these two agents.

Table 1. Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab.*

Study Cohort and Patient No.	No. of Doses of Ipilimumab before ALT–AST Elevation	Time to Onset of ALT–AST Elevation after First Dose of Ipilimumab	Treatment	Time to Resolution of ALT–AST Elevation	Toxicity Relapse with Repeated Ipilimumab
First cohort					
4	1	21 days	Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab permanently discontinued	4 days	NA
5	2	36 days	Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (2 doses)	6 days	No
6†	1	21 days	Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab continued (1 dose)	6 days	No
8	1	19 days	Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (1 dose)	12 days	Yes
Second cohort					
10	1	15 days	Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued	10 days	NA
16‡	1	13 days	Vemurafenib and ipilimumab permanently discontinued	20 days	NA

Jang, S, Atkins M. Lancet Oncol 2013;14:e60–9
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- Phase 1 data show that combinations of dabrafenib + ipilimumab with or without trametinib are not associated with hepatotoxicity

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- The triplo combo ipilimumab/dabrafenib/trametinib is not feasible due to the increase of gastro-intestinal toxicity (bowel perforation)
- Sequential treatment with ipilimumab and targeted therapies may be a more appropriate therapeutic approach

Ackerman A, et al. J Clin Oncol 2012; 30 (suppl): abstract 8569
Ascierto PA, et al. J Transl Med 2012;10: Epub ahead of print
Jang, S, Atkins M. Lancet Oncol 2013;14:e60–9
Ribas A, et al. N Engl J Med 2013;368:1365–6
Puzanov I, et al. J Clin Oncol 2014;32(suppl 5s): abstract 2511

Summary of Published Data in Combination with Targeted Agents (cont'd)

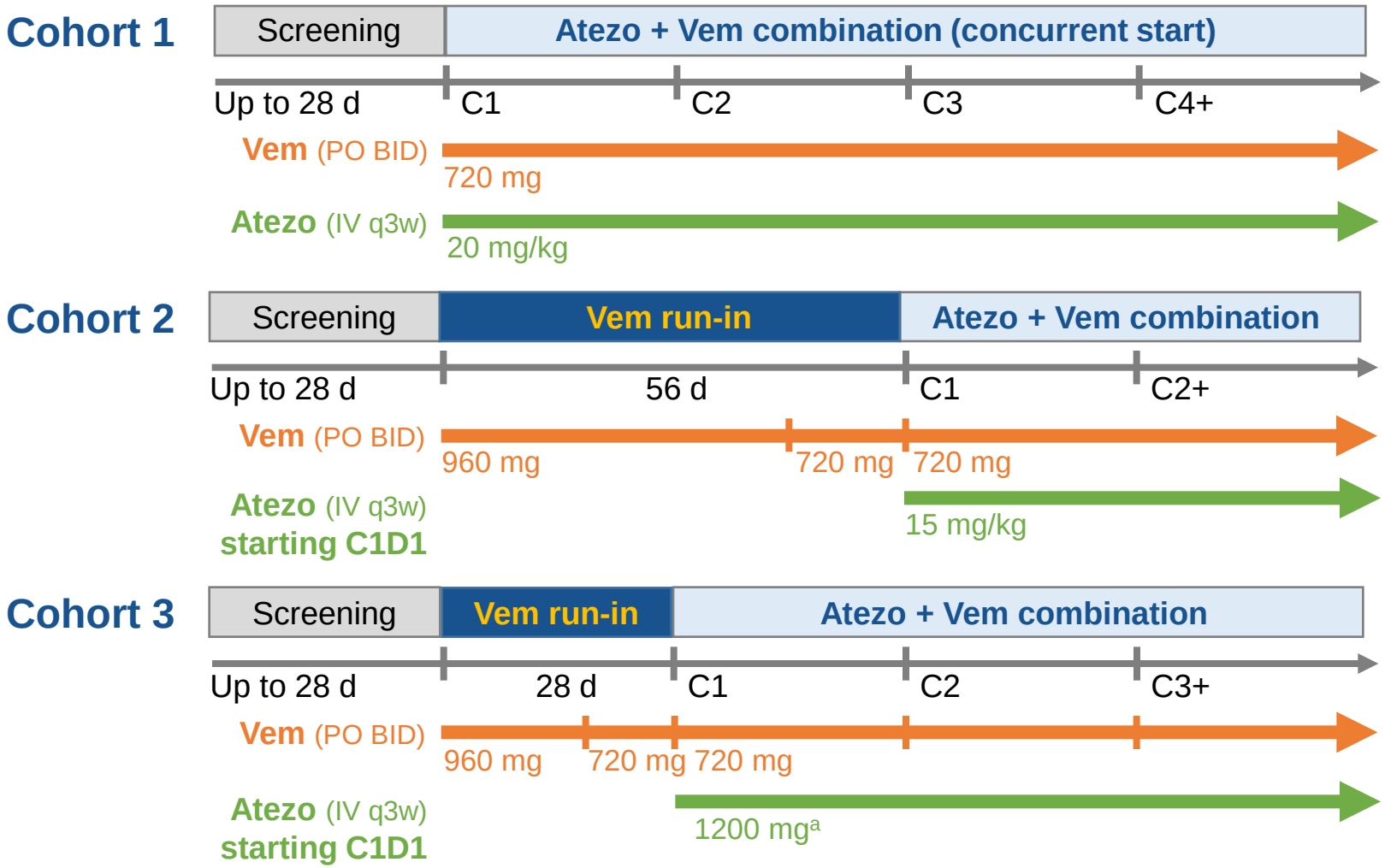
- What about the combo anti-PD-1/PD-L1 with Target Therapy ?

Preliminary clinical safety, tolerability and activity results from a Phase Ib study of atezolizumab (anti-PDL1) combined with vemurafenib in $BRAF^{V600}$ mutant metastatic melanoma

Ryan Sullivan,[1] Omid Hamid,[2] Manish Patel,[3] F. Stephen Hodi,[1] Rodabe Amaria,[4] Peter Boasberg,[2] Jeffrey Wallin,[5] Xian He,[5] Edward Cha,[5] Nicole Richie,[5] Marcus Ballinger,[5] Patrick Hwu[4]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]The Angeles Clinic and Research Institute, Los Angeles, CA; [3]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [4]MD Anderson Cancer Center, Houston, TX; [5]Genentech, Inc., South San Francisco, CA

Study Design

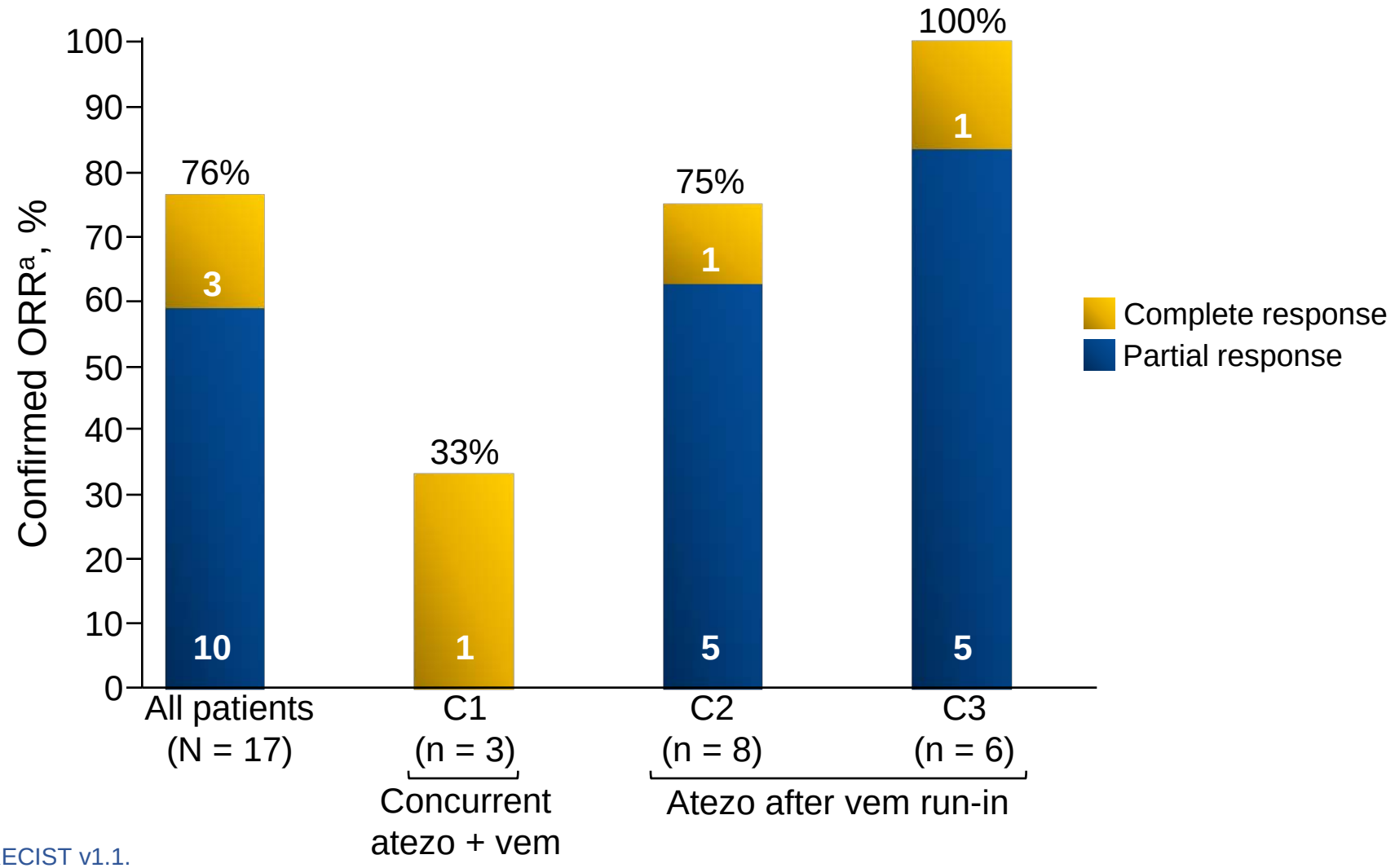


- Treatment continuation until intolerable toxicity or loss of clinical benefit

[a]Weight-based dosing of atezolizumab updated to comparable fixed dose during Cohort 3.

Sullivan R, et al., Atezo + Vem *Melanoma Bridge* 2015

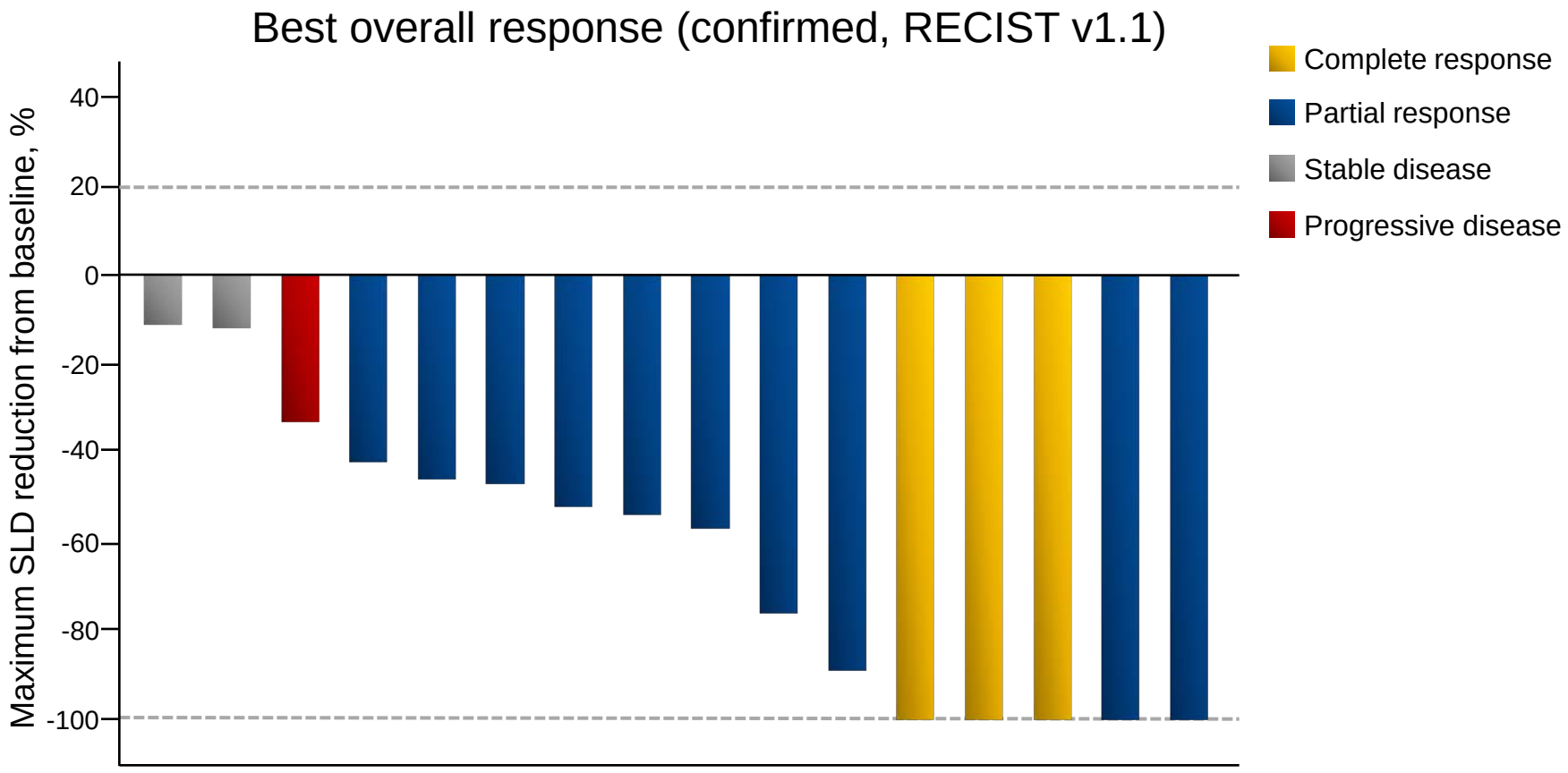
Efficacy: Objective Response Rate



[a]Per RECIST v1.1.
C1, Cohort 1; C2, Cohort 2; C3, Cohort 3.
Numbers within bars represent number of patients responding within each cohort.
Data cut-off September 8, 2015.

Sullivan R, et al., Atezo + Vem *Melanoma Bridge* 2015

Efficacy: Best Change in Tumor Burden

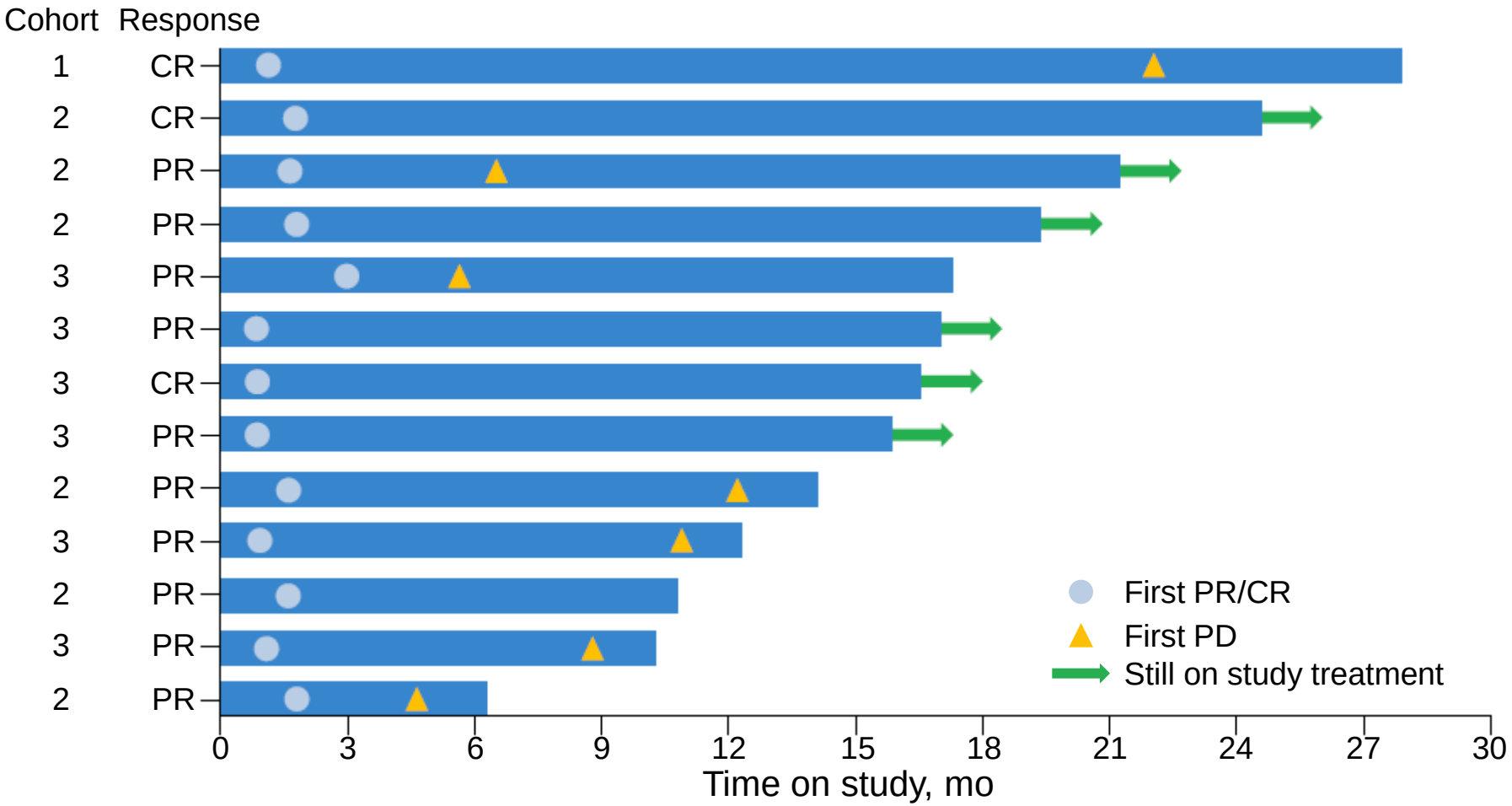


- 16/16 (100%) patients evaluable for tumor response had reduction in target lesions[a]

[a]One additional patient was not evaluable for post-baseline target lesion change.
Data cut-off September 8, 2015.

Sullivan R, et al., Atezo + Vem *Melanoma Bridge* 2015

Efficacy: Duration of Treatment and Response



Median duration of response: 20.9 mo (6.9, NE)

NE; not estimable.
Data cut-off September 8, 2015.

Sullivan R, et al., Atezo + Vem *Melanoma Bridge* 2015

Safety Summary

	All N = 17	Concurrent atezo + vem	Staggered atezo + vem	
		C1 n = 3	C2 n = 8	C3 n = 6
Median safety follow-up, mo	12.3	6.5	10.6	14.2
All treatment-emergent AEs	100%	100%	100%	100%
Grade 3 atezo-related AEs	41%	67%	38%	33%
Grade 3 vem-related AEs (during combination period)	59%	100%	50%	50%

- No treatment-related G4 AEs occurred
- No G5 AEs occurred
- Treatment-related SAEs included pyrexia and dehydration (n = 1), which were resolved
- No atezo-related AEs resulted in treatment discontinuation

Staggered dosing of atezo + vem after vem run-in was better tolerated than concurrent dosing

Safety evaluable population includes all patients who received ≥ 1 dose of atezolizumab.
Data cut-off September 8, 2015.

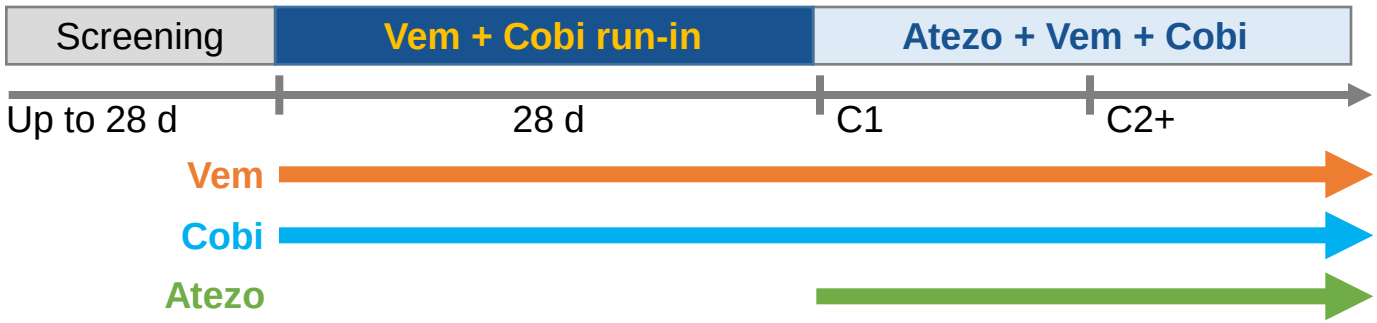
Sullivan R, et al., Atezo + Vem *Melanoma Bridge* 2015

Additional Cohorts: Triple Combination Therapy Including the MEK Inhibitor Cobimetinib

- Improved clinical benefit observed when vemurafenib combined with cobimetinib in patients with unresectable or metastatic *BRAF*^{V600}-mutated melanoma[1]
  - mPFS increased from 7.2 mo to 12.3 mo
  - ORR increased from 50% to 70%
- Vem + cobi treatment resulted in superior OS vs vem + placebo treatment in this patient population[2]
- Triple combination therapy (atezo + vem + cobi) might further enhance clinical benefit

Run-in with vem + cobi, followed by atezo + vem + cobi combination treatment

Cohort 4 and Expansion Phase



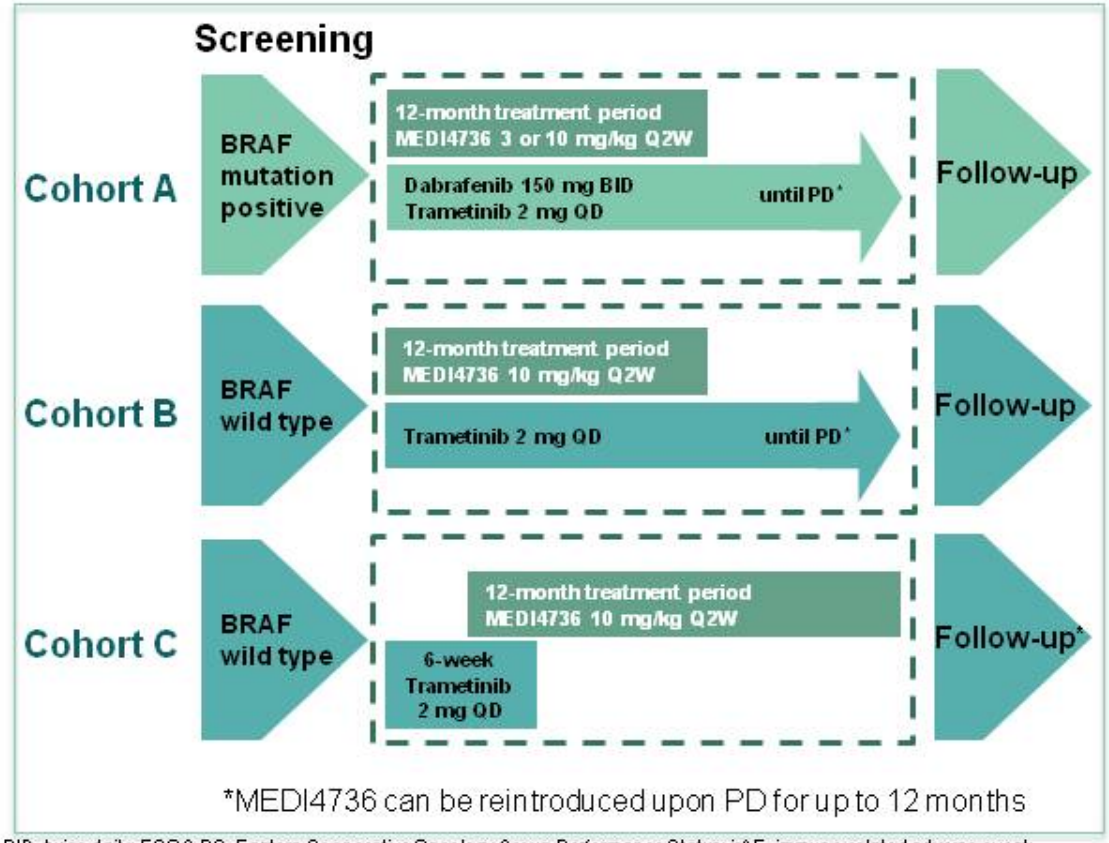
- Currently enrolling patients

Cobi, cobimetinib.

1. COTELLIC (cobimetinib) prescribing information, Genentech, 2015.
2. Atkinson et al., *SMR* 2015.

MEDI4736 in Combination with Targeted Agents

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

PRESENTED AT: ASCO Annual '15 Meeting

Patient baseline demographics

Characteristic	Cohort A (n=26) D + T + M	Cohort B (n=20) T + M	Cohort C (n=19) T → M
Mean age, years (range)	47.2 (23–71)	62.2 (31–85)	58.7 (34–84)
Sex			
Male (%)	14 (54)	13 (65)	10 (53)
ECOG status			
0 (%)	19 (73)	13 (65)	---
1 (%)	5 (19)	7 (35)	---
NA (%)	2 (8)	0 (0)	19 (100)[a]
Mutation status			
BRAF WT (%)	0 (0)	20 (100)	19 (100)
BRAF V600E (%)	19 (73)	0 (0)	0 (0)
BRAF V600E/K (%)	7 (27)	0 (0)	0 (0)
NRAS (%)	0 (0)	3 (15)	6 (32)
Stage at study entry			
Stage III (%)	5 (19)	2 (10)	4 (21)
Stage IV (%)	21 (81)	18 (90)	15 (79)
Median no. prior systemic regimens (range)	0 (0–2)	2 (0–4)	1 (0–4)
Patients who received prior systemic therapy, n (%)	10 (38)	12 (60)	14 (74)
Patients who received prior immunotherapy in adjuvant or metastatic setting, n			
Anti-CTLA-4 (%)	6 (23)	11 (55)	8 (42)
Anti-PD-1 (%)	0 (0)	6 (30)	5 (26)
Cytokine-based therapy (%)	7 (27)	7 (35)	6 (32)

[a]Per protocol, ECOG status for Cohort C was not collected prior to first dose of study drug, but all patients were required to be ECOG 0 to 1 per eligibility criteria

Data cut-off: 7 May 2015

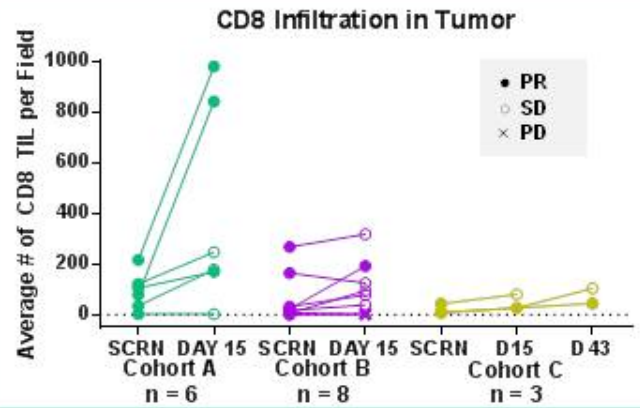
Median follow-up duration:

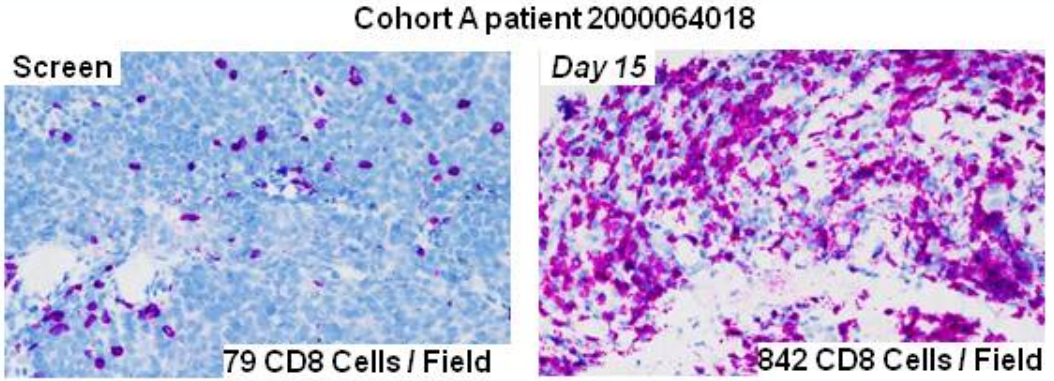
- Cohort A 7.1 mo
- Cohort B 6.8 mo
- Cohort C 3.7 mo

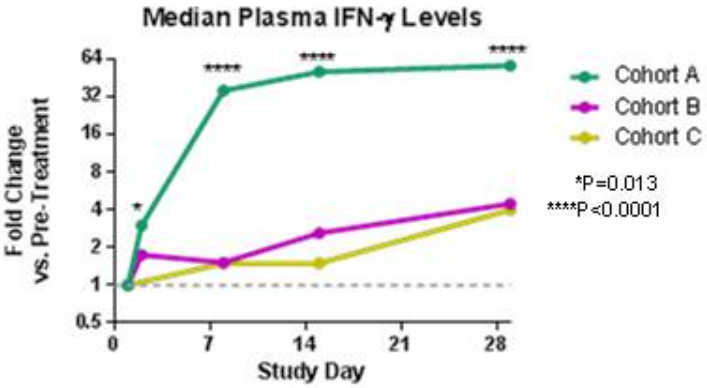
Median exposure duration:

- Cohort A 6.4 mo
- Cohort B 4.1 mo
- Cohort C 2.7 mo

Immune activation post-treatment



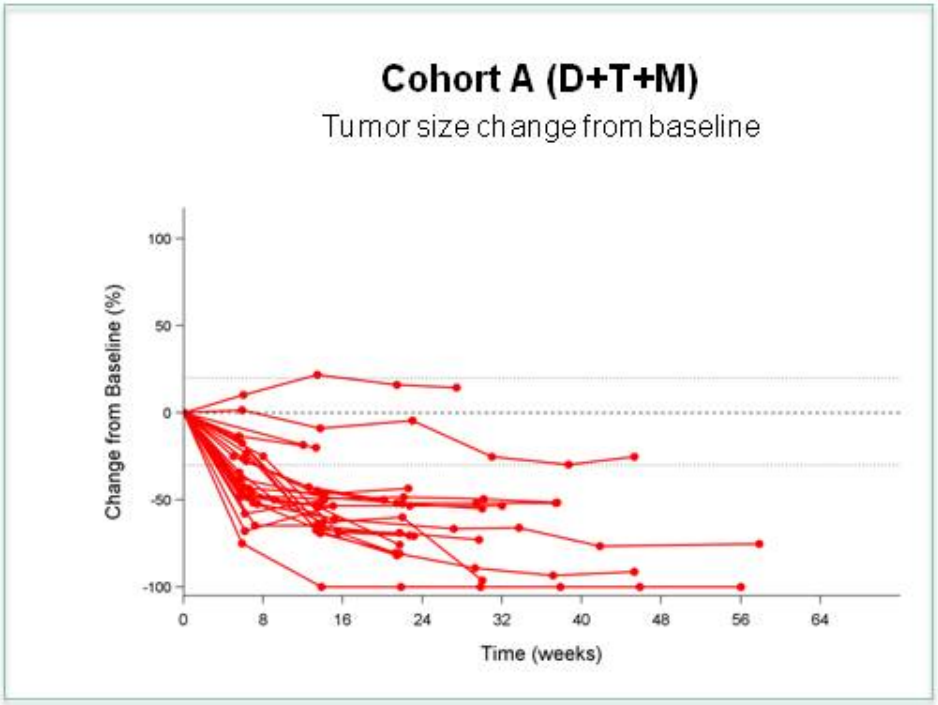




- Evidence of immune activation is observed post-treatment in all cohorts
  - Frequency of tumor-infiltrating CD8 T cells increases post-treatment
  - Levels of interferon gamma and other Th1-associated factors in plasma are increased post-treatment
- More dramatic and consistent changes are observed in Cohort A versus Cohorts B and C

PR, partial response

Tumor size change and time to response: Cohort A



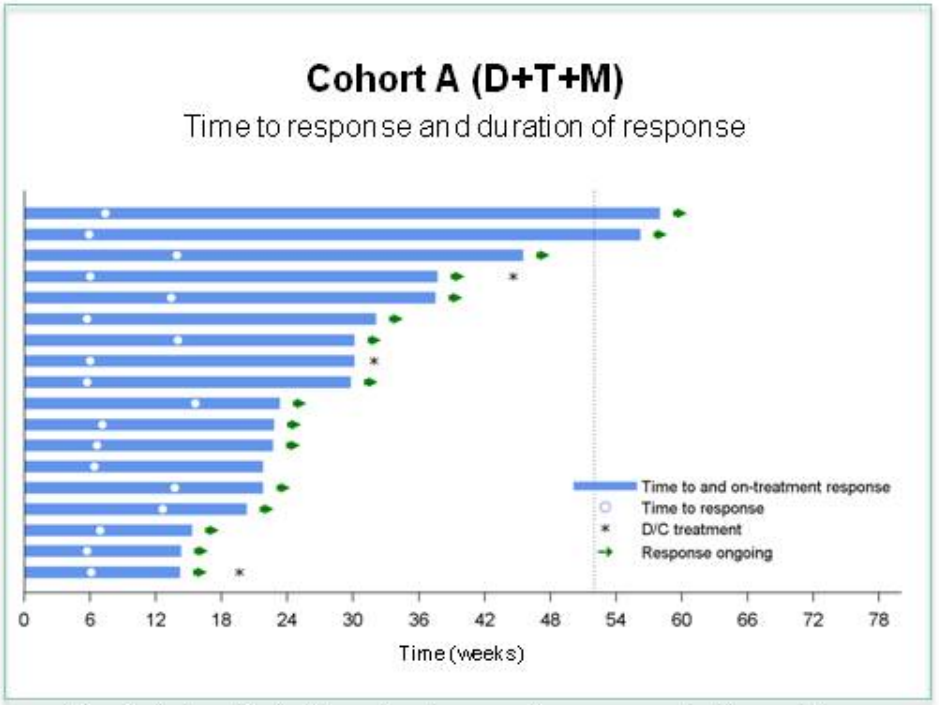
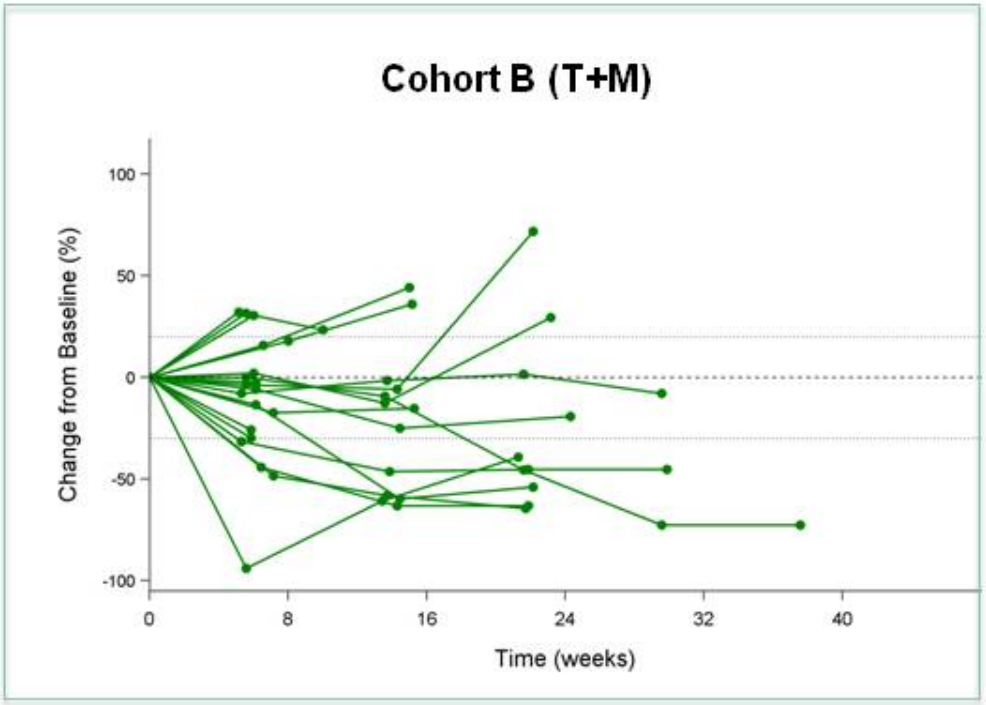
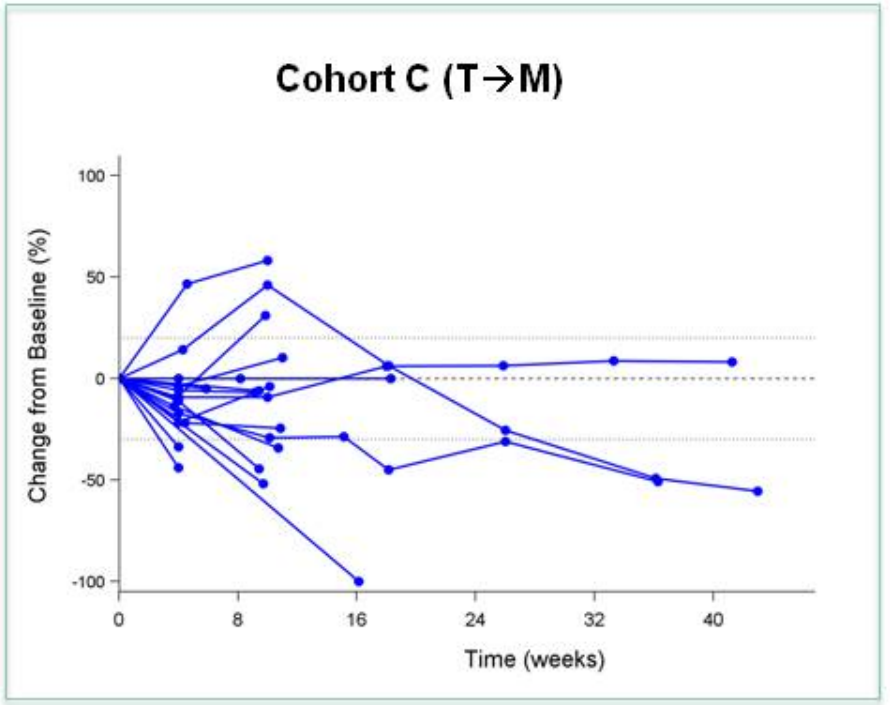


Figure includes subjects with confirmed response in response evaluable population;
D/C treatment=Discontinuation of the regimen

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

Tumor size change from baseline: Cohort B and Cohort C





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

MEDI4736 in Combination with Targeted Agents

Summary of drug-related adverse events

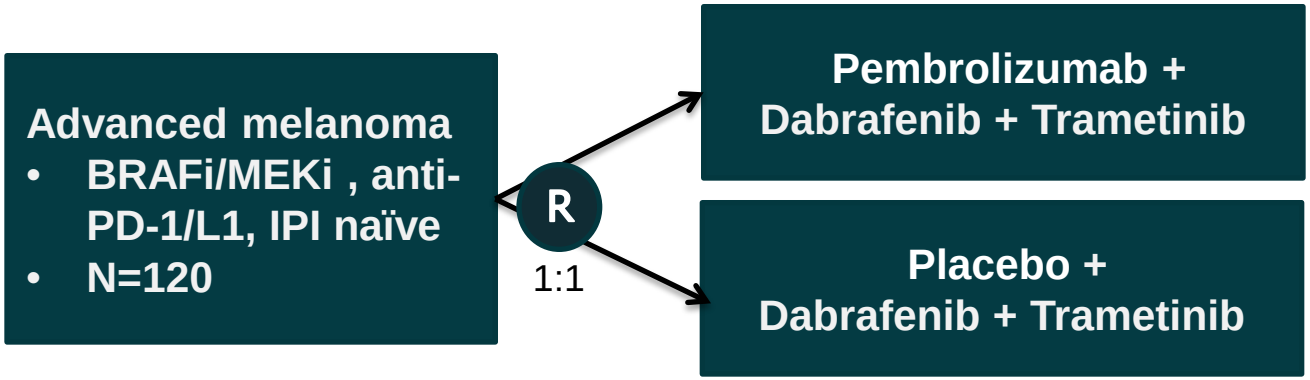
Drug-Related Adverse Event (AE), n (%)[a]	Cohort A (n=26) D + T + M	Cohort B (n=20) T + M	Cohort C (n=19) T → M (sequential)
Any AE	26 (100)	20 (100)	18 (95)
Grade ≥3 AE	12 (46)	9 (45)	9 (47)
Serious AE	8 (31)	4 (20)	4 (21)
AE leading to discontinuation of any drug[b]	3 (12)	3 (15)	4 (21)
AE leading to death	0 (0)	0 (0)	0 (0)
AE related to MEDI4736	14 (54)	7 (35)	8 (42)
AE related to dabrafenib and/or trametinib	22 (85)	19 (95)	15 (79)

- Dose-limiting toxicities were observed in two patients:
  - reversible Grade 3 thrombocytopenia in Cohort A1 (MEDI4736 3 mg/kg)
  - reversible Grade 3 choroidal effusion in Cohort B
- Full doses of all agents were tolerable and chosen for expansion:
  - MEDI4736 10 mg/kg Q2W + dabrafenib 150 mg BID +/or trametinib 2 mg QD

[a]Patients counted once per category regardless of number of events. [b]In Cohort A (n=3): platelet count decreased (n=1), pyrexia (n=1), and pyrexia, myalgia, and arthralgia in 1 patient: In Cohort B (n=3): skin and subcutaneous tissue disorders (n=1), retinal vein occlusion (n=1), and blurred vision and choroidal effusion with ciliary body shutdown in 1 patient; In Cohort C (n=4): elevated LFTs (n=1), creatinine kinase elevation (n=1), skin urticaria (n=1) and lipase increased (n=1).

Data cut-off: 7 May 2015

KEYNOTE-022 Phase 2 Trial Design



- Primary endpoint: PFS
- Interim Analysis for early efficacy signal

Clinicaltrials.gov

Sequencing- Considerations

- **Immunotherapy (IT) and Target Therapy (TT) are not competitive drugs but two important opportunity for our patients**

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- **The outcome of melanoma patients has changed … from 6-9 months to 25-30 months (Combi-D, Combi-V, Keynote001) … this is mainly due to the availability of new treatment ….(sequencing). Patients treated with both the drugs have a better outcome**

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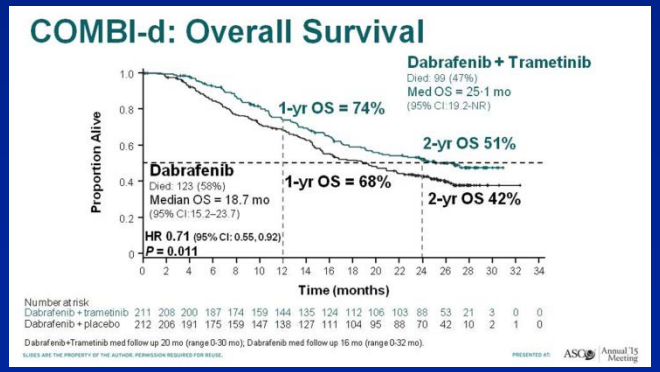
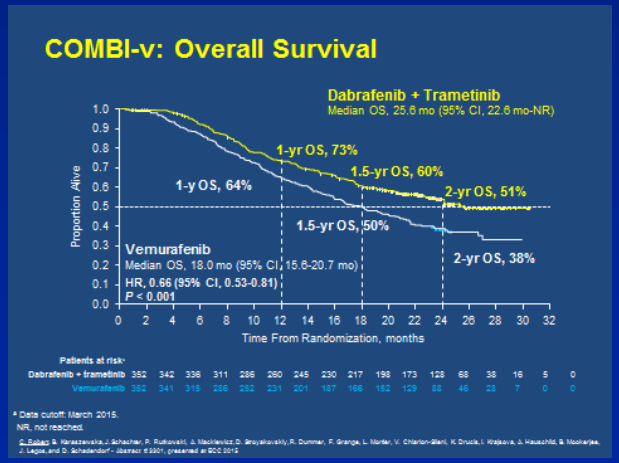
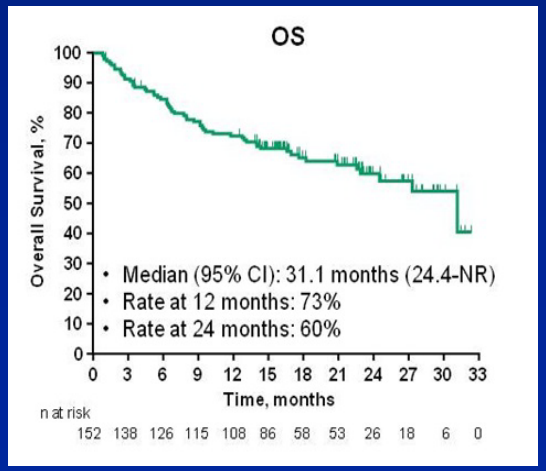
- The outcome of melanoma patients has changed … from 6-9 months to 25-30 months (Combi-D, Combi-V, Keynote001) … this is mainly due to the availability of new treatment ….(sequencing). Patients treated with both the drugs have a better outcome







Sequencing- Considerations

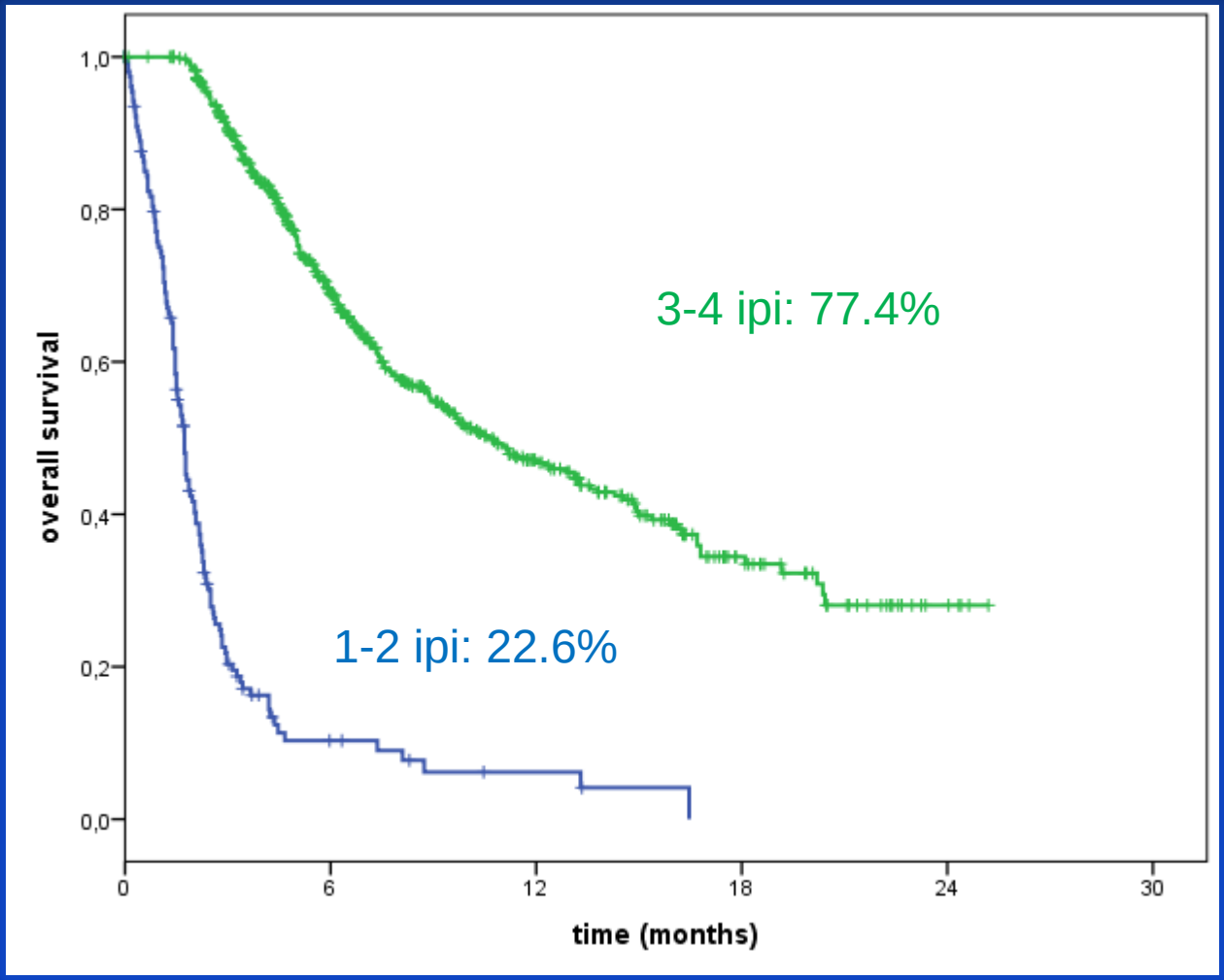
- **Immunotherapy (IT) and Target Therapy (TT) are not competitive drugs but two important opportunity for our patients**

- **The outcome of melanoma patients has changed … from 6-9 months to 25-30 months (Combi-D, Combi-V, Keynote001) … this is mainly due to the availability of new treatment ….(sequencing). Patients treated with both the drugs have a better outcome**

- **IT has a slow action [Ipilimumab-to be effective it should be completed the treatment (4 cycles)] but it's able to achieve long-term response. Anti-PD-1s have a faster action than ipi**

EAP ipilimumab 3 mg/kg

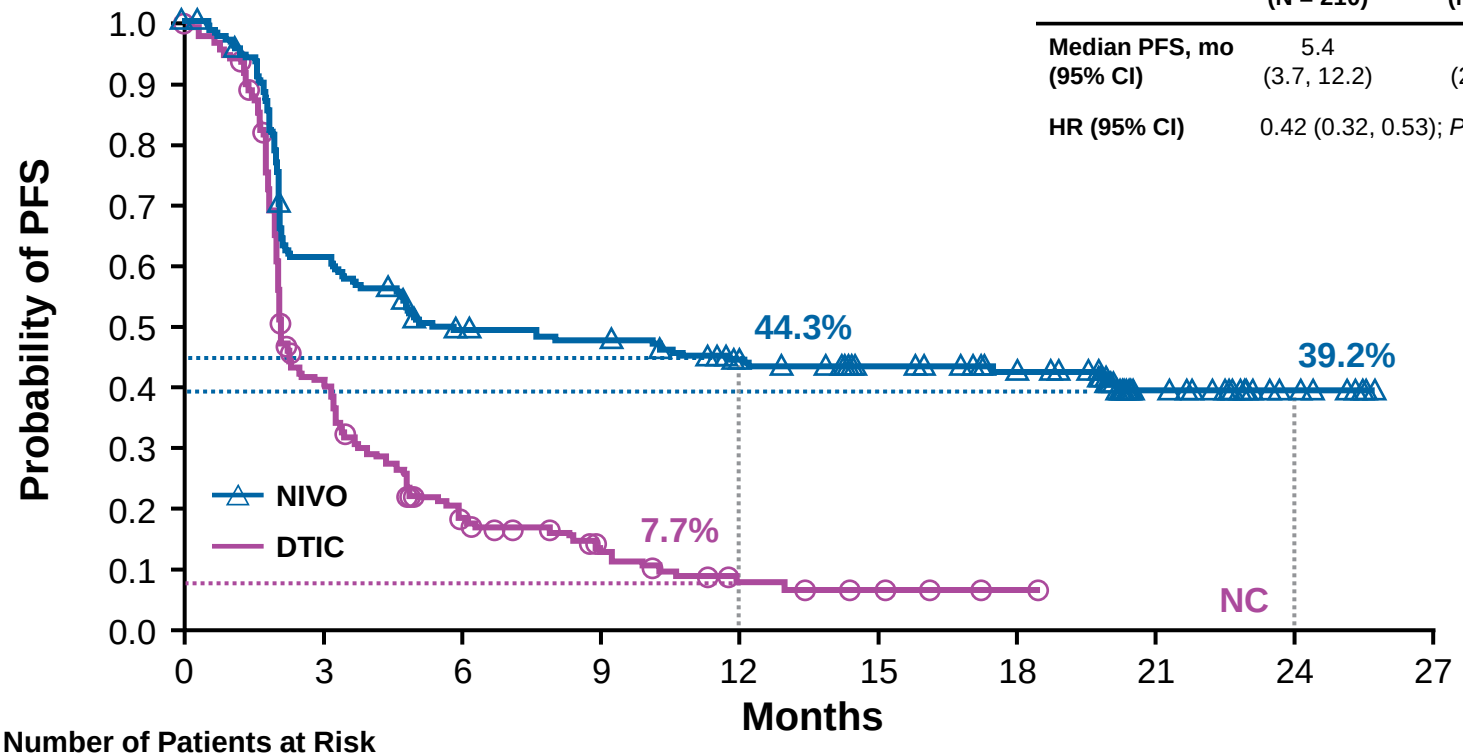
OS for all patients: number of cycles



Ascierto et al. J Trans Med 2014

Progression-Free Survival – NIVO vs DTIC

	NIVO (N = 210)	DTIC (N = 208)
Median PFS, mo (95% CI)	5.4 (3.7, 12.2)	2.2 (2.1, 2.5)
HR (95% CI)	0.42 (0.32, 0.53); *P* < 0.0001	



Number of Patients at Risk

NIVO	210	119	92	88	76	61	52	23	7	0
DTIC	208	75	33	17	7	4	1	0	0	0

CI = confidence interval; HR = hazard ratio; mo = month; NC = not calculated

Sequencing- Considerations

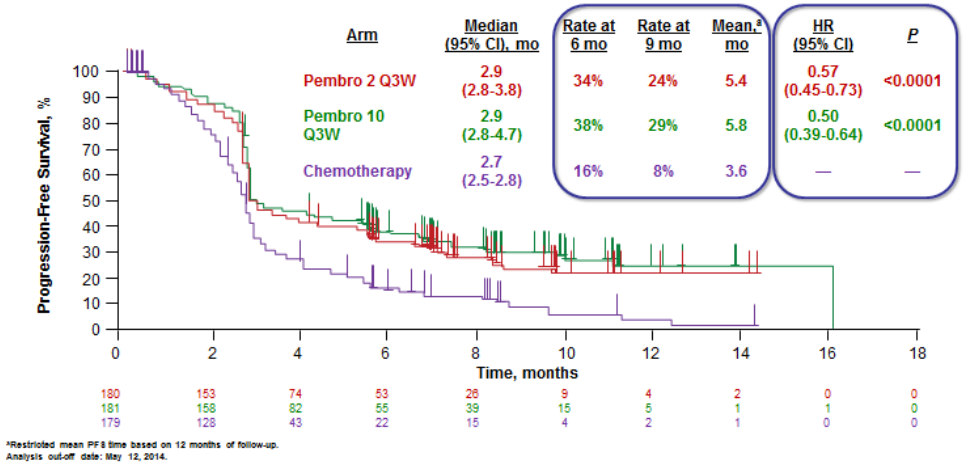
- Immunotherapy (IT) and Target Therapy (TT) are not competitive drugs but two important opportunity for our patients
- The outcome of melanoma patients has changed … from 6-9 months to 25-30 months (Combi-D, Combi-V, Keynote001) … this is mainly due to the availability of new treatment ….(sequencing). Patients treated with both the drugs have a better outcome
- IT has a slow action [Ipilimumab-to be effective it should be completed the treatment (4 cycles)] but it's able to achieve long-term response. Anti-PD-1s have a faster action than ipi
- TT has a faster action but resistance is still a problem. 40% of patients who progress from BRAFi monotherapy has a fast progression which can affect second line treatment. This phenomenon is less evident with the combo BRAFì+MEKì but still a problem

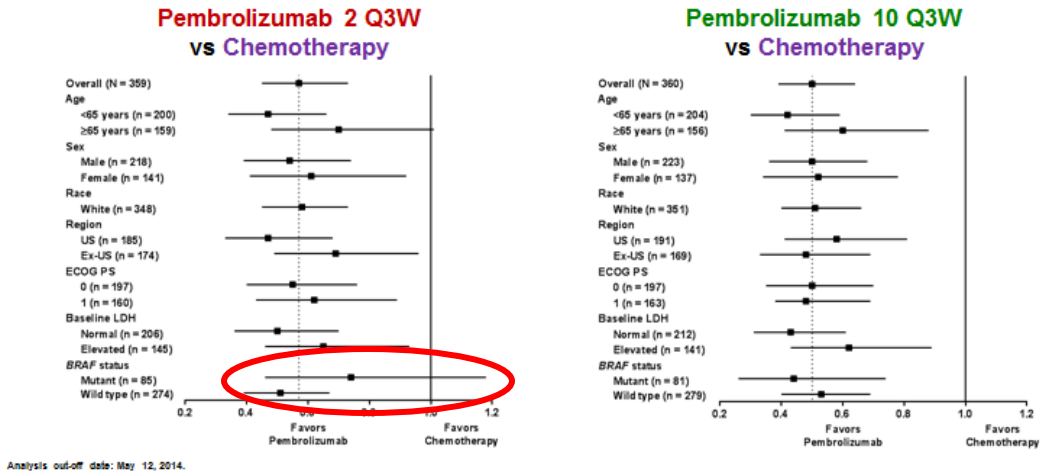
Different evidences of rapid progression disease after BRAF inhibitors treatment

Experience	Patients sample (n)	% of patients with a rapid disease progression kinetics
BRIM-2	39	41%
BRIM-3	42	52%
Ascierto et al.	28	43%
Ackerman et al.	32	50%
Italian ipilimumab EAP	54	41%
Fisher et al.	42	38%

Ascierto et al. J Trans Med 2013

Pembrolizumab: data from the randomized phase II study in ipilimumab refractory advanced melanoma patients (KEYNOTE-002): pembrolizumab (2 mg/kg Q3W and 10 mg/kg Q3W) vs investigator chemotherapy choiche (ICC)





Both pembrolizumab doses substantially improved PFS compared with chemotherapy ($P < 0.0001$).

Mean PFS up to 12 months of follow-up was approximately 2-fold longer with pembrolizumab.

PFS HR was 0,57 for pembro 2 mg/kg Q3W vs ICC, and 0,50 for pembro 10 mg/kg Q3W vs ICC.

ORR was 21% for pembro 2 mg/kg Q3W, 25% for pembro 10 mg/kg Q3W, and 4% for ICC.

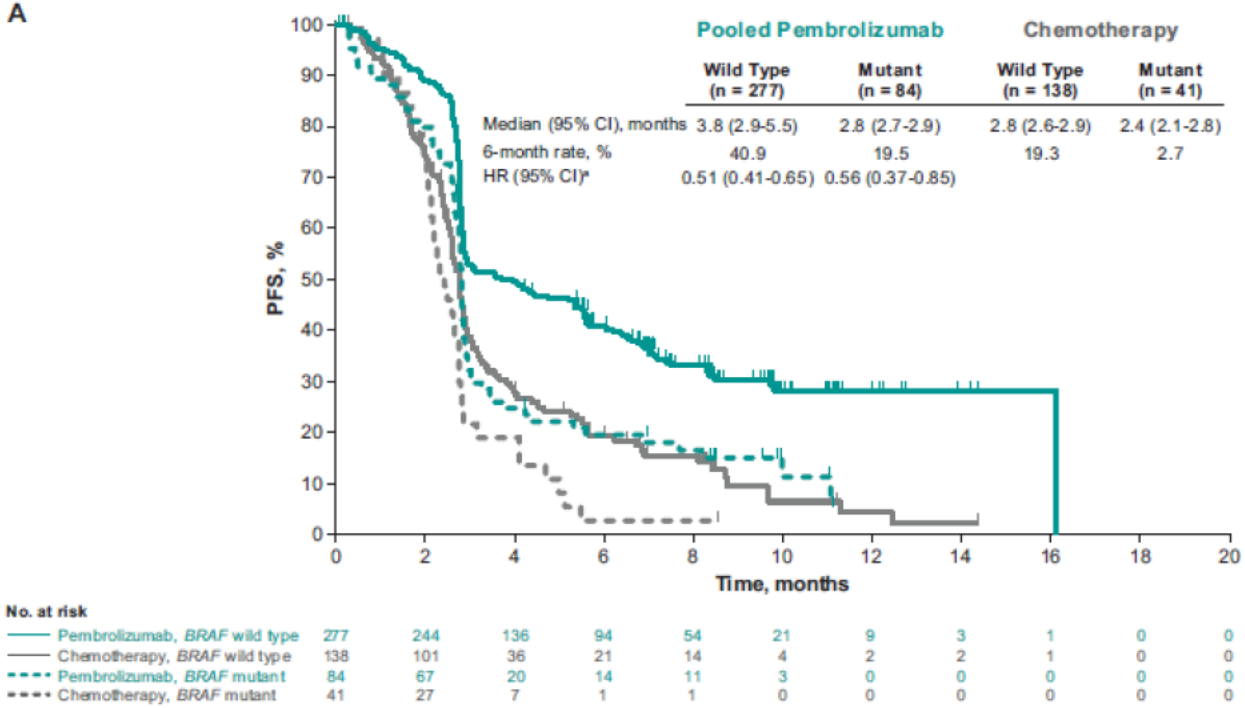
Median duration of response not reached for pembrolizumab, 37 weeks for chemotherapy

There was no significant differences in PFS, ORR, or duration of response between pembrolizumab doses.

Ribas A et al.Lancet Oncol 2015 Jun 23. pii: S1470-2045(15)00083-2

Relationship Between *BRAF*^{V600} Status and PFS (RECIST v1.1, Central Review): KEYNOTE-002

A



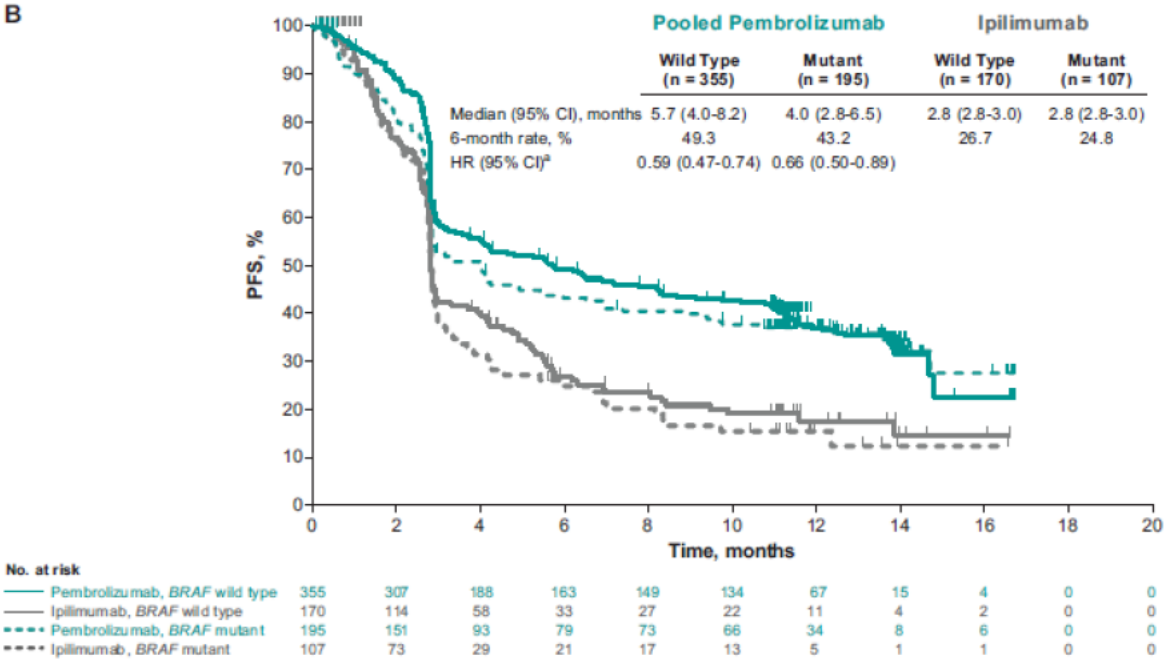
- In KEYNOTE-002, patients with *BRAF*^{V600}–wild-type melanoma had longer PFS than patients with *BRAF*^{V600}-mutant melanoma in the pembrolizumab and chemotherapy arms

BRAFi = BRAF inhibitor; CI = confidence interval; HR = hazard ratio; NR = not reached. [a]Hazard ratios are for the comparison of pembrolizumab versus control for each subgroup.

Puzanov I et al SMR 2015

Relationship Between *BRAF*^{V600} Status and PFS (RECIST v1.1, Central Review): KEYNOTE-006

B



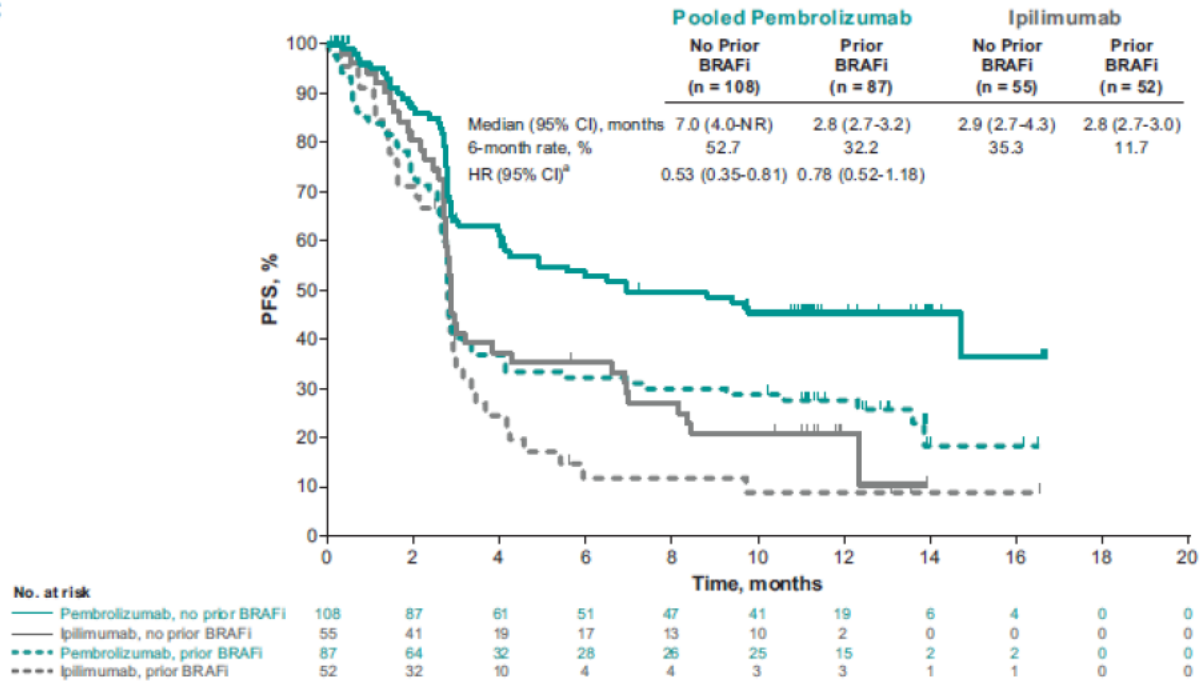
- In KEYNOTE-006, PFS was similar in patients with *BRAF*^{V600}-mutant melanoma and in patients with *BRAF*^{V600}–wild-type melanoma in the pembrolizumab and ipilimumab arms

BRAFi = BRAF inhibitor; CI = confidence interval; HR = hazard ratio; NR = not reached. [a]Hazard ratios are for the comparison of pembrolizumab versus control for each subgroup.

Puzanov I et al SMR 2015

Relationship Between Treatment With Versus Without *BRAF* Inhibitor in *BRAF*^{V600} Mutant Patients and PFS (RECIST v1.1, Central Review): KEYNOTE-006

C

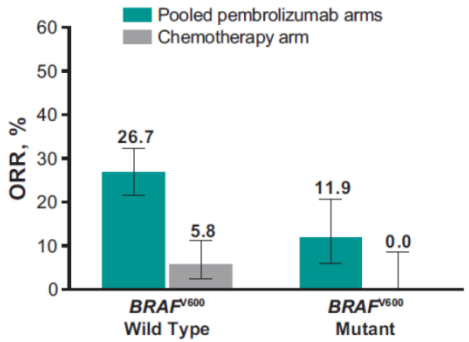


- In patients with *BRAF*^{V600}-mutant melanoma, those who were not treated with a prior BRAF inhibitor had longer PFS than patients who were treated with a prior BRAF inhibitor in the pembrolizumab and ipilimumab arms

BRAFi = BRAF inhibitor; CI = confidence interval; HR = hazard ratio; NR = not reached. [a]Hazard ratios are for the comparison of pembrolizumab versus control for each subgroup.

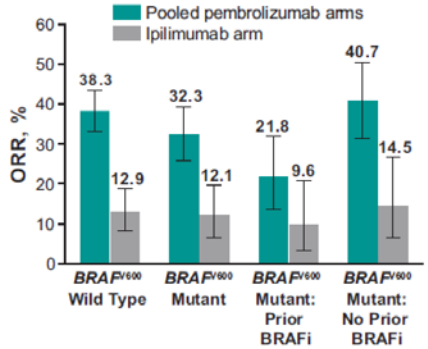
Puzanov I et al SMR 2015

Relationship Between *BRAF*^{V600} Status and ORR (RECIST v1.1, Central Review): KEYNOTE-002



- In KEYNOTE-002, ORR was higher in patients with *BRAF*V600–wild-type melanoma than in patients with *BRAF*V600-mutant melanoma in the pembrolizumab and chemotherapy arms

Relationship Between *BRAF*^{V600} Status, Receiving BRAF Inhibitor Therapy and ORR (RECIST v1.1, Central Review): KEYNOTE-006



- ORR was similar in patients with *BRAF*V600-mutant melanoma and in patients with *BRAF*V600–wild-type melanoma in the pembrolizumab and ipilimumab arms
- ORR was higher in patients with *BRAF*V600-mutant melanoma not treated with a prior BRAF inhibitor compared with patients with *BRAF*V600-mutant melanoma who did receive a prior BRAF inhibitor in the pembrolizumab and ipilimumab arms

Puzanov I et al SMR 2015

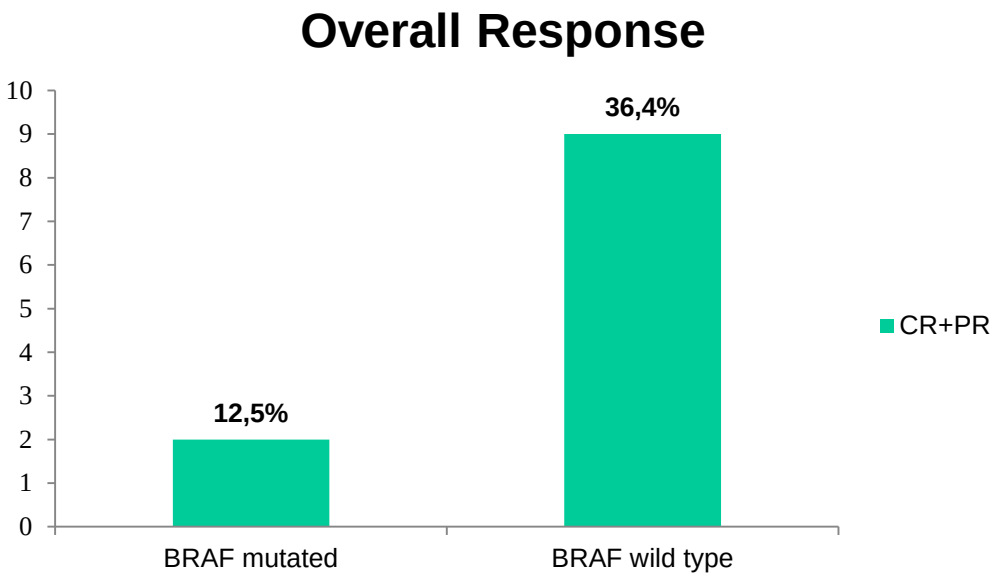
Correlation between BRAF mutational status and clinical response to pembrolizumab in advanced melanoma patients

Ester Simeone[1], Antonio Maria Grimaldi[1], Lucia Festino[1], Diana Giannarelli[2], Marco Palla[1], Corrado Caracò[3], Marcello Curvietto[1], Assunta Esposito[1], Maria Chiara Grimaldi[4], Nicola Mozzillo[3], Paolo Antonio Ascierto[1]

[1]Melanoma, Cancer Immunotherapy and Innovative Therapies O.U. Istituto Nazionale Tumori Fondazione "G. Pascale", Napoli, Italy; [2]Regina Elena National Cancer Institute, Rome, Italy; [3]Unit of Melanoma and Sarcoma Surgery - Istituto Nazionale Tumori Fondazione, Napoli, Italy; [4]Catholic University of Sacred Heart, Roma, Italy; Department of Melanoma, Istituto Nazionale Tumori Fondazione Pascale, IRCCS, Napoli, Italy

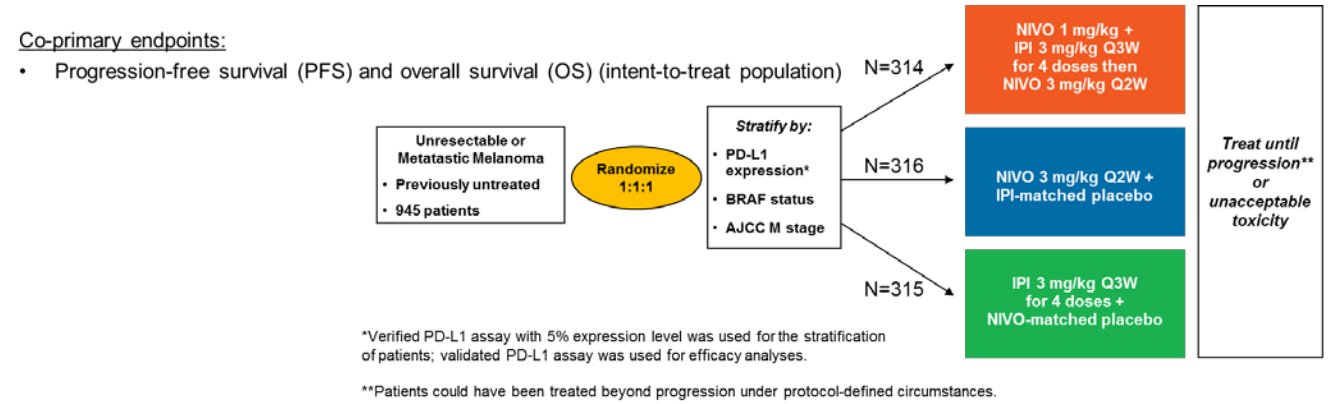
	Responder	Non Responder
Mutated	**2/16 (12,5%)**	**14/16**
Wild Type	**9/26 (36,4%)**	**17/26**

	Mutated	*Non Mutated*
DCR	***3/16 (18,6%)***	***17/26 (65,4%)***



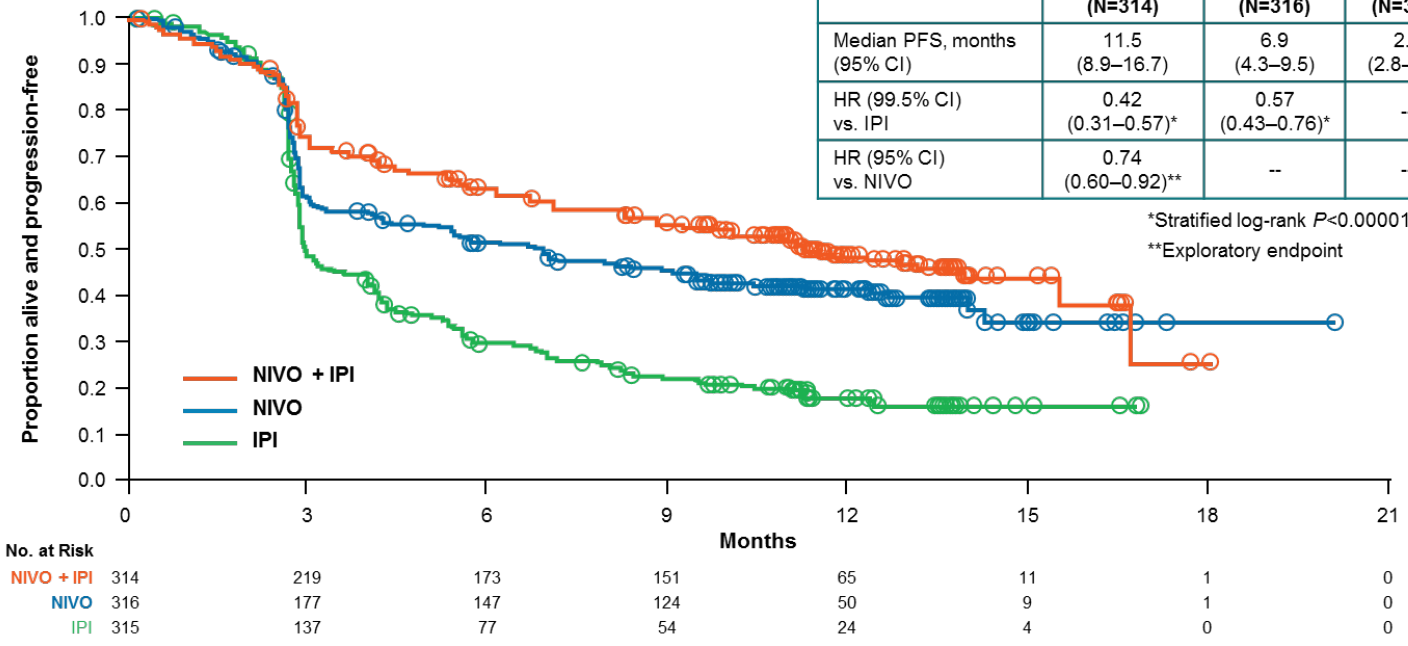
Simeone E et al SMR 2015

Ipilimumab plus nivolumab - results from the three arms randomized phase 3 study in untreated advanced melanoma patients with ipilimumab/nivolumab or nivolumab alone vs ipilimumab alone (CA209-067): NIVO + IPI resulted in a longer PFS



	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

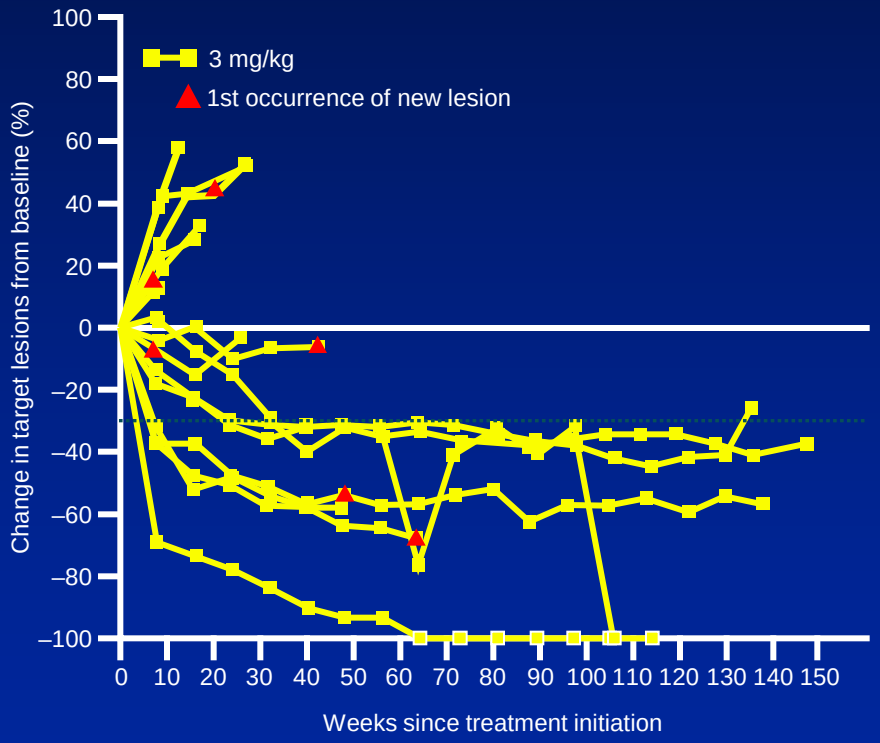
*Stratified log-rank $P<0.00001$ vs. IPI
**Exploratory endpoint



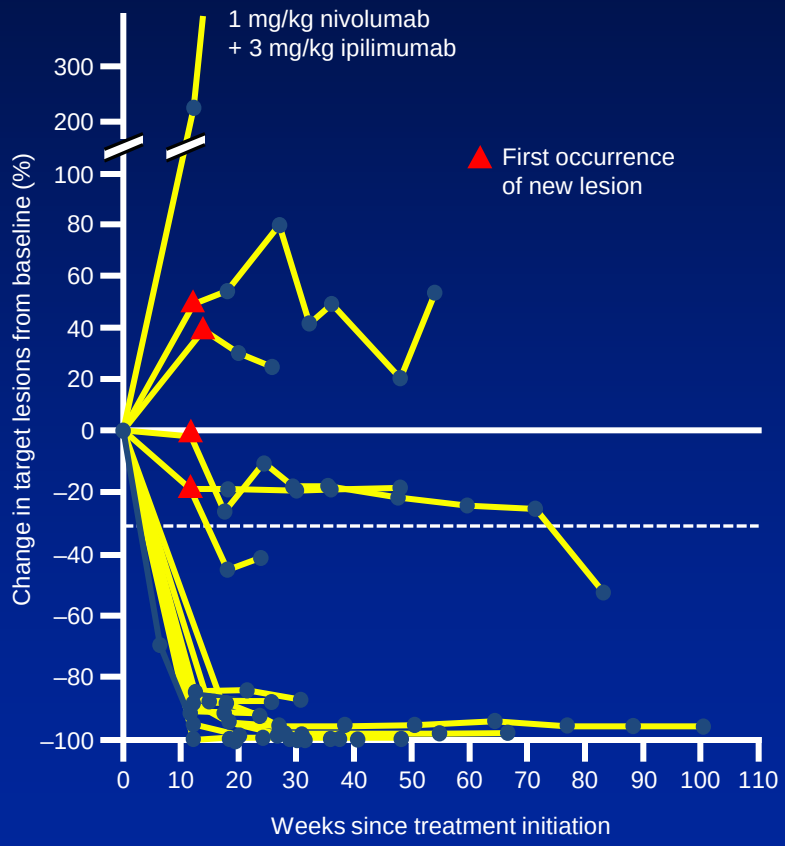
Larkin J et al. N Engl J Med 2015;373:23-34

Changes in Target Lesions: Comparing Nivolumab Alone and in Combination

Nivolumab monotherapy



Nivolumab + ipilimumab



Horizontal line at −30% = threshold for defining objective response (partial tumour regression) in absence of new lesions or non-target disease according to RECIST

Wolchok JD, et al. J Clin Oncol 2013;31(suppl): abstract 9012^;
Sznol M, et al. J Clin Oncol 2013;31(suppl): abstract CRA9006^

How do we sequence ?
Which is the best approach as first ?

Treatment Selection in BRAF-mutant Melanoma

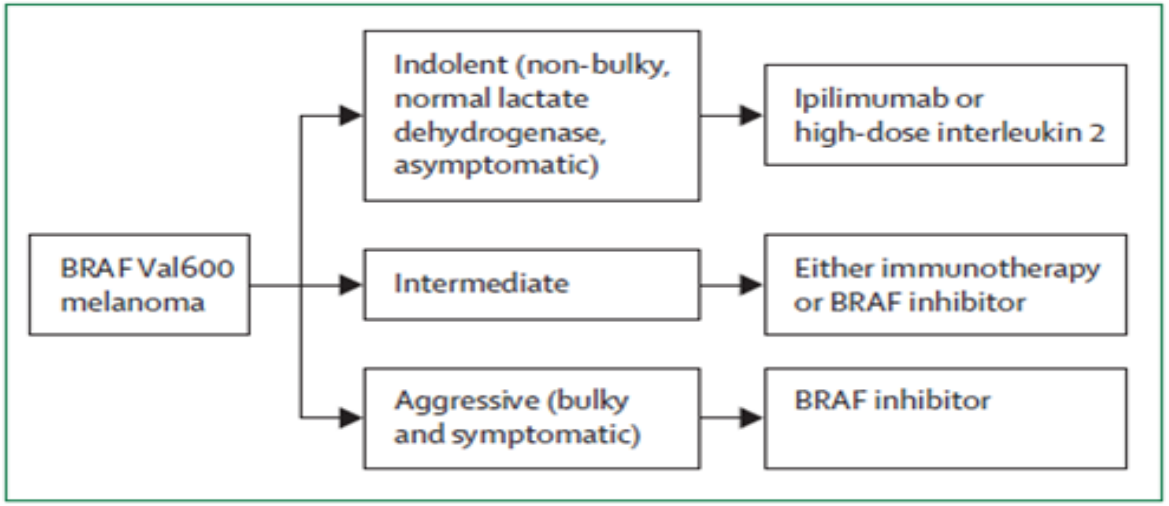
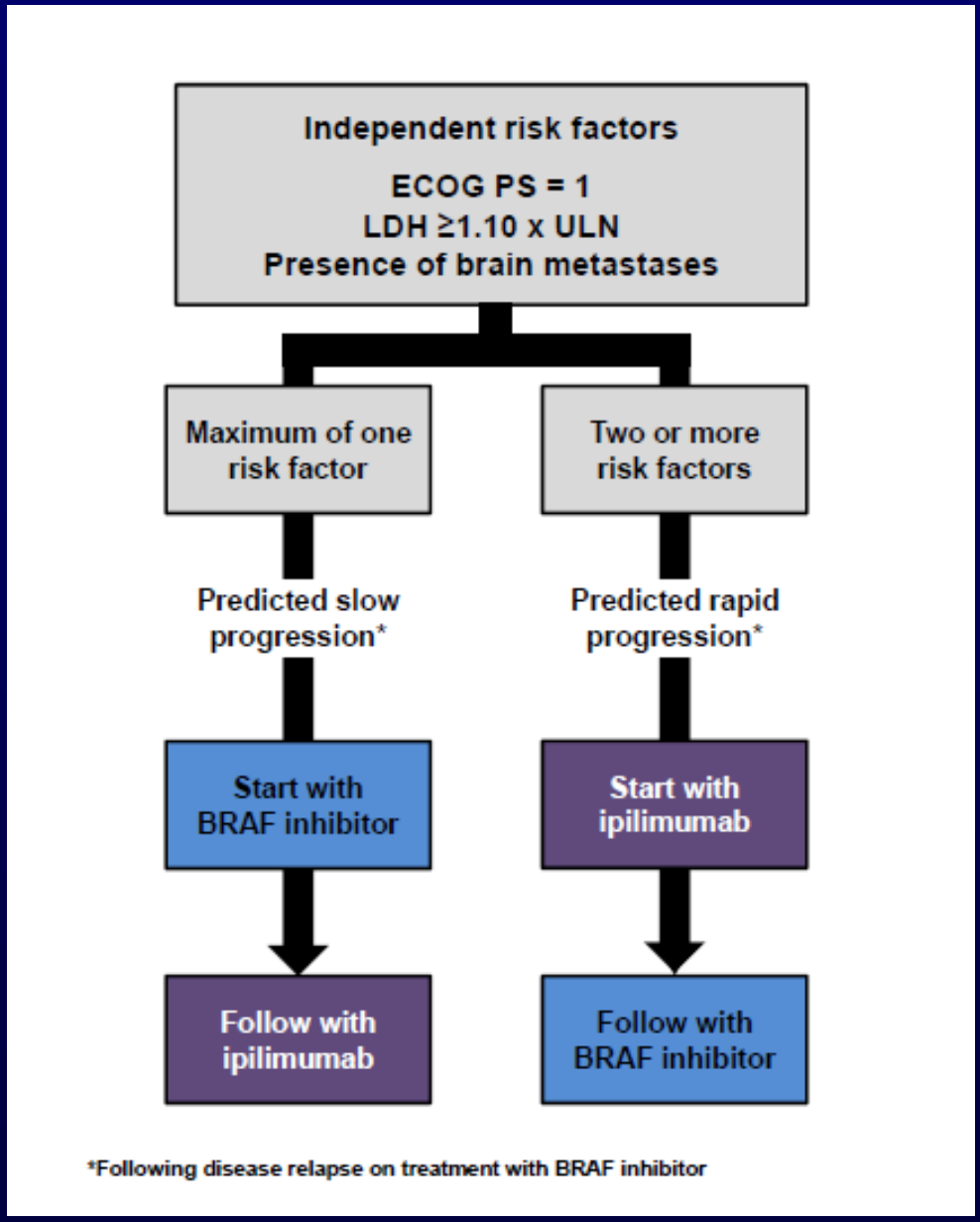


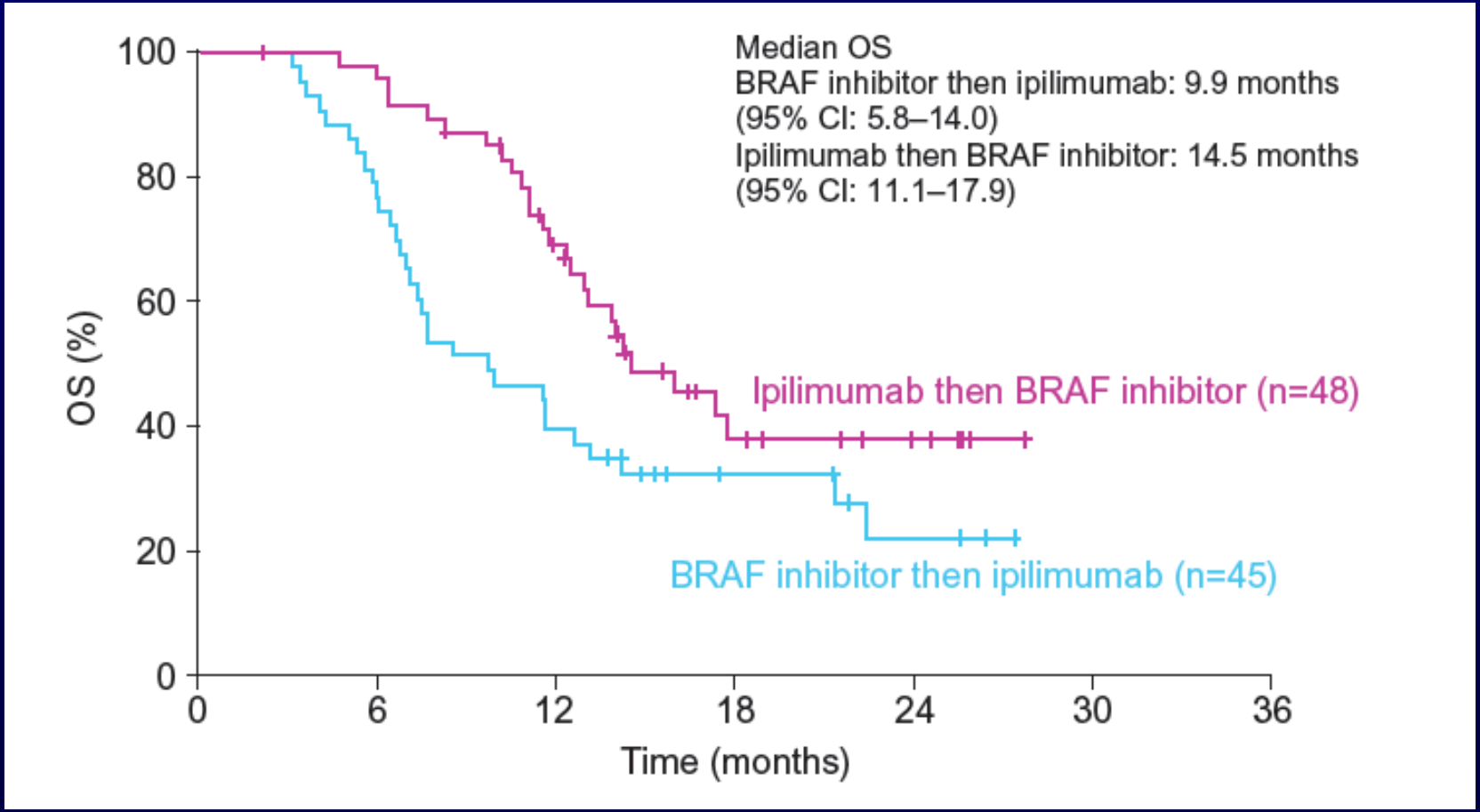
Figure 3: **Suggested initial treatment for patients with metastatic BRAF Val600 mutant melanoma.**
Clinical trials might be appropriate for each category

S Jang,M, Atkins, Lancet Oncol, 2013



Ascierto PA. et al. J Trans Med. 2012; 10: 107

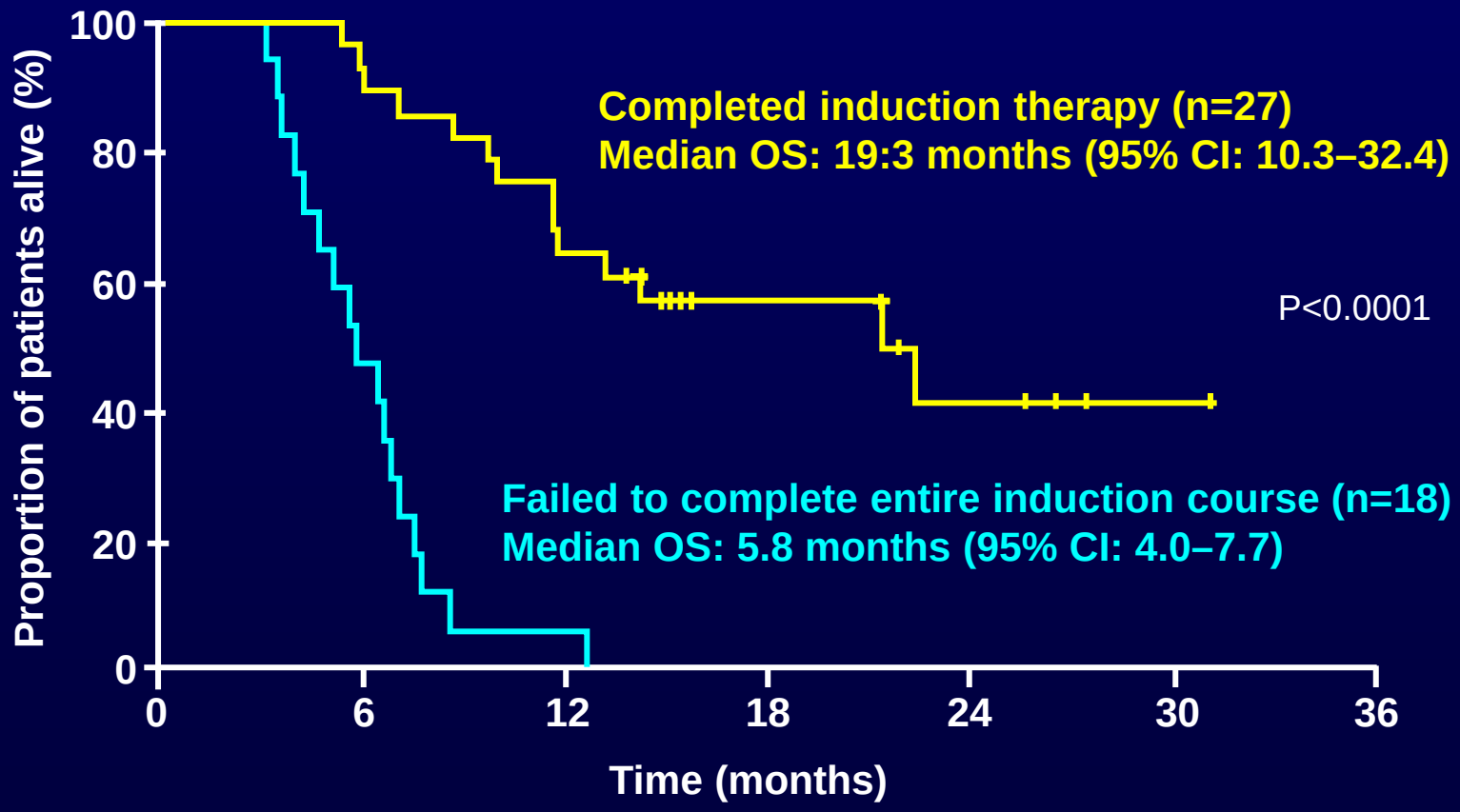
Overall survival for patients who received a BRAF inhibitor followed by ipilimumab or ipilimumab followed by a BRAF inhibitor



Ascierto PA. et al. Cancer Invest. 2014

Benefit of receiving all four doses of ipilimumab

Data from pretreated patients who received ipilimumab within the EAP in Italy suggest the potential for ipilimumab to provide clinical benefit may be improved in patients who complete the entire induction regimen

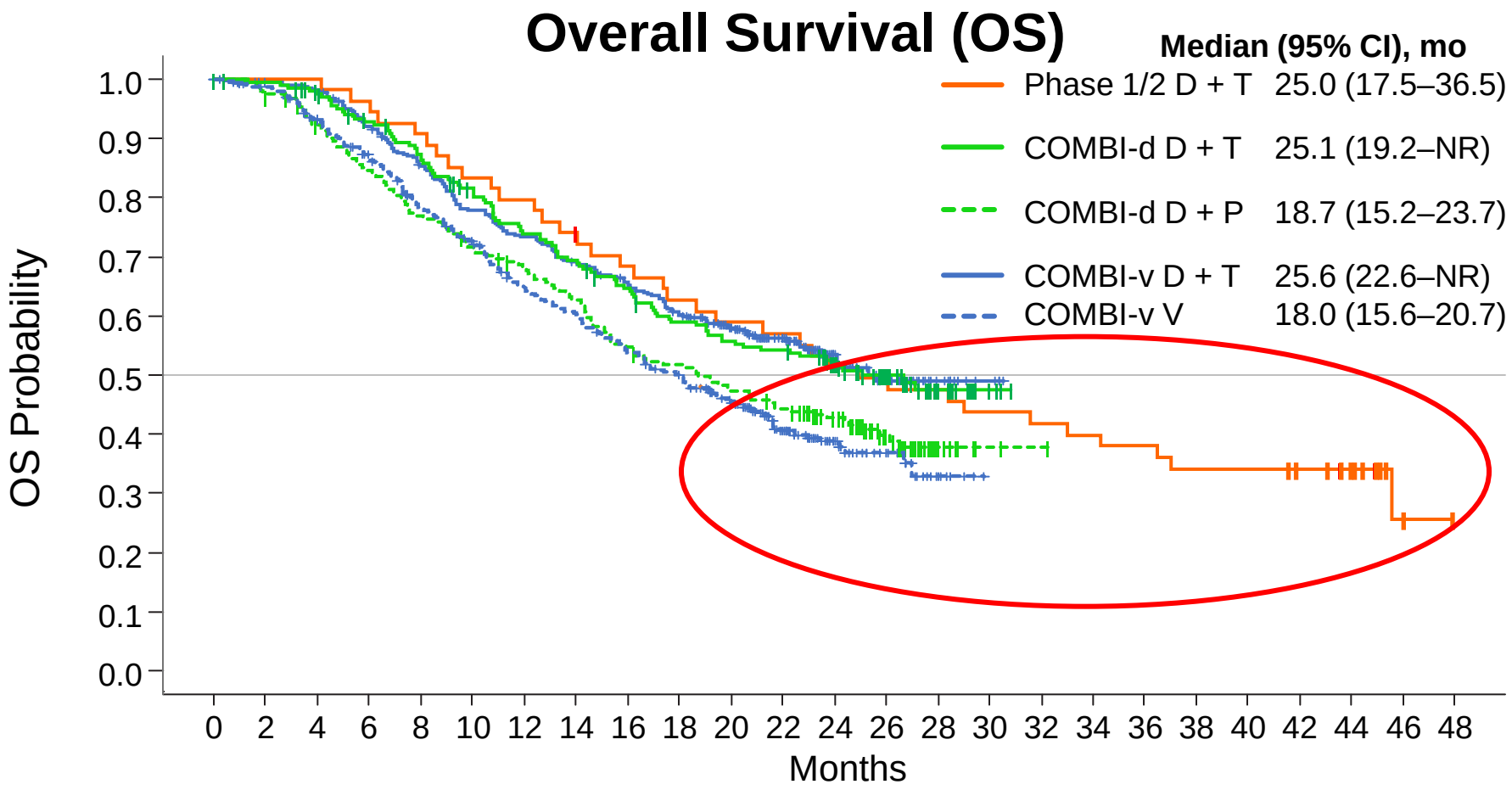


Ascierto et al. Cancer Invest 2014

Introduction

- Phase 1/2: dabrafenib + trametinib[1]
- COMBI-d: dabrafenib + trametinib vs dabrafenib[2]
- COMBI-v: dabrafenib + trametinib vs vemurafenib[3]

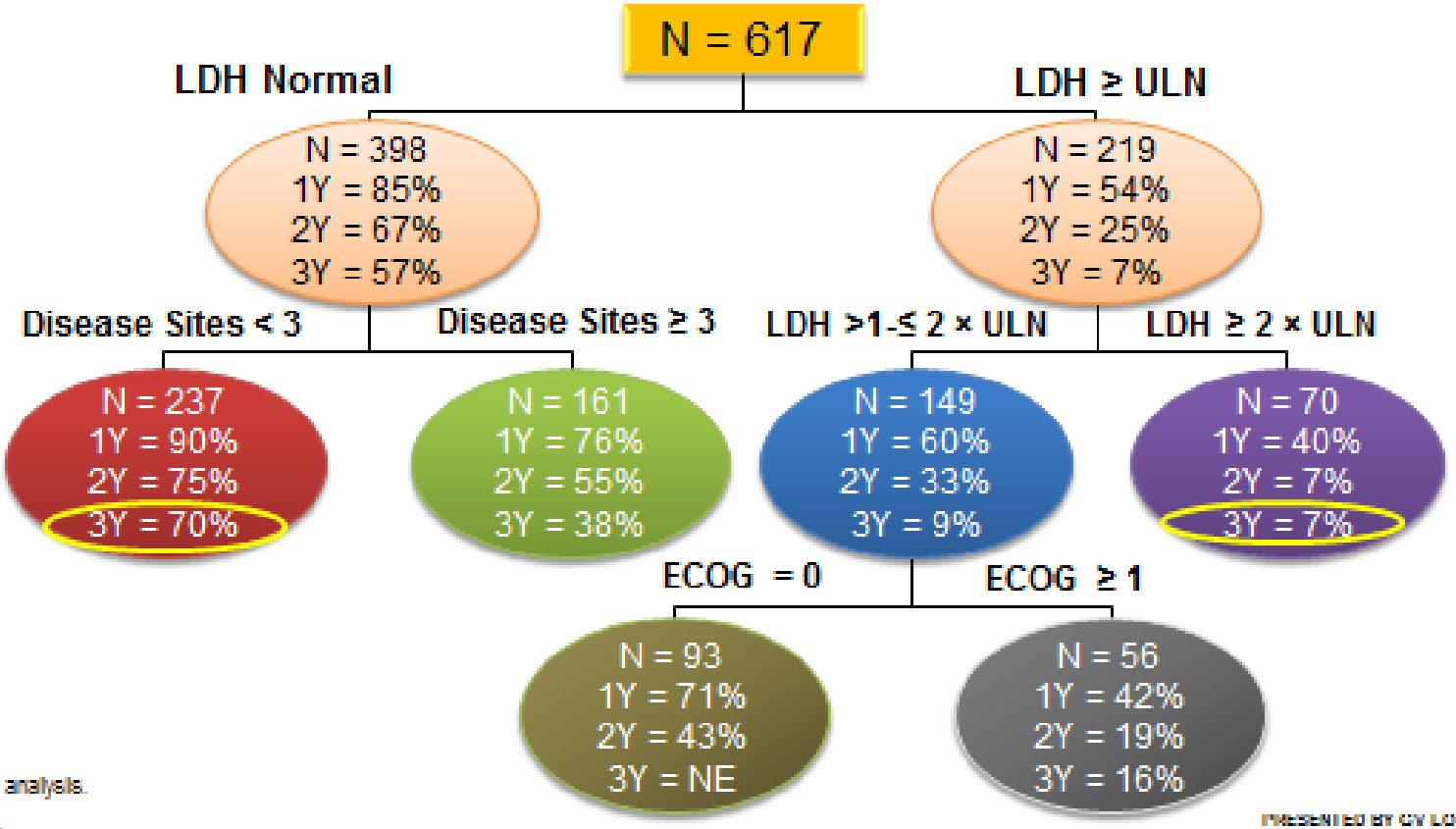
Pooled Analysis



1. Flaherty KT, et al. ASCO. 2014;[abstract 9010]; 2. Long GV, et al. *Lancet.* 2015;386:444-45; 3. Robert C, et al. ECC.

PRESENTED BY GV LONG AT SMR 2015

Five Baseline Factors Influenced OS[a]



[a] Regression tree analysis.

NE, not estimable.

Treatment decision based on patient's characteristic

Patient history (eg, autoimmune disease)

Organ system function, especially cardiac function

Patient's wishes and lifestyle factors

Mutational status

Performance status

Brain mtx

Tumor burden

LDH level

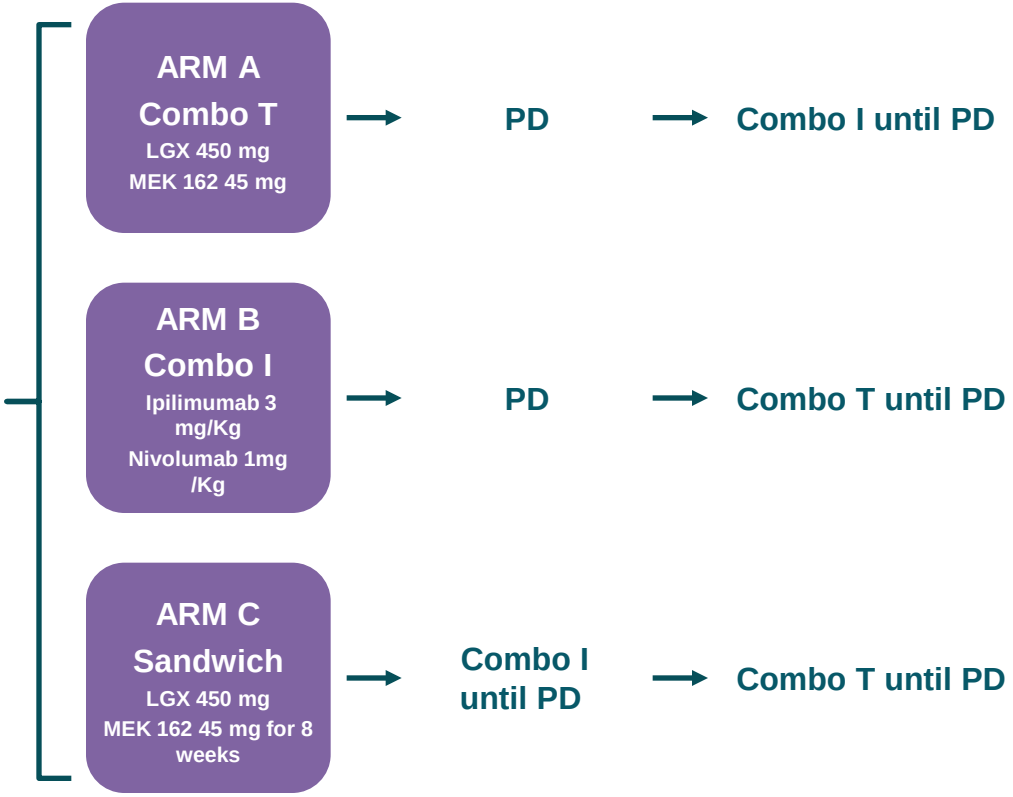
How do we Sequence or Combine Immunotherapies with Targeted Therapies ?

The answer to this question is in a perspective, randomized,

clinical trial

SEquential COMBo Immuno and Target therapy (SECOMBIT) Study (NCT02631447)

- Prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) followed by combo target therapy (encorafenib/ binimetinib) and vice-versa
- Patients affected by metastatic melanoma BRAF V600 mutated
- Sample size 230 pts



This study is designed as a phase II randomized trial with no formal comparative test.

Endpoints:

Primary – OS

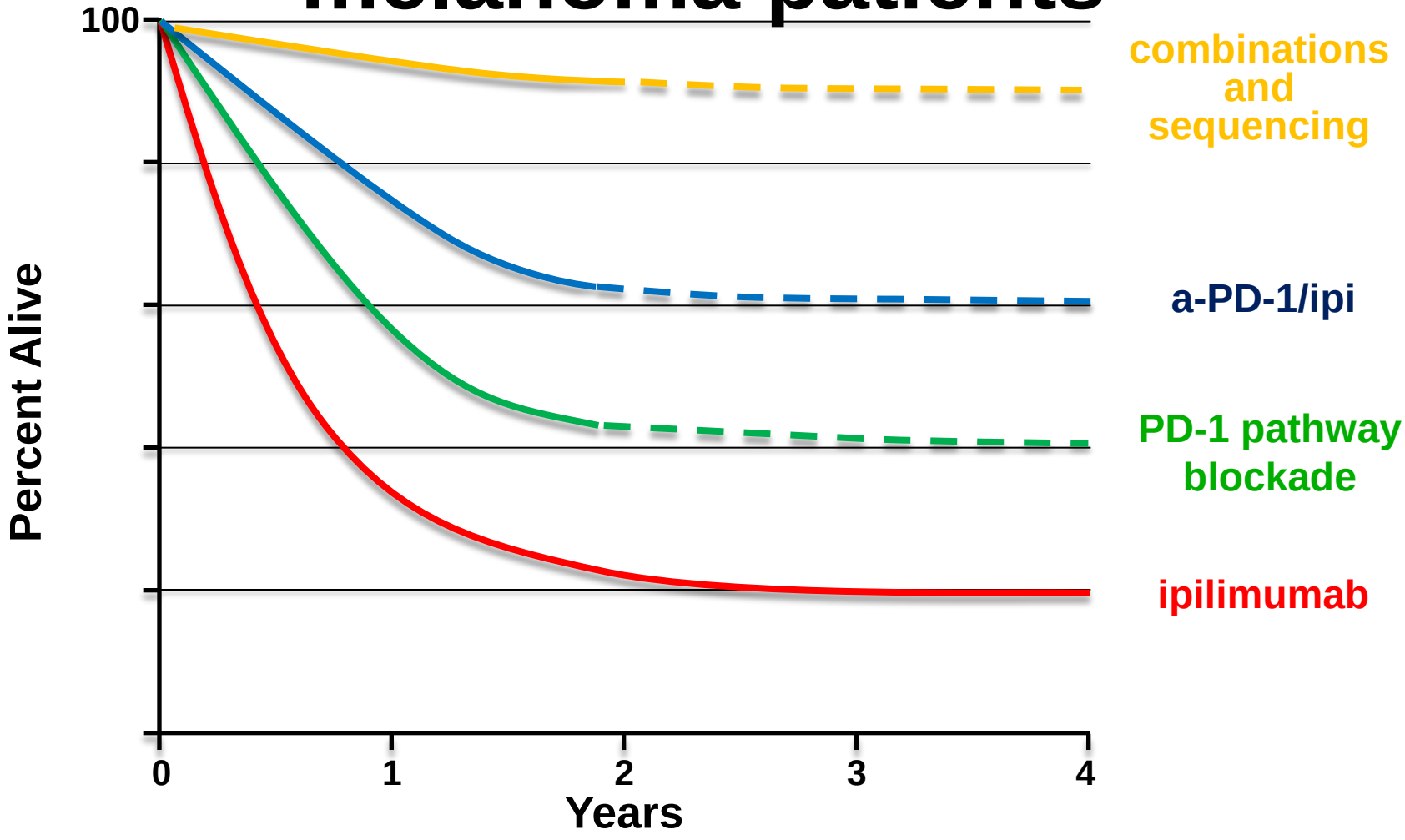
Secondary – PFS, Total PFS (TPFS): the time to the second progression, % patients alive at 2-3 years, BORR;
Duration of Response, Toxicity, Biomarkers study

Steering Committee

P.A. Ascierto (Chair)
R. Dummer
I. Melero
G. Palmieri

www.clinicaltrial.gov

Overall survival for advanced melanoma patients



- Adapted from Walter J. Urba, ASCO 2013

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Susy Esposito
Miriam Paone
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