Combination Therapy

Advances in Cancer Immunotherapy – Aug 22, 2014

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Objectives

- To understand the rationale for the combination of immunotherapies with other forms of therapy
- To explore preclinical data on combination of immunotherapy and targeted therapy
- To provide updated data on the combination of anti-CTLA4 and anti-PD1 therapy
- To summarize currently ongoing clinical trials in multiple malignancies

The Basic Concept of Combination Therapy

- **Concept 1: both A and B show activity**
- Is A+B more efficacious than A followed by B?
- Is A+B more toxic than A followed by B?

- **Concept 2: A is active, B shows minimal to no activity as a single agent**
- Can B enhance the activity of A?

Possible Combinations

- Immunotherapy + targeted therapy
- Immunotherapy + immunotherapy
- Immunotherapy + chemotherapy

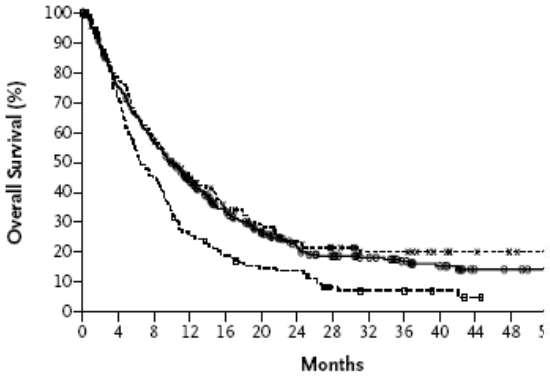
Combining immunotherapy and targeted therapy for melanoma?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

Hodi *et al*. NEJM 2010

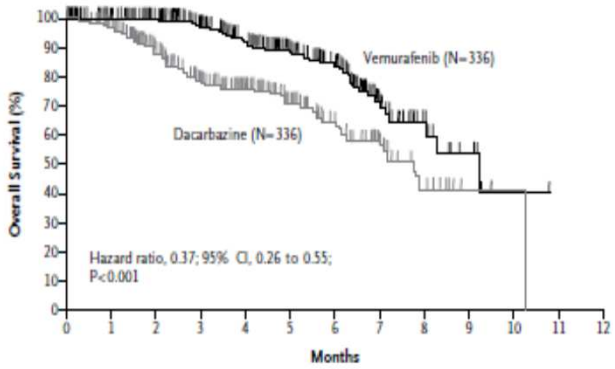


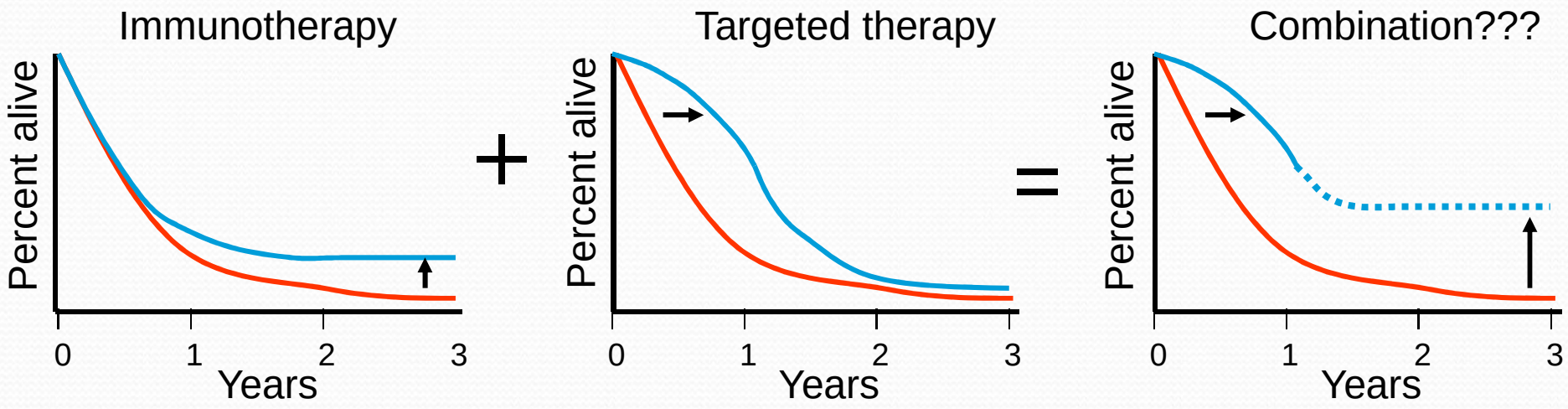
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Chapman *et al*. NEJM 2011



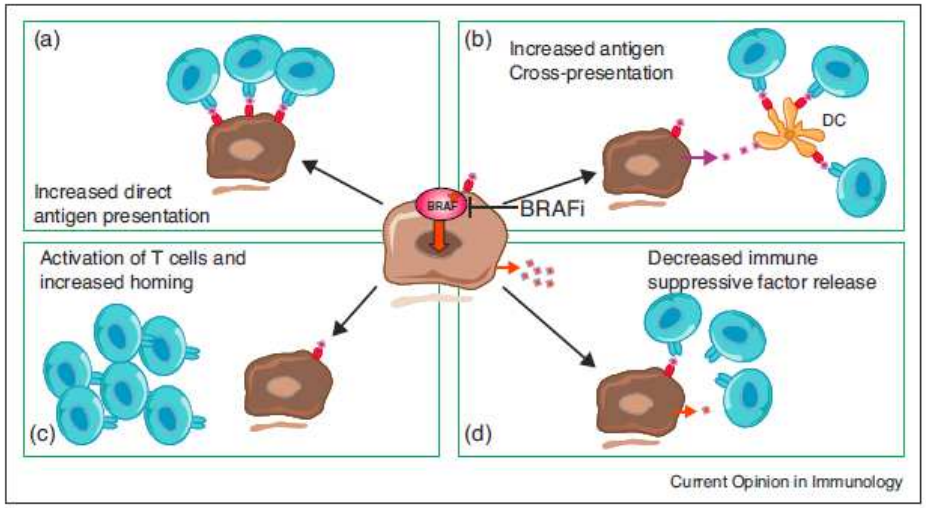


Courtesy of Dr. A. Ribas

Modified from Ribas *et al*. Clinical Cancer Research 2012

BRAF inhibitors as immune sensitizing agents

- BRAF inhibitors could sensitize the immune system by:
  - Increase tumor antigen and MHC expression
  - Increase tumor infiltrating lymphocytes
  - Improve immune effector cell function by inducing paradoxical MAPK activation on T cells
  - Improve the tumor microenviroment by decreasing expression of immune suppressive cytokines and immune regulatory ligands



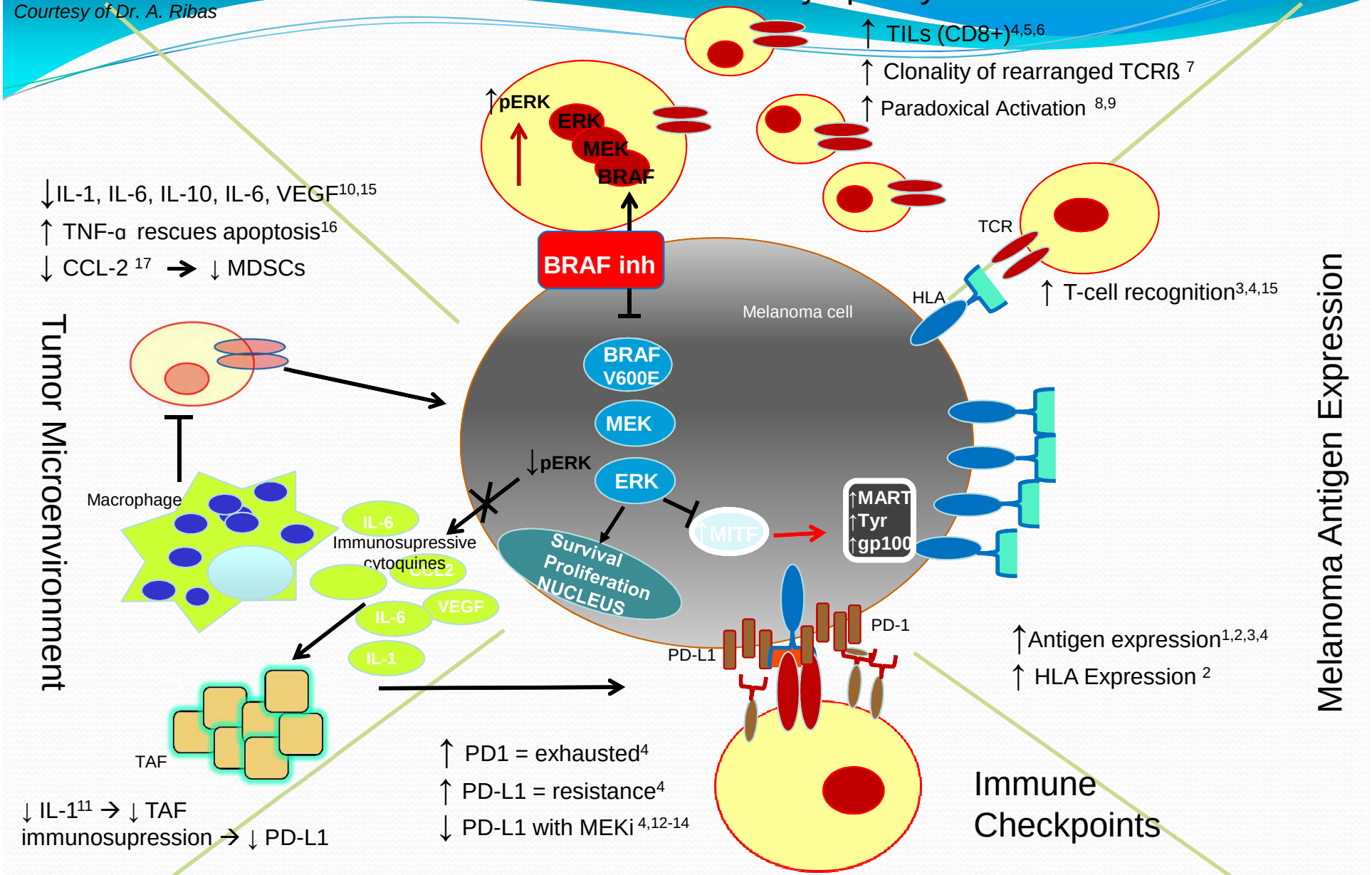
Courtesy of Dr. A. Ribas

1.Kono M. Mol Cancer Res 2006 2. Sapkota B. Oncoimmunology 2013. 3. Boni A. Cancer Res 2010. 4. Frederick DT. Clin Cancer Res 2013. 5. Long GV. Pigment Cell Melanoma Res 2013. 6. Wilmott JS. Clin Cancer Res 2012. 7. Cooper ZA. Oncoimmunology 2013. 8. Comin-Anduix B. Clin Cancer Res 2010. 9. Koya Cancer Research 2012. 10. Sumimoto H. J Exp Med 2006. 11 Khalili JS. Clin Cancer Res 2012. 12. Yamamoto R. Cancer Sci 2009. 13. Berthon C. Cancer Immunol Immunother 2010. 14 Knight DA. J Clin Invest 2013. 15.Liu CCR 2013. 16. Gray-Schopfer VC. Cancer Res 2007. 17. Landsberg, Nature 2012.

Ribas & Wolchok, Curr Opin Immunol 2013
Hu-Lieskovan, Robert, Homet & Ribas JCO 2014

Adapted from Hu-Lieskovan, Robert, Homet, Ribas, J Clin Oncol 2014
Courtesy of Dr. A. Ribas

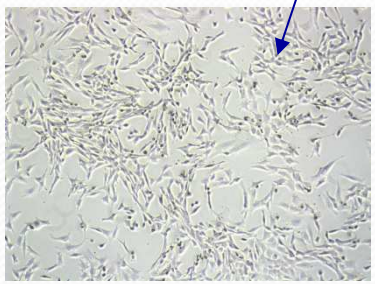
Paradoxical Activation in Lymphocytes

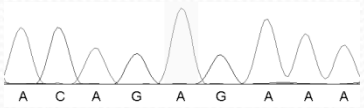


1.Kono M. Mol Cancer Res 2006 2. Sapkota B. Oncoimmunology 2013. 3. Boni A. Cancer Res 2010. 4. Frederick DT. Clin Cancer Res 2013. 5. Long GV. Pigment Cell Melanoma Res 2013. 6. Wilmott JS. Clin Cancer Res 2012. 7. Cooper ZA. Oncoimmunology 2013. 8. Comin-Anduix B. Clin Cancer Res 2010. 9. Koya Cancer Research 2012. 10. Sumimoto H. J Exp Med 2006. 11 Khalili JS. Clin Cancer Res 2012. 12. Yamamoto R. Cancer Sci 2009. 13. Berthon C. Cancer Immunol Immunother 2010. 14 Knight DA. J Clin Invest 2013. 15.Liu CCR 2013. 16. Gray-Schopfer VC. Cancer Res 2007. 17. Landsberg, Nature 2012.

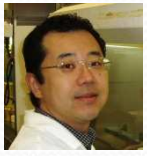
SM1: A $BRAF^{V600E}$-driven melanoma syngeneic to immunocompetent C57BL/6 mice

Goel, Haluska *et al*. Oncogene. 2009





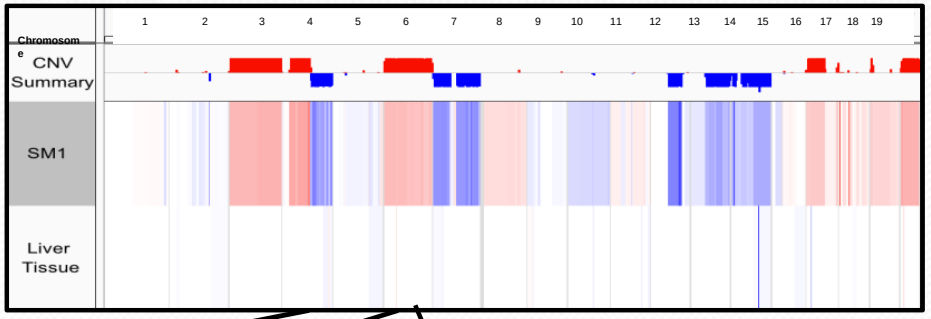
$BRAF^{V600E}$ mutation



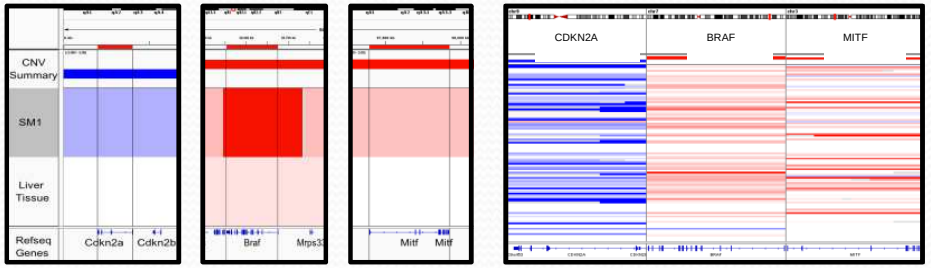
Richard Koya, MD, PhD

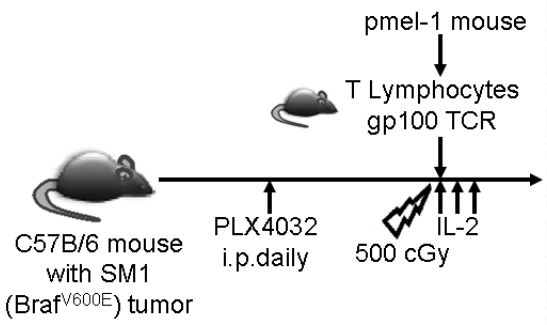
Stephen Mok

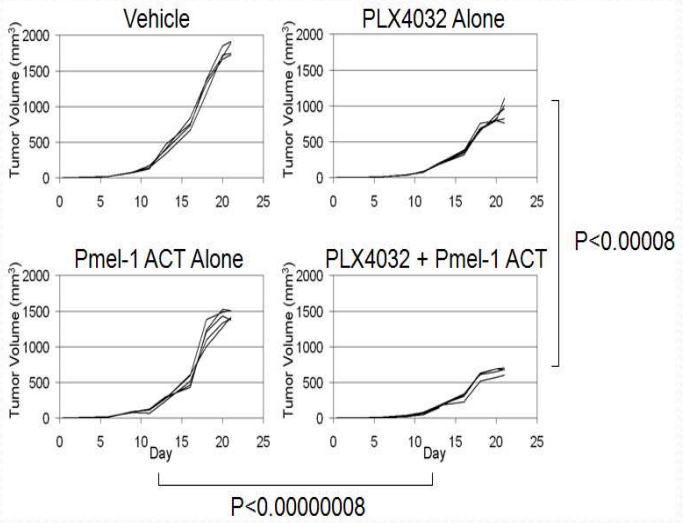
SM1 has genomic alterations similar to human melanoma



Cdkn2a Braf Mitf CNV comparing SM1 with 108 human melanomas





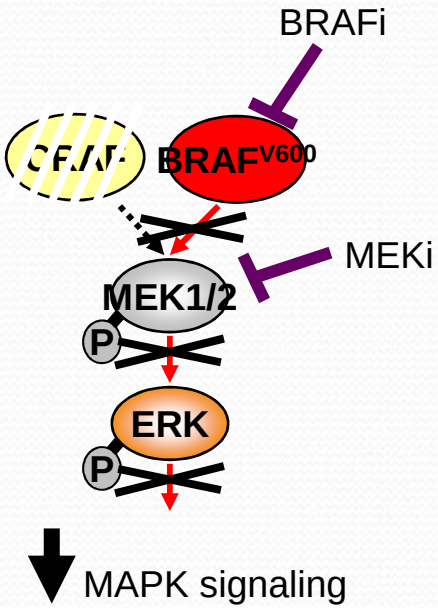


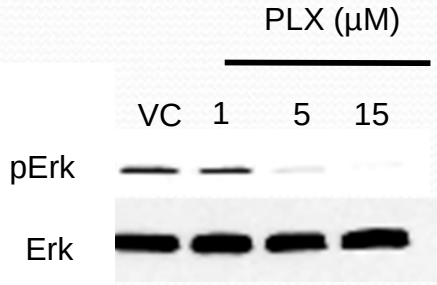
Koya, Mok *et al*. Cancer Res 2012; Knight *et al*. J Clin Inv 2013

Courtesy of Dr. A. Ribas

Paradoxical activation of pERK with exposure of lymphocytes to vemurafenib

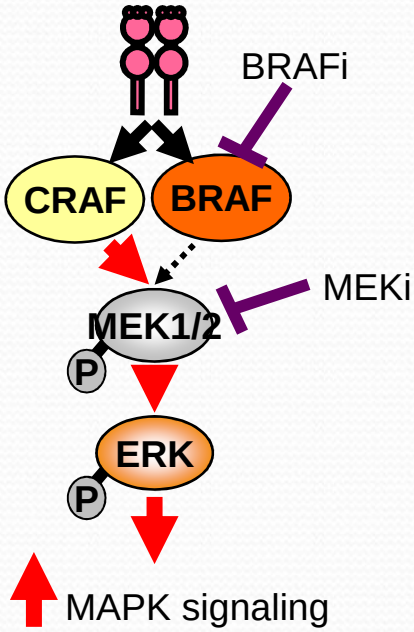
SM1





Courtesy of Dr. A. Ribas

pmel-1



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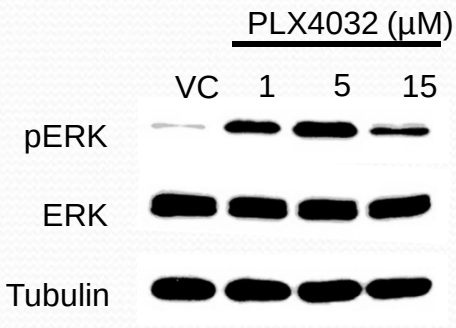
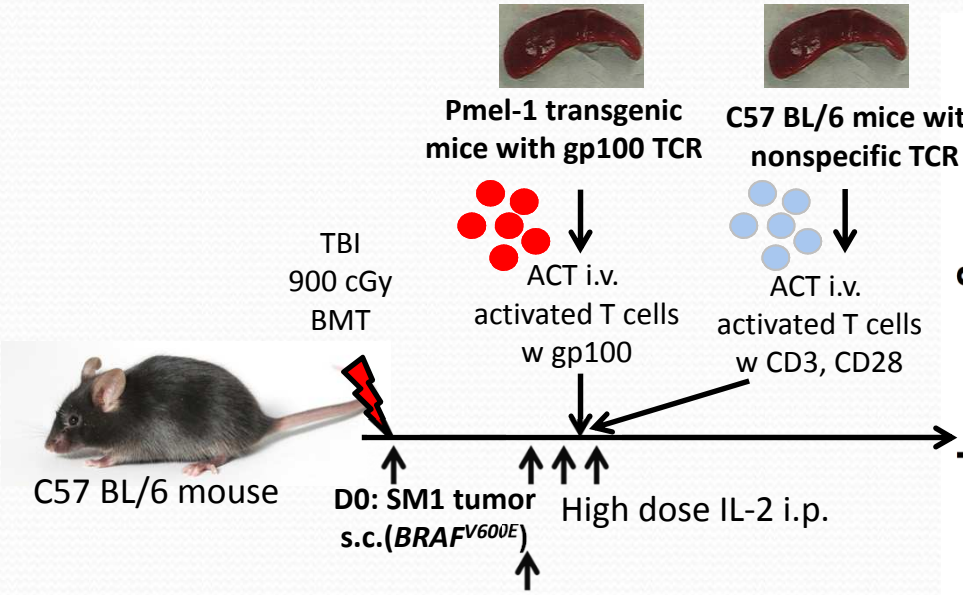


Koya, Mok *et al*. Cancer Res 2012

Enhanced *in vivo* antitumor activity pmel-1 ACT + dabrafenib and/or trametinib



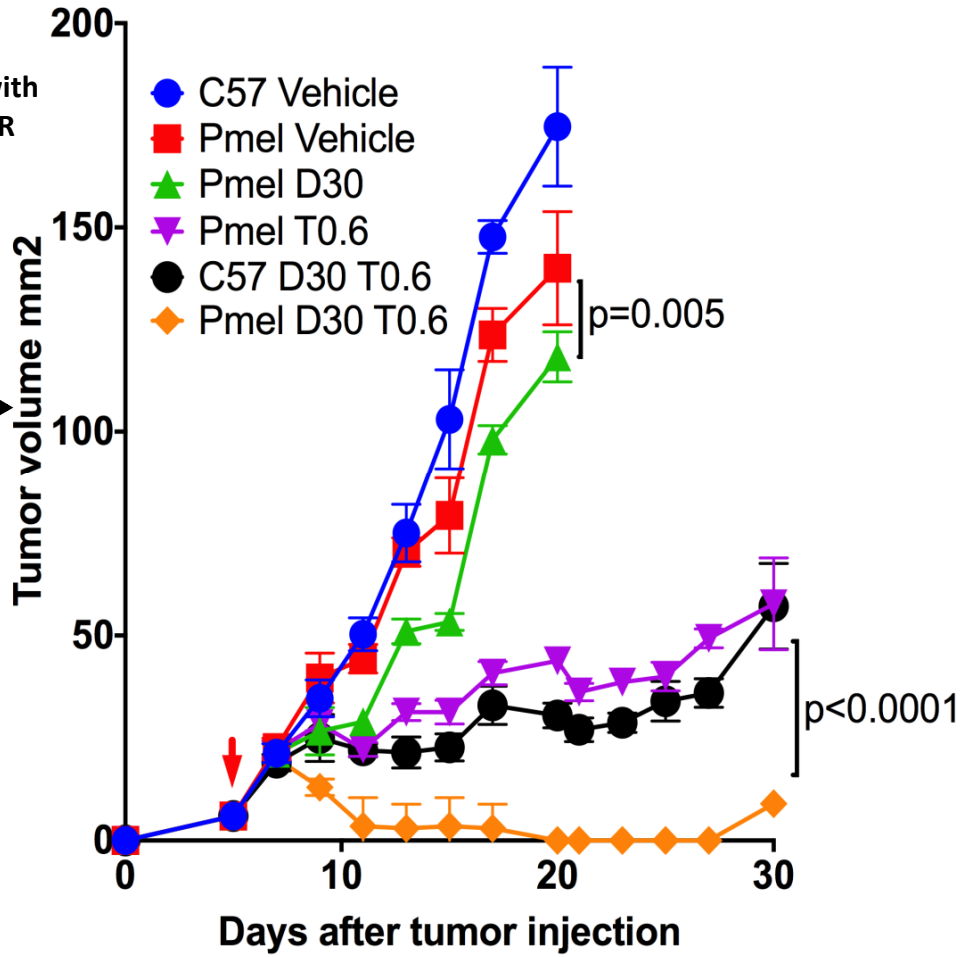
Drug Tx, daily oral gavage

Six groups (N=6):

Pmel ACT+Vehicle (V)
Pmel ACT+D30
Pmel ACT+T0.6
Pmel ACT+D30+T0.6
C57 ACT +V
C57 ACT +D30+T0.6

Siwen Hu-Lieskovan, MD, PhD

Stephen Mok

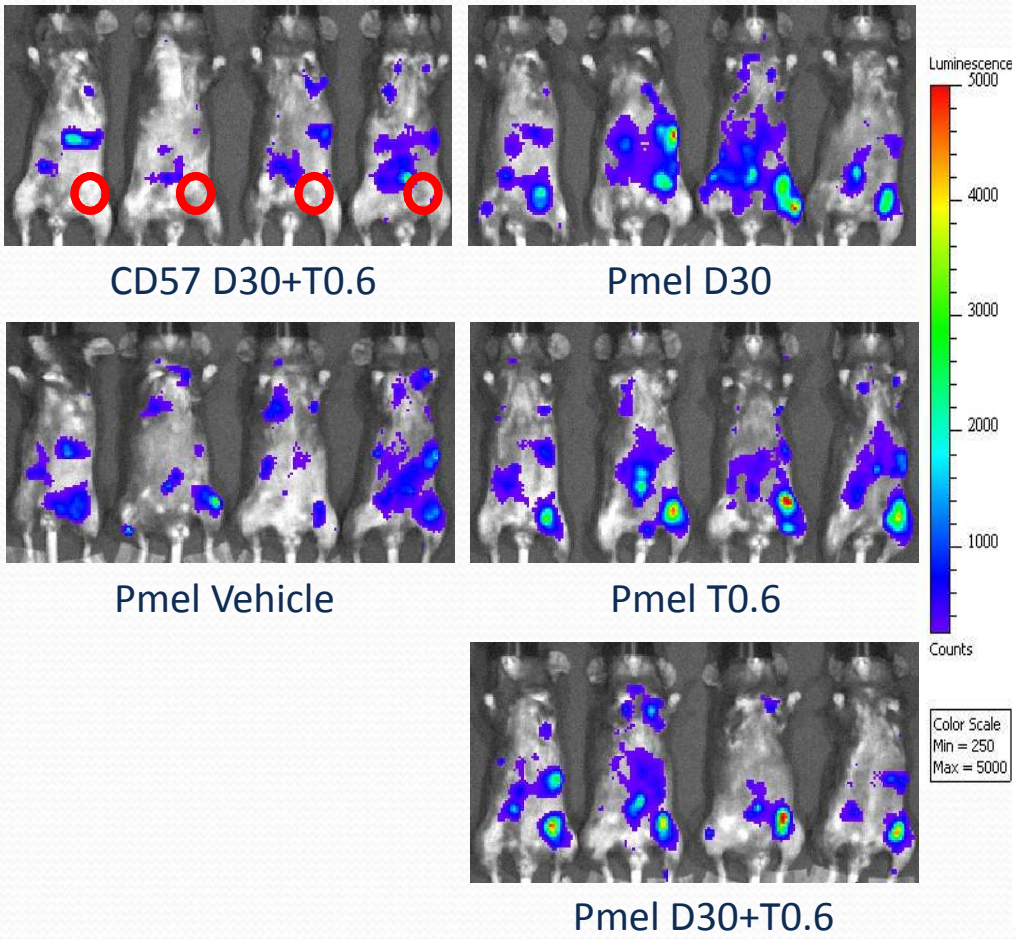


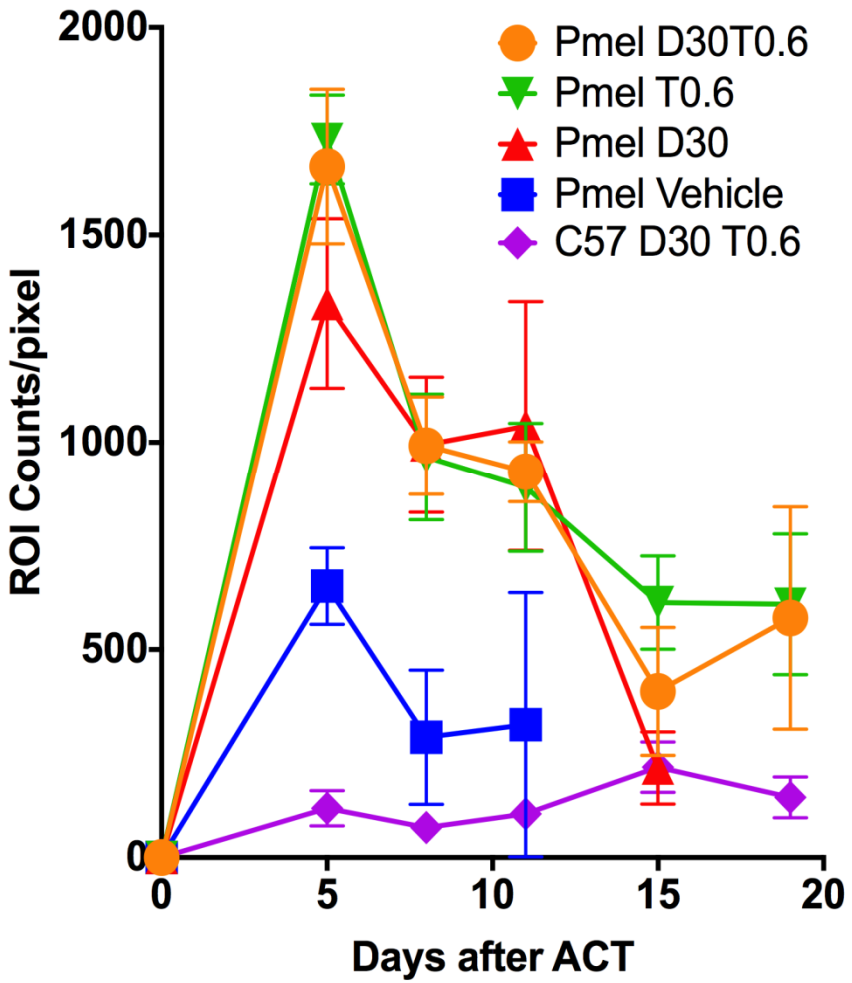
Dabrafenib and trametinib were kindly provided by Drs. Tona Gilmer, Li Liu and Jeff Legos through an MTA with GSK

Courtesy of Dr. A. Ribas

Increased tumor infiltrating T cells pmel-1 ACT + dabrafenib and/or trametinib

Day 5 after ACT
Day 13 after tumor injection





ROI: tumors only (counts/pixel)
Bioluminescent imaging of pmel-1 ACT

Courtesy of Dr. A. Ribas

Liver toxicities with ipilimumab + vemurafenib phase 1 testing

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

* The first cohort started with a run-in period of 1 month of single-agent vemurafenib (960 mg orally twice daily), followed by four infusions of ipilimumab (3 mg per kilogram of body weight every 3 weeks) and concurrent twice-daily doses of vemurafenib. The second cohort received a lower dose of vemurafenib (720 mg twice daily) together with the full dose of ipilimumab. NA denotes not available.
† This patient also had a grade 2 increase in the total bilirubin level.
‡ This patient also had a grade 3 increase in the total bilirubin level.

Ribas A et al. N Engl J Med 2013;368:1365-1366

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Courtesy of Dr. A. Ribas

Anti-PD1 Ab and targeted therapy

BRAF mutated — pembrolizumab + Dabrafenib 150 mg po bid + trametinib 2 mg daily

BRAF wt — pembrolizumab + trametinib 2 mg daily

Randomized phase

BRAF mutated →
- pembrolizumab + Dabrafenib 150 mg po bid + trametinib 2 mg daily
- placebo + Dabrafenib 150 mg po bid + trametinib 2 mg daily

NCT02130466

Pembrolizumab in patients with renal cell carcinoma

- An open-label, 2 part study of **pazopanib** and/or **pembrolizumab** in treatment naïve subjects with advanced RCC. Part 1 consists of a Phase I dose escalation followed by an expansion cohort. Part 2 is a randomized 3-arm Phase II study.

- A Phase 1B, Open Label, Dose Finding Study To Evaluate Safety, Pharmacokinetics And Pharmacodynamics Of **Axitinib** In Combination With **pembrolizumab** In Patients With Advanced Renal Cell Cancer

NCT02014636, NCT02133742

Nivolumab in patients with renal cell carcinoma

- A Phase 1 Study of Nivolumab (BMS-936558) Plus **Sunitinib**, **Pazopanib** or **Ipilimumab** in Subjects With Metastatic Renal Cell Carcinoma

- A Phase 1B, Open Label, Dose Finding Study To Evaluate Safety, Pharmacokinetics And Pharmacodynamics Of **Axitinib** In Combination With **MK-3475** In Patients With Advanced Renal Cell Cancer

NCT01472081

Anti-PDL1 Ab and targeted therapy

MEDI4736 binds to PD-L1 and blocks its interaction with PD-1 and CD80

BRAF mutated	MEDI4736	+	Dabrafenib 150 mg po bid + trametinib 2 mg daily
BRAF wt	MEDI4736	+	trametinib 2 mg daily

BRAF wt	trametinib 2 mg daily	followed by	MEDI4736

NCT02027961

MEDI4736 in patients with lung cancer

- A Phase I, Open-Label, Multicentre Study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of **gefitinib** in combination with **MEDI4736** (anti PD-L1) in Subjects with Non-small cell lung cancer (NSCLC).

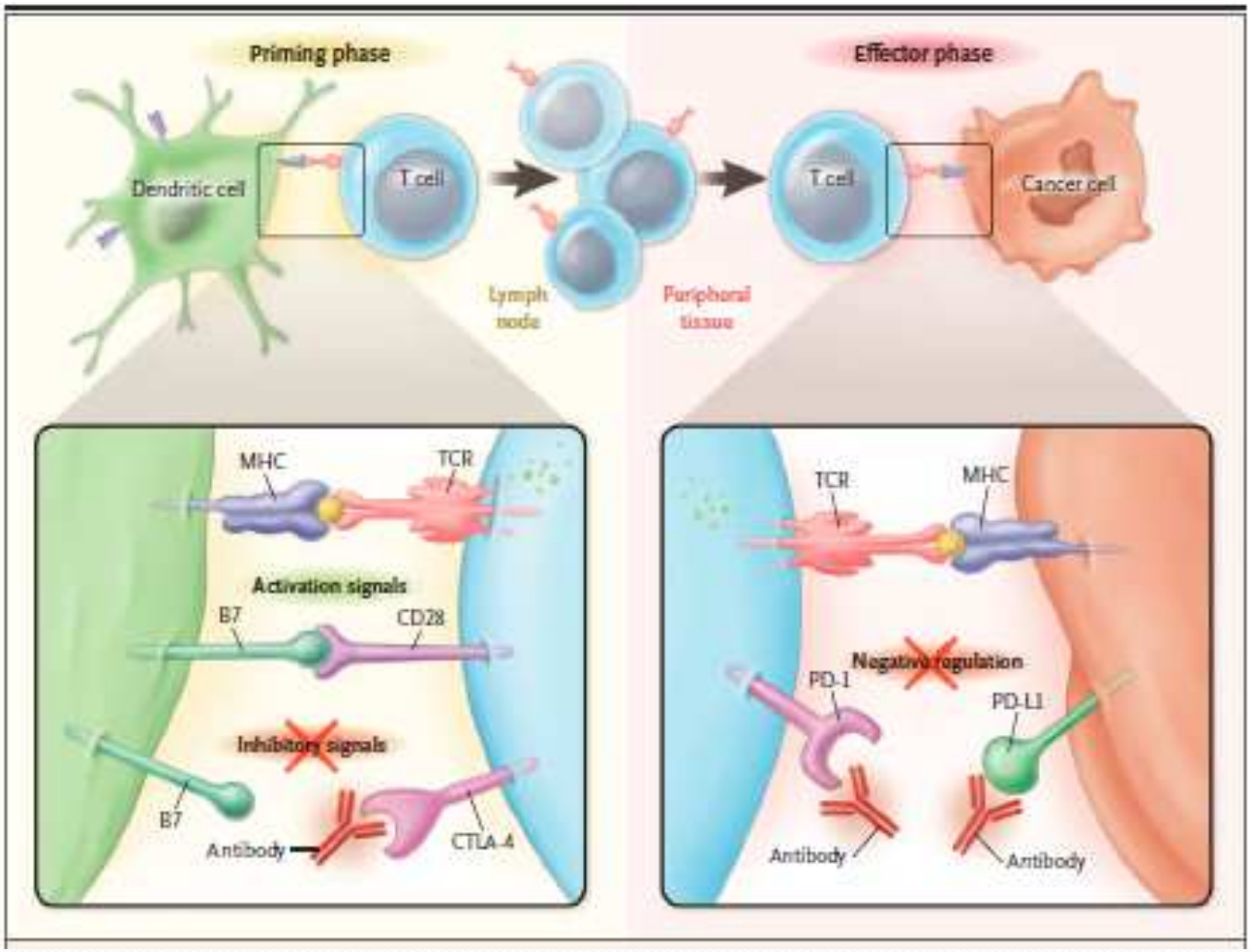
- Multi-arm, Phase Ib, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of **AZD9291** in Combination With Ascending Doses of Novel Therapeutics in Patients With EGFRm+ Advanced NSCLC Who Have Progressed Following Therapy With an EGFR TKI. Group A: **AZD9291 + MEDI4736**

NCT02088112, NCT02143466

EDITORIAL

Tumor Immunotherapy Directed at PD-1

Antoni Ribas, M.D., Ph.D.



NEJM 2012; Jun 28; 366 (26): 2517-9

Anti-CTLA4 + anti-PD1 antibodies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

N Engl J Med 2013;369:122-33.

Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL)

Mario Sznol,[1] Harriet Kluger,[1] Margaret K. Callahan,[2] Michael A. Postow,[2] RuthAnn Gordon,[2] Neil H. Segal,[2] Naiyer A. Rizvi,[2] Alexander M. Lesokhin,[2] Michael B. Atkins,[3] John M. Kirkwood,[4] Matthew M. Burke,[1] Amanda Ralabate,[1] Angel Rivera,[1] Stephanie A. Kronenberg,[2] Blessing U. Agunwamba,[2] William Feely,[5] Quan Hong,[5] Suba Krishnan,[5] Jedd D. Wolchok[2]

[1]Yale University School of Medicine and Yale Cancer Center, New Haven, CT, USA; [2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [3]Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA; [4]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [5]Bristol-Myers Squibb, Princeton, NJ, USA

Presented By Mario Sznol at 2014 ASCO Annual Meeting

Objectives

- To report updated safety, survival, and clinical activity of initial concurrent cohorts 1-3 (N=53) with additional follow-up of ~ 1 year
- To report responses in a new cohort (cohort 8) of 41 patients using Phase 2/3 dosing regimen (last patient, first treatment Nov. 2013)

Concurrent Therapy

Induction: Nivo + IPI every 3 weeks for 4 doses (12 weeks)	→ Cohorts 1, 2, 2a, 3: Nivo every 3 weeks for 4 doses then: Nivo + IPI every 12 weeks for 8 doses
Induction: Nivo + IPI every 3 weeks for 4 doses (12 weeks)	→ Cohort 8: Nivo 3 mg/kg every 2 weeks until disease progression

Sequential Therapy

Prior standard ipilimumab therapy	→ Cohorts 6, 7: Nivo 1 or 3 mg/kg Q2W IV until disease progression

CA209-004 Phase I Study: Dose Cohorts

		Dose (mg/kg),		Treatment Schedule	
Regimen Cohort No.	N	Nivolumab	Ipilimumab	Induction	Maintenance
Concurrent				Nivo Q3W x 8 + IPI Q3W x 4	Nivo + IPI Q12W x 8
1	14	0.3	3		
2	17	1	3		
2a	16	3	1		
3	6	3	3		
8*	41	1	3	Nivo Q3W x 8 + IPI Q3W x 4	Nivo 3 mg/kg Q2W (Max. 48 doses)
Sequenced				Nivo Q2W (Max of 48 doses)	
6	17	1	Prior		
7	16	3	Prior		

*Insufficient follow-up at this data collection to report survival endpoints

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Activity Summary: Concurrent and Sequenced Cohorts from 004

Nivolumab (mg/kg) + IPI (mg/kg)	N	ORR[a], %	CR, %	Aggregate Clinical Activity Rate	≥80% tumor burden reduction at 36 wks[b], %
Concurrent Cohorts 1-3	53	42	17	70	42
0.3 + 3	14	21	14	57	36
1 + 3	17	53	18	65	53
3 + 1	16	44	25	81	31
3 + 3	6	50	0	83	50
1 + 3 [Cohort 8][c]	40	43	10[d]	53	28
Sequenced	33	31	3	44	31

[a]per RECIST, [CR+PR]/N x 100; [b] Best overall response; [c]Cohort 8: Phase 2/3 trial; last patient, first dose Nov 2013. [d]2 confirmed and 2 unconfirmed responses

n: no. response-evaluable pts.

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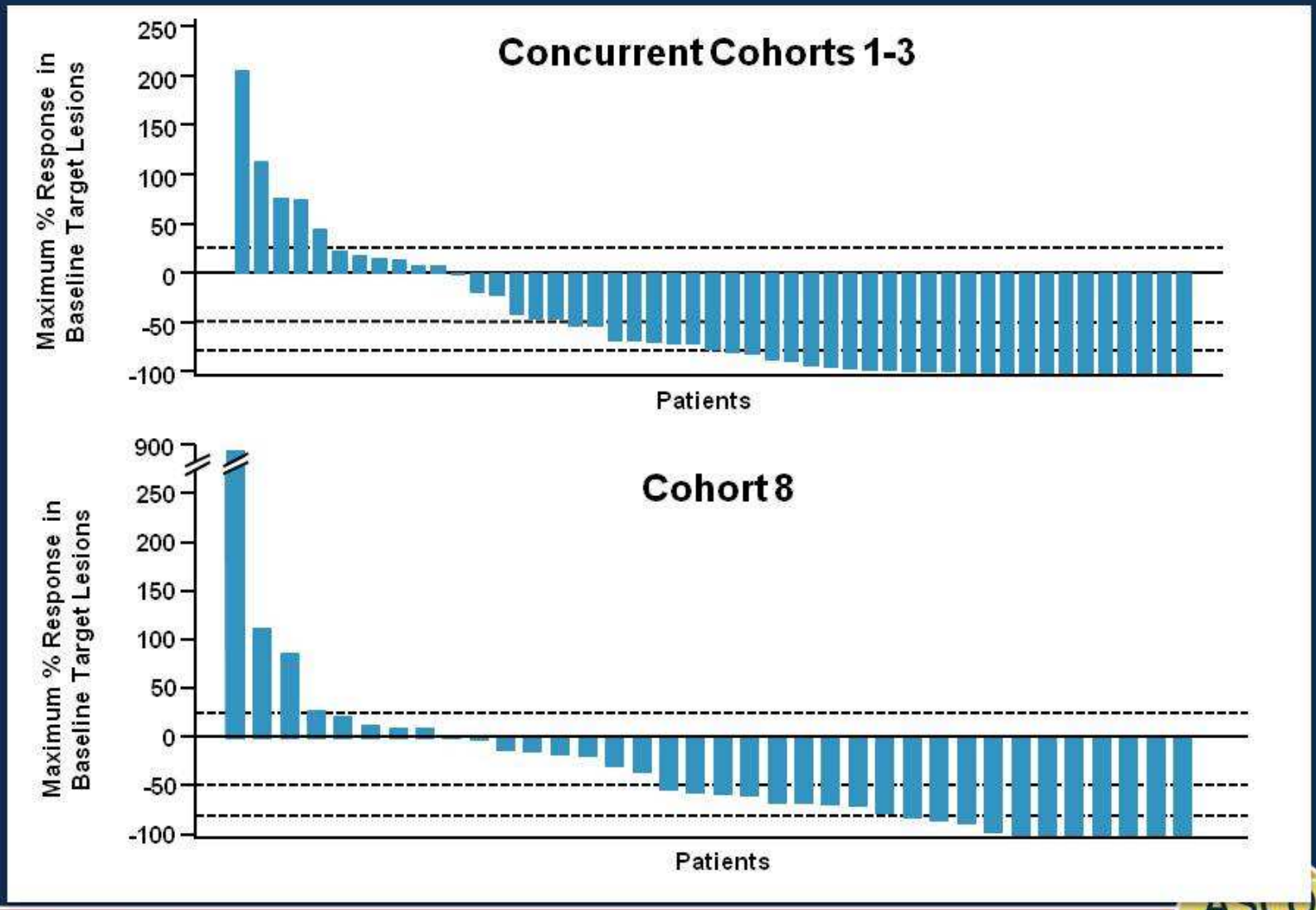
Response in Target Lesions



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Safety Overview

AE, %	Concurrent Cohorts 1-3 n=53		Cohort 8 n = 41		All Concurrent n=94	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
All Related AEs	96	62	95	61	96	62
Select AEs						
Gastrointestinal	43	9	34	20	39	14
Hepatic	30	15	12	12	22	14
Skin	79	4	73	15	77	9
Endocrine	17	4	22	2	19	3
Renal	6	6	0	0	3	3
Other						
Uveitis	6	4	2	2	4	3
Pneumonitis	6	2	2	2	4	2
Lipase increased	26	19	15	10	21	15
Amylase increased	21	6	12	7	17	6

- No new safety signals with 22 months of follow-up for the initial concurrent cohorts
- 22/94 (23%) patients discontinued treatment due to treatment-related adverse events
- 1/94 drug-related death in trial; fatal multi-organ failure (as a result of colitis) in cohort 8

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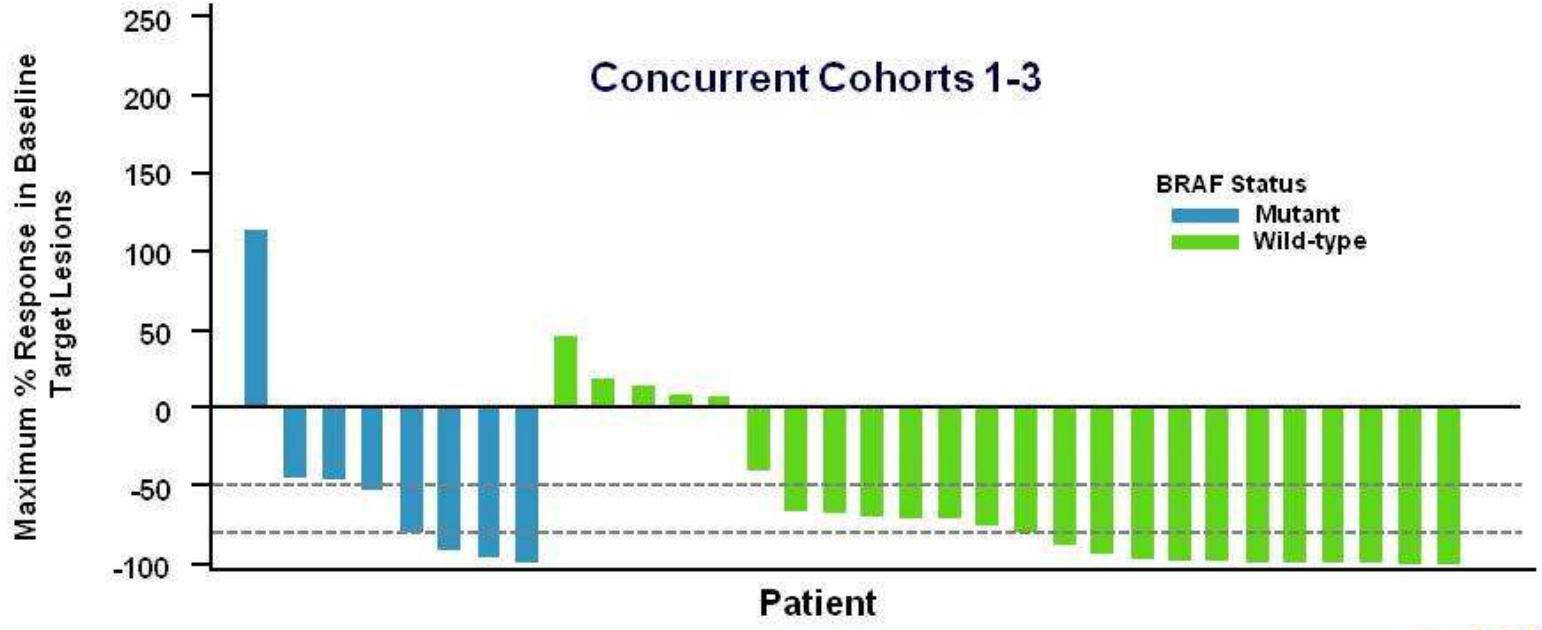
ORR by BRAF Status for Concurrent Cohorts

Nivolumab (mg/kg) + IPI (mg/kg) [n] BRAF Status	Evaluable Samples	ORR, n (%)	
		WT	MT
Concurrent Cohorts 1-3 [53]	36	13/26 (50)	2/10 (20)
Cohort 8 [41; Nivo 1 + IPI3]	38	9/26 (35)	6/12 (50)
Sequenced [33]	24	5/15 (33)	3/9 (33)



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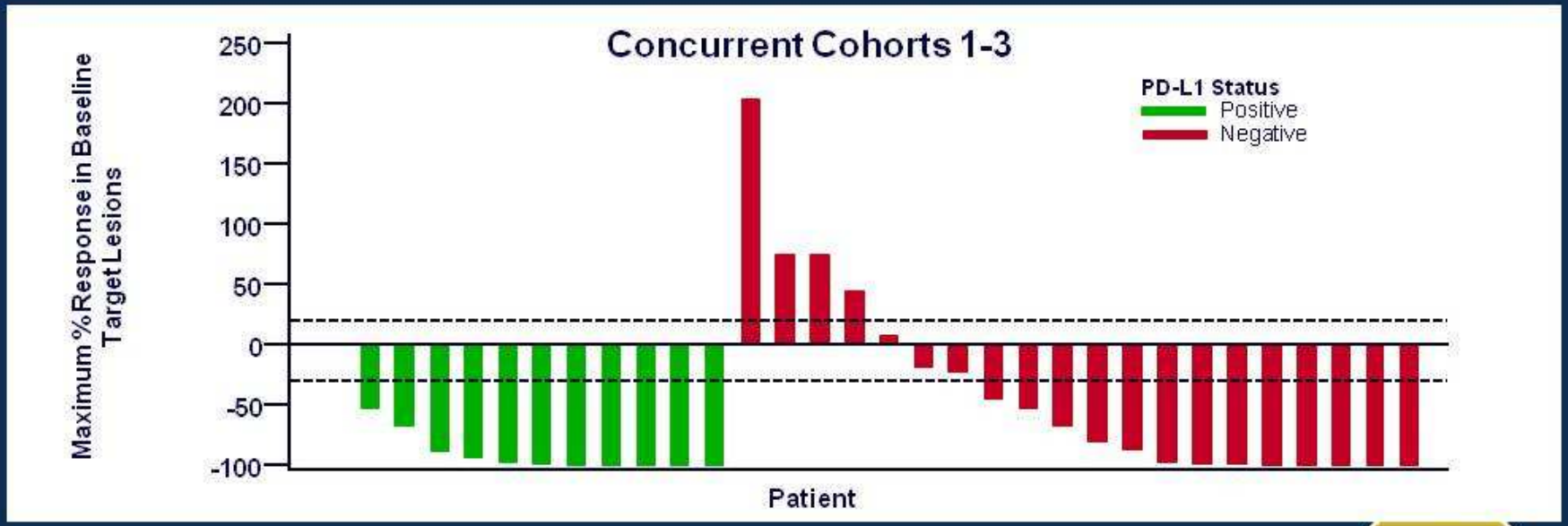
ORR by PD-L1 Status (5% cutoff)

Cohort [n]	Evaluable Samples	ORR, n (%)	
PD-L1 Status		PD-L1+	PD-L1-
Concurrent Cohorts 1-3 [53]	36	8/14 (57)	9/22 (35)
Cohort 8 [41; Nivo1 + IPI3]	20	0/0	8/20 (40)
Sequenced [33]	23	5/8 (63)	3/15 (20)



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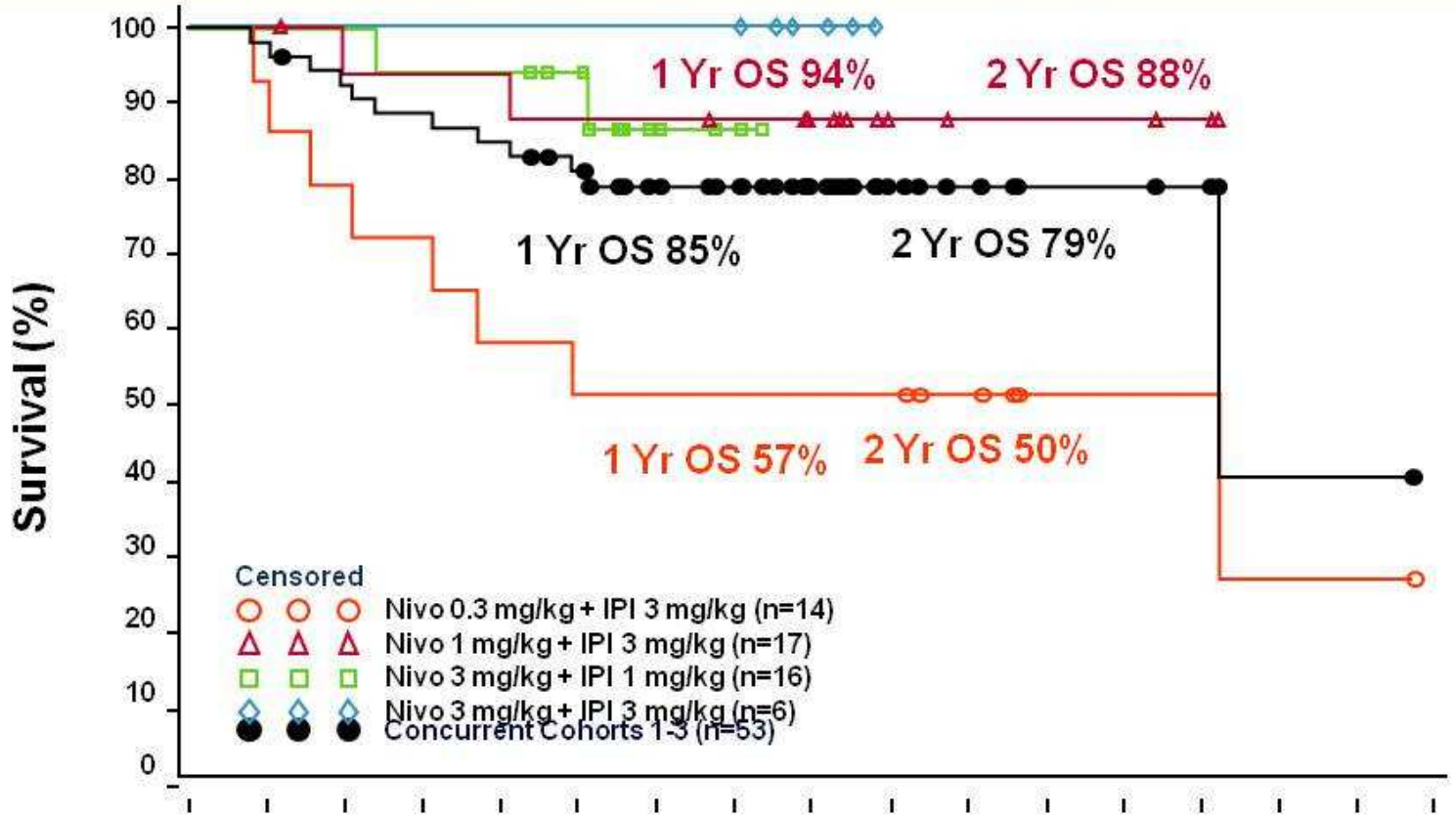
Presented By Mario Sznol at 2014 ASCO Annual Meeting

Overall Survival for Concurrent Therapy by Dose Cohort



Pts at Risk

Nivo 0.3_IPI 3	14	13	11	10	8	7	7	7	7	7	5	2	2	2	1	1	0
Nivo 1 _IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Nivo 3_IPI 1	16	16	15	15	15	13	4	2	0	0	0	0	0	0	0	0	0
Nivo 3_IPI 3	6	6	6	6	6	6	6	6	3	0	0	0	0	0	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

Presented by:

PRESENTED AT: 50th ANNUAL MEETING SCIENCE & SOCIETY

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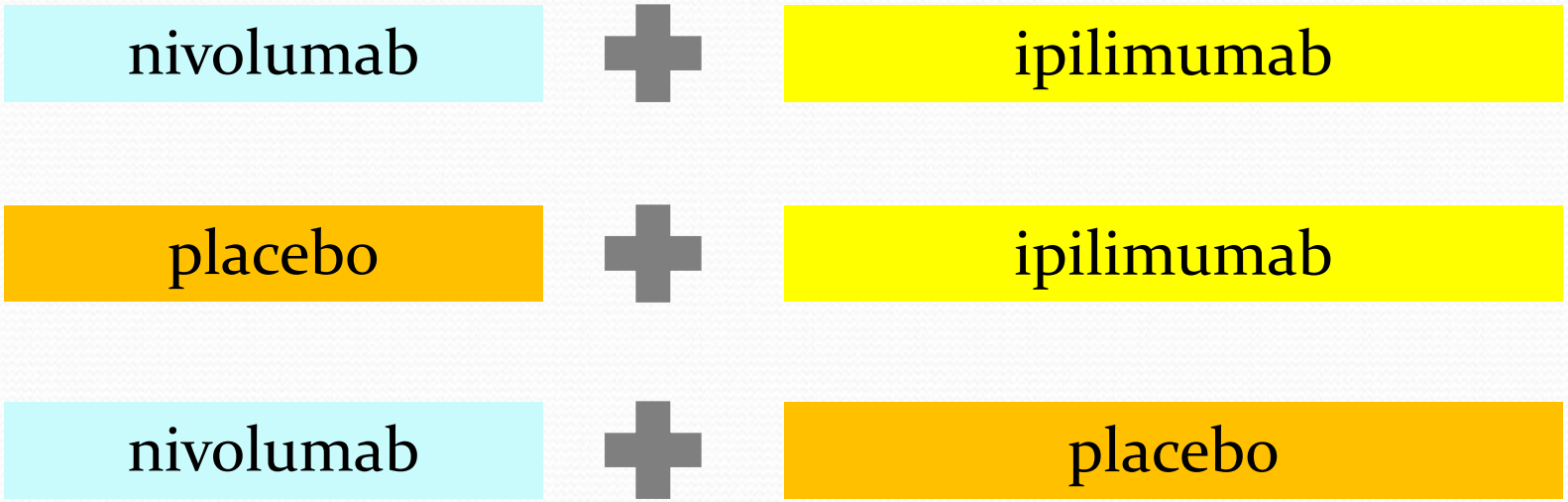
Survival Endpoints for Concurrent and Sequential Therapy by Dose Cohort

Nivolumab (mg/kg) + IPI (mg/kg) [n]	1-yr OS rate, % [Pts at Risk]	2-yr OS rate, % [Pts at Risk]	Median OS, mo	Median PFS, Weeks
Concurrent Cohorts 1-3 [53]	85 [44]	79[19]	40	27
0.3 + 3 [14]	57 [8]	50 [7]	27	13
1 + 3 [17]	94 [15]	88 [9]	NR	36
3 + 1 [16]	94 [15]	NC	NR	58
3 + 3 [6]	100 [6]	NC	NR	34
Cohort 8 [41]	NC	NC	NR	37
Sequenced [33]	70 [23]	NC	NR	23

n: no. treated pts.

NC, not calculated/insufficient follow-up; NR, not reached

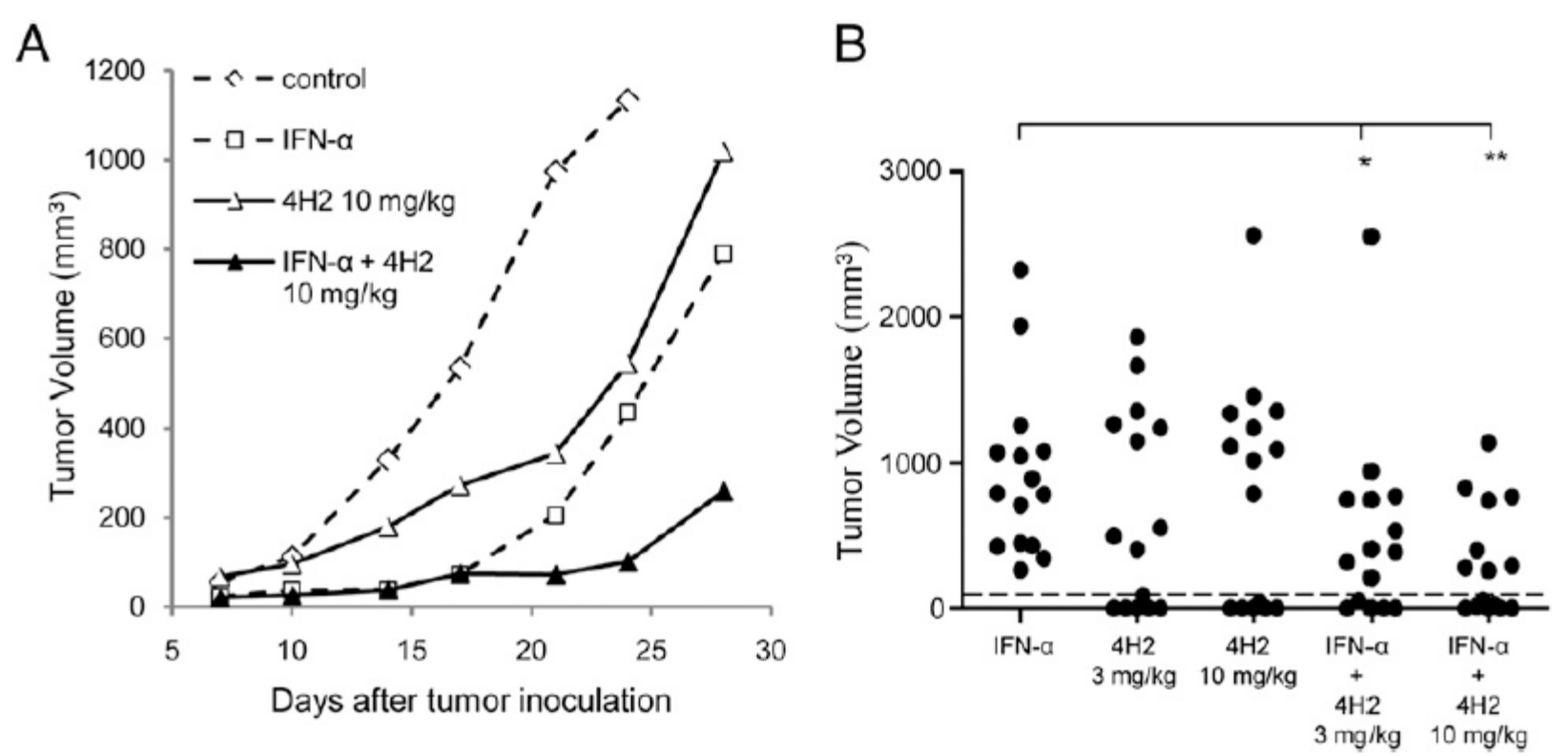
Phase 3 Trial - CheckMate 067



- 915 patients
- Stratified based on PD-L1 expression

NCT01844505

Interferon-α and anti-PD1 antibody



- the potential additive anti-tumor effect of the combination IFNα and anti-PD1

Terawaki S et al J Immunol. 2011 Mar 1;186(5):2772-9.

Interferon-α and pembrolizumab in melanoma and RCC

pembrolizumab + Pegylated IFN-α

pembrolizumab + ipilimumab

NCT02089685

Immunotherapy and chemotherapy

- A Multi-arm Phase I Safety Study of **Nivolumab** in Combination With **Gemcitabine/Cisplatin**, **Pemetrexed/Cisplatin**, **Carboplatin/Paclitaxel,** Bevacizumab Maintenance, **Erlotinib**, **Ipilimumab** or as Monotherapy in Subjects With Stage IIIB/IV Non-small Cell Lung Cancer (NSCLC)

NCT01454102

Other combinations

- Ipilimumab + Talimogene laherparepvec (Tvec) in melanoma
- Pembrolizumab + Talimogene laherparepvec (Tvec) in melanoma
- Nivolumab + dasatinib in CML
- Nivolumab + anti-KIR antibody in solid tumors
- Nivolumab + anti-LAG-3 antibody in solid tumors
- Nivolumab + IL-21 in solid tumors
- aldesleukin + ziv-aflibercept in melanoma
- aldesleukin + vemurafenib in melanoma
- Adoptive cell transfer therapy and ipilimumab in melanoma

Questions

Question 1

- The following mechanisms of sensitization of the immune system by BRAF inhibitors have been described, EXCEPT

  A. Increase in tumor antigen and MHC expression

  B. Increase in tumor infiltrating lymphocytes

  C. Improvement of immune effector cell function by inducing paradoxical MAPK activation on T cells

  D. Inhibition of tumor angiogenesis through VEGF-MAPK pathway

  E. Improvement of the tumor microenviroment by decreasing expression of immune suppressive cytokines and immune regulatory ligands

Question 2

- The phase 1 clinical trial of the combination of vemurafenib and ipilimumab in patients with metastatic melanoma was stopped early because

  A. Of poor accrual

  B. Increased liver toxicity

  C. Increased gastrointestinal toxicity

  D. Increased dermatologic toxicity

  E. Increased frequency of the development of brain metastasis

Question 3

- The updated data on the phase 1 trial of 53 patients treated with anti-PD1 antibody, nivolumab, and anti-CTLA4 antibody, ipilimumab concurrently show the 1-year survival rate of

  A. 15%

  B. 25%

  C. 40%

  D. 65%

  E. 85%