Combining Immunological and Targeted Agents
- *The Way Forward*

***Axel Hoos**, MD, PhD*
VP, Oncology R&D
Head, Immuno-Oncology & Combinations

WIN Symposium, Paris, June 23-24, 2014

Disclosures

- Employee and stock holder of GlaxoSmithKline

- Investigational use of dabrafenib/trametininb in BRAF-mutant colorectal cancer

Objectives

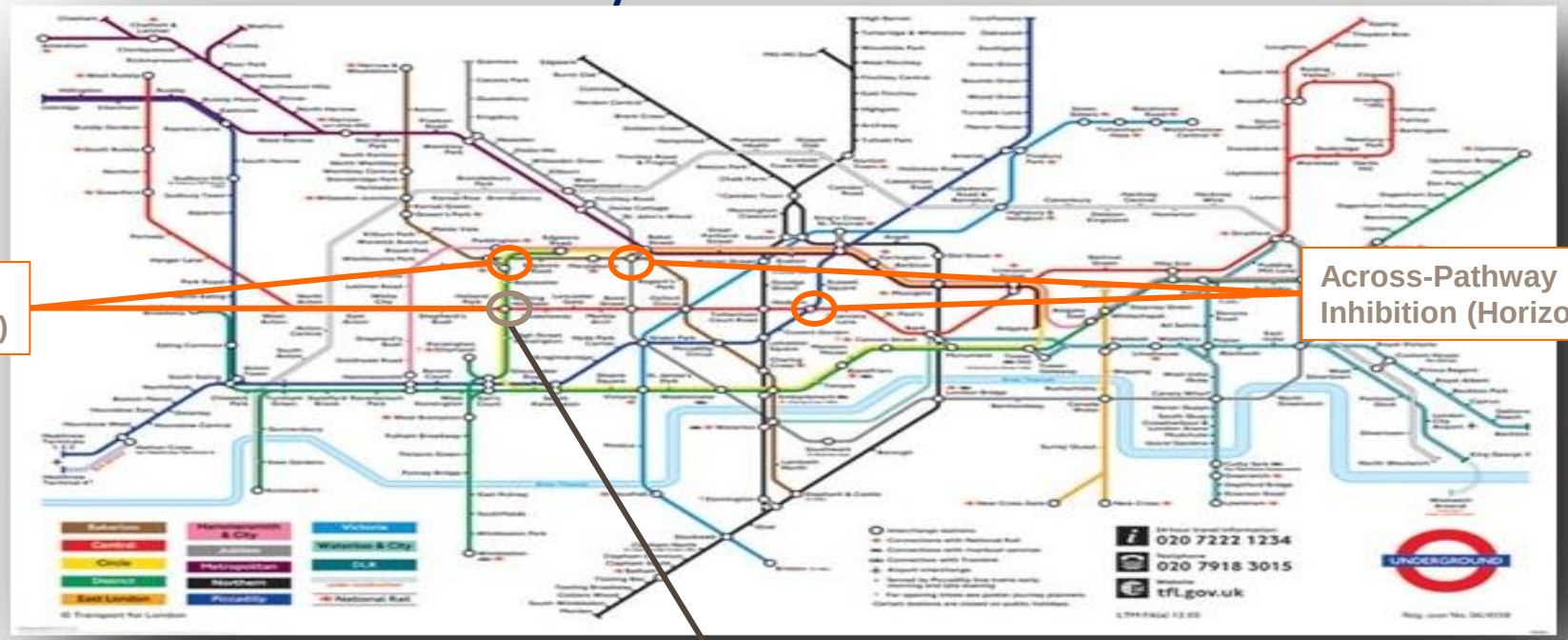
- Role of Targeted Therapies
- Clinical Benefit Hypothesis for Targeted – Immuno Therapy Combinations
- Preparing for Combinations: Characterization of Immune Effects
- First Clinical Results: Lessons learned
- The Way Forward

Combination Therapy

Science-driven Combinations Across Central Mechanisms

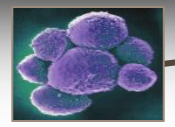
Host Immune System

Pathways in Cancer Cells



Within-Pathway Inhibition (vertical)

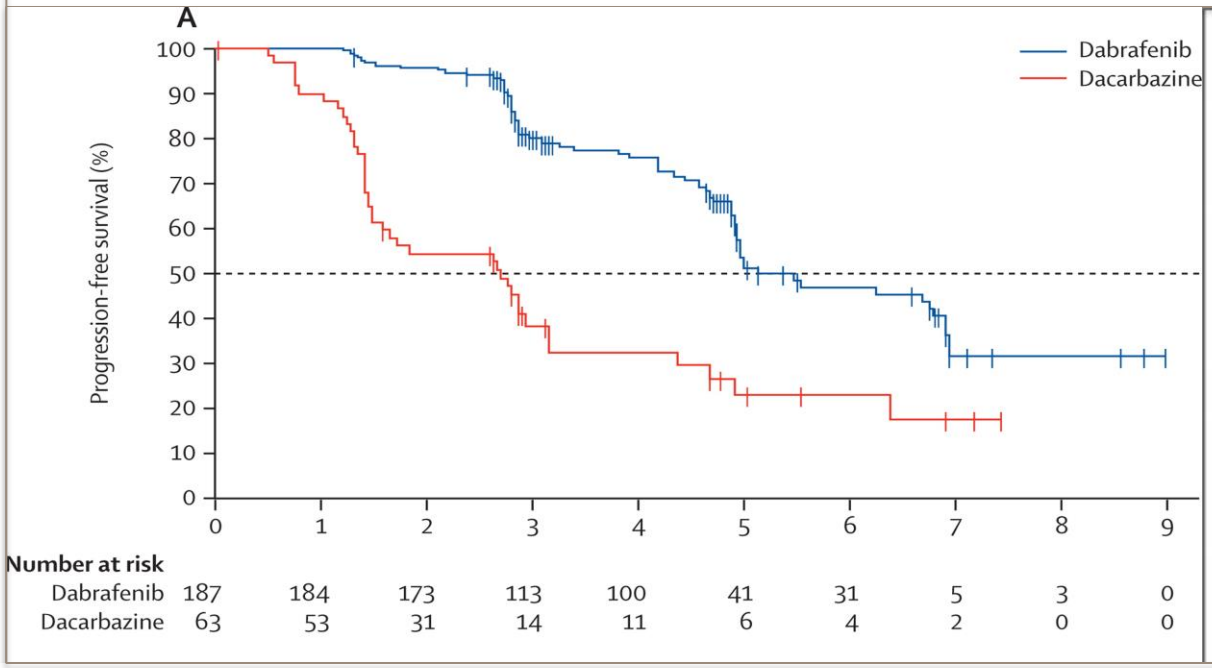
Across-Pathway Inhibition (Horizontal)



Targeted – Immuno Therapy Combination

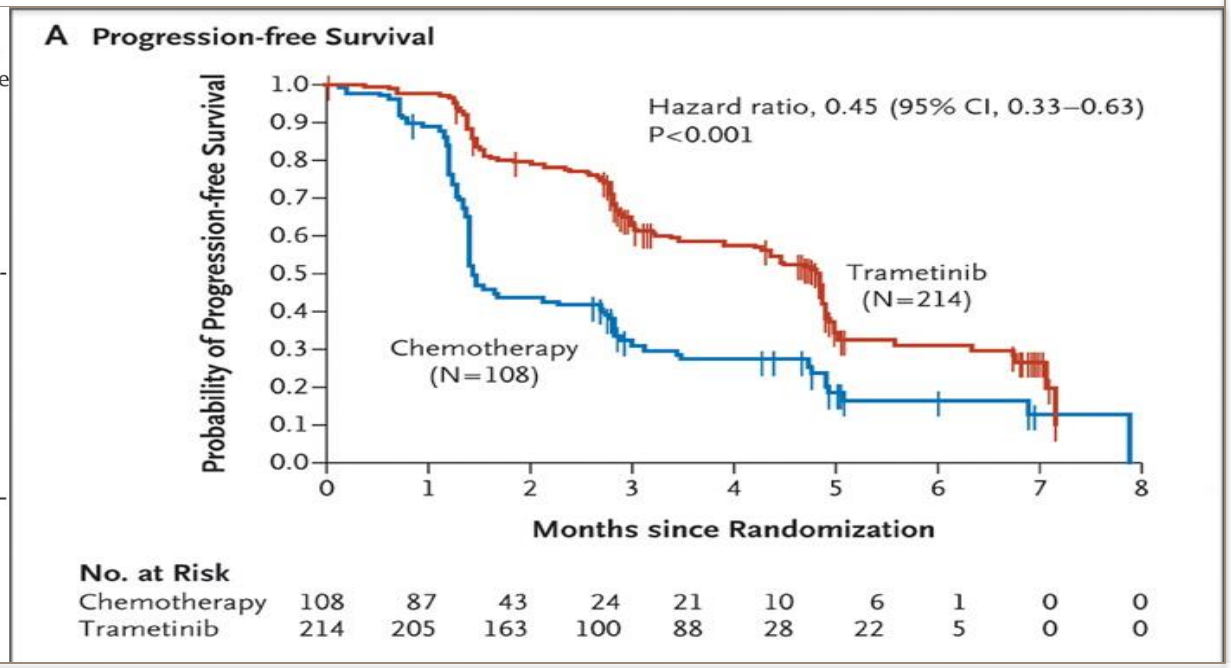
Inhibition of the MAPK Pathway:
BRAF (Dabrafenib) ; MEK (Trametinib)

Phase 3: Dabrafenib PFS



Hauschild A et al. Lancet 2012;380:358-365

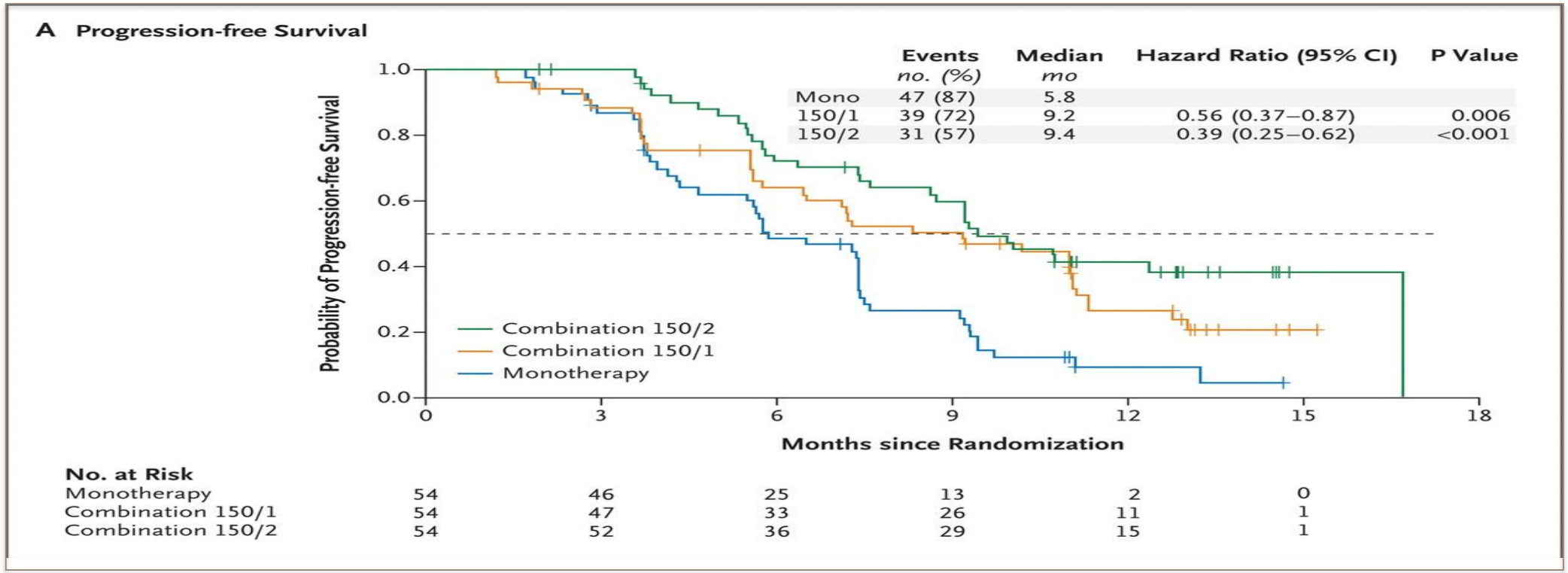
Phase 3: Trametinib PFS



Flaherty KT et al. N Engl J Med 2012;367:107-114

Dual Inhibition of the MAPK Pathway:
BRAF (Dabrafenib) + MEK (Trametinib)

Randomized Phase 2: PFS



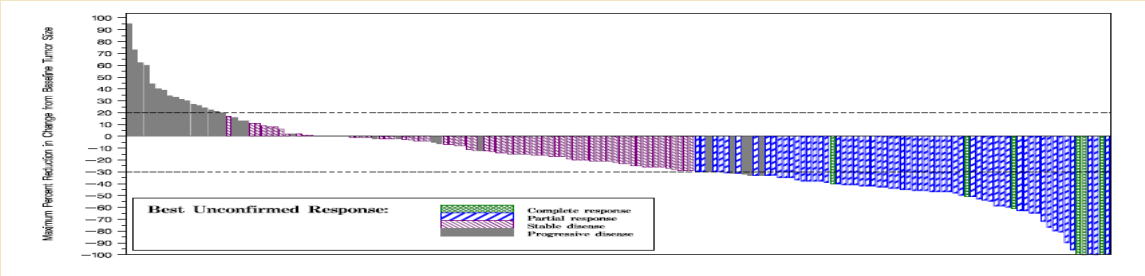
Flaherty KT et al. N Engl J Med 2012;367:1694-1703

The NEW ENGLAND JOURNAL of MEDICINE

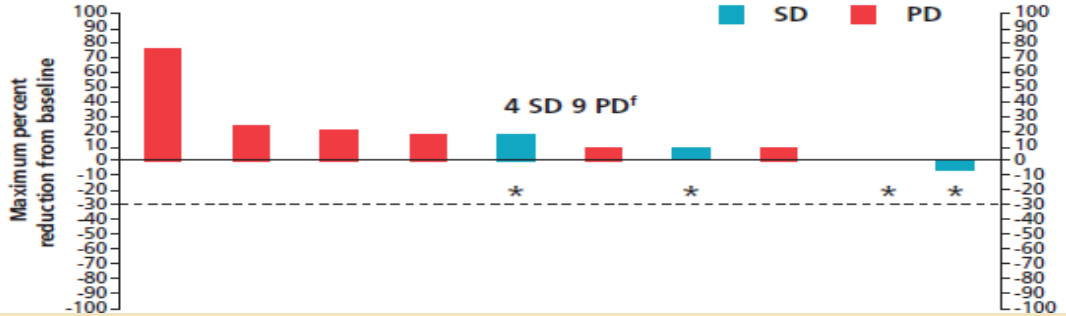
BRAF-mutant tumors are not created equal

Trametinib (MEKi) in BRAF-mutant Melanoma vs. CRC

Melanoma



CRC

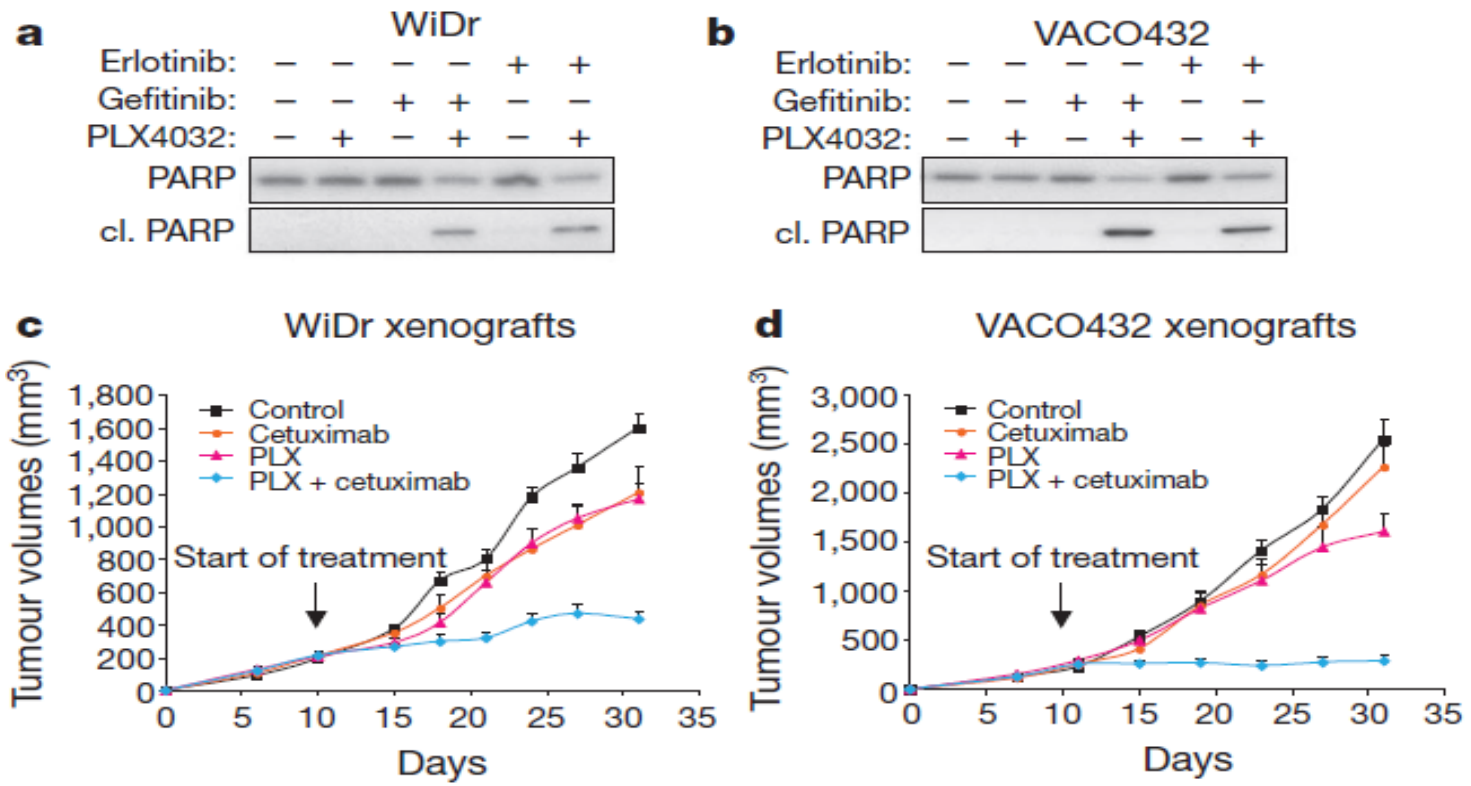


Unconfirmed response rate: 0%
Median PFS: 1.8m

EGFR Feedback in BRAF-mutant CRC

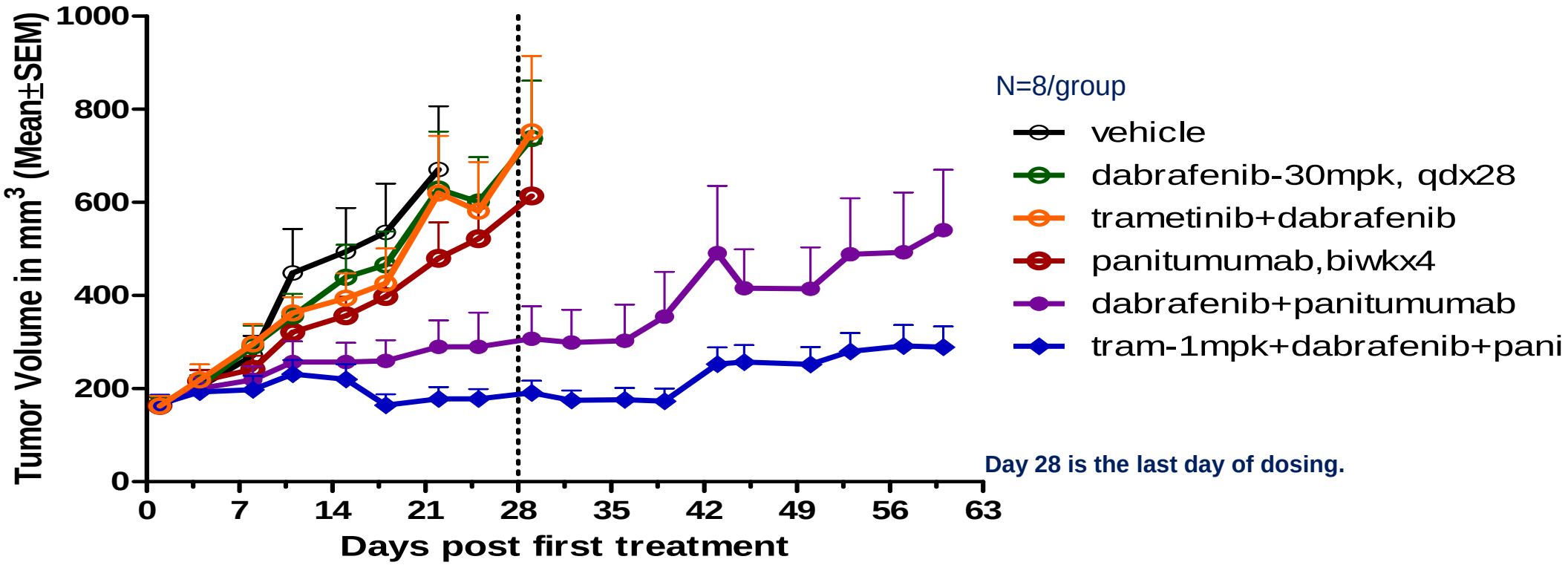
EGFR is activated upon BRAF inhibition in CRC

- Netherlands Cancer Institute (NKI):
  - EGFR identified via synthetic lethality screen in BRAF -mutant cell lines
  - EGFR can mediate resistance of to BRAFi
  - Dual blockade of BRAF and EGFR may overcome resistance



Prahallad *et al*., Nature 2012

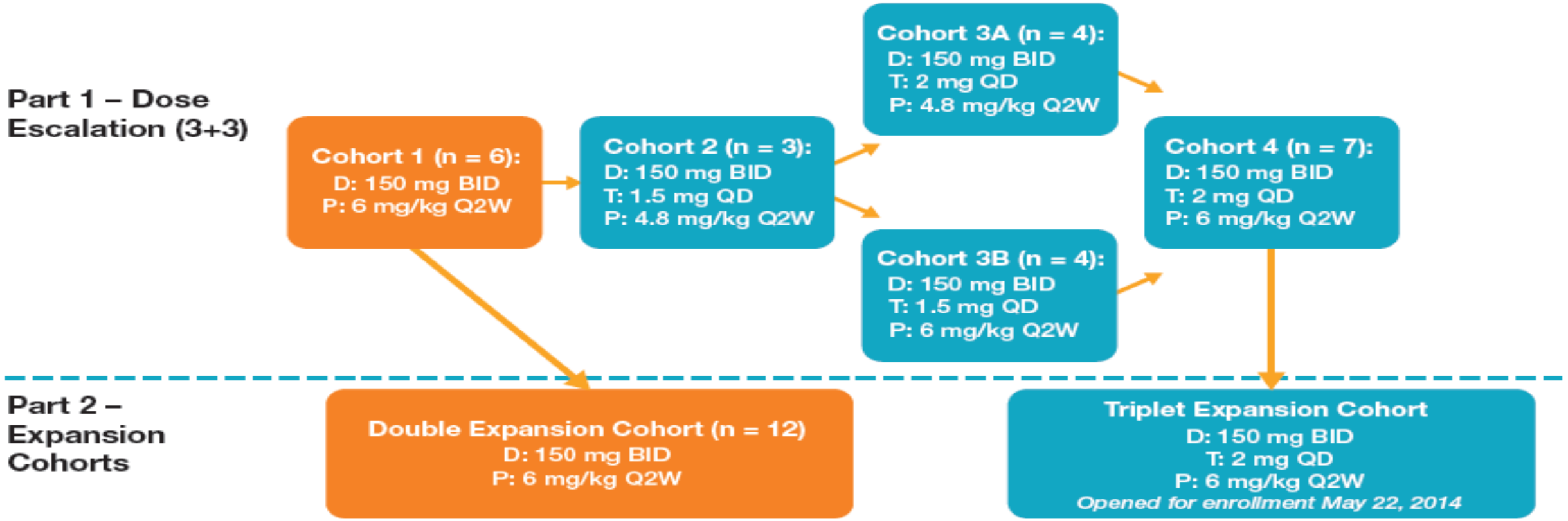
Preclinical In Vivo Efficacy-
$BRAF^{V600E\ \_L584F}/PI3K^{wt}$ Co-012 CRC PDX model



- Dabrafenib mono and dabrafenib/trametinib combo: non-significant tumor growth delay (TGD)
- Panitumumab mono: 70% TGD, 3/8 60-day survivors
- Dabrafenib/panitumumab combo: 108% TGD, 7/8 60-day survivors
- Dabrafenib/trametinib/panitumumab triple combo: 108% TGD, 8/8 60-day survivors

Liu et al, ASCO 2014, Abstract #3513

Open-Label Phase I/ II Study of MEK Inhibitor Trametinib (T), BRAF Inhibitor Dabrafenib (D) and Anti-EGFR Antibody Panitumumab (P) in Combination in Patients with BRAF V600E Mutated Colorectal Cancer



Note: BID, twice daily; QD, once daily; Q2W, every 2 weeks; RP2D/R, recommended phase 2 dose/regimen.

- *Enroll a total of ~20 patients in each cohort at the RP2D/R*
- *Part 1 and Part 2: Pre-dose and on-study biopsies required for pharmacodynamic assessments*
- ***Part 3 of the study (not shown) will be a randomized Phase II study comparing D + P + T, D + P and standard of care.***

Bendell et al, ASCO 2014, Abstract #3515

Safety

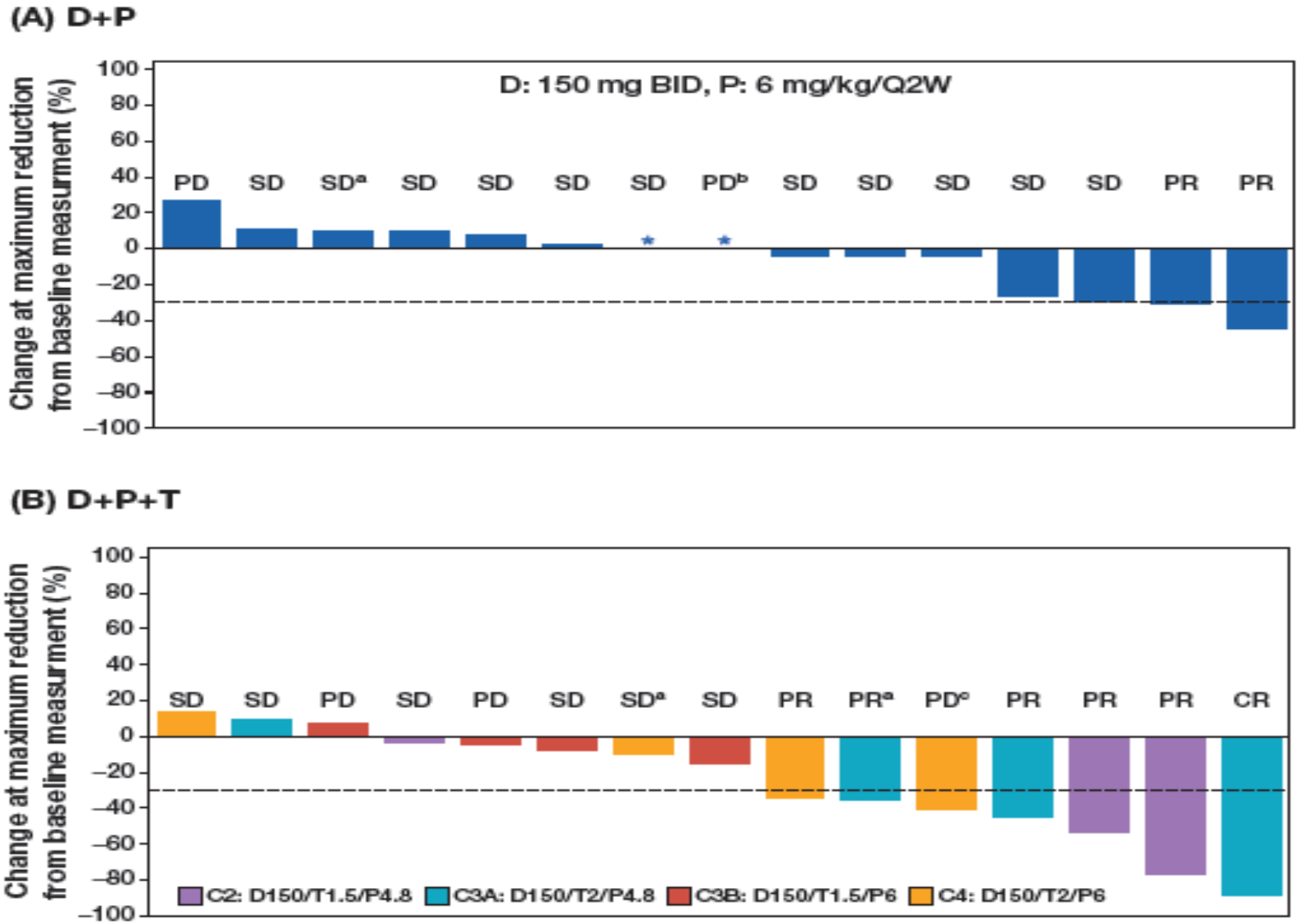
- The doublet and triplet combinations have been well tolerated.
- No DLTs have occurred on study.
- No grade 4-5 AEs were noted.

- Acneiform Rash:
  - D + P: 47% grade 1 rash, 6 % grade 2 rash
  - D + P + T: 25% grade 1 rash; 25% grade 2 rash, 6% grade 3 rash
  - P: 57% grade 1-2 rash, 7% grade 3 rash (per prescribing information)

- Pyrexia:
  - D + P: 0% grade 1, 24% grade 2 pyrexia
  - D + P + T: 13% grade 1, 6% grade 2 pyrexia

Bendell et al, ASCO 2014, Abstract #3515

Maximum Tumor Response



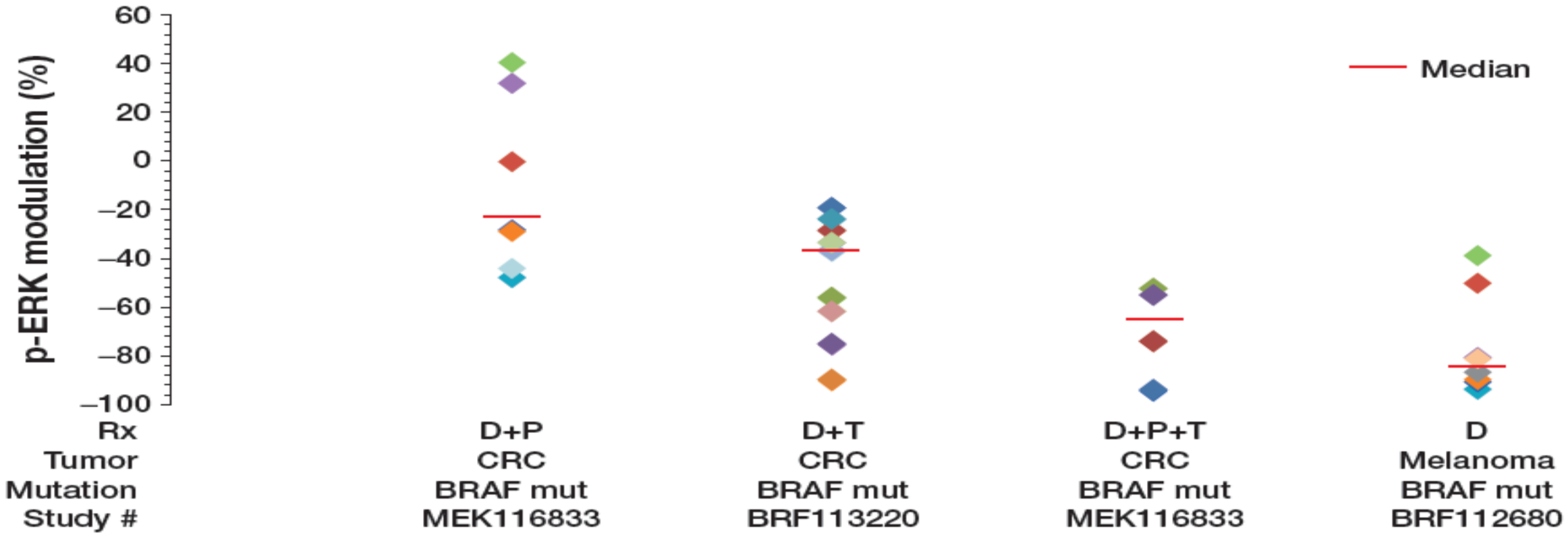
2/15

7/15

Bendell et al, ASCO 2014, Abstract #3515

Bars are grouped by best unconfirmed response. *Indicates maximum reduction from baseline is 0%. [a] Denotes that subject received prior anti-EGFR therapy. [b] denotes progressive disease secondary to presence of new lesion. [c] Patient had a 30% reduction in target lesions but was deemed to have PD due to presence of one new lesion.

Cross-Study Comparison of Phospho-ERK Modulation Between D+P, D+T and D+P+T Therapy in CRC and D Therapy in Melanoma



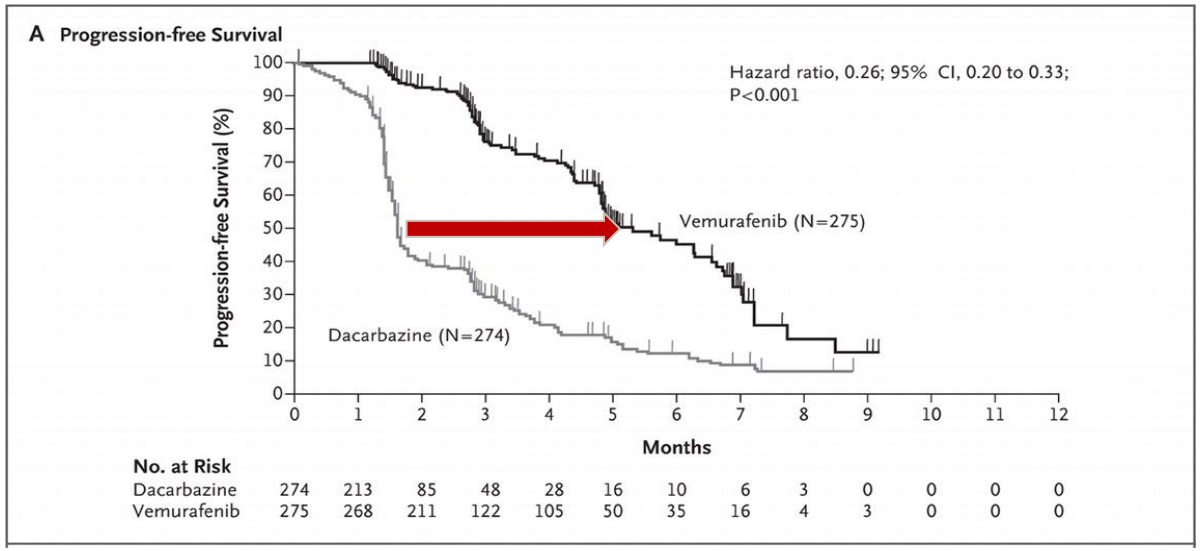
Comparison of p-ERK modulation using dabrafenib based combination therapies in BRAFm CRC and BRAFm melanoma. Treatment in BRAFm CRC was dabrafenib (150 mg BID) , trametinib (1.5-2 mg QD) and/or panitumumab (4.5-6 mg every two weeks). Treatment in BRAFm melanoma was dabrafenib (70 -200 mg BID). Average +/- SD for median pERK decrease in CRC was D+P (n= 7): -11 % (± 35.7%), -28; D+T (n=9): 47 % (± 24 %) , -36.7%; D+P+T (n=2): -84 (± 14%), -84%. Average +/- SD for pERK decrease in melanoma was D (n=8): 76 % (± 20 %), -84%.

Bendell et al, ASCO 2014, Abstract #3515

Targeted – Immuno Therapy Combinations

Clinical Benefit Hypothesis

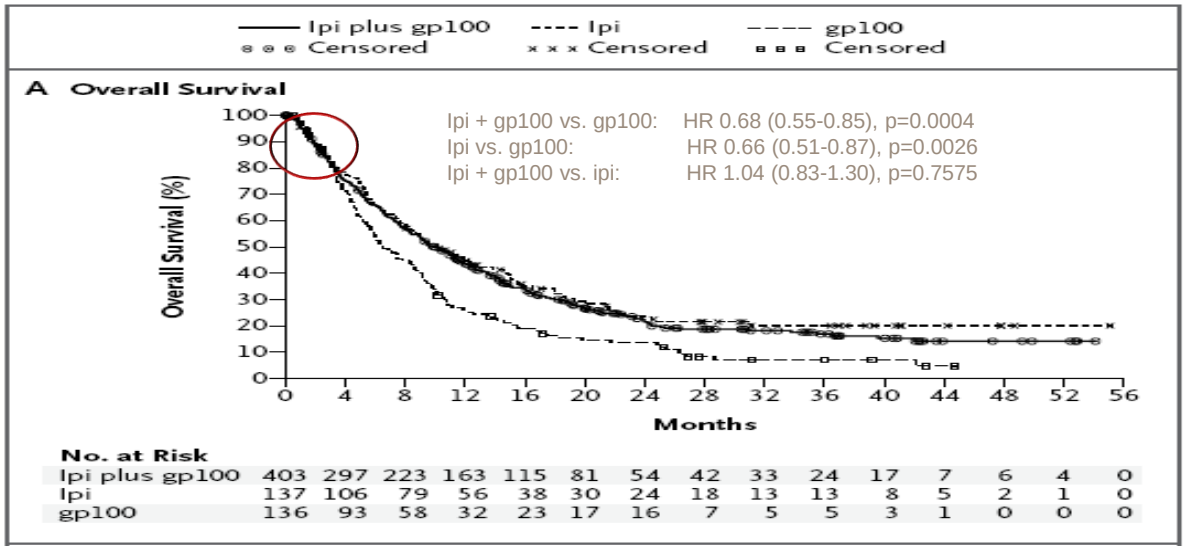
TKI: Vemurafenib (BRAFi)



Chapman et al., New Engl. J. Med. 2011

- Fast response
- Limited durability

IT: Ipilimumab (anti-CTLA-4)



Hodi et al., New Engl. J. Med. 2010

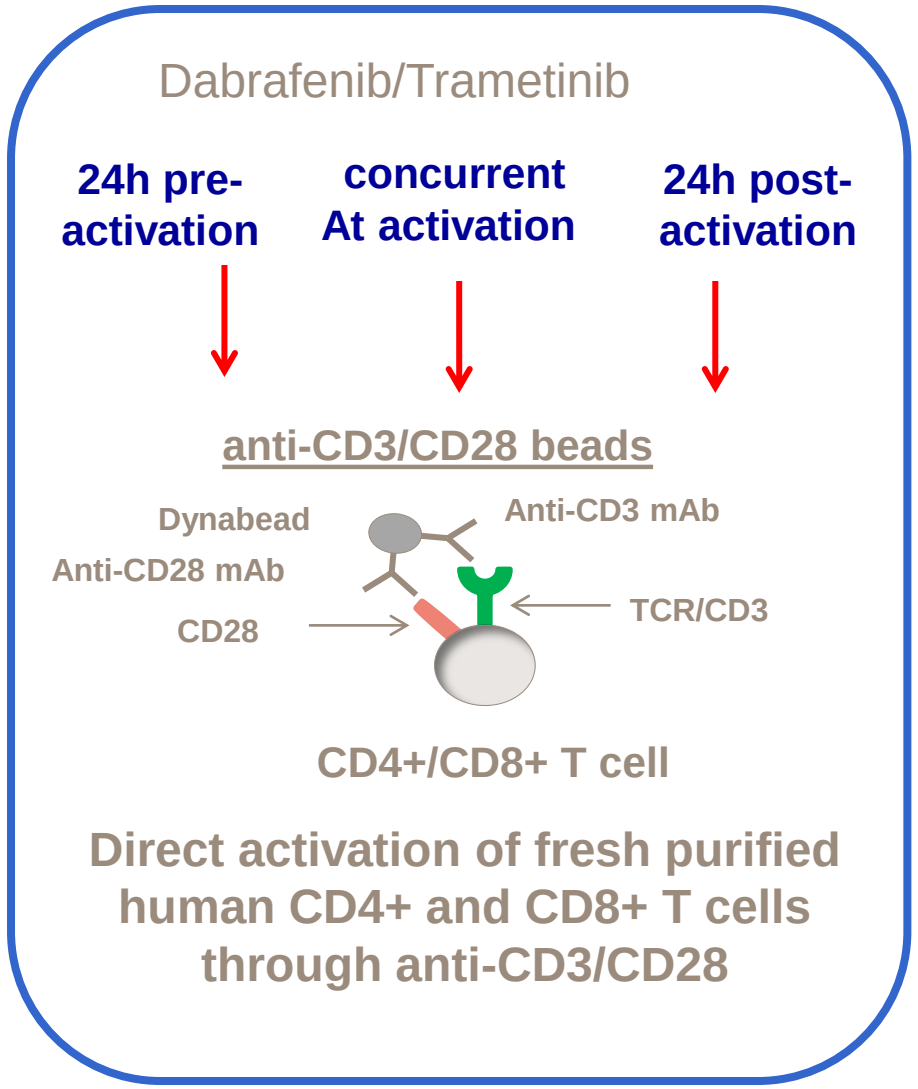
- Delayed effect
- Long durability

Combination: Immediate TKI effects bridge to long-term IT effects
Expected Result: Larger proportion of long-term survivors
Caution: Potential toxicity

Dabrafenib / Trametinib Impact on the Immune System

In-vitro and in-vivo proof of concept Studies

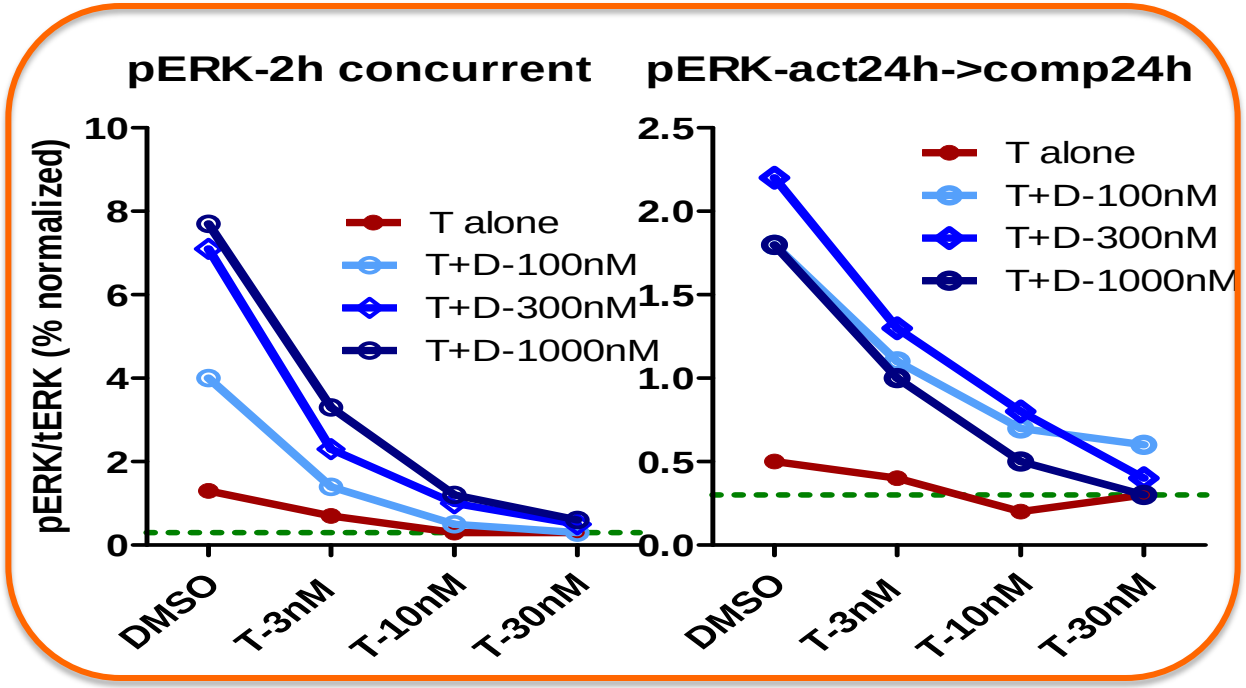
Direct effects of dabrafenib/trametinib on activated human CD4 and CD8 T cells

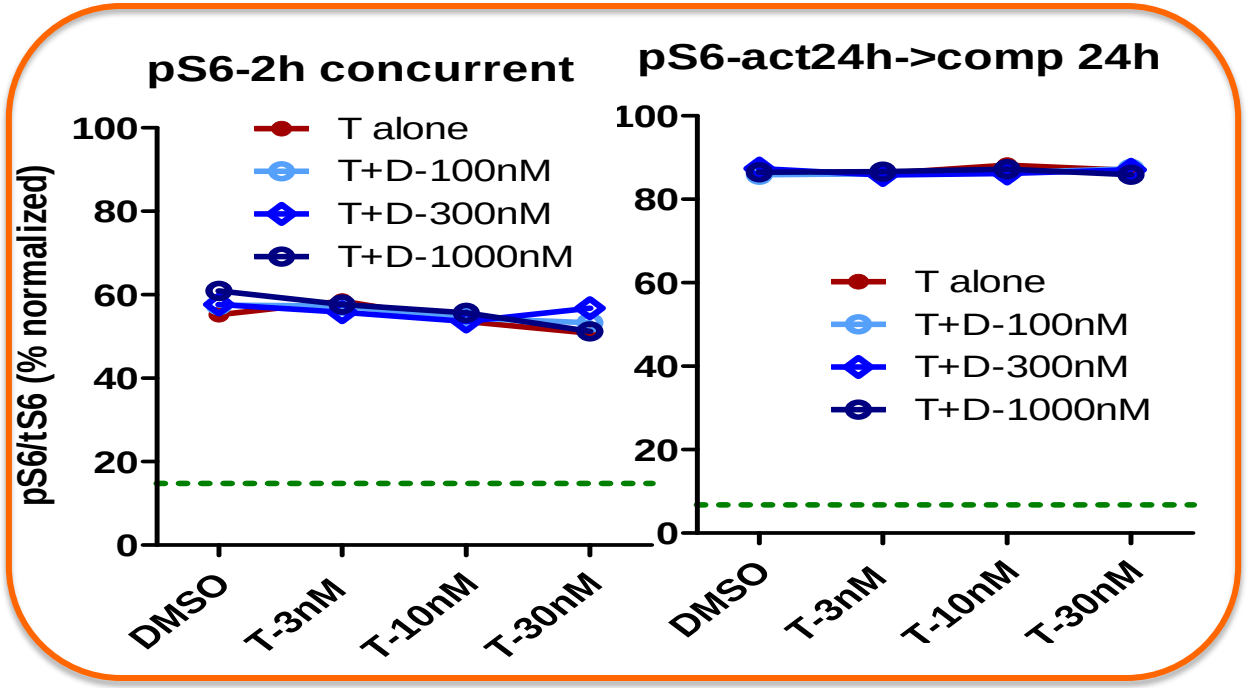


Assays	Dabrafenib	Dabrafenib +Trametinib	Trametinib
Proliferation	No inhibitory	Partially offset trametinib effect	Partial inhibitory, minimal if activated first
Viability	No death	No death	No death
Cytokines	Minimal	Some changes	Some changes
Activation/ exhaustion markers	Minimal	Some changes	Some changes
Signaling	↑ pERK /little change of pS6	partially offset trametinib effect	↓pERK /little inhibition of pS6
Gene expression	Minimal	Some changes	Some changes

MAPK and PI3K/AKT signaling changes by BRAFi/MEKi in human CD4/CD8 T cells and PBMC activated by anti-CD3/CD28

Human CD4 + cells

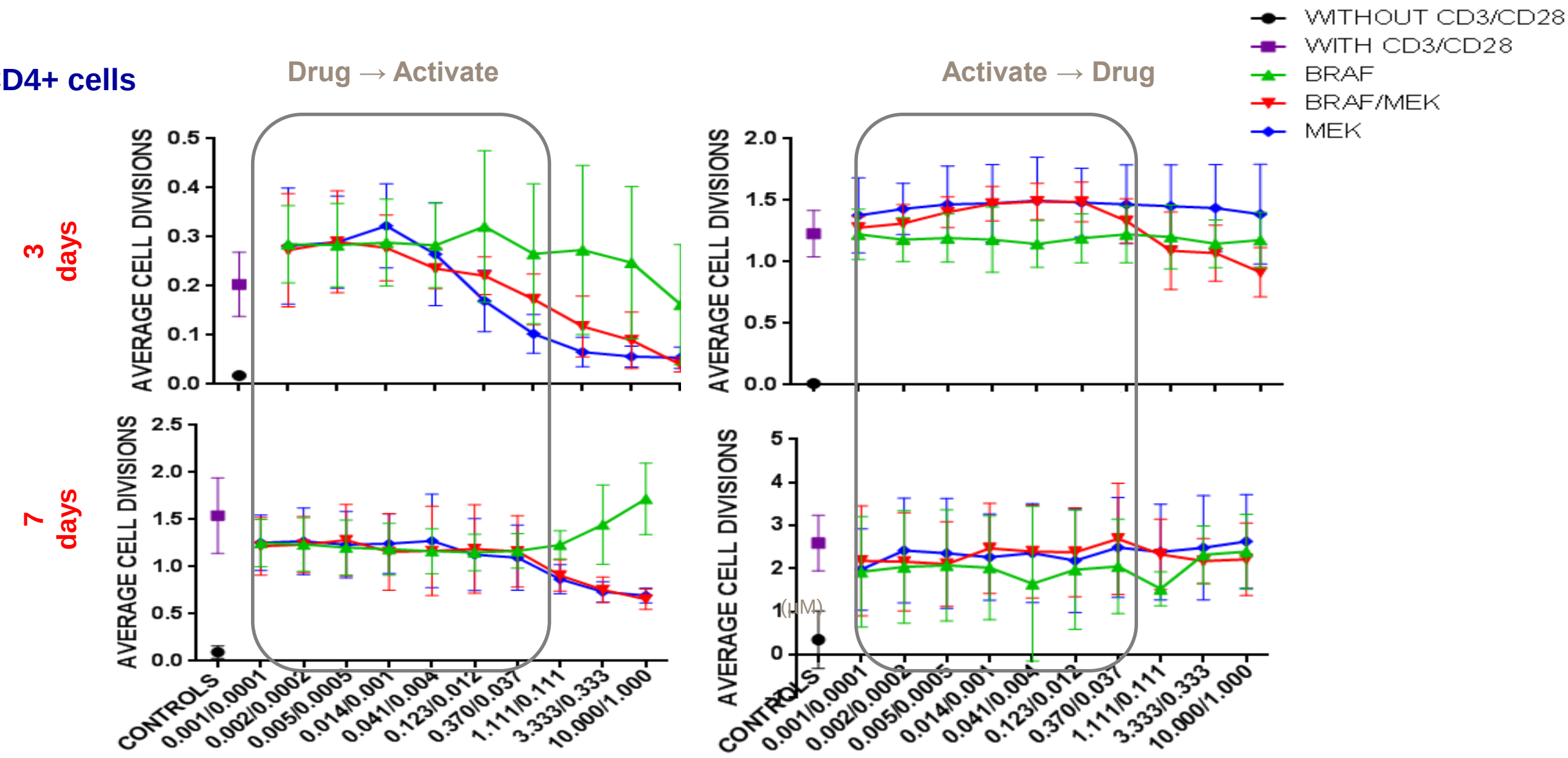




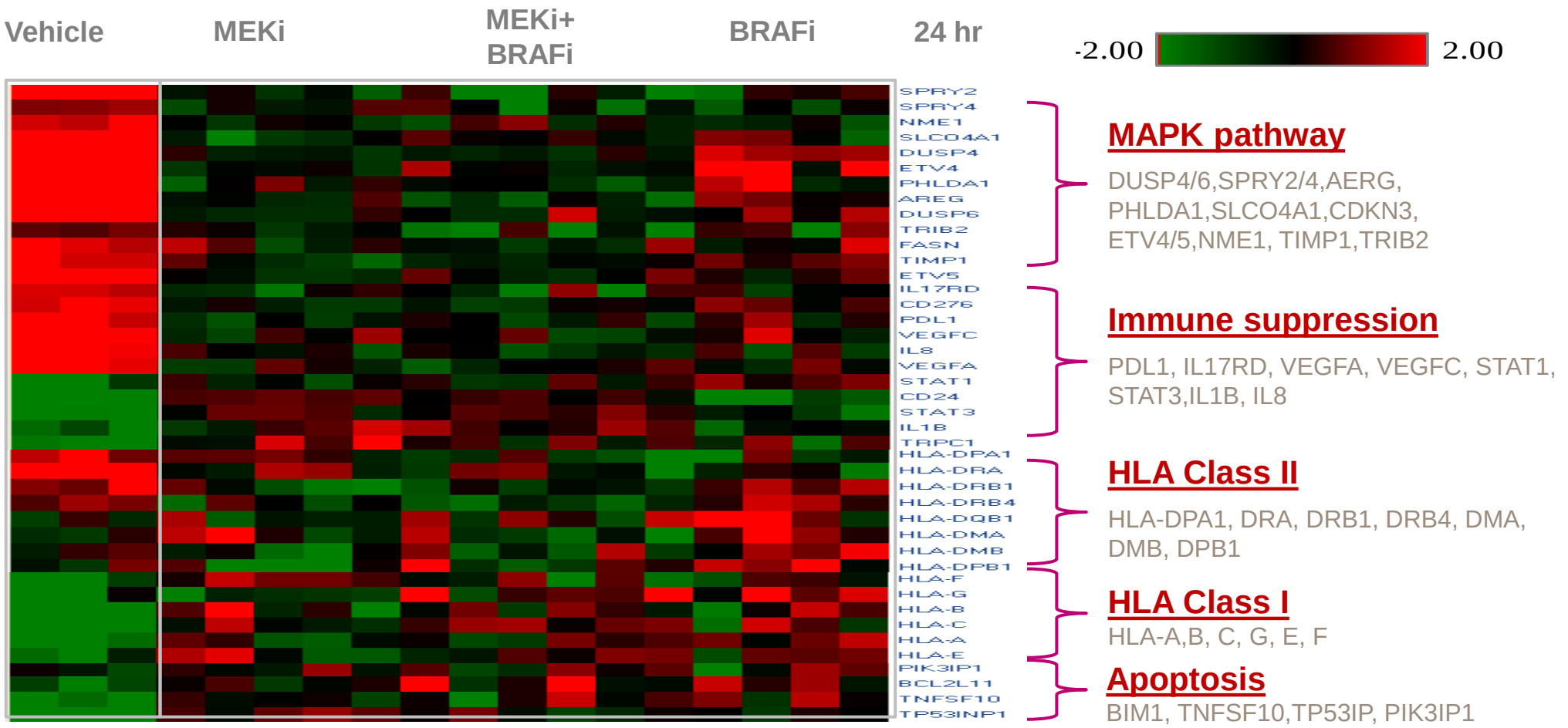
pERK/ERK and pS6/tS6, pAKT/tAKT MSD assays:

- pERK was inhibited by trametinib, however enhanced by dabrafenib independent on activation sequence
- Dabrafenib, trametinib alone and in combination had minimal effect on pS6 and pAKT
- Similar data were observed in both CD4 and CD8 cells and PBMC

Effects of BRAFi/MEKi on cell proliferation in human CD4 and CD8 T cells



Dabrafenib/trametinib inhibited MAPK, reduced immune suppression factors and increased MHC molecule expressions in A375 melanoma cells



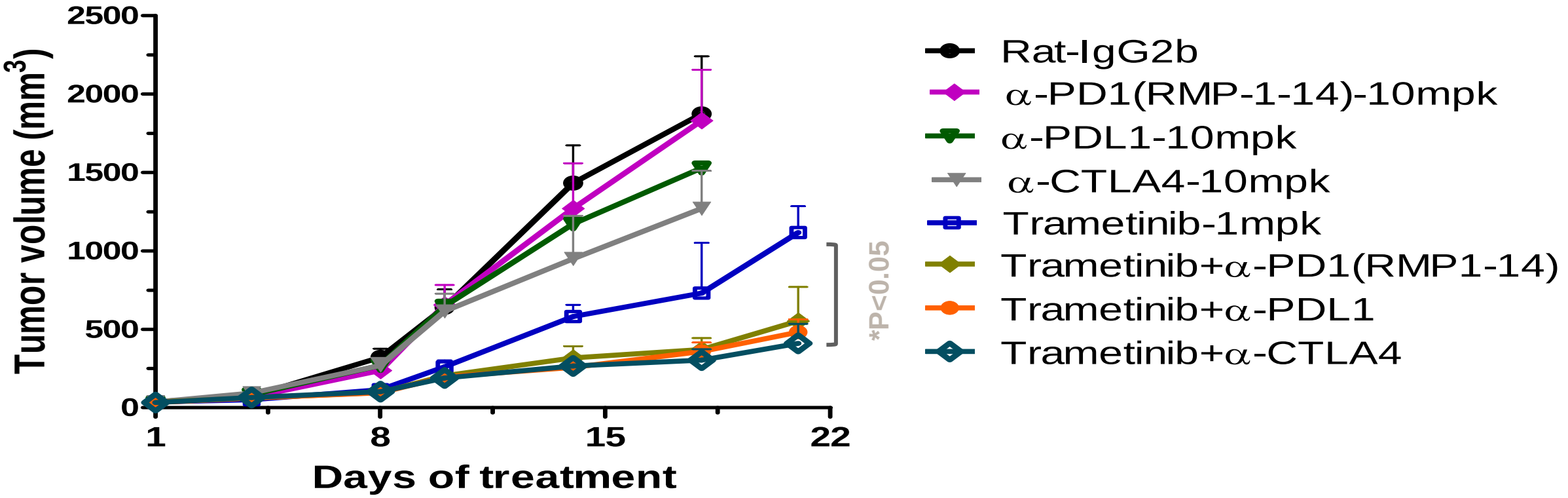
- Dabrafenib/trametinib reduced immune suppression factors and increased MHC molecule expressions in A375 BRAFV600E mutant melanoma cells in vitro and xenograft tumors in vivo
- These effects are correlated with MAPK pathway inhibition

In vitro immune modulation effects on tumor cells

Cancer cells		BRAF /RAS	PD-L1 baseline exp.	Comp. treatment	48 hr treatment changes (mRNA/protein)					
					PD-L1	HLA-I	HLA-II	IL6	IL8	DUSP6
Melanoma $BRAF^{mut}$	YUSIT	V600K	BD	dab./tram.	↓[a]	-	ND	↓	↓	↓
	A375	V600E	low	dab./tram.	↓	↑	↑	↓	↓	↓
	SKMEL24*	V600E	BD	dab./tram.	-	↑	↑	↑	↑	↓
	12R5-1#	V600E	high	dab./tram.	↓	↑	ND	↑	↓	ND
Melanoma $BRAF^{wt}$	CHL-1	WT	BD	trametinib	-[b]	-	-	↓	-	-
	HMVII	$NRAS^{Q61K}$	BD	trametinib	-[b]	↑[c]	-	↓	↓	↓
	SKMEL2	$NRAS^{Q61R}$	BD	trametinib	↓	↑	↑	↑	↓	↓
NSCLC	Calu6*	$KRAS^{Q61K}$	BD	trametinib	-	↑	-	-	↓	↓
	A549	$KRAS^{G12S}$	BD	trametinib	-[b]	↑	-	↑	-	↓
	H358	$KRAS^{G12C}$	Medium	trametinib	↓	↑[c]	-	↑	↓	↓

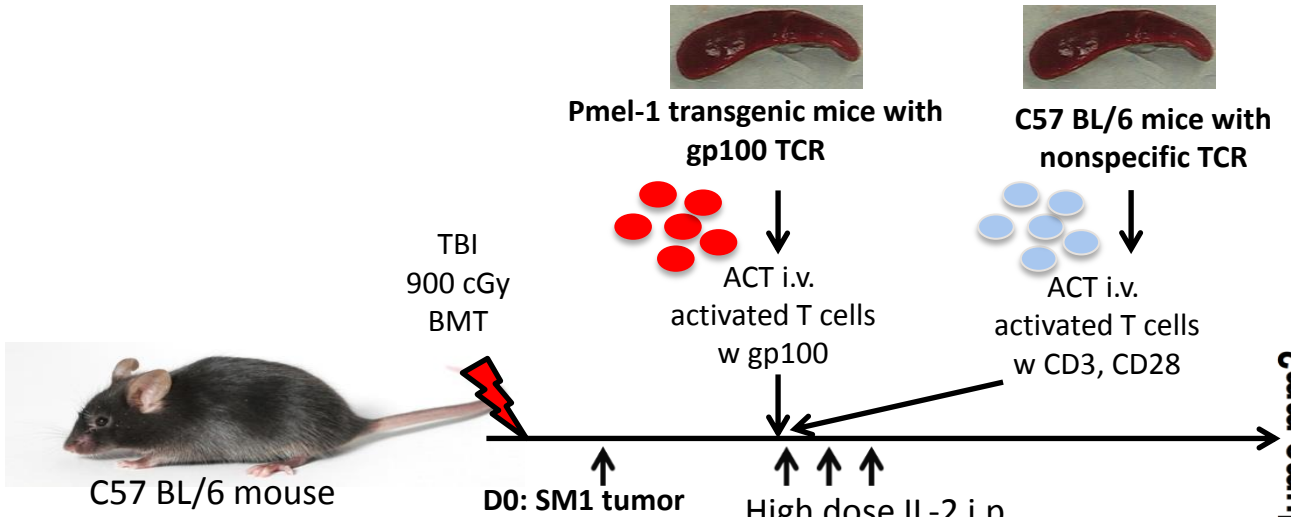
- **Trametinib/dabrafenib reduced a subset of tumor suppression factors and increased the expression of HLA molecules and tumor antigens (eg NY-ESO-1,MART1) in $BRAF^{V600}$ mutant melanoma lines.**
- **Trametinib increased expression of HLA molecules in most tumor cell lines tested.**

Trametinib+ immuno-modulators enhanced efficacy in CT-26 ($KRAS^{G12D}$) murine CRC in female BALB/c syngeneic model



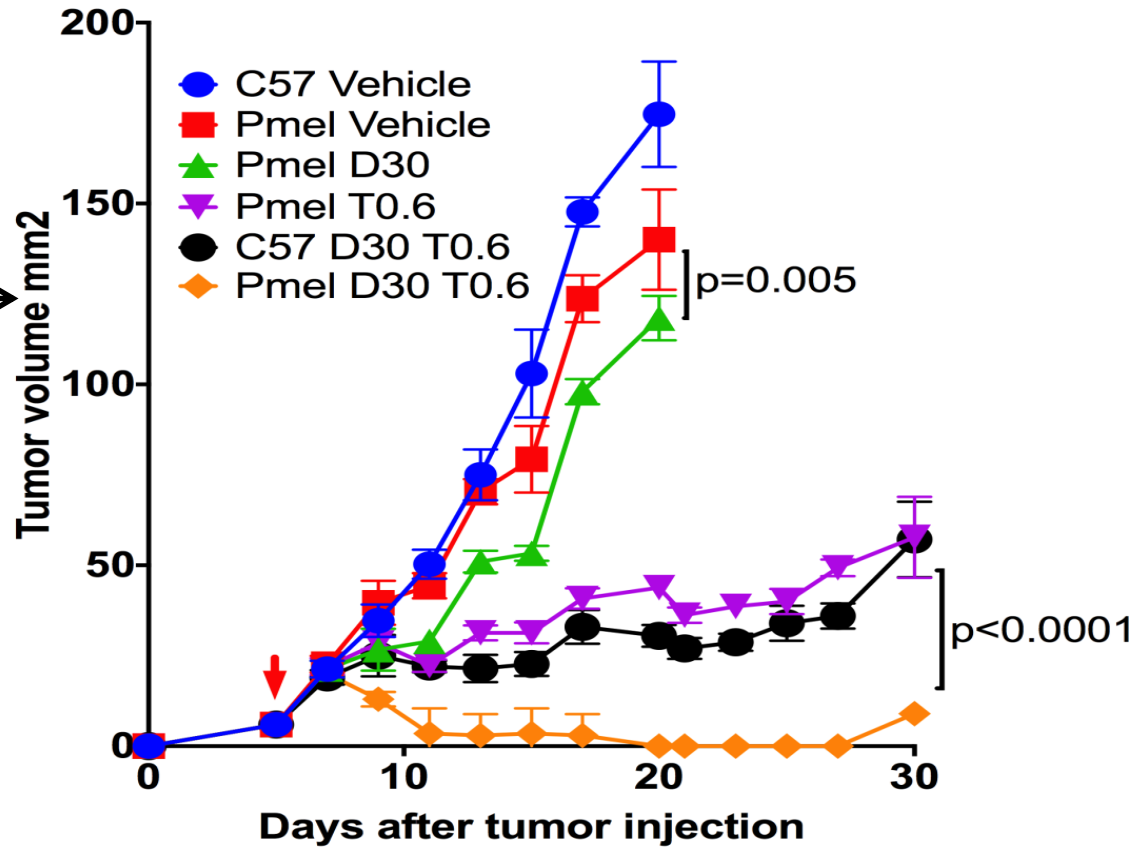
Treatments began at day 12 after cell implant. Mice (n = 10/group) were treated with trametinib at 1 mg/kg, orally QDx21days, or anti-mouse antibodies, Rat-IgG2a, αPD-1 (RMP1-14 clone, rat IgG2a), αPD-L1 (10F.9G2 clone, rat IgG2b), αCTLA-4 (9D9 clone, mouse IgG2b) at 10 mg/kg, i.p. twice weekly x 3 weeks.

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



SM1: *BRAF*^{V600E}-driven melanoma syngeneic to immunocompetent C57BL/6 mice (Koya et al. Cancer Res 2012)

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



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

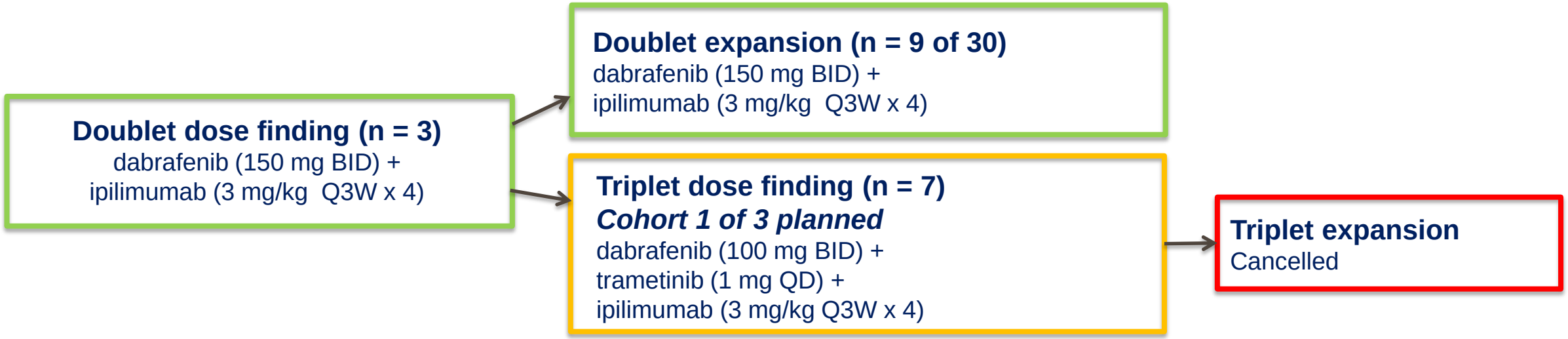
Siwen Hu-Lieskovan and Toni Ribas et al, ASCO, 2014

Courtesy of Toni Ribas

Resulting Clinical Programs in Melanoma

- Dabrafenib/Trametinib + Ipilimumab
- Dabrafenib/Trametininb + Lambrolizumab (partnership with Merck)
- Dabrafenib/Trametinib + PDL-1 (partnership with MedImmune/AZ)

Phase I study of the BRAF inhibitor dabrafenib (D) ± the MEK inhibitor trametinib (T) in combination with ipilimumab (I) for V600E/K mutation-positive unresectable or metastatic melanoma (MM)



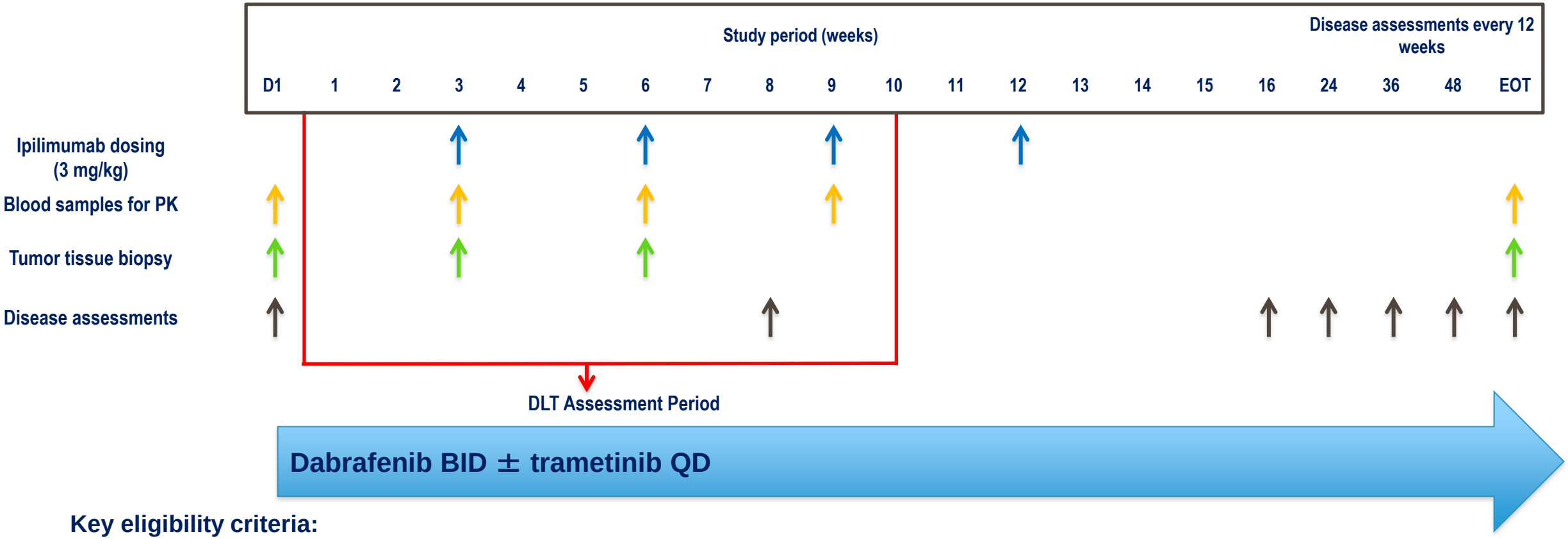
Primary objective: *to characterize the safety of dabrafenib ± trametinib when administered in combination with ipilimumab.*

Secondary Objectives: *to characterize the efficacy, PK, and PD of dabrafenib ± trametinib and ipilimumab.*

BID, twice daily; PD, pharmacodynamics; PK, pharmacokinetics;
Q3W, every 3 weeks; QD, once daily

Puzanov et al, ASCO 2014, Abstract #2511

Study design



Key eligibility criteria:

- Adults with advanced BRAF V600E or V600K –positive MM
- ≤1 previous therapy
- no prior BRAF, MEK or immunotherapy
- ECOG 0-1.

Puzanov et al, ASCO 2014, Abstract #2511

Safety Summary

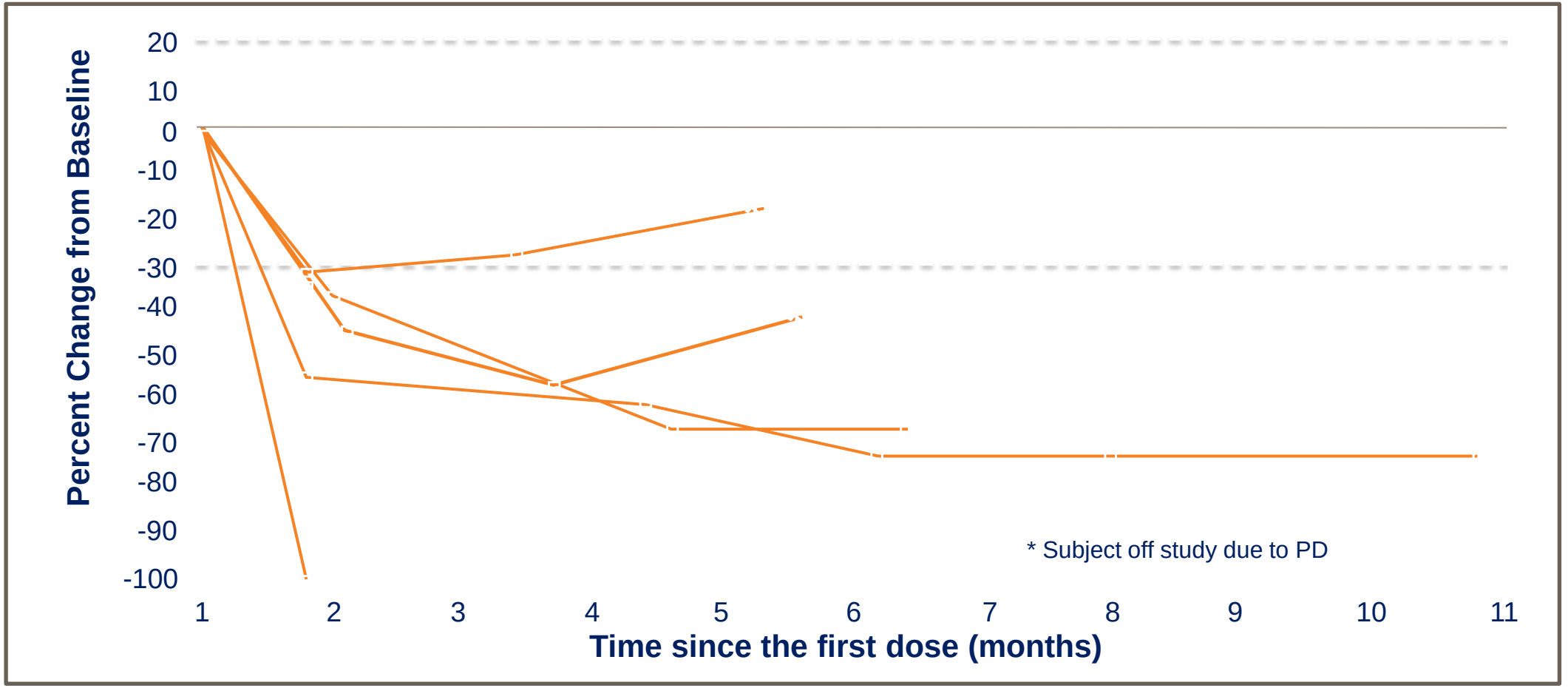
- ***Doublet:*** Dabrafenib + ipilimumab are well tolerated at standard doses
  - –No DLTs detected.
  - –Infrequent and manageable transaminase elevations
    - One (1) of 8 patients had Grade 3 event which resolved to grade 1 after 1 week of high dose steroids.

- ***Triplet:*** First cohort (N = 7) low dose dabrafenib and trametinib, standard dose ipilimumab: 2 cases of colitis / perforation
  - –One case of colitis refractory to steroids during taper: multiple perforations
  - –Cohort closed due to DLTs.

Puzanov et al, ASCO 2014, Abstract #2511

Preliminary clinical activity in doublet arm

Investigator-Assessed Change from Baseline SPD for Index Lesions



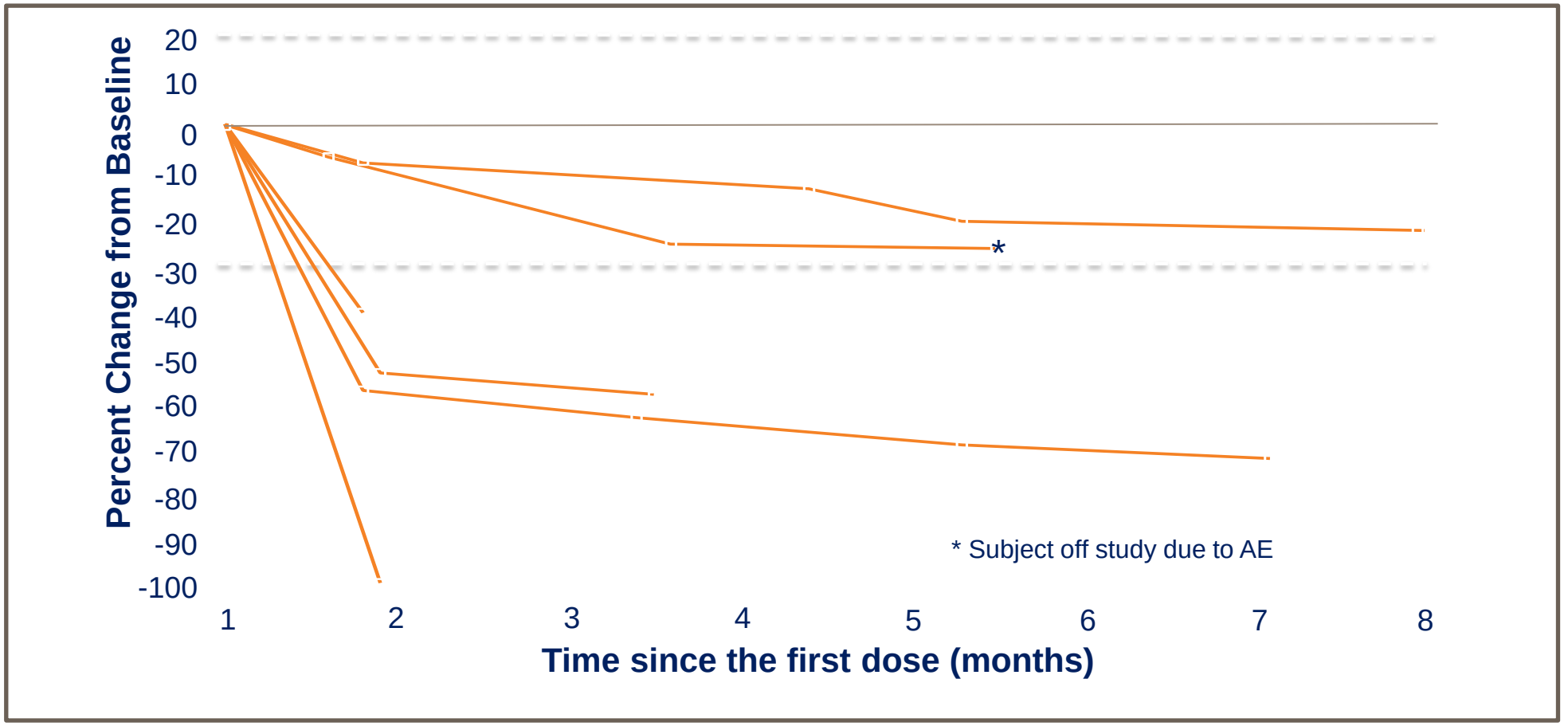
All evaluable subjects in the doublet arm (n=6) had a reduction in SPD

SPD = Sum Product Diameters

Puzanov et al, ASCO 2014, Abstract #2511

Preliminary clinical activity in triplet arm

Investigator-Assessed Change from Baseline SPD for Index Lesions



All evaluable subjects in the triplet arm (n=6) had a reduction in SPD

SPD = Sum Product Diameters

Puzanov et al, ASCO 2014, Abstract #2511

Study Summary

- Dabrafenib and ipilimumab, at standard doses, have been well tolerated in combination
  - No new toxicities were detected
  - A single event of elevated transaminases resolved to grade 1 in 1 week on high dose steroids
- Concurrent administration of dabrafenib, trametinib and ipilimumab was associated with grade 3 colitis with perforation in 2 of 7 patients
  - Concurrent administration is no longer being explored
  - Sequential administration of ipilimumab and trametinib in combination with dabrafenib is under consideration.
- Combinations appear highly active although longer follow-up is needed.

Puzanov et al, ASCO 2014, Abstract #2511

The Way Forward

- Targeted Therapies have great strengths in inducing fast and high response rates but are prone to resistance
- Immunotherapies may offer desired long-term benefit

- Characterization of Targeted Therapy effects beyond the tumor enables rational combinations
- The now well-studied BRAF/MEK inhibitors may offer a model for systematic characterization of other targeted therapies (e.g. epigenetic compounds)

- Safety monitoring and management is paramount for clinical success
- Preliminary clinical activity data is encouraging
- Drug sequencing may be a vital component for complex combinations
- Multiple combinations studies are under way to answer key questions

Acknowledgements

Patients and their families

Clinical Investigators

Academic Collaborators

GSK Team