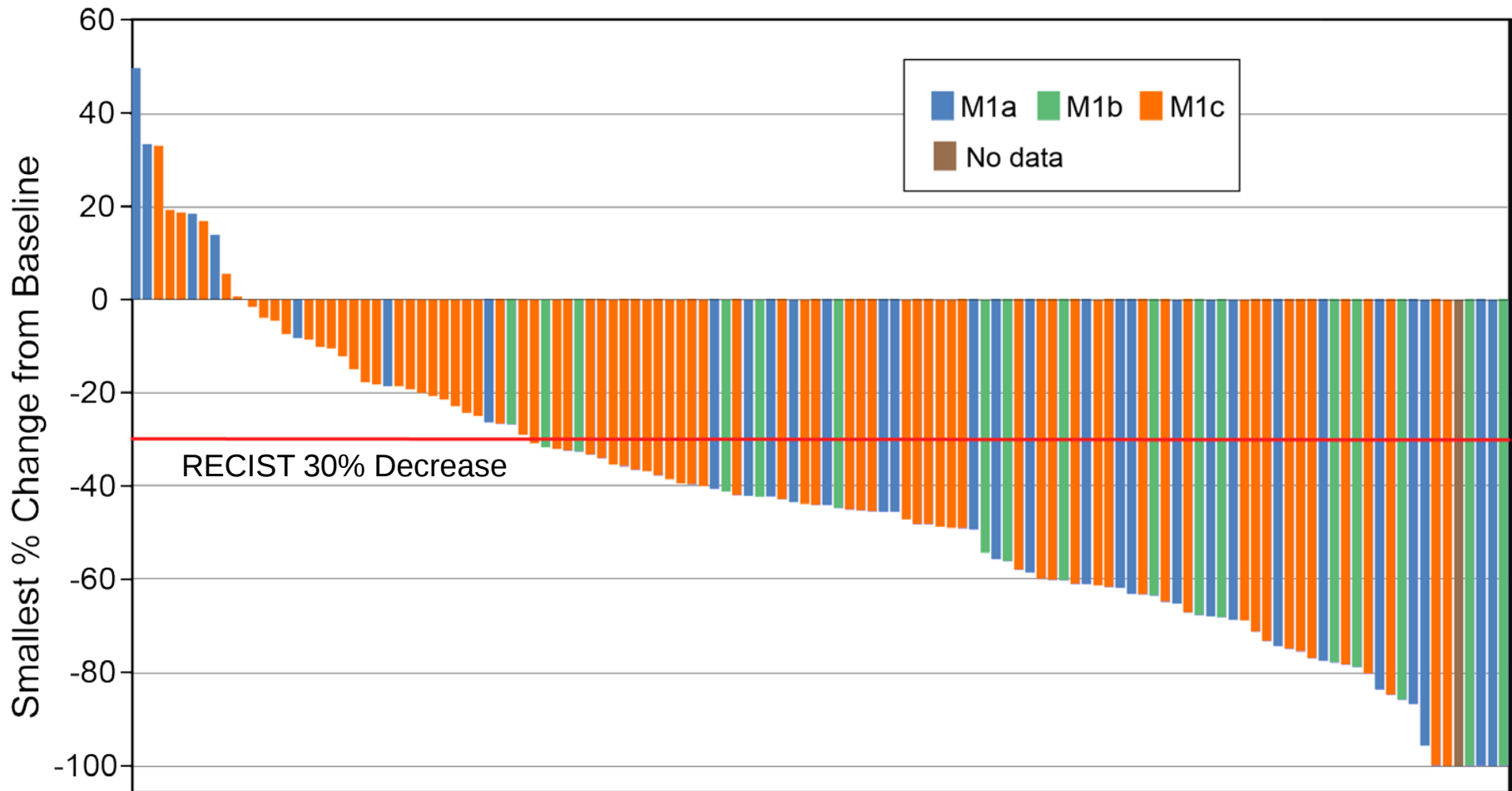


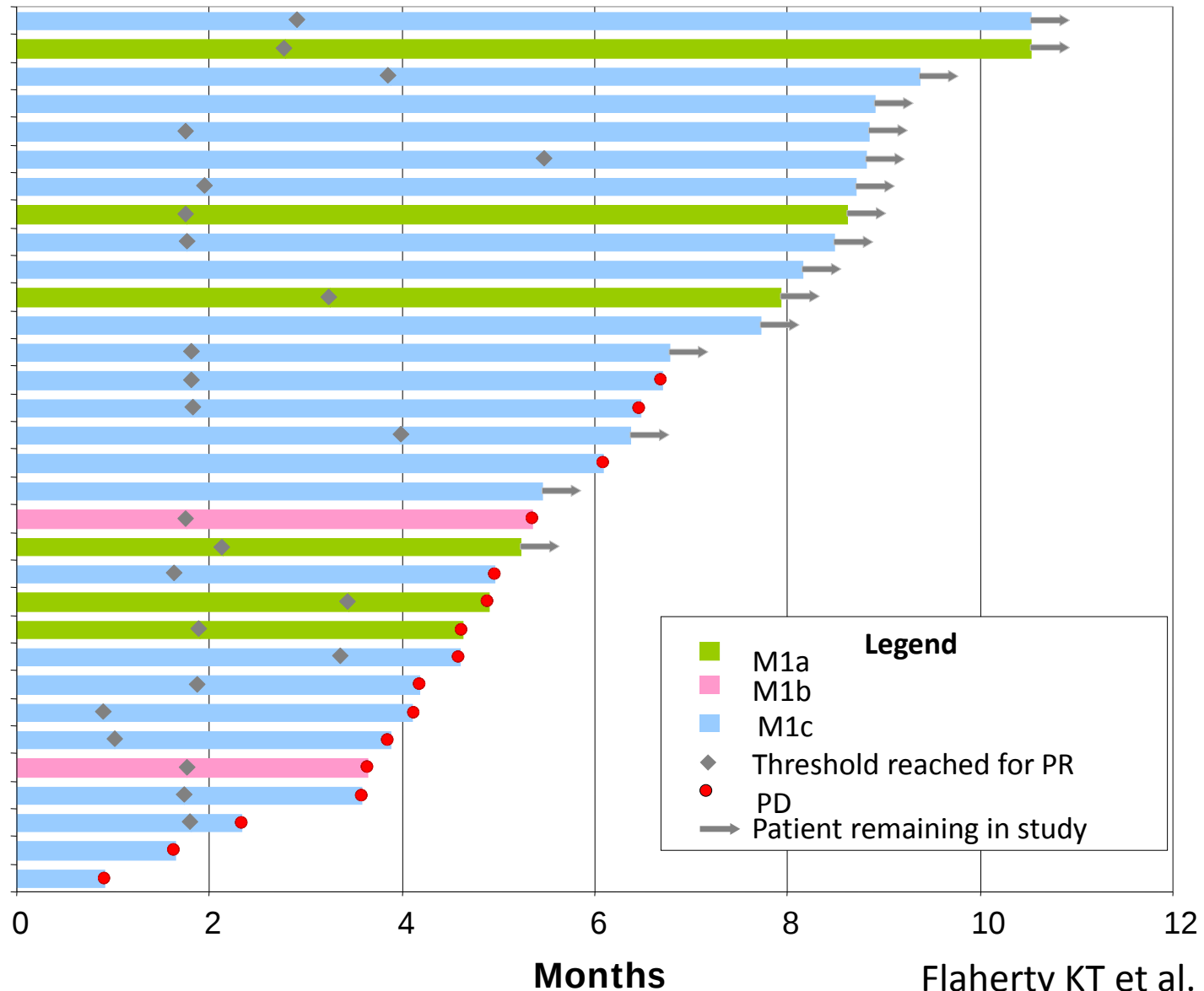
Signal transduction and anti-angiogenic therapy combinations with immunotherapy

Keith T. Flaherty, M.D.
Massachusetts General Hospital
Cancer Center

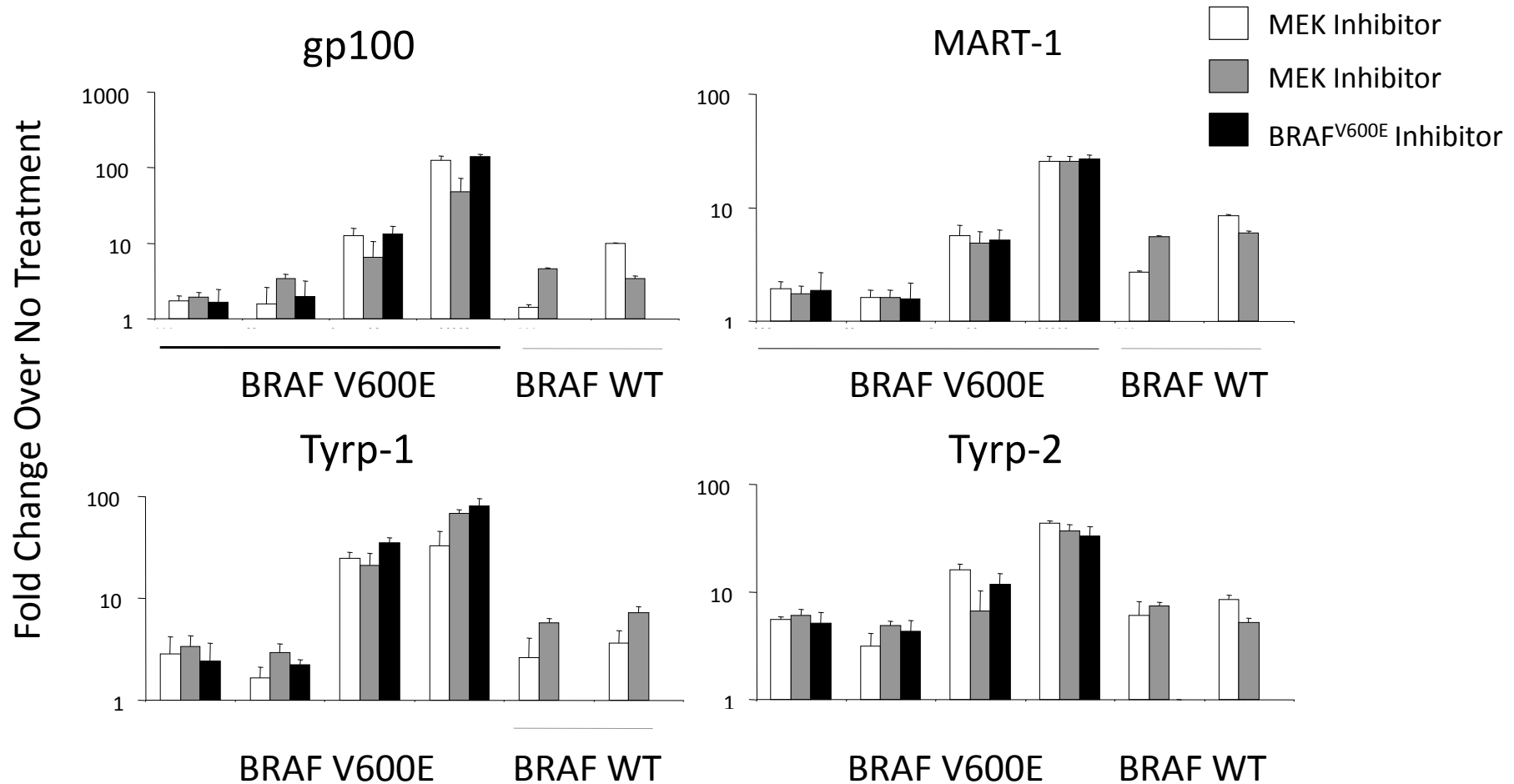
Change in tumor size in 122 ^{V600E}BRAF mutant melanoma patients treated with vemurafenib



Progression-free survival for 32 BRAF mutant melanoma patients treated with vemurafenib

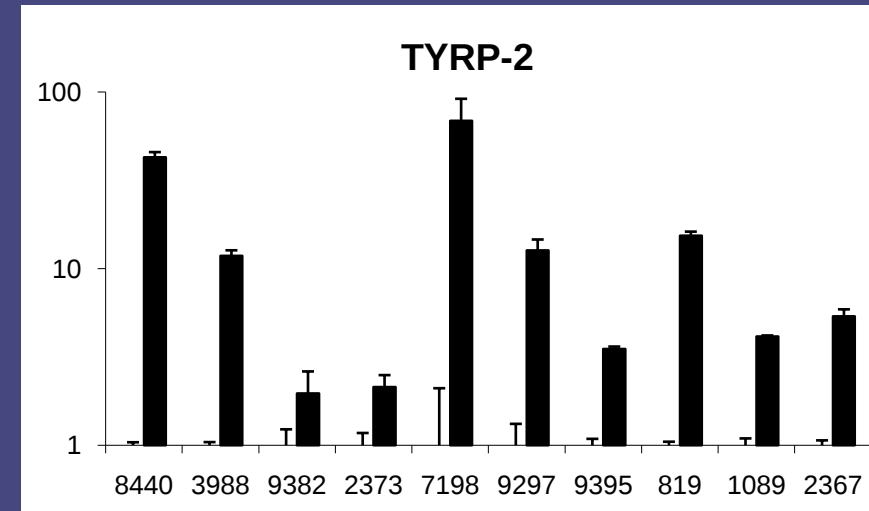
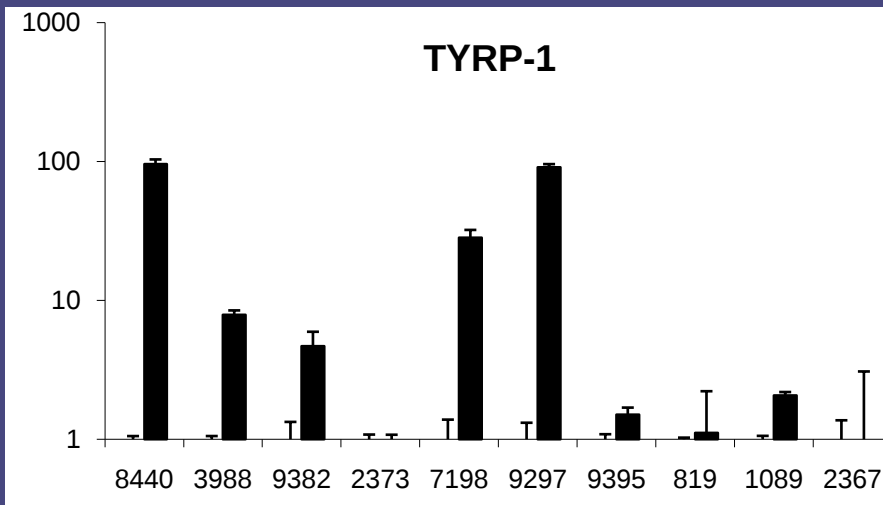
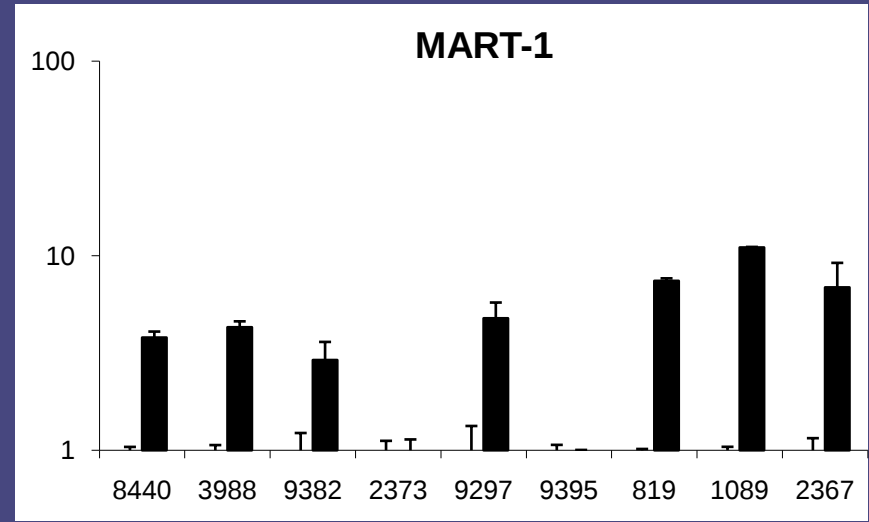
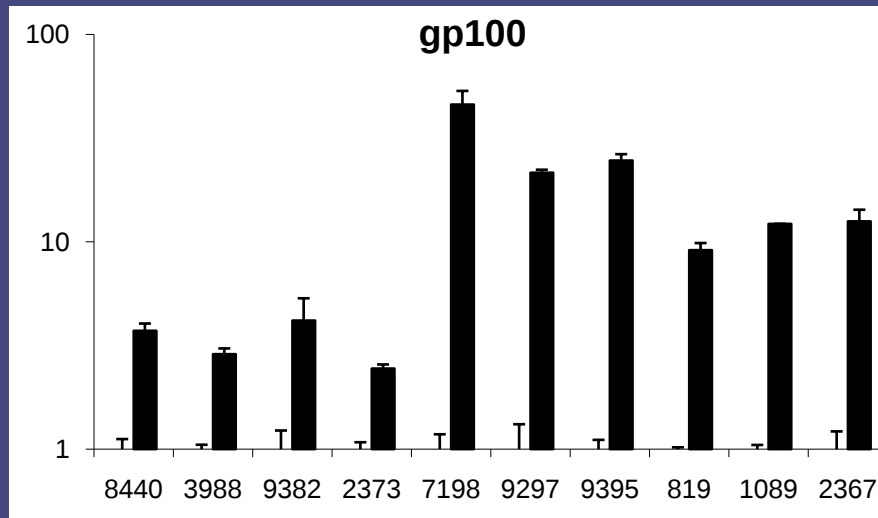


BRAF/MAPK Inhibition Increases Melanocyte Differentiation Antigen (MDA) Expression in Melanoma Cell Lines

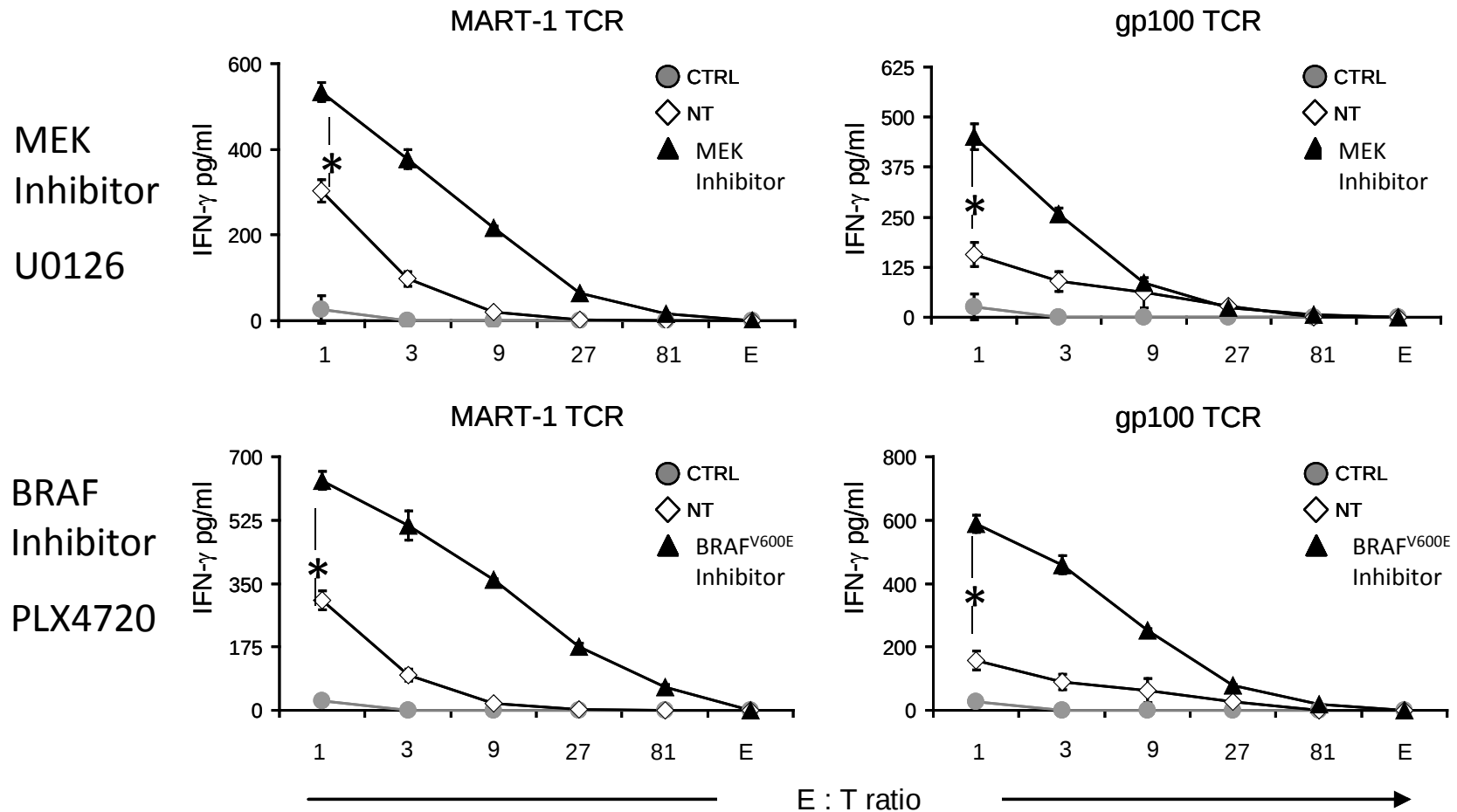


Treatment with a Selective BRAF Inhibitor of Increases MDA mRNA Expression in Tumors of Patients with Metastatic Melanoma

Fold Change Over No Treatment



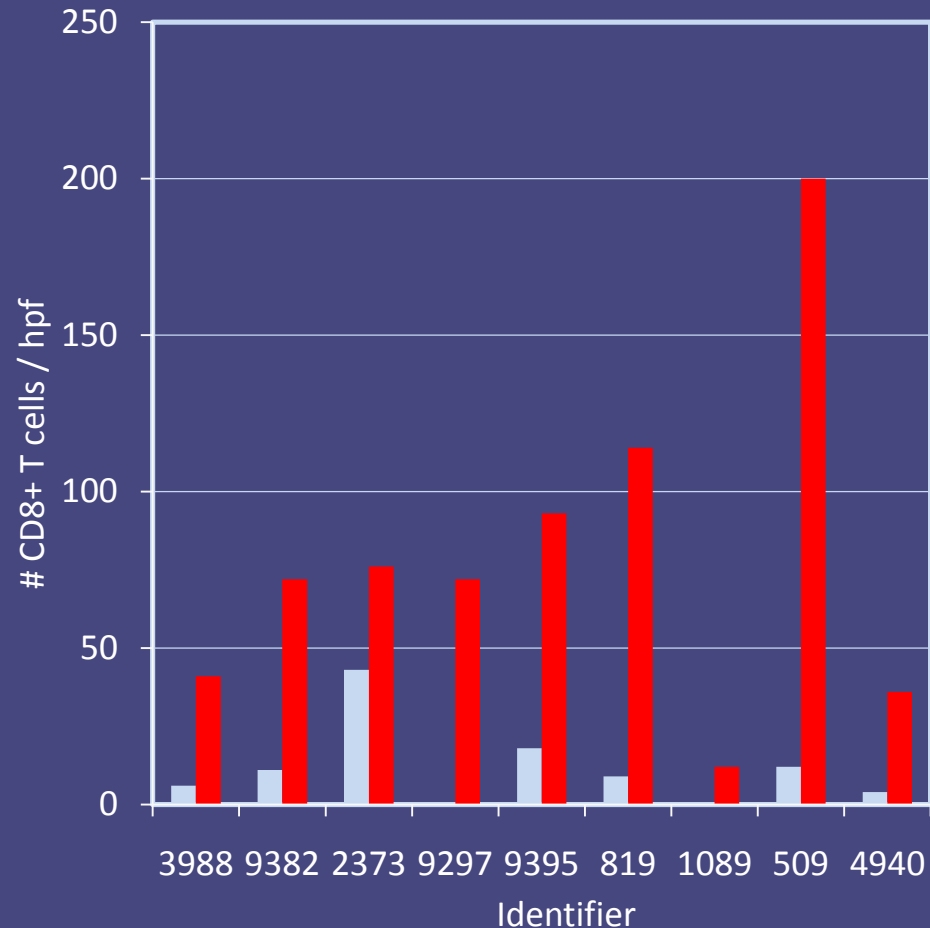
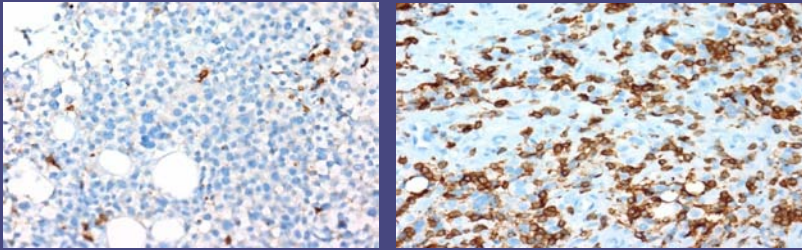
BRAF/MAPK Inhibition Increases Recognition of Melanoma Cells by Antigen-Specific T Cells



P<0.05

Treatment with a Selective Inhibitor of BRAF^{V600E} Increases CD8+ T Cell Infiltrate in Tumors of Patients with Metastatic Melanoma

CD8+ T cells (40X)

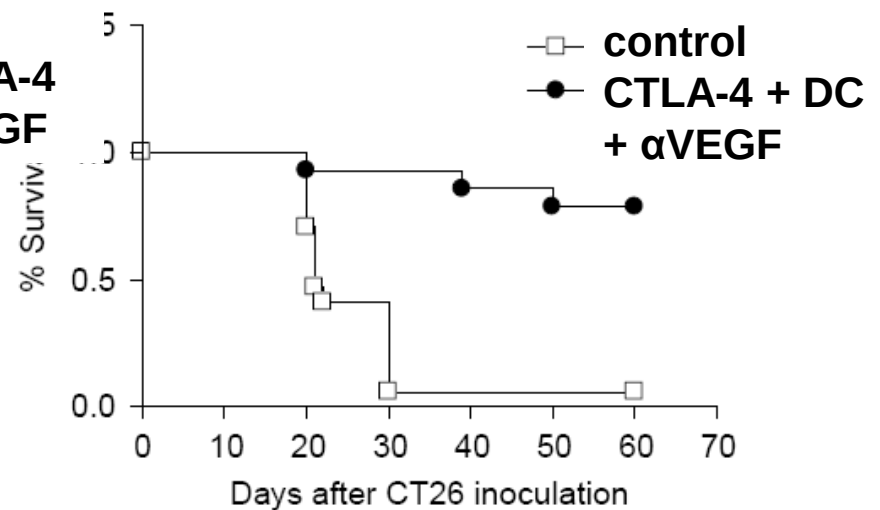
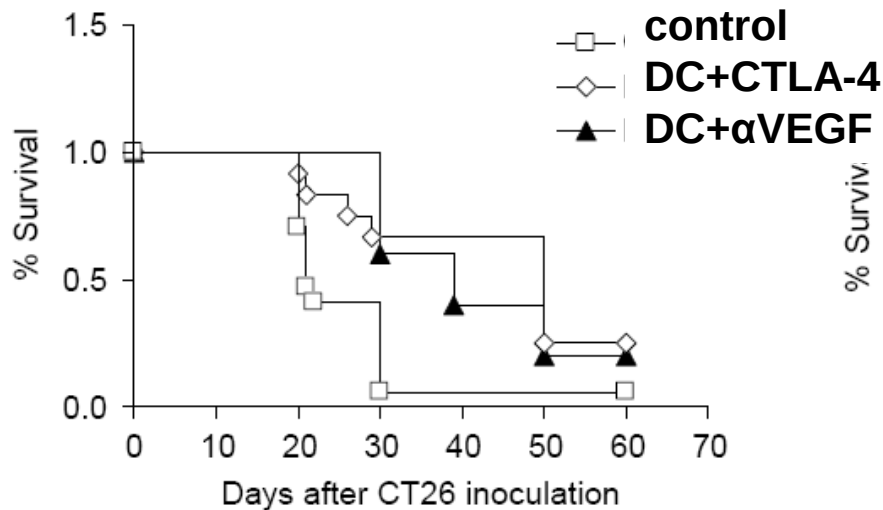
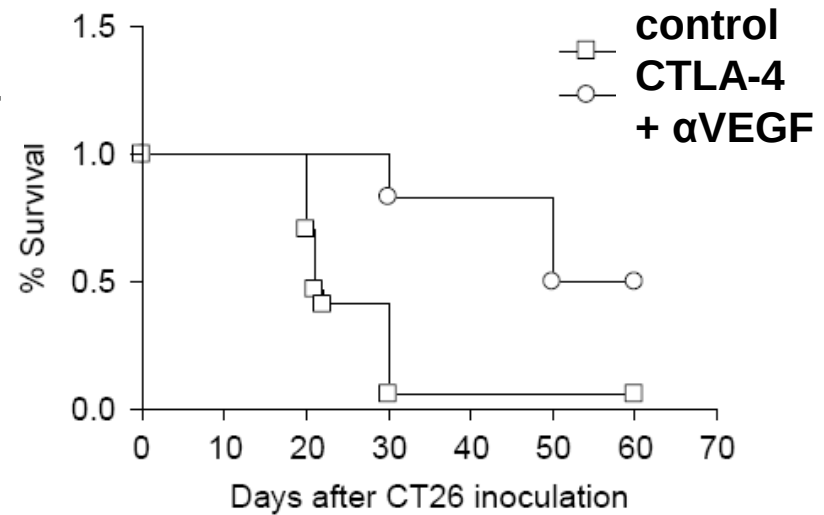
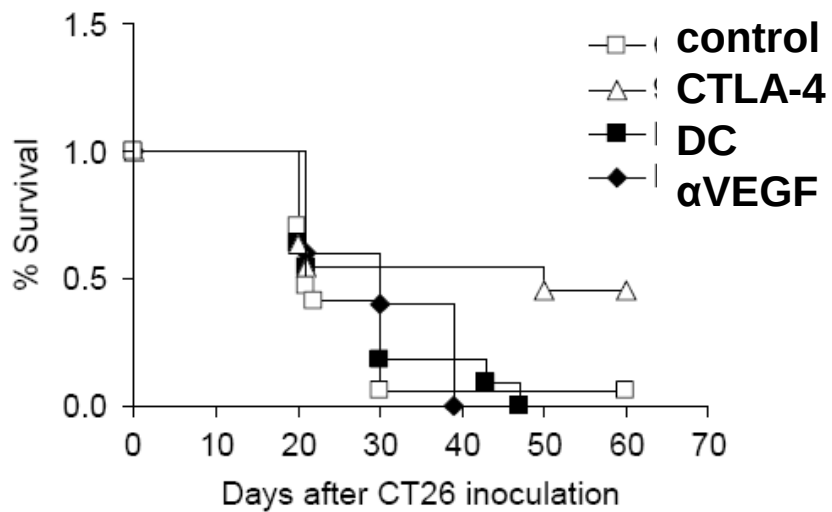


Phase I Trial of Ipilimumab (CTLA-4) plus Bevacizumab (VEGF)

FS Hodi, P Friedlander, M Atkins, D McDermott, D
Lawrence, N Ibrahim, X Wu, J Zhou, A Giobbie-Hurder,
G Murphy, T Hollman, EF Velazquez, S Russell, P Dipro,
J Yap, A Van Den Abbeele

Dana-Farber Cancer Institute, Beth Israel-Deaconess
Medical Center, Massachusetts General Hospital,
Brigham and Women's Hospital

Anti-tumor immunity & anti-angiogenesis



Ipilimumab Plus Bevacizumab Phase I Clinical Trial

- Cohort 1: 10 mg/kg ipilimumab plus 7.5 mg/kg bevacizumab
- Cohort 2: 10 mg/kg ipilimumab plus 15 mg/kg bevacizumab
 - Induction: Every 3 weeks x 4 cycles
 - Maintenance: Bevacizumab continued every 3 weeks, ipilimumab continued every 3 months

Ipilimumab Plus Bevacizumab: Inflammatory Adverse Events 22 Patients

- Giant cell (temporal) arteritis
- Palpable purpura (small vessel inflammation)
- 5 cases hypophysitis
- 3 cases thyroiditis
- Grade 4 hepatitis
- Alopecia areata
- 2 cases bilateral uveitis/retinitis
- Grade 2 colitis

Ipilimumab Plus Bevacizumab:

Clinical Efficacy

22 patients

Best overall response by RECIST:

- 6 partial responses (27%)
 - 1 complete response (5%)
 - 7 durable stable disease (32%)
 - 8 progressive disease (36%)
-
- Median follow up = 14 months
 - 6-month PFS = 59%, 95% CI (36% to 76%)
 - 1-year OS = 72%, 95% CI (48% to 86%)

Alterations in Infiltrating Immune Cells as a Function of Therapy

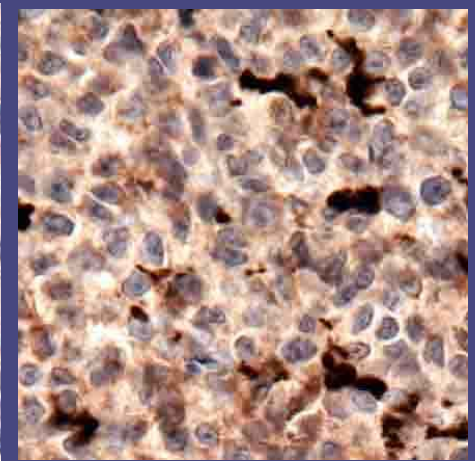
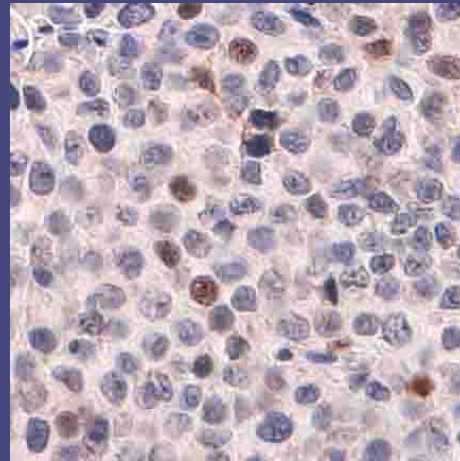
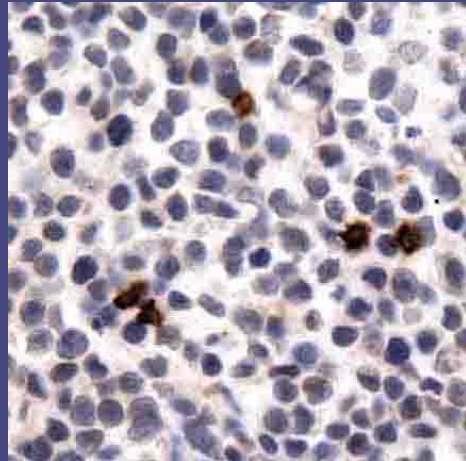
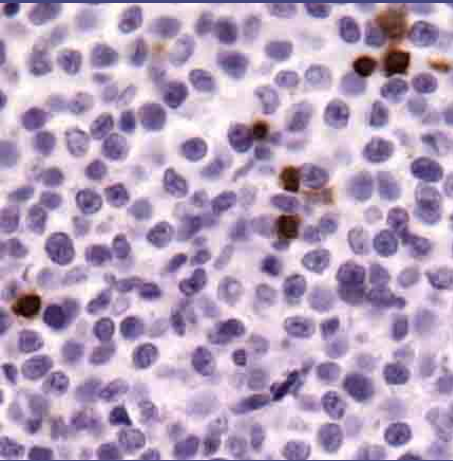
CD3

CD8

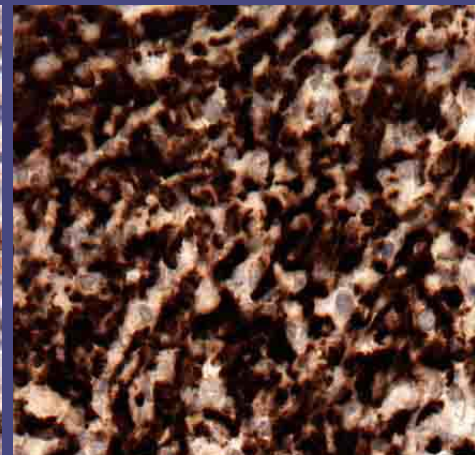
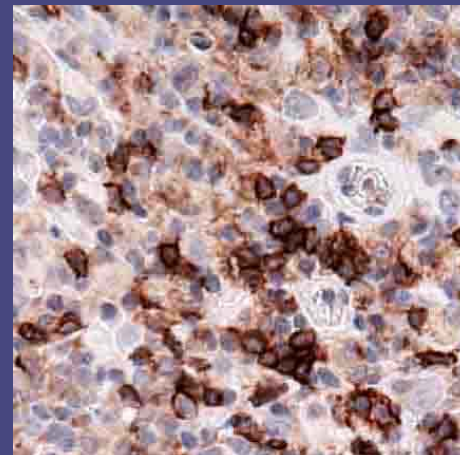
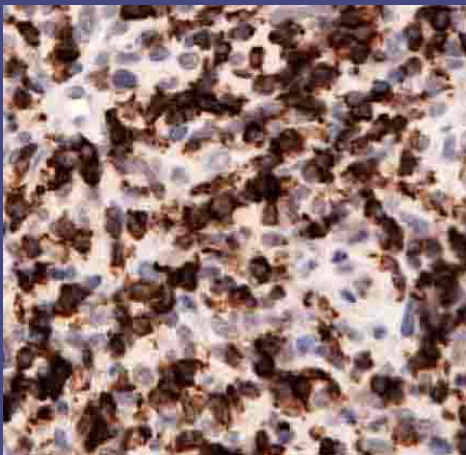
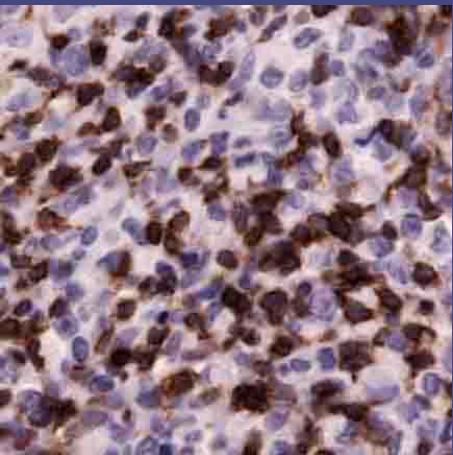
CD4

CD163

Pre-Treatment



Post-Treatment



Building on BRAF inhibition

