Targeted Therapies in Cancer: Is Targeting the Same Mutation Relevant Across Histology and Tumor Type?

Shivaani Kummar, M.D., FACP
DeArmond Endowed Chair of Cancer Research
Professor & Head, Division of Hematology & Medical Oncology
Co-Director, Center for Experimental Therapeutics
Knight Cancer Institute,
Oregon Health & Science University

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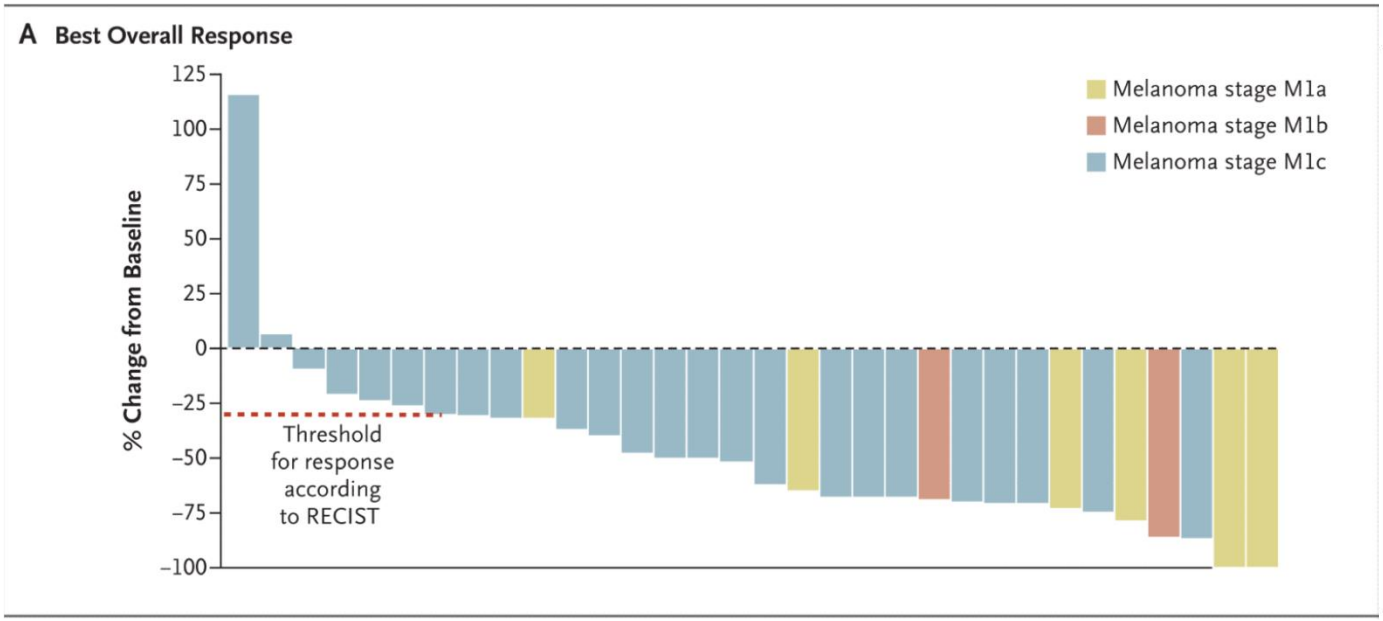
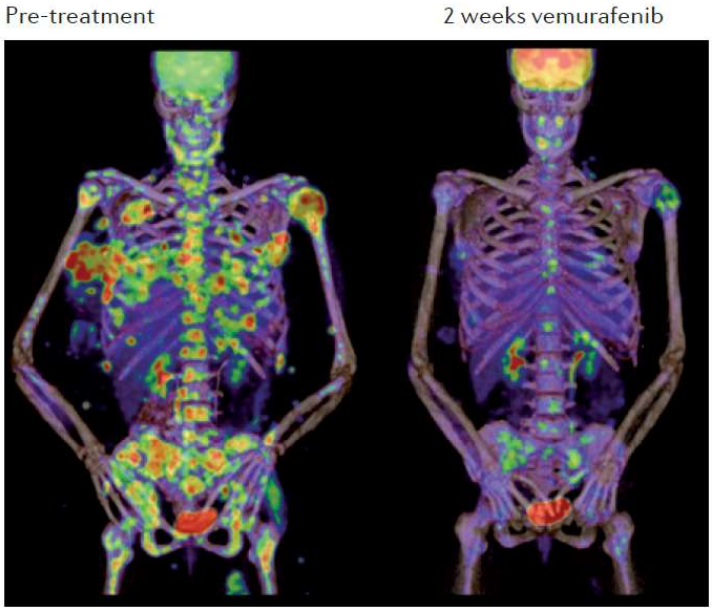
Vemurafenib in BRAF V600E mutant melanoma

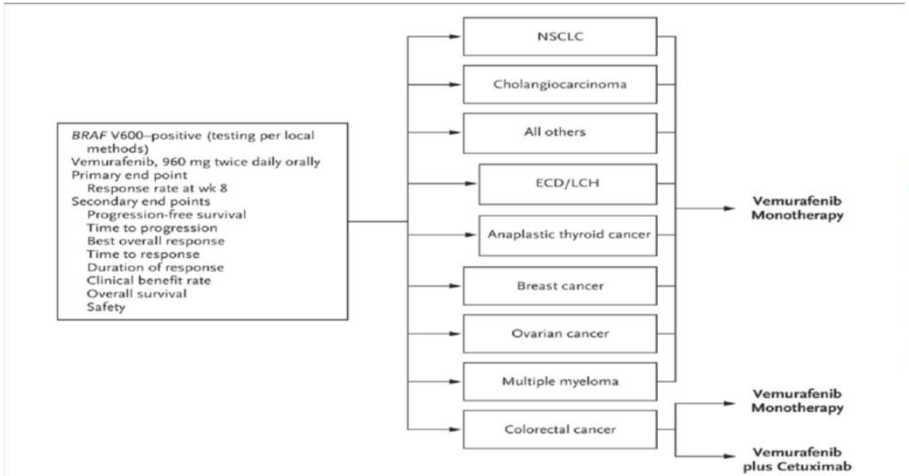
ORR: 75% (24/32 pts in expansion); median PFS 7 mos

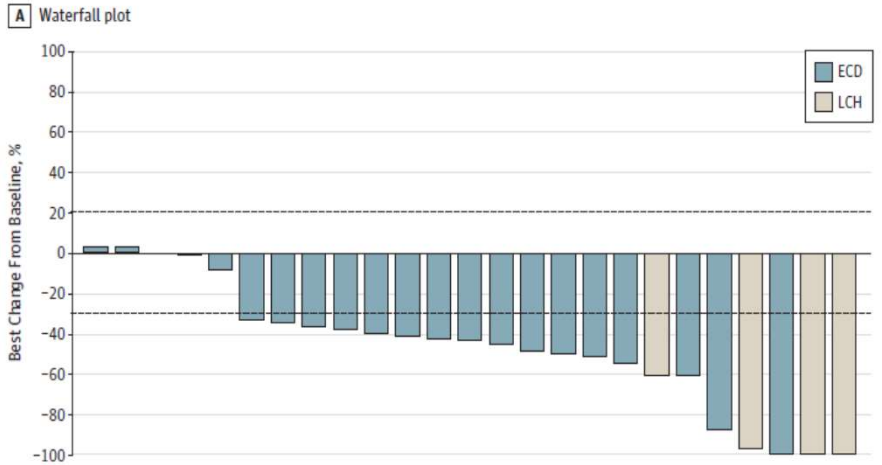


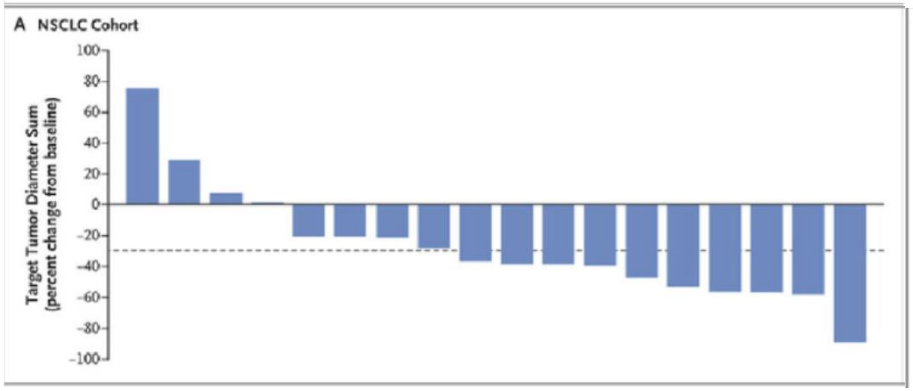


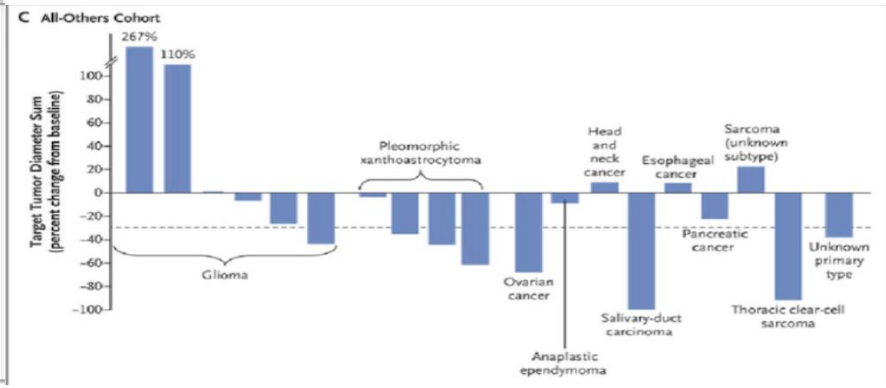
Flaherty KT, et al. N Engl J Med. 2010; 363(9): 809–819

Vemurafenib for non-melanoma BRAFV600+ cancers



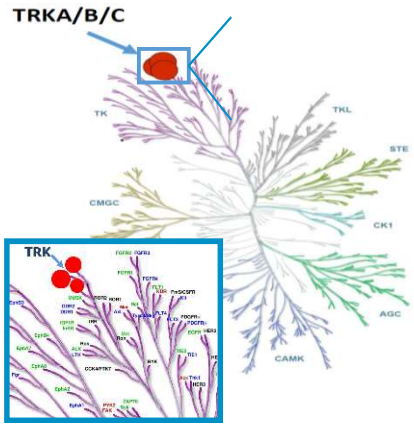


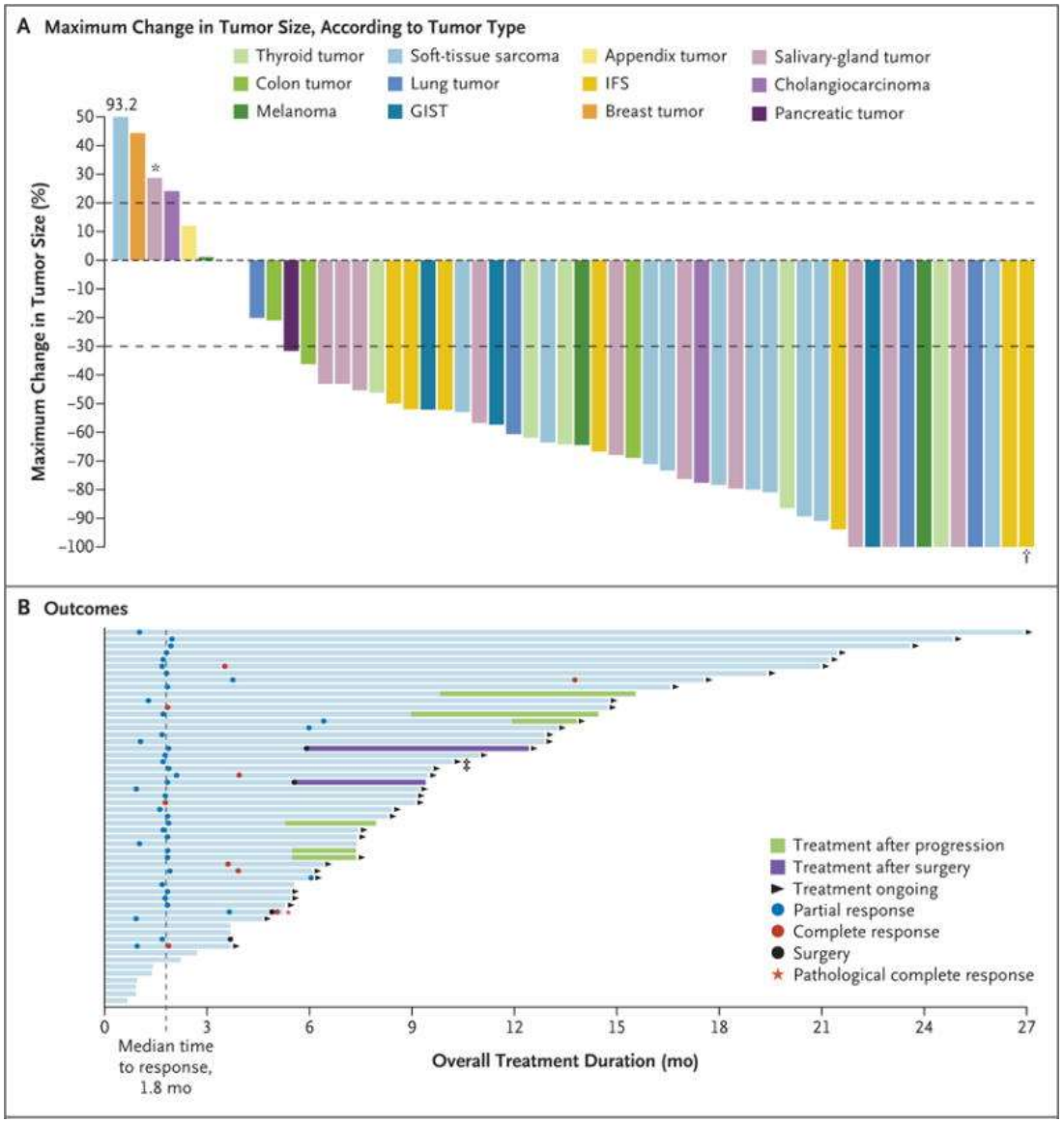




New Engl Journal of Med 2015; 373(8):726; *JAMA Oncol*. 2018;4(3):384

Larotrectinib is a highly selective TRK inhibitor with potency against TRKA, TRKB, and TRK C





Larotrectinib is FDA approved for Patients with Advanced Solid Tumors Harboring an NTRK Gene Fusion (tissue-agnostic indication)

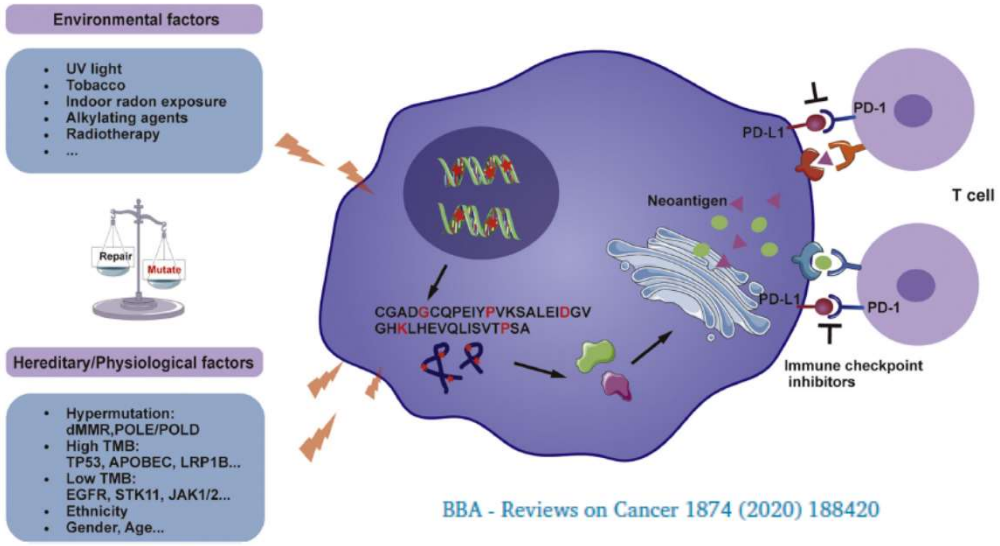
Drilon A, et al. N Engl J Med. 2018 Feb 22;378(8):731-739

FDA approvals for Tissue Agnostic Indications

- Pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
- Larotrectinib and Entrectinib is a kinase inhibitor indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity.
- Pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

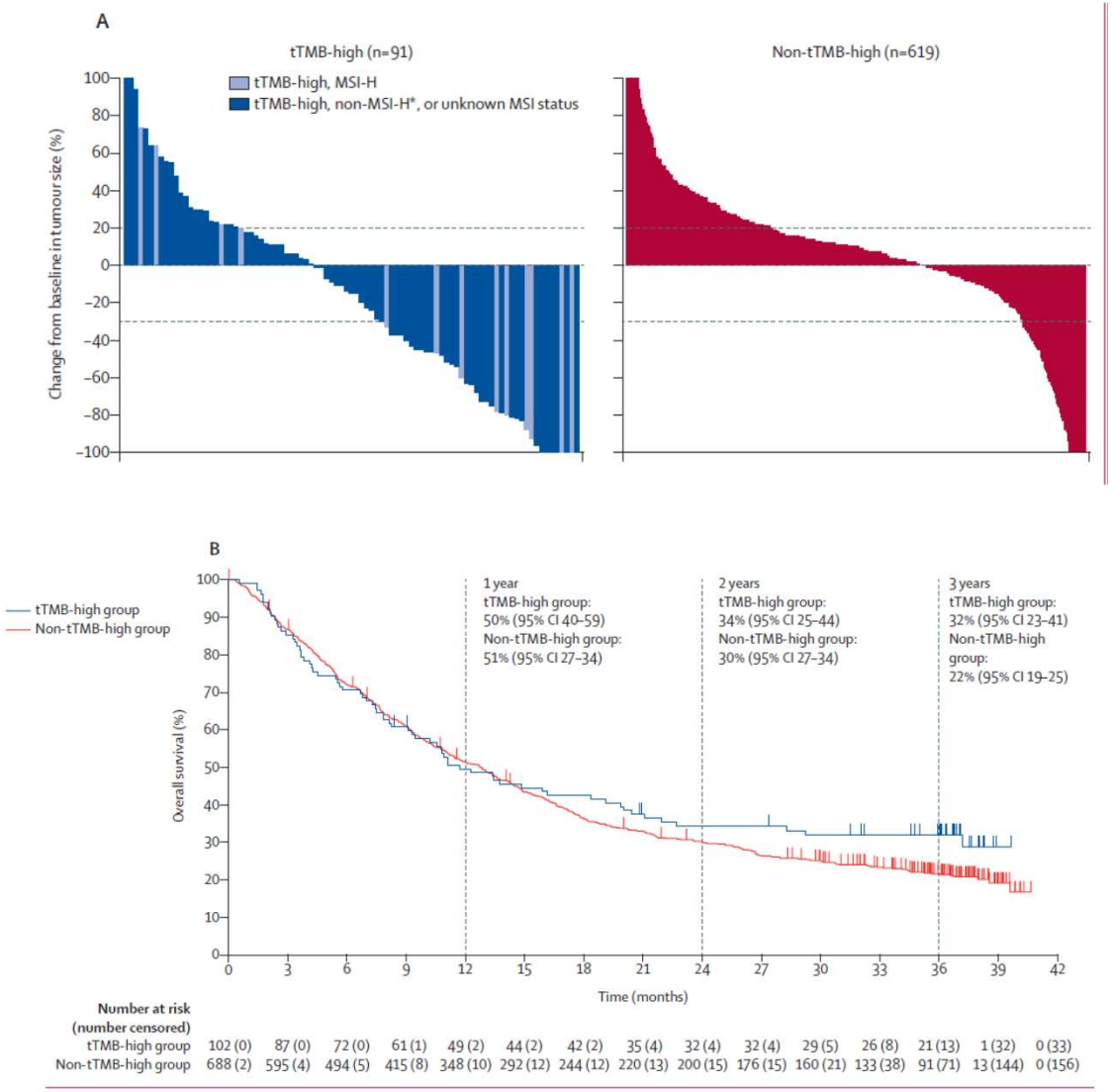
Tumor Mutational Burden

- TMB is the number of somatic, coding, base substitutions (synonymous and nonsynonymous) and short insertions and deletions (indels) per megabase of tumor genome examined.
- TMB is a continuous variable



BBA - Reviews on Cancer 1874 (2020) 188420

- KEYNOTE 158: multi-cohort, open-label, non-randomized, phase 2 study of pembrolizumab for the treatment of advanced solid tumors with Tissue TMB (tTMB) of at least 10 mut/Mb using the FoundationOne CDx assay.(Marabelle A, et al. *Lancet Oncol* 2020; 21: 1353–65)
- 10 cohorts of patients, 81 centers in 21 countries
- 102 patients tTMB-H; 688 patients (non-tTMB-H)



ORR tTMB-H
including MSI-H 29%
excluding MSI-H 28%

ORR non-tTMB-H 6%

DOR not reached for tTMB-H group,
33.1 month in the non-tTMB-H group

Median OS for tTMB-H group was 11.7 mos,
12.8 mos for the non-tTMB-H group

3 year OS 32% tTMB-H group,
22% in the non-tTMB-H group

15% patients had grade 3-5 adverse events, including colitis and pneumonitis.

TMB cut-off of 10 mut/Mb

- Study enrolled patients in 10 cohorts-
  - Biliary cancer -0 patients were TMB-H,
  - Pleural mesothelioma only 1 pt was
  - Anal cancer- 1/14 patients with TMB-H responded while 9/84 non-TMB-H group responded.
    - Median TMB was higher in responders versus non-responders in this disease group, however overall median TMB was below the cut-off of 10.
- WES of 3534 primary tumors in the TCGA and 696 metastatic tumors: TMB values in prostate cancer (range 0.03 -14.3 mut/Mb), bladder cancer (0.04-99.68 mut/Mb). (Fernandez EM, et al. JCO PO 2019)

TMB cut-off of 10 mut/Mb- is this ideal?

- Having a cut-off allows us to treat patients who may derive benefit; especially important for relatively rare tumors
- What about the 6% ORR in patients in the non-tTMB cohort?
  - Values for TMB vary between different malignancies
  - Given the range of TMB scores should we divide tumors into categories that have higher values of TMB versus middle or lower ranges and use different cut-offs to test immune targeted agents to really figure out which patients are likely to respond?
- Is TMB a stand alone biomarker of response?
  - KEAP1-driven co-mutations (KEAP1, STK11, SMARCA4, PBRM1) leading to resistance to immunotherapy even in TMB-H settings in lung adenocarcinomas;
  - KALRN mutations predicting response to immunotherapy

Tissue agnostic versus histology driven approach

- Concept of 'high' TMB deriving benefit from checkpoint therapy may be tissue agnostic but should cut-offs be histology driven?
- Depends on the target and agent- larotrectinib versus vemurafenib
  - Importance of target may be disease context dependent
  - Vemurafenib in BRAF V600E melanoma vs colorectal cancer): BRAF(V600E) inhibition caused feedback activation of EGFR in colon cancer [Prahallad A, et al. Nature 2012; 483(7387):100]
  - Is target a genetic event such as a fusion or protein expression (dynamic, varies across histologies, biology may be different)

- *BASKET trials need to have independent cohorts based on histology; data can be pooled depending on clinical observations*