

Annotation of Identified Variants

File Name: my_data.txt

Clinical Variant 1

Gene Name: BRAF

Protein Change: K601E

Coordinates: chr7:g.140453134T>C

Variant Annotation

Variant annotation not found...

Evidence Statements

Evidence statement 1

Preclinical study in 293H cell line. Ectopic expression of V600E, L597R/Q/S, and K601E mutants elevated phospho-MEK and ERK levels. Vemurafenib treatment of all of the BRAF mutant-expressing cells led to a decrease in phospho-MEK and ERK protein levels. Treatment with MEK inhibitor GSK1120212 led to a more dramatic decrease in phospho-ERK signaling.

Evidence statement 2

In a study of 197 metastatic melanoma patients, BRAF mutations were identified in 95 patients including V600E (n=70), V600K (n=19), K601E (n=1) and D594N (n=1). Patients were treated with a specific RAF inhibitor (dabrafenib), which improved overall survival of patients with BRAF mutations ($P<0.003$), compared to non-treated patients with BRAF mutations. Patients having BRAF mutations without RAF inhibitor treatment were associated with reduced overall survival (11.1 mo vs. 46.1 mo for wild-type, $P=0.006$).

Evidence statement 3

The phase 2a MyPathway study assigned patients with HER2, EGFR, BRAF or SHH alterations to treatment with pertuzumab plus trastuzumab, erlotinib, vemurafenib, or vismodegib, respectively. Of 26 patients with BRAF V600E mutations, objective responses were seen in 12 patients (46%; 95% CI, 27% to 67%). Only one of 23 patients (4%; 95% CI, 0% to 22%) with other non-V600 BRAF mutations had a PR (pancreas cancer with a CUX1-BRAF fusion). Non-responding BRAF mutations included: K601E (n = 6), G464V (n = 2), G469A (n = 2), G496A (n = 2), N581S (n = 2), and one each for G466V, G596R, G606E, L597Q, P731T, intron 9 rearrangement, intron 10 rearrangement, and MACF1- and WASFL-BRAF fusion.

Evidence statement 4

In a retrospective study from 20 institutes in 4 countries, the efficacy of BRAF inhibitor and/or MEK inhibitor in patients with melanoma harboring BRAF nonV600E/K mutations were evaluated. Treated with BRAF inhibitor monotherapy, response rate were 27%(4/15) for V600R, 100%(2/2) for V600D, 0% (0/2) for V600_K601>E, 0% (0/1) for V600G, 0% (0/1) for V600L, 0% (0/1) for V600_S602>DT, 0% (0/5) for L597, 0% (0/6) for K601E, 0% (0/2) for G469, 0% (0/1) for G593D, and 0% (0/1) for T599_V600insT. Treated with MEK inhibitor monotherapy, response rate were 100% (1/1) for L597, and 0% (0/1) for K601E. Treated with BRAF inhibitor and MEK inhibitor combination therapy, response rate were 55% (16/29) for V600R, 67% (2/3) for V600D, 50% (1/2) for V600_K601>E, 50% (1/2) for V600M, 22% (2/9) for L597, 25% (1/4) for K601E, 67% (2/3) for G469, and 0% (0/1) for A598V.

Additional information

Total Number of Variants Processed: 5

The Number of Clinical Annotations: 1