Project
Assessment of 8q gains in MODUL (15-224, MO29112)

Requester
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FMI Identifier
DBI_20210208_B.1

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Overview:

This query examines paired tumor tissue and progression liquid biopsies in MODUL. We provide a table of paired samples with a flag for 8q gains.

This analysis identified 8q gains in 3/8 (38%) of control samples and 3/21 (14%) of experimental samples. Although nominally different, the result is not statistically significant at p=0.3 by the Fisher's exact test.

Specifics:

- Datafreeze: Q1_2021_Pharma
- Study: MODUL (15-224, MO29112)

8q gains were defined using an experimental methodology described in DBI_20200824_F.1. To be consistent with the previous query, the chromosomal gain region was defined as 8:46000001:147000000, as was discovered in the IMBLAZE370 query.

Caveats:
Notes for liquid biopsy results:
The sensitivity of FoundationOne Liquid is highly dependent on the ctDNA content in a sample. Samples with low or no ctDNA will have fewer variant calls. Please also note that copy number modeling is also dependent on ctDNA fraction. Samples with low ctDNA have a reduced likelihood of having a called amplification. Deletions are not called on liquid biopsy samples. TMB calling and local/met status is not available on FoundationOne Liquid.

Notes for CTF:
Please note that for newer samples, the value given in this column may not be the "MSAF" (Maximum Somatic Allele Fraction) but may instead be the Tumor Fraction Estimate (TFE) from the copy number profile. When TFE can be confidently called, it is preferably used. Otherwise,

the output from the latest version of our MSAF caller (described in more detail below) is returned.

MSAF calling is a method of estimating the fraction of circulating tumor DNA (ctDNA) in plasma samples from subjects with cancer. MSAF is determined by calculating the allele fraction for all known somatic, likely somatic, and variant of unknown significance (VUS) substitution alterations detected at >2000X median unique coverage by non-PCR duplicate read pairs. Subsequently, the ExAC database, which contains 60,706 unrelated individuals sequenced as part of various disease-specific and population genetic studies, is queried with the identified alterations. Any alteration that is seen greater than 2 times in the ExAC database is removed from the alteration list for MSAF calculation as it is likely a germline alteration; in addition, dbSNP variants are excluded. The MSAF is estimated as the highest somatic allele fraction.

Please note, a sample's MSAF, if estimated as the highest somatic allele fraction, will never be between 0.4 and 0.6 since variants with an allele frequency in this range are excluded as potential germline variants. Additionally, a sample can have an MSAF of 0 and still have a variant if that variant is predicted germline. Furthermore, for technical reasons, a subset of samples will not have a calculated MSAF (these will be shown as '.').

Finally, please be aware that MSAF can be artificially inflated if a variant is found on an amplified allele or is under LOHx (copy neutral LOH).

Data Description:

Samples Tab: summary of sample characteristics

trf	Unique permanent sample identifier for the progression liquid sample; this id will not change between queries.
baseline_TRF	Unique identifier for the tissue baseline sample, as provided to us for the query
treatment	Treatment arm, as provided to us for the query
8q gain	Flag indicating whether the sample has a gain of 8q (see specifics)