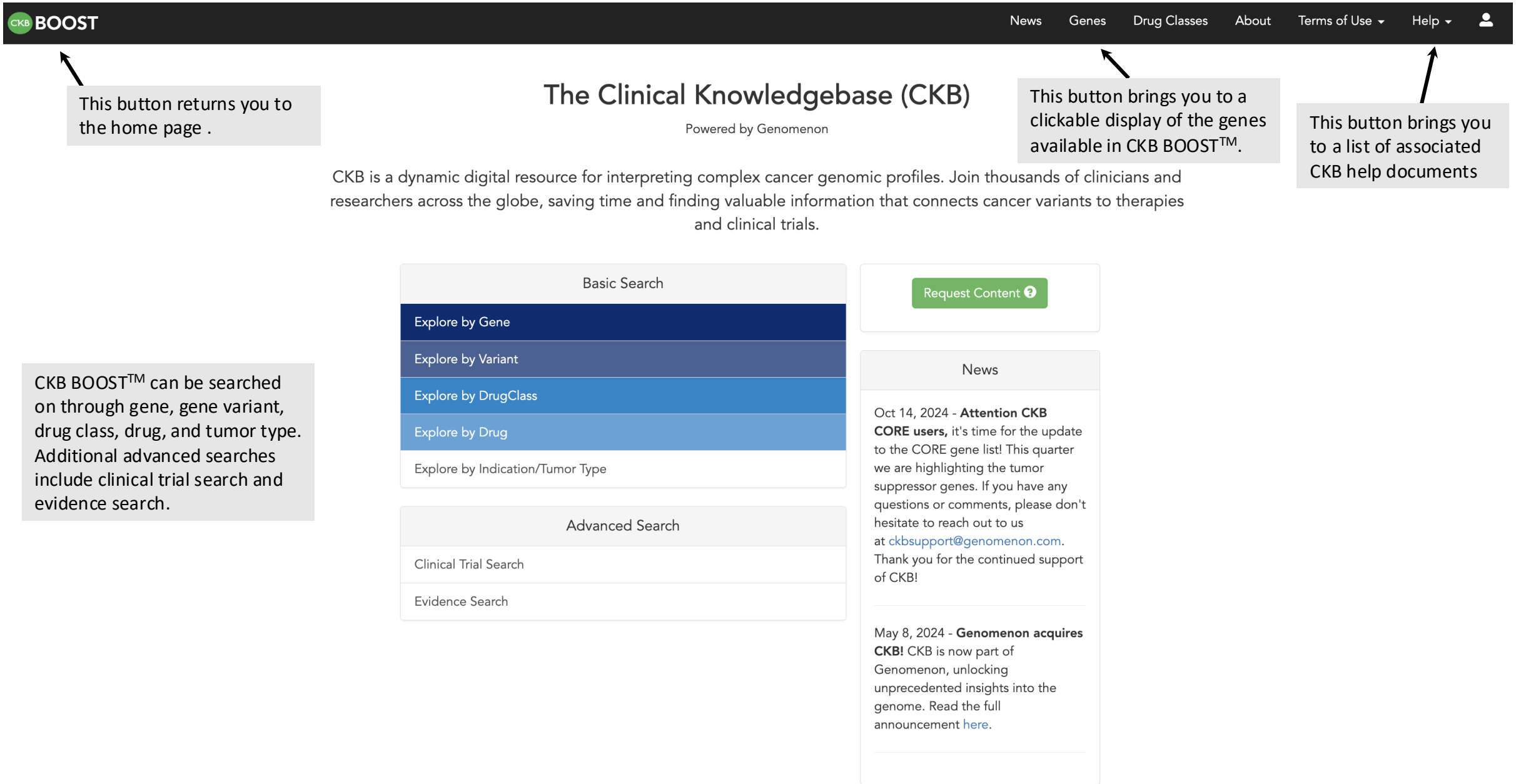
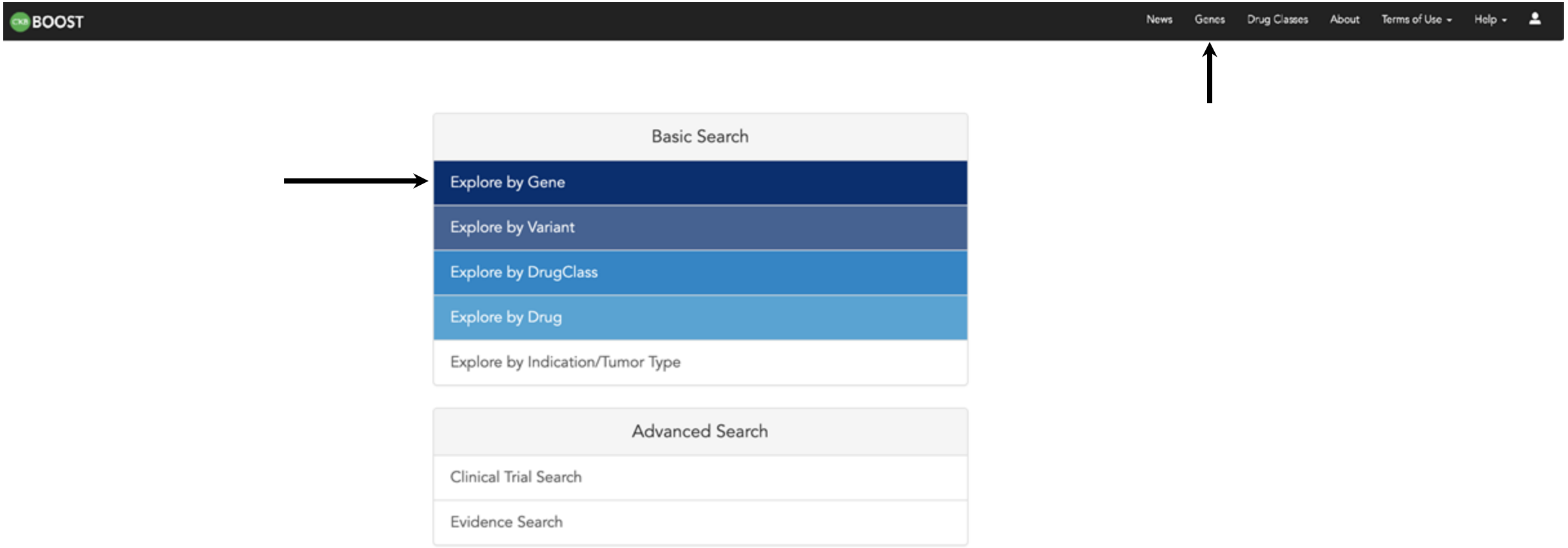
The Cancer Knowledgebase (CKB) Tutorial
CKB BOOST™

https://ckbhome.genomenon.com/

Getting Started

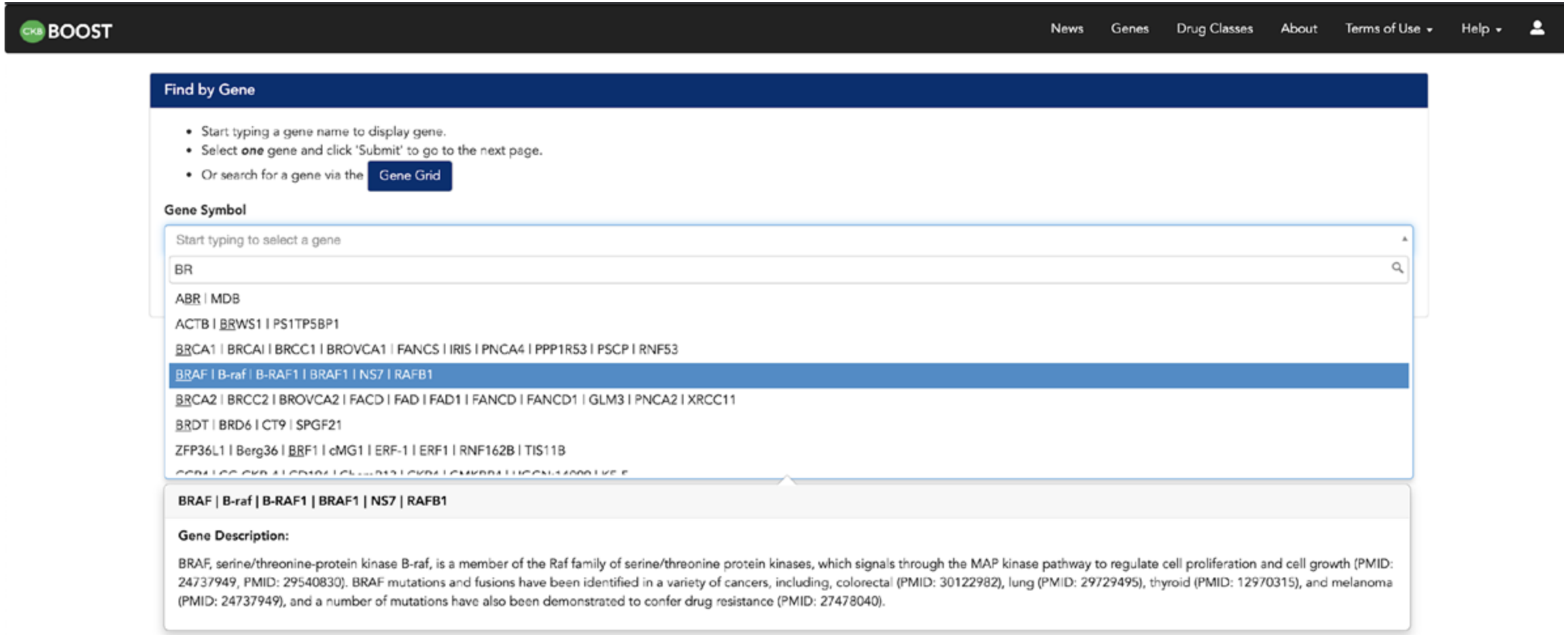


Explore By Gene



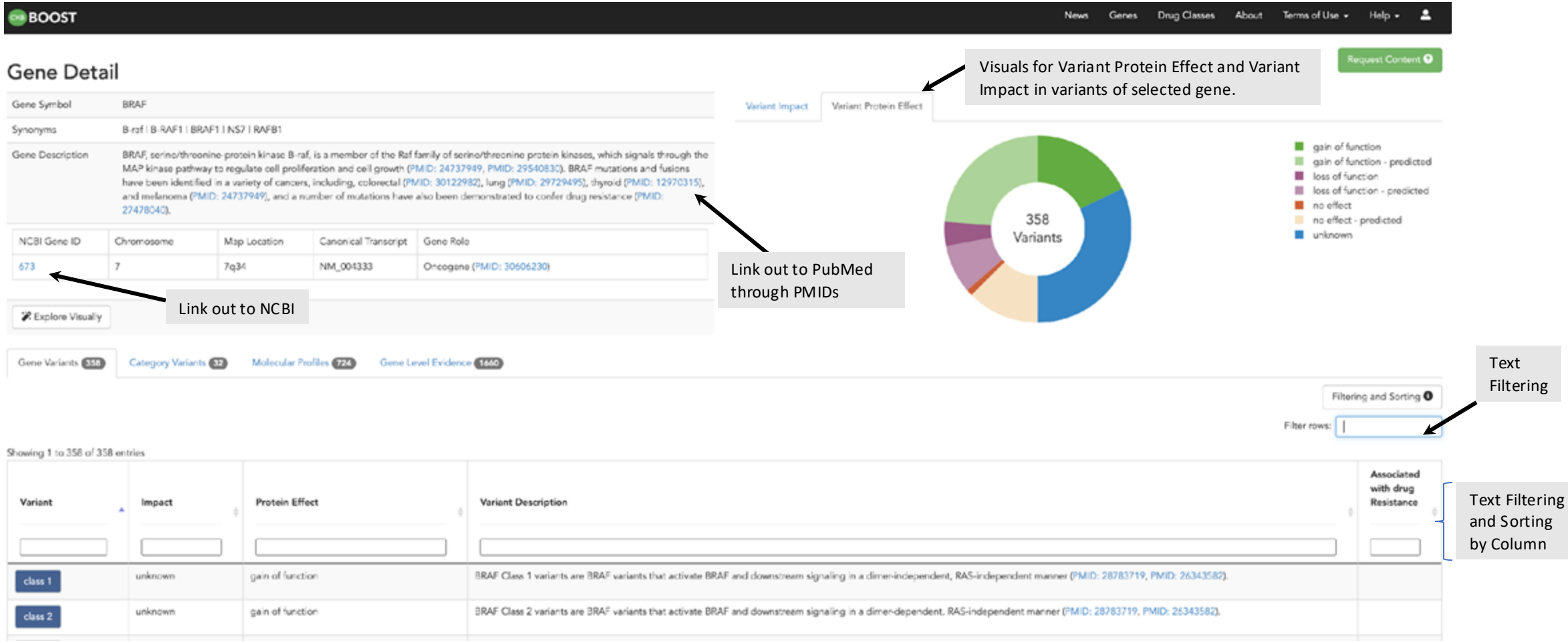
- Clicking on the “Explore by Gene” button will bring you to a page where you can search for content related to all the genes in CKB.
- Clicking on the “Genes” link in the toolbar will bring you to a clickable list of genes with available content.

Explore By Gene



Typing in the search box will trigger a drop-down list of genes. Genes in CKB are given HGNC approved names, but associated synonyms are also available for searching. **Click** on the desired gene name to select for searching. This will bring you to the “Gene Detail Page” for the selected gene.

Explore By Gene



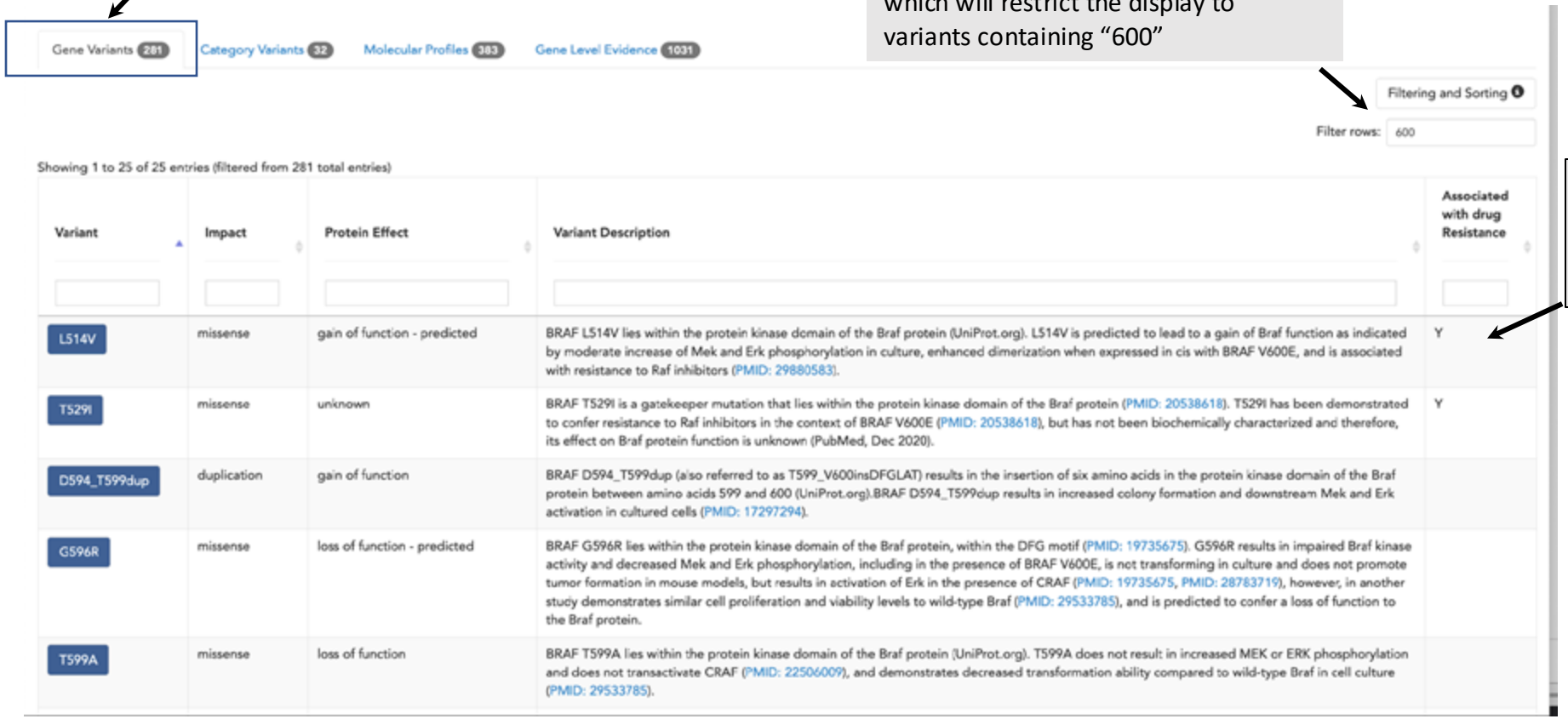
- The header of the page contains data relevant to the gene, as well as a link out to the NCBI Gene page (Entrez ID), chromosome and map location, the canonical transcript, and its role in cancer. There are also visuals for types of variant protein effects and variant impact for the selected gene.
- Below, there are 4 tabs related to different areas of content:
  - The 'Gene Variants ' tab lists all annotated gene variants associated with the selected gene.
  - The 'Category Variants' tab lists all annotated category variants associated with the selected gene.
  - The 'Molecular Profiles' tab contains all molecular profiles (which contain one or more gene variants) associated with the selected gene.
  - The 'Gene Level' Evidence tab lists all annotated evidence associated with the selected gene.
- All pages also incorporate filtering and sorting capability to enable easy content searching.

Explore By Gene

Gene Variant Tab

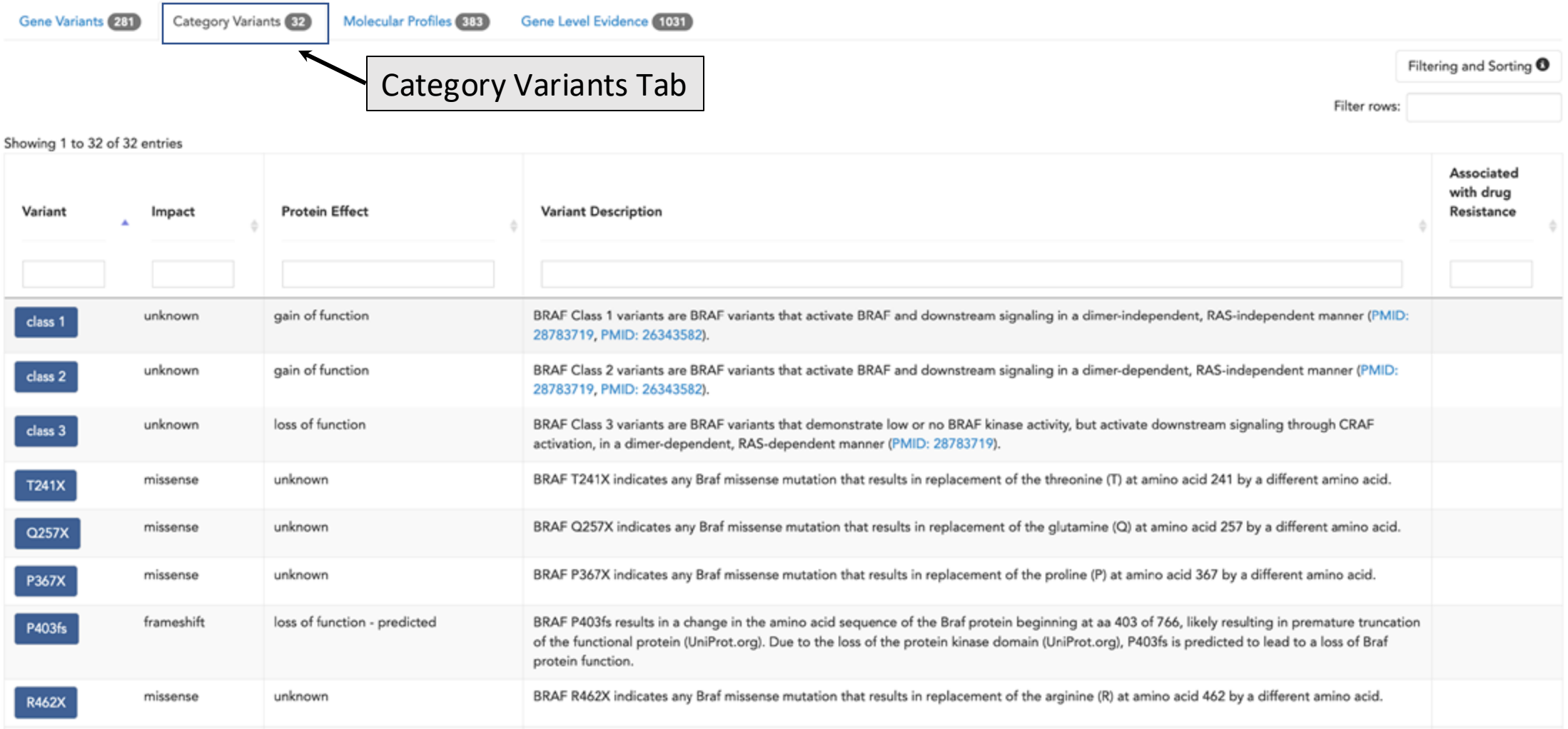
You can filter on any relevant text here. In this example, we've filtered on 600, which will restrict the display to variants containing "600"

Variants associated with drug resistance will have 'Y' in this column.



The **Gene Variant** tab lists gene variants for the selected gene, their impact on the protein (corresponding to variant type), their effect on the intrinsic activity of the protein, and an annotated description. Links in blue will navigate to outside content. Content can be sorted or filtered. Clicking on the blue "gene variant" buttons will bring you to the Gene Variant Detail Page.

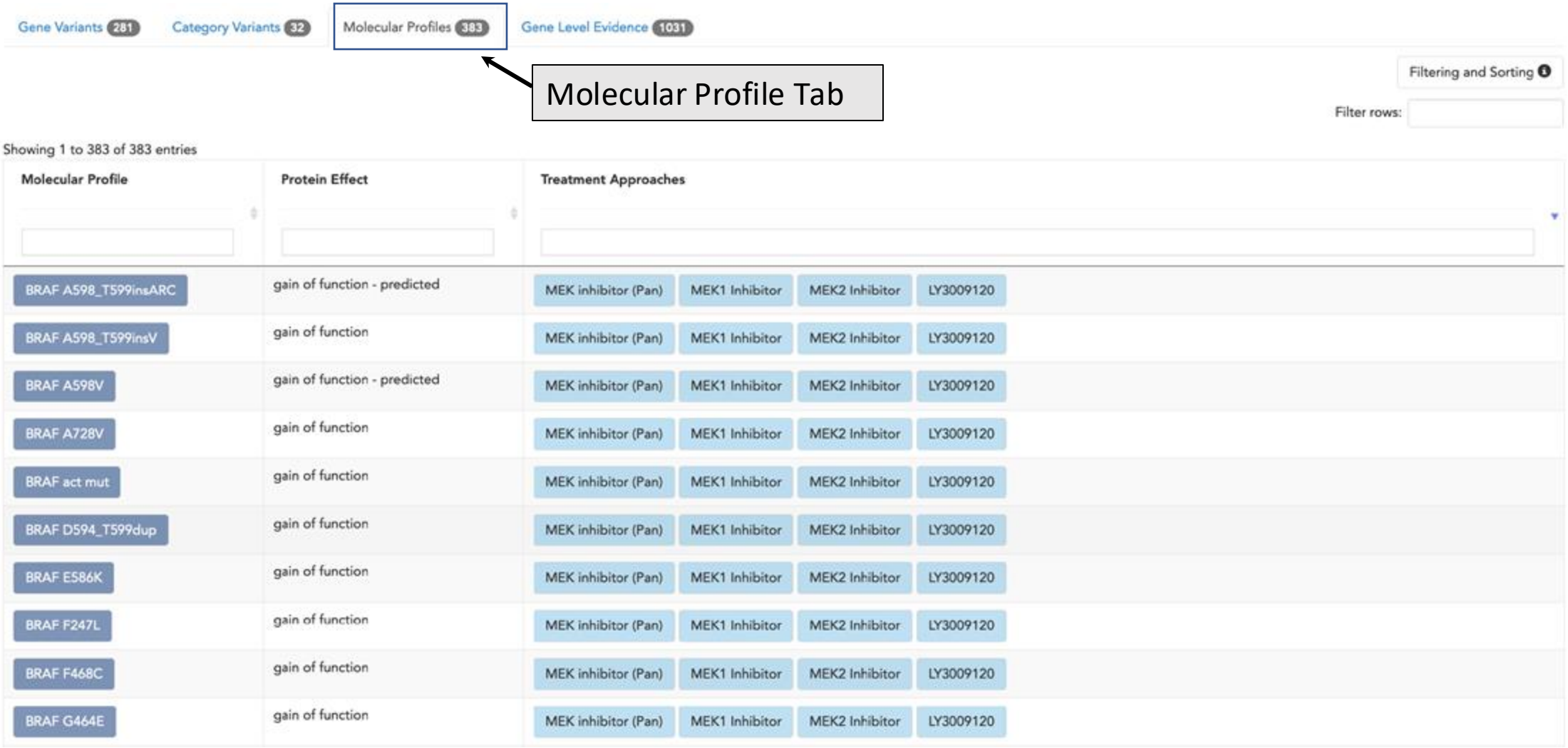
Explore By Gene



Variant	Impact	Protein Effect	Variant Description	Associated with drug Resistance
class 1	unknown	gain of function	BRAF Class 1 variants are BRAF variants that activate BRAF and downstream signaling in a dimer-independent, RAS-independent manner (PMID: 28783719, PMID: 26343582).	
class 2	unknown	gain of function	BRAF Class 2 variants are BRAF variants that activate BRAF and downstream signaling in a dimer-dependent, RAS-independent manner (PMID: 28783719, PMID: 26343582).	
class 3	unknown	loss of function	BRAF Class 3 variants are BRAF variants that demonstrate low or no BRAF kinase activity, but activate downstream signaling through CRAF activation, in a dimer-dependent, RAS-dependent manner (PMID: 28783719).	
T241X	missense	unknown	BRAF T241X indicates any Braf missense mutation that results in replacement of the threonine (T) at amino acid 241 by a different amino acid.	
Q257X	missense	unknown	BRAF Q257X indicates any Braf missense mutation that results in replacement of the glutamine (Q) at amino acid 257 by a different amino acid.	
P367X	missense	unknown	BRAF P367X indicates any Braf missense mutation that results in replacement of the proline (P) at amino acid 367 by a different amino acid.	
P403fs	frameshift	loss of function - predicted	BRAF P403fs results in a change in the amino acid sequence of the Braf protein beginning at aa 403 of 766, likely resulting in premature truncation of the functional protein (UniProt.org). Due to the loss of the protein kinase domain (UniProt.org), P403fs is predicted to lead to a loss of Braf protein function.	
R462X	missense	unknown	BRAF R462X indicates any Braf missense mutation that results in replacement of the arginine (R) at amino acid 462 by a different amino acid.	

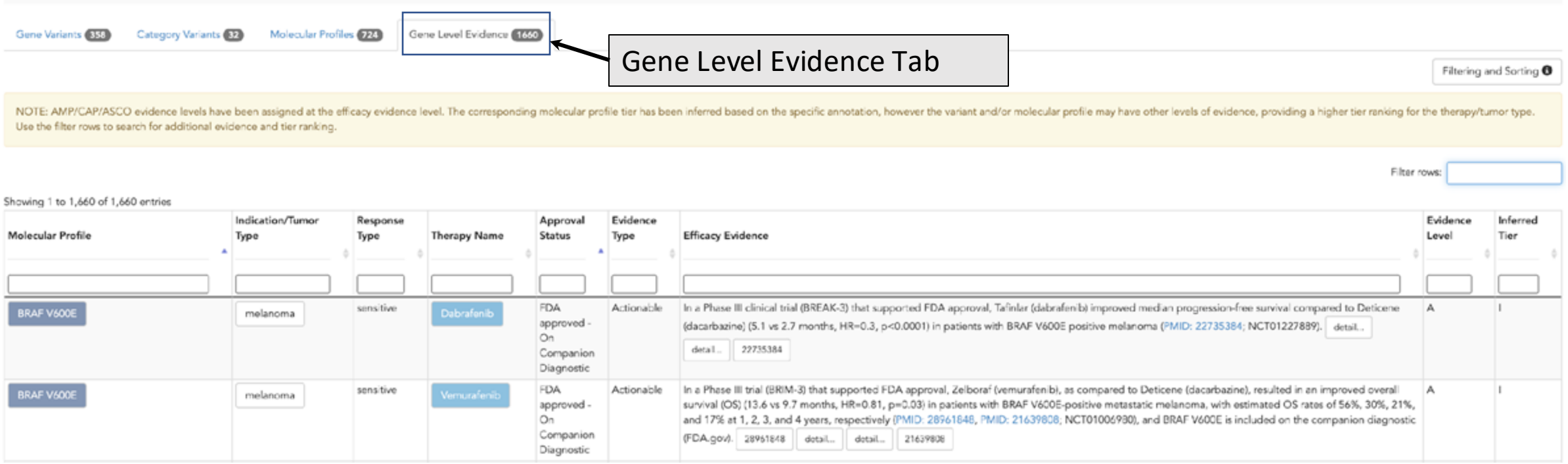
The **Category Variants** tab displays all category variants associated with the selected gene. Category variants can be classified as functional and/or positional. Functional category variants include act mut and inact mut. Examples of positional variants include exon, codon, and short form frameshifts. Category variants can include member variants and can be used to identify relevant efficacy evidence. For more information about category variants, click here.

Explore By Gene



The **Molecular Profile** tab displays all molecular profiles associated with the selected gene, which can contain one or more gene variants. If appropriate, any related treatment approaches are listed. Treatment approaches are either Drug Classes or individual Therapies that have been assigned to variants based on evidence from the literature. Clicking on these buttons will bring you to the "Profile Treatment Approach Detail" page.

Explore By Gene

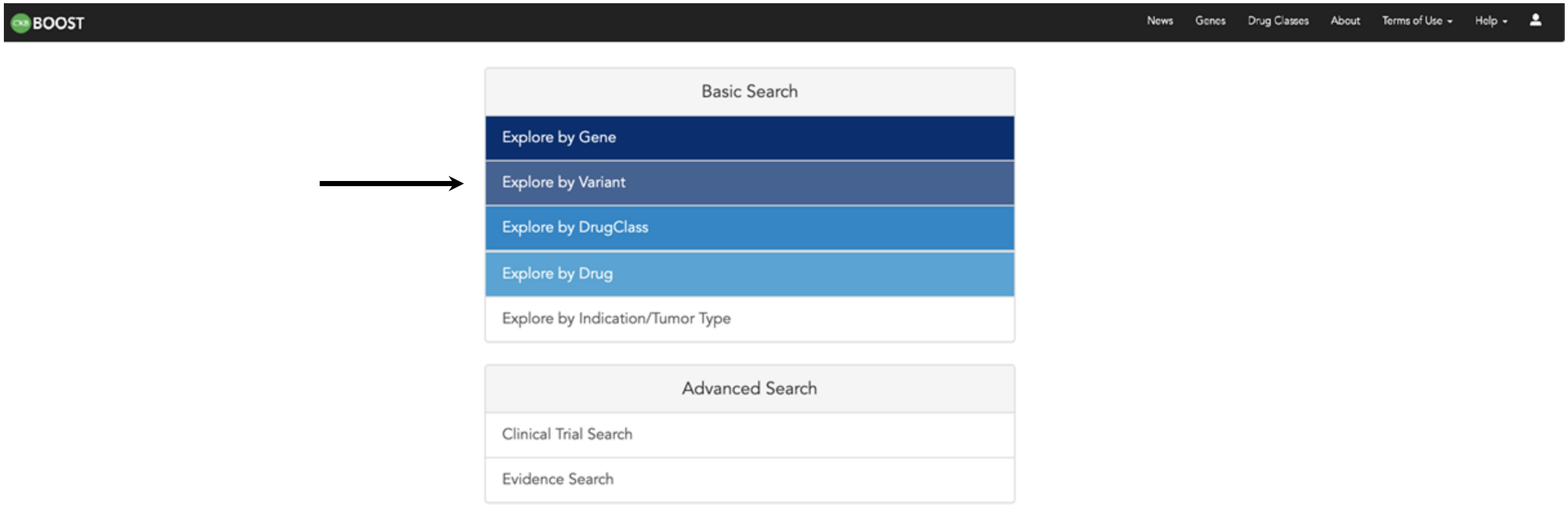


The **Gene Level Evidence** tab displays all annotated evidence associated with gene variants in the selected gene. Links in blue go out to PubMed for the associated references.

There are multiple 'Evidence Types' . The majority are "Actionable", meaning there is an association between a gene variant and therapy. Other evidence types are :"Prognostic" (variant association with disease outcome), "Diagnostic" (variant association with disease diagnosis), "Risk Factor" (germline variant association with risk of disease onset), and "Emerging" (variant as a potential therapeutic target).

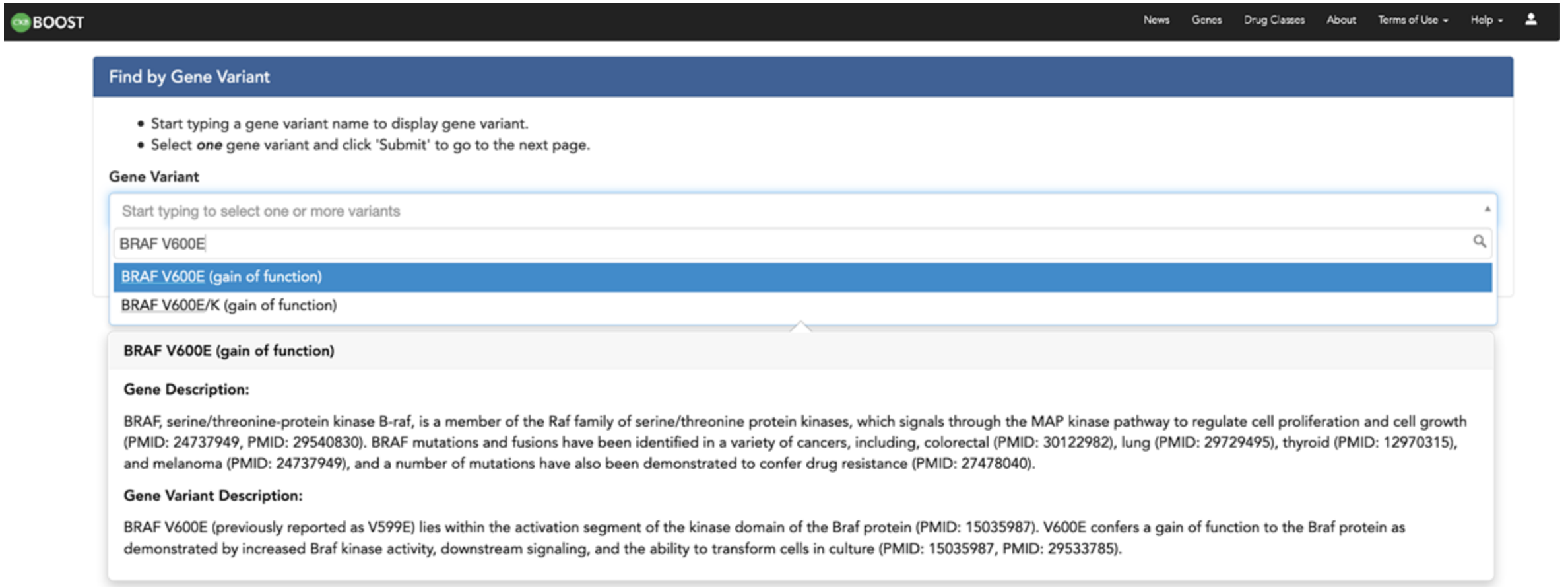
The last two columns of the 'Gene Level Evidence' tab includes the evidence level and inferred tier for the evidence annotation based on the AMP/CAP/ASCO guidelines for somatic variant reporting. The corresponding molecular profile is inferred based on the specific annotation but could have a higher inferred tier depending on the evidence.

Explore By Gene Variant



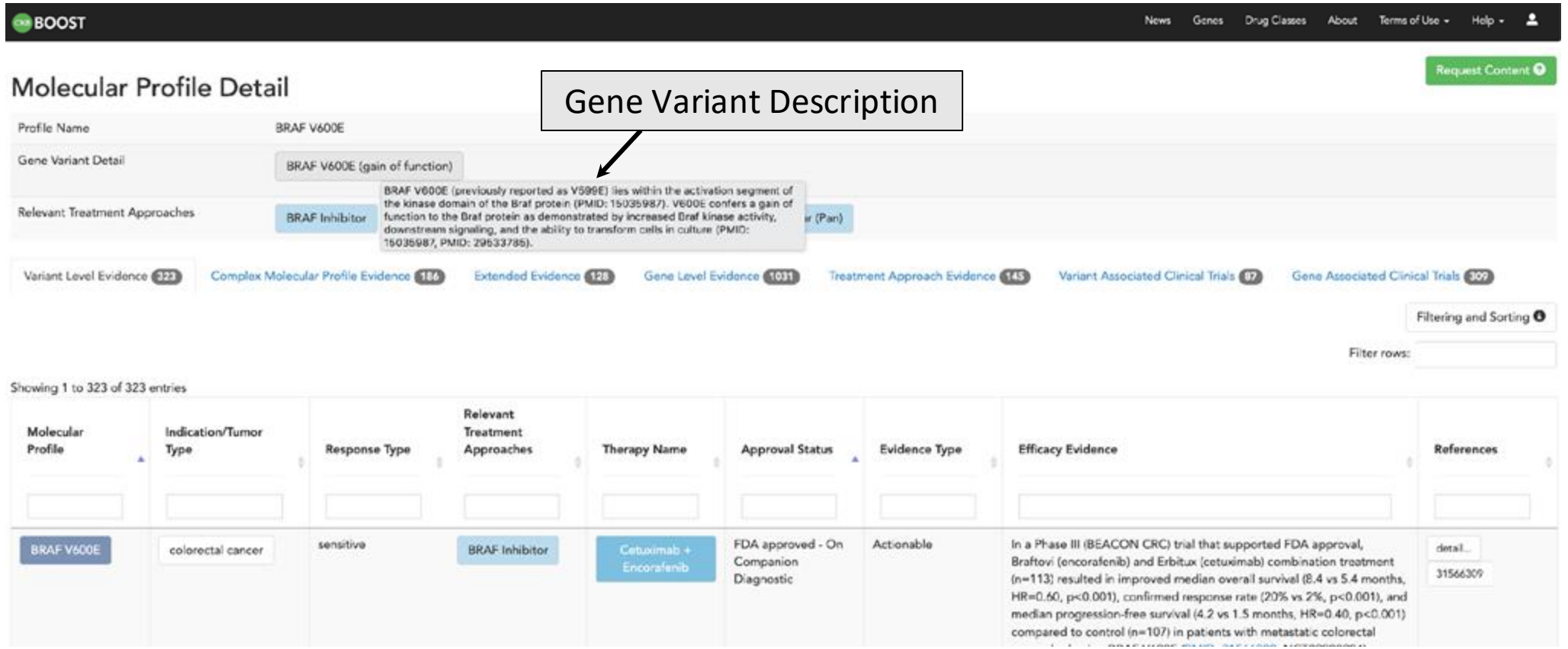
- Clicking on the “Explore by Variant” button will bring you to a page where you can search for content related to a gene variant.

Explore By Gene Variant



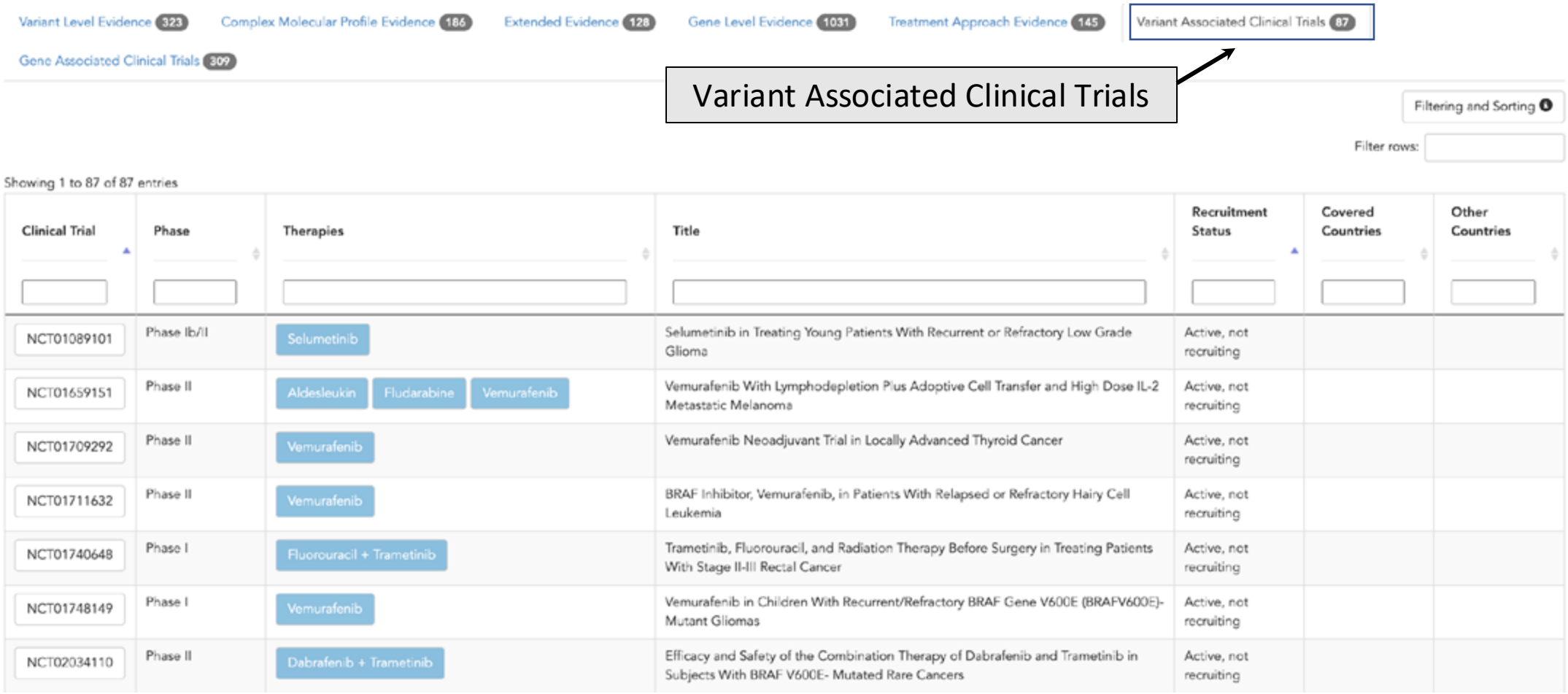
Typing in the search box will trigger a drop-down list of gene variants. Gene variants in CKB follow HGVS nomenclature. **Click** on the desired gene variant to select for searching. This will bring you to the “Molecular Profile Detail Page” for the selected gene variant.

Explore By Gene Variant



- To view the gene variant description, hover over the variant button next to Gene Variant Detail in the header.
- Below, there are 7 tabs related to different areas of content:
  - The 'Variant Level Evidence ' tab lists all annotated evidence that includes only the gene variant in the molecular profile.
  - The 'Complex Molecular Profile Evidence' tab lists all annotated evidence that includes the gene variant plus one or more other variants in the molecular profile.
  - The 'Extended Evidence' tab lists all annotated evidence that includes the category variant(s) in which the gene variant is a member.
  - The 'Gene Level Evidence' tab lists all annotated evidence associated with the gene.
  - The 'Treatment Approach Evidence' tab lists all the annotated evidence related to the Relevant Treatment Approaches listed in the header under Gene Variant Detail.
  - The 'Variant Associated Clinical Trials' tab lists all the trials that include the gene variant as a variant requirement.
  - The 'Gene Associated Clinical Trials' tab lists all the trials that include a any variant in the associated gene.
- All pages also incorporate filtering and sorting capability to enable easy content searching.

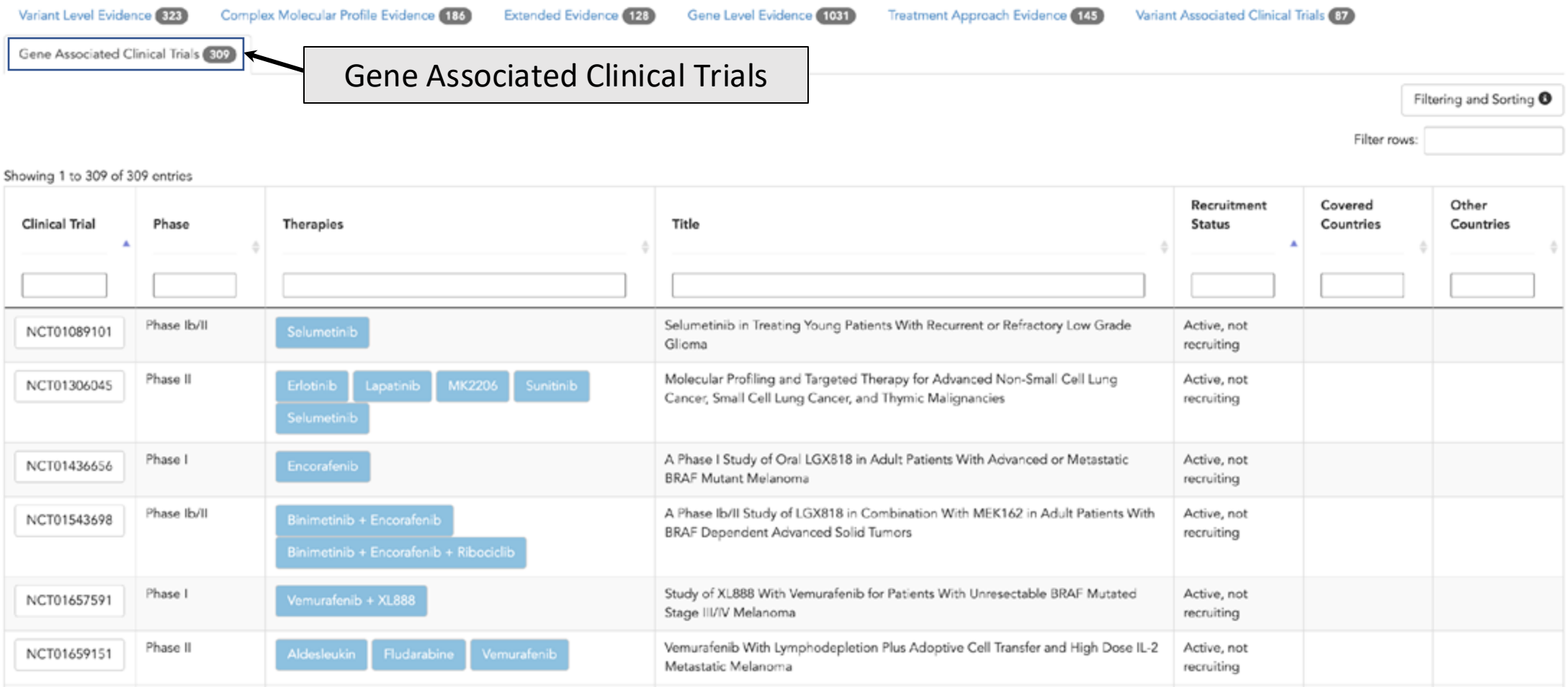
Explore By Gene Variant



Clinical Trial	Phase	Therapies	Title	Recruitment Status	Covered Countries	Other Countries
NCT01089101	Phase Ib/II	Selumetinib	Selumetinib in Treating Young Patients With Recurrent or Refractory Low Grade Glioma	Active, not recruiting		
NCT01659151	Phase II	Aldesleukin, Fludarabine, Vemurafenib	Vemurafenib With Lymphodepletion Plus Adoptive Cell Transfer and High Dose IL-2 Metastatic Melanoma	Active, not recruiting		
NCT01709292	Phase II	Vemurafenib	Vemurafenib Neoadjuvant Trial in Locally Advanced Thyroid Cancer	Active, not recruiting		
NCT01711632	Phase II	Vemurafenib	BRAF Inhibitor, Vemurafenib, in Patients With Relapsed or Refractory Hairy Cell Leukemia	Active, not recruiting		
NCT01740648	Phase I	Fluorouracil + Trametinib	Trametinib, Fluorouracil, and Radiation Therapy Before Surgery in Treating Patients With Stage II-III Rectal Cancer	Active, not recruiting		
NCT01748149	Phase I	Vemurafenib	Vemurafenib in Children With Recurrent/Refractory BRAF Gene V600E (BRAFV600E)-Mutant Gliomas	Active, not recruiting		
NCT02034110	Phase II	Dabrafenib + Trametinib	Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib in Subjects With BRAF V600E- Mutated Rare Cancers	Active, not recruiting		

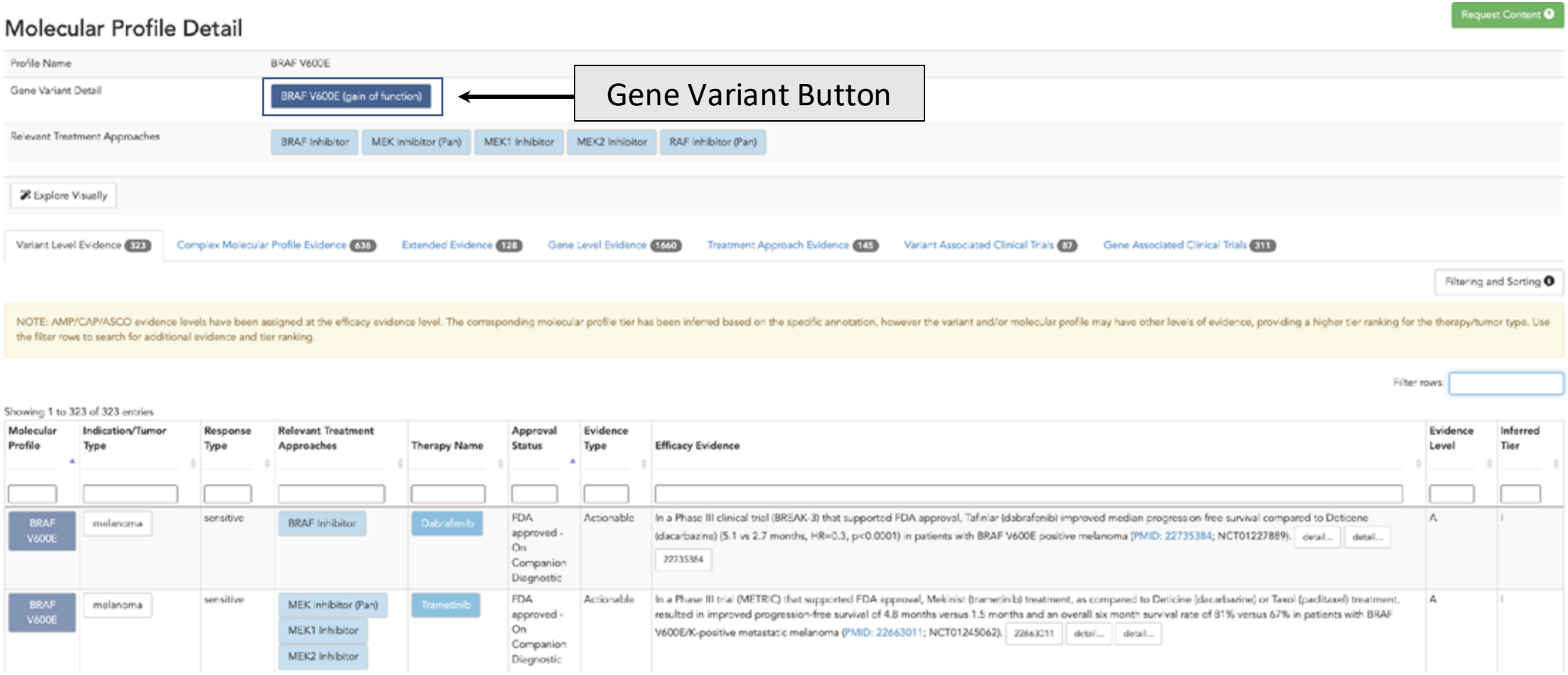
The **Variant Associated Clinical Trials** tab displays clinical trials that include the selected gene variant as a variant requirement. NCTID buttons navigate to the 'Clinical Trial Detail Page'. Recruitment status updates daily.

Explore By Gene Variant



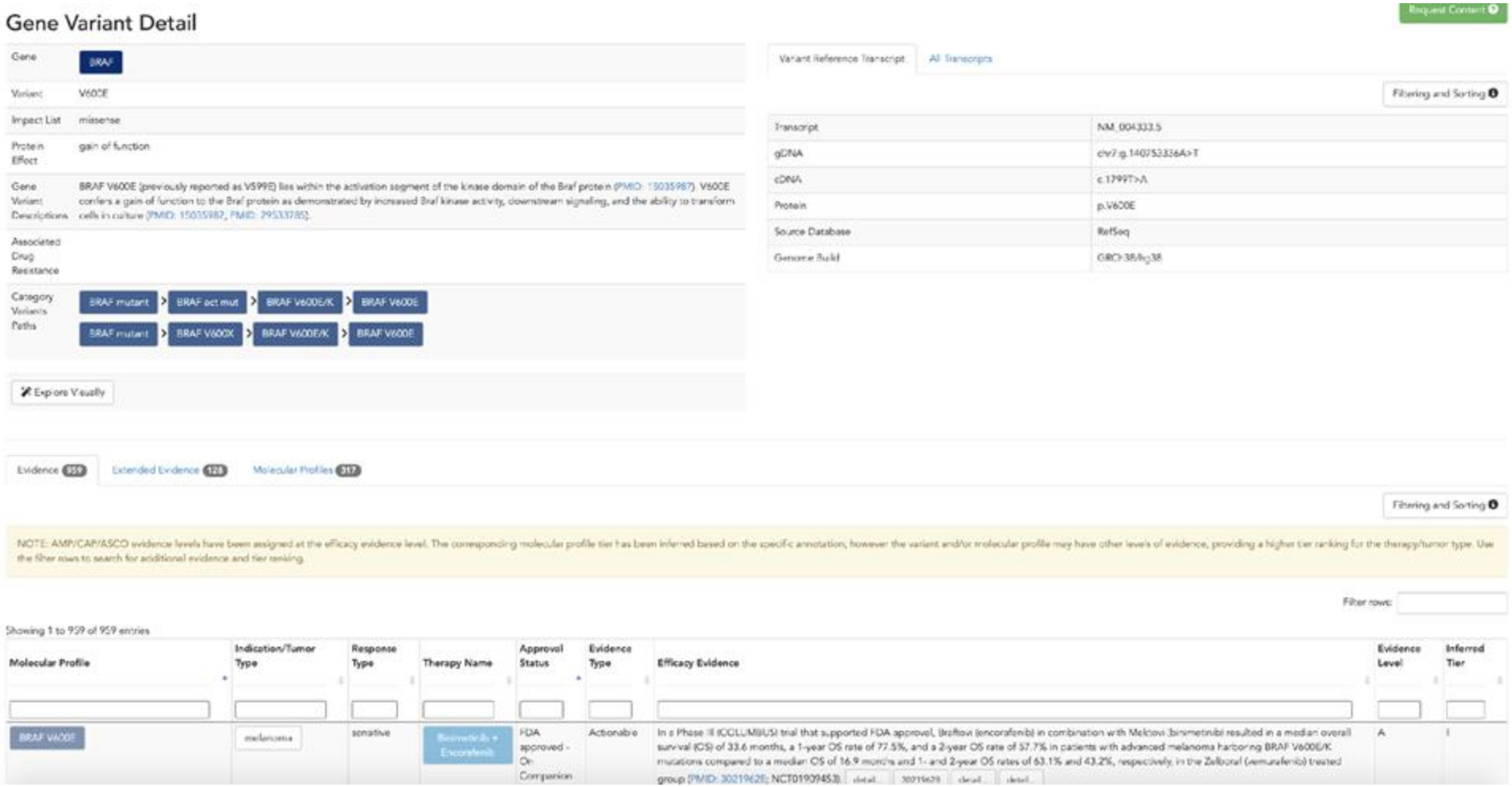
The **Gene Associated Clinical Trials** tab displays clinical trials that include any gene variant specific to the gene for the selected gene variant. NCTID buttons navigate to the 'Clinical Trial Detail Page'. Recruitment status updates daily.

Explore By Gene Variant



To view the gene variant detail page, click on the gene variant button next to 'Gene Variant Detail' in the top header

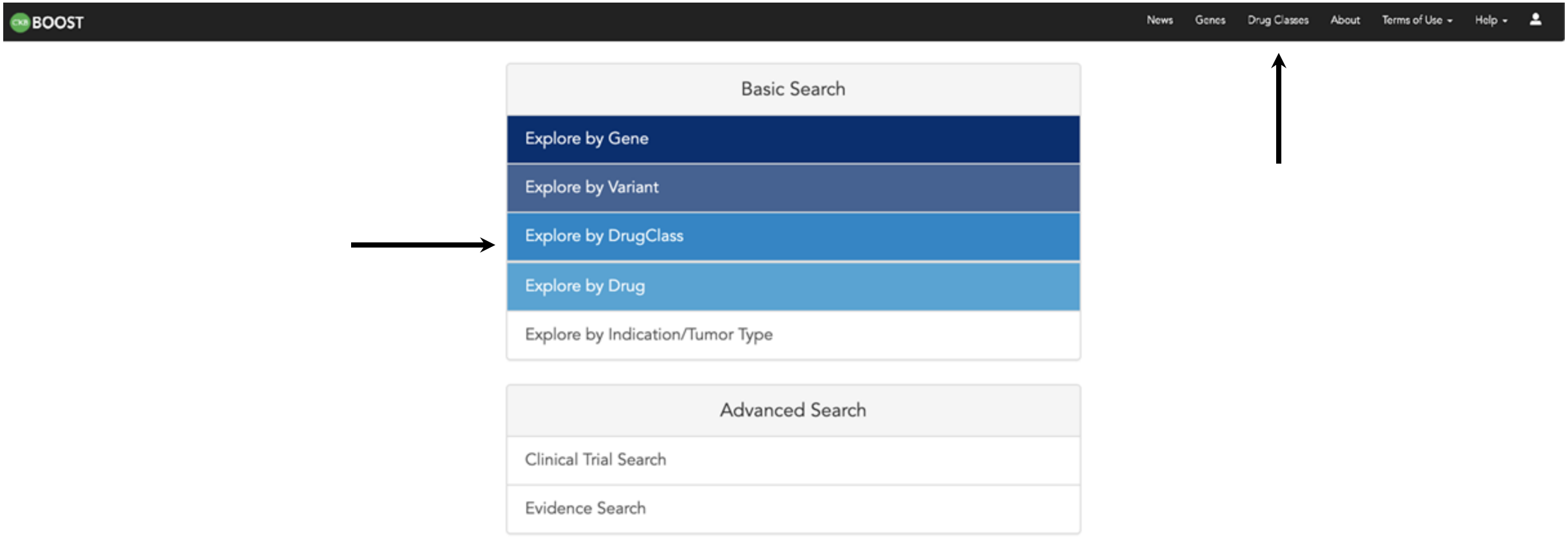
Explore By Gene Variant



The header includes the variant description, the category variants in which the specific gene variant is a member, and to the right, the variant reference transcript and a second tab with other relevant transcripts. There are three tabs below the header.

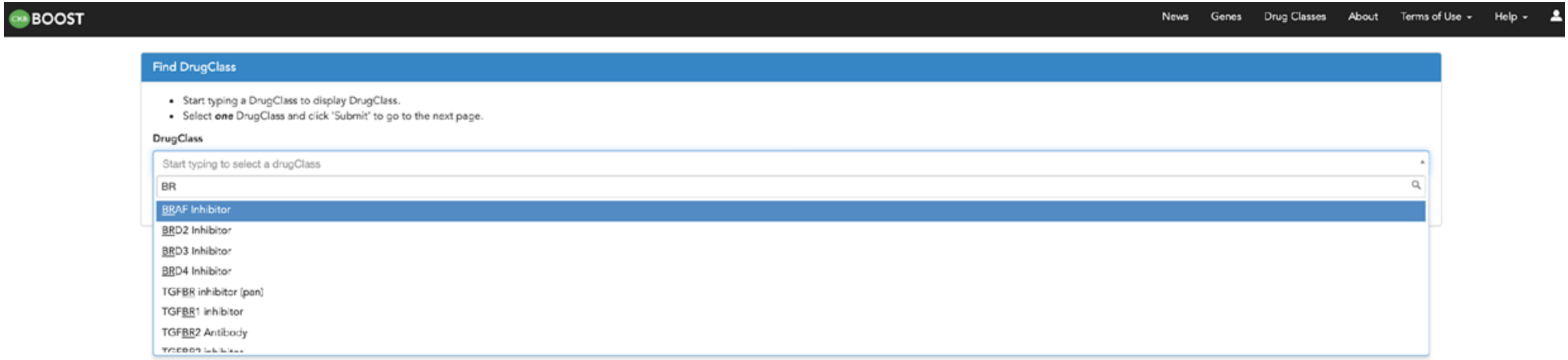
- The ‘Evidence’ tab lists all the evidence annotations specific to the gene variant selected and includes both single and complex molecular profiles.
- The ‘Extended Evidence’ tab lists all the evidence annotations specific to the category variant(s) in which the selected gene variant belongs.
- The ‘Molecular Profiles’ tab lists all the molecular files that include the selected gene variant.

Explore By Drug Class



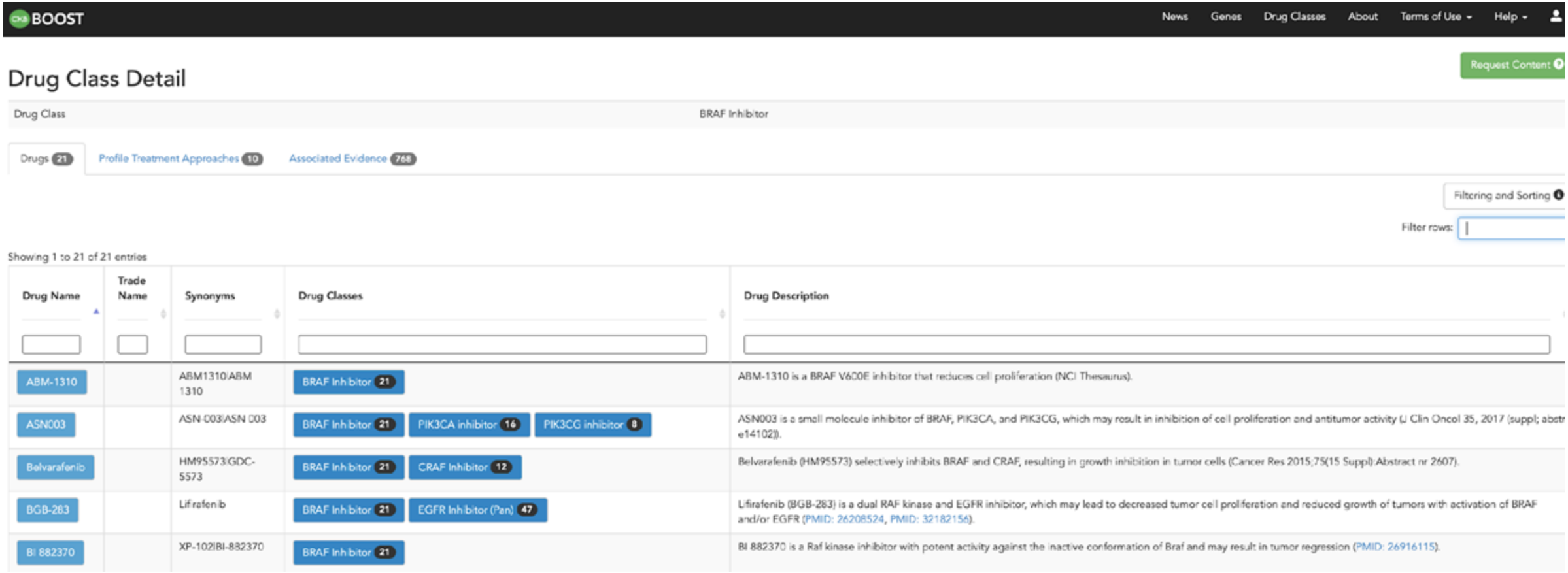
Clicking on the “Explore by Drug Class” button will bring you to a page where you can search for content based on drugs. Drug classes can be explored through the ‘Drug Class’ grid found on the top header next to ‘Genes’. Drug classes are named based on the drug target.

Explore By Drug Class



Typing a drug target (i.e. BRAF), will trigger a drop down list. **Click** to select the desired drug class. This will bring you to the "Associated Evidence and Clinical Trials " page for that drug.

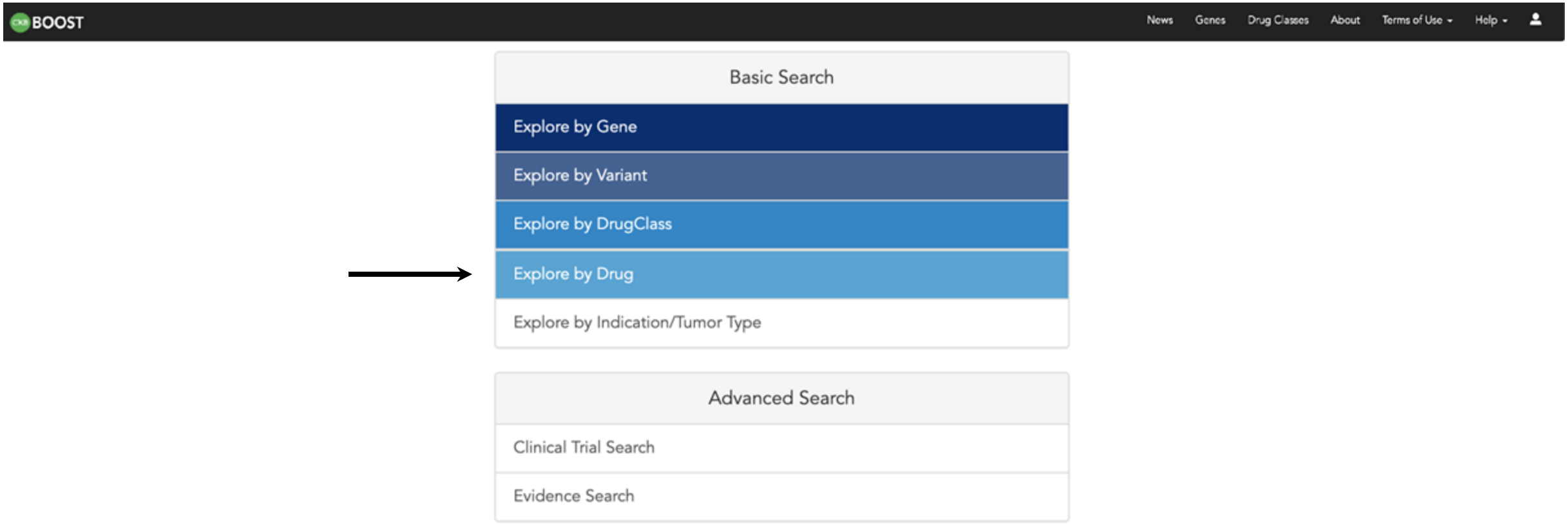
Explore By Drug Class



Typing a drug target (i.e. BRAF), will trigger a drop down list. **Click** to select the desired drug class. This will bring you to the "Drug Class Detail" page for that drug. There are three tabs on this page.

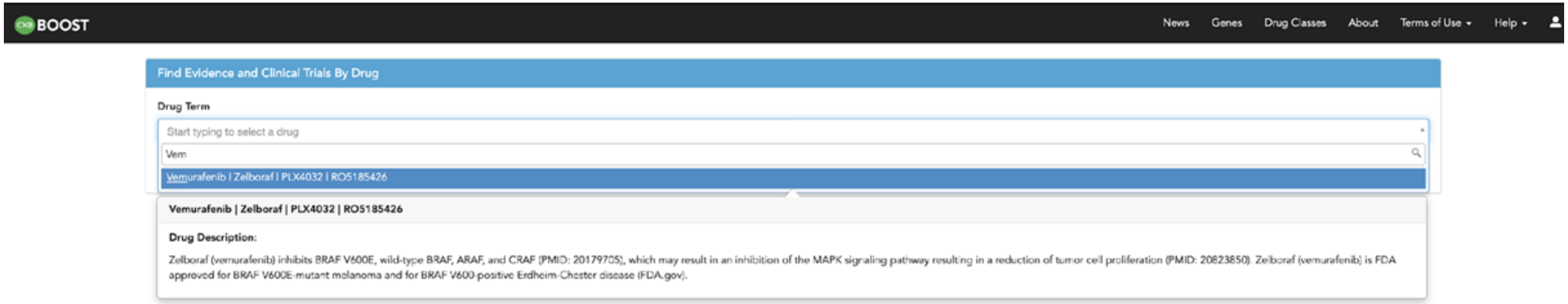
- The 'Drugs' tab lists all the drugs that are members of the selected drug class.
- The 'Profile Treatment Approaches' tab lists all the molecular profiles that include the selected drug class as a treatment approach.
- The 'Associated Evidence' tab lists all the evidence that includes a drug that is a member of that drug class.

Explore By Drug



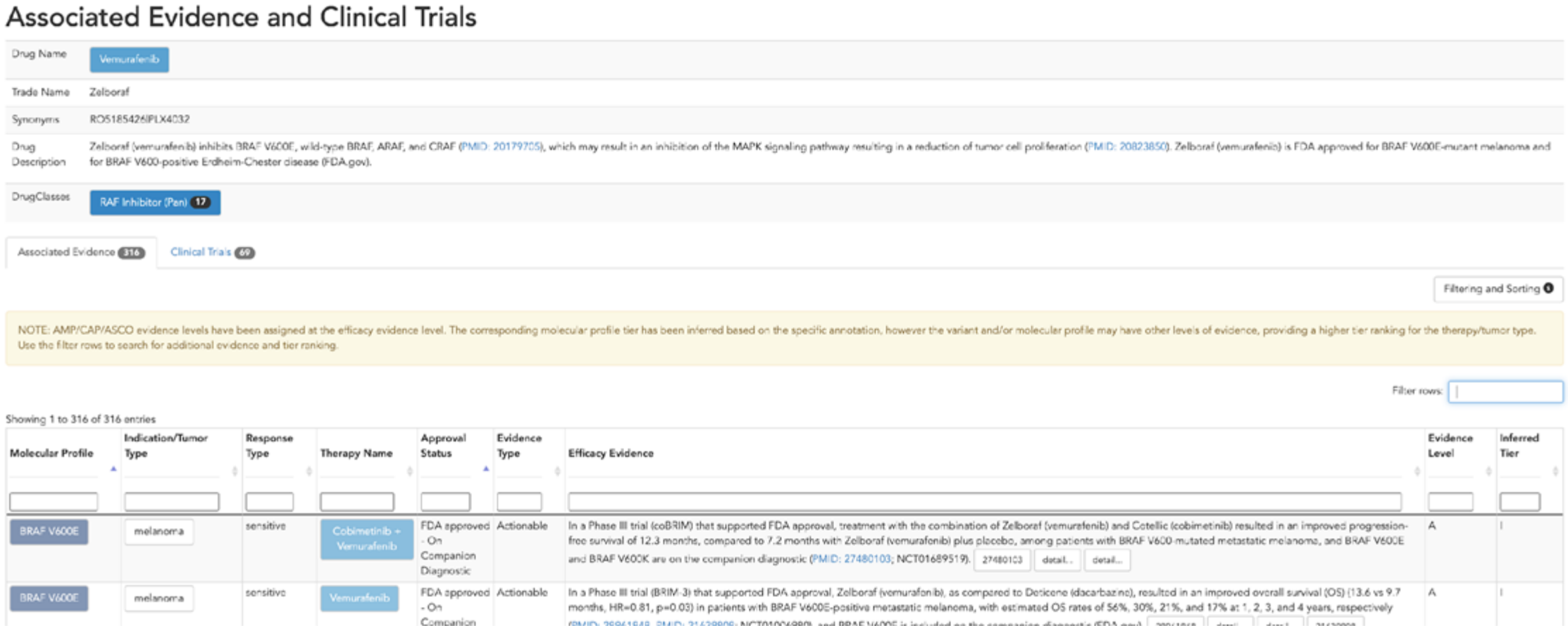
Clicking on the “Explore by Drug” button will bring you to a page where you can search for content based on drugs.

Explore By Drug



Typing a drug term, including trade name or synonym, will trigger a drop down list. **Click** to select the desired drug. This will bring you to the “Associated Evidence and Clinical Trials “ page for that drug.

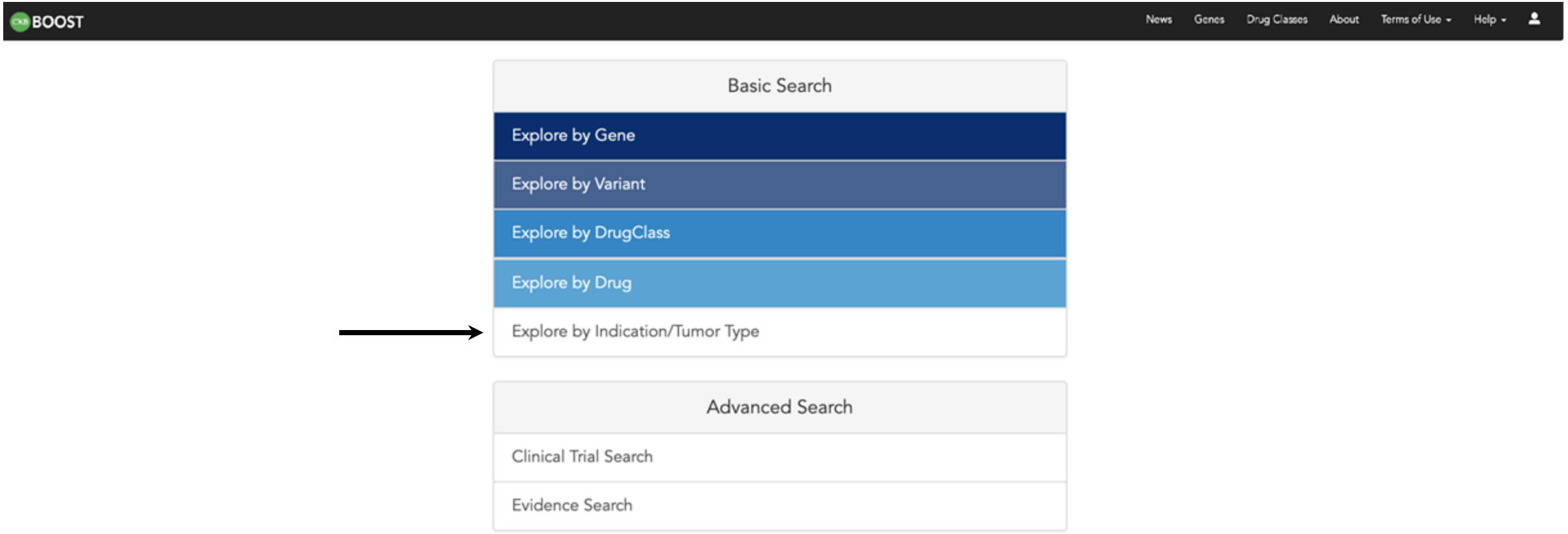
Explore By Drug



Below the header are two tabs related to different areas of content:

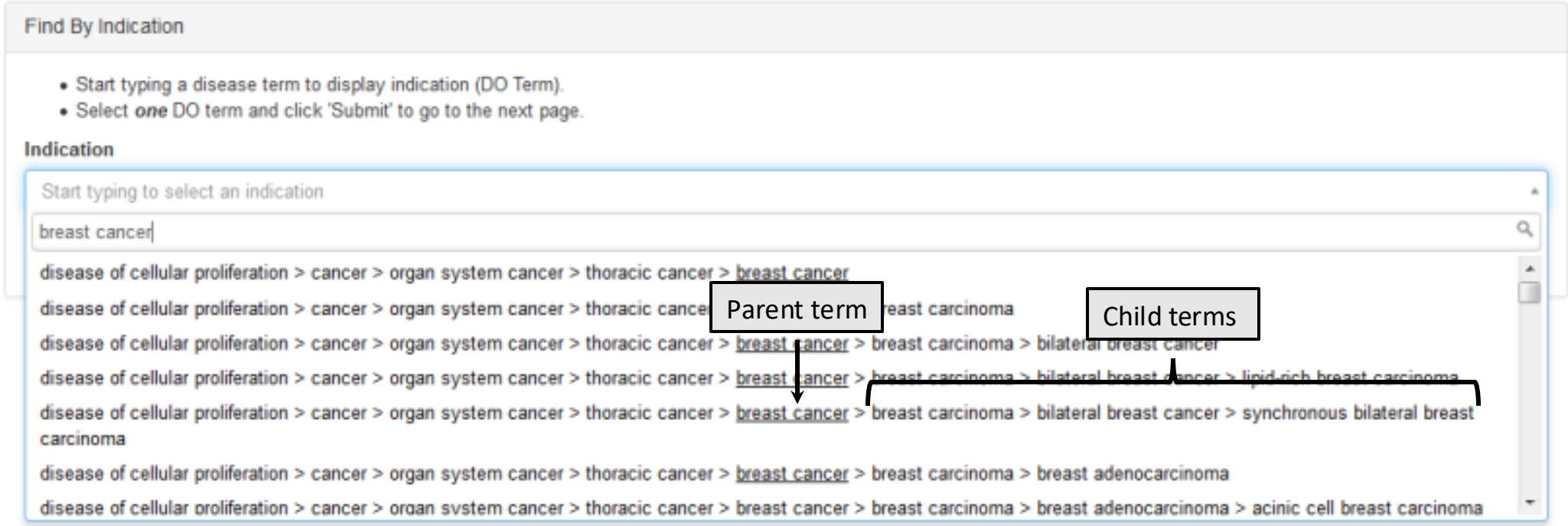
- The ‘Associated Evidence’ tab displays all efficacy evidence associated with selected drug, similar to what is displayed with gene.
- The ‘Clinical Trials‘ tab displays all clinical trials associated with the selected drug, alone or in combination therapy.

Explore By Indication



Clicking on the “Explore by Indication” button will bring you to a page where you can search for content based on disease terms.

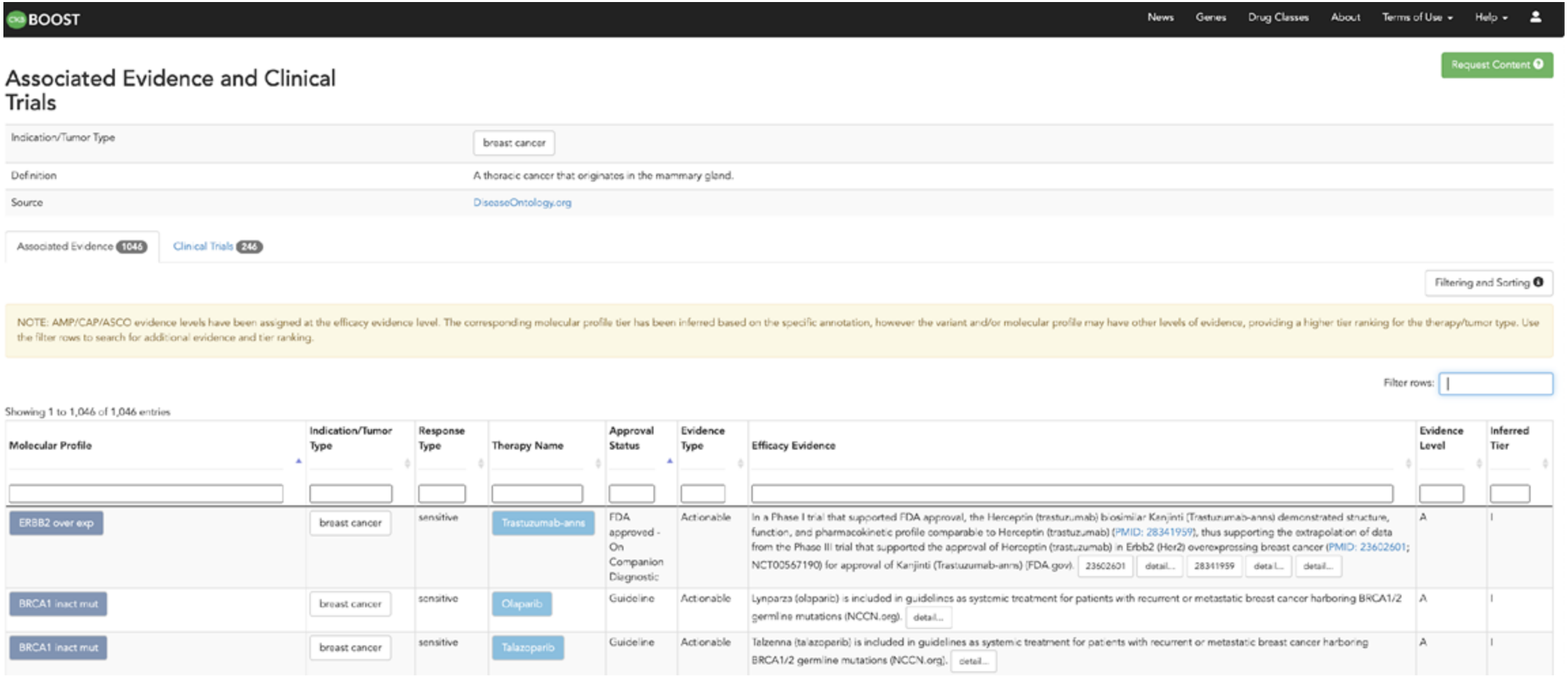
Explore By Indication



Typing in the indication search box will bring up a drop down list of disease terms. Disease terms in CKB are incorporated from the Disease Ontology (http://disease-ontology.org), which is a hierarchical disease ontology, composed of parent terms (ex. “breast cancer”), and child terms (ex. “synchronous bilateral breast carcinoma”).

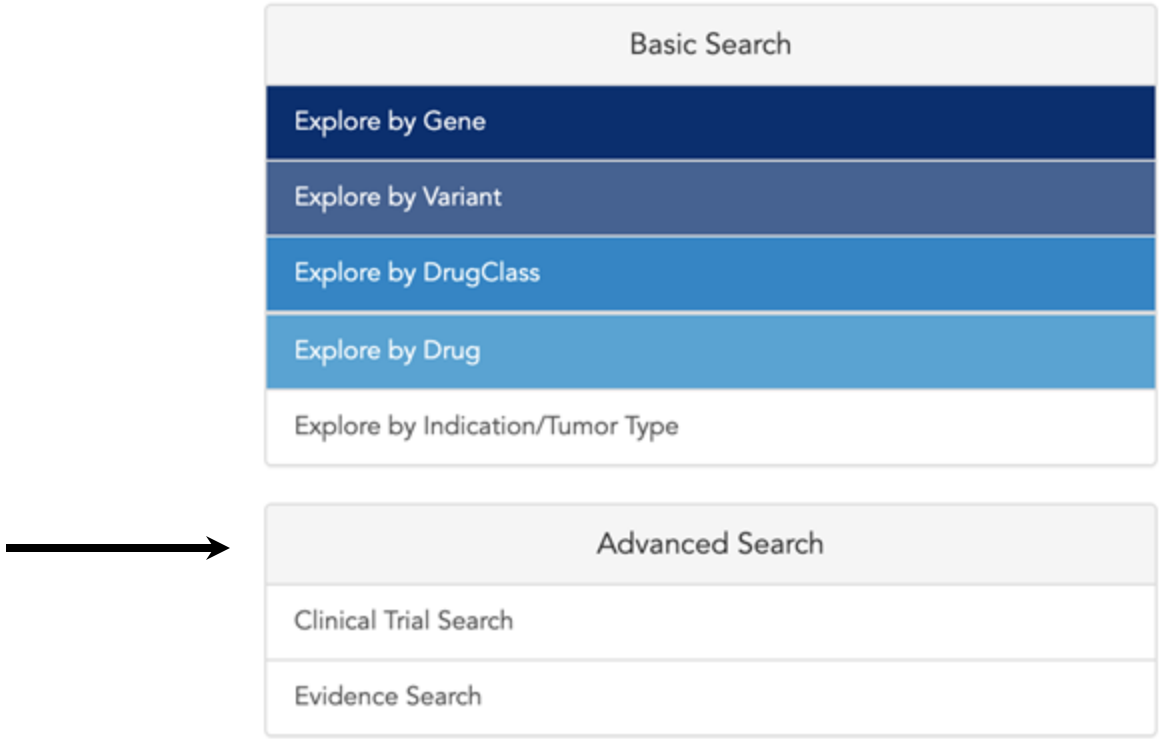
Select a term from the drop down list to begin the search. Results returned will pertain only to the indication searched, and not “child” terms (those beneath the chosen term in the hierarchy).

Explore By Indication



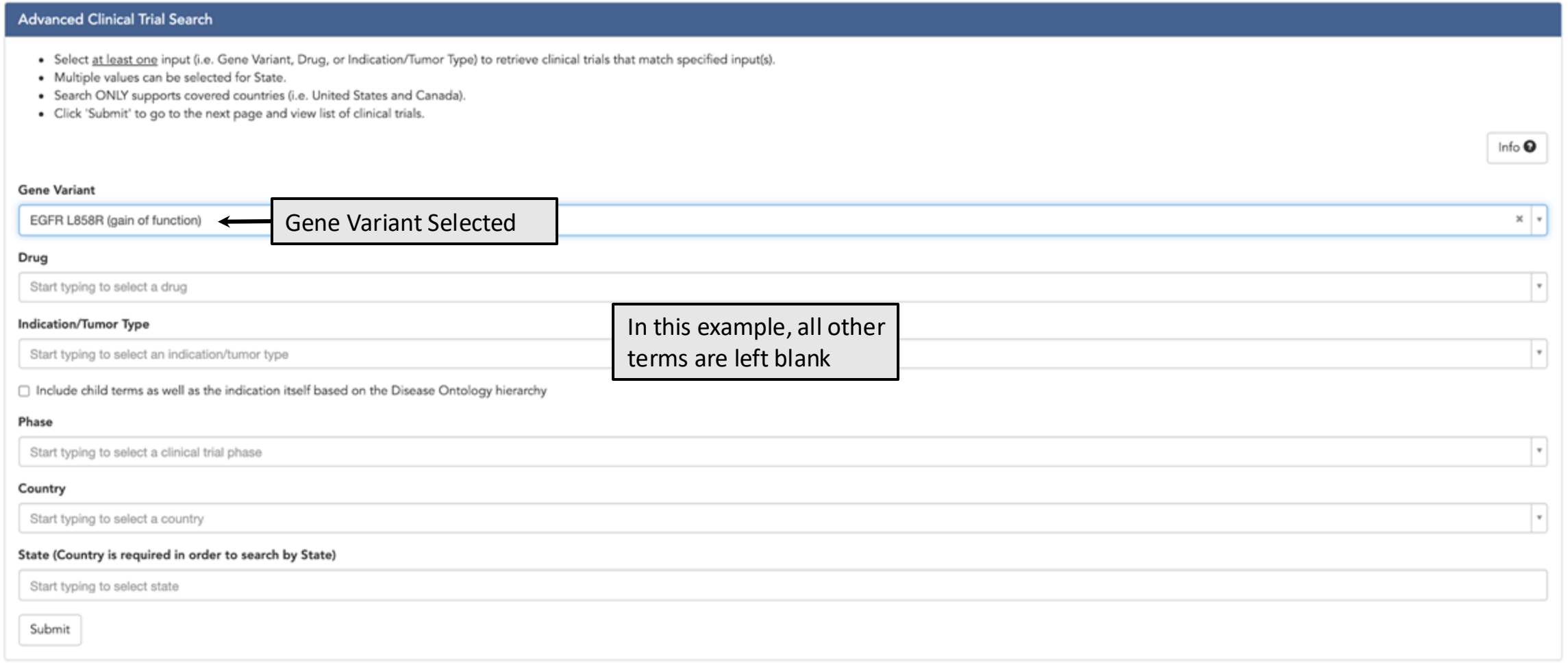
There are 2 tabs on the returned results page : ‘Associated Evidence’ and ‘Clinical Trials’, which display results pertaining to the disease term searched, similar to the results for “Explore by Drug”.

Advanced Searching



There are two “Advanced Search” options, which allow the user to search on multiple search parameters simultaneously. The ‘Clinical Trial Search’ returns clinical trials that match the search term, and the ‘Evidence Search’ return matching annotated evidence. Clicking on either of these buttons will bring you to the search page.

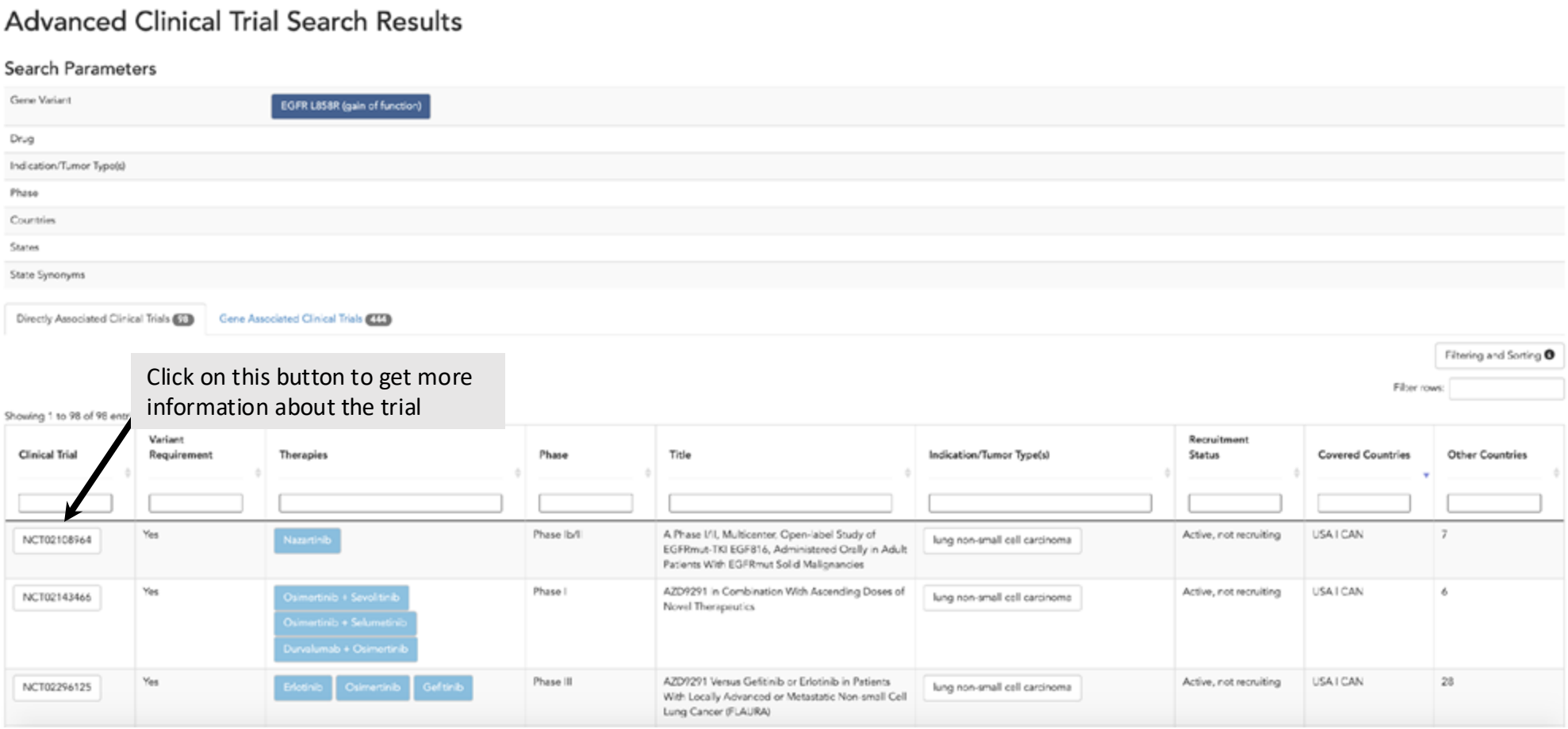
Advanced Clinical Trials Search



The Advanced Clinical Trial Search enables the user to search for clinical trials based on 'gene variant', 'drug', 'indication', clinical trial 'phase', 'country', and/or 'state'. A user must select **at least one** attribute from either 'gene variant', 'drug', or 'Indication/Tumor Type' to search on. Selecting only a 'gene variant' will return all clinical trials that match that gene variant, regardless of all other attributes.

Once you have selected the desired search terms, click 'Submit' to begin the search.

Advanced Clinical Trials Search

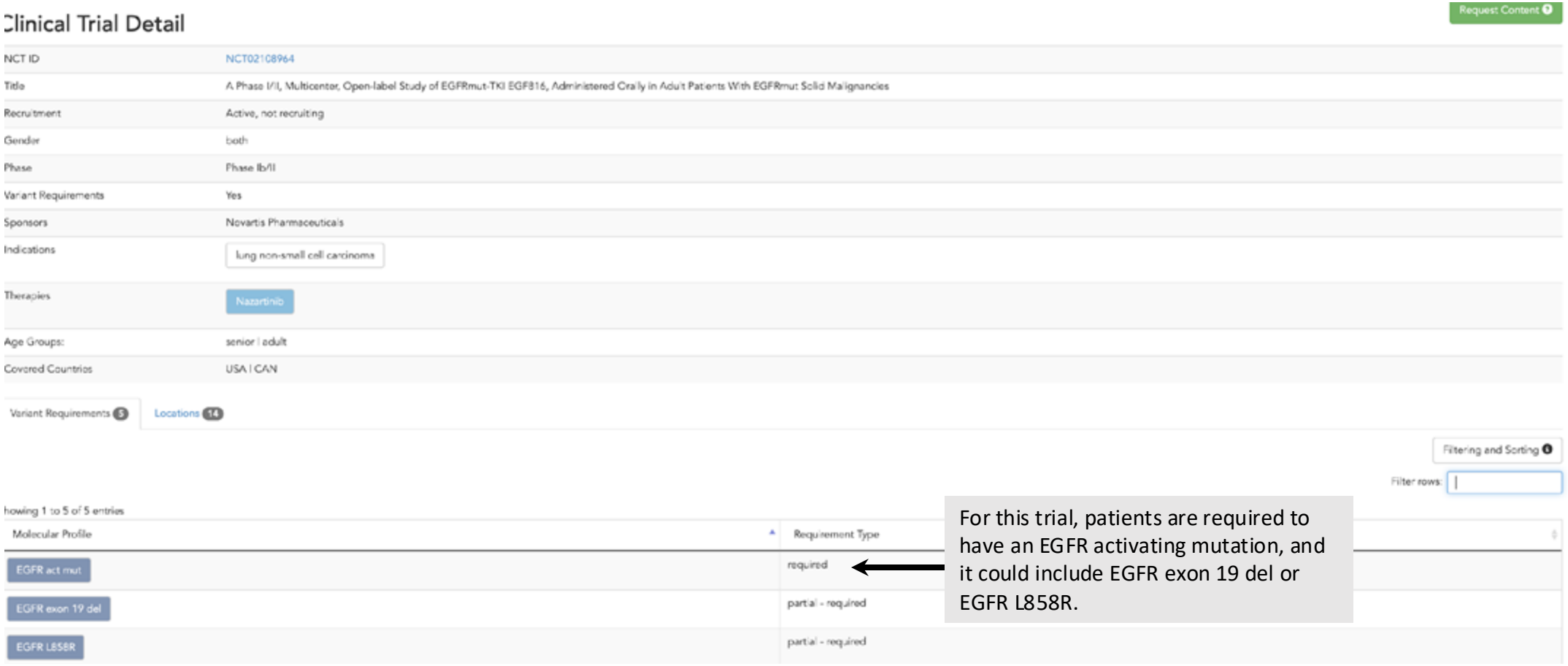


- The header of the **Advanced Clinical Trials Search Results** page lists the search parameters. Fields left blank in the search will be blank in the header. Clinical trial results will pertain to the searched terms.

- When gene variant is used as a search parameter, the results page will have 2 tabs: “Directly Associated Clinical Trials’ and ‘Gene Associated Clinical Trials’. The ‘Directly Associated Clinical Trials ‘ tab will display clinical trials with ‘variant requirement’ matching the searched variant. The ‘Gene Associated Clinical Trials ‘ tab will display all clinical trials with variant requirements related to the Gene of the searched variant. Searches lacking gene variant selection will not have a “Gene Associated Clinical Trials ‘ tab.

- Clicking the white clinical trial button will bring you to the “Clinical Trial Detail” Page, which contains more detail about the trial, including specifics on variant requirements.

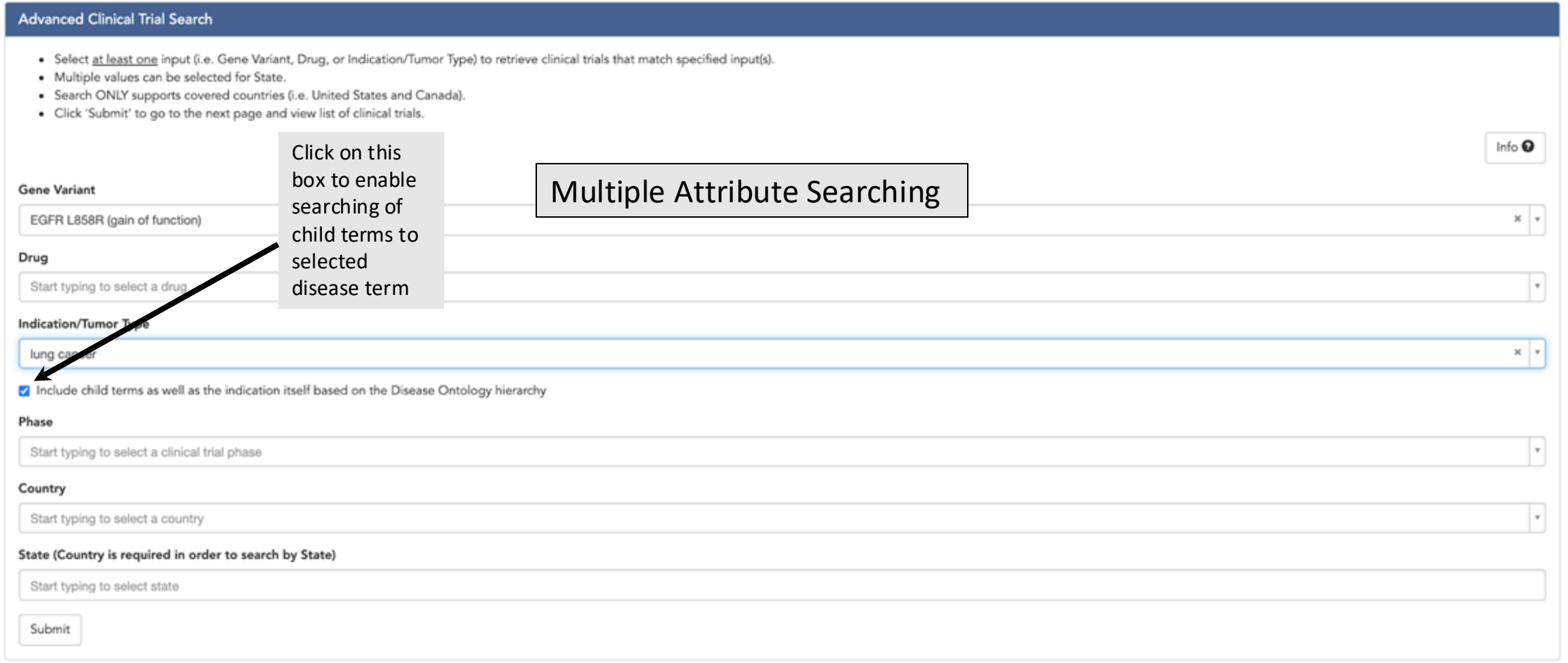
Advanced Clinical Trials Search



The **Clinical Trial Detail** page lists additional information about the clinical trial, curated from clinicaltrials.gov, including the sponsor and variant requirements. The specific variant requirements are listed in the table. Requirement types can be “required” (variant is required for enrollment), “excluded” (variant is excluded from enrollment), “partial” (variant is required or excluded for a subset of the enrollment population).

The second tab ’Locations’ lists the locations of the trial, which are imported from clinicaltrials.gov.

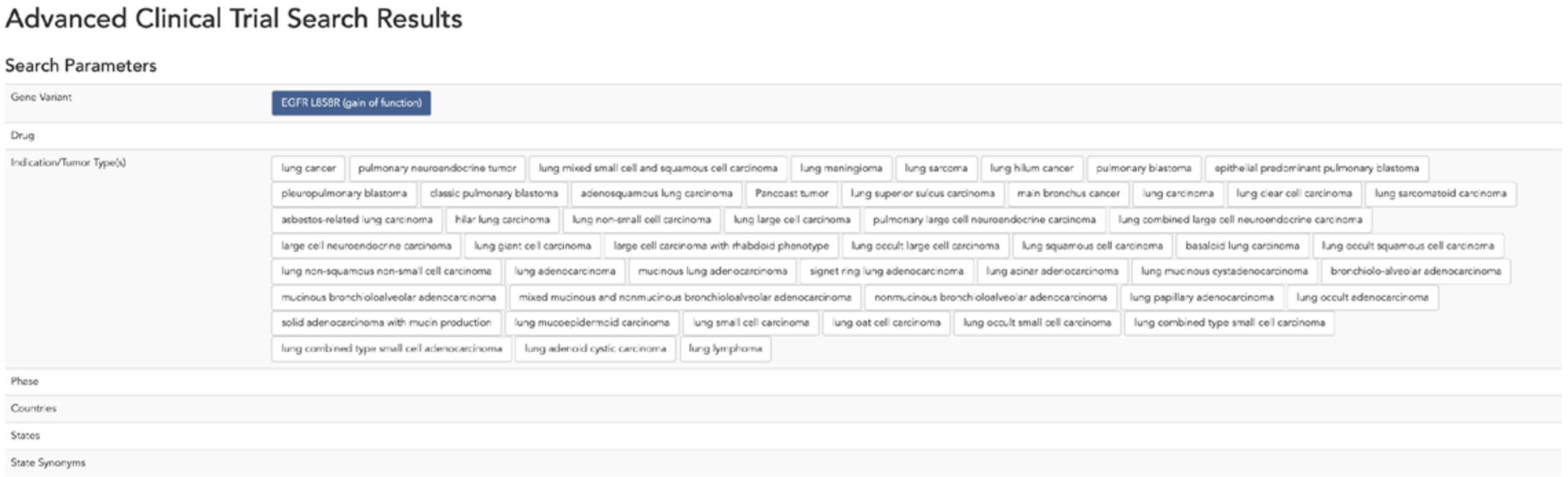
Advanced Clinical Trials Search



Users can also search using multiple attributes. Typing in each box will trigger a drop-down list of terms from which to select. Results returned will relate to ALL items selected ('AND' searching).

When choosing an indication, users have the option to include child terms (those below the selected term in the hierarchy). To enable this function, click the box below. In this example, all child terms for "lung cancer" will be searched on in addition to the parent term. Hit 'Submit' to begin the search. All results returned will pertain to the combination of terms selected.

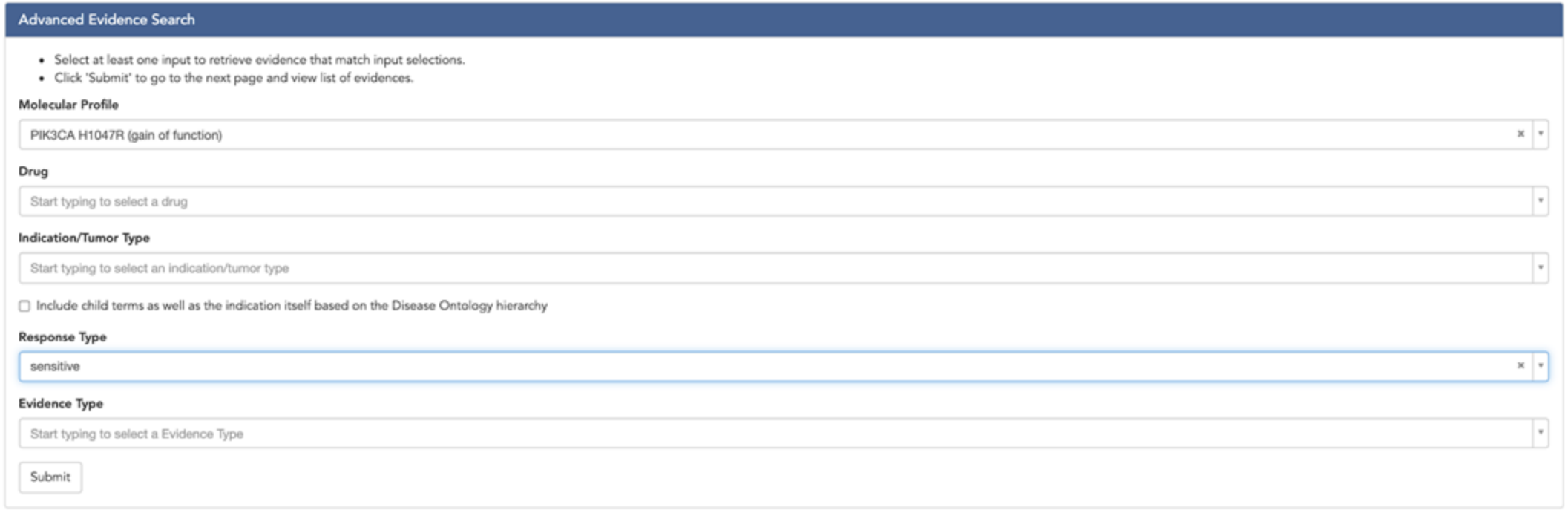
Advanced Clinical Trials Search



When the “include child terms” button is selected, the header of the results page will list the selected indication as well as all child terms included in the search.

In this example, ‘gene variant’ and ‘indication’ were used as search parameters. Other fields were left blank. Results returned will pertain to the gene variant selected **AND** one of the listed indication terms.

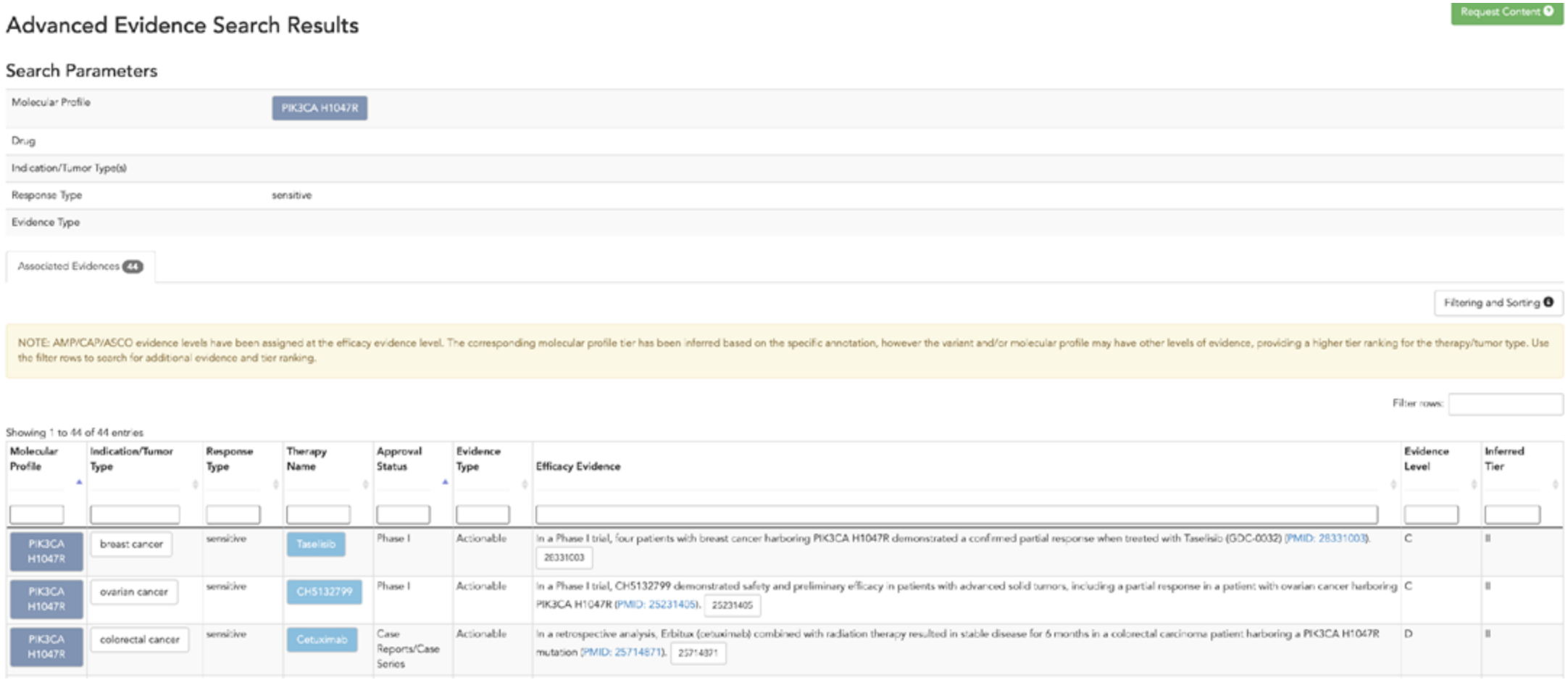
Advanced Evidence Search



The Advanced Evidence Search operates in a similar way to the Advanced Clinical Trial Search and enables the user to search for annotated *evidence* related to 'molecular profile', 'drug', 'indication', and/or clinical trial 'phase'. A user can select **one or more** of these attributes to search on.

Once you have selected the desired search terms, click 'Submit' to begin the search. Results returned will pertain to **all** attributes selected.

Advanced Evidence Search



Request Content

Advanced Evidence Search Results

Search Parameters

Molecular Profile	PIK3CA H1047R
Drug	
Indication/Tumor Type(s)	
Response Type	sensitive
Evidence Type	

Associated Evidences 44

Filtering and Sorting

NOTE: AMP/CAP/ASCO evidence levels have been assigned at the efficacy evidence level. The corresponding molecular profile tier has been inferred based on the specific annotation, however the variant and/or molecular profile may have other levels of evidence, providing a higher tier ranking for the therapy/tumor type. Use the filter rows to search for additional evidence and tier ranking.

Filter rows:

Showing 1 to 44 of 44 entries

Molecular Profile	Indication/Tumor Type	Response Type	Therapy Name	Approval Status	Evidence Type	Efficacy Evidence	Evidence Level	Inferred Tier
PIK3CA H1047R	breast cancer	sensitive	Taselisib	Phase I	Actionable	In a Phase I trial, four patients with breast cancer harboring PIK3CA H1047R demonstrated a confirmed partial response when treated with Taselisib (GDC-0032) (PMID: 28331003). 28331003	C	II
PIK3CA H1047R	ovarian cancer	sensitive	CH5132799	Phase I	Actionable	In a Phase I trial, CH5132799 demonstrated safety and preliminary efficacy in patients with advanced solid tumors, including a partial response in a patient with ovarian cancer harboring PIK3CA H1047R (PMID: 25231405). 25231405	C	II
PIK3CA H1047R	colorectal cancer	sensitive	Cetuximab	Case Reports/Case Series	Actionable	In a retrospective analysis, Erbitux (cetuximab) combined with radiation therapy resulted in stable disease for 6 months in a colorectal carcinoma patient harboring a PIK3CA H1047R mutation (PMID: 25714871). 25714871	D	II

The **Advanced Evidence Search Results** page lists all evidence that matches **all** search terms. In this example, evidence annotations that have both the response type: “sensitive” **and** contains the molecular profile: “PIK3CA H1047R” are returned.