IntelliSpace Genomics

Challenges in Genomic Aberration Detection and Interpretation in Solid Tumors and Evidence-based Approaches for Targeted Therapy

Nevenka Dimitrova, PhD, CTO Genomics, Healthcare Informatics, Philips
Sheryl Elkin, PhD, N-of-One

Philips Healthcare Informatics – Genomics
AMP Webinar March 14, 2017

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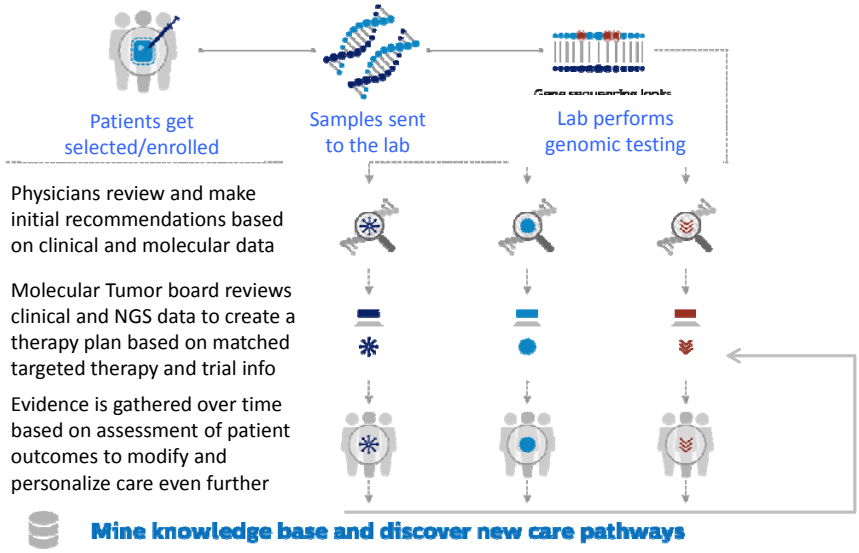
Precision Medicine



- A Retrospective Analysis of Precision Medicine Outcomes in Patients With Advanced Cancer Reveals Improved Progression-Free Survival Without Increased Health Care Costs.
Haslem DS, Van Norman SB, Fulde G, Knighton AJ, Belnap T, Butler AM, Rhagunath S, Newman D, Gilbert H, Tudor BP, Lin K, Stone GR, Loughmiller DL, Mishra PJ, Srivastava R, Ford JM, Nadauld LD. J Oncol Pract. 2016 Sep 6. pii: JOPR011486

- Precision medicine in pediatric oncology: Lessons learned and next steps.
Mody RJ, Prensner JR, Everett J, Parsons DW, Chinnaiyan AM. Pediatric Blood Cancer. 2017 Mar;64(3). doi: 10.1002/pbc.26288. Review.

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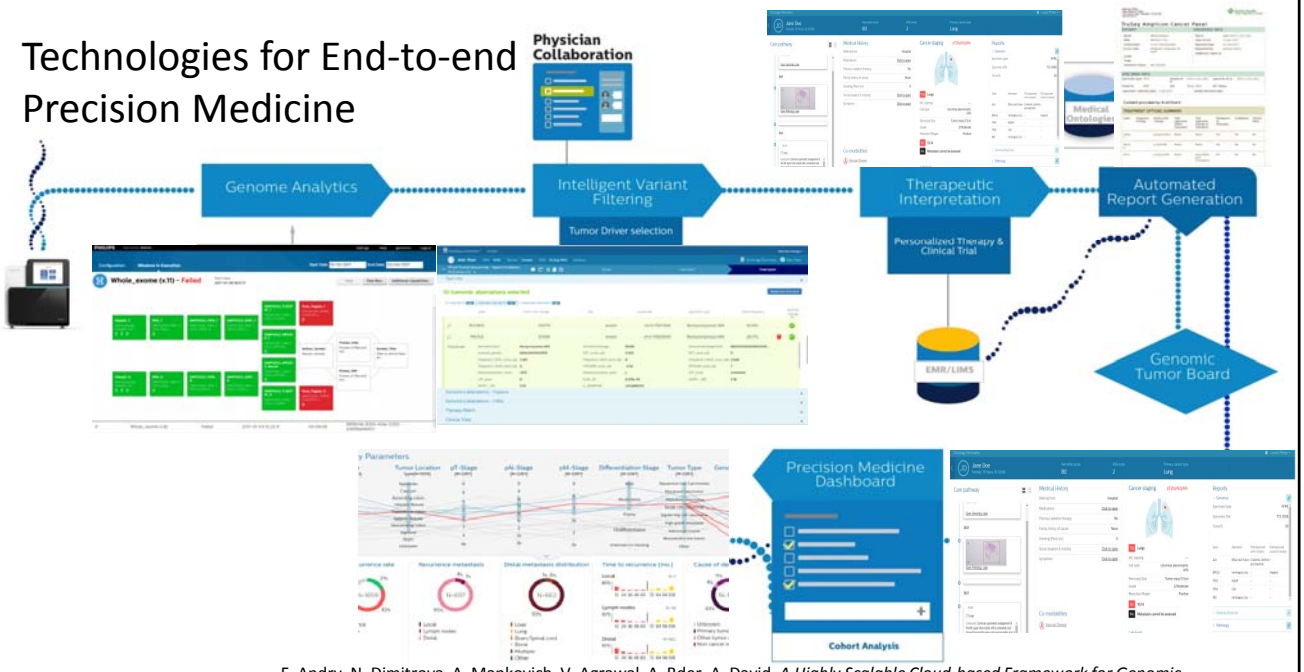
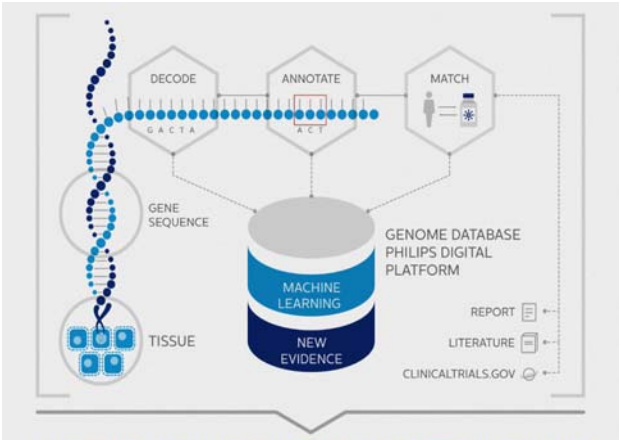
Technologies for End-to-end Precision Medicine



F. Andry, N. Dimitrova, A. Mankovich, V. Agrawal, A. Bder, A. David, *A Highly Scalable Cloud-based Framework for Genomic Processing*, 9th Int.Conf. Biomedical Engineering Systems and Technologies (BIOSTEC 2016) - BIOINFORMATICS, pp. 198-206, Rome,

The End-to-end Platform

IntelliSpace Genomics ***Clinical*** Workflows



IntelliSpace Genomics ***Research*** Workflows

SONIC HEDGEHOG Pathway | WNT Pathway | PI3K Pathway | NOTCH Pathway

Cancer Subtyping | InFflo Network Analysis | Autoencoder Deep learning | Single Cell Phylo

Generate and validate hypotheses

GENOME ANALYTICS

SECURE PHILIPS HEALTHSUITE DIGITAL PLATFORM

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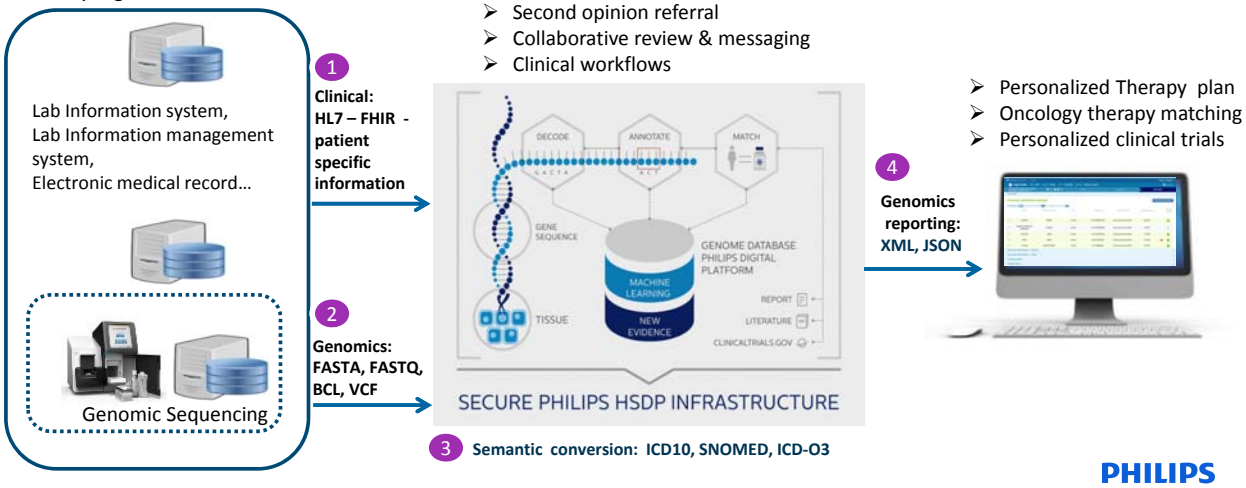
The IntelliSpace Genomics Platform

Interoperability

- Synthesize clinical information
- Analyze genomics data



- Genomics decode, persistence
- Genomics annotation
- Second opinion referral
- Collaborative review & messaging
- Clinical workflows

- Personalized Therapy plan
- Oncology therapy matching
- Personalized clinical trials

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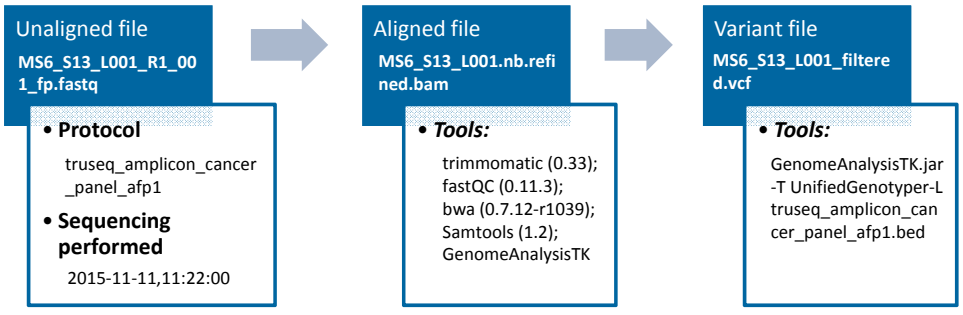
Audit and reproducibility

Controlled processing of raw next generation sequencing data using automated pipelines with quality checks, traceability

- Best in class algorithms
- Molecular test agnostic



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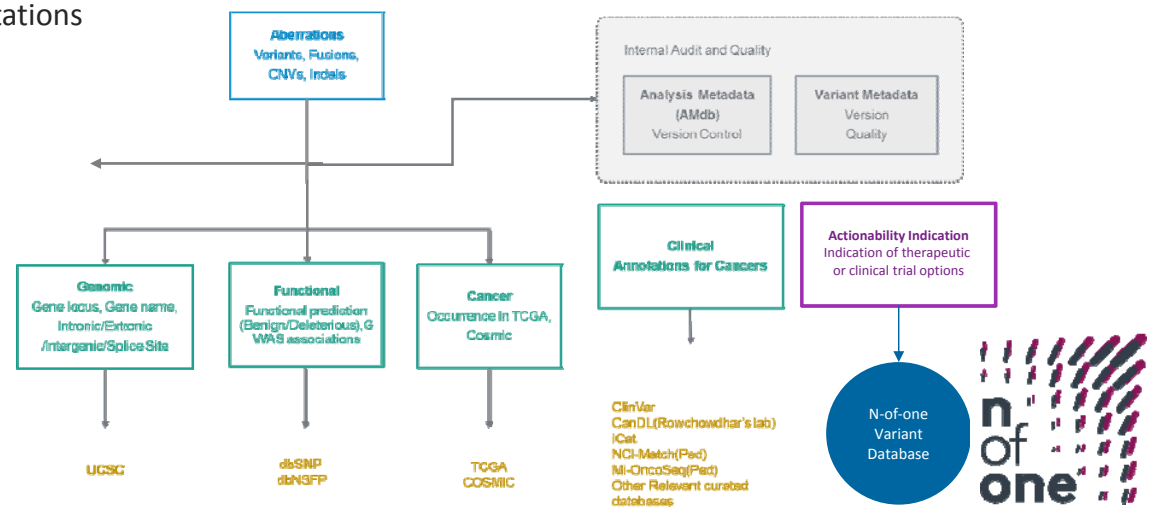
Informed annotation

Variant annotation with therapy-indication - genomic, functional, and cancer-specific annotations



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N-of-One: Clinical Interpretation of Molecular Diagnostic Tests

- Acknowledged leader with 8-year track record of success
- High quality, patient-specific, data-driven therapeutic strategies with reproducible methodology
- Utilized by hospital and commercial labs worldwide: all size panels and on multiple test platforms
- Tens of thousands of patient cases interpreted across hundreds of cancer types
- Industry-leading proprietary tools, platform and database
- Experienced team of practicing oncologists and Ph.D. scientists

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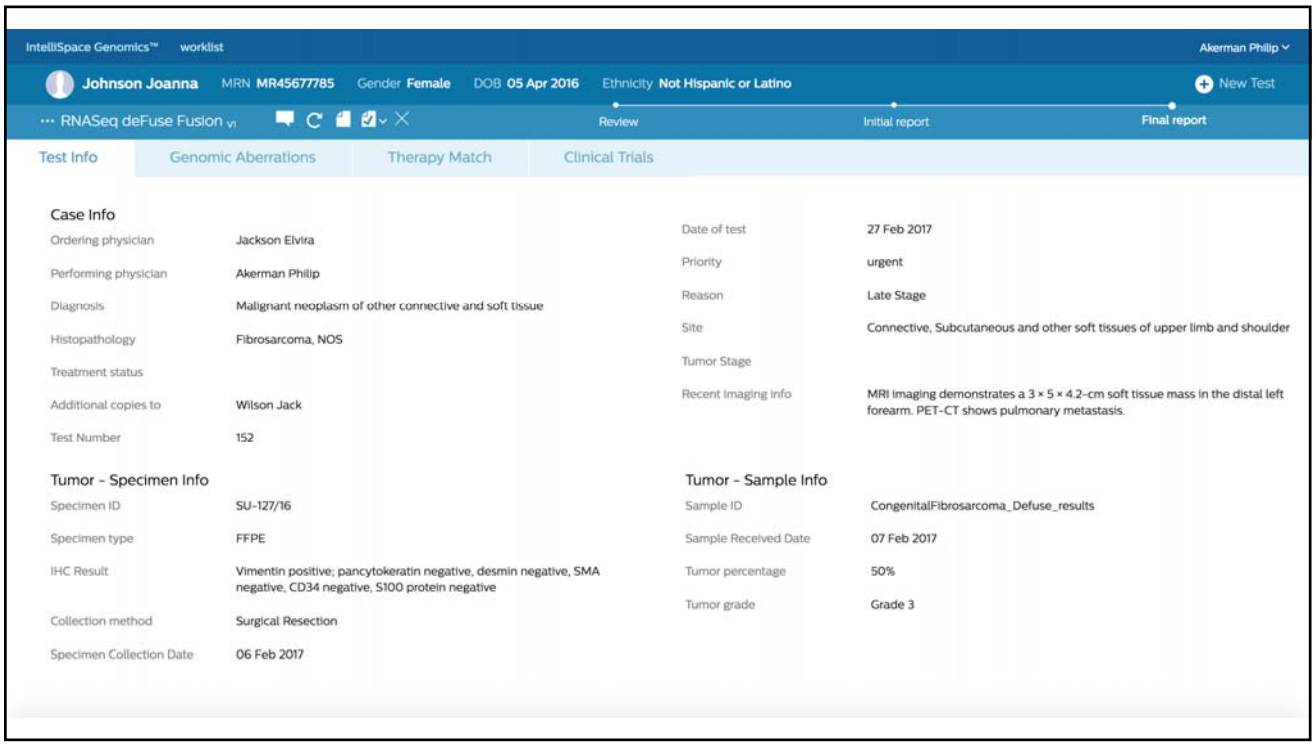
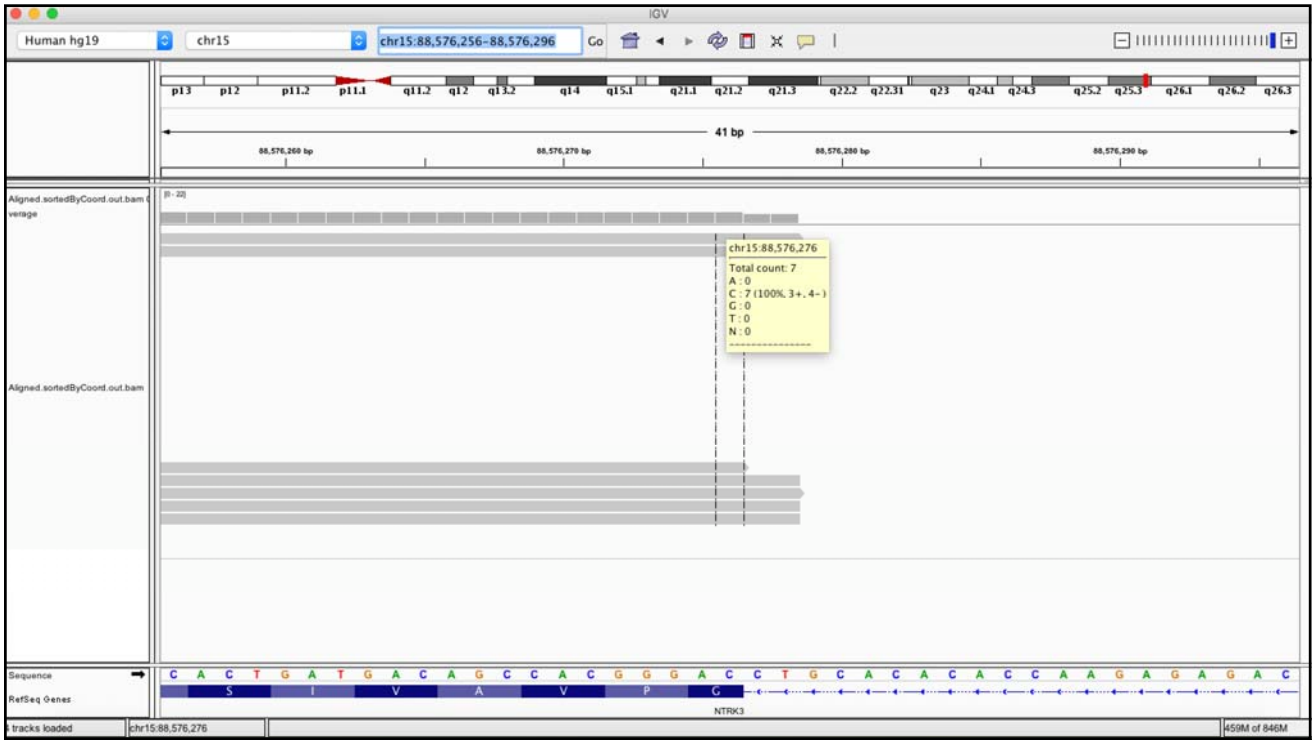

IntelliSpace Genomics™ worklist
Akerman Philip
Johnson Joanna MRN MR45677785 Gender Female DOB 05 Apr 2016 Ethnicity Not Hispanic or Latino
New Test
RNASeq deFuse Fusion v1
Review
Initial report
Final report
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
Case Info
Ordering physician Jackson Elvira
Performing physician Akerman Philip
Diagnosis Malignant neoplasm of other connective and soft tissue
Histopathology Fibrosarcoma, NOS
Treatment status
Additional copies to Wilson Jack
Test Number 152
Date of test 27 Feb 2017
Priority urgent
Reason Late Stage
Site Connective, Subcutaneous and other soft tissues of upper limb and shoulder
Tumor Stage
Recent Imaging Info MRI imaging demonstrates a 3 × 5 × 4.2-cm soft tissue mass in the distal left forearm. PET-CT shows pulmonary metastasis.
Tumor - Specimen Info
Specimen ID SU-127/16
Specimen type FFPE
IHC Result Vimentin positive; pancytokeratin negative, desmin negative, SMA negative, CD34 negative, S100 protein negative
Collection method Surgical Resection
Specimen Collection Date 06 Feb 2017
Tumor - Sample Info
Sample ID CongenitalFibrosarcoma_Defuse_results
Sample Received Date 07 Feb 2017
Tumor percentage 50%
Tumor grade Grade 3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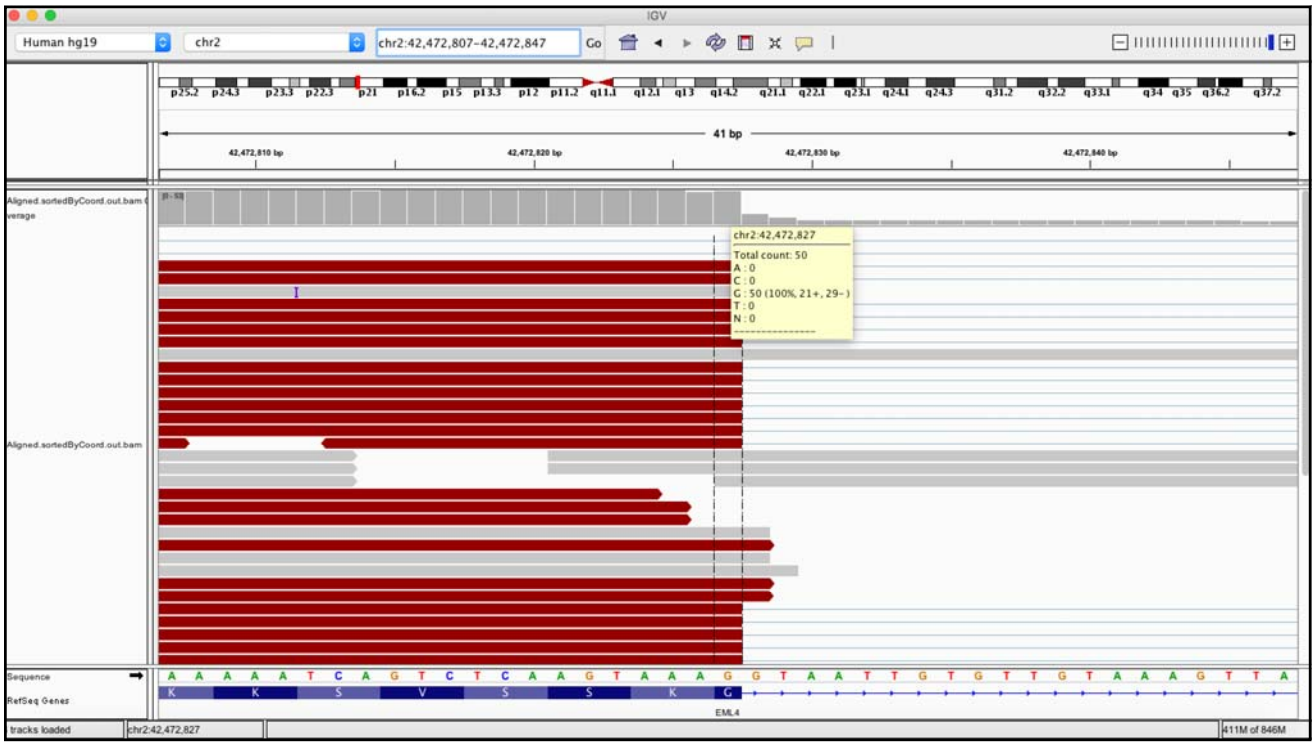
Human hg19
chr15
chr15:88,576,256-88,576,296
Go
41 bp
chr15:88,576,276
Total count: 7
A : 0
C : 7 (100%, 3+, 4-)
G : 0
T : 0
N : 0
Aligned.sortedByCoord.out.bam
Sequence
RefSeq Genes
NTRK3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C : 0
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T : 0
N : 0
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RefSeq Genes
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tracks loaded
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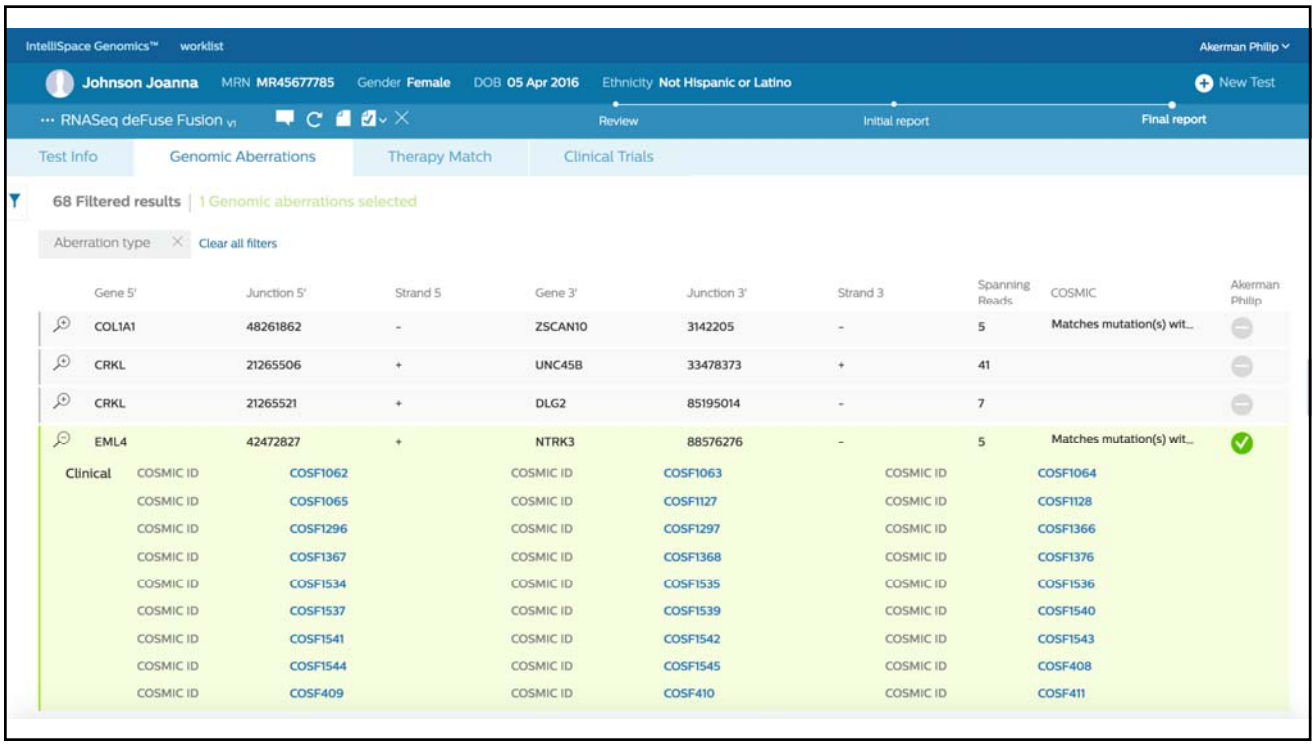
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Initial report
Final report
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
68 Filtered results | 1 Genomic aberrations selected
Aberration type
Clear all filters
Gene 5' Junction 5' Strand 5 Gene 3' Junction 3' Strand 3 Spanning Reads COSMIC Akerman Philip
COL1A1 48261862 - ZSCAN10 3142205 - 5 Matches mutation(s) wit...
CRKL 21265506 + UNC45B 33478373 + 41
CRKL 21265521 + DLG2 85195014 - 7
EML4 42472827 + NTRK3 88576276 - 5 Matches mutation(s) wit...
Clinical
COSMIC ID COSF1062 COSMIC ID COSF1063 COSMIC ID COSF1064
COSMIC ID COSF1065 COSMIC ID COSF1127 COSMIC ID COSF1128
COSMIC ID COSF1296 COSMIC ID COSF1297 COSMIC ID COSF1366
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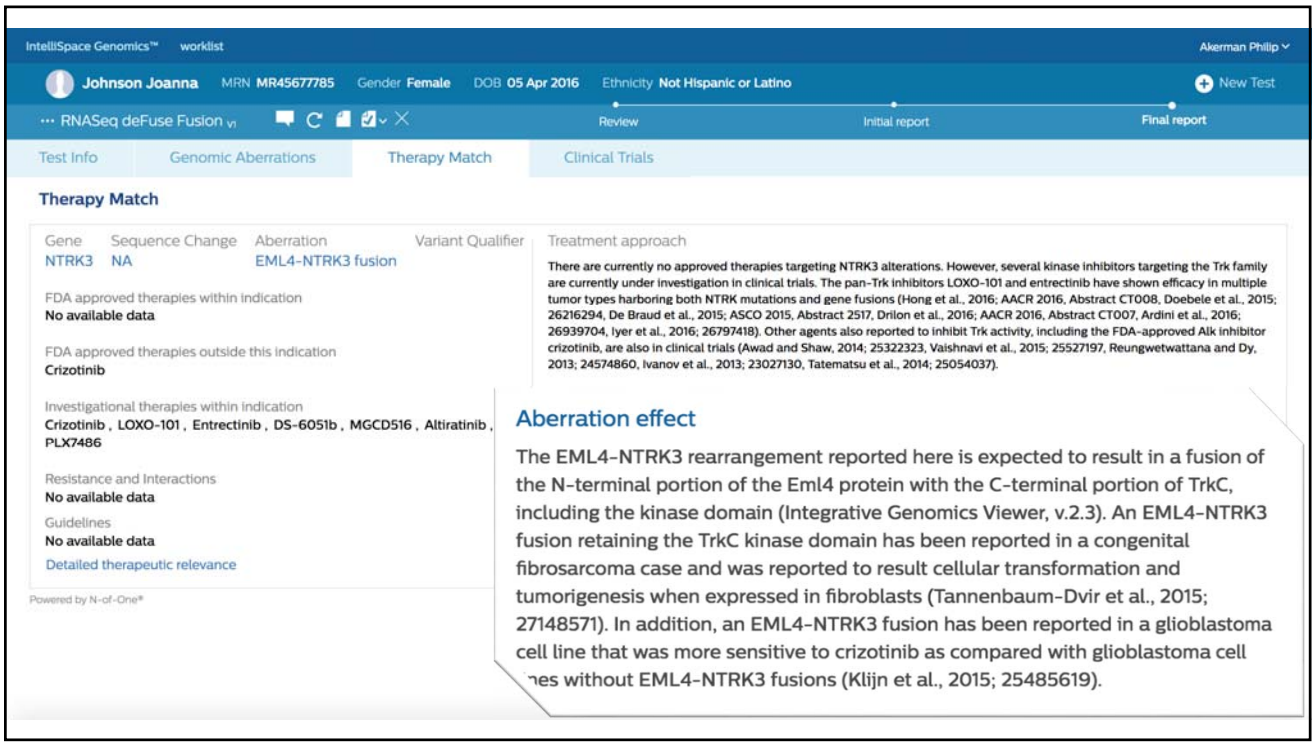
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Therapy Match
Clinical Trials
Therapy Match
Gene NTRK3
Sequence Change NA
Aberration EML4-NTRK3 fusion
Variant Qualifier
Treatment approach
There are currently no approved therapies targeting NTRK3 alterations. However, several kinase inhibitors targeting the Trk family are currently under investigation in clinical trials. The pan-Trk inhibitors LOXO-101 and entrectinib have shown efficacy in multiple tumor types harboring both NTRK mutations and gene fusions (Hong et al., 2016; AACR 2016, Abstract CT008, Doebele et al., 2015; 26216294, De Braud et al., 2015; ASCO 2015, Abstract 2517, Drilon et al., 2016; AACR 2016, Abstract CT007, Ardini et al., 2016; 26939704, Iyer et al., 2016; 26797418). Other agents also reported to inhibit Trk activity, including the FDA-approved Alk inhibitor crizotinib, are also in clinical trials (Awad and Shaw, 2014; 25322323, Vaishnavi et al., 2015; 25527197, Reungwetwattana and Dy, 2013; 24574860, Ivanov et al., 2013; 23027130, Tatematsu et al., 2014; 25054037).
FDA approved therapies within indication
No available data
FDA approved therapies outside this indication
Crizotinib
Investigational therapies within indication
Crizotinib , LOXO-101 , Entrectinib , DS-6051b , MGCD516 , Altiratinib , PLX7486
Resistance and Interactions
No available data
Guidelines
No available data
Detailed therapeutic relevance
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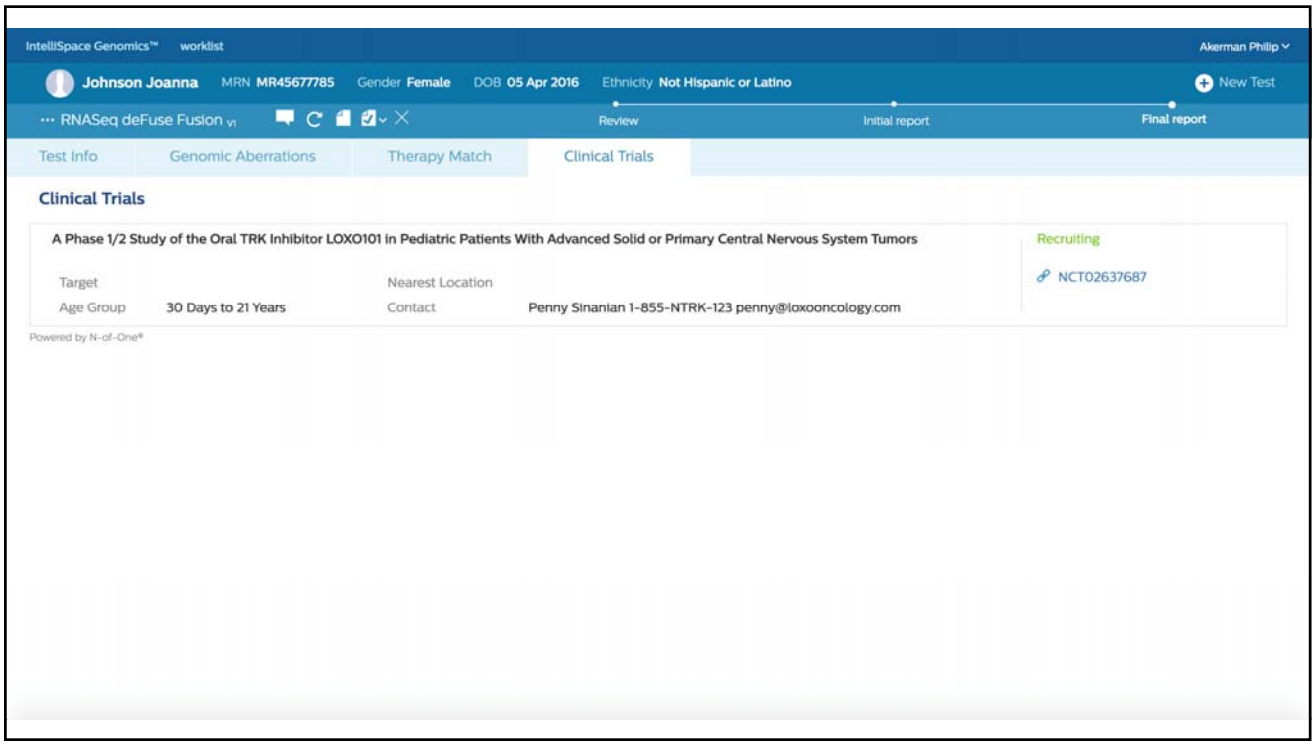
Aberration effect
The EML4-NTRK3 rearrangement reported here is expected to result in a fusion of the N-terminal portion of the Eml4 protein with the C-terminal portion of TrkC, including the kinase domain (Integrative Genomics Viewer, v.2.3). An EML4-NTRK3 fusion retaining the TrkC kinase domain has been reported in a congenital fibrosarcoma case and was reported to result cellular transformation and tumorigenesis when expressed in fibroblasts (Tannenbaum-Dvir et al., 2015; 27148571). In addition, an EML4-NTRK3 fusion has been reported in a glioblastoma cell line that was more sensitive to crizotinib as compared with glioblastoma cell lines without EML4-NTRK3 fusions (Klijn et al., 2015; 25485619).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Final report
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
Clinical Trials
A Phase 1/2 Study of the Oral TRK Inhibitor LOXO101 in Pediatric Patients With Advanced Solid or Primary Central Nervous System Tumors
Recruiting
NCT02637687
Target
Age Group 30 Days to 21 Years
Nearest Location
Contact Penny Sinanian 1-855-NTRK-123 penny@loxooncology.com
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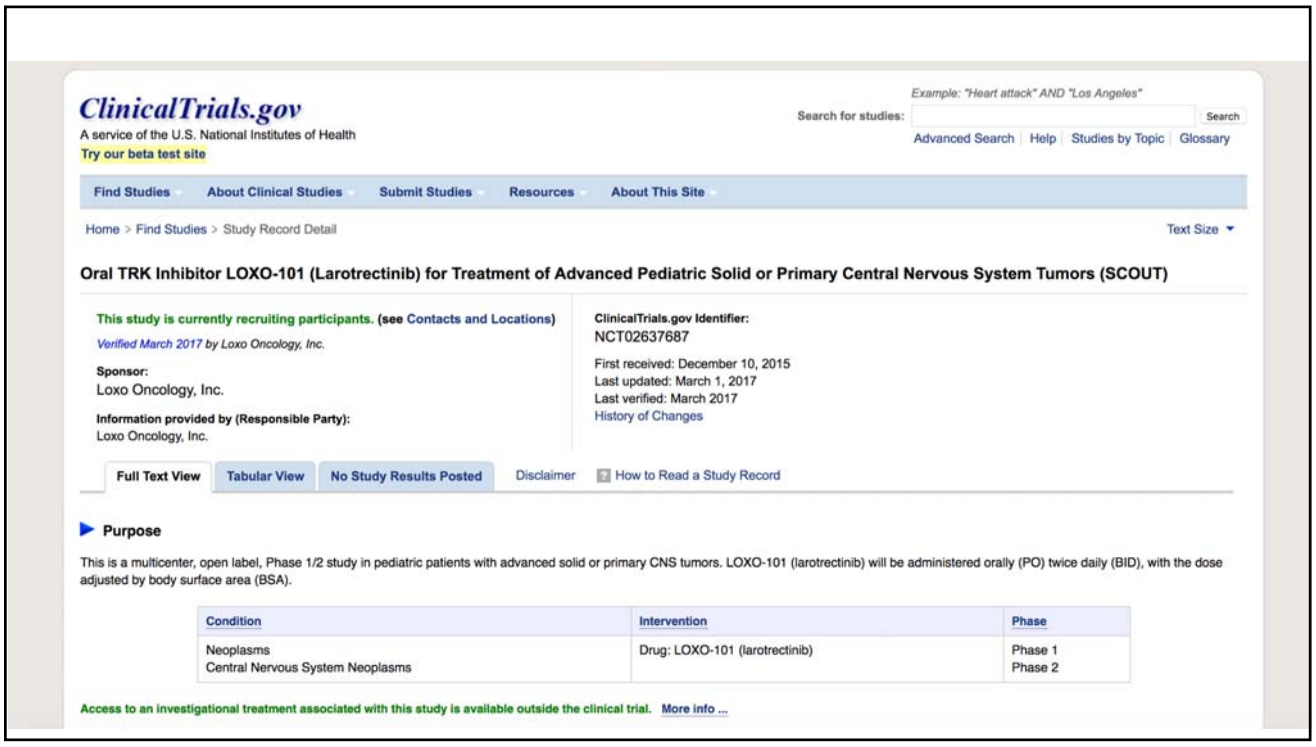

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Home > Find Studies > Study Record Detail

Text Size

Oral TRK Inhibitor LOXO-101 (Larotrectinib) for Treatment of Advanced Pediatric Solid or Primary Central Nervous System Tumors (SCOUT)

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2017 by Loxo Oncology, Inc.

Sponsor:
Loxo Oncology, Inc.

Information provided by (Responsible Party):
Loxo Oncology, Inc.

ClinicalTrials.gov Identifier:
NCT02637687

First received: December 10, 2015
Last updated: March 1, 2017
Last verified: March 2017
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

This is a multicenter, open label, Phase 1/2 study in pediatric patients with advanced solid or primary CNS tumors. LOXO-101 (larotrectinib) will be administered orally (PO) twice daily (BID), with the dose adjusted by body surface area (BSA).

Condition	Intervention	Phase
Neoplasms Central Nervous System Neoplasms	Drug: LOXO-101 (larotrectinib)	Phase 1 Phase 2

Access to an investigational treatment associated with this study is available outside the clinical trial. More info ...

Detailed Description:

This is a multicenter, open label, Phase 1/2 study in pediatric patients with advanced solid or primary CNS tumors. LOXO-101 (larotrectinib) will be administered orally (PO) twice daily (BID), with the dose adjusted by body surface area (BSA).

Dose Escalation Phase will proceed through the planned 4 dose levels, or until the MTD is reached, or until the Sponsor determines that a suitable dose has been achieved based on PK exposure..

Expansion Cohorts may be enrolled to better characterize safety and efficacy in patients with specific abnormalities in the NTRK genes or proteins.

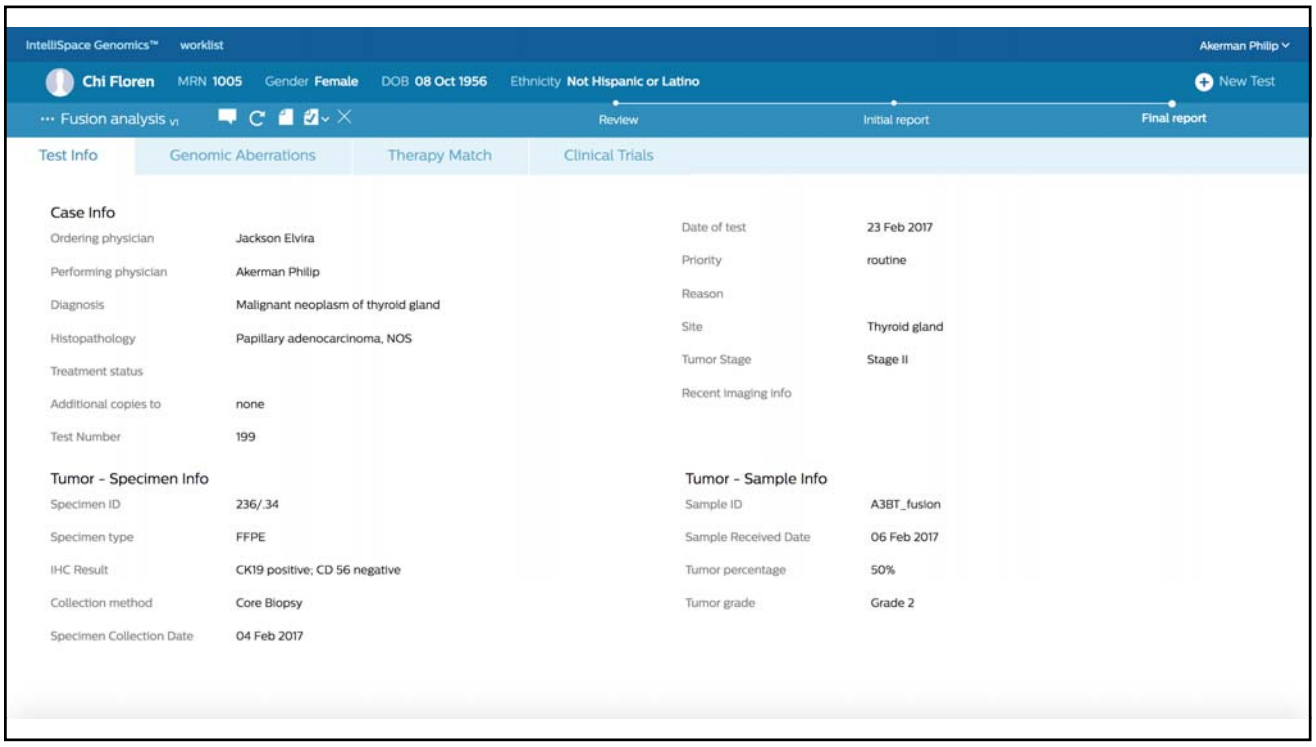
Eligibility

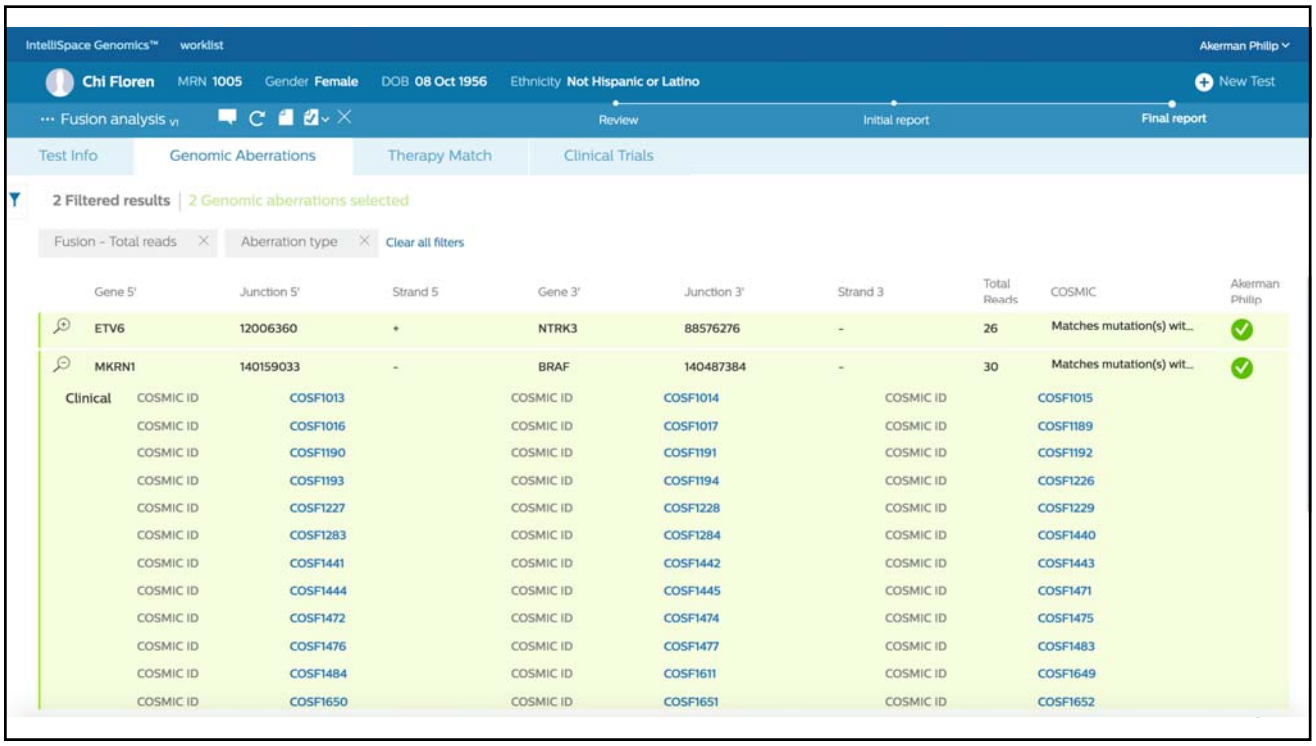
Ages Eligible for Study: 1 Month to 21 Years (Child, Adult)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Pediatric patients ≥ 1 year old on Cycle 1 Day 1 (C1D1)
- Phase 1 only: Between 1 and 21 years of age at C1D1 with a locally advanced or metastatic solid tumor or primary CNS tumor that has relapsed, progressed or was nonresponsive to available therapies and for which no standard or available systemic curative therapy, or ≥1 month old with a diagnosis malignancy and with a documented NTRK fusion that has progressed or was nonresponsive to available therapies, and for which no standard or available curative therapy exists or patients with locally advanced infantile fibrosarcoma who would require, in the opinion of the Investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection
- Phase 2 only: Ages >/= 1 month of age at C1D1 with a locally advanced or metastatic infantile fibrosarcoma, Patients with locally advanced infantile fibrosarcoma who would require, in the opinion of the Investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection enrollment or ages 1 month through 21 years of age at C1D1 with a locally advanced or metastatic solid tumor or primary CNS tumor that has relapsed, progressed or was nonresponsive to available therapies and for which no standard or available systemic curative therapy with a documented NTRK gene fusion (identified through molecular assays as routinely performed at CLIA or other similarly-certified laboratories) or (including Expansion Phase) potential patients older than 21 years of age with a tumor diagnosis with histology typical of a pediatric patient and an NTRK fusion may be considered for enrollment following discussion between the local site Investigator and the Sponsor's Medical Monitor.
- Karnofsky (those 16 years old or older) or Lansky (those younger than 16 years) performance score of at least 50
- Adequate hematologic function: Absolute neutrophil count (ANC) ≥ 1.0 109/L, platelet count ≥ 100.0 109/L and hemoglobin ≥ 8.0 g/dL (patients with bone marrow involvement will not be evaluable for hematologic DLT and can enroll with ANC ≥ 0.75 109/L, platelet count ≥ 50.0 109/L and hemoglobin ≥ 8.0 g/dL)
- Adequate hepatic function: Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 upper limit of normal (ULN) for age (patients with documented Gilbert's Disease may be enrolled with Sponsor approval).


IntelliSpace Genomics™ worklist
Akerman Philip
Chi Floren MRN 1005 Gender Female DOB 08 Oct 1956 Ethnicity Not Hispanic or Latino
New Test
Fusion analysis v1
Review
Initial report
Final report
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
Case Info
Ordering physician Jackson Elvira
Performing physician Akerman Philip
Diagnosis Malignant neoplasm of thyroid gland
Histopathology Papillary adenocarcinoma, NOS
Treatment status
Additional copies to none
Test Number 199
Date of test 23 Feb 2017
Priority routine
Reason
Site Thyroid gland
Tumor Stage Stage II
Recent Imaging Info
Tumor - Specimen Info
Specimen ID 236/_34
Specimen type FFPE
IHC Result CK19 positive; CD 56 negative
Collection method Core Biopsy
Specimen Collection Date 04 Feb 2017
Tumor - Sample Info
Sample ID A3BT_fusion
Sample Received Date 06 Feb 2017
Tumor percentage 50%
Tumor grade Grade 2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Genomic Aberrations
Therapy Match
Clinical Trials
2 Filtered results | 2 Genomic aberrations selected
Fusion - Total reads
Aberration type
Clear all filters
Gene 5' Junction 5' Strand 5 Gene 3' Junction 3' Strand 3 Total Reads COSMIC Akerman Philip
ETV6 12006360 + NTRK3 88576276 - 26 Matches mutation(s) wit...
MKRN1 140159033 - BRAF 140487384 - 30 Matches mutation(s) wit...
Clinical
COSMIC ID COSF1013 COSMIC ID COSF1014 COSMIC ID COSF1015
COSMIC ID COSF1016 COSMIC ID COSF1017 COSMIC ID COSF1189
COSMIC ID COSF1190 COSMIC ID COSF1191 COSMIC ID COSF1192
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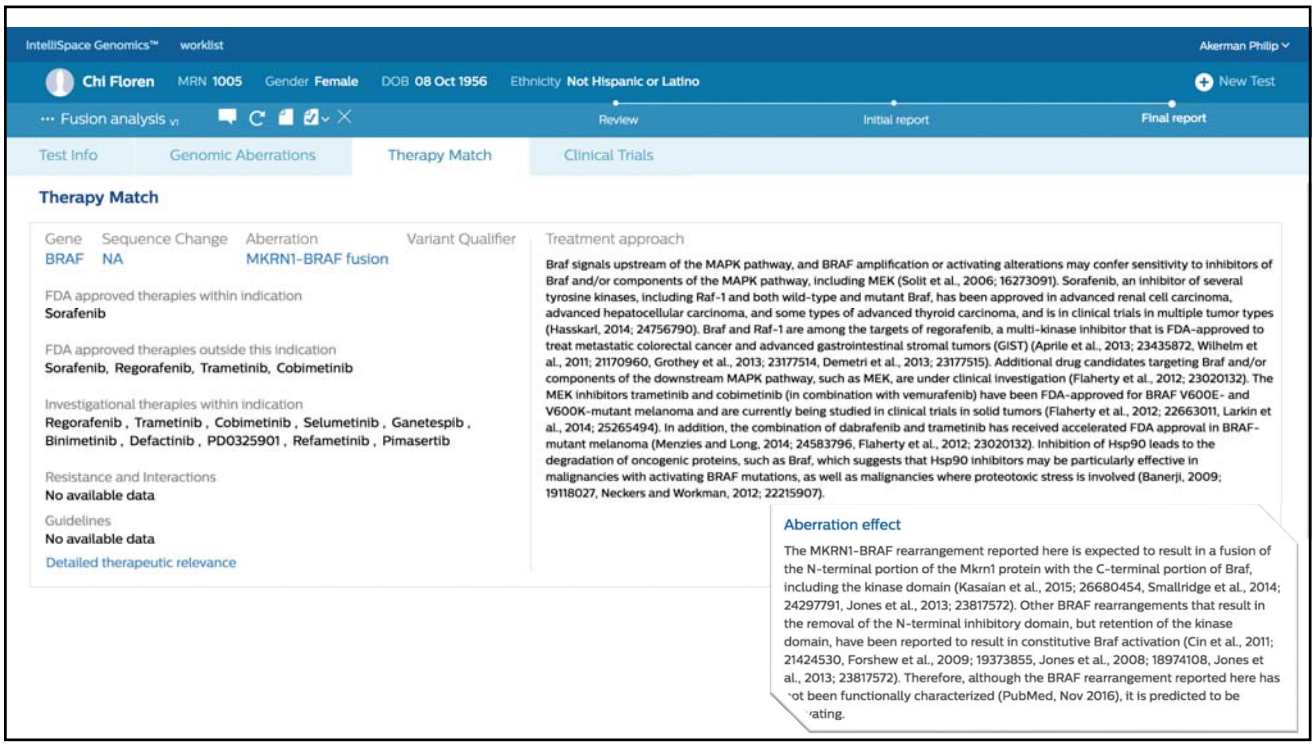
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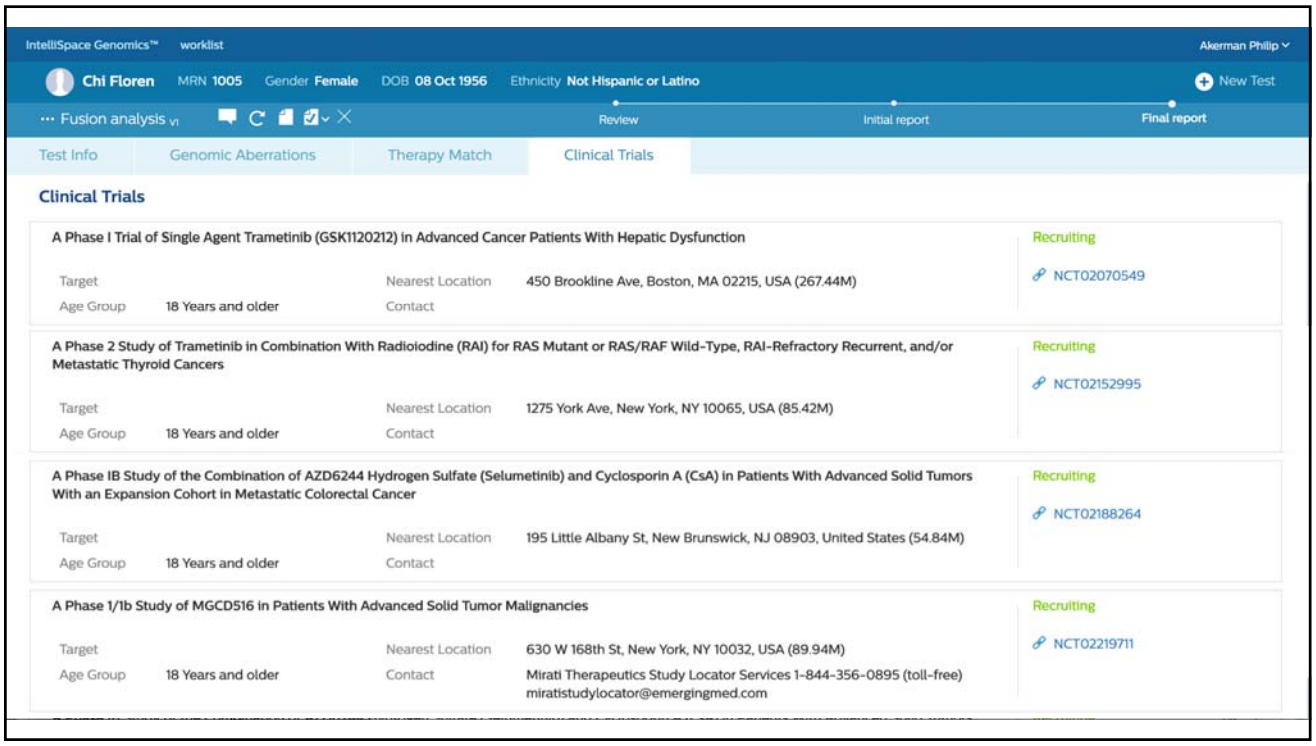
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
Therapy Match
Gene Sequence Change Aberration Variant Qualifier
BRAF NA MKRN1-BRAF fusion
FDA approved therapies within indication
Sorafenib
FDA approved therapies outside this indication
Sorafenib, Regorafenib, Trametinib, Cobimetinib
Investigational therapies within indication
Regorafenib , Trametinib , Cobimetinib , Selumetinib , Ganetespib , Binimetinib , Defactinib , PD0325901 , Refametinib , Pimasertib
Resistance and Interactions
No available data
Guidelines
No available data
Detailed therapeutic relevance
Treatment approach
Braf signals upstream of the MAPK pathway, and BRAF amplification or activating alterations may confer sensitivity to inhibitors of Braf and/or components of the MAPK pathway, including MEK (Solit et al., 2006; 16273091). Sorafenib, an inhibitor of several tyrosine kinases, including Raf-1 and both wild-type and mutant Braf, has been approved in advanced renal cell carcinoma, advanced hepatocellular carcinoma, and some types of advanced thyroid carcinoma, and is in clinical trials in multiple tumor types (Hasskarl, 2014; 24756790). Braf and Raf-1 are among the targets of regorafenib, a multi-kinase inhibitor that is FDA-approved to treat metastatic colorectal cancer and advanced gastrointestinal stromal tumors (GIST) (Aprile et al., 2013; 23435872, Wilhelm et al., 2011; 21170960, Grothey et al., 2013; 23177514, Demetri et al., 2013; 23177515). Additional drug candidates targeting Braf and/or components of the downstream MAPK pathway, such as MEK, are under clinical investigation (Flaherty et al., 2012; 23020132). The MEK inhibitors trametinib and cobimetinib (in combination with vemurafenib) have been FDA-approved for BRAF V600E- and V600K-mutant melanoma and are currently being studied in clinical trials in solid tumors (Flaherty et al., 2012; 22663011, Larkin et al., 2014; 25265494). In addition, the combination of dabrafenib and trametinib has received accelerated FDA approval in BRAF-mutant melanoma (Menzies and Long, 2014; 24583796, Flaherty et al., 2012; 23020132). Inhibition of Hsp90 leads to the degradation of oncogenic proteins, such as Braf, which suggests that Hsp90 inhibitors may be particularly effective in malignancies with activating BRAF mutations, as well as malignancies where proteotoxic stress is involved (Banerji, 2009; 19118027, Neckers and Workman, 2012; 22215907).
Aberration effect
The MKRN1-BRAF rearrangement reported here is expected to result in a fusion of the N-terminal portion of the Mkrn1 protein with the C-terminal portion of Braf, including the kinase domain (Kasaian et al., 2015; 26680454, Smallridge et al., 2014; 24297791, Jones et al., 2013; 23817572). Other BRAF rearrangements that result in the removal of the N-terminal inhibitory domain, but retention of the kinase domain, have been reported to result in constitutive Braf activation (Cin et al., 2011; 21424530, Forshew et al., 2009; 19373855, Jones et al., 2008; 18974108, Jones et al., 2013; 23817572). Therefore, although the BRAF rearrangement reported here has ot been functionally characterized (PubMed, Nov 2016), it is predicted to be ating.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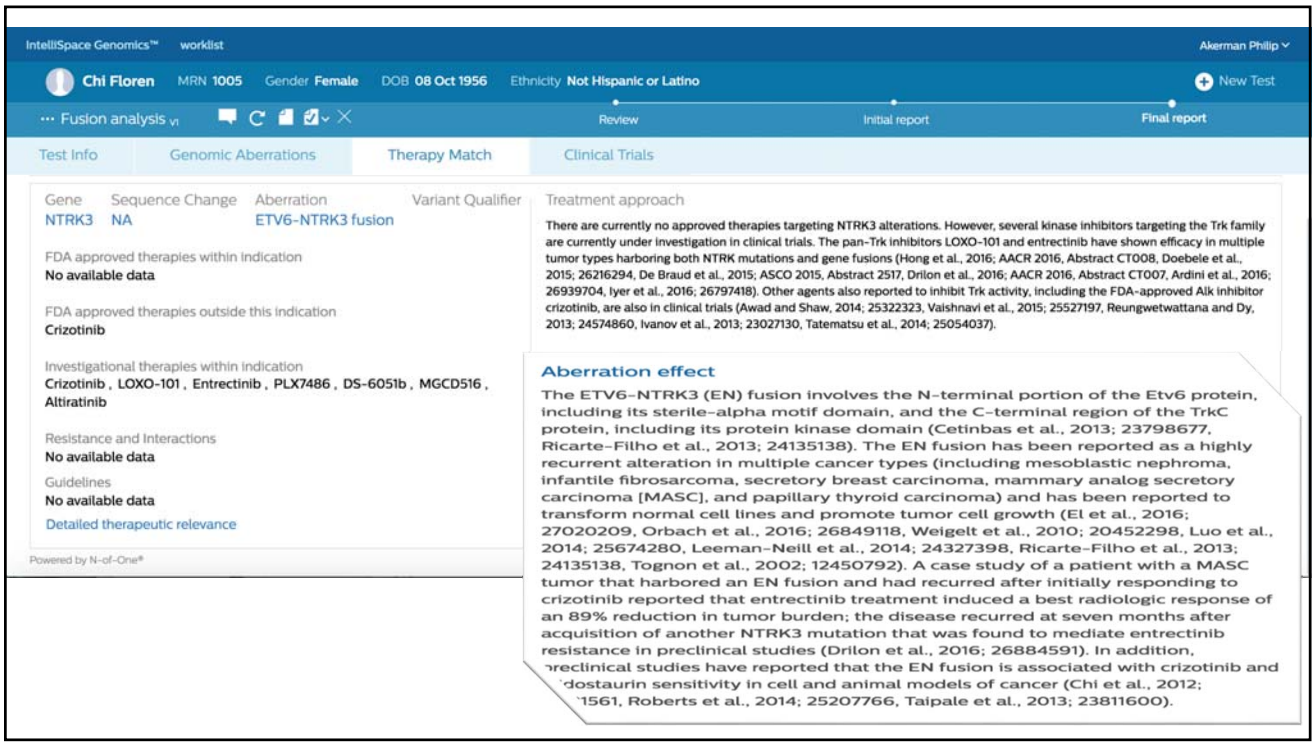
Therapy Match
Clinical Trials
Clinical Trials
A Phase I Trial of Single Agent Trametinib (GSK1120212) in Advanced Cancer Patients With Hepatic Dysfunction
Recruiting
NCT02070549
Target
Age Group 18 Years and older
Nearest Location 450 Brookline Ave, Boston, MA 02215, USA (267.44M)
Contact
A Phase 2 Study of Trametinib in Combination With Radioiodine (RAI) for RAS Mutant or RAS/RAF Wild-Type, RAI-Refractory Recurrent, and/or Metastatic Thyroid Cancers
Recruiting
NCT02152995
Target
Age Group 18 Years and older
Nearest Location 1275 York Ave, New York, NY 10065, USA (85.42M)
Contact
A Phase IB Study of the Combination of AZD6244 Hydrogen Sulfate (Selumetinib) and Cyclosporin A (CsA) in Patients With Advanced Solid Tumors With an Expansion Cohort in Metastatic Colorectal Cancer
Recruiting
NCT02188264
Target
Age Group 18 Years and older
Nearest Location 195 Little Albany St, New Brunswick, NJ 08903, United States (54.84M)
Contact
A Phase 1/1b Study of MGCD516 in Patients With Advanced Solid Tumor Malignancies
Recruiting
NCT02219711
Target
Age Group 18 Years and older
Nearest Location 630 W 168th St, New York, NY 10032, USA (89.94M)
Contact Mirati Therapeutics Study Locator Services 1-844-356-0895 (toll-free) miratistudylocator@emergingmed.com


IntelliSpace Genomics™ worklist
Akerman Philip
Chi Floren MRN 1005 Gender Female DOB 08 Oct 1956 Ethnicity Not Hispanic or Latino
New Test
Fusion analysis v1
Review
Initial report
Final report
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
Gene
NTRK3
Sequence Change
NA
Aberration
ETV6-NTRK3 fusion
Variant Qualifier
Treatment approach
There are currently no approved therapies targeting NTRK3 alterations. However, several kinase inhibitors targeting the Trk family are currently under investigation in clinical trials. The pan-Trk inhibitors LOXO-101 and entrectinib have shown efficacy in multiple tumor types harboring both NTRK mutations and gene fusions (Hong et al., 2016; AACR 2016, Abstract CT008, Doebele et al., 2015; 26216294, De Braud et al., 2015; ASCO 2015, Abstract 2517, Drilon et al., 2016; AACR 2016, Abstract CT007, Ardini et al., 2016; 26939704, Iyer et al., 2016; 26797418). Other agents also reported to inhibit Trk activity, including the FDA-approved Alk inhibitor crizotinib, are also in clinical trials (Awad and Shaw, 2014; 25322323, Vaishnavi et al., 2015; 25527197, Reungwetwattana and Dy, 2013; 24574860, Ivanov et al., 2013; 23027130, Tatematsu et al., 2014; 25054037).
FDA approved therapies within indication
No available data
FDA approved therapies outside this indication
Crizotinib
Investigational therapies within indication
Crizotinib , LOXO-101 , Entrectinib , PLX7486 , DS-6051b , MGCD516 , Altiratinib
Resistance and Interactions
No available data
Guidelines
No available data
Detailed therapeutic relevance
Aberration effect
The ETV6-NTRK3 (EN) fusion involves the N-terminal portion of the Etv6 protein, including its sterile-alpha motif domain, and the C-terminal region of the TrkC protein, including its protein kinase domain (Cetinbas et al., 2013; 23798677, Ricarte-Filho et al., 2013; 24135138). The EN fusion has been reported as a highly recurrent alteration in multiple cancer types (including mesoblastic nephroma, infantile fibrosarcoma, secretory breast carcinoma, mammary analog secretory carcinoma [MASC], and papillary thyroid carcinoma) and has been reported to transform normal cell lines and promote tumor cell growth (El et al., 2016; 27020209, Orbach et al., 2016; 26849118, Weigelt et al., 2010; 20452298, Luo et al., 2014; 25674280, Leeman-Neill et al., 2014; 24327398, Ricarte-Filho et al., 2013; 24135138, Tognon et al., 2002; 12450792). A case study of a patient with a MASC tumor that harbored an EN fusion and had recurred after initially responding to crizotinib reported that entrectinib treatment induced a best radiologic response of an 89% reduction in tumor burden; the disease recurred at seven months after acquisition of another NTRK3 mutation that was found to mediate entrectinib resistance in preclinical studies (Drilon et al., 2016; 26884591). In addition, preclinical studies have reported that the EN fusion is associated with crizotinib and dostaurin sensitivity in cell and animal models of cancer (Chi et al., 2012; 1561, Roberts et al., 2014; 25207766, Taipale et al., 2013; 23811600).
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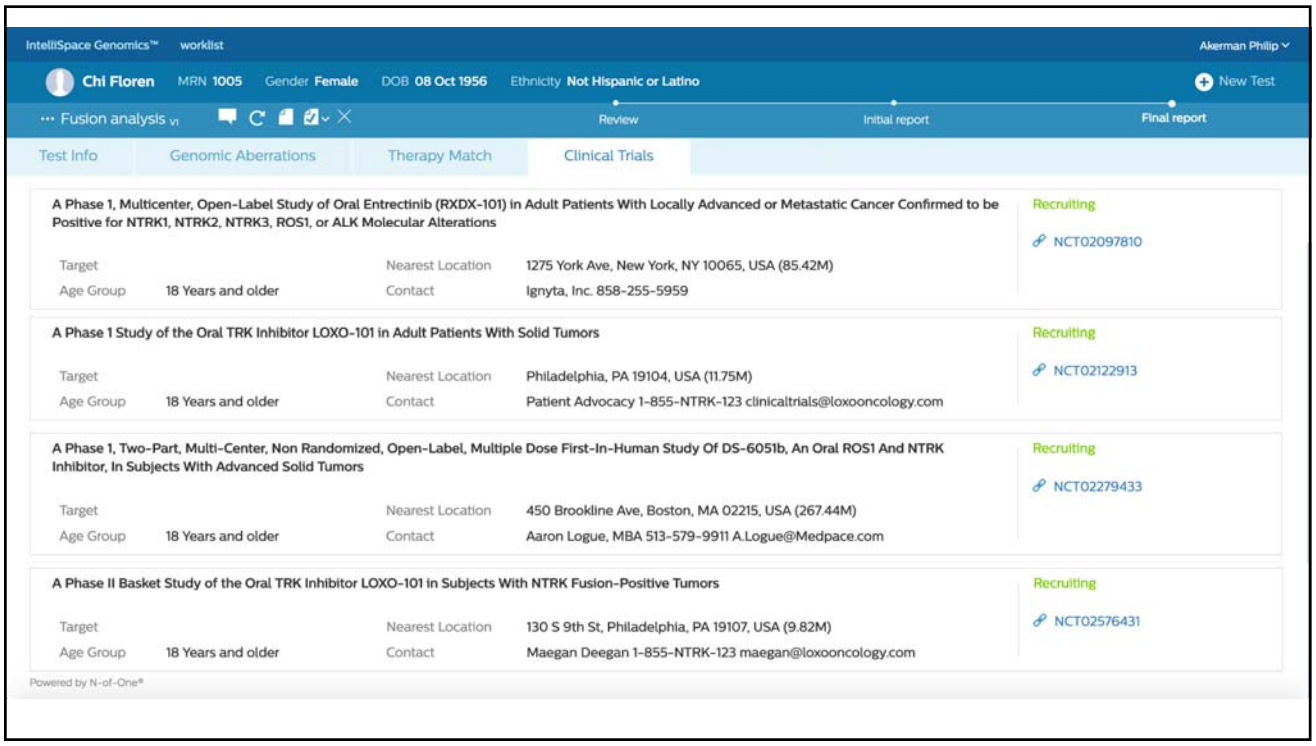
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Genomic Aberrations
Therapy Match
Clinical Trials
A Phase 1, Multicenter, Open-Label Study of Oral Entrectinib (RXDX-101) in Adult Patients With Locally Advanced or Metastatic Cancer Confirmed to be Positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK Molecular Alterations
Recruiting
NCT02097810
Target
Age Group 18 Years and older
Nearest Location 1275 York Ave, New York, NY 10065, USA (85.42M)
Contact Ignyta, Inc. 858-255-5959
A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients With Solid Tumors
Recruiting
NCT02122913
Target
Age Group 18 Years and older
Nearest Location Philadelphia, PA 19104, USA (11.75M)
Contact Patient Advocacy 1-855-NTRK-123 clinicaltrials@loxooncology.com
A Phase 1, Two-Part, Multi-Center, Non Randomized, Open-Label, Multiple Dose First-In-Human Study Of DS-6051b, An Oral ROS1 And NTRK Inhibitor, In Subjects With Advanced Solid Tumors
Recruiting
NCT02279433
Target
Age Group 18 Years and older
Nearest Location 450 Brookline Ave, Boston, MA 02215, USA (267.44M)
Contact Aaron Logue, MBA 513-579-9911 A.Logue@Medpace.com
A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-Positive Tumors
Recruiting
NCT02576431
Target
Age Group 18 Years and older
Nearest Location 130 S 9th St, Philadelphia, PA 19107, USA (9.82M)
Contact Maegan Deegan 1-855-NTRK-123 maegan@loxooncology.com
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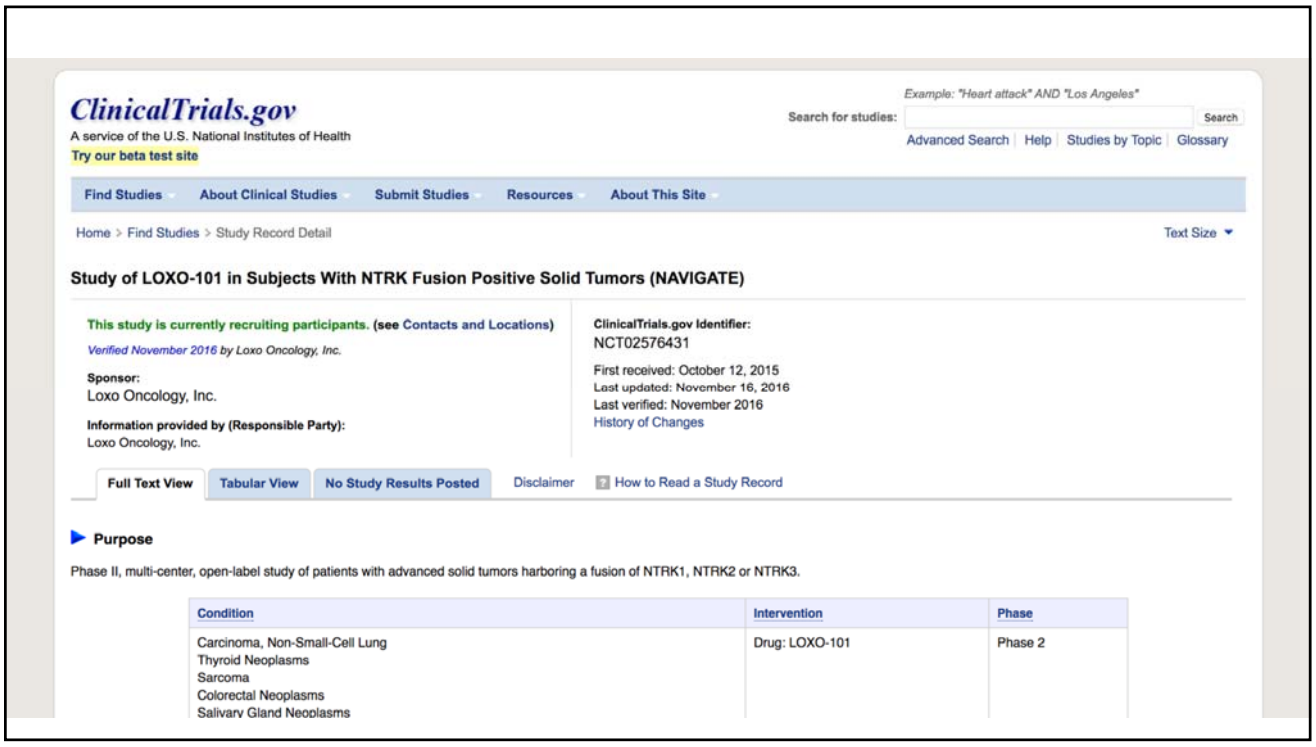

ClinicalTrials.gov

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Home > Find Studies > Study Record Detail

Text Size

Study of LOXO-101 in Subjects With NTRK Fusion Positive Solid Tumors (NAVIGATE)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2016 by Loxo Oncology, Inc.

Sponsor:
Loxo Oncology, Inc.

Information provided by (Responsible Party):
Loxo Oncology, Inc.

ClinicalTrials.gov Identifier:
NCT02576431

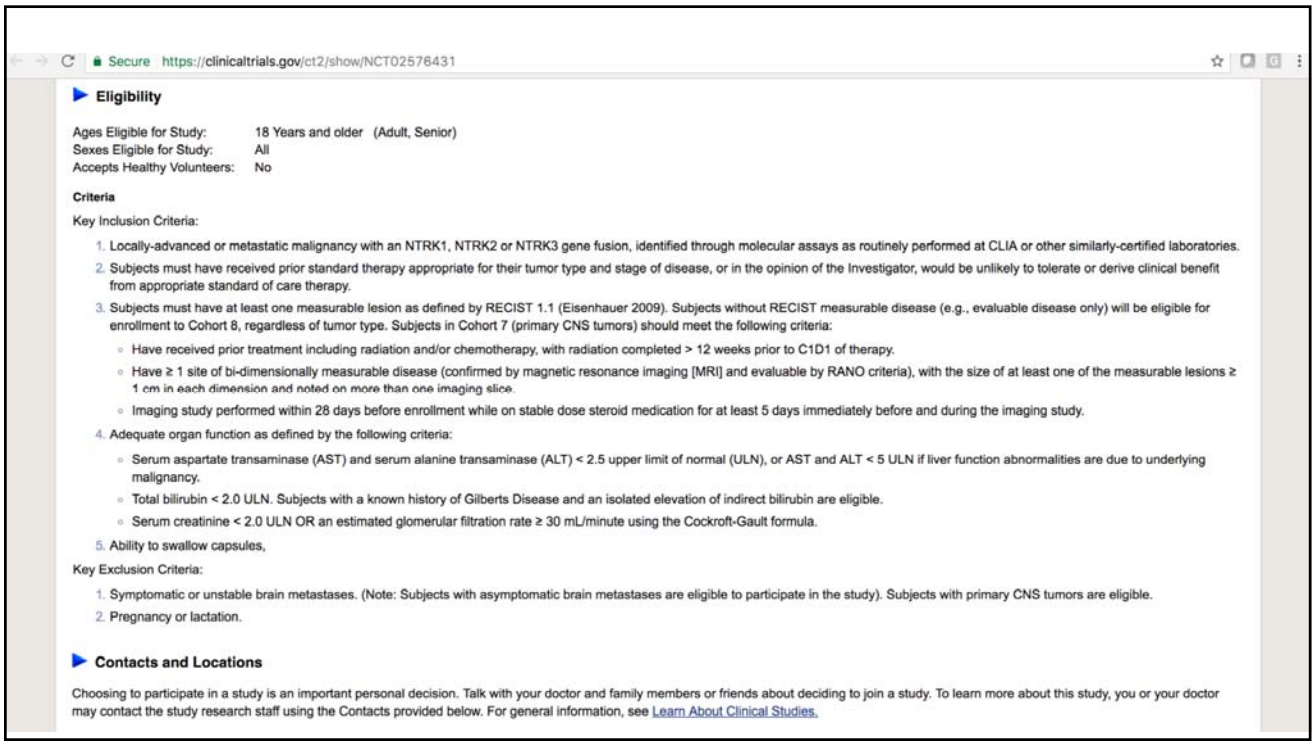
First received: October 12, 2015
Last updated: November 16, 2016
Last verified: November 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

Phase II, multi-center, open-label study of patients with advanced solid tumors harboring a fusion of NTRK1, NTRK2 or NTRK3.

Condition	Intervention	Phase
Carcinoma, Non-Small-Cell Lung Thyroid Neoplasms Sarcoma Colorectal Neoplasms Salivary Gland Neoplasms	Drug: LOXO-101	Phase 2



Secure https://clinicaltrials.gov/ct2/show/NCT02576431

Eligibility

Ages Eligible for Study: 18 Years and older (Adult, Senior)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria

Key Inclusion Criteria:

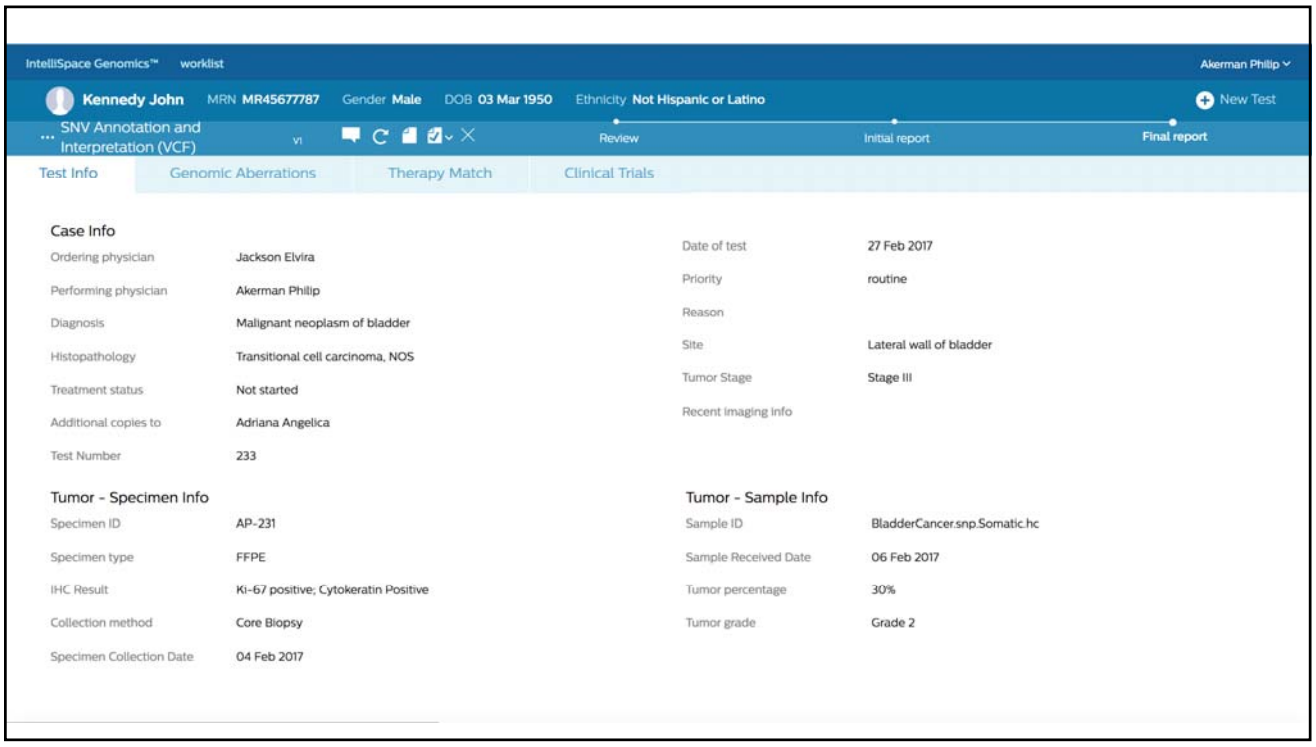
1. Locally-advanced or metastatic malignancy with an NTRK1, NTRK2 or NTRK3 gene fusion, identified through molecular assays as routinely performed at CLIA or other similarly-certified laboratories.
2. Subjects must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy.
3. Subjects must have at least one measurable lesion as defined by RECIST 1.1 (Eisenhauer 2009). Subjects without RECIST measurable disease (e.g., evaluable disease only) will be eligible for enrollment to Cohort 8, regardless of tumor type. Subjects in Cohort 7 (primary CNS tumors) should meet the following criteria:
   - Have received prior treatment including radiation and/or chemotherapy, with radiation completed > 12 weeks prior to C1D1 of therapy.
   - Have ≥ 1 site of bi-dimensionally measurable disease (confirmed by magnetic resonance imaging [MRI] and evaluable by RANO criteria), with the size of at least one of the measurable lesions ≥ 1 cm in each dimension and noted on more than one imaging slice.
   - Imaging study performed within 28 days before enrollment while on stable dose steroid medication for at least 5 days immediately before and during the imaging study.
4. Adequate organ function as defined by the following criteria:
   - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) < 2.5 upper limit of normal (ULN), or AST and ALT < 5 ULN if liver function abnormalities are due to underlying malignancy.
   - Total bilirubin < 2.0 ULN. Subjects with a known history of Gilberts Disease and an isolated elevation of indirect bilirubin are eligible.
   - Serum creatinine < 2.0 ULN OR an estimated glomerular filtration rate ≥ 30 mL/minute using the Cockroft-Gault formula.
5. Ability to swallow capsules,

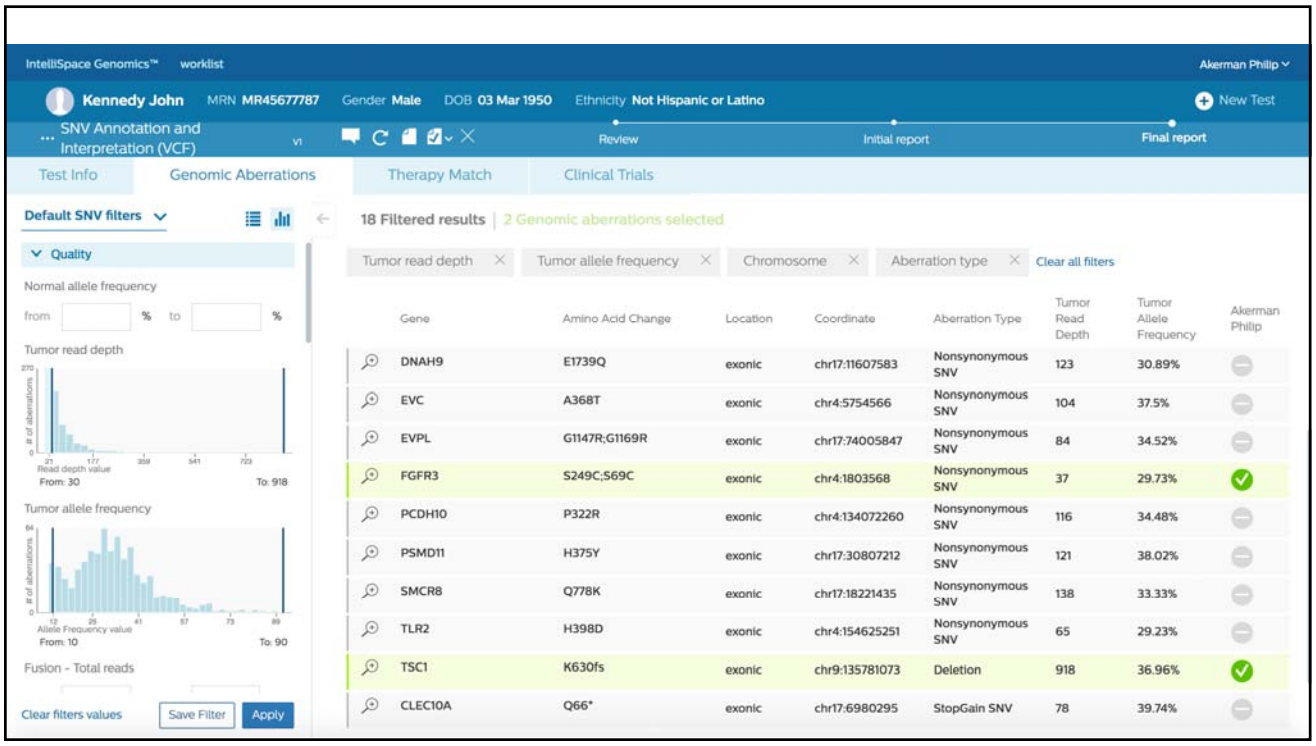
Key Exclusion Criteria:

1. Symptomatic or unstable brain metastases. (Note: Subjects with asymptomatic brain metastases are eligible to participate in the study). Subjects with primary CNS tumors are eligible.
2. Pregnancy or lactation.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.


IntelliSpace Genomics™ worklist
Akerman Philip
Kennedy John MRN MR45677787 Gender Male DOB 03 Mar 1950 Ethnicity Not Hispanic or Latino
New Test
SNV Annotation and Interpretation (VCF) v1
Review
Initial report
Final report
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
Case Info
Ordering physician Jackson Elvira
Performing physician Akerman Philip
Diagnosis Malignant neoplasm of bladder
Histopathology Transitional cell carcinoma, NOS
Treatment status Not started
Additional copies to Adriana Angelica
Test Number 233
Date of test 27 Feb 2017
Priority routine
Reason
Site Lateral wall of bladder
Tumor Stage Stage III
Recent imaging info
Tumor - Specimen Info
Specimen ID AP-231
Specimen type FFPE
IHC Result Ki-67 positive; Cytokeratin Positive
Collection method Core Biopsy
Specimen Collection Date 04 Feb 2017
Tumor - Sample Info
Sample ID BladderCancer.snp.Somatic.hc
Sample Received Date 06 Feb 2017
Tumor percentage 30%
Tumor grade Grade 2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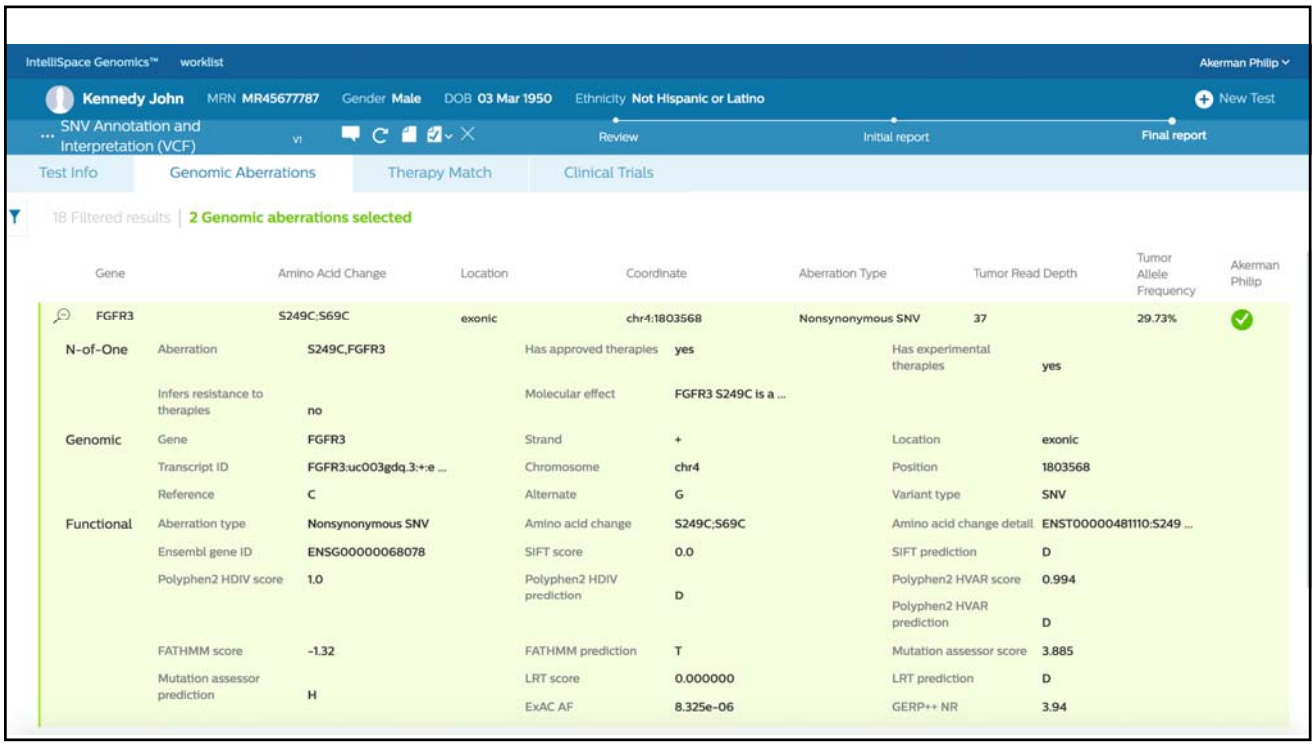
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
Default SNV filters
Quality
Normal allele frequency
from % to %
Tumor read depth
Read depth value
From: 30 To: 918
Tumor allele frequency
Allele Frequency value
From: 10 To: 90
Fusion - Total reads
Clear filters values
Save Filter
Apply
18 Filtered results | 2 Genomic aberrations selected
Tumor read depth
Tumor allele frequency
Chromosome
Aberration type
Clear all filters
Gene Amino Acid Change Location Coordinate Aberration Type Tumor Read Depth Tumor Allele Frequency Akerman Philip
DNAH9 E1739Q exonic chr17:11607583 Nonsynonymous SNV 123 30.89%
EVC A368T exonic chr4:5754566 Nonsynonymous SNV 104 37.5%
EVPL G1147R;G1169R exonic chr17:74005847 Nonsynonymous SNV 84 34.52%
FGFR3 S249C;S69C exonic chr4:1803568 Nonsynonymous SNV 37 29.73%
PCDH10 P322R exonic chr4:134072260 Nonsynonymous SNV 116 34.48%
PSMD11 H375Y exonic chr17:30807212 Nonsynonymous SNV 121 38.02%
SMCR8 Q778K exonic chr17:18221435 Nonsynonymous SNV 138 33.33%
TLR2 H398D exonic chr4:154625251 Nonsynonymous SNV 65 29.23%
TSC1 K630fs exonic chr9:135781073 Deletion 918 36.96%
CLEC10A Q66* exonic chr17:6980295 StopGain SNV 78 39.74%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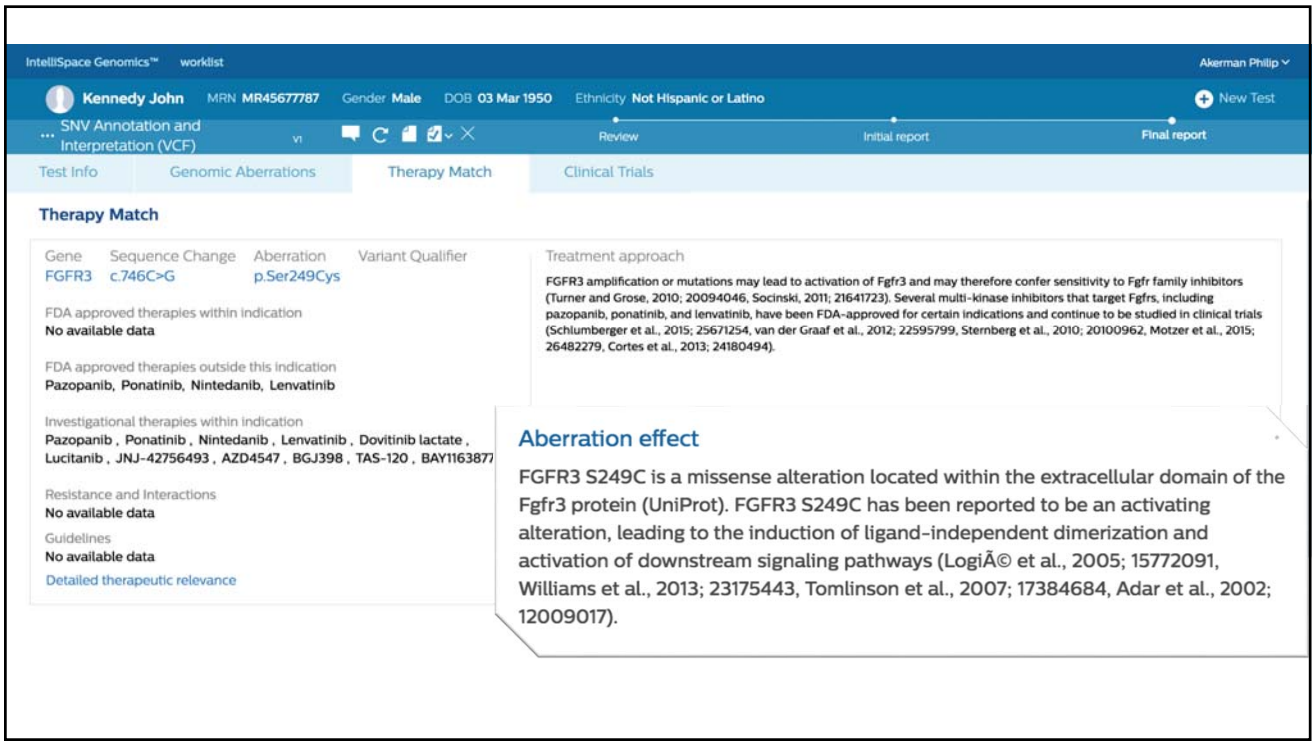
Initial report
Final report
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
18 Filtered results | 2 Genomic aberrations selected
Gene
Amino Acid Change
Location
Coordinate
Aberration Type
Tumor Read Depth
Tumor Allele Frequency
Akerman Philip
FGFR3
S249C;S69C
exonic
chr4:1803568
Nonsynonymous SNV
37
29.73%
N-of-One
Aberration S249C,FGFR3
Has approved therapies yes
Has experimental therapies yes
Infers resistance to therapies no
Molecular effect FGFR3 S249C is a ...
Genomic
Gene FGFR3
Strand +
Location exonic
Transcript ID FGFR3:uc003gdq.3:+:e ...
Chromosome chr4
Position 1803568
Reference C
Alternate G
Variant type SNV
Functional
Aberration type Nonsynonymous SNV
Amino acid change S249C;S69C
Amino acid change detail ENST00000481110:S249 ...
Ensembl gene ID ENSG00000068078
SIFT score 0.0
SIFT prediction D
Polyphen2 HDIV score 1.0
Polyphen2 HDIV prediction D
Polyphen2 HVAR score 0.994
Polyphen2 HVAR prediction D
FATHMM score -1.32
FATHMM prediction T
Mutation assessor score 3.885
Mutation assessor prediction H
LRT score 0.000000
LRT prediction D
ExAC AF 8.325e-06
GERP++ NR 3.94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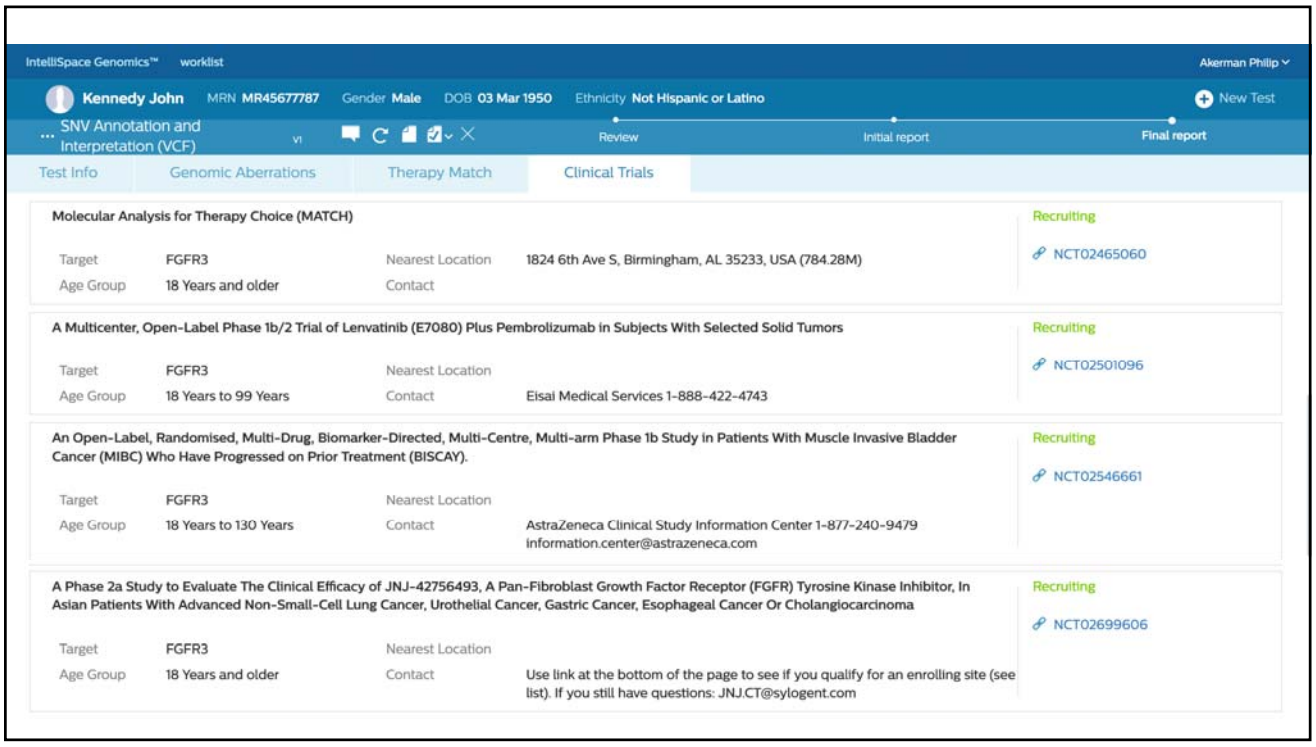
Initial report
Final report
Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
Therapy Match
Gene Sequence Change Aberration Variant Qualifier
FGFR3 c.746C>G p.Ser249Cys
FDA approved therapies within indication
No available data
FDA approved therapies outside this indication
Pazopanib, Ponatinib, Nintedanib, Lenvatinib
Investigational therapies within indication
Pazopanib , Ponatinib , Nintedanib , Lenvatinib , Dovitinib lactate , Lucitanib , JNJ-42756493 , AZD4547 , BGJ398 , TAS-120 , BAY1163877
Resistance and Interactions
No available data
Guidelines
No available data
Detailed therapeutic relevance
Treatment approach
FGFR3 amplification or mutations may lead to activation of Fgfr3 and may therefore confer sensitivity to Fgfr family inhibitors (Turner and Grose, 2010; 20094046, Socinski, 2011; 21641723). Several multi-kinase inhibitors that target Fgfrs, including pazopanib, ponatinib, and lenvatinib, have been FDA-approved for certain indications and continue to be studied in clinical trials (Schlumberger et al., 2015; 25671254, van der Graaf et al., 2012; 22595799, Sternberg et al., 2010; 20100962, Motzer et al., 2015; 26482279, Cortes et al., 2013; 24180494).
Aberration effect
FGFR3 S249C is a missense alteration located within the extracellular domain of the Fgfr3 protein (UniProt). FGFR3 S249C has been reported to be an activating alteration, leading to the induction of ligand-independent dimerization and activation of downstream signaling pathways (LogiÃ© et al., 2005; 15772091, Williams et al., 2013; 23175443, Tomlinson et al., 2007; 17384684, Adar et al., 2002; 12009017).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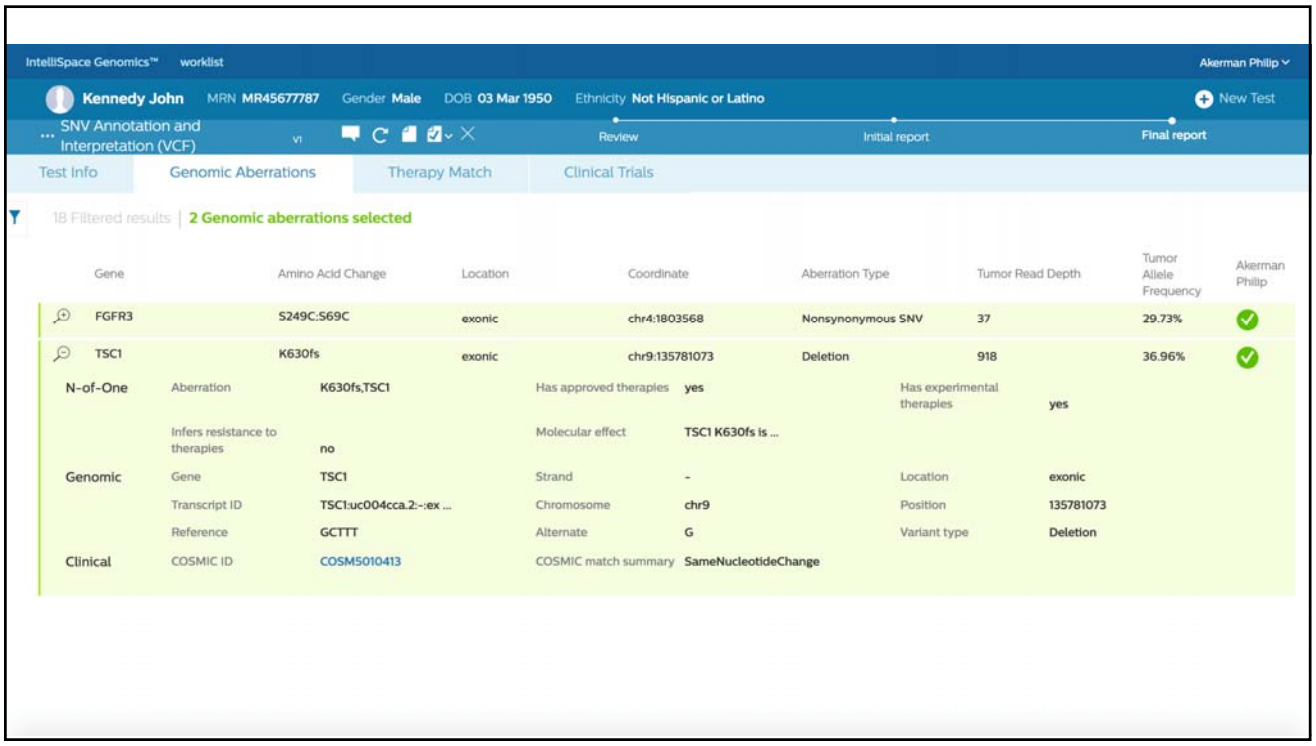
Genomic Aberrations
Therapy Match
Clinical Trials
Molecular Analysis for Therapy Choice (MATCH)
Recruiting
Target FGFR3
Age Group 18 Years and older
Nearest Location 1824 6th Ave S, Birmingham, AL 35233, USA (784.28M)
Contact
NCT02465060
A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors
Recruiting
Target FGFR3
Age Group 18 Years to 99 Years
Nearest Location
Contact Eisai Medical Services 1-888-422-4743
NCT02501096
An Open-Label, Randomised, Multi-Drug, Biomarker-Directed, Multi-Centre, Multi-arm Phase 1b Study in Patients With Muscle Invasive Bladder Cancer (MIBC) Who Have Progressed on Prior Treatment (BISCAY).
Recruiting
Target FGFR3
Age Group 18 Years to 130 Years
Nearest Location
Contact AstraZeneca Clinical Study Information Center 1-877-240-9479 information.center@astrazeneca.com
NCT02546661
A Phase 2a Study to Evaluate The Clinical Efficacy of JNJ-42756493, A Pan-Fibroblast Growth Factor Receptor (FGFR) Tyrosine Kinase Inhibitor, In Asian Patients With Advanced Non-Small-Cell Lung Cancer, Urothelial Cancer, Gastric Cancer, Esophageal Cancer Or Cholangiocarcinoma
Recruiting
Target FGFR3
Age Group 18 Years and older
Nearest Location
Contact Use link at the bottom of the page to see if you qualify for an enrolling site (see list). If you still have questions: JNJ.CT@sylogent.com
NCT02699606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Clinical Trials
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Gene
Amino Acid Change
Location
Coordinate
Aberration Type
Tumor Read Depth
Tumor Allele Frequency
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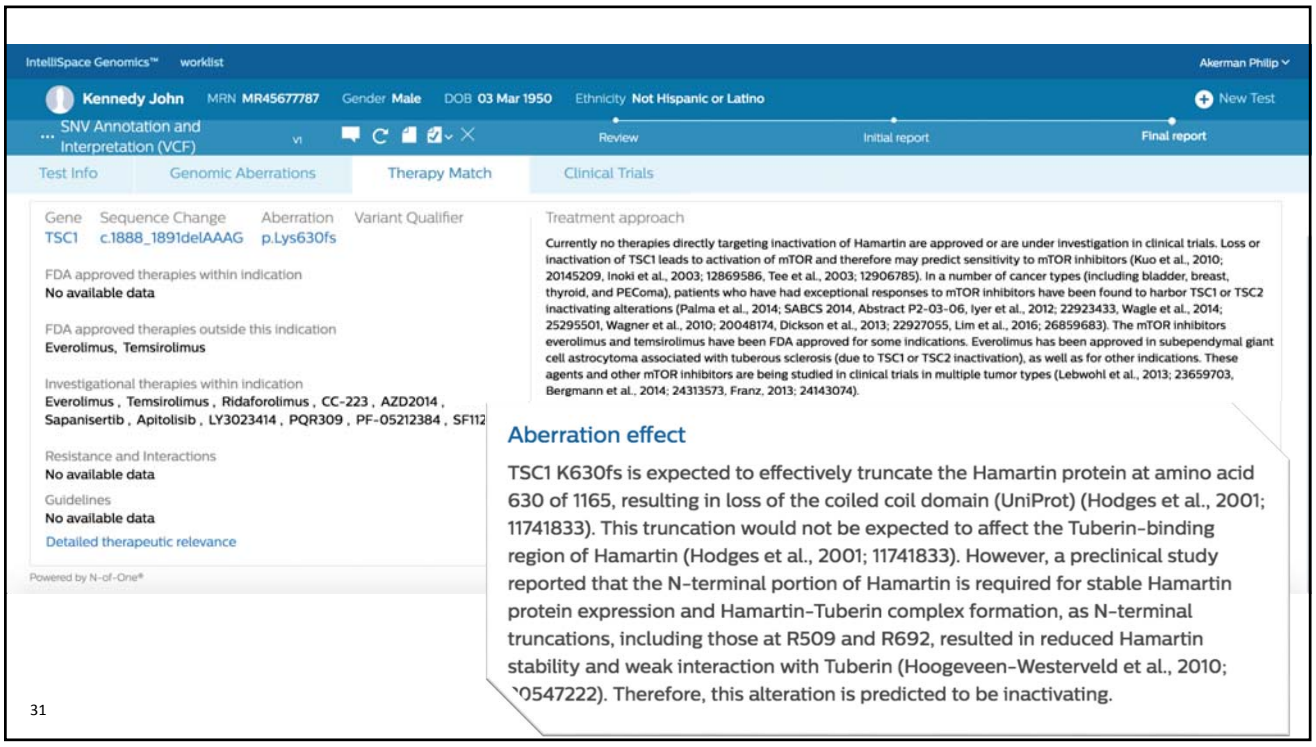
TSC1 K630fs exonic chr9:135781073 Deletion 918 36.96%
N-of-One
Aberration K630fs,TSC1
Has approved therapies yes
Has experimental therapies yes
Infers resistance to therapies no
Molecular effect TSC1 K630fs is ...
Genomic
Gene TSC1
Strand -
Location exonic
Transcript ID TSC1:uc004cca.2:-:ex ...
Chromosome chr9
Position 135781073
Reference GCTTT
Alternate G
Variant type Deletion
Clinical
COSMIC ID COSM5010413
COSMIC match summary SameNucleotideChange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Test Info
Genomic Aberrations
Therapy Match
Clinical Trials
Gene Sequence Change Aberration Variant Qualifier
TSC1 c.1888_1891delAAAG p.Lys630fs
Treatment approach
Currently no therapies directly targeting inactivation of Hamartin are approved or are under investigation in clinical trials. Loss or inactivation of TSC1 leads to activation of mTOR and therefore may predict sensitivity to mTOR inhibitors (Kuo et al., 2010; 20145209, Inoki et al., 2003; 12869586, Tee et al., 2003; 12906785). In a number of cancer types (including bladder, breast, thyroid, and PEComa), patients who have had exceptional responses to mTOR inhibitors have been found to harbor TSC1 or TSC2 inactivating alterations (Palma et al., 2014; SABCS 2014, Abstract P2-03-06, Iyer et al., 2012; 22923433, Wagle et al., 2014; 25295501, Wagner et al., 2010; 20048174, Dickson et al., 2013; 22927055, Lim et al., 2016; 26859683). The mTOR inhibitors everolimus and temsirolimus have been FDA approved for some indications. Everolimus has been approved in subependymal giant cell astrocytoma associated with tuberous sclerosis (due to TSC1 or TSC2 inactivation), as well as for other indications. These agents and other mTOR inhibitors are being studied in clinical trials in multiple tumor types (Lebwohl et al., 2013; 23659703, Bergmann et al., 2014; 24313573, Franz, 2013; 24143074).
FDA approved therapies within indication
No available data
FDA approved therapies outside this indication
Everolimus, Temsirolimus
Investigational therapies within indication
Everolimus , Temsirolimus , Ridaforolimus , CC-223 , AZD2014 , Sapanisertib , Apitolisib , LY3023414 , PQR309 , PF-05212384 , SF112
Resistance and Interactions
No available data
Guidelines
No available data
Detailed therapeutic relevance
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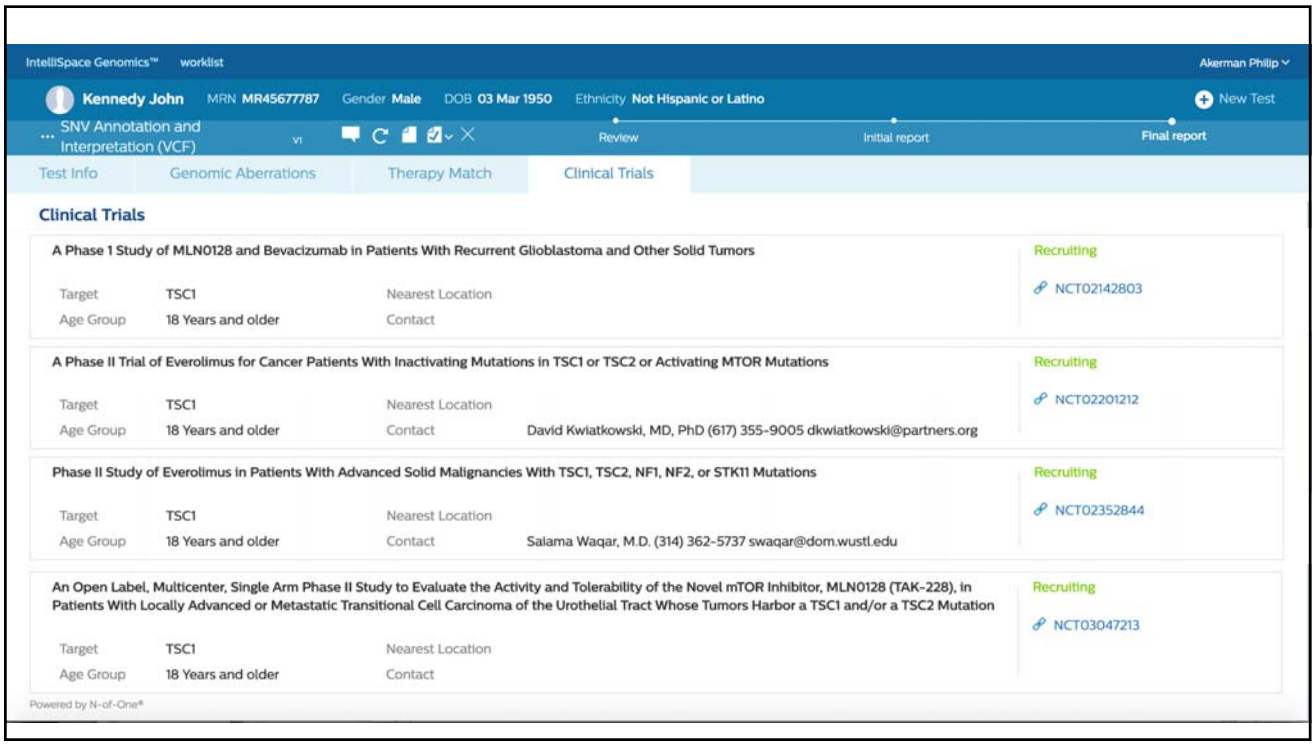
Aberration effect
TSC1 K630fs is expected to effectively truncate the Hamartin protein at amino acid 630 of 1165, resulting in loss of the coiled coil domain (UniProt) (Hodges et al., 2001; 11741833). This truncation would not be expected to affect the Tuberin-binding region of Hamartin (Hodges et al., 2001; 11741833). However, a preclinical study reported that the N-terminal portion of Hamartin is required for stable Hamartin protein expression and Hamartin-Tuberin complex formation, as N-terminal truncations, including those at R509 and R692, resulted in reduced Hamartin stability and weak interaction with Tuberin (Hoogeveen-Westerveld et al., 2010; 20547222). Therefore, this alteration is predicted to be inactivating.

31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Genomic Aberrations
Therapy Match
Clinical Trials
Clinical Trials
A Phase 1 Study of MLN0128 and Bevacizumab in Patients With Recurrent Glioblastoma and Other Solid Tumors
Recruiting
Target TSC1
Age Group 18 Years and older
Nearest Location
Contact
NCT02142803
A Phase II Trial of Everolimus for Cancer Patients With Inactivating Mutations in TSC1 or TSC2 or Activating MTOR Mutations
Recruiting
Target TSC1
Age Group 18 Years and older
Nearest Location
Contact David Kwiatkowski, MD, PhD (617) 355-9005 dkwiatkowski@partners.org
NCT02201212
Phase II Study of Everolimus in Patients With Advanced Solid Malignancies With TSC1, TSC2, NF1, NF2, or STK11 Mutations
Recruiting
Target TSC1
Age Group 18 Years and older
Nearest Location
Contact Salama Waqar, M.D. (314) 362-5737 swaqar@dom.wustl.edu
NCT02352844
An Open Label, Multicenter, Single Arm Phase II Study to Evaluate the Activity and Tolerability of the Novel mTOR Inhibitor, MLN0128 (TAK-228), in Patients With Locally Advanced or Metastatic Transitional Cell Carcinoma of the Urothelial Tract Whose Tumors Harbor a TSC1 and/or a TSC2 Mutation
Recruiting
Target TSC1
Age Group 18 Years and older
Nearest Location
Contact
NCT03047213
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- Clinical interpretation - patient-specific, evidence-driven treatment strategies
- Biomarker specific clinical trial matching

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