TruSight™ Oncology 500 Solid Tumor

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601 Genome Way
Huntsville, AL
35806

HUDSONALPHA DISCOVERY
SEQUENCING + BIOINFORMATICS™

STUDY	DISEASE	PARTICIPANT	REPORT DATE	REPORT STATUS
haib20SL6185	Uncertain diagnosis	6185-SL-0021		Final

CLINICALLY RELEVANT RESULTS

Tier I - Strong Clinical Significance

No variants were reported for this classification tier.

Tier II - Potential Clinical Significance

VARIANT	CLINICAL IMPACT
NRAS p.Q61K c.181C>A C NM_002524.4 **VAF** % 9.6 **DEPTH** 228	**May benefit from** — Binimetinib *in Lentigo maligna, Superficial spreading melanoma, Nodular malignant melanoma of skin, Superficial spreading malignant melanoma of skin, Nodular melanoma, Acral lentiginous malignant melanoma of skin, Desmoplastic malignant melanoma, or Malignant melanoma of skin* **Not likely to benefit from** — Panitumumab or Cetuximab *in Malignant tumor of colon, Primary adenocarcinoma of colon, or Malignant tumor of rectum* **Unfavorable Prognosis in** — Myelodysplastic syndrome (clinical) or Myelodysplastic syndrome

INTERPRETATION

(1) Binimetinib is useful in certain circumstances as a single agent for metastatic or unresectable NRAS mutated tumors that have progressed after prior immune checkpoint inhibitor therapy. (2) In patients who were previously untreated or had prior failure of immunotherapy, binimetinib was associated with a response rate of 15%, and demonstrated a modest improvement in PFS with no improvement in OS compared with single-agent dacarbazine. (3) Binimetinib has also been shown to

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VARIANT	CLINICAL IMPACT
	INTERPRETATION
	provide improved response rates and PFS compared with DTIC (dacarbazine) in a phase 3 randomized trial in patients with unresectable stage IIIC or stage IV melanoma with NRAS Q61R/K/L mutations.

MLH1

p.S252*
c.755C>A

C

NM_000249.3
VAF % 19.6
DEPTH 163

May benefit from

— Ipilimumab + Nivolumab or Nivolumab *in Malignant tumor of colon, Primary adenocarcinoma of colon, or Malignant tumor of rectum*

— Ipilimumab + Nivolumab *in Adenocarcinoma of small intestine or Adenocarcinoma of rectum*

— Nivolumab *in Carcinoma, undifferentiated, Endometrioid carcinoma, Carcinosarcoma of uterus, Adenocarcinoma of small intestine, Adenocarcinoma of rectum, or Endometrial carcinoma*

— Pembrolizumab *in Malignant tumor of colon, Osteosarcoma of bone, Invasive micropapillary carcinoma of breast, Primary malignant neoplasm of endometrium, Malignant fibrous histiocytoma, Endometrial carcinoma, Adenocarcinoma of prostate, Siewert type II adenocarcinoma of esophagogastric junction, Adenocarcinoma of cervix, Adenocarcinoma of pancreas, Ewing's sarcoma of bone, Primary adenocarcinoma of colon, Malignant tumor of fallopian tube, Squamous cell carcinoma of vulva, Malignant tumor of small intestine, Adenocarcinoma of rectum, Infiltrating lobular carcinoma of breast, Malignant tumor of rectum, Malignant tumor of ovary, Seminoma - category, Carcinosarcoma of uterus, Mixed ductal and lobular carcinoma of breast, Adenocarcinoma of small intestine, Malignant tumor of biliary tract, Malignant tumor of esophagus, Malignant tumor of adrenal gland, Adenocarcinoma of esophagus, Infiltrating carcinoma with ductal and lobular features, Germ cell tumor, nonseminomatous, Squamous cell carcinoma of esophagus, Hepatocellular carcinoma, Malignant tumor of pancreas, Malignant tumor of testis, Malignant epithelial tumor of ovary, Malignant tumor of breast, Infiltrating duct carcinoma of breast, Malignant tumor of unknown origin or ill-defined site, Malignant tumor of cervix, Small cell carcinoma of lung, Inflammatory carcinoma of breast, Primary malignant neoplasm of the peritoneum, Carcinoma of esophagus, Siewert type III adenocarcinoma of esophagogastric junction, Malignant tumor of gallbladder, Siewert type I adenocarcinoma of esophagogastric junction, Cholangiocarcinoma of biliary tract, Primary malignant clear cell tumor of ovary, Carcinoma of cervix, Carcinosarcoma of ovary, Malignant retroperitoneal tumor, Malignant tumor of stomach, Malignant tumor of prostate, Dedifferentiated chondrosarcoma, Carcinoma, undifferentiated, Endometrioid carcinoma, Chondrosarcoma of bone, Malignant tumor of penis, Adenosquamous carcinoma of cervix, Endometrioid carcinoma ovary,*

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VARIANT	CLINICAL IMPACT
	Mucinous carcinoma of breast, Adenocarcinoma of stomach, or Mesenchymal chondrosarcoma **Favorable Prognosis in** — Malignant tumor of colon, Primary adenocarcinoma of colon, or Malignant tumor of rectum INTERPRETATION Pembrolizumab is used as single-agent third-line therapy in patients with microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) or tumor mutational burden-high (TMB-H) tumors (useful in certain circumstances)
CTNNB1 p.S33Y c.98C>A C NM_001904.3 VAF % 32.4 DEPTH 247	**Diagnostic of** — Medulloblastoma INTERPRETATION (1) Description: Medulloblastomas are WHO grade IV tumors that predominantly arise from the cerebellum in pediatric patients, but can also occur in adults. The WHO committee on CNS tumors now recommends subclassification of these tumors into four distinct groups: i) WNT-activated; ii) SHH-activated and TP53-mutant; iii) SHH-activated and TP53-wildtype; and iv) non-WNT/non-SHH. (2) Detection: Virtually all WNT-driven medulloblastomas will contain mutations in either CTNNB1 or, less commonly, APC (the latter mutation may be germline if the patient has Turcot syndrome). WNT-driven tumors will also usually contain monosomy 6. Differentiating between WNT-activated, SHH-activated, and non-WNT/non-SHH tumors is best classified by expression arrays, DNA methylation arrays, or an immunohistochemistry panel composed of beta-catenin, GAB1, and YAP1. (3) Molecular profiling to identify clinically relevant subtypes is recommended to encourage opportunities for clinical trial.
GATA2 p.G200Vfs*18 c.599delG	**Unfavorable Prognosis in** — Myelodysplastic syndrome (clinical) or Myelodysplastic syndrome

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VARIANT	CLINICAL IMPACT

C

NM_032638.4
VAF % 10.6
DEPTH 321

INTERPRETATION

Genes frequently somatically mutated in MDS include GATA2. Nonsense or Frameshift or Splice site mutations in GATA2 are associated with a poor prognosis.

PIK3CA

p.E545K
c.1633G>A

C

NM_006218.2
VAF % 7
DEPTH 143

May benefit from

— Alpelisib *in Human epidermal growth factor 2 negative carcinoma of breast, Malignant tumor of breast, Infiltrating duct carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Hormone receptor positive malignant neoplasm of breast, Infiltrating carcinoma with ductal and lobular features, or Infiltrating lobular carcinoma of breast*

INTERPRETATION

(1) Alpelisib is recommended for treatment of recurrent or stage IV (M1) hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative disease with no visceral crisis in postmenopausal women or premenopausal women treated with ovarian ablation/suppression, as second-line therapy or beyond in combination with fulvestrant if PIK3CA mutation positive (preferred regimen). (2) Men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis.

PIK3CA

p.H1047R
c.3140A>G

C

NM_006218.2
VAF % 14.9
DEPTH 235

May benefit from

— Alpelisib *in Human epidermal growth factor 2 negative carcinoma of breast, Malignant tumor of breast, Infiltrating duct carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Hormone receptor positive malignant neoplasm of breast, Infiltrating carcinoma with ductal and lobular features, or Infiltrating lobular carcinoma of breast*

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INTERPRETATION

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KIT

p.D816V
c.2447A>T

C

NM_000222.2
VAF % 7.6
DEPTH 171

May benefit from

— Midostaurin *in Chronic myelomonocytic leukemia or Myelodysplastic/ myeloproliferative disease*

Not likely to benefit from

— Imatinib *in Aggressive systemic mastocytosis*

Diagnostic of

— Gastrointestinal stromal tumor

INTERPRETATION

Comprehensive molecular studies investigating the mechanisms of resistance to sunitinib are limited by the small number of patients who are surgical candidates after their disease failed to respond to two different TKI therapies. Nevertheless, available evidence (both clinical and preclinical) indicates that while sunitinib is very sensitive to adenosine triphosphate (ATP)-binding pocket mutations that confer resistance to imatinib, it has little activity against other imatinib-resistant mutations in the KIT activation loop.

TET2

p.L1329M
c.3985C>A

Unfavorable Prognosis in

— Myeloproliferative disorder or Myeloproliferative neoplasm

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VARIANT	CLINICAL IMPACT

C

NM_001127208.2
VAF % 34.5
DEPTH 113

INTERPRETATION

(1) TET2 or TP53 mutations have also been associated with a worsened overall prognosis and an increased rate of leukemic transformation. (2) Mutations in several genes (ASXL1, TET2, TP53, SRSF2, and IDH1 or IDH2) and other chromosomal abnormalities (eg, aberrations in chromosomes 1q and 9p) have been associated with transformation to AML.

SDHA

c.1794+119delA

Diagnostic of

— Paraganglioma, malignant or Gastrointestinal stromal tumor

C

NM_004168.2
VAF % 38.7
DEPTH 204

INTERPRETATION

(1) Morphologic diagnosis based on microscopic examination of histologic sections remains the gold standard for sarcoma diagnosis. However, several ancillary techniques are useful in support of morphologic diagnosis, including IHC, classical cytogenetics, electron microscopy, and molecular genetic testing. Molecular genetic testing has emerged as an ancillary testing approach since many sarcoma types harbor characteristic genetic aberrations. Recurrent genetic aberrations in sarcoma include, germline SDH subunit mutations in familial gastric GIST and paraganglioma associated with Carney-Stratakis syndrome. (2) Carney-Stratakis syndrome is an autosomal-dominant familial syndrome characterized by a predisposition to GISTs and paragangliomas. Germline loss-of-function mutations within the succinate dehydrogenase (SDH) gene subunits (SDHB, SDHC, and SDHD) have been identified in individuals with GISTs associated with Carney-Stratakis syndrome. In an analysis of 11 patients from 9 families presenting with GIST and paragangliomas associated with Carney-Stratakis syndrome, Pasini and colleagues identified germline mutations in SDHB, SDHC, or SDHD genes in 8 patients (from 7 untreated families) with GISTs.

EGFR

p.G719S
c.2155G>A

May benefit from

— Bevacizumab-bvzr + Erlotinib, Bevacizumab + Erlotinib, or Bevacizumab-awwb + Erlotinib *in Nonsquamous nonsmall cell neoplasm of lung, Adenocarcinoma of lung, or Large cell carcinoma of lung*

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VARIANT	CLINICAL IMPACT
C NM_005228.3 VAF % 23.4 DEPTH 197	— Afatinib + Cetuximab, Erlotinib, Afatinib, Erlotinib + Ramucirumab, Dacomitinib, Osimertinib, or Gefitinib *in Squamous cell carcinoma of lung, Adenocarcinoma of lung, Non-small cell lung cancer, Epidermal growth factor receptor positive non-small cell lung cancer, Large cell carcinoma of lung, or Non-small cell carcinoma*

INTERPRETATION

(1) Ramucirumab in combination with erlotinib for sensitizing EGFR mutation-positive recurrent, advanced or metastatic disease as (a) first-line therapy, (b) continuation of therapy following disease progression on combination of erlotinib and ramucirumab for asymptomatic disease, symptomatic brain lesions, or isolated symptomatic systemic lesions. (2) For the 2020 update (Version 2), the NCCN NSCLC Panel recommends erlotinib/ramucirumab as a first-line therapy option for patients with EGFR-positive metastatic NSCLC (category 2A, other recommended intervention) based on clinical data. (3) There are no data to support using erlotinib (with or without ramucirumab or bevacizumab), gefitinib, afatinib, or dacomitinib after progression on first-line therapy with osimertinib. (4) The most commonly described mutations in EGFR (exon 19 deletions, p.L858R point mutation in exon 21) are associated with responsiveness to EGFR tyrosine kinase inhibitor (TKI) therapy; most recent data indicate that tumors that do not harbor a sensitizing EGFR mutation should not be treated with EGFR TKI in any line of therapy. Many of the less commonly observed alterations in EGFR, which cumulatively account for ~10% of EGFR-mutated NSCLC (ie, exon 19 insertions, p.L861Q, p.G719X, p.S768I) are associated with responsivelness to EGFR TKI therapy, although the number of studied patients is lower. The extent to which this association is true in squamous cell carcinoma is less well defined. (5) Note: Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

VARIANT	May benefit from
BRAF p.V600E c.1799T>A C NM_004333.4 VAF % 8.4 DEPTH 263	— Vemurafenib, Dabrafenib, Cobimetinib + Vemurafenib, Binimetinib + Encorafenib, Atezolizumab + Cobimetinib + Vemurafenib, or Trametinib *in Malignant melanoma, metastatic, Malignant melanoma, or Metastatic malignant melanoma* — Dabrafenib *in Superficial spreading melanoma, Squamous cell carcinoma of lung, Non-small cell carcinoma, Hurthle cell carcinoma of thyroid, Desmoplastic malignant melanoma, Lentigo maligna, Nodular malignant melanoma of skin, Follicular thyroid carcinoma, Adenocarcinoma of lung, Superficial spreading malignant melanoma of skin, Non-small cell lung cancer, Nodular melanoma, Acral lentiginous malignant*

VARIANT	CLINICAL IMPACT

melanoma of skin, Large cell carcinoma of lung, Papillary thyroid carcinoma, or Malignant melanoma of skin

— Vemurafenib *in Superficial spreading melanoma, Squamous cell carcinoma of lung, Hurthle cell carcinoma of thyroid, Non-small cell carcinoma, Desmoplastic malignant melanoma, Lentigo maligna, Hairy cell leukemia, Nodular malignant melanoma of skin, Follicular thyroid carcinoma, Superficial spreading malignant melanoma of skin, Hairy cell leukemia (clinical), Adenocarcinoma of lung, Nodular melanoma, Non-small cell lung cancer, Erdheim-Chester disease, Acral lentiginous malignant melanoma of skin, Large cell carcinoma of lung, Papillary thyroid carcinoma, Polyostotic sclerosing histiocytosis, or Malignant melanoma of skin*

— Trametinib *in Malignant melanoma - category or Malignant melanoma of skin*

— Encorafenib + Panitumumab or Cetuximab + Encorafenib *in Malignant tumor of colon, Primary adenocarcinoma of colon, Adenocarcinoma of rectum, or Malignant tumor of rectum*

— Pembrolizumab, Ipilimumab + Talimogene laherparepvec, Ipilimumab, Nivolumab, Ipilimumab + Nivolumab, Cobimetinib + Vemurafenib, Atezolizumab + Cobimetinib + Vemurafenib, or Binimetinib + Encorafenib *in Lentigo maligna, Superficial spreading melanoma, Nodular malignant melanoma of skin, Superficial spreading malignant melanoma of skin, Nodular melanoma, Acral lentiginous malignant melanoma of skin, Desmoplastic malignant melanoma, or Malignant melanoma of skin*

— Cobimetinib + Vemurafenib *in Dysembryoplastic neuroepithelial tumor, Ganglioglioma, anaplastic, Pilocytic astrocytoma, Low grade glioma, or Pleomorphic xanthoastrocytoma*

— Dabrafenib + Trametinib *in Superficial spreading melanoma, Malignant melanoma, metastatic, Squamous cell carcinoma of lung, Dysembryoplastic neuroepithelial tumor, Pilocytic astrocytoma, Non-small cell carcinoma, Desmoplastic malignant melanoma, Anaplastic thyroid carcinoma, Lentigo maligna, Nodular malignant melanoma of skin, Adenocarcinoma of lung, Superficial spreading malignant melanoma of skin, Ganglioglioma, anaplastic, Non-small cell lung cancer, Malignant melanoma, Nodular melanoma, Acral lentiginous malignant melanoma of skin, Low grade glioma, Large cell carcinoma of lung, Metastatic malignant melanoma, Malignant melanoma of skin, or Pleomorphic xanthoastrocytoma*

— Bevacizumab-bvzr, Bevacizumab-awwb, Bevacizumab, or Atezolizumab *in Nonsquamous nonsmall cell neoplasm of lung, Adenocarcinoma of lung, or Large cell carcinoma of lung*

— Pembrolizumab or Ipilimumab + Nivolumab *in Squamous cell carcinoma of lung, Adenocarcinoma of lung, Non-small cell lung cancer, Large cell carcinoma of lung, or Non-small cell carcinoma*

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	Not likely to benefit from — Panitumumab or Cetuximab *in Malignant tumor of colon, Primary adenocarcinoma of colon, or Malignant tumor of rectum* **Unfavorable Prognosis in** — Malignant tumor of colon, Primary adenocarcinoma of colon, Adenocarcinoma of rectum, Malignant tumor of rectum, or Papillary thyroid carcinoma **Diagnostic of** — Hairy cell leukemia or Hairy cell leukemia (clinical) INTERPRETATION (1) BRAF exon 15 mutation (V600E) has also been reported in a small subset of patients with intestinal high-risk GISTs lacking KIT/PDGFRA mutations. (2) In the absence of KIT and PDGFRA mutations, only a subset of patients with advanced GISTs benefit from imatinib, although tumors known to be SDH deficient or having alternative drivers (eg, NF1, BRAF) are unlikely to benefit from imatinib.
EZH2 p.G395Efs*29 c.1184delG C NM_004456.4 VAF % 20.3 DEPTH 231	**Unfavorable Prognosis in** — Myelodysplastic syndrome (clinical), Myelodysplastic/myeloproliferative disease, or Myelodysplastic syndrome INTERPRETATION (1) Genes frequently somatically mutated in MDS include EZH2. Nonsense or Frameshift mutations in EZH2 are independently associated with a poor prognosis in MDS and MDS/MPN. (2) Mutations of TP53, EZH2, ETV6, RUNX1, and ASXL1 have been shown to predict decreased OS in multivariable models adjusted for IPSS or IPSS-R risk groups in several studies of distinct cohorts.
PTCH1 p.S1203Afs*52 c.3606delC C	**May benefit from** — Vismodegib *in Medulloblastoma*

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VARIANT	CLINICAL IMPACT
NM_000264.3 **VAF** % 30.8 **DEPTH** 357	INTERPRETATION (1) Vismodegib is a recommended treatment for recurrence as a single agent (useful in certain circumstances) in patients who have received prior chemotherapy and have mutations in the sonic hedgehog pathway. (2) SHH-pathway inhibitors that have been evaluated in phase II trials including adults with recurrent medulloblastoma include vismodegib and sonidegib. Patients in these trials with SHH-activated disease were more likely to respond than patients with non-SHH disease.
KRAS p.G13D c.38G>A C **NM_033360.2** **VAF** % 15.1 **DEPTH** 251	**Not likely to benefit from** — Panitumumab or Cetuximab *in Malignant tumor of colon, Primary adenocarcinoma of colon, or Malignant tumor of rectum* — Panitumumab *in Metastasis from malignant tumor of colon or Metastasis from malignant tumor of rectum* — Erlotinib, Osimertinib, or Gefitinib *in Non-small cell lung cancer or Non-small cell carcinoma* **Unfavorable Prognosis in** — Non-small cell lung cancer or Non-small cell carcinoma INTERPRETATION The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab.
KRAS p.G12D c.35G>A C **NM_033360.2** **VAF** % 8.5 **DEPTH** 246	**Not likely to benefit from** — Panitumumab or Cetuximab *in Malignant tumor of colon, Primary adenocarcinoma of colon, or Malignant tumor of rectum* — Panitumumab *in Metastasis from malignant tumor of colon or Metastasis from malignant tumor of rectum* — Erlotinib, Osimertinib, or Gefitinib *in Non-small cell lung cancer or Non-small cell carcinoma*

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VARIANT	CLINICAL IMPACT

Unfavorable Prognosis in

— Malignant tumor of unknown origin or ill-defined site, Non-small cell lung cancer, or Non-small cell carcinoma

INTERPRETATION

(1) The NCCN Colon/Rectal Cancer Panel believes that RAS mutation status should be determined at diagnosis of stage IV disease. (2) Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab. The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab. (3) A sizable body of literature has shown that these KRAS exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy. (4) Patients with known KRAS or NRAS mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified.

BRCA2

p.K1691Nfs*15
c.5073delA

C

NM_000059.3
VAF % 28
DEPTH 143

May benefit from

— Bevacizumab + Olaparib or Niraparib *in Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Primary malignant clear cell tumor of ovary, Malignant tumor of ovary, Primary malignant neoplasm of the peritoneum, Malignant epithelial tumor of ovary, or Carcinosarcoma of ovary*

— Rucaparib *in Malignant tumor of prostate, Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Primary malignant clear cell tumor of ovary, Malignant tumor of ovary, Adenocarcinoma of prostate, Malignant epithelial tumor of ovary, Primary malignant neoplasm of the peritoneum, or Carcinosarcoma of ovary*

— Talazoparib *in Human epidermal growth factor 2 negative carcinoma of breast, Malignant tumor of breast, Infiltrating duct carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Infiltrating carcinoma with ductal and lobular features, or Infiltrating lobular carcinoma of breast*

— Olaparib *in Human epidermal growth factor 2 negative carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Primary malignant clear cell tumor of ovary, Adenocarcinoma of prostate, Malignant epithelial tumor of ovary, Carcinosarcoma of ovary, Malignant tumor of prostate, Malignant tumor of breast, Adenocarcinoma of pancreas, Infiltrating duct carcinoma of*

VARIANT	CLINICAL IMPACT

breast, Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Infiltrating carcinoma with ductal and lobular features, Infiltrating lobular carcinoma of breast, Malignant tumor of ovary, or Primary malignant neoplasm of the peritoneum

Unfavorable Prognosis in

— Malignant tumor of prostate or Primary malignant neoplasm of prostate

INTERPRETATION

(1) INDICATIONS AND USAGE: Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (2) CLINICAL STUDIES: First-Line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma: The efficacy of Lynparza was evaluated in POLO (NCT02184195), a randomized (3:2), double-blind placebo-controlled, multi-center trial. Patients were required to have metastatic pancreatic adenocarcinoma with a deleterious or suspected deleterious germline BRCA mutation (gBRCAm) and absence of disease progression after receipt of first-line platinum-based chemotherapy for at least 16 weeks. The major efficacy outcome measure was PFS by BICR using RECIST, version 1.1 modified to assess patients with clinical complete response at entry who were assessed as having no evidence of disease unless they had progressed based on the appearance of new lesions. Additional efficacy outcome measures were OS and ORR. All patients had a deleterious or suspected deleterious germline BRCA-mutation as detected by the Myriad BRACAnalysis or BRACAnalysis CDx at a central laboratory only (n=106), local BRCA test only (n=4), or both local and central testing (n=44). Among the 150 patients with central test results, 30% had a mutation in BRCA1; 69% had a mutation in BRCA2; and 1 patient (1%) had mutations in both BRCA1 and BRCA2. An improvement in PFS was demonstrated for the Lynparza arm (median PFS= 7.4 months) over the Placebo arm (median PFS= 3.8 months). Of the Patients with Measurable Disease, Objective Response Rate (95% CI) was 23% (14, 34) for patients administered Lynparza (n=78) and 12% (4, 23) for patients administered Placebo (n=52).

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VARIANT	CLINICAL IMPACT

BRCA2

p.N1784Tfs*7
c.5351delA

C

NM_000059.3
VAF % 42.4
DEPTH 170

May benefit from

— Bevacizumab + Olaparib or Niraparib *in Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Primary malignant clear cell tumor of ovary, Malignant tumor of ovary, Primary malignant neoplasm of the peritoneum, Malignant epithelial tumor of ovary, or Carcinosarcoma of ovary*

— Rucaparib *in Malignant tumor of prostate, Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Primary malignant clear cell tumor of ovary, Malignant tumor of ovary, Adenocarcinoma of prostate, Malignant epithelial tumor of ovary, Primary malignant neoplasm of the peritoneum, or Carcinosarcoma of ovary*

— Talazoparib *in Human epidermal growth factor 2 negative carcinoma of breast, Malignant tumor of breast, Infiltrating duct carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Infiltrating carcinoma with ductal and lobular features, or Infiltrating lobular carcinoma of breast*

— Olaparib *in Human epidermal growth factor 2 negative carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Primary malignant clear cell tumor of ovary, Adenocarcinoma of prostate, Malignant epithelial tumor of ovary, Carcinosarcoma of ovary, Malignant tumor of prostate, Malignant tumor of breast, Adenocarcinoma of pancreas, Infiltrating duct carcinoma of breast, Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Infiltrating carcinoma with ductal and lobular features, Infiltrating lobular carcinoma of breast, Malignant tumor of ovary, or Primary malignant neoplasm of the peritoneum*

Unfavorable Prognosis in

— Malignant tumor of prostate or Primary malignant neoplasm of prostate

INTERPRETATION

(1) INDICATIONS AND USAGE: Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (2) CLINICAL STUDIES: First-Line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma: The efficacy of Lynparza was evaluated in POLO (NCT02184195), a randomized (3:2), double-blind placebo-controlled, multi-center trial. Patients were required to have

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VARIANT	CLINICAL IMPACT

INTERPRETATION

metastatic pancreatic adenocarcinoma with a deleterious or suspected deleterious germline BRCA mutation (gBRCAm) and absence of disease progression after receipt of first-line platinum-based chemotherapy for at least 16 weeks. The major efficacy outcome measure was PFS by BICR using RECIST, version 1.1 modified to assess patients with clinical complete response at entry who were assessed as having no evidence of disease unless they had progressed based on the appearance of new lesions. Additional efficacy outcome measures were OS and ORR. All patients had a deleterious or suspected deleterious germline BRCA-mutation as detected by the Myriad BRACAnalysis or BRACAnalysis CDx at a central laboratory only (n=106), local BRCA test only (n=4), or both local and central testing (n=44). Among the 150 patients with central test results, 30% had a mutation in BRCA1; 69% had a mutation in BRCA2; and 1 patient (1%) had mutations in both BRCA1 and BRCA2. An improvement in PFS was demonstrated for the Lynparza arm (median PFS= 7.4 months) over the Placebo arm (median PFS= 3.8 months). Of the Patients with Measurable Disease, Objective Response Rate (95% CI) was 23% (14, 34) for patients administered Lynparza (n=78) and 12% (4, 23) for patients administered Placebo (n=52).

BRCA2

p.I2675Dfs*6
c.8021dupA

C

NM_000059.3
VAF % 10.8
DEPTH 157

May benefit from

— Bevacizumab + Olaparib or Niraparib *in Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Primary malignant clear cell tumor of ovary, Malignant tumor of ovary, Primary malignant neoplasm of the peritoneum, Malignant epithelial tumor of ovary, or Carcinosarcoma of ovary*

— Rucaparib *in Malignant tumor of prostate, Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Primary malignant clear cell tumor of ovary, Malignant tumor of ovary, Adenocarcinoma of prostate, Malignant epithelial tumor of ovary, Primary malignant neoplasm of the peritoneum, or Carcinosarcoma of ovary*

— Talazoparib *in Human epidermal growth factor 2 negative carcinoma of breast, Malignant tumor of breast, Infiltrating duct carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Infiltrating carcinoma with ductal and lobular features, or Infiltrating lobular carcinoma of breast*

— Olaparib *in Human epidermal growth factor 2 negative carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Primary malignant clear cell tumor of ovary, Adenocarcinoma of prostate, Malignant epithelial tumor of ovary, Carcinosarcoma of ovary, Malignant tumor of prostate, Malignant tumor of breast, Adenocarcinoma of pancreas, Infiltrating duct carcinoma of*

VARIANT	CLINICAL IMPACT

breast, Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Infiltrating carcinoma with ductal and lobular features, Infiltrating lobular carcinoma of breast, Malignant tumor of ovary, or Primary malignant neoplasm of the peritoneum

Unfavorable Prognosis in

— Malignant tumor of prostate or Primary malignant neoplasm of prostate

INTERPRETATION

(1) INDICATIONS AND USAGE: Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (2) CLINICAL STUDIES: First-Line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma: The efficacy of Lynparza was evaluated in POLO (NCT02184195), a randomized (3:2), double-blind placebo-controlled, multi-center trial. Patients were required to have metastatic pancreatic adenocarcinoma with a deleterious or suspected deleterious germline BRCA mutation (gBRCAm) and absence of disease progression after receipt of first-line platinum-based chemotherapy for at least 16 weeks. The major efficacy outcome measure was PFS by BICR using RECIST, version 1.1 modified to assess patients with clinical complete response at entry who were assessed as having no evidence of disease unless they had progressed based on the appearance of new lesions. Additional efficacy outcome measures were OS and ORR. All patients had a deleterious or suspected deleterious germline BRCA-mutation as detected by the Myriad BRACAnalysis or BRACAnalysis CDx at a central laboratory only (n=106), local BRCA test only (n=4), or both local and central testing (n=44). Among the 150 patients with central test results, 30% had a mutation in BRCA1; 69% had a mutation in BRCA2; and 1 patient (1%) had mutations in both BRCA1 and BRCA2. An improvement in PFS was demonstrated for the Lynparza arm (median PFS= 7.4 months) over the Placebo arm (median PFS= 3.8 months). Of the Patients with Measurable Disease, Objective Response Rate (95% CI) was 23% (14, 34) for patients administered Lynparza (n=78) and 12% (4, 23) for patients administered Placebo (n=52).

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VARIANT	CLINICAL IMPACT

BRCA1

p.R1443*
c.4327C>T

C

NM_007294.3
VAF % 26.5
DEPTH 234

May benefit from

— Bevacizumab + Olaparib or Niraparib *in Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Primary malignant clear cell tumor of ovary, Malignant tumor of ovary, Primary malignant neoplasm of the peritoneum, Malignant epithelial tumor of ovary, or Carcinosarcoma of ovary*

— Rucaparib *in Malignant tumor of prostate, Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Primary malignant clear cell tumor of ovary, Malignant tumor of ovary, Adenocarcinoma of prostate, Malignant epithelial tumor of ovary, Primary malignant neoplasm of the peritoneum, or Carcinosarcoma of ovary*

— Talazoparib *in Human epidermal growth factor 2 negative carcinoma of breast, Malignant tumor of breast, Infiltrating duct carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Infiltrating carcinoma with ductal and lobular features, or Infiltrating lobular carcinoma of breast*

— Olaparib *in Human epidermal growth factor 2 negative carcinoma of breast, Invasive micropapillary carcinoma of breast, Mixed ductal and lobular carcinoma of breast, Primary malignant clear cell tumor of ovary, Adenocarcinoma of prostate, Malignant epithelial tumor of ovary, Carcinosarcoma of ovary, Malignant tumor of prostate, Malignant tumor of breast, Adenocarcinoma of pancreas, Infiltrating duct carcinoma of breast, Malignant tumor of fallopian tube, Endometrioid carcinoma ovary, Mucinous carcinoma of breast, Inflammatory carcinoma of breast, Infiltrating carcinoma with ductal and lobular features, Infiltrating lobular carcinoma of breast, Malignant tumor of ovary, or Primary malignant neoplasm of the peritoneum*

Unfavorable Prognosis in

— Malignant tumor of prostate

INTERPRETATION

(1) INDICATIONS AND USAGE: Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (2) CLINICAL STUDIES: The efficacy of Lynparza was evaluated in OlympiAD (NCT02000622), an open-label randomized (2:1) study in patients with gBRCAm HER2-negative metastatic breast

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VARIANT | CLINICAL IMPACT

INTERPRETATION

cancer. Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have progressed on at least 1 endocrine therapy (adjuvant or metastatic), or have disease that the treating healthcare provider believed to be inappropriate for endocrine therapy. No prior treatment with a PARP inhibitor was permitted. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). The major efficacy outcome measure was PFS assessed by blinded independent central review (BICR) using RECIST version 1.1. Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx and 297 were confirmed to have deleterious or suspected deleterious gBRCAm statusstatus; 202 were randomized to the Lynparza arm and 95 to the healthcare provider's choice of chemotherapy arm. A statistically significant improvement in PFS was demonstrated for the Lynparza arm (median PFS= 7 months) compared to the chemotherapy arm (median PFS= 4.2 months). An exploratory analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results.

SMARCA4

p.S122Lfs*7
c.363dupC

C

NM_001128849.1
VAF % 8.6
DEPTH 222

Diagnostic of

— Undifferentiated sarcoma

INTERPRETATION

(1) PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS: SMARCA4 mutation in a small subset of Undifferentiated Uterine Sarcoma. (2) HALLMARKS FOR HISTOLOGIC DIAGNOSIS: Infiltrative sheets of pleomorphic epithelioid and/or spindle cells. SMARCA4-deficient subset consists of epithelioid/rhabdoid cells associated with myxoid matrix. lymphovascular space invasion (LVSI), high MI (mitotic index), and necrosis are common (3) TESTS NEEDED TO CONFIRM DIAGNOSIS: IHC panel of CD10, BCOR, cyclin D1, desmin, SMA, pan-CK, EMA, BRG1, INI1, pan-Trk, ALK, HMB45, melan A, SOX10, and STAT6 is recommended to exclude other tumor types. Absence of ESS associated fusions by FISH and/or targeted RNA sequencing is recommended. Absent CK expression and BRG1 loss (SMARCA4) and/or SMARCA4 mutation detectable by DNA sequencing is confirmatory of SMARCA4-deficient tumors. (4) ER

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VARIANT	CLINICAL IMPACT
	INTERPRETATION
	and/or PR expression may correlate with improved survival. MI >=11/mm2 is associated with decreased survival.

RUNX1

p.M267I
c.801G>A

C

NM_001754.4
VAF % 8.8
DEPTH 340

Unfavorable Prognosis in

— Acute myeloid leukemia or Acute myeloid leukemia, disease

INTERPRETATION

(1) Non- acute promyelocytic leukemia AML (Non-APL AML) with the genetic abnormality mutated RUNX1 is categorized as Poor/Adverse risk category. These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes. (2) AML (Acute Myeloid Leukemia) with RUNX1 mutation is associated with a poorer prognosis. (3) Other candidate genes that are associated with an adverse impact on outcome are TET2 and RUNX1. (4)The runt-related transcription factor 1 (RUNX1) gene, encoding a myeloid transcription factor, is mutated in approximately 10% of de novo AML cases and associated with adverse prognoses. (5) In a study examining the impact of multiple RUNX1 mutations and loss of wild-type RUNX1 in AML, both loss of wild-type RUNX1 (OS, 5 months) and having more than or equal to 1 RUNX1 mutation (14 months) had an adverse impact on prognosis compared to 1 RUNX1 mutation (22 months; P < .002 and .048, respectively). (6) Both NCCN and the ELN classify patients with wild-type NPM1 and FLT3-ITDhigh, mutated TP53, mutated RUNX1, or mutated ASXL1 as having poor risk. However, mutated RUNX1 or ASXL1 should not be used as poor-risk prognostic markers if they co-occur with favorable-risk AML subtypes. (7) Prognostic impact of the biomarker is treatment-dependent and may change with new therapies.

BCOR

p.Q1208Tfs*8
c.3621dupA

C

NM_001123385.1
VAF % 14.3
DEPTH 105

Unfavorable Prognosis in

— Myelodysplastic syndrome (clinical) or Myelodysplastic syndrome

INTERPRETATION

Genes frequently somatically mutated in MDS include BCOR. Nonsense or Frameshift or Splice Site mutations in BCOR are associated with a poor prognosis.

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Other Biomarkers

BIOMARKER	CLINICAL IMPACT

TMB

INTERPRETATION

384.3
muts/Mb

MSI

INTERPRETATION

79.6%
Unstable Sites

POTENTIAL CLINICAL TRIALS

No relevant clinical trials were reported.

CLASSIFICATION AND LEVELS OF EVIDENCE

The variant classification system used in this report is based on joint consensus recommendations of the Association for Molecular Pathology, American Society of Clinical Oncology, and the College of American Pathologists (J Mol Diagn 2017, 19:4-23). Tiers IA, IB, IIC, IID, III and IV describe variant categories of descending clinical significance in the patient. Variants in Tier IV are not reported in accordance with the consensus recommendations.

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IA	IB	IIC	IID
Variant of strong clinical significance, Level A evidence (FDA approved therapy or practice guideline in patient's tumor type)	Variant of strong clinical significance, Level B Evidence (consensus in the field based on well-powered studies in patient's tumor type)	Variant of potential clinical significance, Level C evidence (FDA approved therapy or practice guideline in other tumor type(s), evidence from multiple small published studies, or based on availability of investigational therapies)	Variant of potential clinical significance, Level D evidence (case reports or preclinical studies)

III	Variant of uncertain clinical significance
IV	Benign or likely benign variant

TEST DETAILS

REPORTED GENES

A total of 523 genes were subjected to targeted next generation sequencing analysis. Details available upon request.

CGW VERSION

CGW_v6.13.1

DATABASE DETAILS

The versions, releases, builds, dates of the following databases were used to generate this report.

- Genomic Build: GRCh37.p13
- Genomic Annotation Sources: NCBI RefSeq v105
- dbSNP: 149
- COSMIC: v91
- gnomAD: r2.1
- ExAC: v1.0
- dbNSFP: 3.5c
- NHLBI ESP: v.0.0.30
- ClinVar: 20190603

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METHODOLOGY

Assay Methods: The test was performed using the Illumina TruSight ™ Oncology 500 (TSO500) targeted hybrid-capture based next generation sequencing assay. It employs Unique molecular identifiers (UMI) to enable detection of variants, present in solid tumor, formalin-fixed paraffin-embedded (FFPE) tumor, and cfDNA samples, at low VAFs with a high degree of sensitivity and specificity. TSO500 is designed to detect multiple classes of mutations including single-nucleotide variants (SNVs), multi-nucleotide variants (<3bp), small Insertions (1-18bp)/Deletions (1-27bp) and Copy Number Variants (CNVs). The assay also detects, quantitatively, microsatellite instability (MSI) and tumor mutational burden (TMB). Fusions are detected in RNA (TSO500 Solid Tumor reports only). DNA and RNA (TSO500 Solid Tumor reports) or cfDNA (cfDNA reports) extractions are performed and RNA is then reverse transcribed to cDNA. The genomic DNA and cDNA (TSO500 Solid Tumor reports) or cfDNA (TSO500 cfDNA reports) are sheared to prepare sequencing libraries. The regions of interest are hybridized to biotinylated probes, magnetically pulled down with streptavidin-coated beads, and eluted to enrich the library pool. Finally, libraries are normalized, then pooled and sequenced on an Illumina NextSeq or NovaSeq instrument.

Secondary Analysis Methods: The DNA and RNA data is analyzed using the Illumina Software TSO500 v2.1 Local App or the cfDNA data is analyzed using the Illumina Software TSO500 v3 Dragen Server pipeline at Discovery Life Sciences. Further processing of data for interpretation and annotation using a customized analysis pipeline within the Clinical Genomics Workspace software platform from PierianDx is then performed.

Variant Calling: Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen) and classified as per the AMP classification system into tiers IA, IB, IIC, IID, III and IV. These tiers are stratified by clinical utility ('actionability' for clinical decision-making as to diagnosis, prognosis, treatment options, and carrier status) and previously reported data in the medical literature. Variations found in gnomAD (https://gnomad.broadinstitute.org/) that have ≥1% minor allele frequency (except those that are also in ClinVar denoted as clinically relevant, used in a clinical diagnostic assay, or reported as a mutation in a publication) are classified as known polymorphisms. Small variant calls in the HLA-A, KMT2B, KMT2C, and KMT2D genes are filtered out due to potential mis-mapping as a result of sequence homology with other genomic regions.

Notes:

- This assay does not detect complex structural alterations or large indels, with the exception of a subset of clinically relevant complex EGFR exon 19 indels that are specifically targeted. Variants located outside of targeted capture regions will not be detected.

- It is possible that pathogenic variants may not be reported by one or more of the tools because of the parameters used. However, tool parameters were optimized to maximize specificity and sensitivity.

DISCLAIMER

The results provided in this report are for Research Use Only (RUO) and informational in nature. The information contained in this report cannot be used for patient treatment and/or prognostic decisions. All interpretations are made by the PierianDx Clinical Knowledgebase. No interpretations of variants have been made by Discovery Life Sciences.

The RUO assay was performed using tumor tissue; it is therefore not possible to determine whether variants detected are somatic or germline in origin unless a matched germline normal sample was analyzed using the same RUO assay

and a tumor/normal pair VCF was generated prior to PierianDx interpretation or, in cases where tumor-only sample was analyzed, a tumor-only informed bioinformatics pipeline was used to generate the VCF prior to PierianDx interpretation.

High confidence Variant Allele Fraction (VAF) cutoffs for the results provided in this report were set at 5% based on RUO verification studies performed at Discovery Life Sciences.

PATIENT AND ORDER DETAILS

PATIENT

SEX

ETHNICITY

RACE

SPECIMEN

SPECIMEN TYPE

Nucleic acid specimen

EXT. SPECIMEN ID

% TUMOR IN SELECTED AREA

CASE

REVIEW STATUS

Final

DATE ACCESSIONED

12/04/2020 16:44

DATE REPORTED

ACCESSION NUMBER

6185-SL-0021_rerun