Deciphering Anticancer Drugs

The Increasing Role of Pharmacogenomics and Pharmacogenetics in Treatment Optimization

Danica Wasney

November 18, 2022

Presenter Disclosure

- Faculty/Speaker: Danica Wasney

- Relationships with financial sponsors:
  - Speaker Honoraria: Apobiologix

Mitigating Potential Bias

- Not Applicable

Equity Commitment

- In preparing for this presentation, I have considered the Health Equity Resource for Presenters provided by the conference planning committee.

- This was provided to help presenters reflect on how these topics and content can have good effects or bad effects on people or populations that are underserved.

Genes Tested

A total of 97 regions of interest from 31 genes were assessed for point mutations and small indels.

Gene (transcript)	Exon(s)	Amino acids
AKT1 (NM_001014432.1)	3	16-59
ALK (NM_004304.4)	21-23,25	1120-1215; 1248-1279
AR (NM_000044.4)	5,8	725-773, 870-920
BRAF (NM_004333.5)	11,15	439-478; 581-620
CTNNB1 (NM_001098209.1)	3	5-81
EGFR (NM_005228.4)	18-21	688-875
ERBB2 (NM_004448.3)	8	301-541
ESR1 (NM_001122742.1)	8	518-595
FGFR1 (NM_023110.2)	12,14	518-555; 619-659
FGFR2 (NM_000141.4)	7,12,14	251-313;522-558;622-662
FGFR3 (NM_000142.4)	7,12,14	247-310;512-549;613-653
FOXL2 (NM_023067.3)	1	1-376 (full CDS)
GNA11 (NM_002067.4)	5	202-245
GNAQ (NM_002072.4)	5	202-245
GNAS (NM_000516.5)	8	196-229
HRAS (NM_005343.3)	2-3	1-97

Gene (transcript)	Exon(s)	Amino acids
IDH1 (NM_001282386.1)	4	41-136
IDH2 (NM_002168.3)	4	126-178
KIT (NM_000222.2)	2,9-11,13-15,17	23-112;411-592;624-745; 798-828
KRAS (NM_004985.4)	2-4	1-150
MAP2K1 (NM_002755.3)	2,11	27-97; 357-394
MAP2K2 (NM_030662.3)	2,2	31-101
MET (NM_001127500.2)	11-16,20-21	807-1132; 1285-1403
NRAS (NM_002524.4)	2-4	1-150
PDGFRA (NM_006206.5)	12,14-15,18,23	552-596;631-719;814-854;1041-1089
PIK3CA (NM_006218.3)	10,21	514-555; 979-1069
PTEN (NM_000314.6)	1-9	1-403 (full CDS)
RET (NM_020975.5)	11,16	628-712; 911-934
SMO (NM_005631.4)	6,9	381-422; 489-591
STK11 (NM_000455.4)	1-9	1-433 (full CDS)
TP53 (NM_000546.5)	2-11	1-394 (full CDS)

Learning Objectives

1) Describe the importance of certain genetic mutations for optimizing selection of anticancer therapies
2) Differentiate between somatic and germline genetic mutations and their relevance to anticancer drugs
3) Identify potential eligible medications for a patient based on a Next Generation Sequencing (NGS) report
4) Using case-based examples, list recent PODP formulary additions based on high microsatellite instability (MSI-H)/deficiency in mismatch repair (dMMR), BRCA mutation, NTRK mutation, etc.

Question #1

- Let's get to know the attendees!

My profession is:

A. Pharmacist/Pharmacy Tech or Assistant
B. Physician
C. Nurse
D. Allied Health

Question #2

- Chemotherapy is standard of care for 1st line treatment of patients with metastatic colorectal cancer (mCRC) that is deficient in Mismatch Repair (dMMR).

A. True

B. False

Definitions

Pharmacogenetics

- The study of variability in drug response due to heredity

- Examples in Hem-Onc:
  - **CYP2D6 polymorphism**
    - CPY2D6 "poor metabolizers" receiving tamoxifen for early breast cancer have poorer clinical outcomes (PFS, OS) than "extensive" or "intermediate" metabolizers
  - **DPYD genotype variant**
    - DPYD gene variants associated with DPD deficiency are linked to a 25.6 times increased risk of fluoropyrimidine-related mortality

Schroth W, et al. JAMA 2009
Sharma BB, et al. The Oncologist 2021

Pharmacogenomics

- **Genome**: entire set of DNA instructions found in a cell
- **Genomics**: biology field studying all of the DNA of an organism; identifies and characterizes all the genes and functional elements in an organism's genome
- **Pharmacogenomics:** Using a patient's genomic information to tailor drug selection used in medical management, providing a more individualized approach

genome.gov/genetics-glossary

Germline Mutations

- "**From the patient**"
- **Inherited** genetic alteration from occurring in the germ cells
- Present in every cell in the body
- Can be passed on to future children
- May be present in other family members
- Testing aims to identify mutations that predispose to later-onset diseases (e.g. breast, ovarian, prostate cancers)
- Tested via cheek swab or blood sample (not tumour tissue)

BRCA1
BRCA2

Somatic Mutations

- "**From the Cancer**"
- **Acquire** in DNA with
- Occur i omatic cell
- Neither inherited nor transmitted
- Can be prognosti dictive of clinical course of diagnos se to therapy
- Testing aims to identify "drivers" of cancer grov ay have therapeuti (e.g drugs)
- Tested via sample of malignant tissue (e.g. IHC, FISH, NGS)

ALK

EGFR

ROS-1

NTRK

BRAF

Testing Modalities

- Goal: finding an "actionable mutation/target" for which there is a drug of known clinical activity/benefit/tolerability

Immunohistochemistry (IHC)

- Most common application of immunostaining
- Involves the process of selectively identifying target antigens (proteins) in cells of a tissue section by exposing the cell to select antibodies (probes)
- Staining the cell then shows presence of/intensity of uptake in the tissue sample of the target antigen

- Example: estrogen receptor/ progesterone receptor expression in breast cancer tissue

In Situ Hybridization

- Technique that localizes a sequence of DNA or RNA in a sample (affixed to a glass slide) then exposes the sample to a fluorescent "probe" – a small piece of single stranded DNA tagged with a dye designed to adhere to a specific target section of DNA
  - The labeled probe finds and binds to its matching sequence in the sample

Example: HER2/neu amplification in breast cancer tissue

Next Generation Sequencing (NGS)

- Laboratory technique for determining the exact sequence of nucleotides in a DNA molecule
  - key to understanding the function of genes and other parts of the genome
- "Next generation" sequencing is a version of DNA sequencing that is more efficient/less expensive version of original
- Can look at 1000s of genes up to the whole genome; can evaluate DNA or RNA; DNA tends to be used most but requires the most cells to evaluate; 2-4 weeks turnaround time

- Example: Q31 Hotspot Tumour Panel

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SUMMARY OF TEST RESULTS Positive

Individual Variant Interpretations

Gene ***EGFR***

Exon # 19

Nucleotide NM_005228.5
c.2252_2275delCATCTCCGA
AAGCCAACAAGGAAA

Amino Acid p.Thr751_Glu758del
(p.T751_E758del)

Allelic Fraction 36.0%

Classification **Tier 1A**

Assessment **Pathogenic**

Interpretation

EGFR encodes the Epidermal growth factor receptor (Egfr), a receptor tyrosine kinase that functions as an oncogene. Egfr activates signaling pathways, such as the Ras/Raf/MAPK and PI3K pathways, and stimulates the cell to grow and divide [13]. Amplification, mutation, and overexpression of EGFR may cause excessive proliferation and tumor formation [3, 2]. EGFR activating mutations or amplification may predict sensitivity to Egfr-targeted therapies, including inhibitors of multiple ErbB family members, and several have received FDA approval in some tumor types [9, 12, 14]. Small in-frame deletions in exon 19 and the exon 21 missense mutation L858R account for approximately 40% of all EGFR alterations in non-small cell lung cancer [7, 4]. In-frame insertions within exon 20 of EGFR are found in over 4% of non-small cell lung cancer and associated with resistance to tyrosine kinase inhibitors [1, 8, 10, 16, 17].

Question #3:

- Clinical trials that evaluate actionable driver mutations and targeted therapies have historically underrepresented people from racial or ethnic-minority populations

A. True

B. False

Integrating genomics into clinical oncology: Ethical and social challenges from proponents of personalized medicine

2014

PRECISION MEDICINE

By Latrice G. Landry, Nadya Ali, David R. Williams, Heidi L. Rehm, and

Lack Of Diversity In Genomic Databases Is A Barrier To Translating Precision Medicine Research Into Practice

2018

JAMA Network | Open.

2020

Original Investigation | Diversity, Equity, and Inclusion

Racial and Ethnic Disparities Among Participants in Precision Oncology Clinical Studies

asco special art

Increasing Racial and Ethnic Diversity in Cancer Clinical Trials: An American Society of Clinical Oncology and Association of Community Cancer Centers Joint Research Statement

2022

ASCO-ACCC Joint Statement - 2022

- "*Increasing Racial and Ethnic Diversity in Cancer Clinical Trials*"
- 2-8% of adults with cancer enroll onto trials
  - Tend to be younger, healthier, urban, less diverse racially/ethnically
  - Are results generalizable to all if not representing all?
- Greatest barrier to enrollment: clinicians are not routinely offering clinical trials as a treatment option to all potentially eligible patients
- Barriers are many and include selection bias by clinicians, social determinants of health for patients (logistics, costs, exclusion criteria), institutional barriers (travel)

J Clin Oncol 2022; 40:2163-71.

Access to Testing

- If a new therapy requires confirmation of a driver mutation, cost of testing to identify potentially eligible patients must be integrated into funding
- Differs by tumour type/mutation:
  - Those with established actionable driver mutations likely have reflexive testing in place (e.g. NSCLC)
  - Those with emerging actionable driver mutations likely require reactive/requested testing in place (e.g. NTRK)
  - Funding for testing for systemic therapies that are not provincially funded differs
    - Some tests are covered by manufacturer access programs
    - Some tests require self-funding by patients (including third party insurance coverage)

Patient Cases

- Sources for potential directed-treatment options:
  - **Pathology Report(s)** (ARIA)
    - Surgical Pathology (histologic diagnosis)
    - Next Generation Sequencing Report ("Q31 Hotspot")
    - Immunohistochemistry (IHC)
  - **PODP Formulary** (SharePoint)
    - Searchable database to identify treatments by DSG, drug, regimen, ID#
    - Provides criteria for use, direct links to RRO, drug dose alerts
  - **PODP Funding Algorithms** (SharePoint)
    - Emerging library of algorithms providing an overview of funded therapies and sequences for specific diagnoses

Patient Case - Lung Cancer

- 77 y.o. male
- Prior Stage IIIA NSCLC (right lung) 2 years ago; ALK, EGFR negative; PD-L1 TPS: 60-70%
- Received 1 cycle of adjuvant PEMEtrexed-CISplatin
  - discontinued due to acute nephrotoxicity (CISplatin)
- May 2022: recurrent disease identified on routine follow-up CT (contralateral lung [left])
- June 2022: CT-guided biopsy of left lung lesion
- July 2022: PET: Intense uptake left lower lobe, right lung, right scapula, bilateral hilar and subcarinal lymph nodes

NGS @ CCMB: "Q31 Hotspot"

Shared health
Soins communs
Manitoba

Diagnosis: Non-small cell lung carcinoma

Specimen Type: FFPE Tissue

Primary Tumour Site: Lung

Tumour content (%): 40

Test Performed: Q31 Hotspot Tumour Panel

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GNAS (NM_000516.5)	8	196-220	*TP53* (NM_000546.5)	2-11	1-394 (full CDS)
HRAS (NM_005343.3)	2-3	1-97			

SUMMARY OF TEST RESULTS **Negative**

EGFR negative,
ALK negative,
MET negative,
RET negative

PD-L1 BIOMARKER RESULTS

(Tumour Proportion Score TPS): <1%

Patient Case - Lung Cancer

- Based on Q31 Hotspot and IHC results, targeted therapy is not appropriate
- From past treatment, chemotherapy-induced nephrotoxicity persists (**CrCl = 23 mL/min**)
- All other baseline hematology/biochemistry unremarkable
- Medical Oncologist offers:
  - Triplet therapy with **pembrolizumab, PACLitaxel, and CARBOplatin (PODP Formulary ID: 477)**
    - **100% dose for pembrolizumab, PACLitaxel**
    - **80% dose for CARBOplatin**
- Two cycles so far; no delays or worsening labs

PODP

Non-Small Cell Lung Cancer, Advanced; 1st Line

Indication Medications

CISplatin gemcitabine pembrolizumab CARBOplatin PACLitaxel DOCEtaxel

FORMULARY

pembrolizumab plus platinum-doublet chemotherapy, for the first-line treatment of patients with:

- Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC), Non-Squamous or Squamous cell histology **AND**
- No known epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations **AND**
- Any PD-L1 expression level (including unknown) **AND**
- Good performance status

Treatment with pembrolizumab plus platinum-doublet chemotherapy is intended for 4 cycles.
Following this, pembrolizumab should continue to a maximum of 2 years from start of treatment with chemotherapy, OR until confirmed disease progression or unacceptable toxicity, whichever comes first.

Exclusion criterion:

- Disease relapse within 6 months of completing durvalumab for Stage IIIB disease

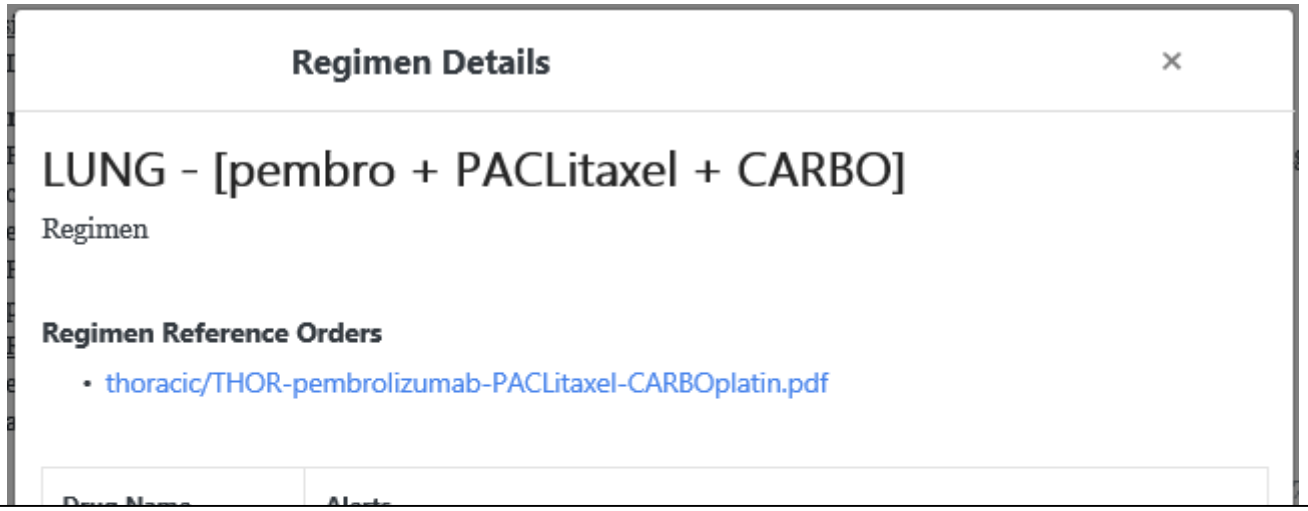
Important Notes:

1. Funded dosing for this indication is pembrolizumab 2 mg/kg (up to a maximum of 200 mg) every 21 days. After completing chemotherapy, pembrolizumab maintenance may also be prescribed at a dose of 4 mg/kg (up to a maximum of 400 mg) every 6 weeks.
2. For patients with PD-L1 of 50% or greater, the choice of 1st line treatment with either single-agent pembrolizumab or pembrolizumab in combination with platinum doublet chemotherapy is left at the physician's discretion.
3. Re-Treatment: Patients who complete pembrolizumab treatment (either at the end of the 2-year treatment duration or earlier) with stable disease or better are eligible for re-treatment with up to 17 additional doses of pembrolizumab (e.g. one additional year) if they subsequently experience disease progression.

Id: 477

Regimens:

LUNG - [pembro + DOCEtaxel + CARBOplatin]	LUNG - [pembro + gemcitabine + CARBOplatin]	LUNG - [pembro + gemcitabine + CISplatin]
LUNG - [pembro + PACLitaxel + CARBO]	LUNG - [pembrolizumab q 21 days (maintenance)]	LUNG - [pembrolizumab q 42 days (maintenance)]



Regimen Details

LUNG - [pembro + PACLitaxel + CARBO]

Regimen

Regimen Reference Orders

- thoracic/THOR-pembrolizumab-PACLitaxel-CARBOplatin.pdf

ADULT

Updated: November 1, 2022

Regimen Reference Order

THOR – pembrolizumab + PACLitaxel + CARBOplatin

ARIA: LUNG - [pembro + PACLitaxel + CARBO]
LUNG - [pembrolizumab q 21 days (maintenance)]
LUNG - [pembrolizumab q 42 days (maintenance)]

Planned Course: **pembrolizumab + PACLitaxel + CARBOplatin every 21 days for 4 cycles, followed by pembrolizumab every 21 days up to 31 cycles or until disease progression or unacceptable toxicity (maximum 2 years of therapy)**

OR

pembrolizumab + PACLitaxel + CARBOplatin every 21 days for 4 cycles, followed by pembrolizumab every 42 days up to 16 cycles or until disease progression or unacceptable toxicity (maximum 2 years of therapy)

Indication for Use: **Lung Cancer Non-Small Cell Squamous Metastatic**

Patient Case – Colorectal Cancer

- 78 y.o. female
- Abdominal pain in Spring 2021 led to imaging which confirmed a large pericolonic mass into transverse colon
  - Necrotic – differential: lymphoma vs. primary CRC vs. GIST
- Concern for bowel perforation with neoadjuvant chemotherapy
- Biopsy via colonoscopy confirmed poorly differentiated carcinoma
- Extended right hemicolectomy led to further pathological assessment: IHC for MMR

Mismatch Repair (MMR) and Microsatellite Instability (MSI)

- Genetic subset of colorectal cancer tumors with mismatch-repair deficiency (dMMR)
  - 15% of all patients with colorectal cancer (both sporadic and hereditary)
    - Sporadic dMMR: methylation of the *MLH1* gene promoter
    - Hereditary dMMR: germline mutations in the *MLH1* and *MSH2* genes

Mismatch Repair (MMR) and Microsatellite Instability (MSI)

- Results in the inability of cells to recognize and repair spontaneous mutations, resulting in a very high tumor mutation burden and altered microsatellite sequences that render these tumors high in microsatellite instability (MSI-H)
- Mounting evidence suggests that MSI-H–dMMR tumors are less responsive to conventional chemotherapy

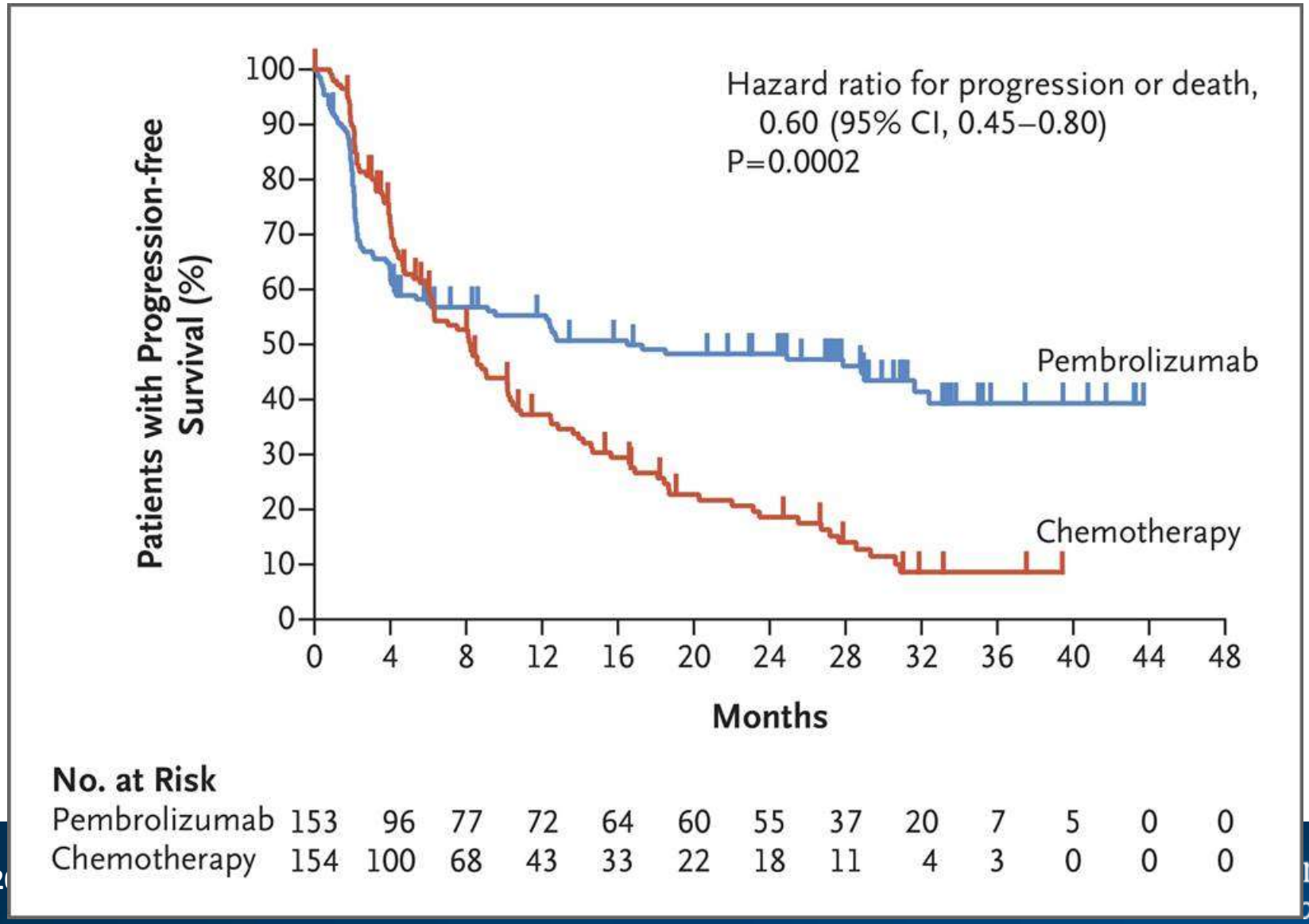
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

- KEYNOTE 177
- Compared pembrolizumab to various chemotherapy options (FOLFIRI, FOLFOX6, bevacizumab + FOLFIRI or FOLFOX6, cetuximab + FOLFIRI or FOLFOX6) for 1st line treatment of mCRC

KEYNOTE 177


Hazard ratio for progression or death,
0.60 (95% CI, 0.45–0.80)
P=0.0002
Pembrolizumab
Chemotherapy
Patients with Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 4 8 12 16 20 24 28 32 36 40 44 48
Months
No. at Risk
Pembrolizumab 153 96 77 72 64 60 55 37 20 7 5 0 0
Chemotherapy 154 100 68 43 33 22 18 11 4 3 0 0 0

Back to our Case: dMMR

- Performed via Immunohistochemistry (IHC) of surgical specimen
- Tests expression of 4 MMR proteins that work in pairs (MSH2 with MSH6; MLH1 with PMS2); if one is lost, the other is usually lost; confirms dMMR

ADDENDUM
COLORECTAL CARCINOMA RESECTION MISMATCH REPAIR (MMR) PROTEIN EXPRESSION

NATURE OF SPECIMEN: Colon

IHC performed on block: **A13**

RESULTS:

MLH1: **Loss** of nuclear positivity, tumor cells
PMS2: **Loss** of nuclear positivity, tumor cells
MSH2: Intact nuclear positivity, tumor cells
MSH6: Intact nuclear positivity, tumor cells

Interpretation:
…this tumor is MSI high, showing loss of nuclear staining for MLH1 and PMS2.

BRAF immunohistochemistry (anti-BRAF V600E, clone VE1) has been ordered and results will be reported as a supplemental report.

Questions

- Do we have enough information to select a 1st line treatment?

- Which 1st line treatment is optimal for this patient?

PODP Formulary ID: 570

Colorectal Cancer, Advanced/Metastatic; MSI-High/dMMR; 1st line

FORMULARY

pembrolizumab monotherapy, for the first line treatment of patients with:

- Metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer **AND**
- No prior treatment for metastatic MSI-H/dMMR colorectal cancer **AND**
- Good performance status

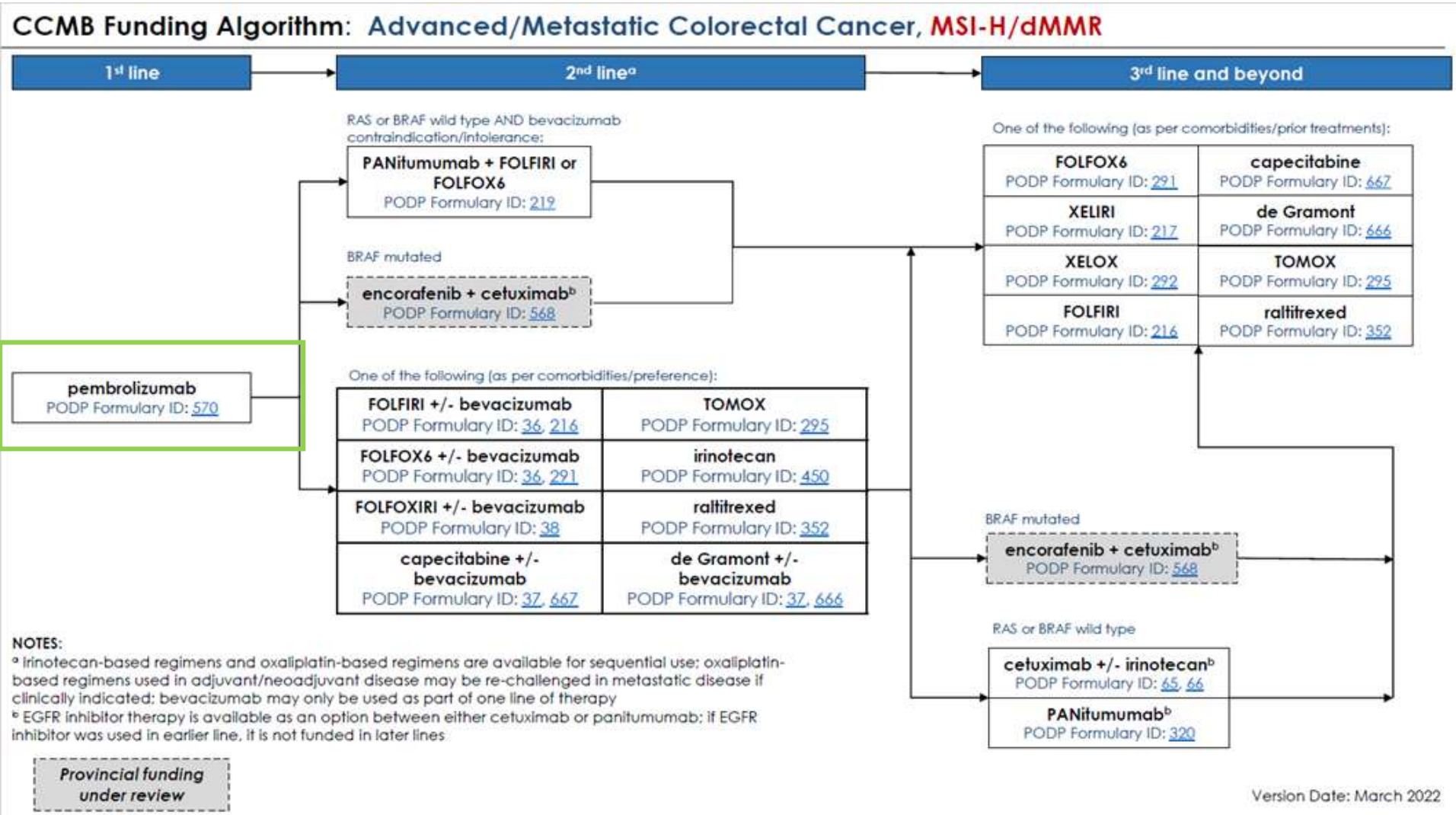
Treatment should continue until confirmed disease progression or unacceptable toxicity to a maximum of 2 years or 35 doses, whichever comes first.

Regimens:

GAST - [pembrolizumab q 21 days]

Reference:
Andre T, Shiu KK, et al. "Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer." *N Engl J Med* 2020; 383 (23):2207-18.

mCRC Funding Algorithm - dMMR

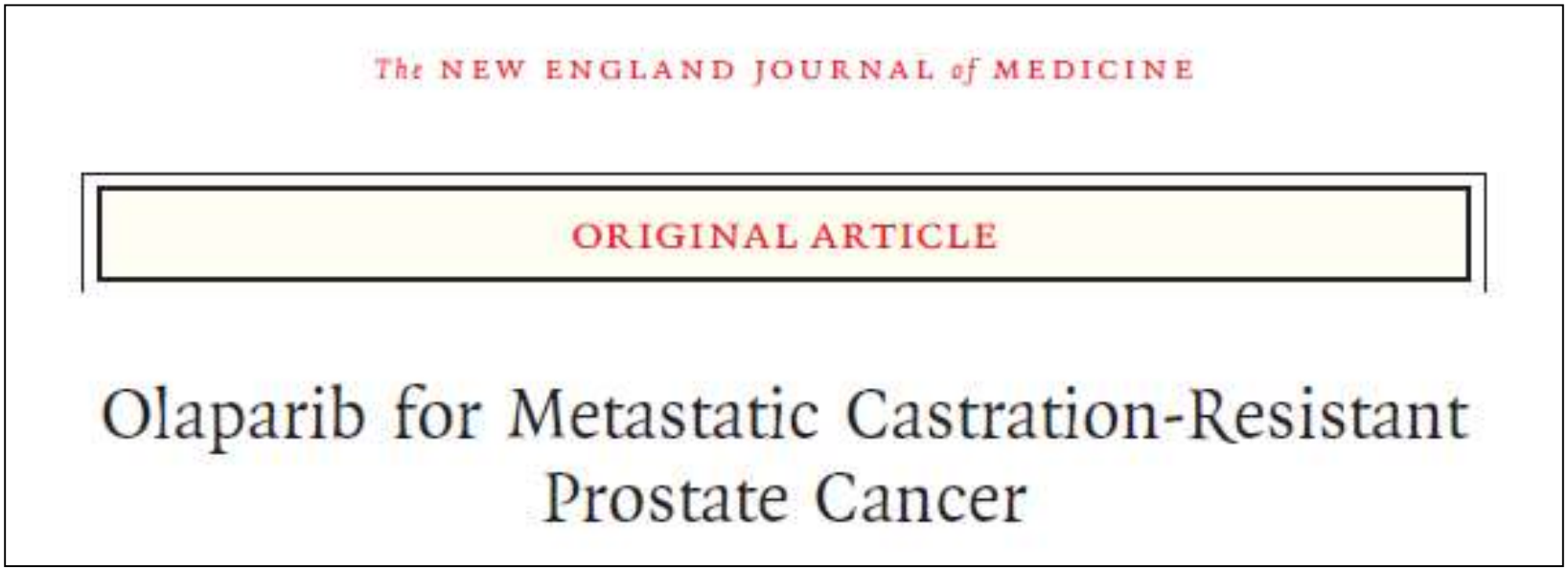


CancerCare Manitoba
ActionCancerManitoba

BRCA mutation

- BRCA1 and BRCA2 are tumor suppressor genes
- Common functional link between BRCA1/2 proteins is the homologous recombination repair (HRR) pathway
  - Promotes DNA double-strand break (DSB) repair
- Deleterious mutations in BRCA gene are known to be pathogenic
  - Interfere with BRCA1/2's DNA repair function
- Alteration can occur in germline or somatic cells
- BRCA1 or BRCA2 mutations are mutually exclusive
- Associated with ovarian, breast, and prostate cancers

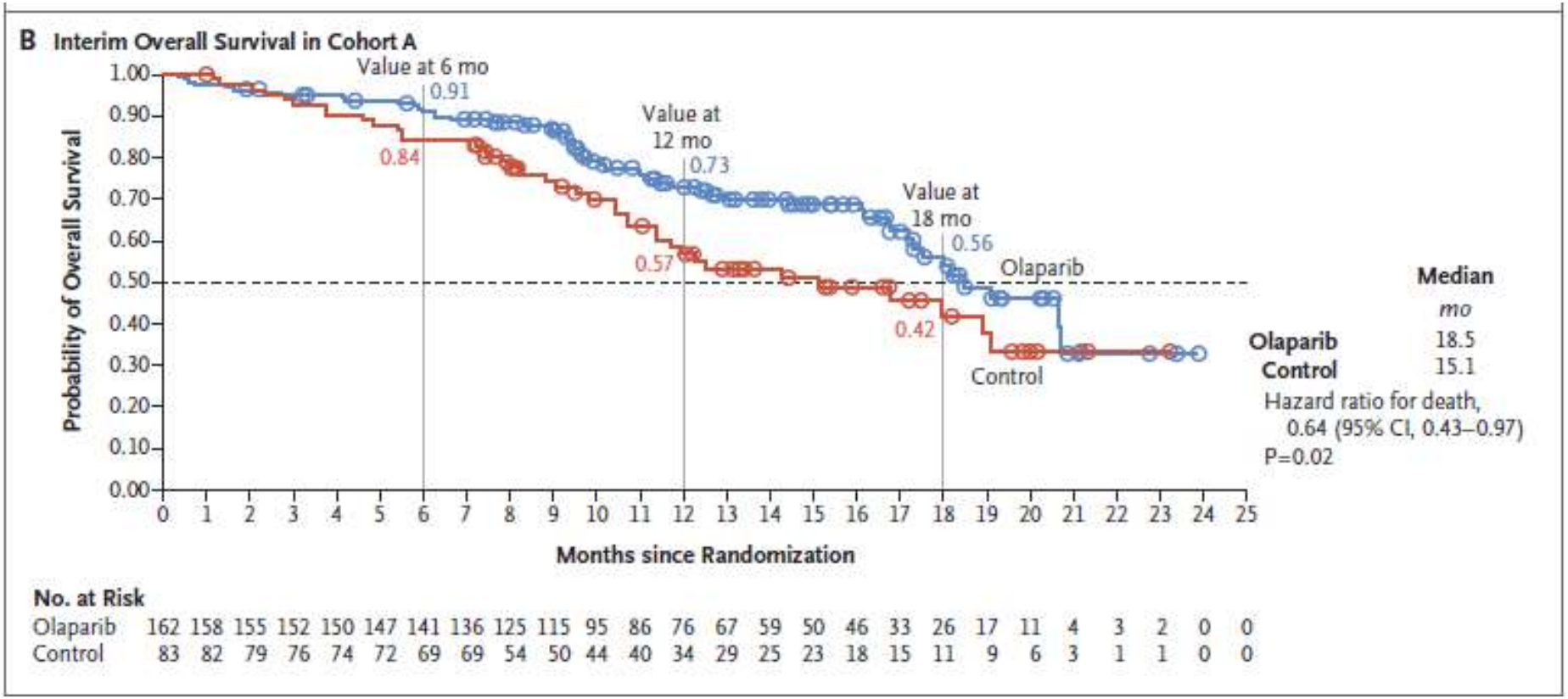
BRCA mutation



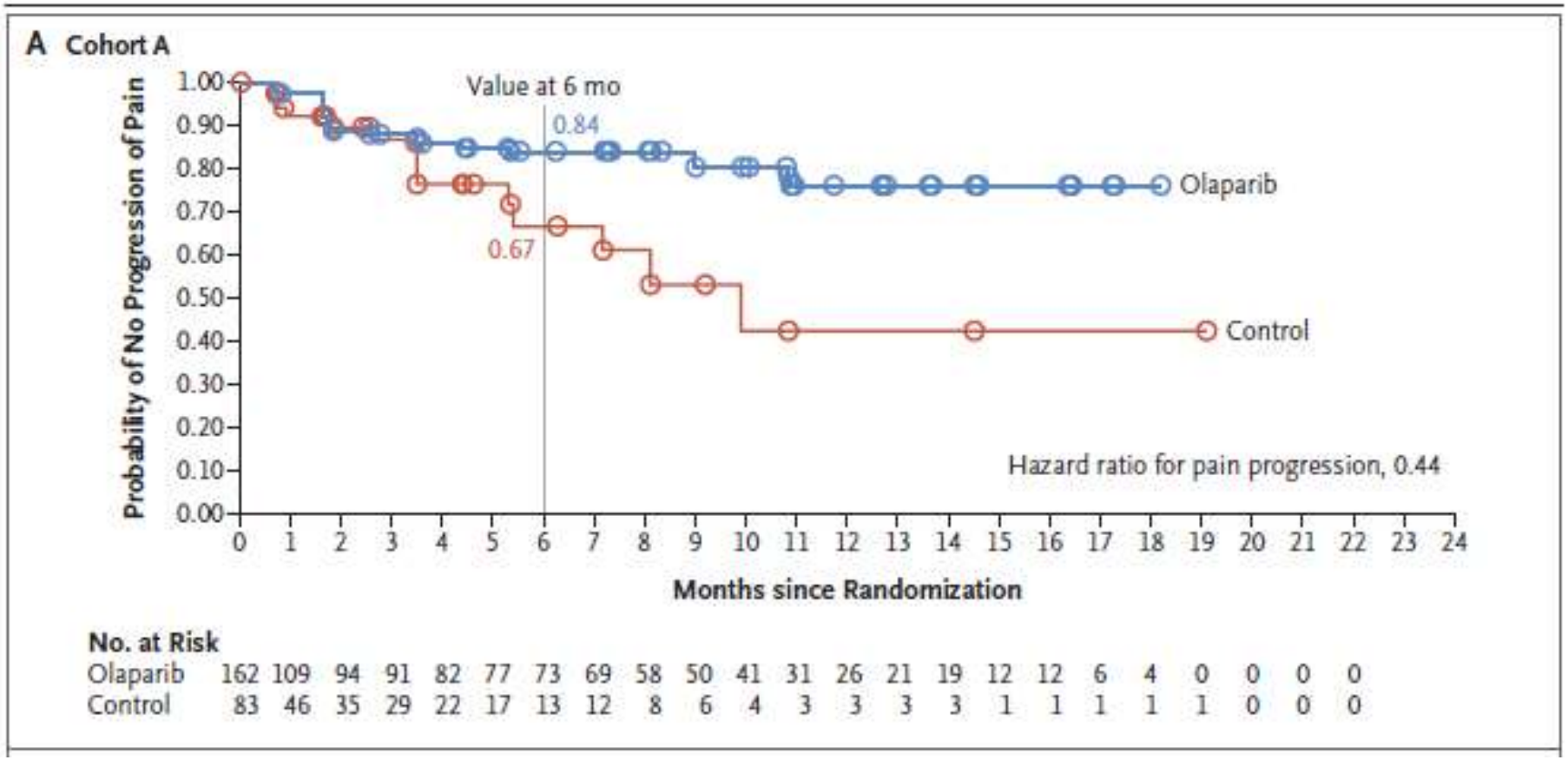
Cohort A: *Patients with at Least One Alteration in* BRCA1, BRCA2, *or* ATM *(Cohort A)*

olaparib tablets (300 mg twice daily) or the prespecified physician's choice of enzalutamide (160 mg once daily) or abiraterone (1000 mg once daily, plus prednisone at a dose of 5 mg twice daily) (control group).

BRCA mutation



BRCA mutation



Patient Case – Prostate Cancer

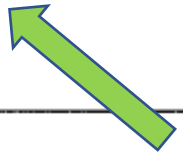
- 62 y.o. male
- Diagnosed with locally advanced prostate cancer in 2020; initiated ADT with goserelin and RT
- 2021: retroperitoneal recurrence; initiated enzalutamide for metastatic castrate-resistant prostate cancer (mCRPC)
- Summer 2022: enlarging retroperitoneal disease; PSA increase; screened for clinical trial enrollment – includes NGS testing assessment for potential BRCA, ATM mutations

"FoundationOne Liquid CDx"

FoundationOne® Liquid CDx CTA interrogates 324 genes, including the complete exonic sequence of 309 genes and select introns of 15 genes (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity across the entire coding region unless otherwise noted.

STUDY
Partner Name **Clovis Oncology**
Partner Study ID **CO-338-063 FACT CF3**
FMI Study ID **FoundationOneLiquidDx-BPA-PRO-20-2011**

TEST
FMI Test Order # **ORD-1100289-01**
Test Type **FoundationOne Liquid AB1**
Report Date **04 Jun 2021**



STUDY-RELATED DELETERIOUS ALTERATION(S)

GENE	ALTERATION
BRCA1	None
BRCA2	K2472fs*7

Prostate Cancer, Metastatic, Castration-Resistant (mCRPC); BRCA/ATM mutation

Indication Medications

olaparib

RESTRICTED

olaparib monotherapy, for the treatment of patients with:

- Metastatic castration-resistant prostate cancer (mCRPC) **AND**
- Deleterious or suspected deleterious germline and/or somatic mutations in the homologous recombination repair (HRR) genes *BRCA* or *ATM* **AND**
- Disease progression following prior treatment with a new hormonal agent / androgen receptor-axis-targeted agent (ARTA) **AND**
- Good performance status

Treatment should continue until confirmed disease progression or unacceptable toxicity.

Request Information

Request Form

- *HCD Program Eligible*

Request Form to Use: "Restricted Drug Form - GENITOURINARY DSG"

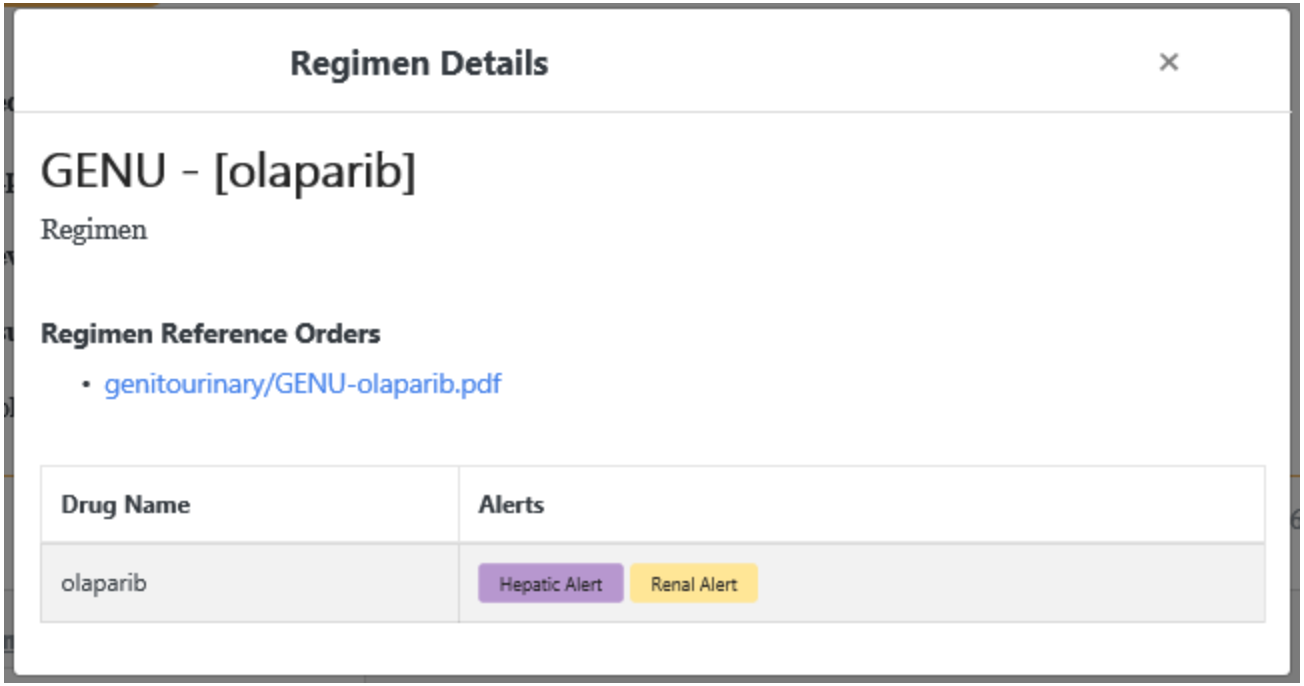
Supporting Documentation: Confirmation of BRCA/ATM mutation

Reviewed by: Genitourinary DSG Chair, or Designate

Usual Duration of Approval: 5 years, then reassess

olaparib dispensed by CancerCare Manitoba Pharmacy

Id: 561



ADULT ORAL

Updated: May 31, 2022

Regimen Reference Order – GENU – olaparib

ARIA: GENU - [olaparib]

Planned Course: Twice daily until disease progression or unacceptable toxicity (1 cycle = 30 days)

Indication for Use: BRCA or ATM Mutated Castration-Resistant Prostate Cancer

NTRK

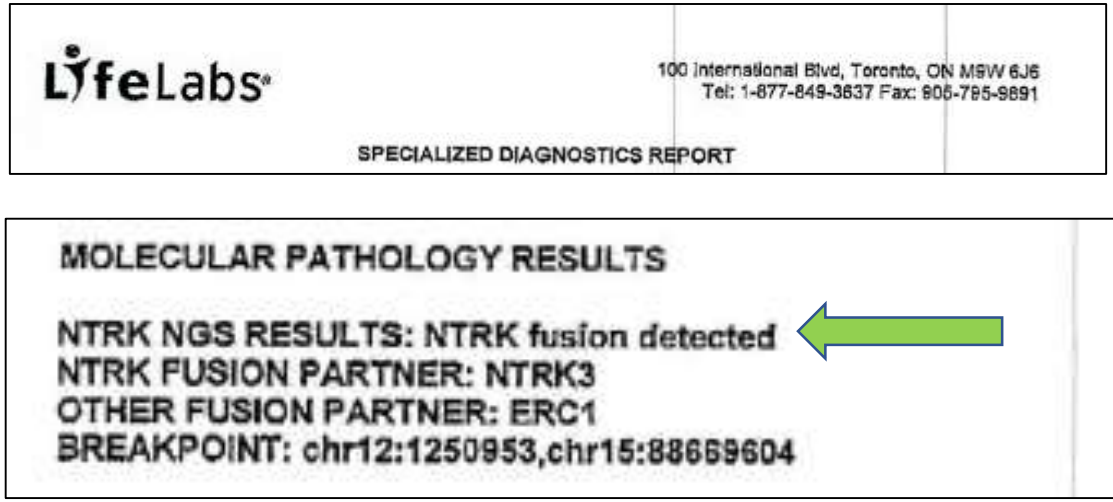
- Neutrotrophic Tyrosine Kinase (NTRK) is an oncogene whose gene products (the TRK family of receptors) express cell surface receptor tyrosine kinases that bind to neurotrophic ligands.
- TRK activation results in the autophosphorylation of intracellular tyrosine residues (signals MAPK, PI3K, PKC pathways downstream)
- Somatic NTRK mutations have been identified in multiple tumour types – colorectal, lung, breast, melanoma, AML, neuroblastoma
- Fusions involving *NTRK1, NTRK2, NTRK3* proteins is common mechanism for TRK oncogenic activation

NTRK

- Two NTRK tyrosine kinase inhibitors under review for funding:
  - Entrectinib
  - Larotrectinib
- Studies for NTRK inhibitors have been "tumour agnostic"
  - Basket trials of small numbers of patients of different diagnoses
- Place in therapy is after "all other satisfactory treatment options" have been used (interpretation of that definition is variable)
- Only larotrectinib has approval in pediatrics

NTRK

- Not included in Q31 Hotspot
- Both agents have manufacturer access programs at this time
- NTRK NGS testing is not provincially funded at this time



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SPECIALIZED DIAGNOSTICS REPORT

MOLECULAR PATHOLOGY RESULTS

NTRK NGS RESULTS: NTRK fusion detected
NTRK FUSION PARTNER: NTRK3
OTHER FUSION PARTNER: ERC1
BREAKPOINT: chr12:1250953,chr15:88669604

Question #4

- Which drug is "mismatched" with its intended mechanism/target:

A. Entrectinib – NTRK fusion mutation

B. Olaparib – BRCA mutation

C. Pembrolizumab – CTLA-4

D. Pembrolizumab – deficiency in MMR

Question #5

- In the electronic health record (e.g. ARIA), pertinent diagnostic information about potential gene mutations/drug targets can be found in:

A. Surgical Pathology

B. "Q31 Hotspot" Tumour Panel

C. Immunohistochemistry

D. All of the above

Take Home Messages

- Terms pharmcogenetics, pharmacogenomics, are often used interchangeably
- Available clinical trial evidence in pharmacogenomics often underrepresents the diversity in the general population
- More and more systemic therapies listed on PODP Formulary have demonstrated evidence of benefit when patient-specific and tumour-specific targets are identified
- Current access to testing varies by tumour type and mutation/target

Resources

- **oncoKB.org**
  - US-based website documenting therapeutic level of evidence for various systemic therapies (MSKCC)
- **genome.gov**
  - US-based website with glossary of terms related to genomic topics
- **CPICgx.org**
  - Clinical Pharmacogenetics Implementation Consortium
  - Guidelines for implementing pharmacogenetic testing into clinical practice
- **CADTH.ca**
  - Canadian agency providing evidence-based reviews of emerging anticancer drugs for Canadian jurisdictions
- **Mypathologyreport.ca**
  - Canadian website with patient-directed information to understand pathology reports; content created by Canadian pathologists and patients