Precision Oncology Comes of Age: Tumor-Agnostic Approaches

Colleen Lewis, MSN, ANP-BC, AOCNP®

R. Donald Harvey, PharmD, BCOP, FCCP, FHOPA

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

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  - Consultant: Takeda, Bristol-Myers Squibb, GlaxoSmithKline
- Ms. Lewis
  - Consultant: Genentech

Learning Objectives

1. Identify clinical trial designs, including basket trials, that enable development of tumor-agnostic therapies
2. Evaluate how testing methodologies, including next-generation sequencing, support the advancement of precision medicine
3. Interpret tumor-agnostic treatment approaches, such as those aimed at managing patients with tumors that have high microsatellite instability (MSI-H) or neurotrophic receptor tyrosine kinase (NTRK) fusions

Changes in Oncology Drug Development

- Two dominant therapeutic directions
  - Targeted (molecularly specified) agents
    - Small molecules, monoclonal antibodies
  - Immunotherapeutics
    - Multiple agents, targets, approaches
- “Seamless” drug development
  - Evolution of the continuous phase I trial

Challenges

- Each potential new therapy is typically tested independently from other therapies seeking to treat the same condition
- For every new trial, the protocol must be reviewed by a number of oversight entities
  - New phase III trials require an average of 36 administrative or regulatory approvals and average more than 2 years

Challenges

- Approximately 4-8% of adult cancer patients enroll in clinical trials
  - Inability to meet accrual goals is a frequent factor causing trials to close, wasting time, money, and limited patient resources
- New therapies molecularly targeted against specific mutations may be present in only a fraction of the patient population

Seamless Drug Development

- Blurring of phases of trials/removal of later-phase trials
  - Bendamustine, crizotinib, osimertinib
- Pembrolizumab
  - Phase I initiated 2011
  - Early activity signals led to rapid expansion of cohorts
  - Total phase I population = 1200 patients
  - Led to approval in 2 diseases and a companion diagnostic
- More efficient enrollment, lower total sample size in development

Prowell TM, et al. *N Engl J Med*. 2016;374:2001-3.

Seamless Drug Development

- Design concerns emerge

Questions Regarding the Design of Large First-in-Human Cancer Trials.

- Is there a compelling rationale for including multiple expansion cohorts?
- Is the sample-size range consistent with the stated objectives and end points?
- Is there an appropriate statistical analysis plan for all stated end points?
- Are the eligibility criteria appropriately tailored to the expansion cohorts?
- Is there a defined end to the trial, in terms of both efficacy and futility?
- Is there a system in place to communicate with all investigators in a timely fashion?
- Does the informed consent reflect the current knowledge of safety and efficacy of the investigational drug and other agents in the same class?
- If the trial may be used for regulatory approval, is there an independent oversight committee?
- If the trial may be used for regulatory approval, has there been communication with regulatory agencies?

Prowell TM, et al. *N Engl J Med*. 2016;374:2001-3.

Seamless Drug Development: Mind the Gap(s)

- Decreased trial population
- Rapid acceleration of dose derivation and adoption for licensing trials
- Clinical pharmacology studies

Precision Medicine Strategies in Oncology

- Cancer focused and/or patient focused
- Cancer-based approaches
  - Tumor genomics
  - Immune profiling
    - Population vs individual
- Patient-based approaches
  - Individualized dose
    - Pharmacogenomic data
    - Therapeutic drug monitoring
    - Reactive to adverse events

Precision Medicine: Historical Examples

- Breast cancer
  - Estrogen-receptor status, HER2 status
- Pharmacogenomics
  - Irinotecan – UGT1A1

DOSAGE AND ADMINISTRATION

- **Do not substitute ONIVYDE for other drugs containing irinotecan HCl. (2.1)**
- Recommended dose of ONIVYDE is 70 mg/m^2 intravenous infusion over 90 minutes every two weeks. (2.2)
- Recommended starting dose of ONIVYDE in patients homozygous for UGT1A1*28 is 50 mg/m^2 every two weeks. (2.2)
- There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. (2.2)

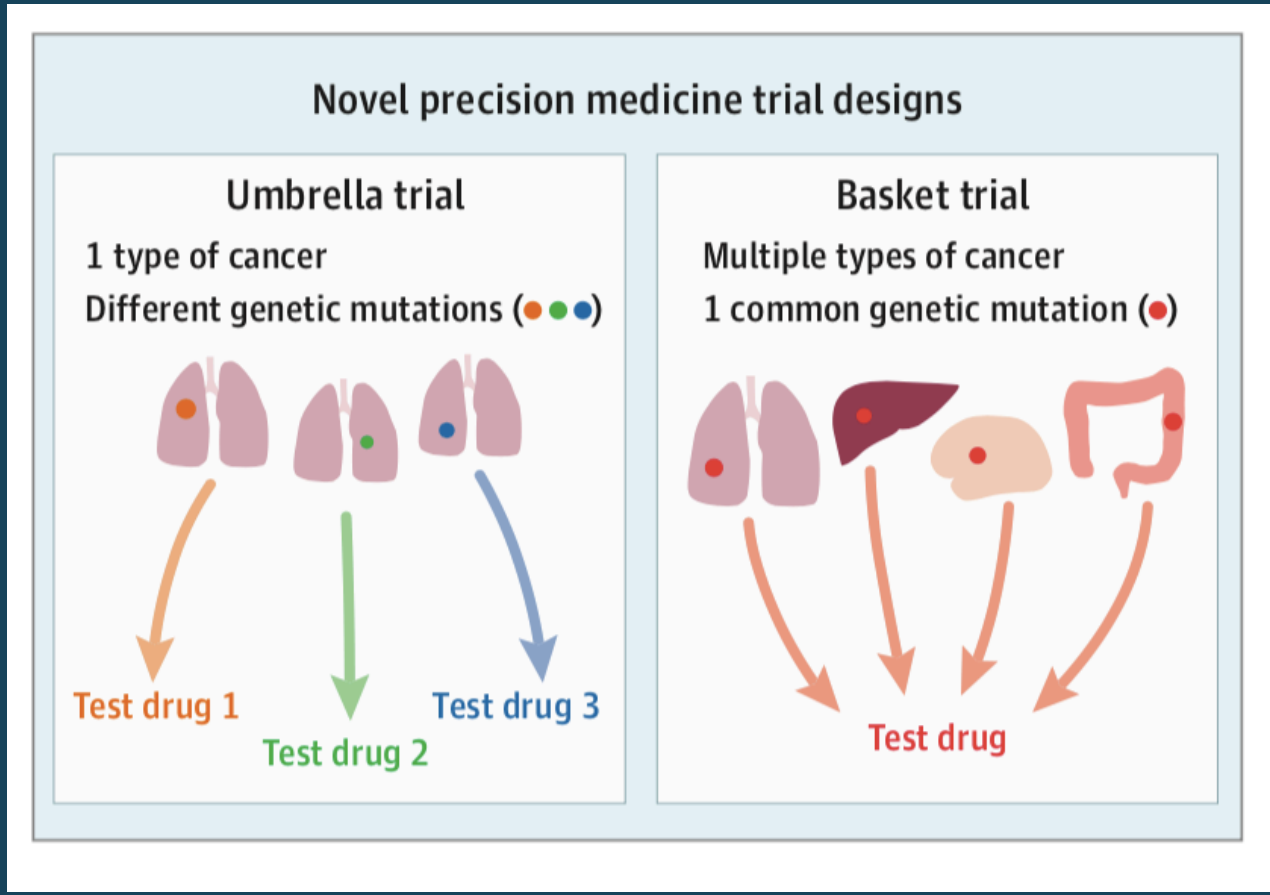
Prescribing information, ONIVYDE (irinotecan liposome injection).

Individualizing Therapy: Benefits and Drawbacks

- Benefits
  - Improved likelihood of depth and duration of response
  - Prevention/mitigation of adverse events
  - Potential for lower doses
- Drawbacks
  - Effort to identify population of interest
  - By definition, excludes patients
  - Cost of additional testing

Trial Designs Focused on Precision Approaches

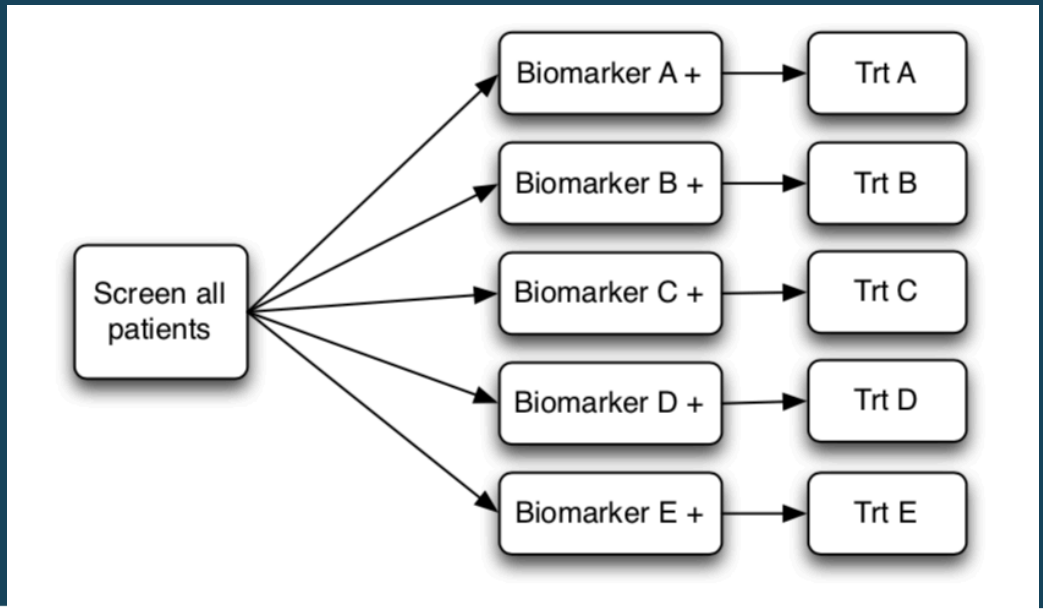
- Master protocol types
  - Umbrella
  - Basket

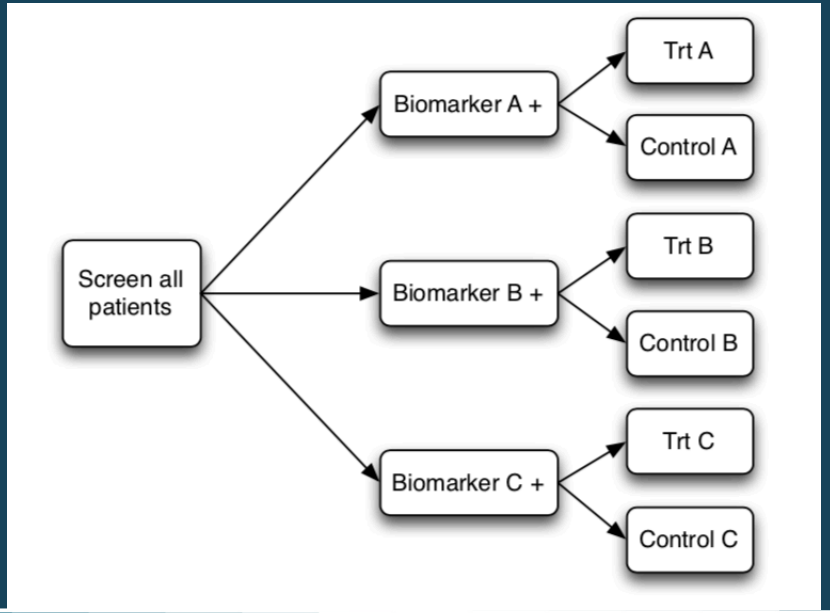


West H. *JAMA Oncol*. 2017;3(3):423.

Trial Designs Focused on Precision Approaches

- Umbrella
  - Single histology, multiple biomarkers each attached to treatment
  - Example: The ASCO Targeted Agent and Profile Utilization Registry (TAPUR) trial, Lung-MAP trial (SWOG)
  - Next generation trials – I-PREDICT (combinations), TARGET (circulating DNA), WINTHER (RNA sequencing and adjacent tissue profiling)





ASCO = American Society of Clinical Oncology.
LeTourneau C, et al. *Nature Medicine* 2019;25:711-12.

Trial Designs Focused on Precision Approaches: Umbrella Trials

Strengths

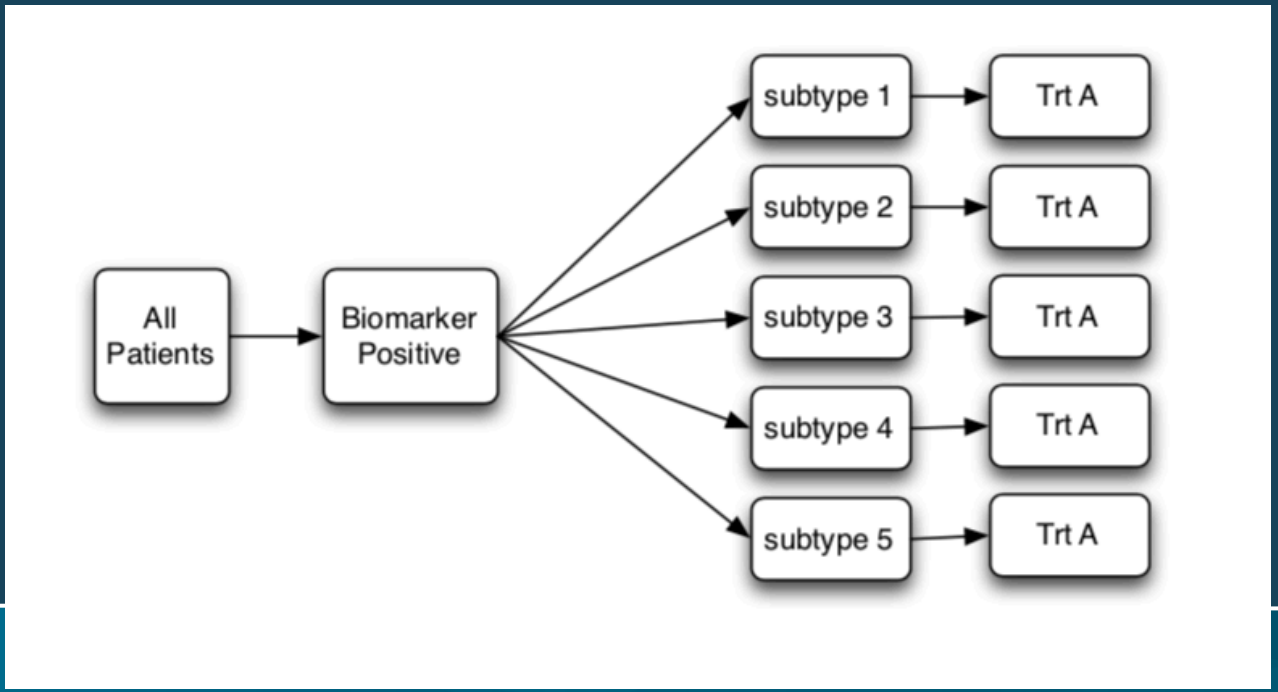
- When biomarker prevalence is low, improves screen success rate with multiple arms
- Flexible design can easily add or drop arms

Weaknesses

- May require large number of drugs and biomarkers
- Development of multiplex assay more complex than single biomarker
- Often requires regulatory review of both drugs and assay

Trial Designs Focused on Precision Approaches

- Basket (= bucket, tumor agnostic)
  - Single treatment, single biomarker, different histologies/anatomic sites
  - Example: Larotrectinib for patients with NTRK gene fusion



Trial Designs Focused on Precision Approaches: Basket Trials

Strengths

- Can be more efficient than multiple histology specific enrichment trials
- If treatment already approved in another disease, can quickly learn if efficacy translates to other indications
- Only need to develop one assay for the trial

Weaknesses

- Disease subtype is often prognostic so choice of endpoints is limited
- Without a comparative arm, can't distinguish predictive from prognostic
- Some baskets may have small sample sizes if mutation is rare

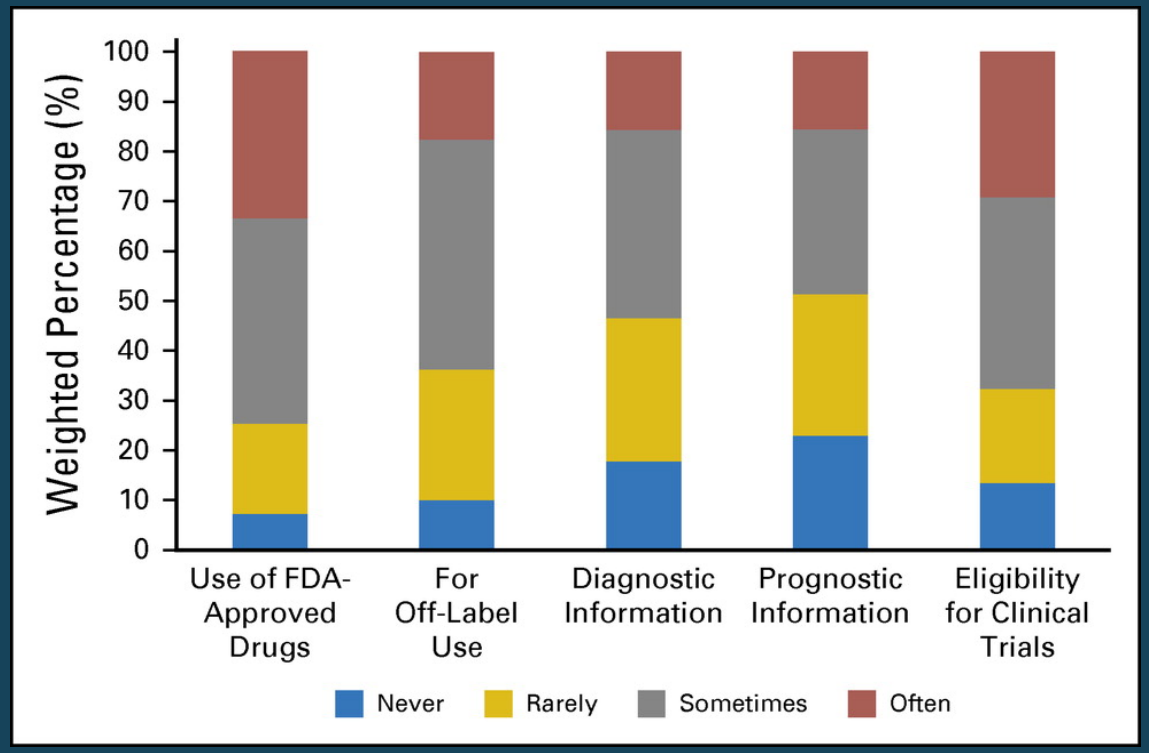
Individual Patient Management Strategies

Next Generation Sequencing (NGS): Oncology

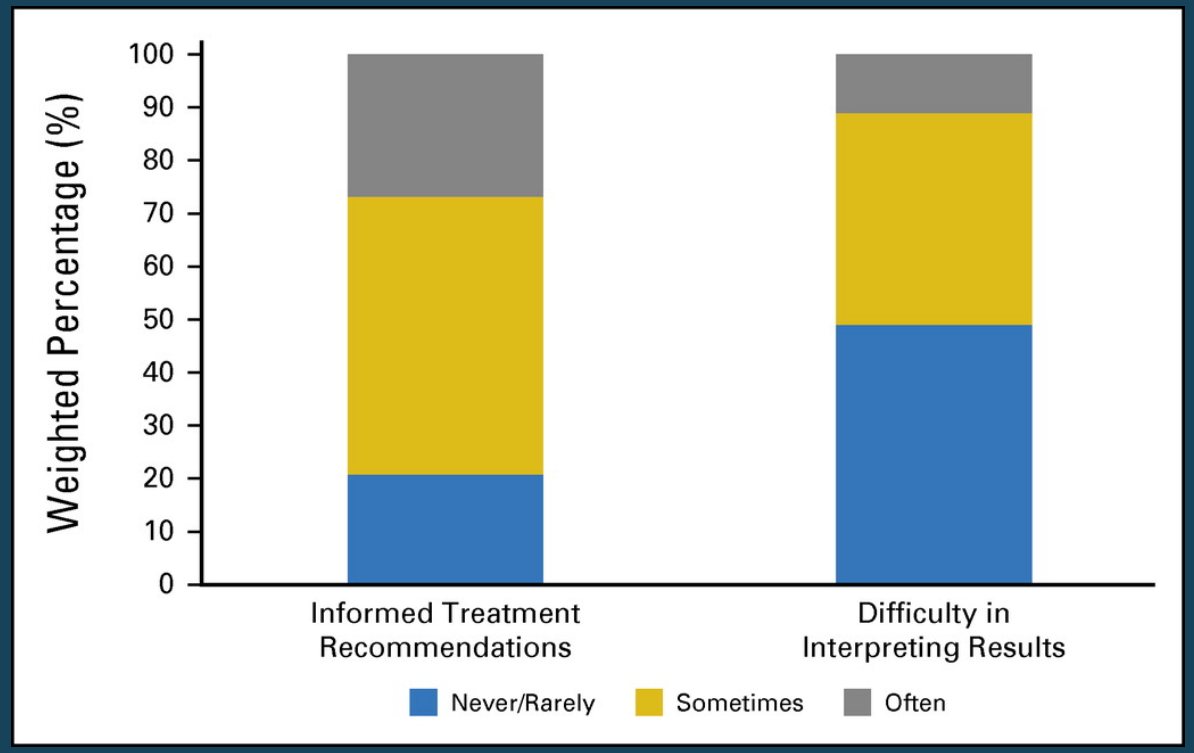
- Developed to obtain genomic data in a timely and cost-effective way based on the data learned from previous whole exome sequencing based comprehensive studies.
- Clinically important genes are examined.
- First choice for individual cancer patient care, when introducing NGS technology into daily practice.

Nagahashi M, et al. *Cancer Sci*. 2019;110(1):6-15.

Clinical Use of NGS: Current Landscape



Use of NGS tests by clinical purpose over the past 12 months among oncologists in the United States.



Use of NGS testing over the past 12 months among oncologists in the United States.

2017 National Survey of Precision Medicine in Cancer Treatment

Freedman AN, et al. *J Clin Oncol Precision Oncol*. 10.1200/PO.18.00169

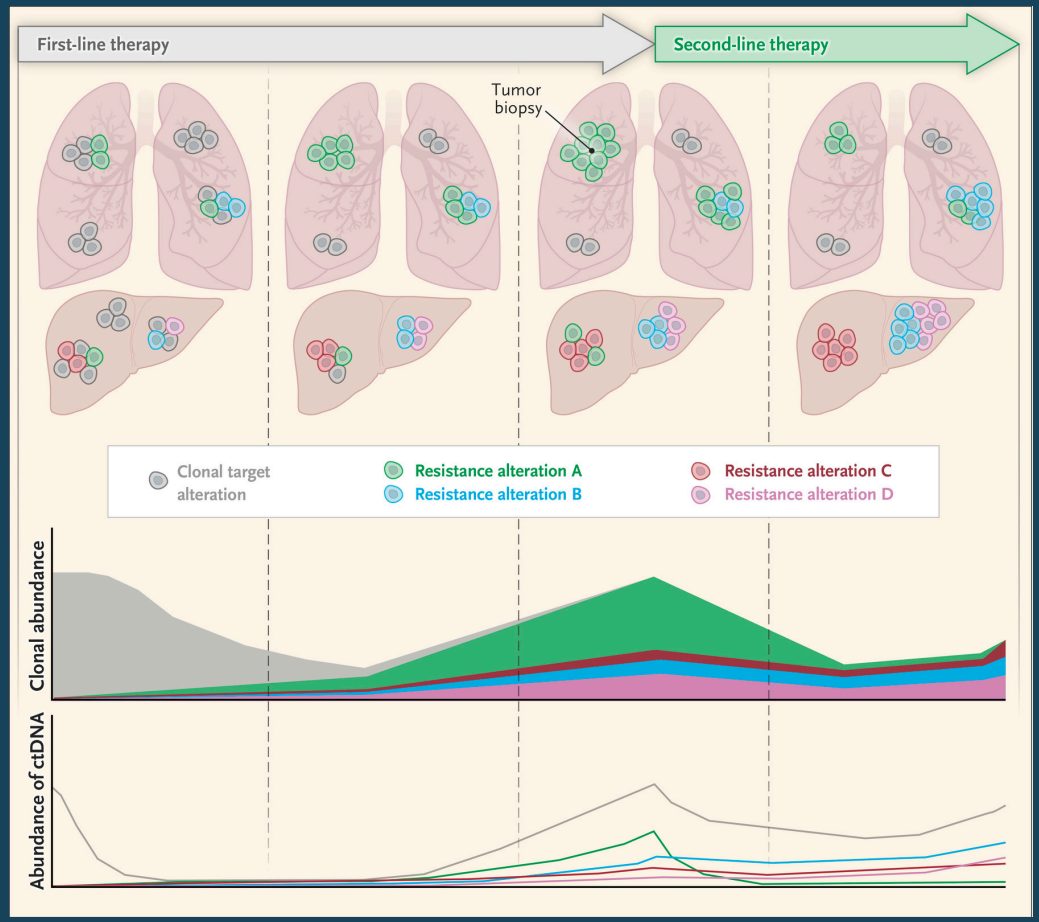
Tissue Testing

- Current gold standard, allows for histologic interpretation and non-DNA-based alterations (hormone receptors)
- Tumor heterogeneity: Biopsy may capture partial genomic landscape of tumor
- Can misguide interpretation and treatment decisions
- Radiation and DNA-damaging agents can impact genomic heterogeneity of recurrent/metastatic disease
    - Repeat biopsy?
- Patients may require multiple samples over time to assess evolving changes
- High-quality specimens are required for best information

Corcoran R, et al. *N Engl J Med*. 2018;379:1754-65; Miles G, et al. *Semin Oncol*. 2015;42(5):713-23.

Liquid Biopsies

- Circulating tumor DNA (ctDNA) is a portion of cell-free DNA, fragmented DNA in the noncellular component of blood – detectable ctDNA can vary
- Newer data show more concordance of tissue and blood samples
- 15% of patients with metastatic cancer may not have sufficient ctDNA levels to allow for mutational profiling from plasma
- Early diagnosis, serial testing
- Monitoring of resistance
  - EGFR T790M in lung cancer



Corcoran R, et al. *N Engl J Med*. 2018;379:1754-65.

NGS: When to Order

- Archival tissue available?
- Age of tissue?
  - Archival surgical tissue should be < 5-7 years old
- New biopsy required for other clinical reasons?
- Biopsies: post neoadjuvant therapy, unresectable patients, progression, core specimen required
- Patients at high risk for recurrence
- Insurance considerations

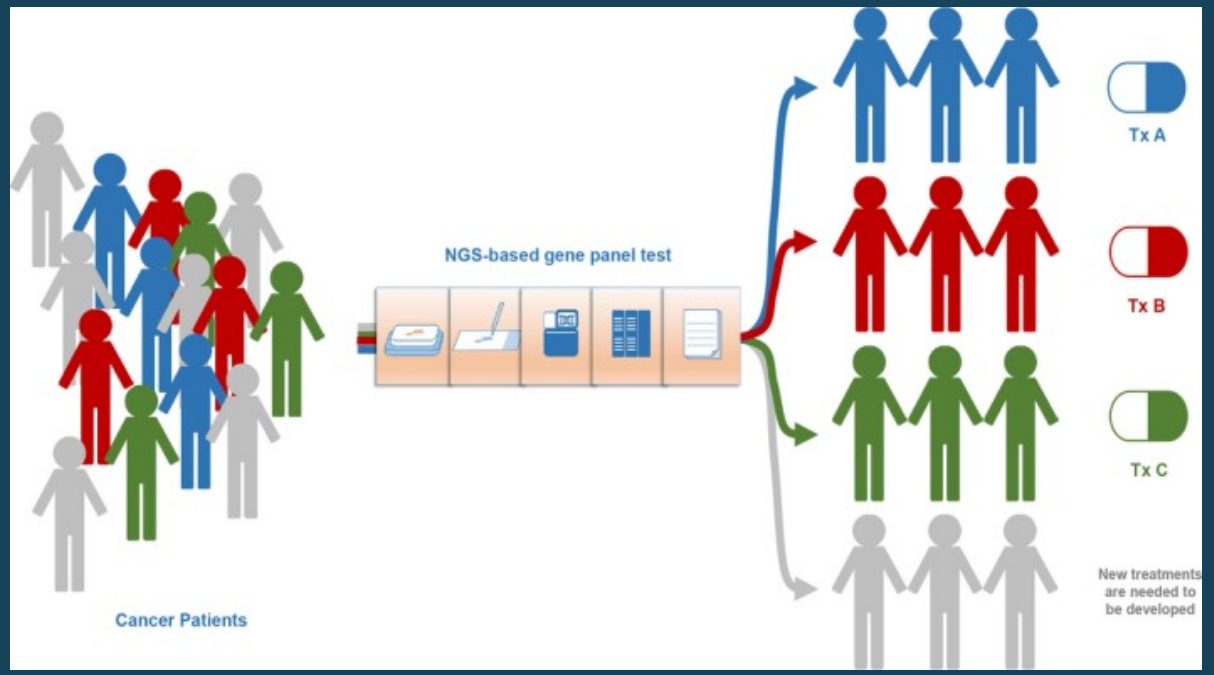
CMS.gov
Centers for Medicare & Medicaid Services

Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)

- Recurrent, metastatic, relapsed, refractory, or stage III or IV cancer
- Not been previously tested using the same NGS test for the same primary diagnosis of cancer
- Repeat testing using the same NGS test only when a new primary cancer diagnosis
- Patient decided to seek further cancer treatment (e.g., therapeutic chemotherapy)

NGS: Interpretation of Results

- No mutations/no actionable mutations
- Mutation that may help select therapy or is associated with resistance to molecular therapies
- Multiple actionable mutations
- Driver vs passenger mutations
- Challenge
  - Discordance with blood-based ctDNA and other platforms
    - RNA-based testing, depth of reads



Nagahashi M, et al. *Cancer Sci*. 2019;110(1):6-15.

Multiple Mutations: Where Do You Start?

- 1/15/19: patient with locally advanced unresectable pancreatic adenocarcinoma
  1/21/19 to 5/15/19: FOLFIRINOX
- Feb 2019 referred from community oncologist
- NGS ordered, MSI-high
- 5/15/19: Restaging with PD
- 6/14/19: Nivolumab c1, d1 q4wk
- 8/30/19: CT CAP: PR (decreased primary pancreatic lesion with increased tumor necrosis)

CT-CAP = CT chest, abdomen, pelvis; FOLFIRINOX = fluorouracil, irinotecan, oxaliplatin; PD = progressive disease.

Testing on Foundation Medicine platform

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Microsatellite status - MSI-High	Pembrolizumab	Atezolizumab
		Avelumab
		Cemiplimab-rwlc
		Durvalumab
		Nivolumab
10 Trials *see p. 20*		
Tumor Mutational Burden - TMB-Intermediate (19 Muts/Mb)	No therapies or clinical trials. see Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ERBB2 - V842I	none	Ado-trastuzumab emtansine
		Afatinib
		Dacomitinib
		Lapatinib
		Neratinib
		Pertuzumab
		Trastuzumab
		Trastuzumab-dkst
		Trastuzumab-dttb
		Trastuzumab-pkrb
9 Trials *see p. 23*		Trastuzumab-qyyp
PIK3CA - R108H	none	Everolimus
10 Trials *see p. 26*		Temsirolimus
ARID1A - R1223C, P2083H	none	none
6 Trials *see p. 22*		
IDH1 - R132C	none	none
1 Trial *see p. 25*		

Common Mutations, No Therapies

- *TP53* mutation, ~50% of cancer patients
- *KRAS*, ~ 25% of all cancer patients
  - 90% of pancreatic cancer, 35-45% colon cancer
- *APC*

Colon cancer patient

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - TMB-Low (3 Muts/Mb)	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
KRAS - G12D	▲ Cetuximab[1]	none
10 Trials *see p. 7*	▲ Panitumumab[1]	

1. Patient may be resistant to indicated therapy

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

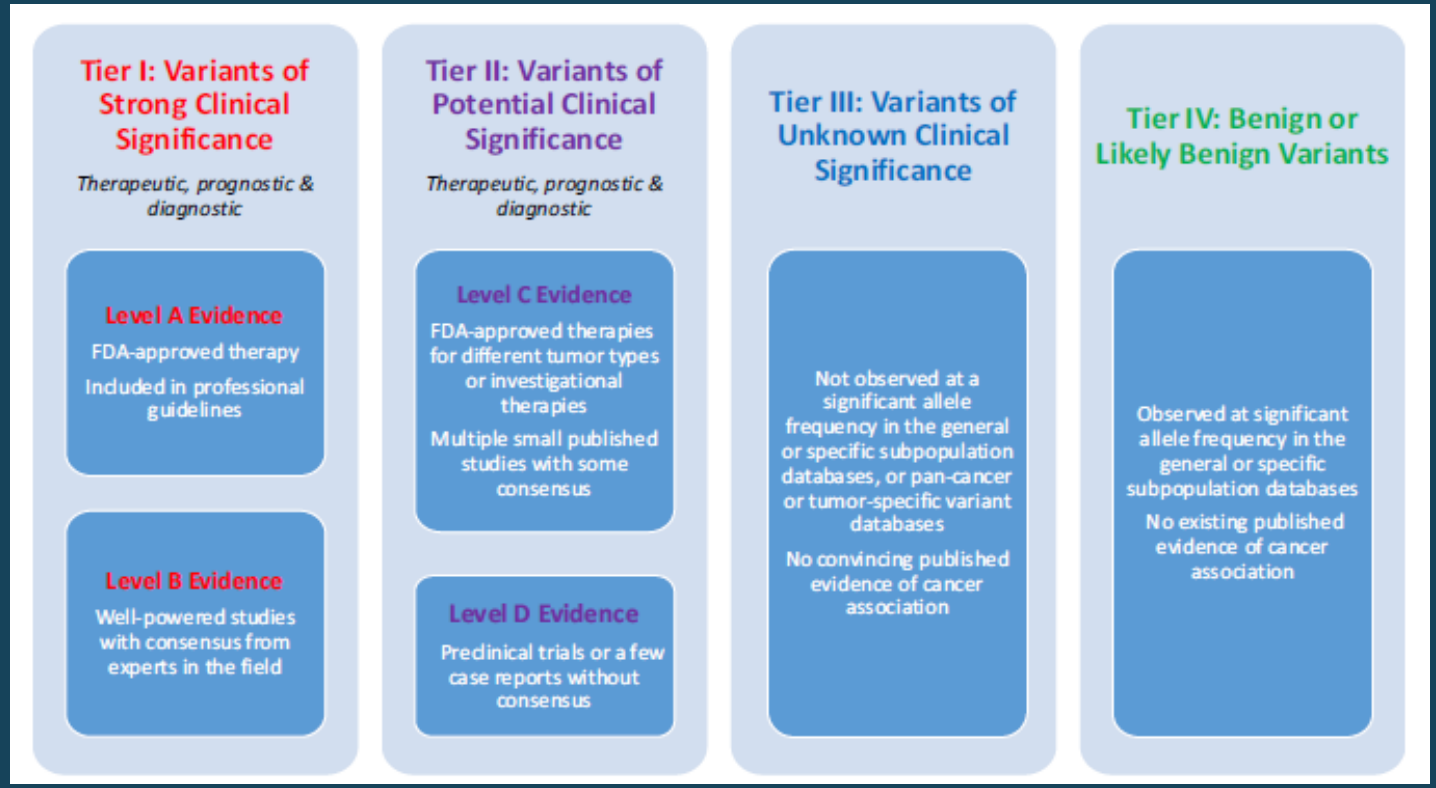
APC - E855*, Q1429* ..... p. 3
ARFRP1 - amplification - equivocal ..... p. 4
GNAS - amplification - equivocal ..... p. 4
NRAS - wildtype ..... p. 4
TP53 - I251N ..... p. 5

A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists

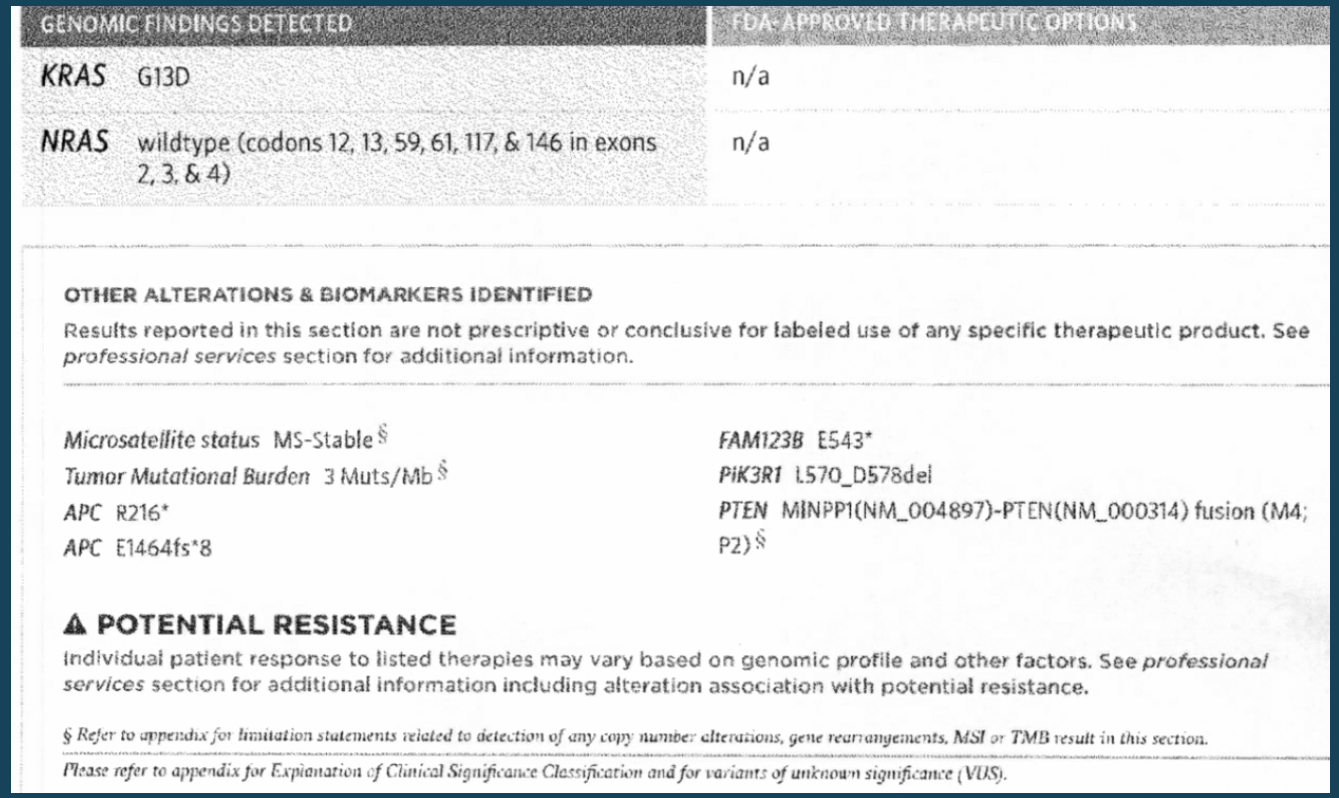
Guidelines to interpret and report sequence variants in cancer.

Primary resources to effectively assess clinical significance of a particular variant:

- Peer-reviewed literature
- Clinical practice guidelines
- Large-scale cancer mutation databases



Li MM, et al. *J Mol Diagn.* 2017;19(1):4-23.



GENOMIC FINDINGS DETECTED		FDA-APPROVED THERAPEUTIC OPTIONS
KRAS	G13D	n/a
NRAS	wildtype (codons 12, 13, 59, 61, 117, & 146 in exons 2, 3, & 4)	n/a

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §
Tumor Mutational Burden 3 Muts/Mb §
APC R216*
APC E1464fs*8
FAM123B E543*
PIK3R1 L570_D578del
PTEN MINPP1(NM_004897)-PTEN(NM_000314) fusion (M4; P2) §

⚠ POTENTIAL RESISTANCE

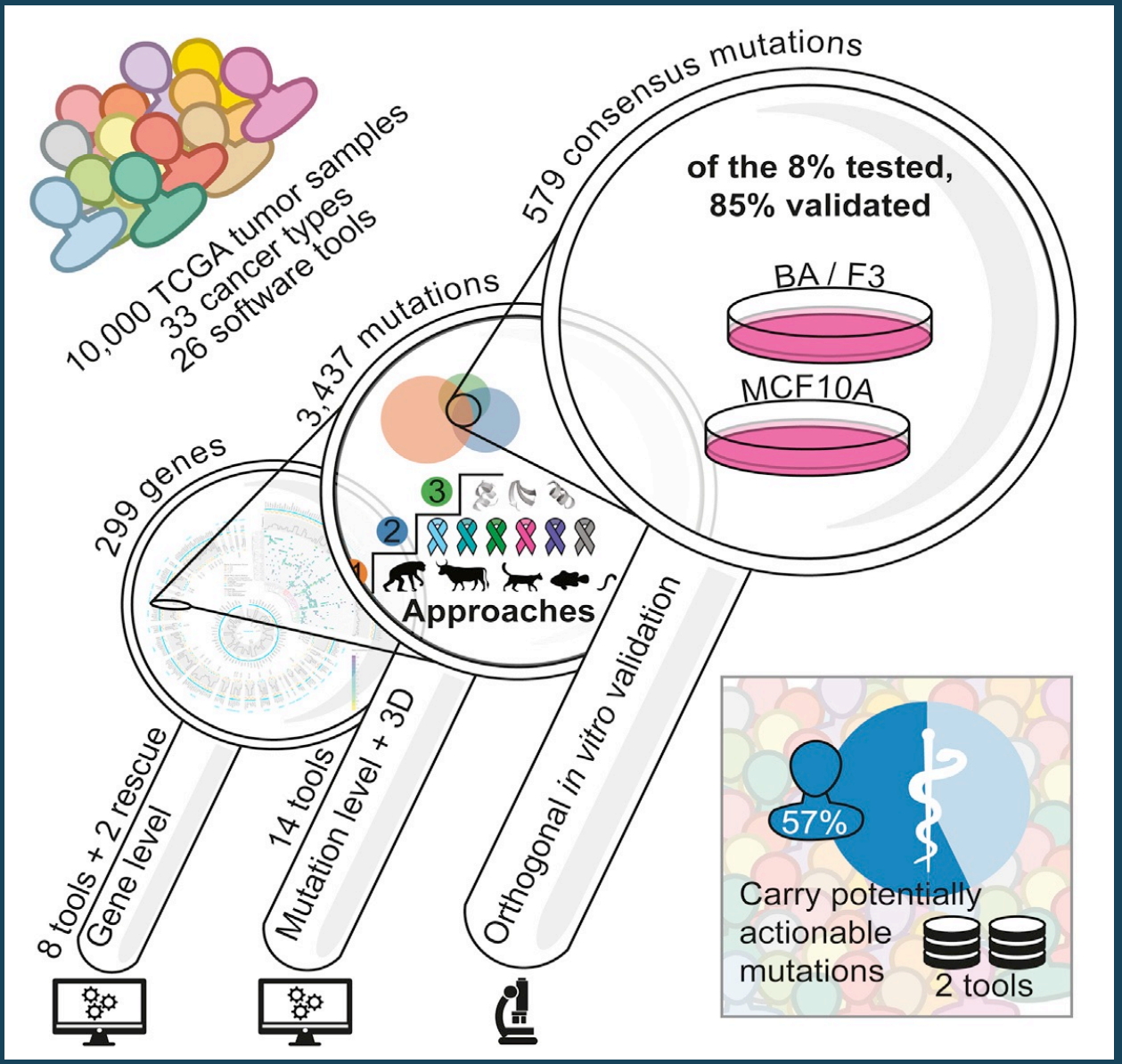
Individual patient response to listed therapies may vary based on genomic profile and other factors. See *professional services* section for additional information including alteration association with potential resistance.

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

- Stage IV cecal adenocarcinoma, *KRAS* mutant, MSS
- 11/28/17 – 3/20/18: FOLFOX
- 4/23/18: Re-do right colectomy and abdominal wall resection and excisional biopsy of a pelvic mass
- 6/6/18 – 7/17/18: FOLFIRI → PD
- 8/18 – 11/18: Regorafenib started and NGS requested (using April 2018 tissue)
- 11/30/18 – 1/11/19: Tipiracil and trifluridine/bevacizumab
- 3/14/19: Started phase II metformin/nivolumab trial, enrolling CRC MSS patients
- 5/16/19: PD
- 5/19: Started duvelisib, PI3K inhibitor
- 7/19: PD

CRC = colorectal cancer; MSS = microsatellite stable.



Questions remain:

- Interactions among mutations
- Reliable ways to identify driver vs passenger mutations
- Implications for therapeutics

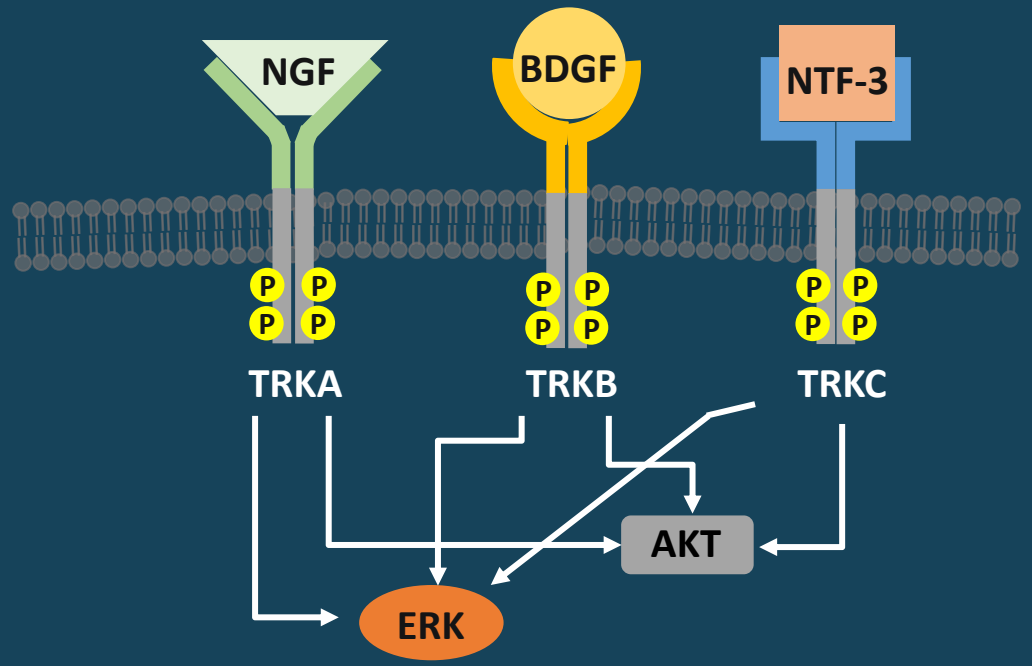
Bailey MH, et al. *Cell.* 2018;173:371-85.

Drug-Specific Examples

NTRK Genes and the Neurotrophin Proteins

- Sympathetic nervous system development is orchestrated by neurotrophins (NTs) and respective neurotrophin receptors
- 3 neurotrophin receptors are encoded by 3 distinct genes

NT Receptor	Gene	Normal Function in Adults
TRKA	*NTRK1*	Pain, thermoregulation
TRKB	*NTRK2*	Movement, memory, mood, appetite, body weight
TRKC	*NTRK3*	Proprioception



- **Fusions of any *NTRK* genes (*NTRK1/2/3*) are oncogenic drivers**

Amatu. *ESMO Open*. 2016;1:e000023; Loewenthal. *Pediatr Res.* 2005;57:587; Razzoli. *Genes Brain Behav.* 2011;10:424. Inoue. *Blood Cells Mol Dis.* 2003;30:157.

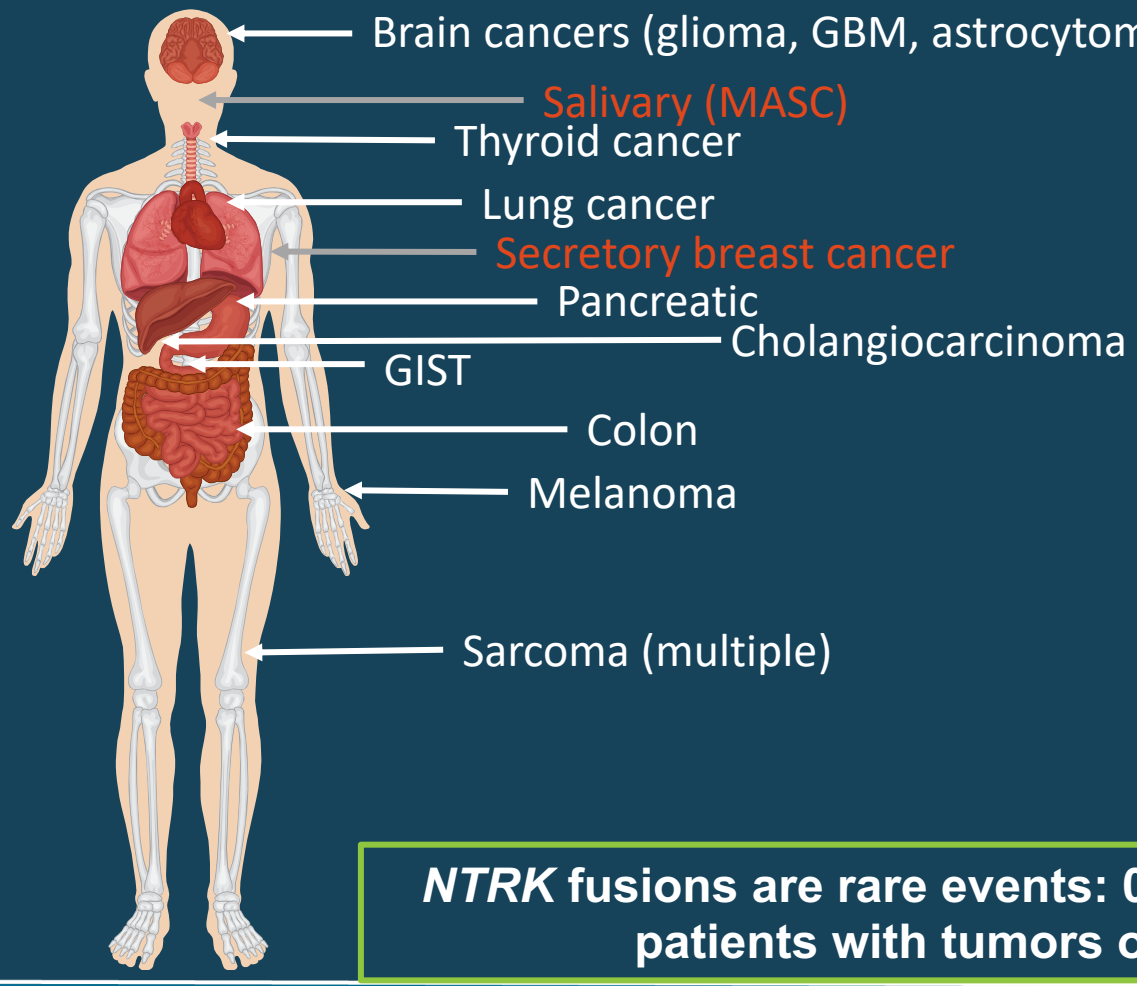
NTRK Fusion vs Other *NTRK* Gene Mutations

- Gene fusion
  - Change to the location of the coding gene on the chromosome
  - No change to DNA protein code of the kinase part
  - Typically results in uncontrollably active kinase enzyme function
- For *NTRK* genes, **FUSIONS** are activating and predictive of response to TRK inhibitors

- Gene mutation
  - Change to DNA coding sequence
  - Location on chromosome unchanged
  - May or may not result in a functionally abnormal protein
- For *NTRK* genes, mutations do NOT lead to benefit with TRK inhibiting drugs: The coding mutation may not be the oncogenic stimulus

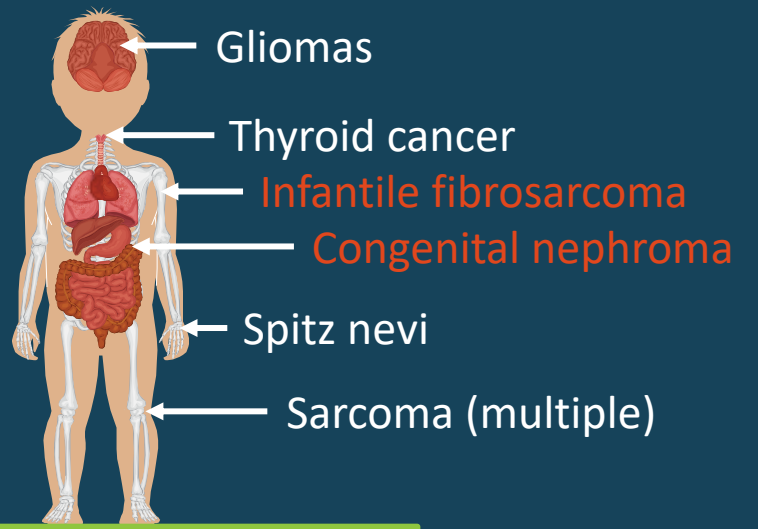
Latysheva. *Nucleic Acids Res*. 2016;44:4487. Supek. *Cell*. 2014;156:1324. Amatu. *ESMO Open*. 2016;1:e000023.

TRK Fusions Present in Adults and Children



Common cancer with low TRK fusion frequency

Rare cancer with high TRK fusion frequency



***NTRK* fusions are rare events: 0.21% across 11,116 patients with tumors of all types**

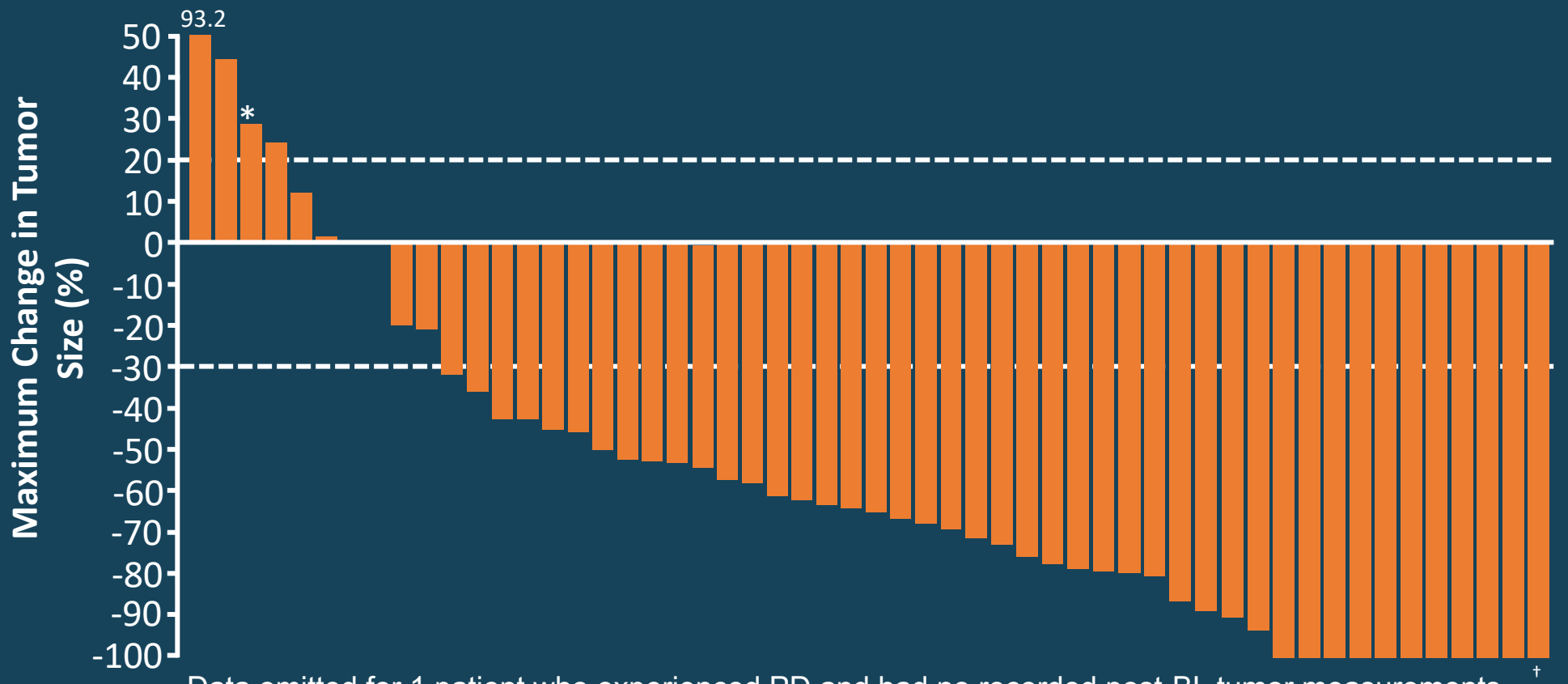
Amatu. *ESMO Open*. 2016;1:e000023. Urano. *Hum Pathol*. 2015;46:94. Knezevich. *Nat Gen.* 1998;18:184. Watanabe. *Cancer Genet Cytogenet*. 2002;136:10. Hyman. ASCO 2017. Abstr LBA2501. Gatalica. AACR-NCI-EORTC 2017. Abstr A047.

Larotrectinib

- First-in-class selective pan-TRK tyrosine kinase inhibitor approved for advanced solid tumors harboring NTRK gene fusion
  - Potent activity against TRKA, TRKB, TRKC (IC50 of 4.2 to 9.1 nM)
- If > 1 m^2, 100 mg PO BID
  - < 1 m^2, 100 mg/m^2 PO BID
- Formulated as liquid (20 mg/mL) and capsule (25, 100 mg)
- CYP3A4 substrate and mild inhibitor
- Common adverse events (> 20%): fatigue, nausea, dizziness, vomiting, increased AST, cough, increased ALT, constipation, and diarrhea

Drilon A. *Cancer Discov*. 2017;7:963; Prescribing information, VITRAKVI (larotrectinib).

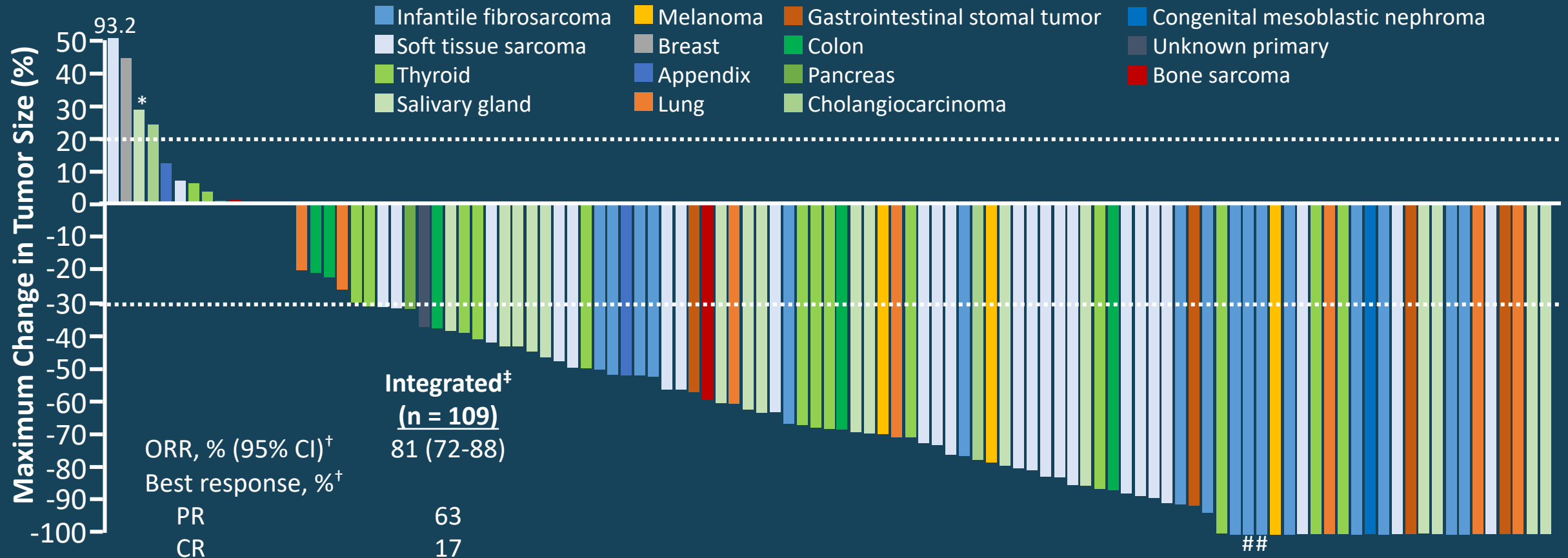
Larotrectinib in TRK Fusion: Positive Cancers



Data omitted for 1 patient who experienced PD and had no recorded post-BL tumor measurements.
*Patient with BL TRK resistance mutation (*NTRK3* G623R) due to previous treatment. †Pathologic CR.

Drilon. *N Engl J Med*. 2018;378:731.

Larotrectinib Activity Across Tumor Types



Lassen. ESMO 2018. Abstr 4090.

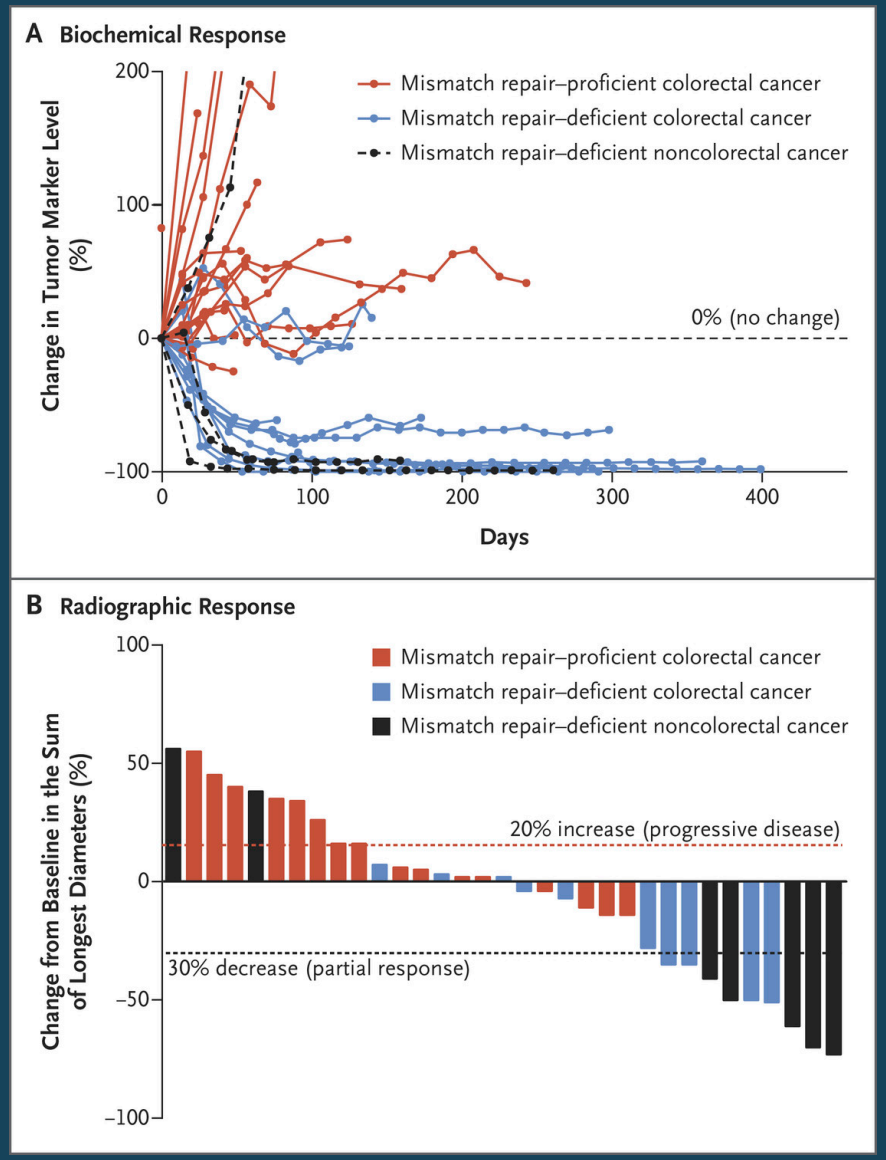
Immune Checkpoint Inhibition and Microsatellite Status

- Microsatellite instability (MSI): Spontaneous loss/gain of nucleotides from repetitive DNA tracts
  - MSI-H is defined as > 30% of repeats unstable
  - Classically associated with CRC (~3-6%)
  - Frequency in other solid tumors
    - Endometrial cancer: 20-30%
    - Other: < 5%
- MSI-H tumors exhibit an unstable/hypermutational nature
  - High levels of checkpoint proteins
  - Theoretically should respond better to immunotherapy
  - Same as mismatch repair deficient (dMMR)
    - PD-L1 expression does not predict response in dMMR patients

Hause RJ, et al. *Nat Med*. 2016;22:1342-50; Gatalica Z, et al. *Fam Cancer*. 2016;15:405-12.

Pembrolizumab

- Approved May 2017
- First approval independent of anatomic site
- Trial N=41 patients
  - 11 MSI-high colon cancer
  - 21 microsatellite stable colon cancer
  - 9 MSI-high other cancers
- Other trials identified a total of 149 patients for FDA review
  - 90 colorectal



Le DT, et al. *N Engl J Med*. 2015;372:2509-20.

Nivolumab +/- Ipilimumab

- Nivolumab approved July 2017
- Combination approved July 2018
  - Regimen: Nivolumab 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks
  - Data from 82 patients with colorectal cancer
  - Overall response rate = 46%
  - Common (≥ 20%) adverse events: fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, dyspnea, decreased appetite, and vomiting

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-ipilimumab-msi-h-or-dmmr-metastatic-colorectal-cancer

Selected Potential Future Precision Targets

- Additional NTRK agents
  - Entrectinib, BAY 2731954
- RET
  - Thyroid cancer, NSCLC, and renal cell carcinomas
  - LOXO-292, BLU-667
- MET
  - Using mutation data rather than tissue staining
  - NSCLC, thyroid, breast, renal, ovarian cancers
  - APL-101, AMG 337, PF-02341066

NSCLC = non-small cell lung cancer

Clinical Pearls

- Tumor agnostic drug development approaches are evolving.
- Deep and prolonged responses are being seen in population subsets.
- NGS can inform treatment decisions, but has limitations.
- Clinical trials are key to understanding clinical application of NGS.

More Questions?

Come see us at Booth #829 (next to the APSHO Booth)
in the Exhibit Hall from **12:50 to 1:30** today.

This has been a SMARTIE presentation.

To access your post-session questions, you can:

- Click on the link that was sent to you via email
- Visit the SMARTIE station
- Go to jadprolive.com/smartie2019