Clinical Pathways Congress + Cancer Care Business Exchange

Evolving Role of Biomarker Testing in Solid Tumors: Implications for Clinical Pathways

Manish A. Shah, MD, FASCO

Bartlett Family Professor of Gastrointestinal Oncology
Chief, Solid Tumor Program
New York-Presbyterian/Weill Cornell Medicine

clinicalpathwayscongress.oncnet.com

Supported by an independent educational grant from Merck & Co., Inc.

Disclosures

- **Manish A. Shah, MD, FASCO:** Research Funding – Bristol Myers Squibb, Merck, Oncolys BioPharma

Learning Objectives

- Describe the importance of biomarker testing and its impact on cancer care delivery and quality measures

- Summarize the latest guidelines and best practices associated with NGS testing methods for diagnostic and prognostic evaluation in a variety of solid tumors

- Identify strategies to address disparities and barriers associated with the cost-effective and optimal use of biomarker testing in solid tumors

NGS = next-generation sequencing.

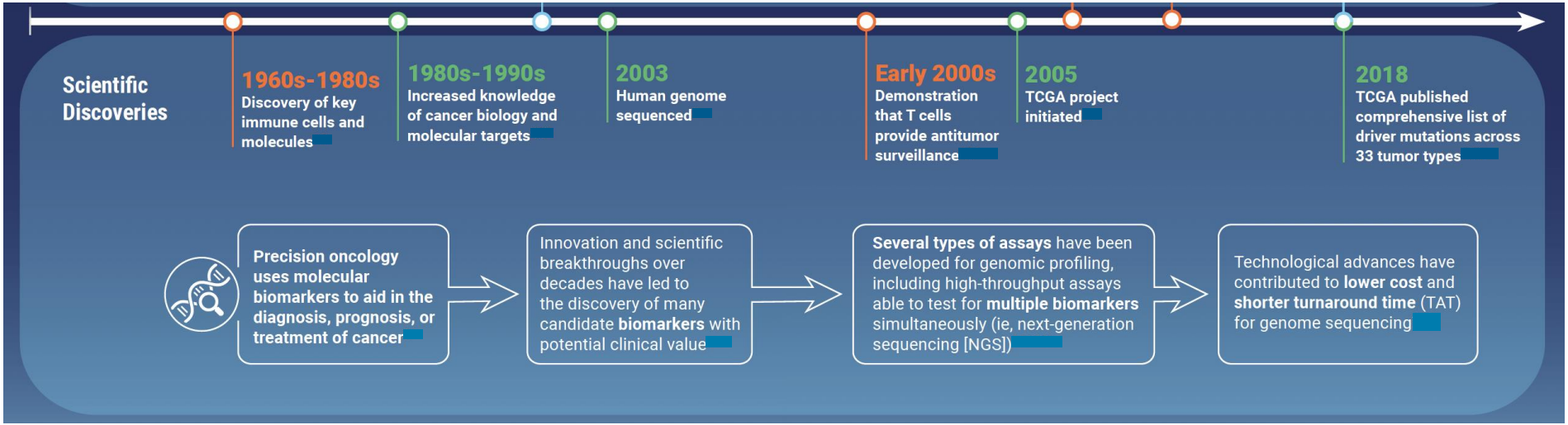
Clinical Pathways Congress + Cancer Care Business Exchange

The Role of Biomarkers and Precision Medicine in Solid Tumor Care

Overview of Biomarker-Directed Therapy

- Precision medicine has rapidly evolved over the last 25 years
- Over 70 FDA-approved drugs require biomarker testing
- Understanding biomarker testing platforms and limitations is critical to appropriate application of novel therapeutics

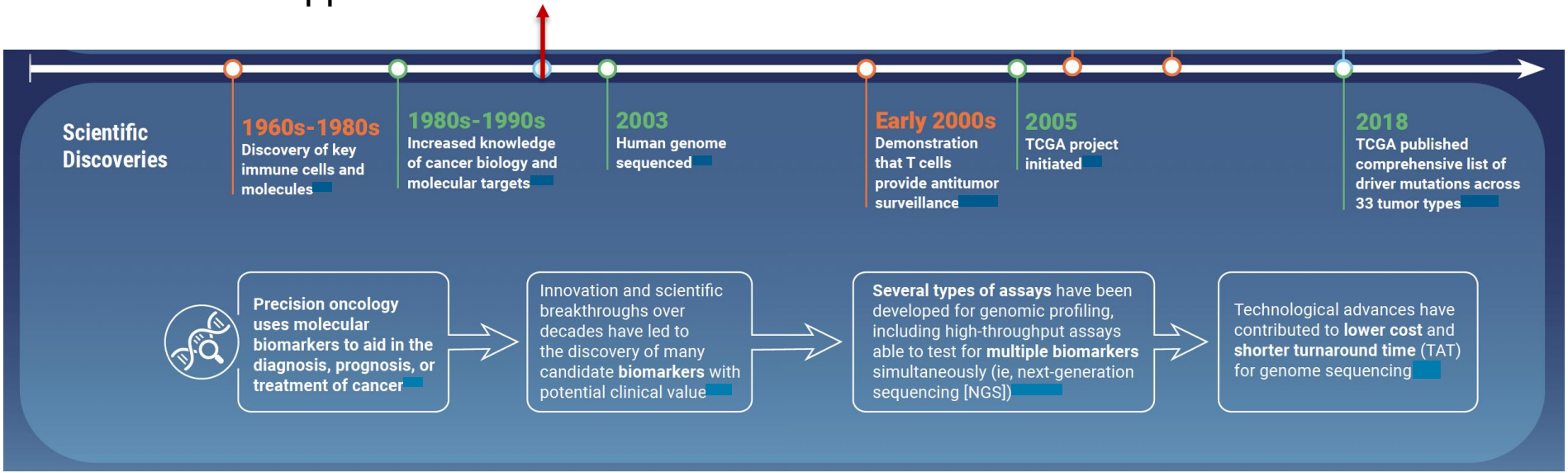
Progress in Precision Oncology Has Accelerated!



TCGA = The Cancer Genome Atlas.

Progress in Precision Oncology Has Accelerated!
But it Is Not a New Concept

Trastuzumab approved for BC in 1998

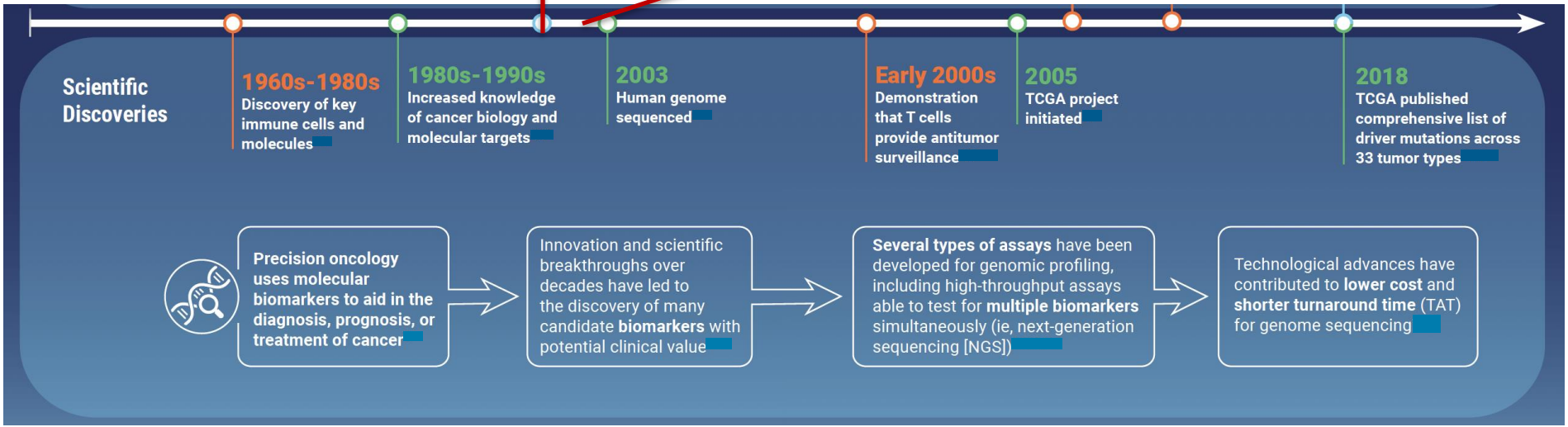


BC = breast cancer.
FDA. Accessed September 3, 2024.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/103792s5354lbl.pdf.

Progress in Precision Oncology Has Accelerated!
But it Is Not a New Concept

Trastuzumab approved for BC in 1998

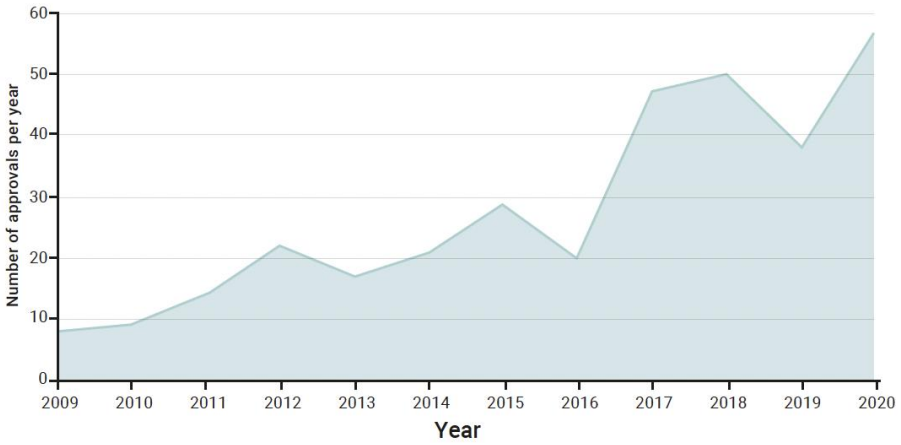
Imatinib approved for GIST in 2002



BC = breast cancer; GIST = gastrointestinal stromal tumor.

FDA. Accessed September 3, 2024.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/103792s5354lbl.pdf;
https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021588Orig1s063lbl.pdf.

Accelerated Development of Precision Medicine



New cancer therapies 2009-2020

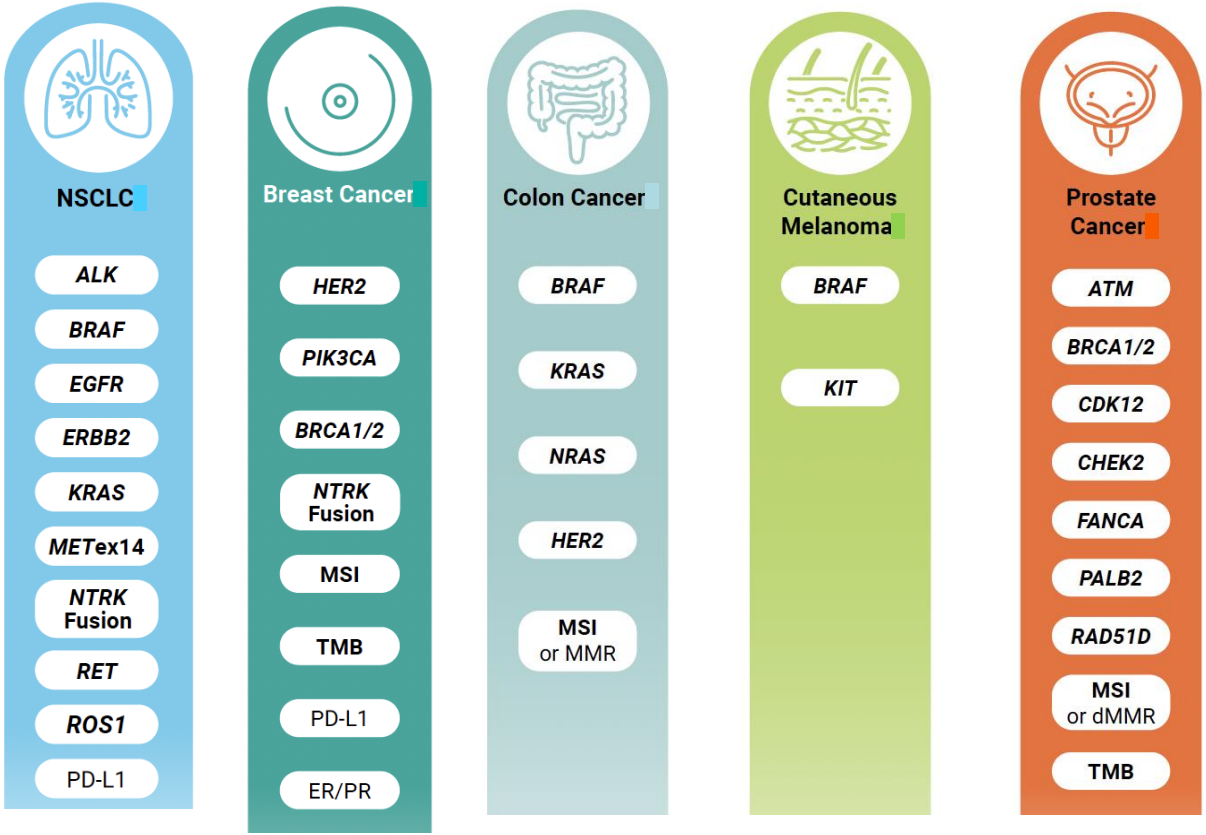
Of the 332 approvals

- >70 require biomarker testing
- Over 28 cancer types

Olivier T, et al. *JAMA Netw Open*. 2021;4(12):e2138793. Chakravarty D, et al. *J Clin Oncol*. 2022;40(11):1231-1258.

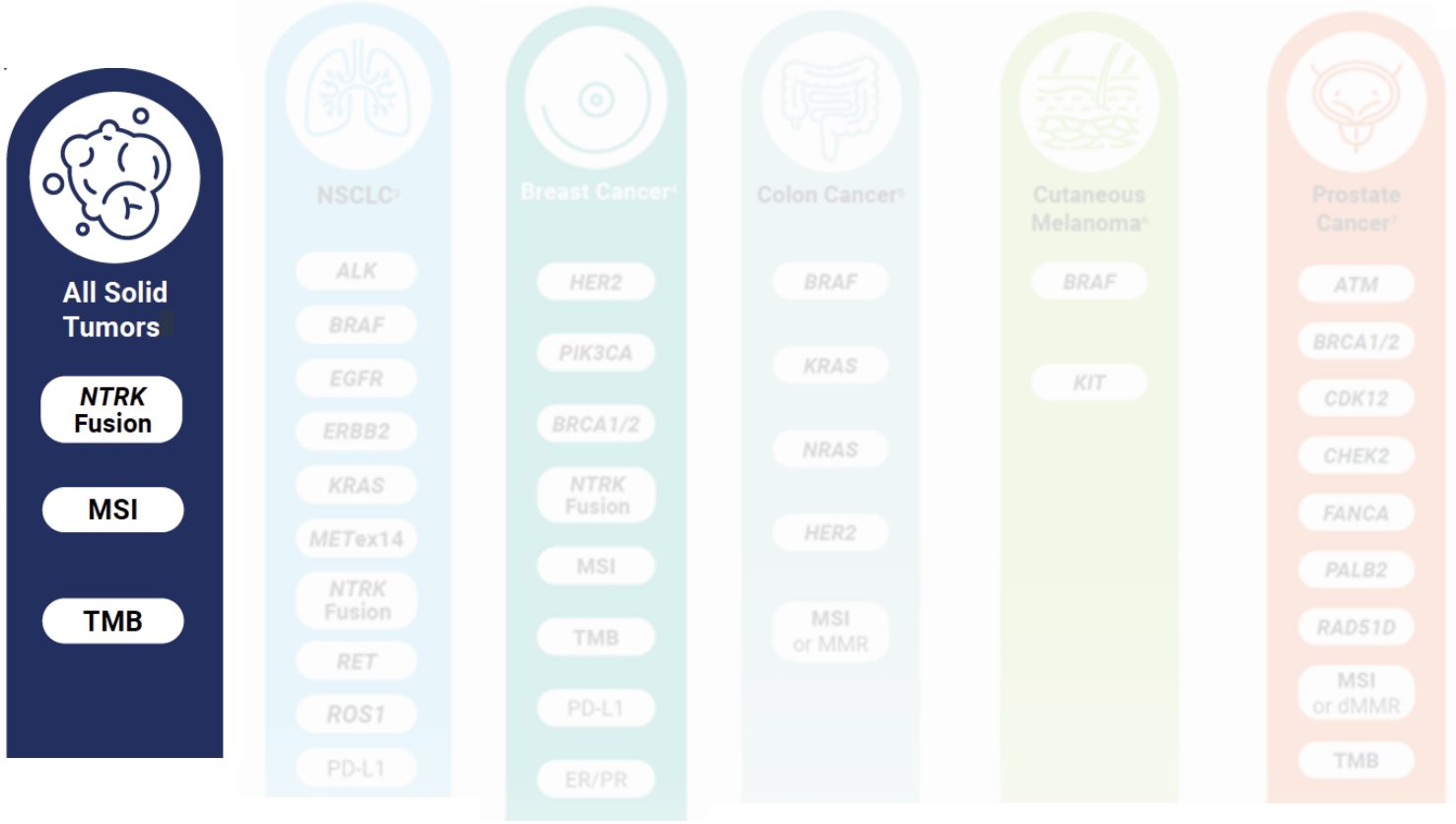
Clinical Pathways Congress + Cancer Care Business Exchange

Tumor-Specific Targets



Chakravarty D, et al. *J Clin Oncol*. 2022;40(11):1231-1258. Siegel RL, et al. *CA Cancer J Clin*. 2023;73(1):17-48. NCCN Guidelines. Accessed September 3, 2024. https://www.nccn.org/guidelines/category_1.

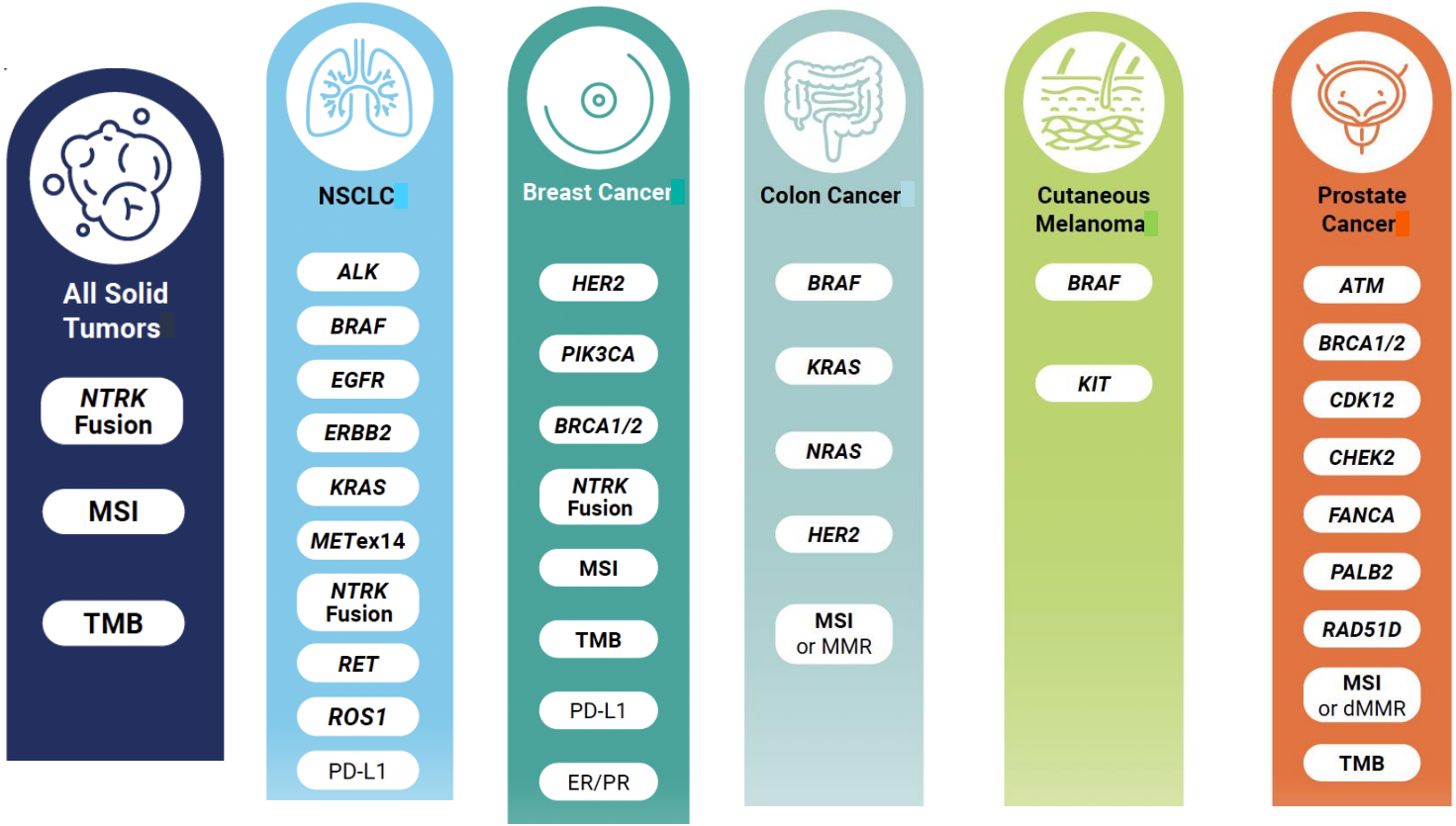
Tumor-Agnostic Targets



Chakravarty D, et al. *J Clin Oncol*. 2022;40(11):1231-1258. Siegel RL, et al. *CA Cancer J Clin*. 2023;73(1):17-48. NCCN Guidelines. Accessed September 3, 2024. https://www.nccn.org/guidelines/category_1.

NCCN Guidelines

Understanding Biomarkers Critical across Solid Tumors



Chakravarty D, et al. *J Clin Oncol*. 2022;40(11):1231-1258. Siegel RL, et al. *CA Cancer J Clin*. 2023;73(1):17-48. NCCN Guidelines. Accessed September 3, 2024. https://www.nccn.org/guidelines/category_1.

Clinical Pathways Congress + Cancer Care Business Exchange

Growing Number of Guideline-Recommended Biomarkers in Multiple Cancer Types

Cancer Type	Targetable Alterations																							
	EGFR mt	*ALK fusion*	*ROS1 fusion*	*BRAF mt*	*ERBB2 (HER2) amp*	*ERBB2 (HER2) mt*	*RET fusion*	*RET mt*	*MET amp & ex 14 skip*	*NTRK fusion*	*MSI high*	*BRCA1/2 g*	*BRCA1/2 somatic*	*KRAS mt exons 2,3,4*	*NRAS mt exons 2,3,4*	*NRAS mt*	*PIK3CA mt*	*KIT mt*	*PALB2*	*NRG1^*	*PDGFRA mt*	*FGFR3 mt*	*FGFR2/3 fusions*	*AR mt*	*IDH1 mt*
NSCLC†	✓	✓	✓	✓	✓	✓	✓		✓	✓				✓											
Colorectal†				✓	✓					✓	✓			✓	✓										
Breast†					✓					✓	✓	✓					✓								
Pancreatic†		✓	✓	✓		✓				✓	✓	✓	✓	✓					✓	✓					
Prostate†											✓	✓	✓						✓						
Ovarian										✓	✓	✓	✓												
Endometrial					✓					✓	✓														
Esophageal Esophagogastric†					✓					✓	✓														
Gastric†					✓					✓	✓														
Cervical										✓	✓														
Cholangiocarcinoma				✓						✓	✓												✓		✓
Melanoma†		✓	✓	✓						✓						✓		✓							
GIST				✓						✓											✓				
Head & Neck					✓					✓														✓	
Bladder																						✓	✓		
Thyroid				✓				✓		✓															
Small bowel										✓	✓														

†NCCN Guidelines suggest that liquid biopsy may be considered for these cancer types under certain conditions, such as when patients are unable to undergo a traditional biopsy or tissue is insufficient for complete testing, upon relapse or progression-depending.

ASCO recommendation as of February 2022:

Multigene panel-based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency-approved therapy

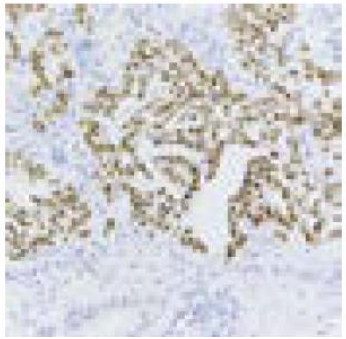
NSCLC = non-small cell lung cancer.

NCCN Guidelines. Accessed September 3, 2024. https://www.nccn.org/guidelines/category_1.
Chakravarty D, et al. *J Clin Oncol*. 2022;40(11):1231-1258.

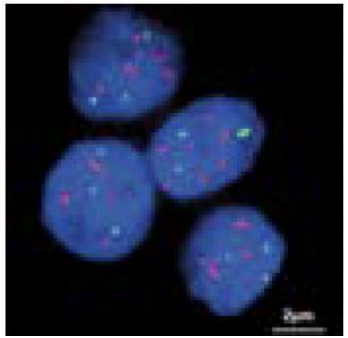
Biomarker Testing Methods

Precision Oncology Methods

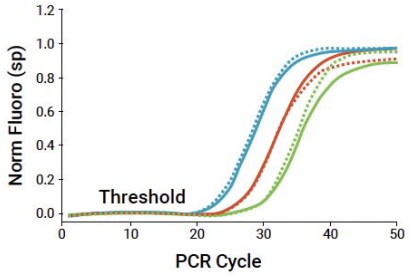
IHC



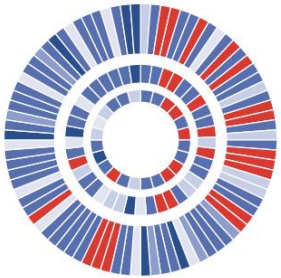
FISH



RT-PCR



NGS



Biomarker testing

- No one platform is perfect for every test
- Knowledge of the limits and expectations of the different platforms is critical

IHC = immunohistochemistry; FISH = fluorescence in situ hybridization; RT-PCR = reverse transcription polymerase chain reaction.

Chakravarty D, et al. *J Clin Oncol*. 2022;40(11):1231-1258.

Clinical Pathways Congress + Cancer Care Business Exchange

Integrating/Refining Biomarker Testing in Clinical Pathways

Biomarker Testing – Multistep Process

Patient's genome

Sample (i.e., biomarker)

Genome sequencing/ testing (i.e., NGS)

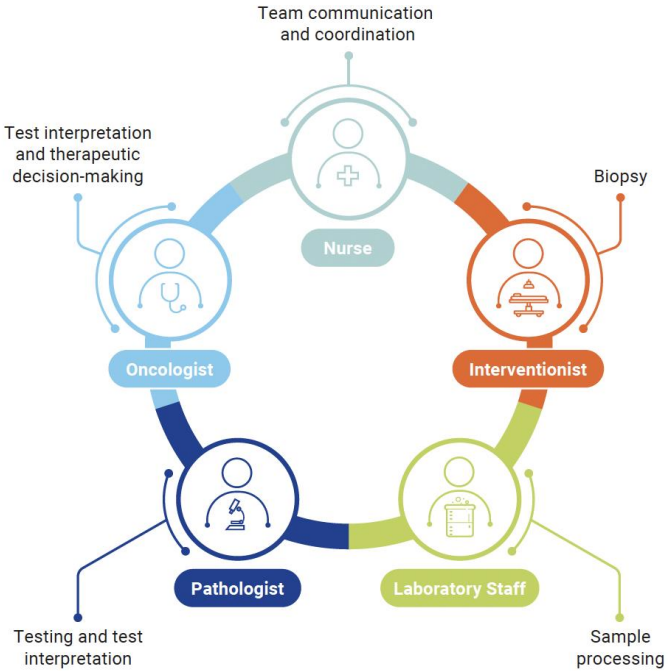
Genome analysis

Pharmacogenetic interpretation

Precision medicine application (diagnostic, treatment, prediction, prevention)

Biomarker Testing – Multistep Process

- Not as simple as ordering a blood test
- Requires a team
- Need to understand what tissue/how much/what type of biopsy, etc



Economic Considerations

Costs are expected to increase exponentially!

- Precision oncology means that we select the right drug for the right target
- Most targets are rare – so few patients will receive the drug

Economic Considerations

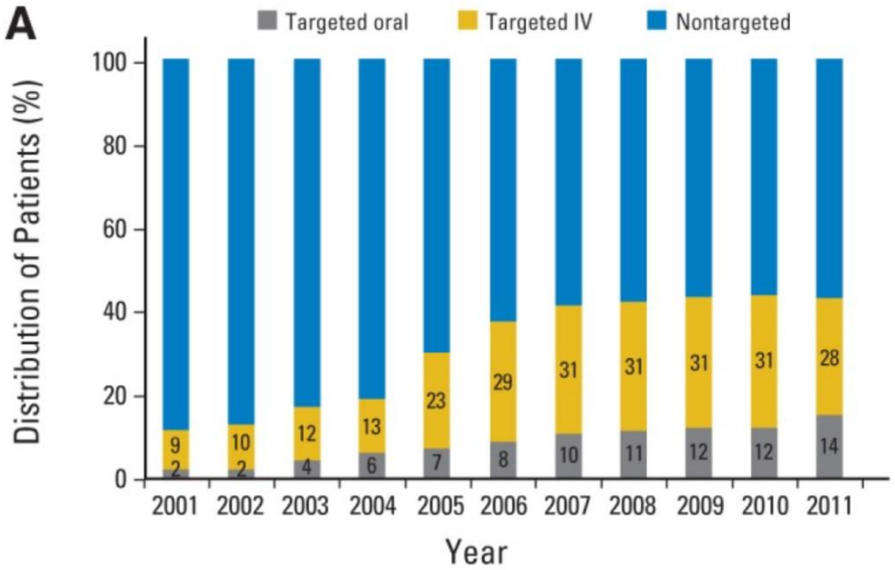
Costs are expected to increase exponentially!

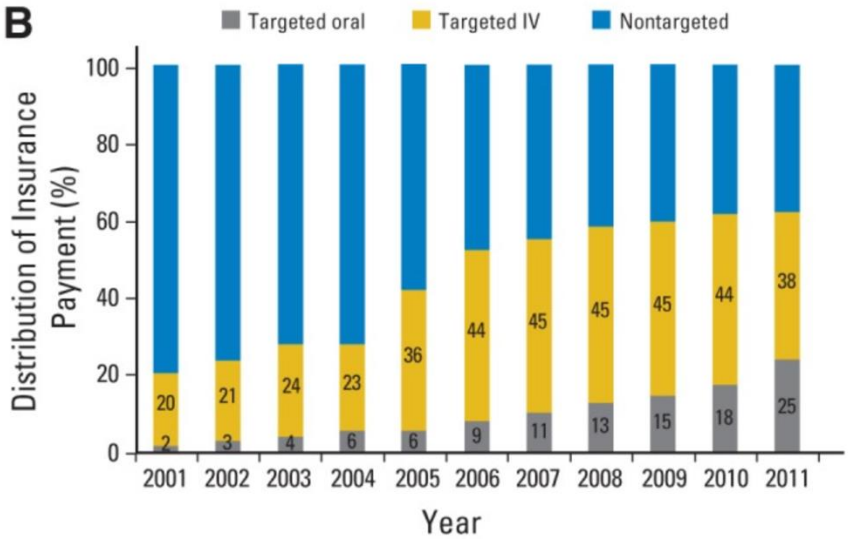
- Drug development costs increase
  - Biomarker validation
  - Increasingly rare population
  - Longer time to identify and enroll patients
  - Approvals require companion diagnostic testing
  - Assay validation and incorporation across pathology labs
  - Value added – difficult to prove

Seo MK, et al. *BMC Cancer*. 2021;21(1):980.

Economic Considerations

Costs of targeted therapy disproportionately increase





Shih YCT, et al. *J Clin Oncol*. 2015;33(19):2190-2196.

Regulatory/Quality Considerations

- Emergence and evolving field of precision medicine require novel policy framework that balances the needs of patients, industry, and science without impeding progress or limiting access

- Recent tumor-agnostic FDA approvals

Regulatory/Quality Considerations

FDA leads the way for regulatory aspects

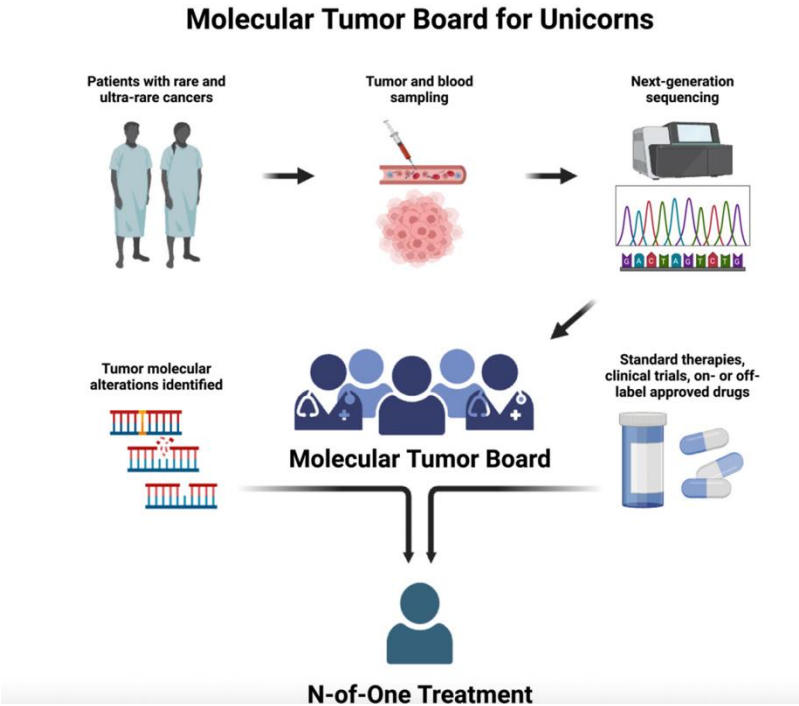
- 1996: Health Insurance Portability and Accountability Act (HIPAA) ensures that personal medical information stored, accessed, or processed adheres to privacy guidelines
- 2015: precisionFDA was introduced – a cloud-based site for community research and development
- 2020: FDA issued several guidance documents on manufacturing and clinical development of gene and cell-based therapeutic products
- 2021: FDA updated guidelines on new products, like the development of antisense oligonucleotides

Mattes WB, et al. *Exp Biol Med* (Maywood) 2018;243(3):256-261. Valla V, et al. *Biomark Insights*. 2021;16:11772719211047763.

Clinical Pathways Congress + Cancer Care Business Exchange

Molecular Tumor Boards

Molecular Tumor Boards



Molecular Tumor Board

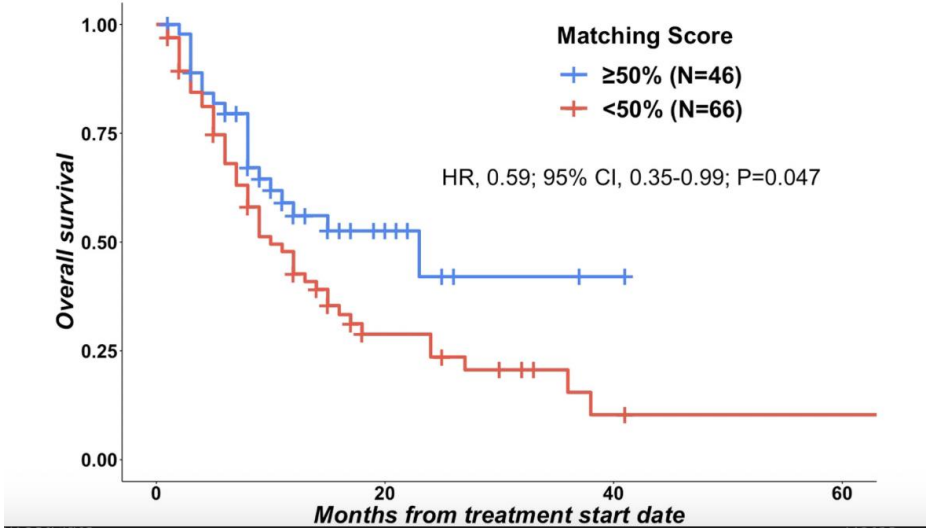
- A multidisciplinary team that integrates molecular profiling to generate personalized treatment plans

Louie BH, et al. *iScience*. 2024;27(8):110465.

Impact on Clinical Decision-Making

A study of 112 patients with rare/ultra-rare tumors

- 41% received treatment with a high degree of matching with their molecular alteration
- Patients who received targeted therapy had a better survival, higher response rate, and better outcomes



HR = hazard ratio; CI = confidence interval.
Louie BH, et al. *iScience*. 2024;27(8):110465.

Clinical Pathways Congress + Cancer Care Business Exchange

Understanding Barriers and Disparities in Biomarker Testing

Barriers to Precision Medicine

- Patient and clinician understanding of testing
- Time it takes to get the test
- Adequate tissue acquisition
- Insurance/cost

Patient Disparities and Considerations

Precision medicine – initially believed to be an opportunity to overcome or address known healthcare disparities, because treatment is based purely on genetic or protein alterations

But disparities have grown

- Insurance/payment for testing
- Mistrust in healthcare system (genetic testing)
- Discordance in patient and clinician understanding about the importance of biomarker testing

Clinical Pathways Congress + Cancer Care Business Exchange

Technology to Optimize Pathways and Biomarker Testing

Value Pathways Powered by NCCN

Oncology clinical pathways integrated into electronic health record (EHR)

- Treatment pathways highlight evidence-based treatment options
- Based on efficacy, toxicity, financial impact to patient and payor
- Refinement of NCCN Guidelines
  - Narrower list; 100% concordant
- Includes incorporation of biomarkers relevant for decision-making
- Embedded in decision support tool

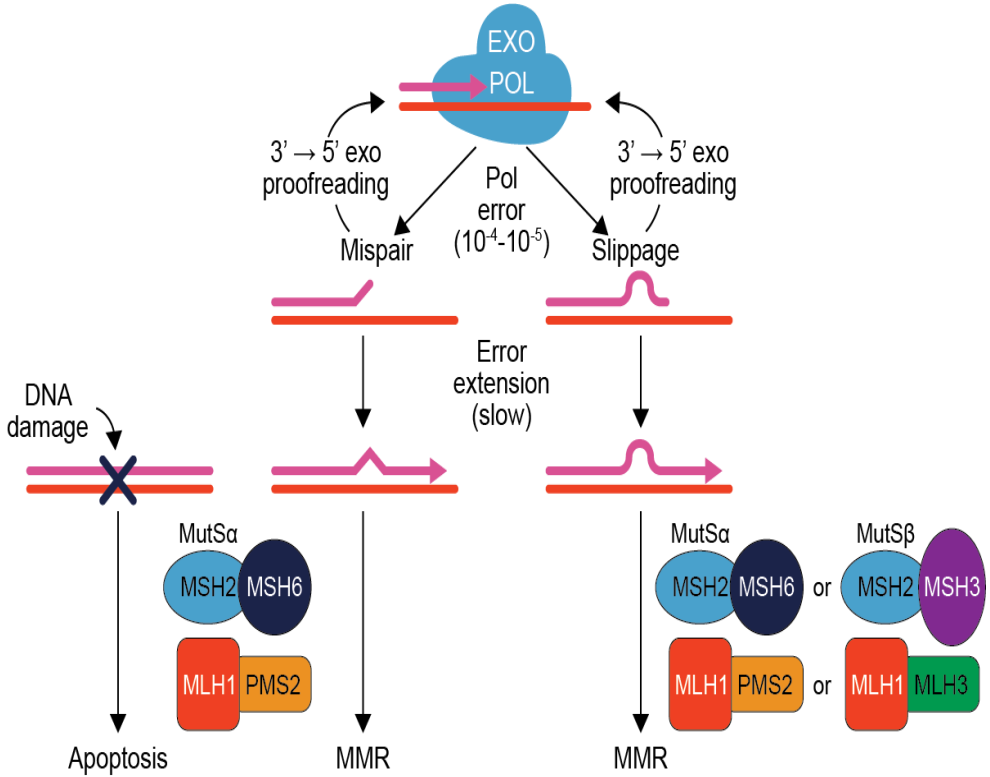
Ginsburg A, et al. *J Clin Pathways*. Accessed September 3, 2024. https://www.hmpgloballearningnetwork.com/site/jcp/article/update-evolution-us-oncology-networks-clinical-pathways-program.

Case Studies and Specific Examples

- Mismatch repair
- *NTRK*
- *HER2*

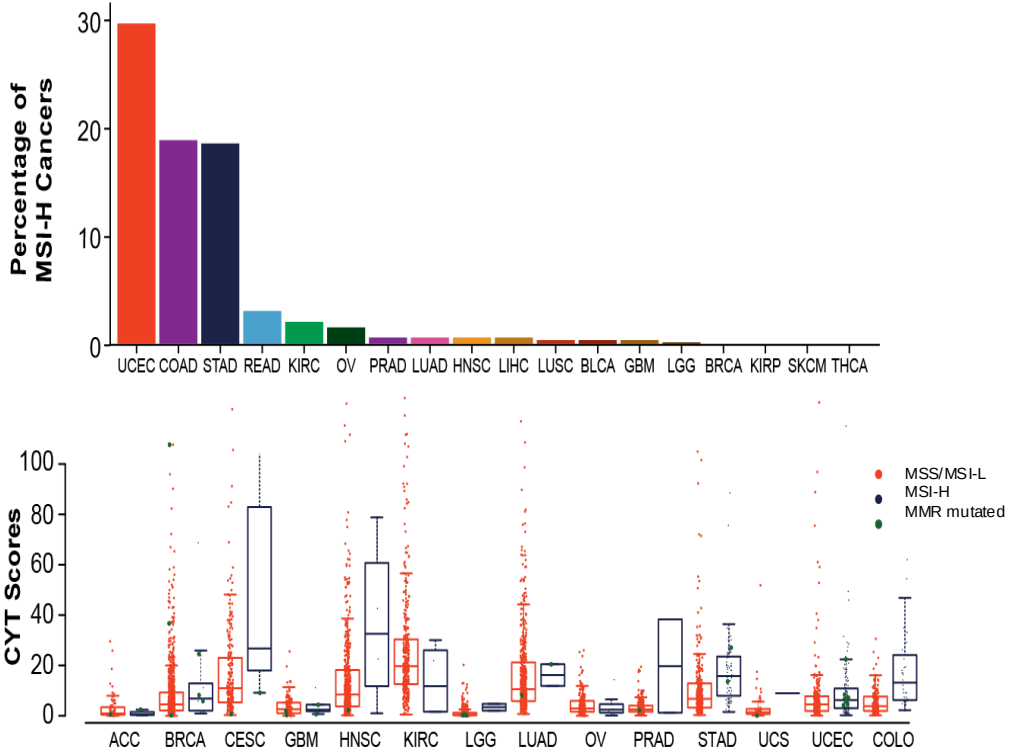
Mismatch Repair

Mismatch Repair Leads to Very High Mutational Burden



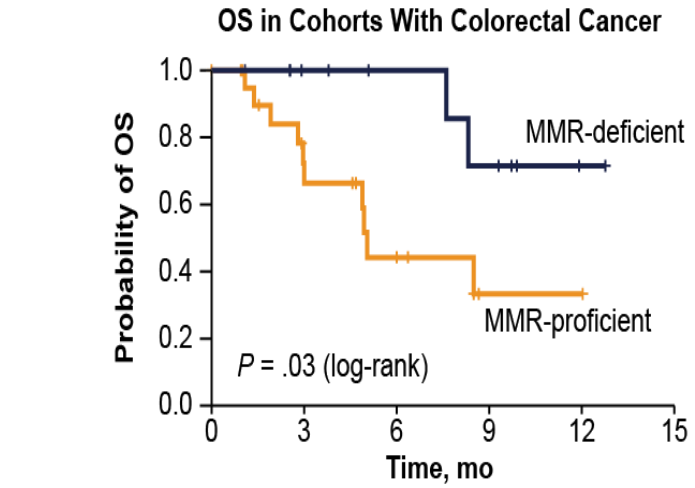
MMR = mismatch repair.

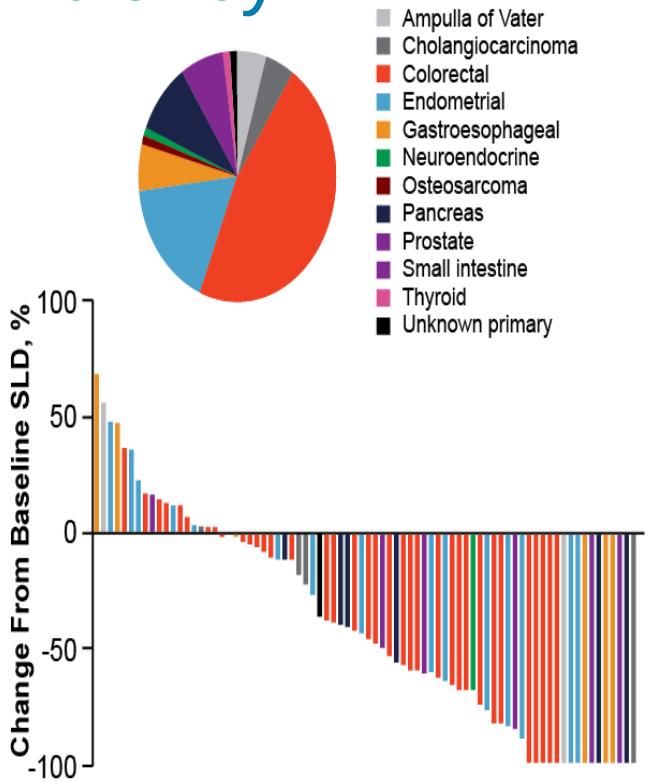
Pan-Cancer Landscape of MMR Deficiency



CYT = cytolytic activity; MSI = microsatellite instability; MSS = microsatellite stability.
Hause RJ, et al. *Nat Med*. 2016;22(11):1342-1350.

Pan-Cancer Landscape of MMR Deficiency





OS = overall survival; SLD = sum of longest diameters.
Le DT, et al. *N Engl J Med*. 2015;372(26):2509-2520.

Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: expanded efficacy analysis from CheckMate 8HW

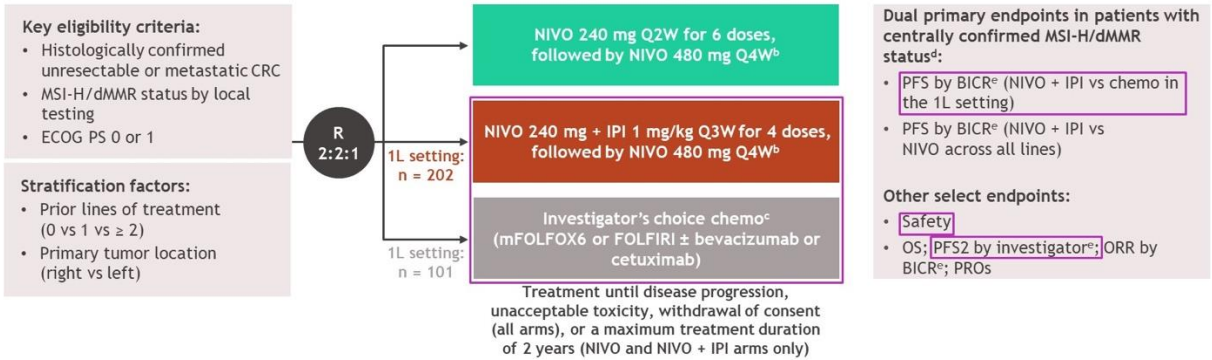
Heinz-Josef Lenz,[1] Sara Lonardi,[2] Elena Elez Fernandez,[3] Eric Van Cutsem,[4] Lars Henrik Jensen,[5] Jaafar Bennouna,[6] Guillermo Ariel Mendez,[7] Michael Schenker,[8] Christelle de la Fouchardiere,[9] Maria Luisa Limon Miron,[10] Takayuki Yoshino,[11] Jin Li,[12] José Luis Manzano Mozo,[13] Giampaolo Tortora,[14] Rocio Garcia-Carbonero,[15] Rohit Joshi,[16] Elvis Cela,[17] Tian Chen,[17] Lixian Jin,[17] Thierry Andre[18]

[1]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [2]Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; [3]Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; [4]University Hospitals Gasthuisberg and University of Leuven (KU Leuven), Leuven, Belgium; [5]University Hospital of Southern Denmark, Vejle Hospital, Vejle, Denmark; [6]Centre Hospitalier Universitaire de Nantes, Nantes, France; [7]Hospital Universitario Fundacion Favaloro, Buenos Aires, Argentina; [8]Centrul de Oncologie Sf Nectarie, Craiova, Romania; [9]Centre Léon Bérard, Lyon Cedex, France; [10]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [11]National Cancer Center Hospital East, Chiba, Japan; [12]Shanghai East Hospital, Shanghai, China; [13]Institut Català d'Oncologia, Badalona, Spain; [14]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [15]Hospital Universitario 12 de Octubre Imas12, Complutense University of Madrid, Madrid, Spain; [16]Cancer Research SA, Adelaide, Australia; [17]Bristol Myers Squibb, Princeton, NJ; [18]Sorbonne Université and Hôpital Saint Antoine, Assistance Publique Hôpitaux de Paris, Paris, France

Lenz HJ, et al. Presented at: ASCO; May 31-June 4, 2024; Chicago, IL. Abstract 3503.

CheckMate 8HW (1L NIVO + IPI vs Chemo) Study Design

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]



- At data cutoff (October 12, 2023), the median follow-up[f] was 31.5 months (range, 6.1-48.4)

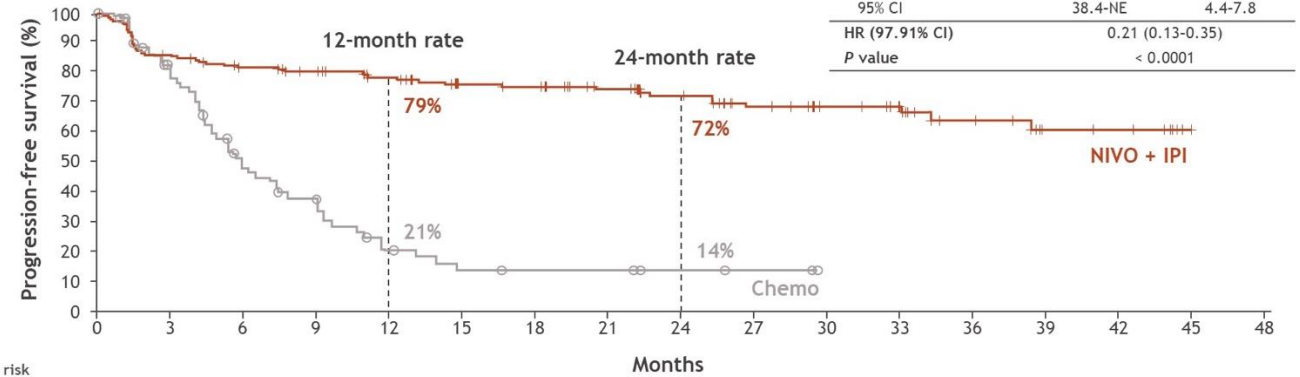
[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and data cutoff.

NIVO = nivolumab; IPI = ipilimumab; CRC = colorectal cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; RECIST = Response Evaluation Criteria in Solid Tumors; PFS = progression-free survival; BICR = blinded independent central review; ORR = objective response rate; PROs = patient-reported outcomes.

Lenz HJ, et al. Presented at: ASCO; May 31-June 4, 2024; Chicago, IL. Abstract 3503.

CheckMate 8HW (1L NIVO + IPI vs Chemo) Progression-Free Survival

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	



No. at risk																
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity and supportive analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

[a]Per BICR. [b]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

Lenz HJ, et al. Presented at: ASCO; May 31-June 4, 2024; Chicago, IL. Abstract 3503.

(1) MMRd solid tumor – use immunotherapy

- In the 2nd-line treatment setting
- 1st-line in CRC
- Non-operative management for rectal cancer

NTRK in Cancer

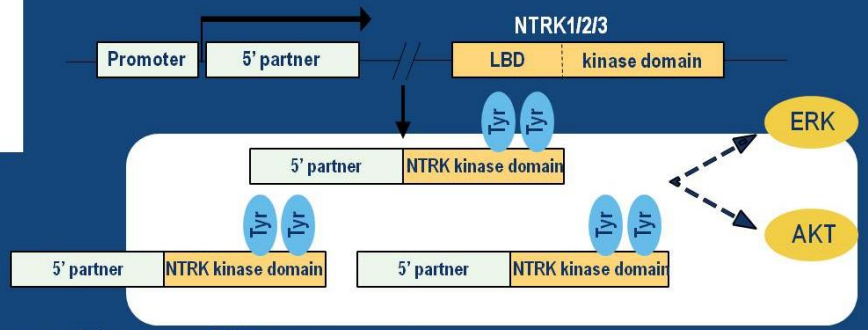
Role of *TRK* in Normal Biology and Cancer

Neurotrophin family of receptors

- **TRKA (*NTRK1*)** → Pain, thermoregulation
- **TRKB (*NTRK2*)** → Movement, memory, mood, appetite, body weight
- **TRKC (*NTRK3*)** → Proprioception

TRK fusions

- Ligand binding domain (LBD) replaced by 5' fusion partner
- Drives overexpression and ligand-independent activation



TRK uncommonly expressed in normal tissues or cancer
Fusion drives abnormally high expression and activation of TRK kinase domain

Manea CA, et al. *Ann Med Surg* (London). 2022;79:103893. Cocco E, et al. *Nat Rev Clin Oncol*. 2018;15(12):731-747.

NTRK Biology

NTRK1, *NTRK2*, and *NTRK3* are common fusion partners with unrelated genes (intrachromosomal or interchromosomal translocation)

- The resulting fusion → ligand-independent receptor activation and uncontrolled activation of downstream pathways

High frequency

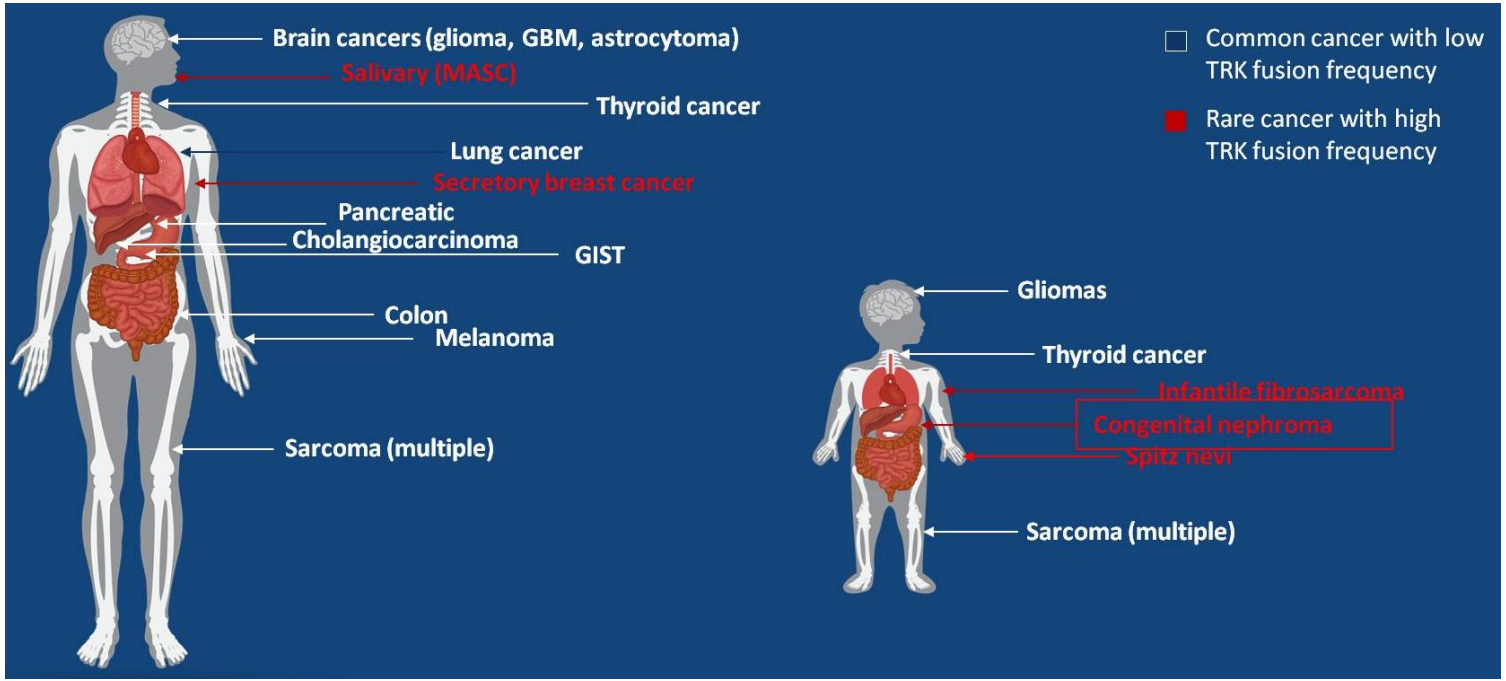
- Infantile fibrosarcoma >90%
- Secretory carcinoma (breast/salivary gland) >90%
- Mesoblastic nephroma >85%

Others

- Pediatric high-grade gliomas 5.3%
- Melanoma, colorectal <1%
- Adult gliomas 0.5-2%

Manea CA, et al. *Ann Med Surg* (London). 2022;79:103893. Cocco E, et al. *Nat Rev Clin Oncol*. 2018;15(12):731-747.

TRK Fusions Found in Diverse Cancer Histologies



GBM = glioblastoma; MASC = mammary analogue secretory carcinoma.

Manea CA, et al. *Ann Med Surg* (London). 2022;79:103893. Cocco E, et al. *Nat Rev Clin Oncol*. 2018;15(12):731-747.

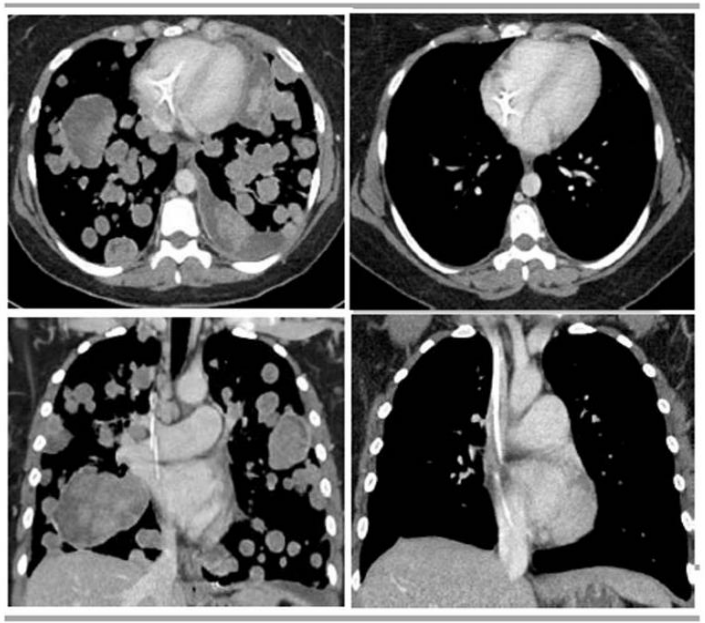
NTRK Inhibitors Approved in 2018

- Larotrectinib and entrectinib – approved in 2018
- Although *NTRK* fusions occur at low frequencies, it is recommended that *NTRK* fusion testing occur in all solid tumors
- Response rates are 60-80%

Manea CA, et al. *Ann Med Surg* (London). 2022;79:103893. Cocco E, et al. *Nat Rev Clin Oncol*. 2018;15(12):731-747.

Patient #1: *LMNA-NTRK1* Fusion Soft-Tissue Sarcoma

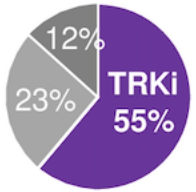
- 42 yo female with undifferentiated sarcoma progressed through epirubicin, ifosfamide, sorafenib, and doxorubicin
- 100mg BID
- Rapid resolution of dyspnea and hypoxemia
- Confirmed partial response



Hong DS. Presented at: ASCO; June 1-5, 2018; Chicago, IL. Education Session.

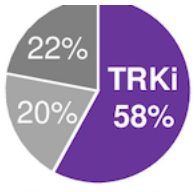
But, Healthcare Providers Generally Do Not Test as Often as They Should

- 43-year-old woman diagnosed with pT4aN0 **colon cancer**; deferred chemotherapy; right lower quadrant mass later recurred, with carcinomatosis and ascites
- Cancer is dMMR/MSI-high, TMB-high, and *NTRK* fusion positive; pembrolizumab started but PD after 2 months; nivolumab/ipilimumab started but PD again after 2 months



N = 85; A6
1.2020-1.2021

- 50-year-old nonsmoker with metastatic **lung adenocarcinoma**
- *EGFR/ALK/ROS1/BRAF* all negative, PD-L1 <1%; patient received carboplatin, pemetrexed, and pembrolizumab but PD
- NGS panel of original biopsy showed *NTRK* fusion



N = 591; A7
2.2020-3.2021

TMB = tumor mutation burden; PD = progressive disease.
Topping R, et al. Presented at: ASCO Quality Care Symposium; September 24-25, 2021; Boston, MA & Virtual. a229.

(1) MMRd solid tumor – use PD-1 inhibition

- In the 2nd-line treatment setting
- 1st-line in CRC
- Non-operative management for rectal cancer

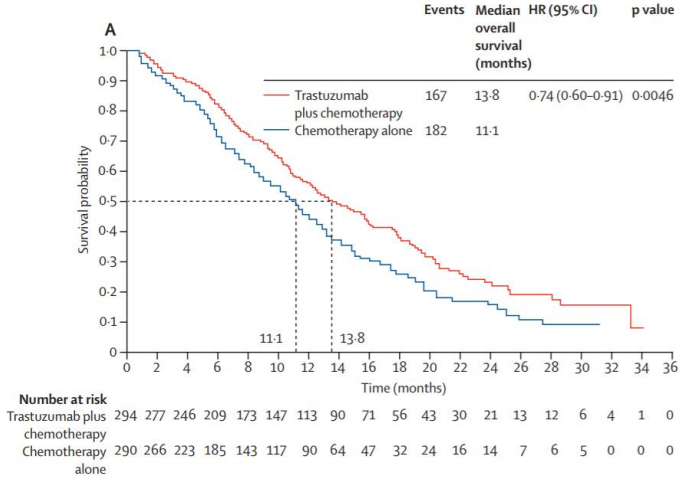
(2) *NTRK* inhibition

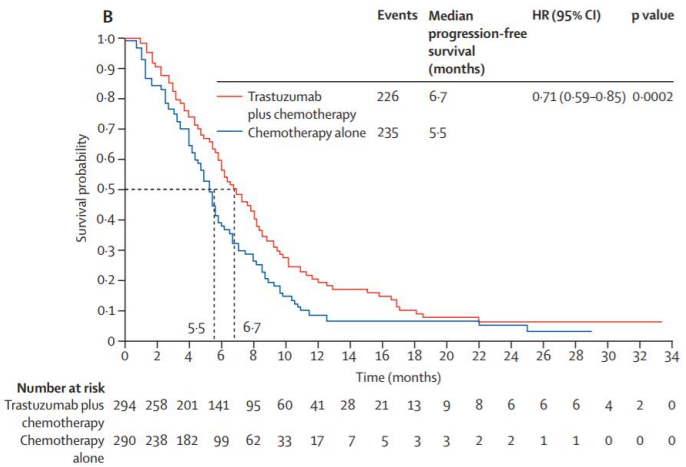
- Even if rare, tumor testing can be important

Targeting *HER2*

Trastuzumab for Gastric Cancer (ToGA): Trastuzumab + Chemo in Advanced *HER2*+ Gastric Cancer

- Primary endpoint: OS
- Trastuzumab + cisplatin/5FU vs cisplatin/5FU





FU = fluorouracil.

Bang YJ, et al. *Lancet*. 2010;376(9742):687-697.

Phase III Clinical Trials of *HER2*-Directed Therapy in Gastric Cancer

First-line → all negative

- JACOB: Capecitabine/cisplatin/trastuzumab +/- pertuzumab (N=780)
- HELOISE: Capecitabine/cisplatin + 2-dose levels of trastuzumab (N=400)

Second-line

- GATSBY: Paclitaxel vs T-DM1 (N=412)
  - T-DM1 was no better than paclitaxel

ClinicalTrials.gov. Accessed September 3, 2024. https://clinicaltrials.gov.

Phase III Clinical Trials of *HER2*-Directed Therapy in Gastric Cancer

First-line → all negative

- JACOB: Capecitabine/cisplatin/trastuzumab +/- pertuzumab (N=780)
- HELOISE: Capecitabine/cisplatin + 2-dose levels of trastuzumab (N=400)

Second-line

- GATSBY: Paclitaxel vs T-DM1 (N=412)
  - T-DM1 was no better than paclitaxel

ALL of these drugs are effective and APPROVED in breast cancer

- Lapatinib
- Pertuzumab
- T-DM1

ClinicalTrials.gov. Accessed September 3, 2024. https://clinicaltrials.gov.

Phase III Clinical Trials of *HER2*-Directed Therapy in Gastric Cancer

First-line → all negative

- JACOB: Capecitabine/cisplatin/trastuzumab +/- pertuzumab (N=780)
- HELOISE: Capecitabine/cisplatin + 2-dose levels of trastuzumab (N=400)

Second-line

- GATSBY: Paclitaxel vs T-DM1 (N=412)
  - T-DM1 was no better than paclitaxel

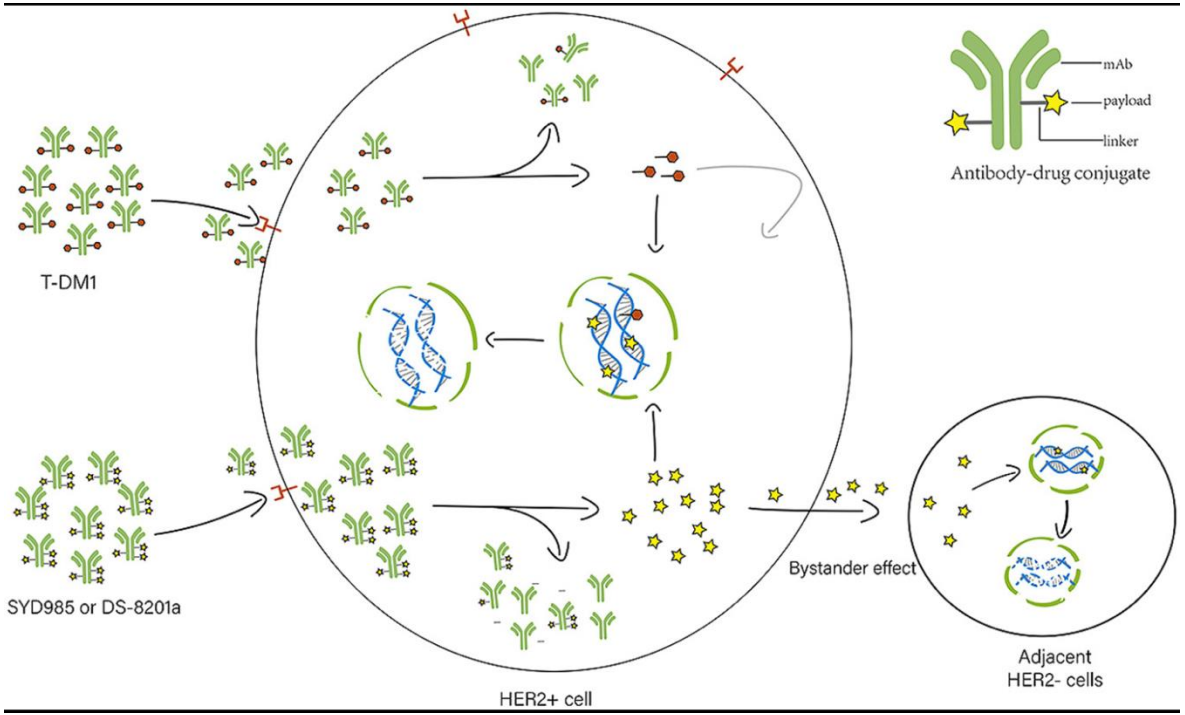
ALL of these drugs are effective and APPROVED in breast cancer

- Lapatinib
- Pertuzumab
- T-DM1

The SAME TARGET in different solid tumors can behave differently

ClinicalTrials.gov. Accessed September 3, 2024. https://clinicaltrials.gov.

Trastuzumab Deruxtecan (DS-8201a)



Adapted from Xu Z, et al. *Eur J Med Chem*. 2019;183:111682.

DESTINY-Breast04

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

Shanu Modi Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, NY, USA

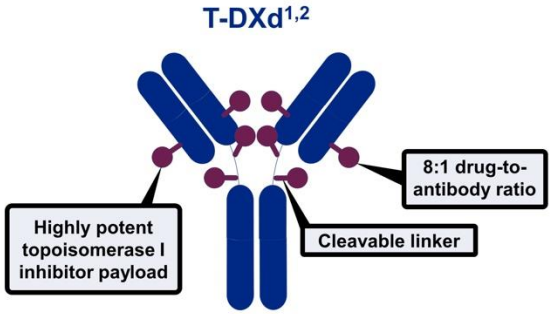
June 5, 2022

Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

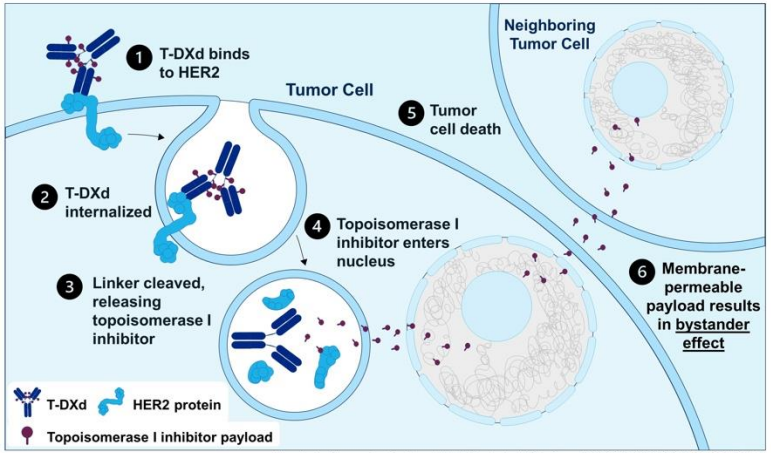
On behalf of the DESTINY-Breast04 investigators

Modi S, et al. Presented at: ASCO; June 3-7, 2022; Chicago, IL. Abstract LBA3.

DESTINY-Breast04: T-DXd MOA, Bystander Effect, and Rationale for Targeting *HER2*-Low mBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

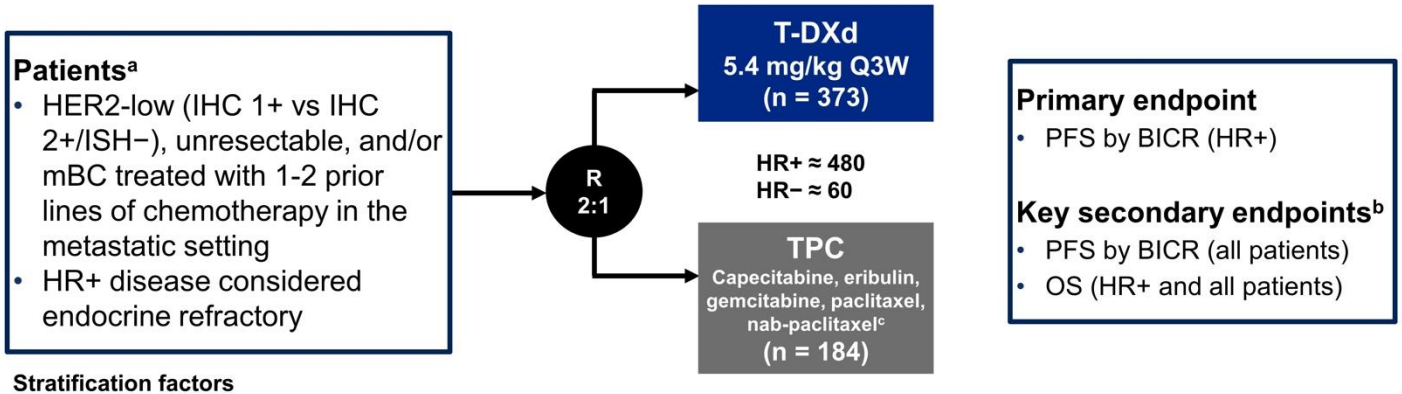
- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.
1. Nakada T, et al. *Chem Pharm Bull.* 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Modi S, et al. *J Clin Oncol.* 2020;38:1887-1896.

Modi S, et al. Presented at: ASCO; June 3-7, 2022; Chicago, IL. Abstract LBA3.

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for *HER2*-Low mBC

An open-label, multicenter study (NCT03734029)

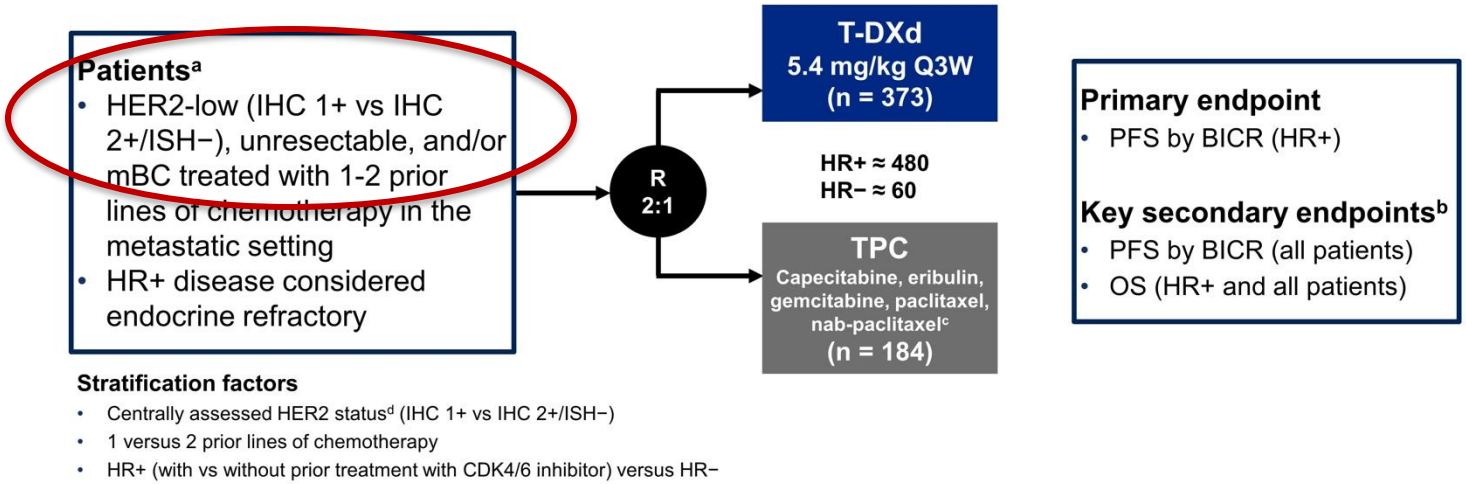


ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines.

Modi S, et al. Presented at: ASCO; June 3-7, 2022; Chicago, IL. Abstract LBA3.

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for *HER2*-Low mBC

An open-label, multicenter study (NCT03734029)

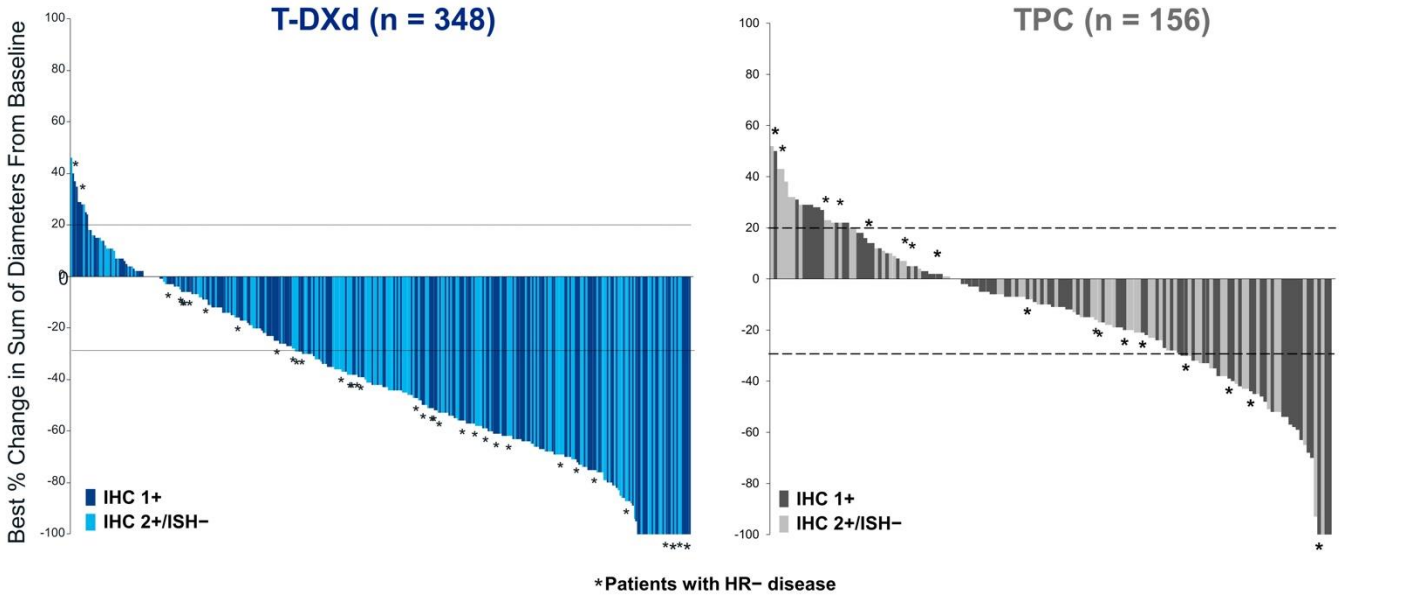


ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines.

Modi S, et al. Presented at: ASCO; June 3-7, 2022; Chicago, IL. Abstract LBA3.

DESTINY-Breast04: Best Change in Target Lesions (All Patients)



*Patients with HR− disease

Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumors in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression, and the lower dashed line indicates a 30% decrease in tumor size (partial response).
HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi S, et al. Presented at: ASCO; June 3-7, 2022; Chicago, IL. Abstract LBA3.

Trastuzumab Deruxtecan

- Approved in breast cancer
- Targets *HER2*
- First to have efficacy in *HER2*-“low” tumors

Target evolution:

HER2-targeted therapy in breast cancer now includes *HER2*-“LOW” tumors

Key Learning Points

(1) MMRd solid tumor – use PD-1 inhibition

- In the 2nd-line treatment setting
- 1st-line in CRC
- Non-operative management for rectal cancer

(2) *NTRK* inhibition

- Even if rare, tumor testing can be important

(3) *HER2*

- Targeting *HER2* is active across cancers – CRC, breast, lung
- Efficacy is not the same across cancers – more effective in breast
- Target evolution

Q&A Session