Advances in Targeted Therapy for Upper GI and Biliary Tract Cancers

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Disclosures

- Pfizer – Consultant
- AstraZeneca – Research support (institutional)
  - **durvalumab**
- Daichii-Sankyo – Advisory Board*
  - **trastuzumab – deruxtecan**
- Cardiff Oncology – Research support (institutional)

Objectives

- Discuss the basics of molecular/genomic testing and targeted therapies in GI oncology
- Review the current landscape of targeted therapies in upper GI and biliary tract cancers
- Discuss practical approaches to integrating targeted therapies into patient care

NATIONAL CANCER INSTITUTE
PRECISION MEDICINE IN CANCER TREATMENT

Discovering unique therapies that treat an individual's cancer based on the specific genetic abnormalities of that person's tumor.

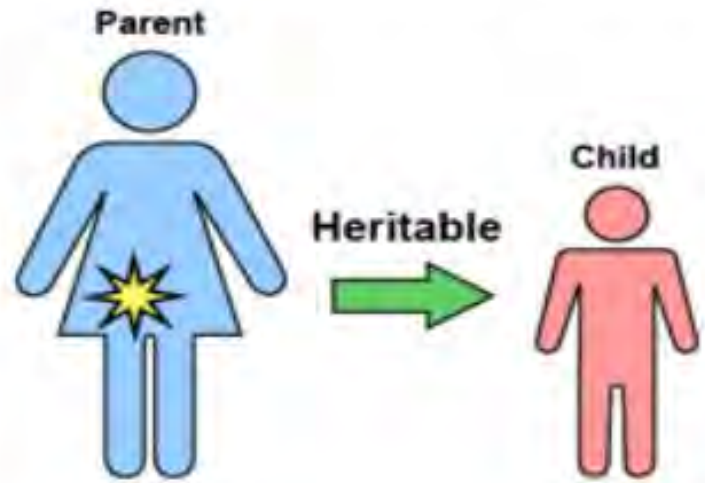
Germline versus Somatic

Somatic mutations
- Occur in ***nongermline*** tissues
- Cannot be inherited

Nonheritable

Mutation in tumor only
(for example, breast)

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome



Mutation in
egg or sperm

All cells
affected in
offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology

Somatic Genomic Testing

- Somatic = Tumor

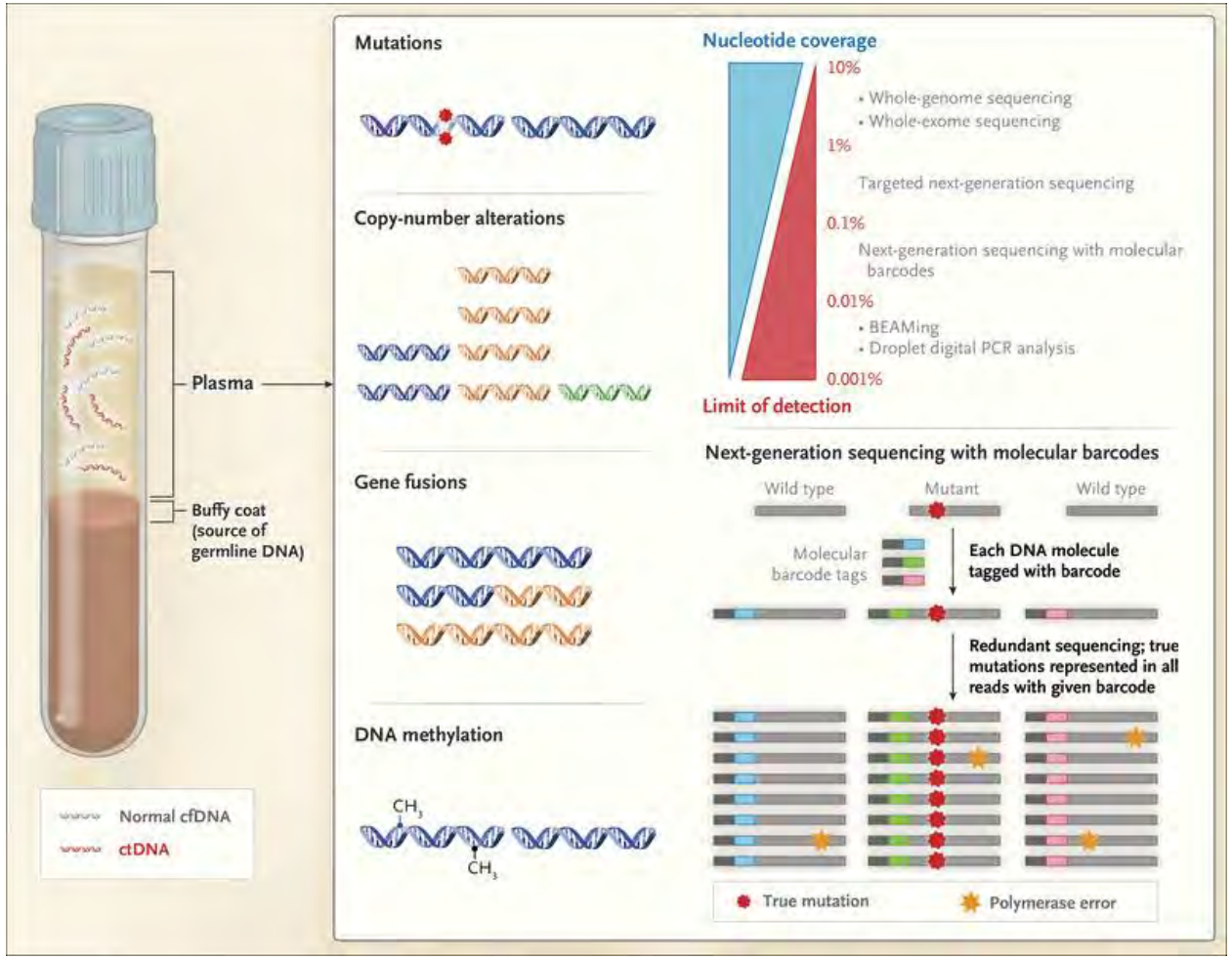
- Must test tumor tissue
  - Tumor biopsy – genomic testing is performed on tumor tissue
  - Liquid biopsy - genomic testing is performed on peripheral blood
    - *May* detect circulating tumor DNA

- Next Generation Sequencing (NGS)
  - Genetic sequencing – DNA, RNA
  - UNMC – Precision Oncology Panel
  - Often use commercial labs – Foundation Medicine, Tempus, Caris, Guardant, etc.

Somatic Genomic/Biomarker Testing

What are we looking for?

- Mutations
- Copy number alterations (amplification)
- Gene fusions
- DNA methylation
- Tumor mutation burden/hypermutability
- RNA expression
- Protein expression (immunohistochemistry)

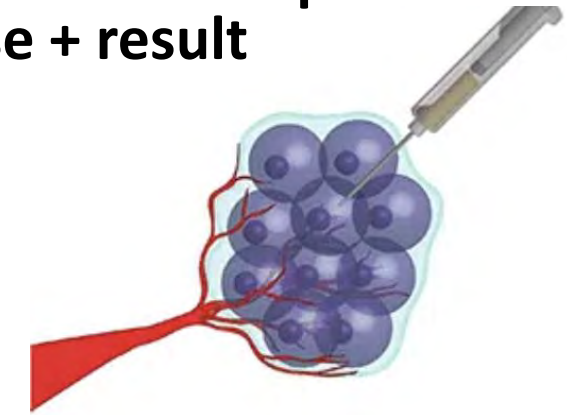


ran RB et al. NEJM, 2018.

NGS: Liquid biopsy vs. Tumor biopsy

Liquid biopsy

- **Non-invasive (blood test)**
- **Longitudinal sampling**
- **May better capture heterogeneity/genomic landscape**
- **May be insensitive – "false negative"**
- **Cannot assess non-DNA biomarkers**
- **Clonal hematopoiesis may cause false + result**



Tumor biopsy

- **Requires "small" specimen, can typically be performed on archival sample**
- **Able to assess non-DNA biomarkers**
- **"Fresh" biopsy requires invasive procedure**
- **More sensitive than liquid biopsy**

Corcoran RB. Nature 2020

Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion

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PURPOSE An ASCO provisional clinical opinion offers timely clinical direction to ASCO's membership following publication or presentation of potentially practice-changing data from major studies. This provisional clinical opinion addresses the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.

CLINICAL CONTEXT An increasing number of therapies are approved to treat cancers harboring specific genomic biomarkers. However, there is a lack of clarity as to when tumor genomic sequencing should be ordered, what type of assays should be performed, and how to interpret the results for treatment selection.

PROVISIONAL CLINICAL OPINION Patients with metastatic or advanced cancer should undergo genomic sequencing in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease. Multigene panel–based assays should be used if more than one biomarker-linked therapy is approved for the patient's disease. Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (*NTRK*) fusions provide a rationale for genomic testing for all solid tumors. Multigene testing may also assist in treatment selection by identifying additional targets when there are few or no genotype-based therapy approvals for the patient's disease. For treatment planning, the clinician should consider the functional impact of the targeted alteration and expected efficacy of genomic biomarker–linked options relative to other approved or investigational treatments.

Current Landscape of Targeted Therapies

- Advanced Upper GI Cancers
- Advanced Biliary Tract Cancers

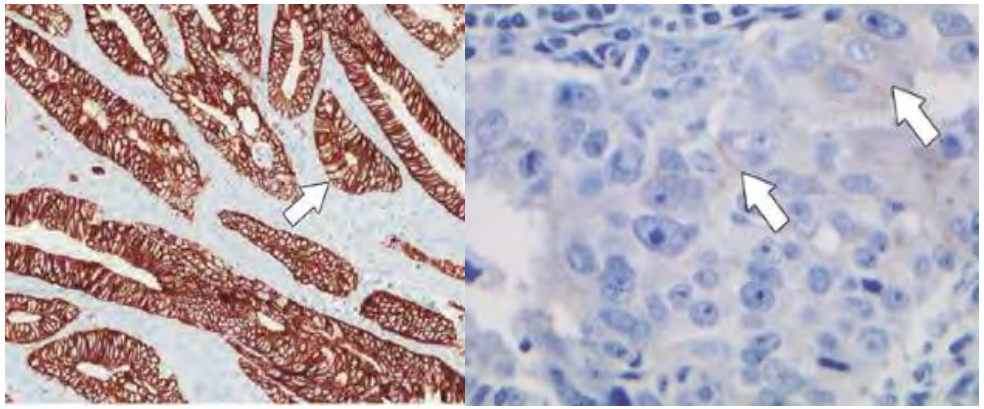
Targeted Therapy in Advanced Gastroesophageal Cancers

- **Critical Biomarkers**
  - **HER2**
  - ***PD-L1***
  - ***Microsatellite instability/mismatch repair deficiency***
    - ***MSI/MMR***

Gastric and GEJ Adenocarcinoma HER2 Overexpression or Amplification

- **~20% of all advanced gastric/GEJ adenocarcinoma have HER2 overexpression or amplification**
- **Can be identified by IHC, FISH or NGS**

Immunohistochemical test detects HER2 protein overexpression



Positive: 3+, Equivocal: 2+, Negative: 0-1+

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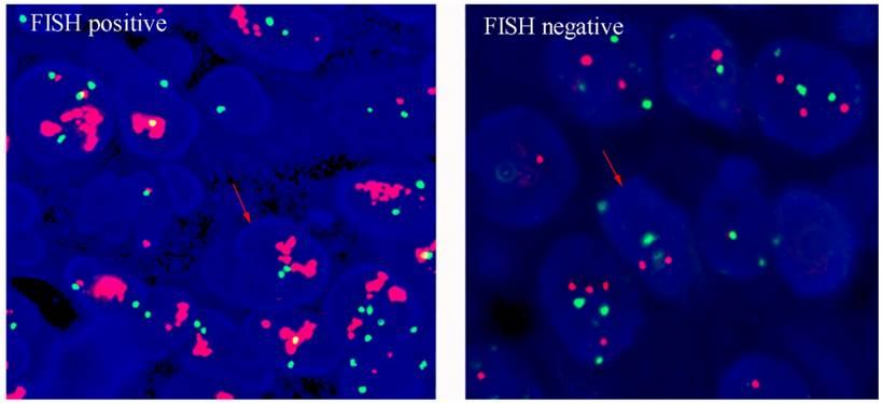
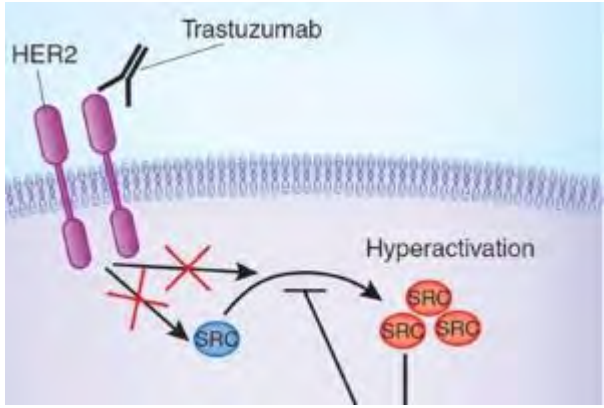
Reflex to FISH

FISH test detects HER2 (*ERBB2* gene) gene overexpression



#of HER2 gene copies relative to centromere 17
Positive: HER2/CEP17 >2.2

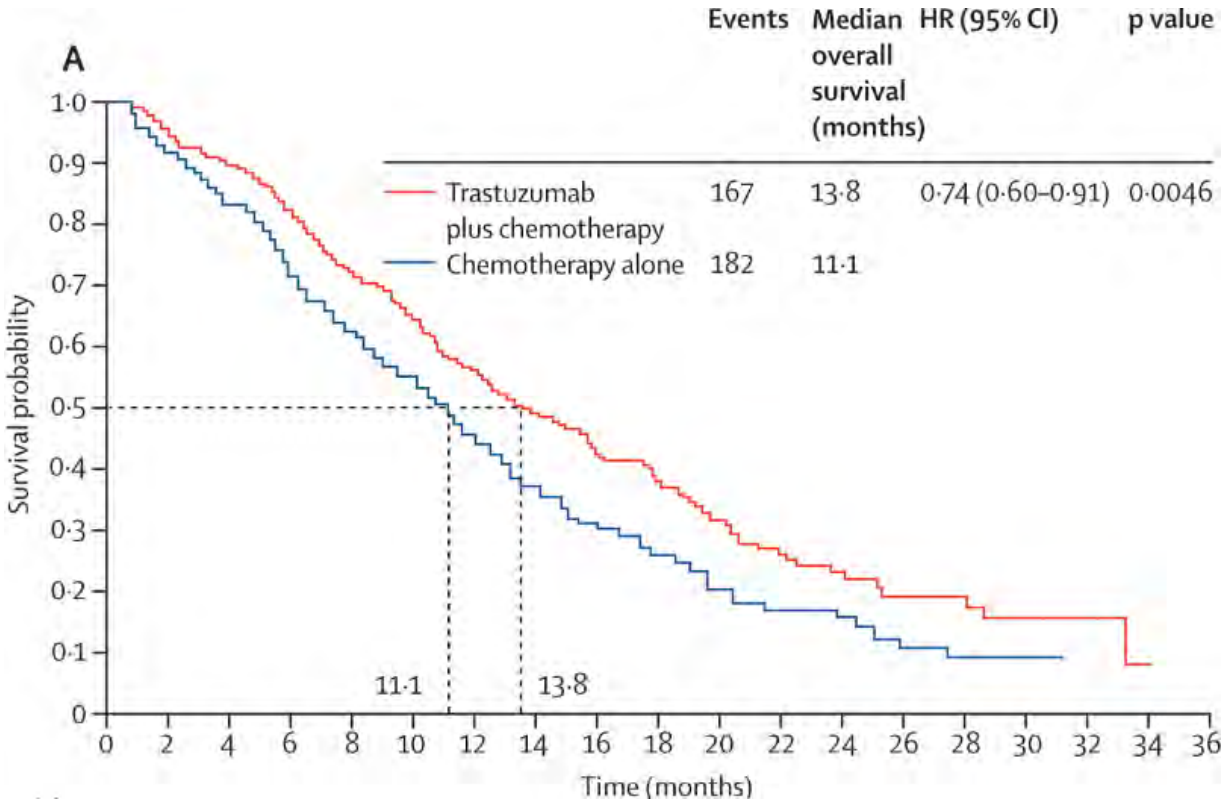
Gastric and GEJ Adenocarcinoma
HER2 Overexpression or Amplification



HER2 overexpression/amplification identifies patients who benefit from first-line trastuzumab + chemotherapy

ToGA (Trastuzumab for Gastric Cancer) compared chemotherapy + trastuzumab to chemotherapy alone for HER2+ advanced gastric and GEJ adenocarcinoma.

Benefit of trastuzumab + chemotherapy: 25% reduction in risk of death



Bang YJ et al. Lancet, 2010.

Gastroesophageal Adenocarcinoma: HER2 Overexpression or Amplification

More recently, trastuzumab + pembrolizumab + platinum-based chemotherapy has emerged as a standard approach to 1st line therapy for HER2+ disease

KEYNOTE 811: Ph3 randomized trial

Trastuzumab + chemo ± pembrolizumab as 1st line tx for HER2+ gastroesophageal adenocarcinoma

5FU+ cisplatin or CapOx

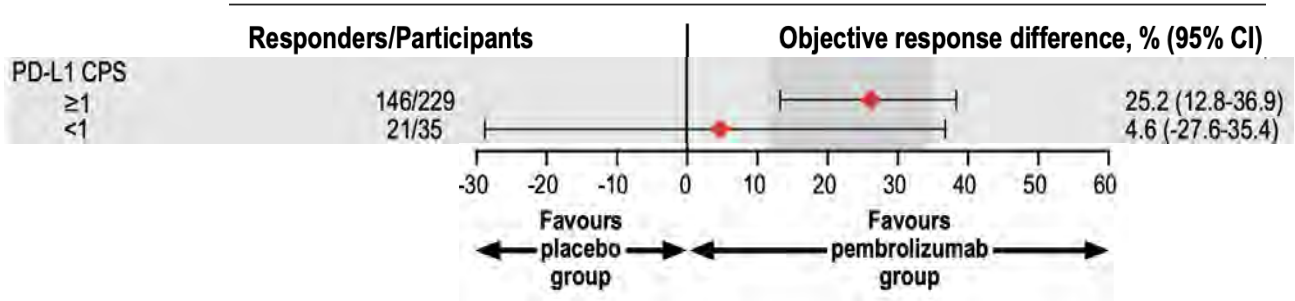
First interim analysis:

- **Objective response rate: 74% vs. 52% (p<0.0001)**
- **Median duration of response 10.6mo vs. 9.5mo**

FDA granted accelerated approval for pembrolizumab with trastuzumab with fluoropyrimidine + platinum containing chemotherapy (May 2021).

***Benefit may not be limited to high PD-L1**

****Pembrolizumab may enhance HER2 specific T-cell responses***

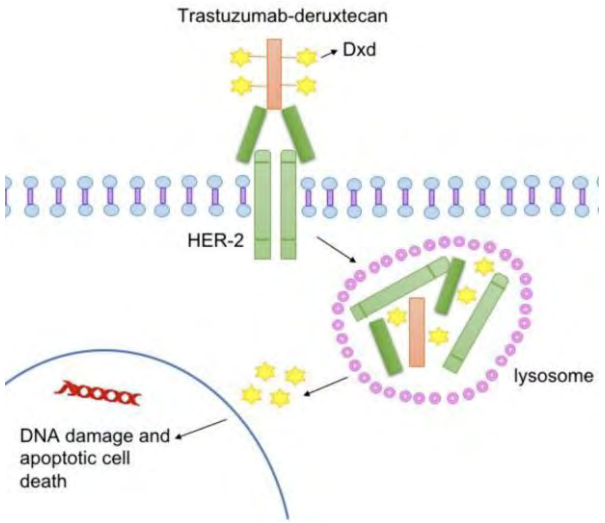


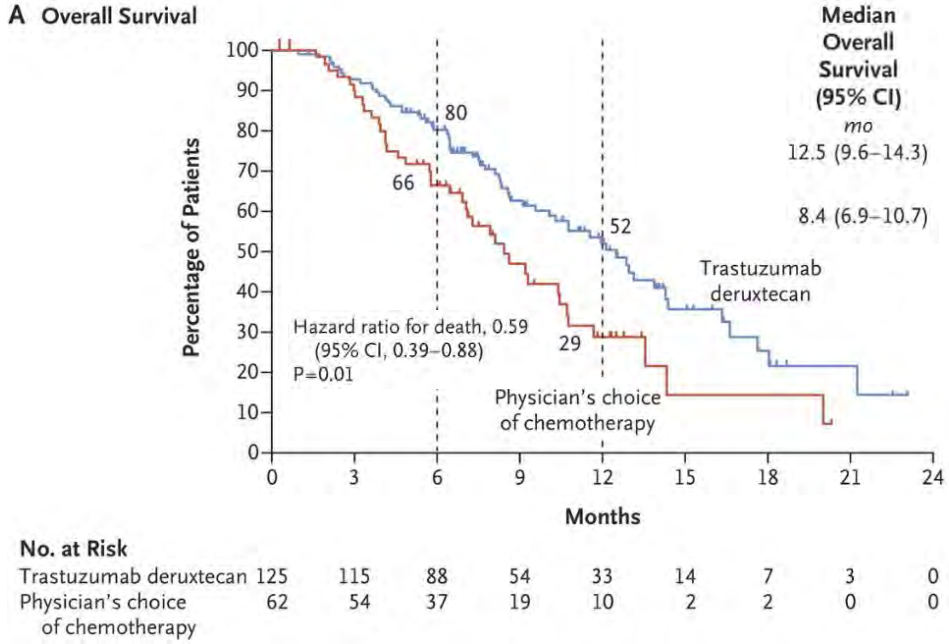
Janjigian YY et al. Nature, 2021.

Gastroesophageal Adenocarcinoma: HER2 Overexpression or Amplification

- Trastuzumab deruxtan – antibody-drug conjugate with anti-HER2 antibody + topoisomerase inhibitor
- DESTINY-Gastric01: randomized Ph2 trial of trastuzumab deruxtecan vs. investigators choice chemotherapy
  - HER2+ disease, progression on at least 2 prior lines of therapy
  - 2:1 randomization
- Primary endpoint: Objective response rate
  - 51% vs. 14% (P<0.001)
  - Improved OS was also noted 12.5 vs. 8.4mo
- Most common G3-4 adverse events:
  - Neutropenia (51% vs. 24%)
  - ~10% had drug-related ILD or pneumonitis
    - 1 drug related death

FDA approved trastuzumab deruxtecan for advanced HER2+ gastric/GEJ adenocarcinoma which has progressed on a prior trastuzumab containing regimen. (Jan 2021)

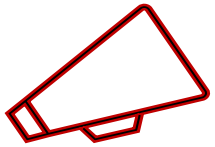




Targeted Therapy in Advanced Gastroesophageal Cancers

- See Dr. Krishnan's talk re: PD-L1, MMR and checkpoint inhibitors

- For advanced HER2 overexpressing or amplified tumors
  - Consider trastuzumab + pembrolizumab + chemotherapy in 1st line setting
  - Consider trastuzumab deruxtecan in later lines
    - Caution re: risk of pneumonitis/ILD including small risk of fatality

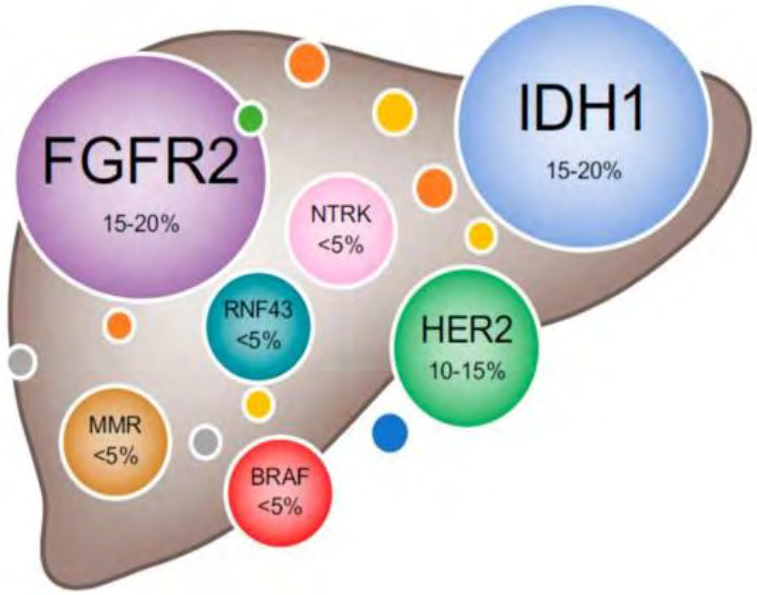


Spoiler Alert: Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer (ASCO Guideline) – *Coming soon*

Targeted therapies in advanced biliary tract cancers

- Molecularly heterogenous group of cancers
- Relatively rich in actionable genomic alterations

Tumor Type	Genomic Alteration	Rate
Large-duct CCA	KRAS mutations TP53 mutations	15-30% 10-40%
Small-duct CCA	IDH1/2 mutations FGFR2 fusions	15-20% 10-20%
Gallbladder and eCCA	KRAS mutations HER2 overexpression/amplification	30-40% 10-15%
All biliary tract	BRAF alterations Homologous recombination deficiency MSI-H/dMMR	3-5% 5-15% 2-5%

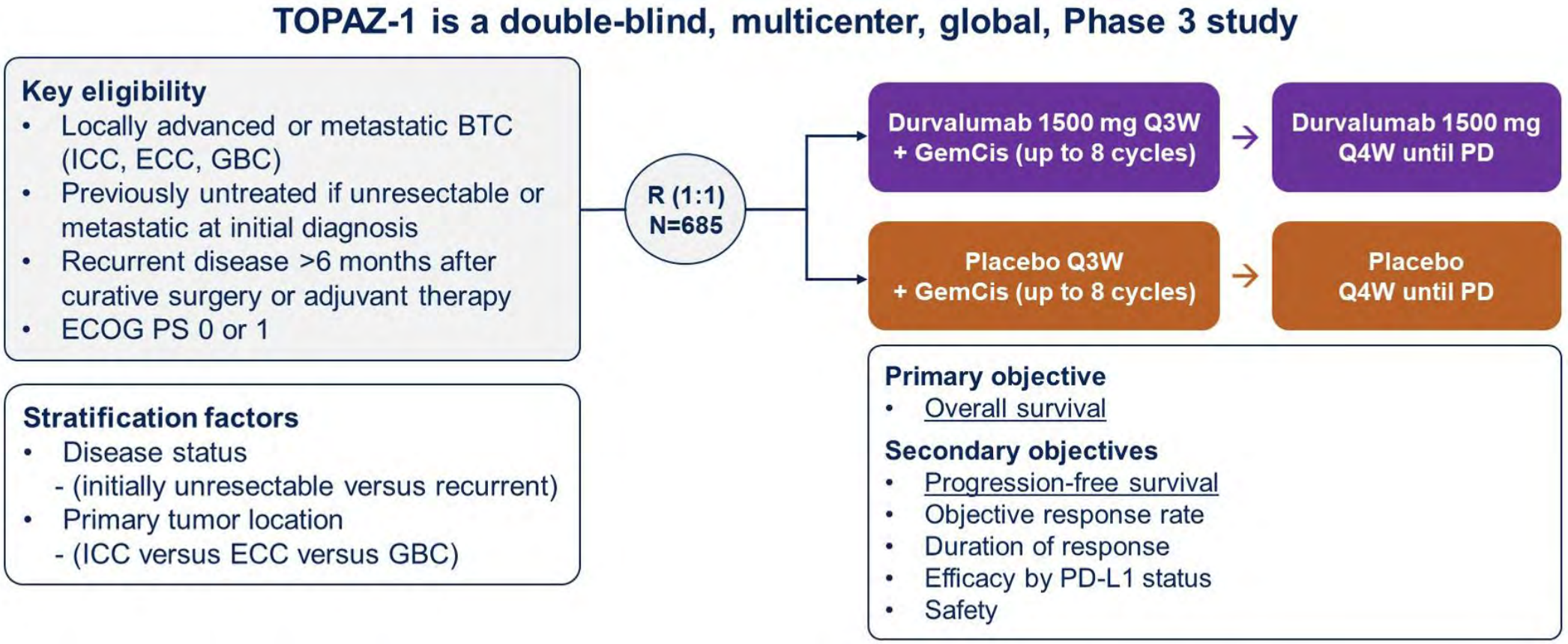


Parsoneni et al. Cancers, 2020.

- Several FDA-approved targeted therapies

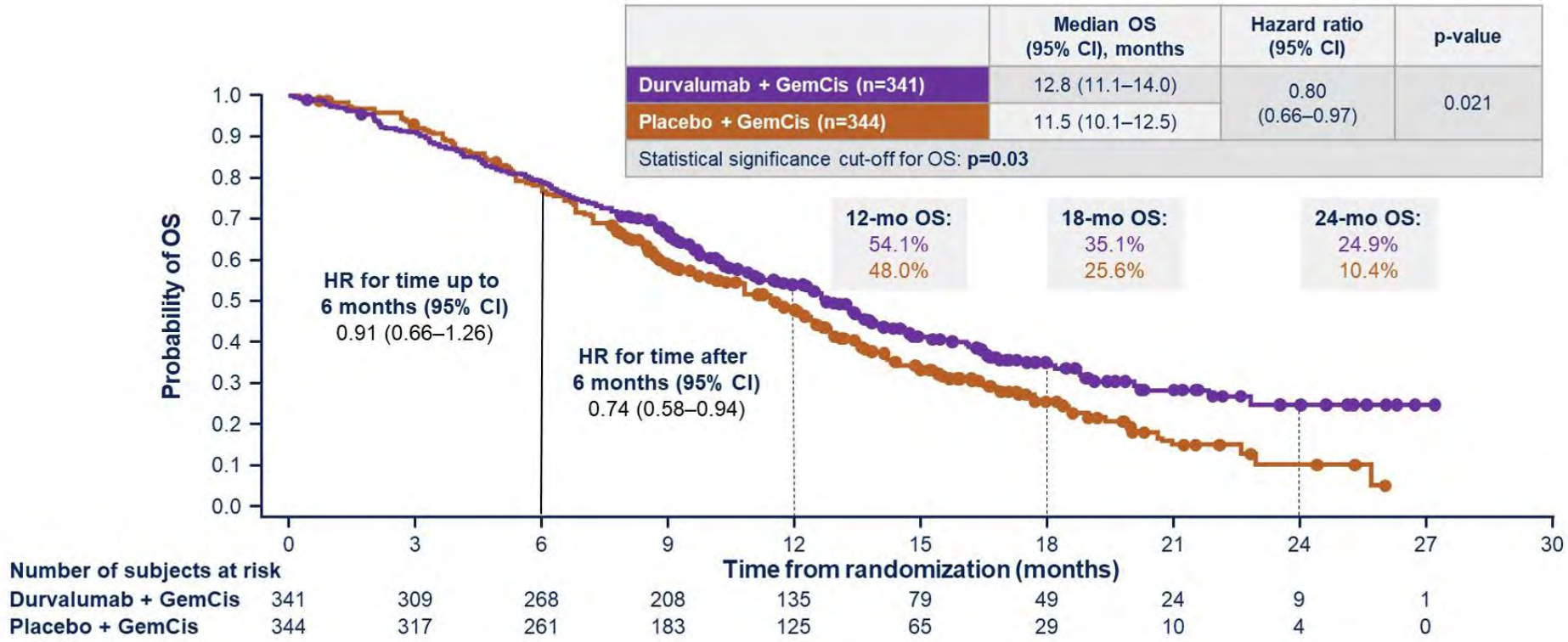
Targeted therapies in advanced biliary tract cancers
Anti-PDL1 + chemo in 1st line

- **Systemic therapy remains the standard of care for treatment of advance biliary tract cancer**
- **TOPAZ-1 tested the benefit of durvalumab (anti PD-L1) in addition to gem-cis in 1st line therapy**



Oh, DY. ASCO GI Symposium 2022.

Targeted therapies in advanced biliary tract cancers
Anti-PDL1 + chemo in 1st line



- **Benefit does not appear limited to tumors w/high PDL1 expression**
- **FDA approved durvalumab in combination with gemcitabine and cisplatin in patients with advanced biliary tract cancer (Sept 2022).**

Oh, DY. ASCO GI Symposium 2022.

Biomarker driven therapy in advanced biliary tract cancers *IDH1* mutations – ClarIDHy Ph3 Randomized Trial

RCT: Efficacy of Ivosidenib for Patients With Advanced Cholangiocarcinoma With *IDH1* Mutation
(oral inhibitor of mutated *IDH1*)

POPULATION

68 Men, 119 Women

Adults with cholangiocarcinoma with *IDH1* mutation and disease progression after 1 or 2 prior treatment regimens

Median age (range), 62 y (33-83 y)

INTERVENTION

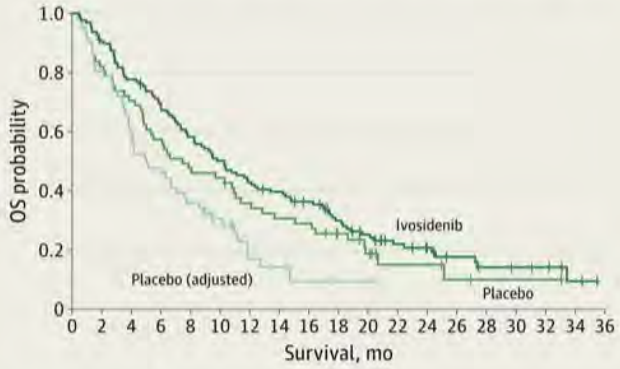
187 Patients randomized

126 Ivosidenib
Ivosidenib, 500 mg once daily

61 Placebo
Placebo medication once daily (43 crossed over from placebo to ivosidenib at time of final analysis)

FINDINGS

Ivosidenib resulted in a favorable overall survival benefit vs placebo



Median overall survival:
Ivosidenib, 10.3 mo (95% CI, 7.8-12.4)
Placebo, 7.5 mo (95% CI, 4.8-11.1)
HR, 0.79 (95% CI, 0.56-1.12); 1-sided *P* =.09;
after adjustment for crossover from placebo to ivosidenib:
HR, 0.49 (95% CI, 0.34-0.70); 1-sided *P* <.001

SETTINGS / LOCATIONS

49 Hospitals in France, Italy, South Korea, Spain, UK, and US

PRIMARY OUTCOME

The primary outcome previously reported was progression-free survival by blinded independent radiology center. The key secondary outcome reported here was overall survival

PFS 2.7 vs. 1.4mo HR 0.37, P<0.001

Ivosidenib is FDA approved for the treatment of *IDH1* mutated cholangiocarcinoma which has progressed on at least one prior line of therapy. (Aug 2021)

ORR: 2 vs. 0%
43 patients crossed over from placebo to ivosidenib.
Most common AEs: anemia, increased bilirubin, hyponatremia

Zhu et al. JAMA Oncology, 2021.

Targeted therapies in advanced biliary tract cancers *FGFR2* alterations

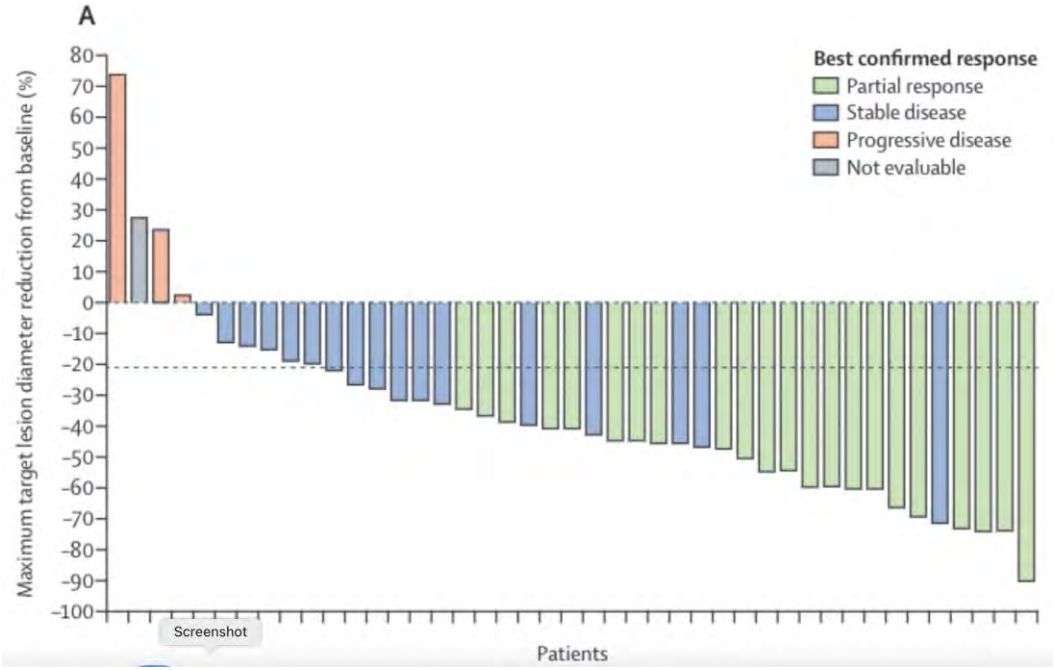
- **Three FGFR inhibitors are FDA approved to treat advanced BTC harboring *FGFR2* fusions or rearrangements:**
  - **All approved based on results of single-arm phase II studies**
  - **Similar adverse event profiles: hyperphosphatemia (~75%), stomatitis, fatigue, alopecia, ocular toxicities (retinal - blurred vision, floaters, detachment)**

	Pemigatinib N=107	Infigratinib N=108	Futibatinib N=1-3
MOA	Inhibits FGFR 1-3	Inhibits FGFR 1-3	Inhibitos FGFR 1-4 (irreversible)
Trial	FIGHT-202 Ph2, multicohort		FOENIX-CCA2
ORR %	35.5%	23%	37%
Median PFS	6.9mo	7.3mo	9 mo
Median OS	21.1mo	-	21.7mo
FDA Approval	May 2021	Aug 2021	Sept 2022

Ghassan AA et al. Lancet, 2020. Javle M et al. Lancet Gastro & Hep, 2021. Goyal L et al. ASCO Annual Meeting, 2022.

Targeted therapies in advanced biliary tract cancers
BRAF Alterations

- Alterations in BRAF are found in 5% of iCCA – most commonly *BRAFV600E*
- Rare Oncology Agnostic Research basket trial – *BRAFV600E* mutated rare cancers treated with dabrafenib and trametinib
  - 43 patients with *BRAFV600E* mutated biliary tract cancers
  - ORR 47%, median duration of response 9 months
  - 6mo PFS 63%, 12mo OS 56%



<u>Tumor agnostic approval:</u> FDA granted accelerated approval to dabrafenib and trametinib for advanced solid tumors with *BRAFV600E* mutation. (July 2022)

Subbiah V et al. Lancet Oncology, 2020.

Targeted therapies in advanced biliary tract cancers

- ***NTRK* fusions – ~1%**
  - **Entrectinib and Larotrectinib are FDA approved (tumor agnostic)**
- **HER2 overexpression/amplification – up to 20%**
  - **Multiple ongoing studies; HER2 directed therapies appear to have activity (response rate)**
- **Immune checkpoint blockade**
  - **In MSS BTC, response rate with nivolumab was 11% (Kim RD, JAMA 2020)**
  - **Tumor agnostic approval for pembrolizumab (dMMR/MSI-H or TMB≥10*)**
    - ***Study did not include any patients with BTC**

FDA approved biomarker directed therapies in advanced biliary tract cancers

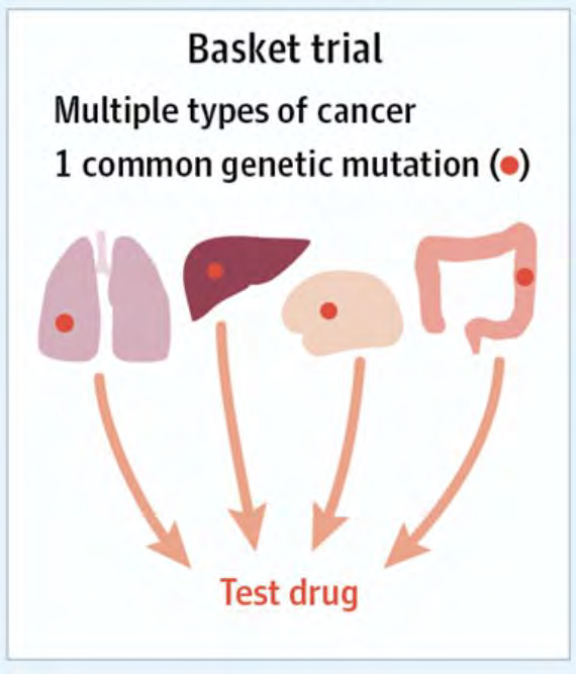
IDH1 mutations	• Ivosidenib
FGFR2 fusions	• Pemigatinib • Infigratinib • Futibatinib
BRAFV600E mutation	• Dabrafenib + trametinib
dMMR/MSI-H +/- high TMB	• Pembrolizumab
NTRK fusions	• **Entrectinib** • **Larotrectinib**

Practical approaches to integrating targeted therapies into patient care

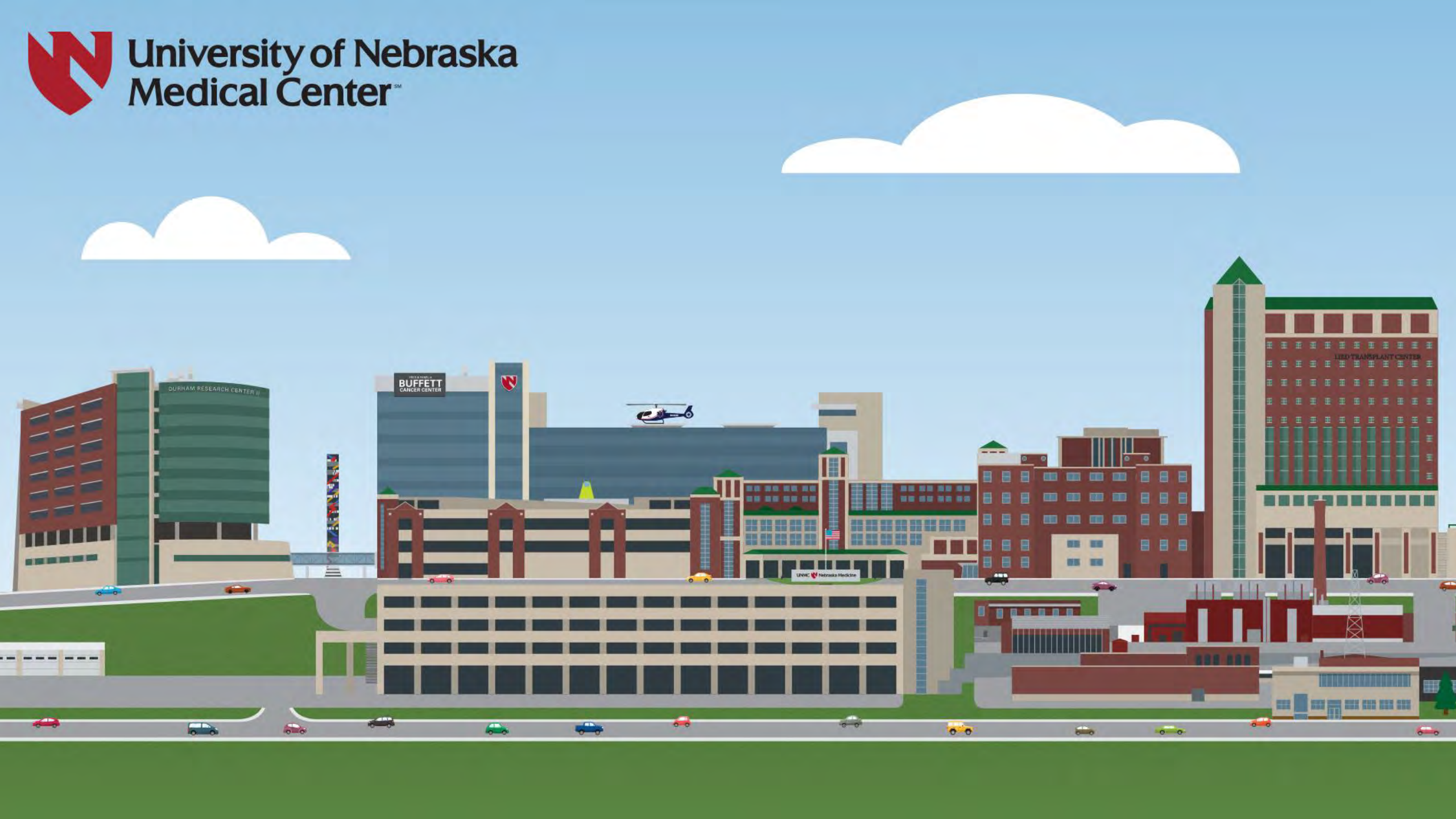
- **Obtaining tissue for molecular profiling**
  - Essential
  - Upper GI tumors – typically easy
  - Biliary tract tumors – may be more challenging; liquid biopsy may have an important role if tumor tissue is inaccessible

- **Identifying actionable targets, selecting optimal therapies**
  - UNMC Molecular tumor board
  - Clinical trials: ex. ASCO's TAPUR trial
  - NGS testing platform

- **Challenges**
  - Financial – insurance coverage is variable, clear disparities in access to NGS
  - Logistic – tracking results, integration into EMR




Cancer care based on your own DNA.
LEARN MORE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