Rare Triple Negative Breast Cancer

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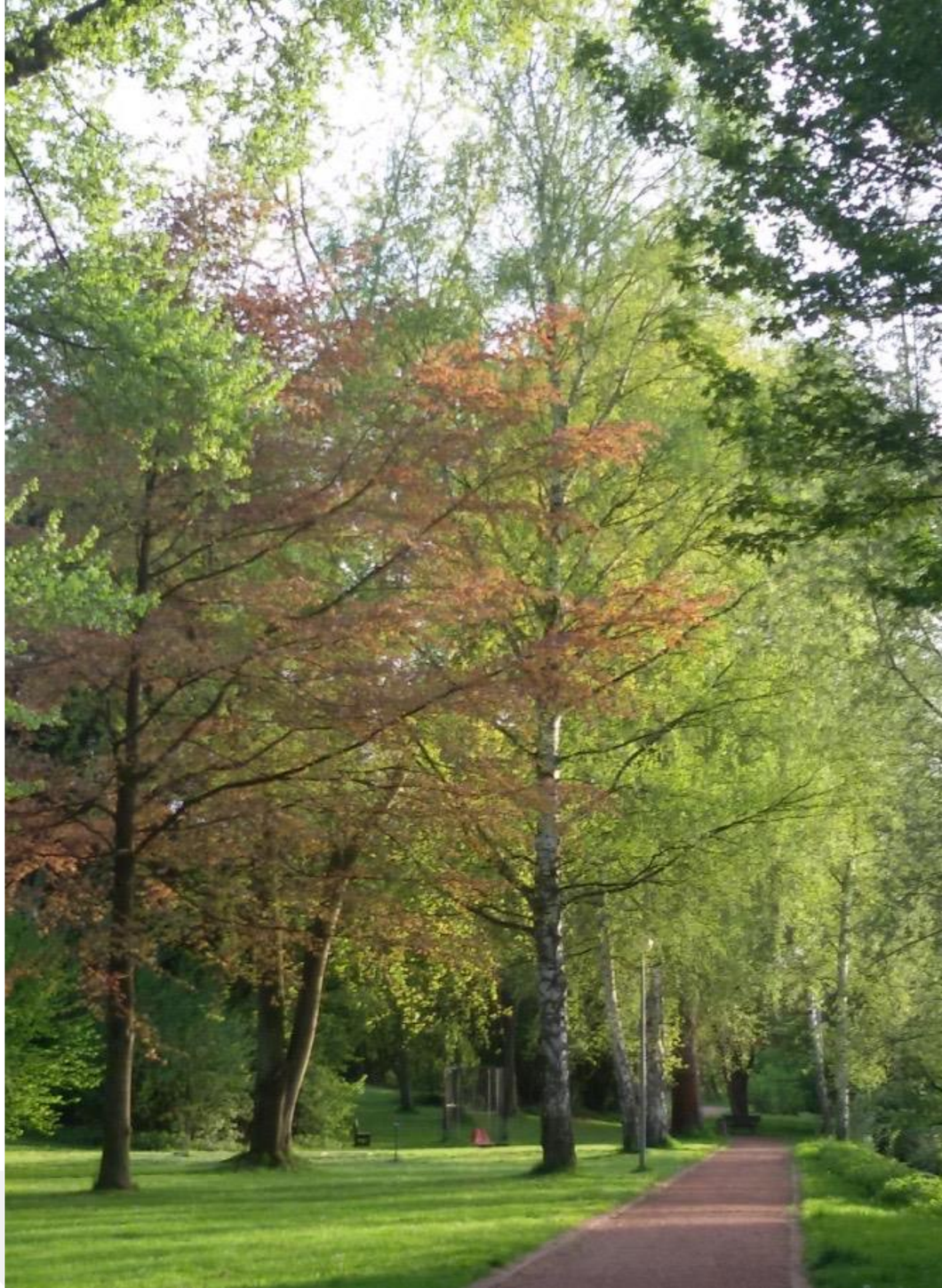
Disclosure of Conflicts of Interest

- Sanofi– research support (to the institution)
- Lilly, Genentech – Consulting
- Beyond Spring Pharmaceuticals – DSMB
- Johnson and Johnson, Gilead Science, Pfizer, Bristol Myers Squibb, Doximity – stock ownership
- Up-to-Date – royalties (husband)

Special Subtypes of Triple Negative Breast Cancer: The Path Ahead

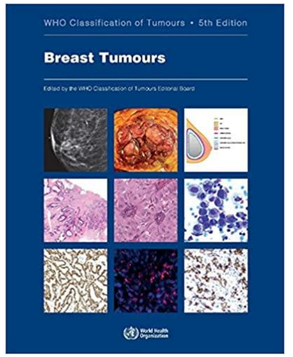
- Overview of less common subtypes of TNBC
- Molecular/clinical features and treatment of special subtypes
- Newer tools for disease management
- Harnessing contemporary research tools to further disease-specific understanding



Take Home Messages

- Given lower prevalence, we have some albeit limited disease-specific information on how to treat special subtypes
- As biologic principals applied to breast cancer – no special type (NST) extend to less common subtypes we can improve our understanding of this group of breast tumors
- We may need to think beyond the randomized trial to further our knowledge in this space

Special Subtypes of Breast Cancer



<u>Invasive breast carcinomas</u>

- Solid papillary carcinoma
- IBC NOS – medullary pattern
- Microinvasive carcinoma
- Invasive lobular carcinoma
- Tubular carcinoma
- Cribriform carcinoma
- Mucinous carcinoma
- Mucinous cystadenocarcinoma
- Invasive micropapillary carcinoma
- Carcinoma with apocrine differentiation
- Metaplastic carcinoma

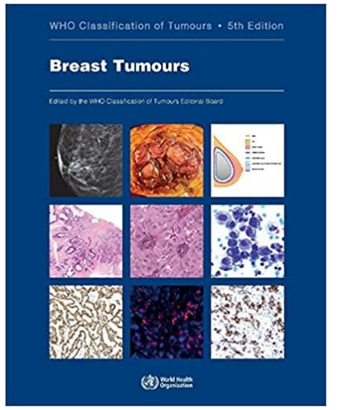
<u>Rare and Salivary gland-type breast tumors</u>

- Acinic cell carcinoma
- Adenoid cystic carcinoma
- Secretory carcinoma
- Mucoepidermoid carcinoma
- Polymorphous adenocarcinoma
- Tall cell carcinoma with reversed polarity

<u>Neuroendocrine neoplasms</u>

- Neuroendocrine tumor
- Neuroendocrine carcinoma

Special Subtypes of Breast Cancer



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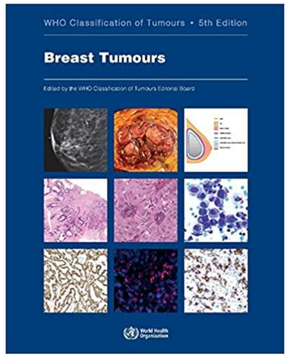

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Neuroendocrine neoplasms

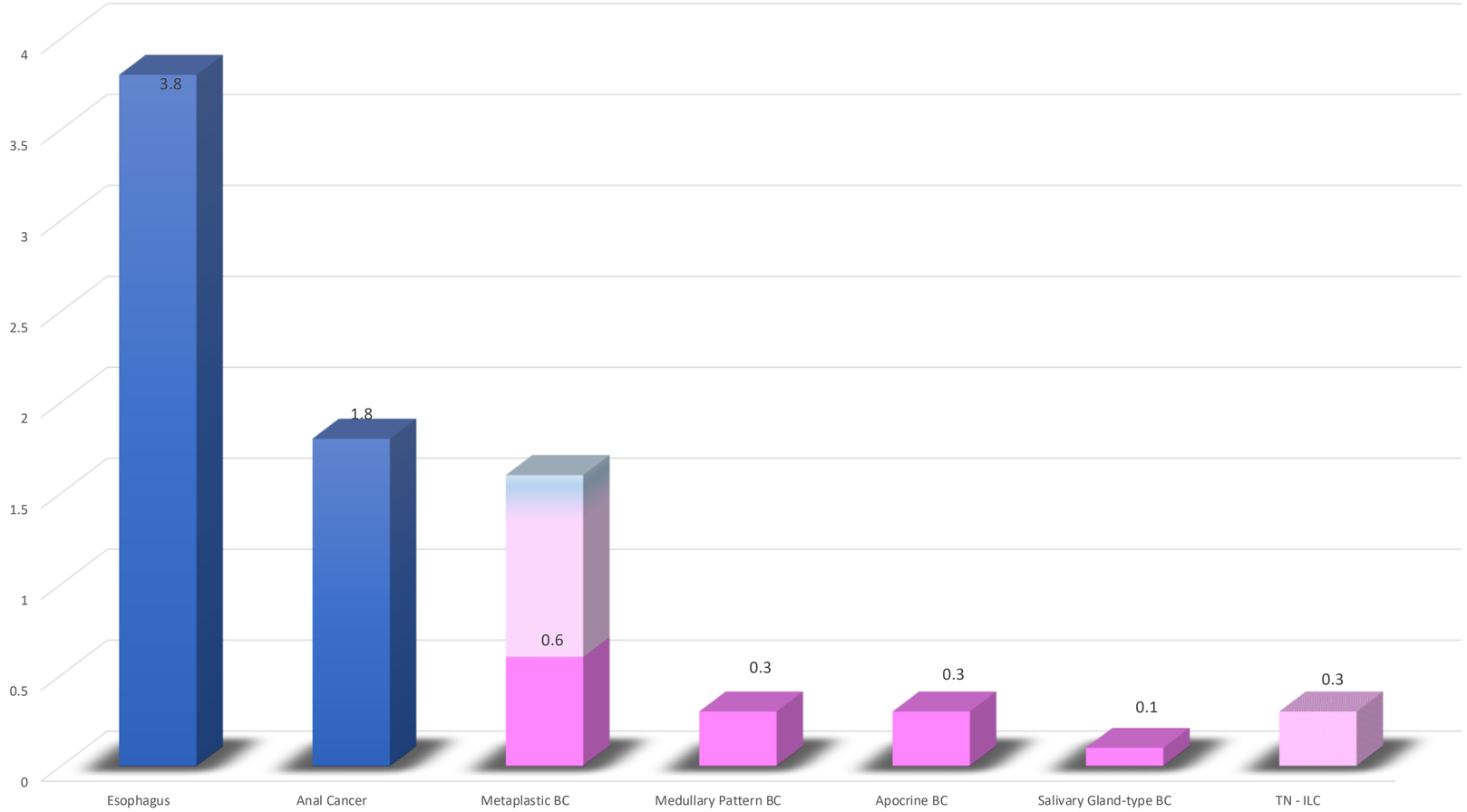
- Neuroendocrine tumor
- Neuroendocrine carcinoma

Special Subtypes of TNBC

	Frequency	ER/PR/ERBB2 expression	Prognosis
Invasive carcinomas of the breast			
IDC NST – Medullary pattern	3-5%	neg/neg/neg	Good
Triple Negative Invasive Lobular Carcinoma	<1%	neg/neg/HER2 mutations; (AR+)	Poor
Carcinoma with apocrine differentiation	<1%	neg/neg/HER2 variable; (AR+)	Data mixed
Metaplastic carcinoma	≅1%	neg/neg/neg	Poor
Salivary gland-type tumors of the breast			
Adenoid cystic carcinoma	0.1-3-5%	neg/neg/neg	Good
Secretory carcinoma	<1%	neg/neg/neg	Good
Neuroendocrine neoplasms of the breast			
Neuroendocrine carcinoma	<1%	neg/neg/neg	Poor

WHO Classification of Tumors, Breast Tumors, 5th Edition; Jenkins S, et al, *Current Oncology Reports* 2021; Mills MN, et al *Eur J Cancer* 2018

How rare are special subtypes of TNBC?

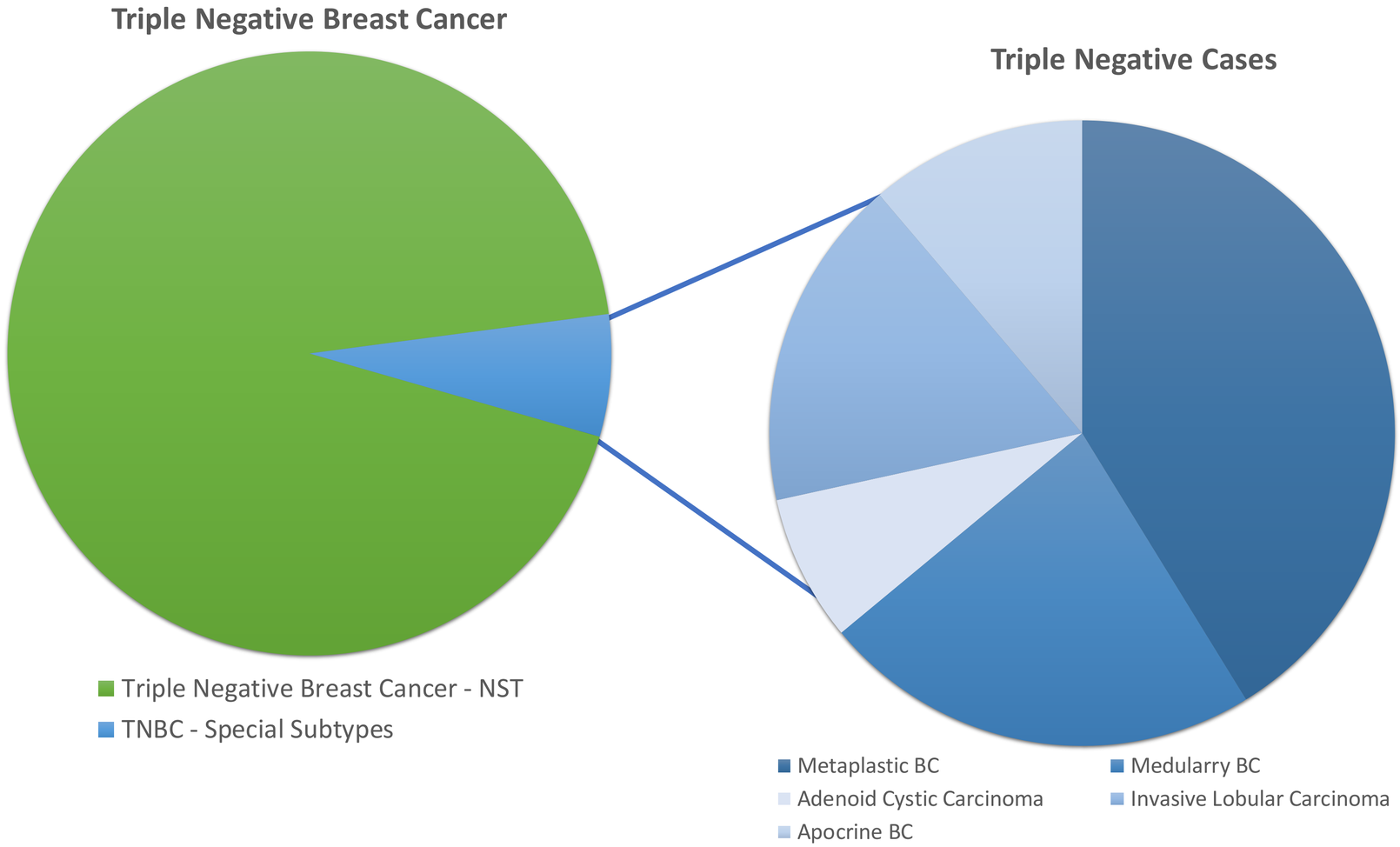


Incidence of rare subtypes likely underestimated, as they are more difficult to diagnose and register

DeSantis, C. *C Cancer J Clin* 2017; Reddy et al, *Breast Cancer Research*, 2020; Saridakis A, *Ann Surg Oncol,* 2021; Pezzi CM, *Ann Surg Oncol,* 2007; Zhao S, et al, Eur J Surg Oncol, 2018; seer.cancer.gov/statfacts/ accessed October 11, 2021

What portion of TNBC are Special Subtypes?

Special Subtypes make up 7% of TNBC in this series based on the NCDB from 2004-2012



Mills MN, et al *Eur J Cancer* 2018

Management of Special Subtypes of Triple Negative Breast Cancer: The Path Ahead

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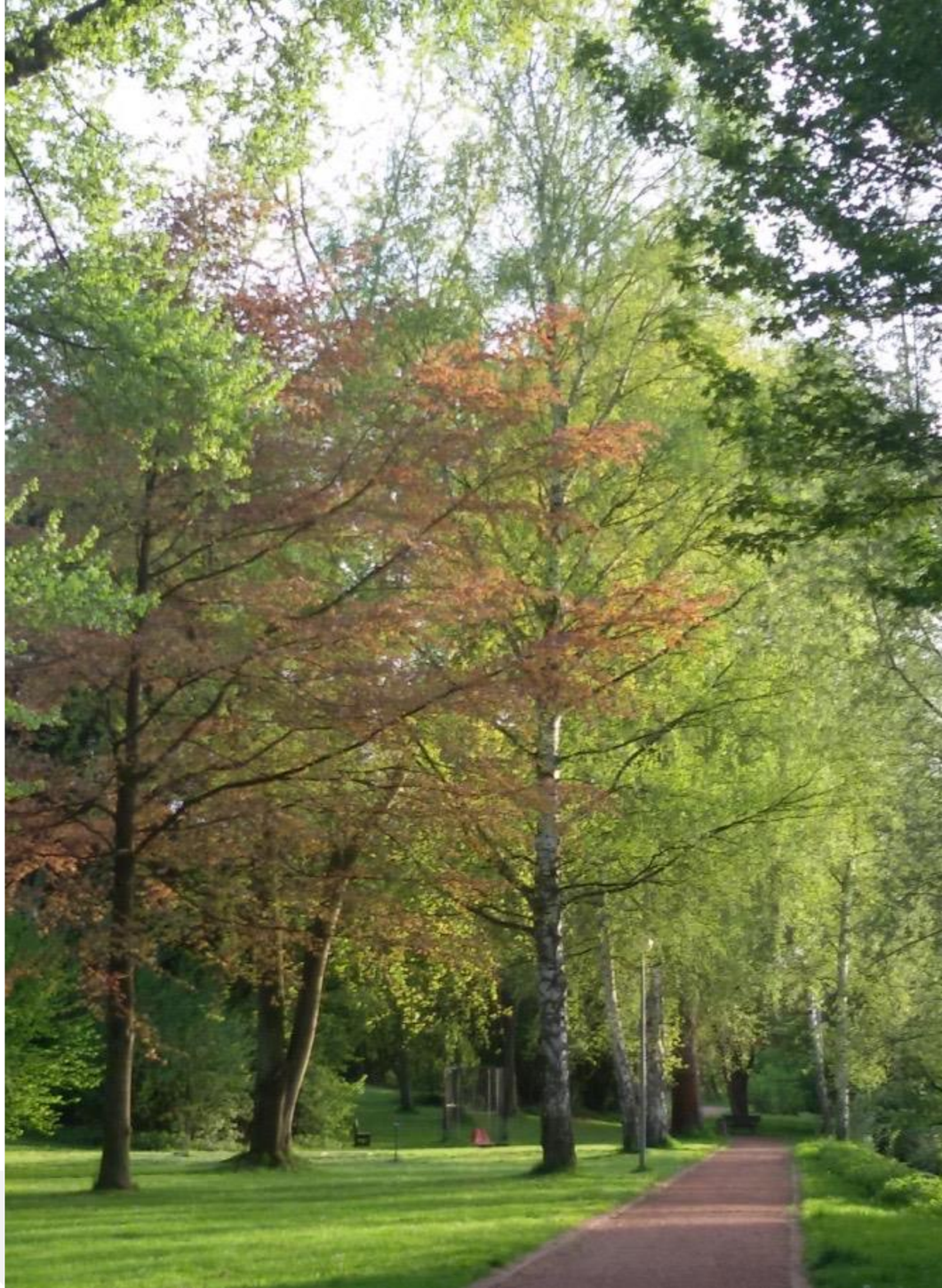


IDC NST – Medullary pattern

(NOT A DISTINCT SUBTYPE as of WHO Classification of Tumors 5th Edition (2019))

Histology

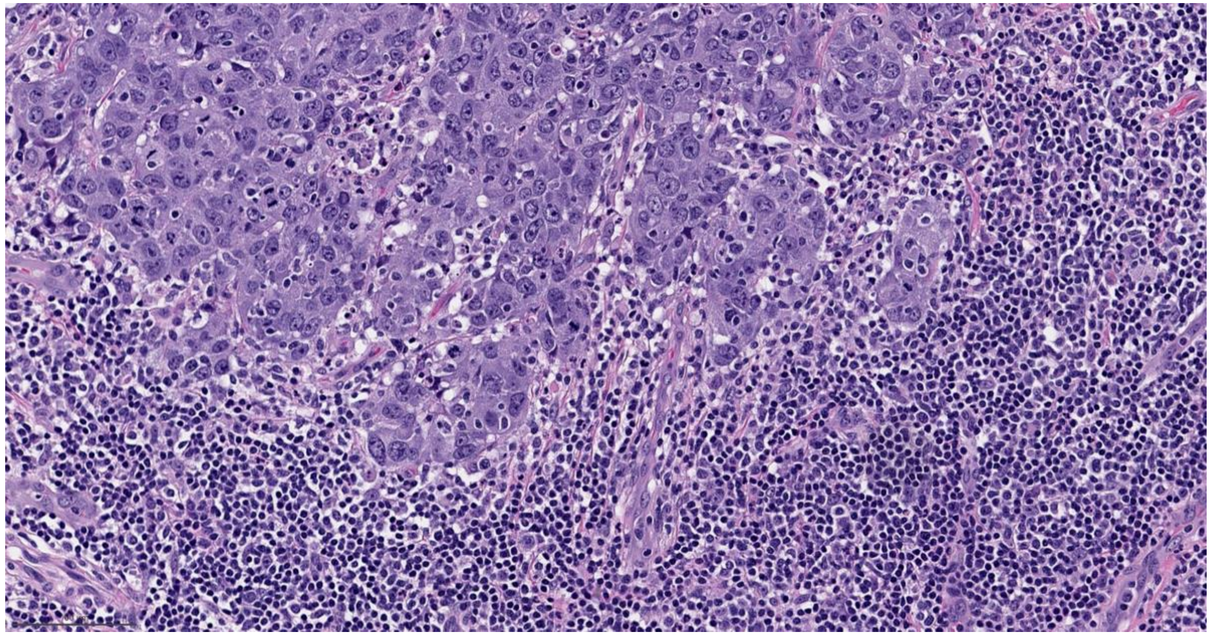


Image courtesy of Hannah Yong Wen, MD, PhD

Molecular Features

- **No longer a separate subtype due to interobserver variability**
- Cytokeratin 5/6 positive
- High rate of TP53 mutations
- Overrepresented in immunomodulatory subtype of TNBC

Purrington KS, *Breast Cancer Res Treat* 2016; Vincent-Salomon A, *Breast Cancer Res*, 2007

IDC NST – Medullary pattern
(NOT A DISTINCT SUBTYPE as of WHO Classification of Tumors 5th Edition (2019))

- Body of literature based on prior classification:
  - Aggressive histopathologic features but good prognosis
  - Over-represented in patients with BRCA1 germline mutations
  - Several studies suggest benefit to chemotherapy may be more limited
  - *Subset of IDC NST eligible for de-escalation studies given good prognosis and TIL-rich tumors?*

Huober J, An*nals of Oncology* 2012; Breast Cancer Linkage Consortium, *Lancet* 1997; Trapani D, *Bre Cancer Res and Treat,* 2021; Mateo, A, An*n Surg Oncol* 2017

Triple Negative Invasive Lobular Carcinoma

Histology

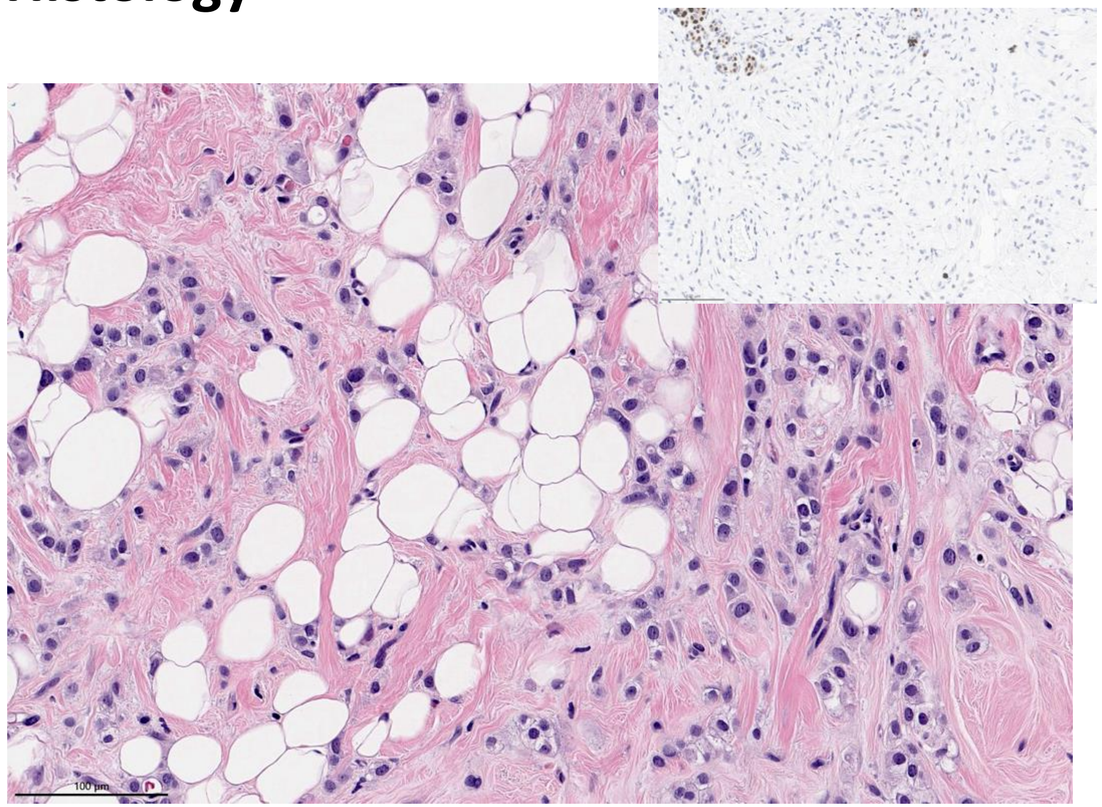


Image courtesy of Hannah Yong Wen, MD, PhD

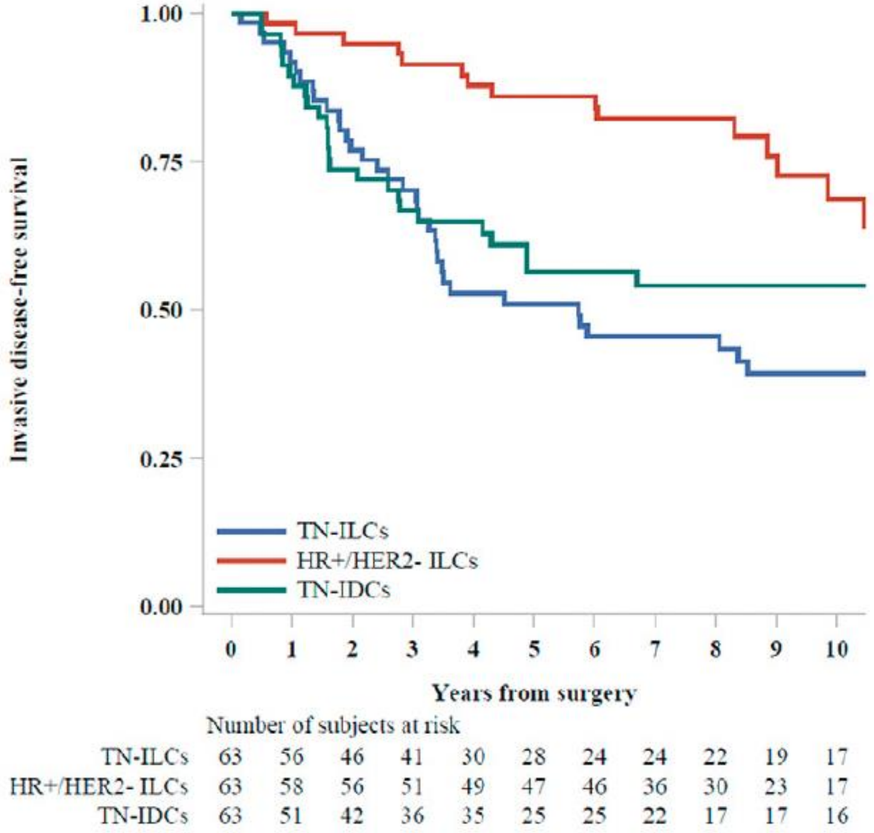
Molecular Features

- Frequent apocrine features
- Frequently express androgen receptor; 74% in recent series
- Approximately 20% with ERBB2 mutations
- Generally, CK5/6 negative

Conforti F et al, *The Breast* 2021

Triple Negative Invasive Lobular Carcinoma – Clinical Features

- Triple Negative ILC represents 1.0 - 2.5 % of ILC cases
- While numbers are small (N=38 -74), triple negative ILC, relative to both triple negative IDC and HR+ ILC:
  - Inferior prognosis
  - Older patient age



Conforti, F. et al, *The Breast*, 2021

Mills MN, et al *Eur J Cancer* 2018; Conforti F et al, *The Breast* 2021 ; Montagna E, et al. *Clin Breast Cancer*, 2013; Flores-Diaz, D, *Breast Cancer Res and Treat*, 2019; Bergeron A, *Modern Pathology*, 2021

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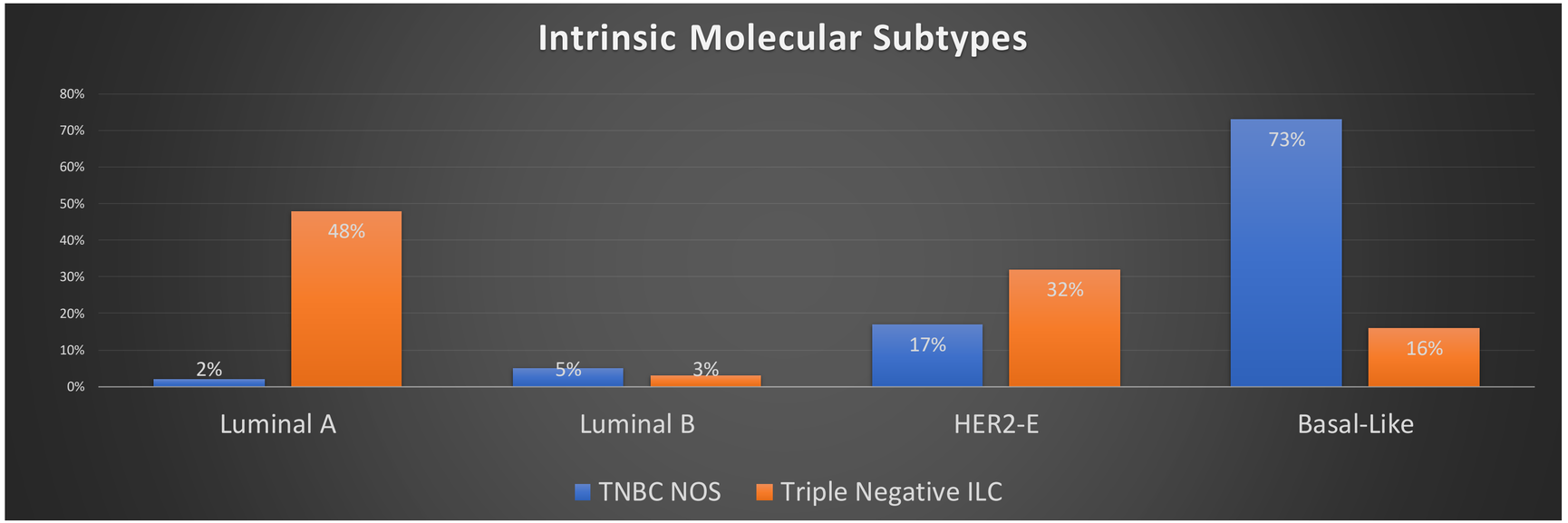
Triple Negative Invasive Lobular Carcinoma



For TN ILC:	**Luminal Type**	**HER2-E/Basal-Like**
Prognosis:	Good	Poor
Express AR:	+++	+
ERBB2 mutated:		+++ (HER2-E)

Other targetable features: PIK3CA, DNA repair pathway derangements, high mutational burden

Cheang M, et. Al, *The Oncologist*, 2015; Conforti F, *The Breast* 2021

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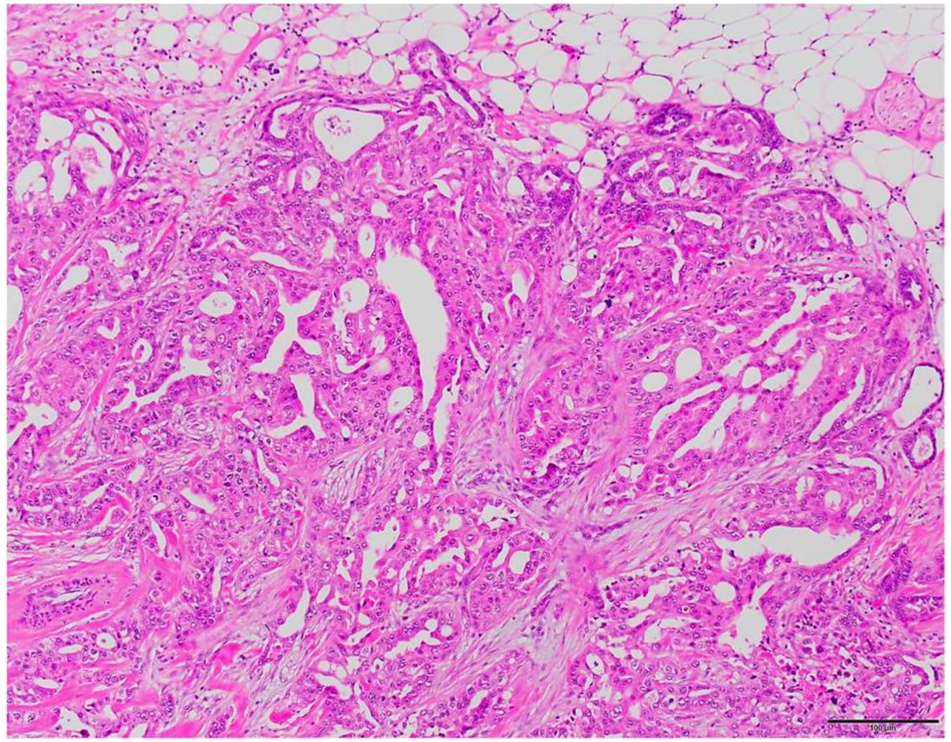
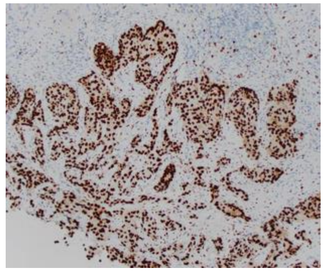
Carcinoma with Apocrine Differentiation

Histology



Images courtesy of Daniel L. Coldren, MD

Molecular Features



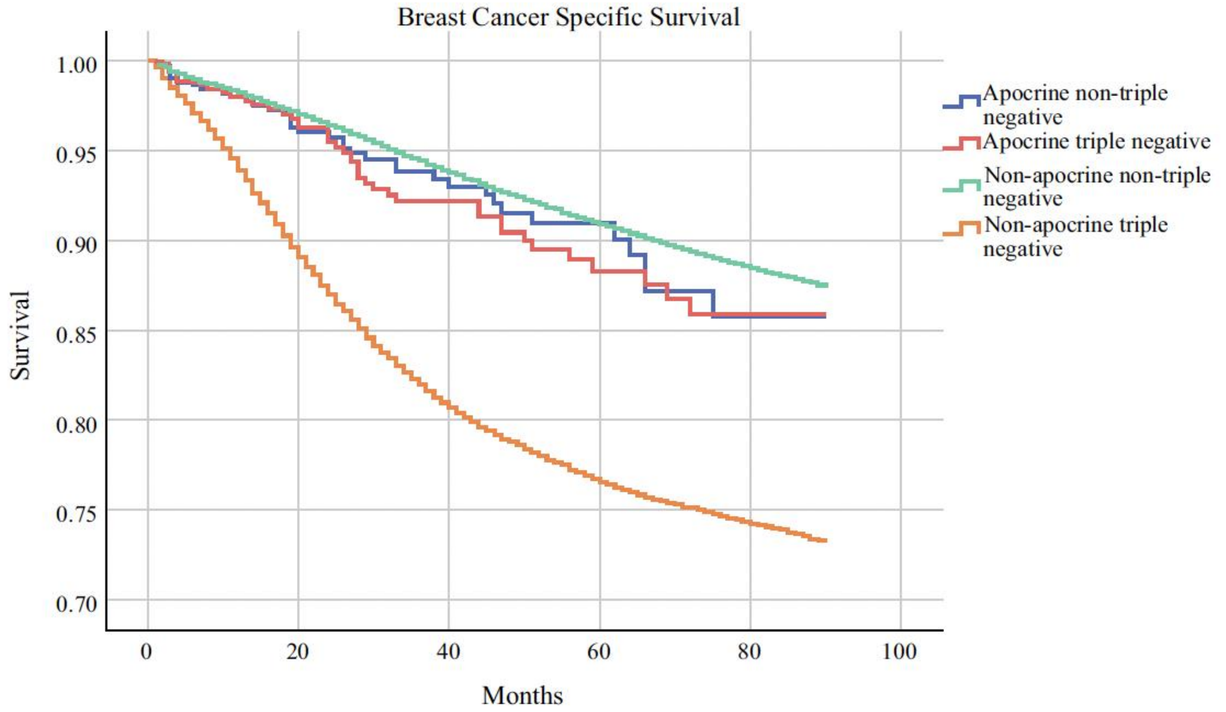
- **AR-positive**

- Express GCPFP-15 an antigen seen in apocrine metaplasia
- Can have HER2 amplification
- Overrepresented in LAR and IM molecular subtypes
- Most are sporadic, but can be see in patients with germline PTEN mutations (Cowden syndrome)

Banneau G,et al, *Breast Canc Research* 2010; Purrington KS et al, *Breast Cancer Res Treat* 2016

Carcinoma with Apocrine Differentiation– Clinical Features

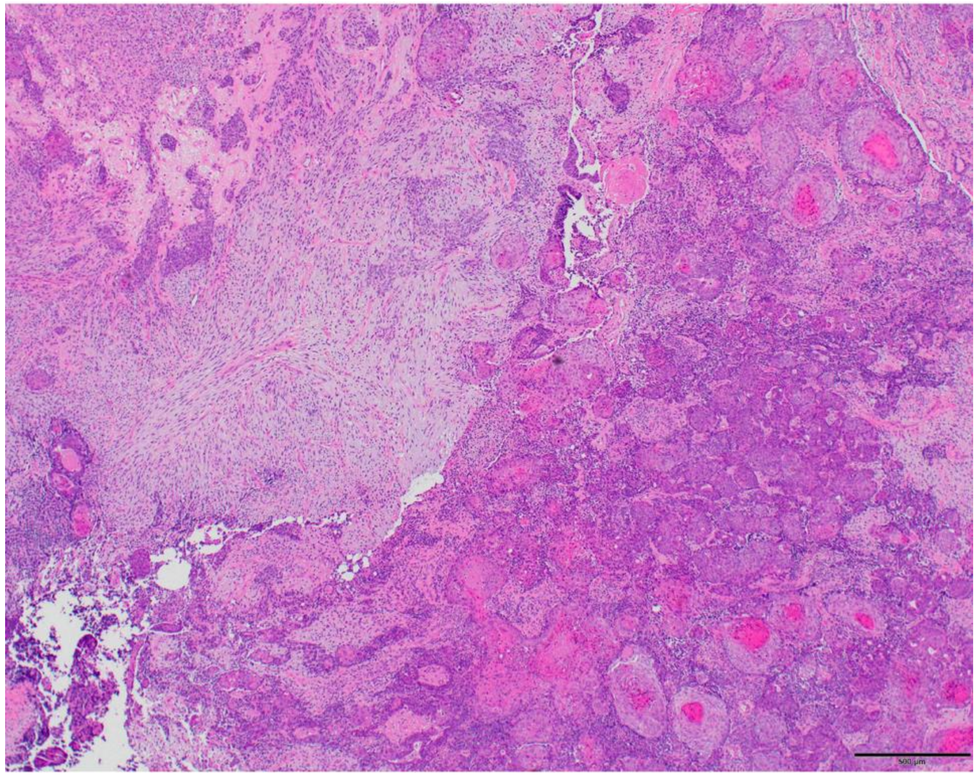
- Relative to non-apocrine TNBC, apocrine triple-negative carcinoma:
  - Occur more commonly in older patients and white patients
  - Characterized by smaller, lower grade tumors
- Comparisons triple negative subtypes support a favorable outcome for patients with apocrine carcinoma
- Retrospective registry analyses support benefit from chemotherapy

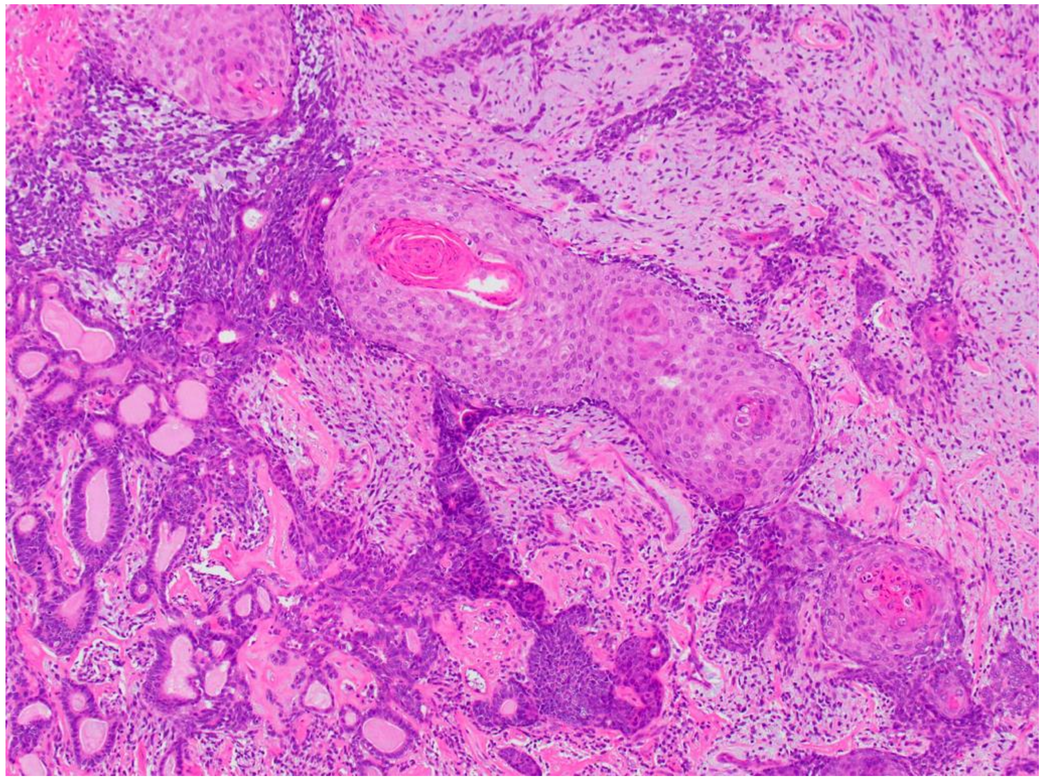


Saridakas A, et al, *Ann Surg Oncol,* 2021

Saridakas A, et al, *Ann Surg Oncol* 2021 ; Arciero CA, *J Surg Oncol,* 2021; Mills MN, et al *Eur J Cancer* 2018 ; Montagna E, et al. *Clin Breast Cancer*, 2013

Metaplastic Carcinoma

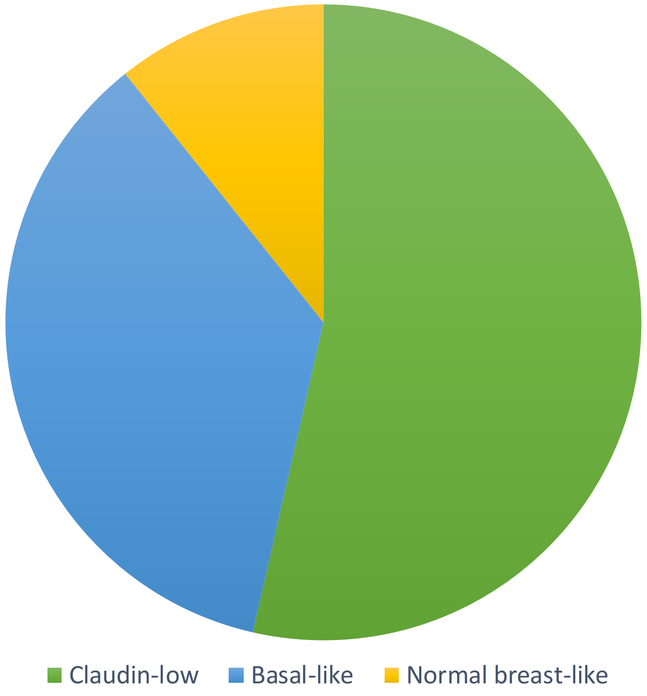




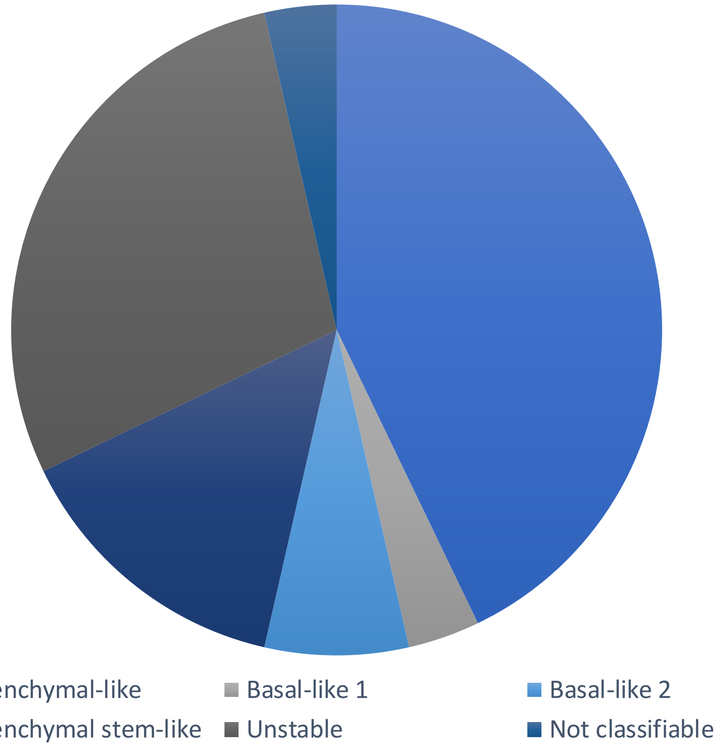
Images courtesy of Daniel L. Coldren, MD

Metaplastic Carcinoma – Molecular Features

Intrinsic Subtype



Triple Negative Subtype



N=28

- Most metaplastic carcinomas are claudin-low or basal-like intrinsic subtypes
- TNBC subtypes most commonly seen in metaplastic carcinoma are mesenchymal and basal-like
- Histologic component impacts molecular subtype

Weigelt et al. *Mod Pathol,* 2014

Metaplastic Carcinoma – Molecular Features

	Chondroid	Spindle	Squamous	TNBC NST
TNBC subtype	Mesenchymal	Predominately mesenchymal stem-like and unstable	Basal-like, claudin-low and normal breast-like	All
BRCAness	Preferentially non-BRCAness	Preferentially non-BRCAness	Preferentially-BRCAness	
TP53 mutation	75%	50%	78%	81%
Mutation in PIK3CA pathway	44%	70%	67%	22%
Mutations in Wnt pathway	56%	50%	44%	28%

Piscuoglio S, et al. *NPJ Breast Cancer* 2017

Metaplastic Carcinoma – Clinical Features

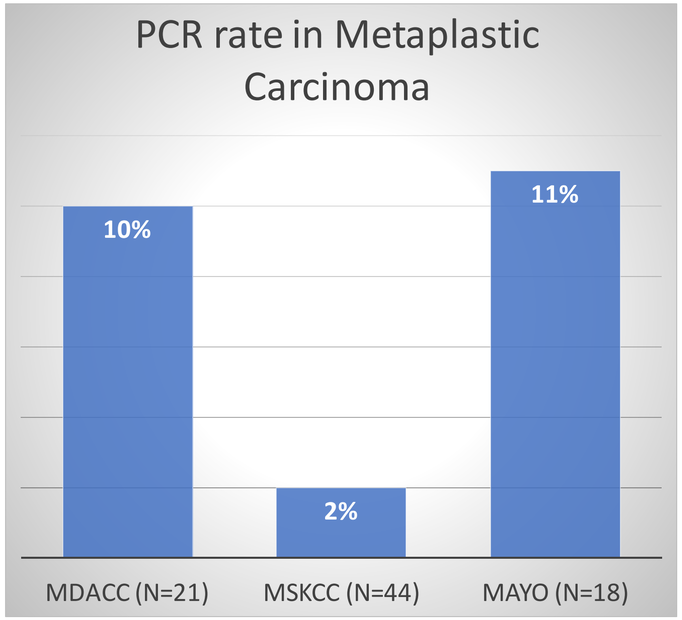
3-year observed survival for MPC diagnosed 2010-2013 as first cancer

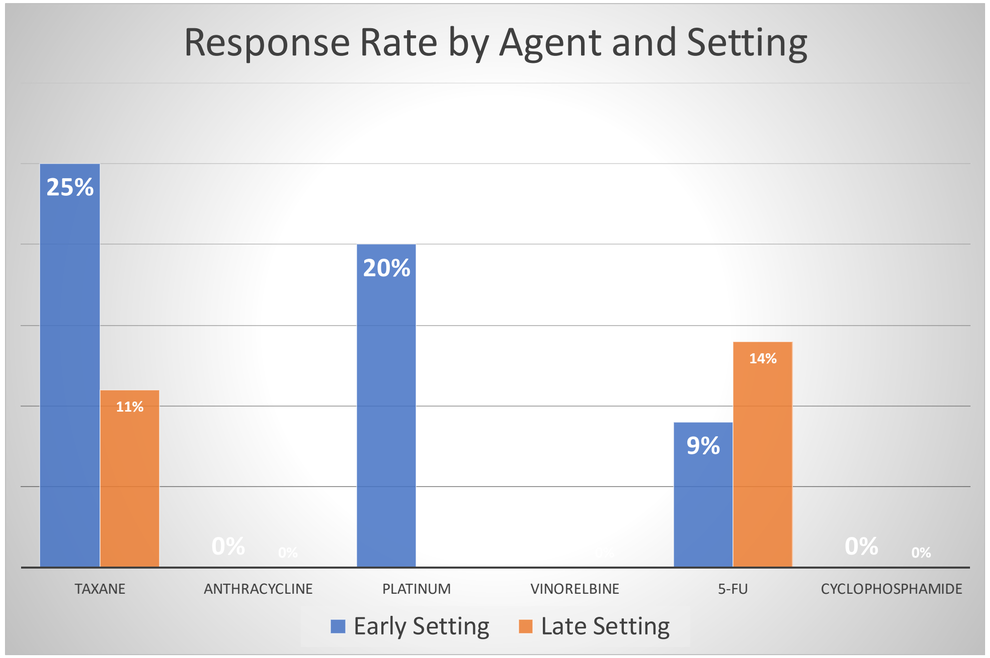
Type	Full Sample, N (OS)	HER2+, N (OS)	TN, N (OS)	HER2-/HR+, N (OS)
MBC				
Stage I-III	872 (76.7%)	47 (91.8%)	601 (75.4%)	224 (77.1%)
Stage I		10 (100%)	136 (91.4%)	59 (92.8%)
Stage II		23 (88.6%)	374 (76.4%)	121 (83.4%)
Stage III		14 (92.2%)	91 (47.1%)	44 (42.2%)
IDC				
Stage I-III	133,612 (92.4%)	22,056 (92.5%)	17,344 (83.8%)	94,212 (94.0%)
Stage I		8,950 (96.3%)	6,540 (93.6%)	55,325 (96.6%)
Stage II		9061 (92.9%)	7,989 (85.0%)	29,937 (92.4%)
Stage III		4,045 (83.6%)	2,815 (58.4%)	8,950 (83.7%)

Schroeder MC, et al, *The Oncologist*, 2018

Metaplastic Carcinoma: Response to Therapy

Low response rates to chemotherapy:





Large registry series still show improved outcomes with chemotherapy and radiation therapy

Hennessy BT, et al , *Ann Oncol* 2006; Wong W, et al, *NPJ Breast* 2021; Al-Hilli Z, et al, *Breast Cancer Res and Treat* 2019; Chen IC et al, *Breast Cancer Res and Treat* 2011; Elimimian EB, et al *JAMA Network Open*, 2021

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Metaplastic Carcinoma
Reports of Exceptional Responses to Novel Therapies

Neoadjuvant:
PARP Inhibition

Patient with T2N0 metaplastic chondrosarcomatous tumor and deleterious BRCA germline mutations had pCR with neoadjuvant talazoparib

Neoadjuvant: IO as per KEYNOTE-522

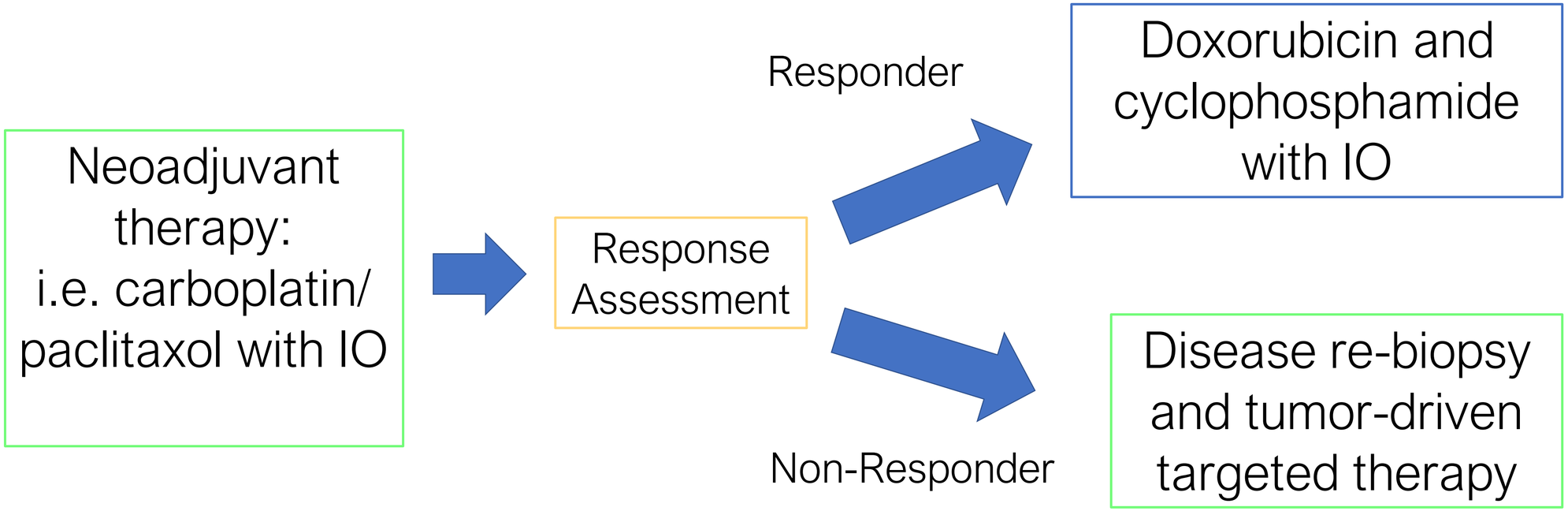
Late Stage: Pathway inhibitors

Case reports of response in the late line setting with:

- Buparlisib
- Dabrafenib and trametinib
- Apatinib

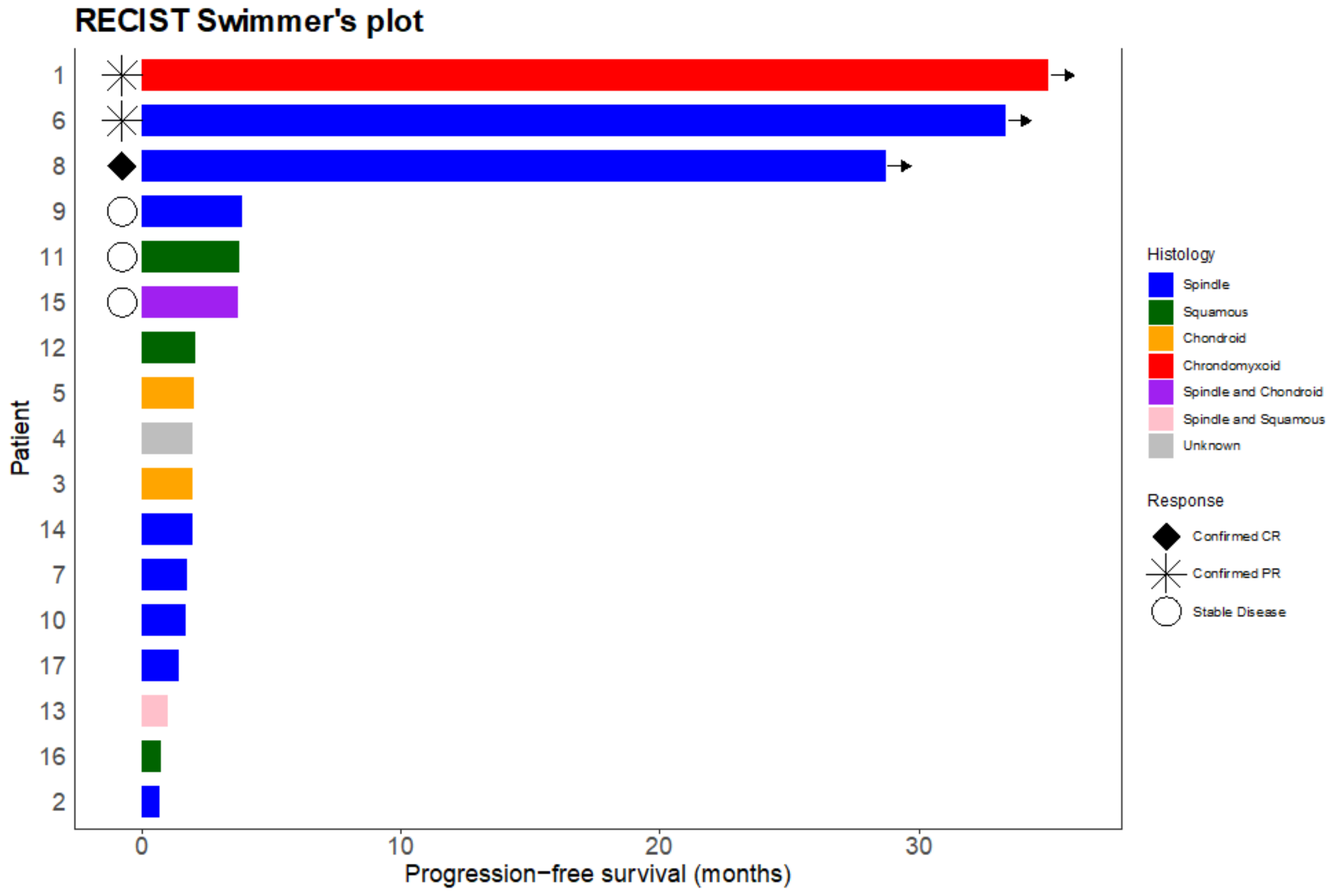
Litton, J et al *JCO*, 2020; Yang MH et al. *J Formos Med Assoc*. 2019; Seo T et al. *Case Rep Oncol* Med. 2020; Zhou Net al, *Oncotarget*, 2016

How might a metaplastic carcinoma trial target these diverse disease vulnerabilities?



Adapted from BIG-NCTN 2021 Annual Retreat

Cohort 36 of the DART Trial (SWOG S1609)
Anti-CTLA-4 and PD-1 Blockade in Advanced Metaplastic BC



- Basket embedded in a larger trial of rare tumors
- Responses ongoing at 28+, 33+ and 34+ months
- All 3 responders developed adrenal insufficiency
- Reponses seen in tumors with low tumor mutational burden, low PD-L1 and absent TILs

Adams S et al, *Clinical Cancer Research,* 2021

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WHO Classification of Tumors, Breast Tumors, 5th Edition; Jenkins S, et al, *Current Oncology Reports* 2021; Mills MN, et al *Eur J Cancer* 2018

Adenoid Cystic Carcinoma

Histology

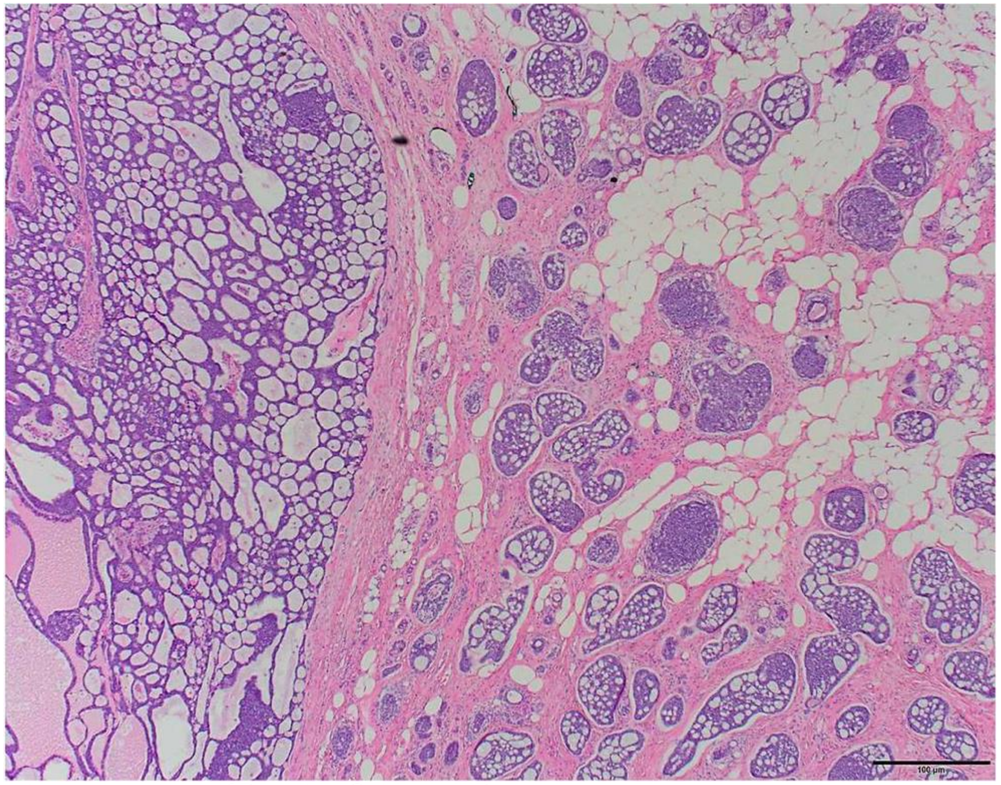


Image courtesy of Daniel L. Coldren, MD

Molecular Features

- Two cell populations, myoepithelial and epithelial
- Frequent *MYB-NFIB* fusion
- *MYBL1 rearrangements or MYB amplification can occur*
- Three subtypes described, classic and the more aggressive, less common, solid-basaloid and high-grade transformational subtypes.

Adenoid Cystic Carcinoma: Clinical Features

- Commonly present as a palpable mass in an older patient
- Despite TNBC phenotype, prognosis for classic subtype is excellent and surgery is generally curative
- Tumors of similar histology/molecular signature arising in the salivary gland have different clinical behavior
- Retrospective data suggest no/marginal benefit to chemotherapy
- Reports on solid-basaloid subtype and high-grade transformational subtype suggest more aggressive clinical course

Foshini PM, et al, *Int Jour Surg Path,* 2016; Schwartz CJ, et al, Mo*dern Pathology*, 2021; Cima L, *Vichows Archiv*, et al 2021; Pareja F, *Modern Pathology*, et al, 2021; Elimimian E, et al *JAMA Network Open*, 2021; Trapani D, et al, *Breast Cancer Research and Treatment,* 2021

Secretory Carcinoma

Histology

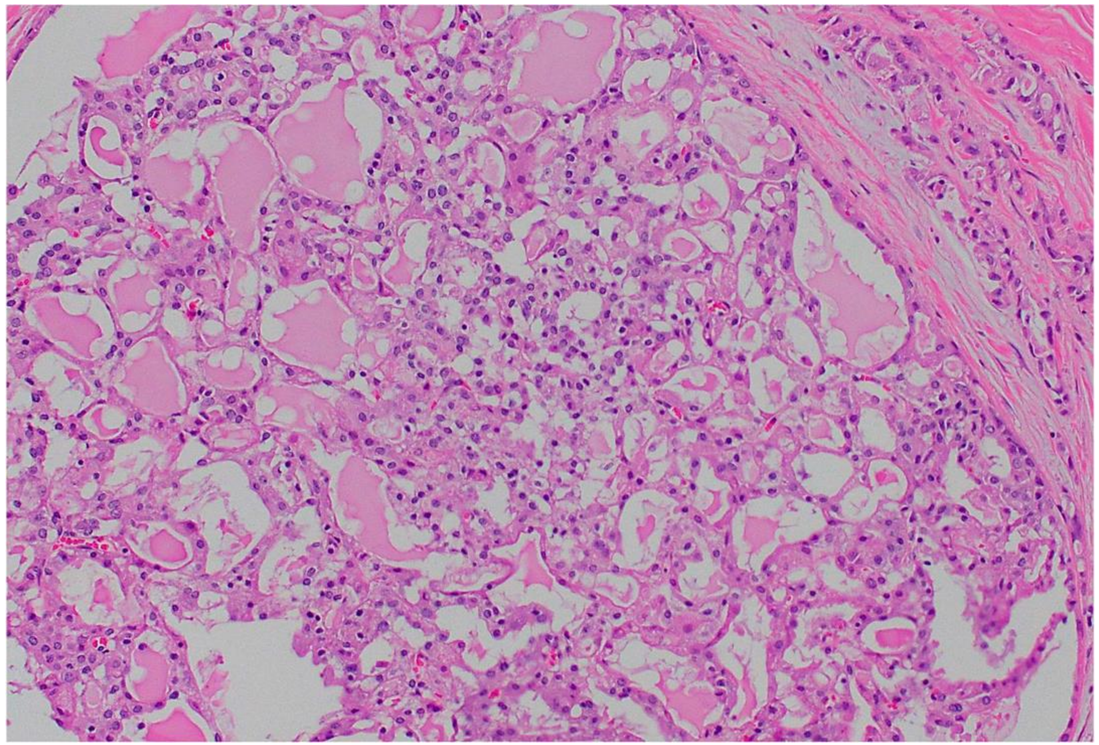


Image courtesy of Daniel L. Coldren, MD

Molecular Features

- Characteristic t(12;15)(p13;q25) translocation
- Resulting in pathognomonic *ETV6-NTRK3* fusion gene

Secretory Carcinoma: Clinical Features

- Present with a slow-growing, often painless mobile mass
- Can be associated with nipple discharge
- Can occur in children, though mean age is 30-50's
- Prognosis is usually excellent, and disease managed with local therapies
- Distant metastases, while rare, can occur.
- Case report of successful treatment with TRK inhibitor used to treat breast tumor with *NTRK* fusions (larotrectinib)

Li D, et al, *Modern Pathology* 2012; Gong P, et al, *Scientific Reports* 2021; Tavassoli FA, et al, *Cancer,* 1980; Shukla N et al, *JCO Precision Oncology*, 2017

Neuroendocrine Carcinoma

Histology

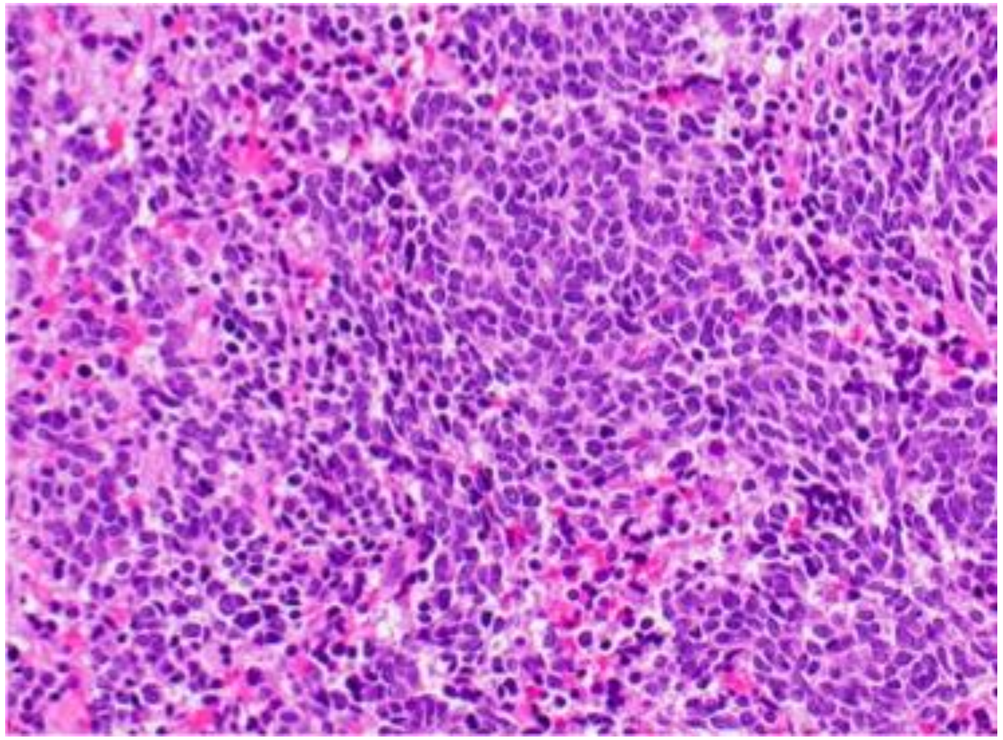


Image courtesy of Daniel L. Coldren, MD

Molecular Features

- To be identified as a pure neuroendocrine carcinoma greater than 90% neuroendocrine neoplasm is required
- NEC, in contrast to NET, tends to be hormone receptor negative
- Series of 58 tumors found 33% had PIK3CA mutations

Shin SJ , et al, *Am J Surg Path*, 2000; McCullar B, et al, *Breast Cancer Res Treat*., 2016

Neuroendocrine Carcinoma – Clinical Features

- Account for 3-10% of extrapulmonary small cell carcinomas
- Presence of DCIS or other mammary carcinoma supports breast origin
- Breast is an extrapulmonary small cell site more likely to present with limited disease
- Survival with local and regional disease is superior to stage matched patients with SCLC
- Can be eligible for small cell lung cancer trials

Hare F, et al *Springerplus*, 2015; Dores GM, et al, *BMC Cancer*, 2015; Wong YNS, et al, BMC Cancer 2009

Management of Special Subtypes of Triple Negative Breast Cancer: The Path Ahead

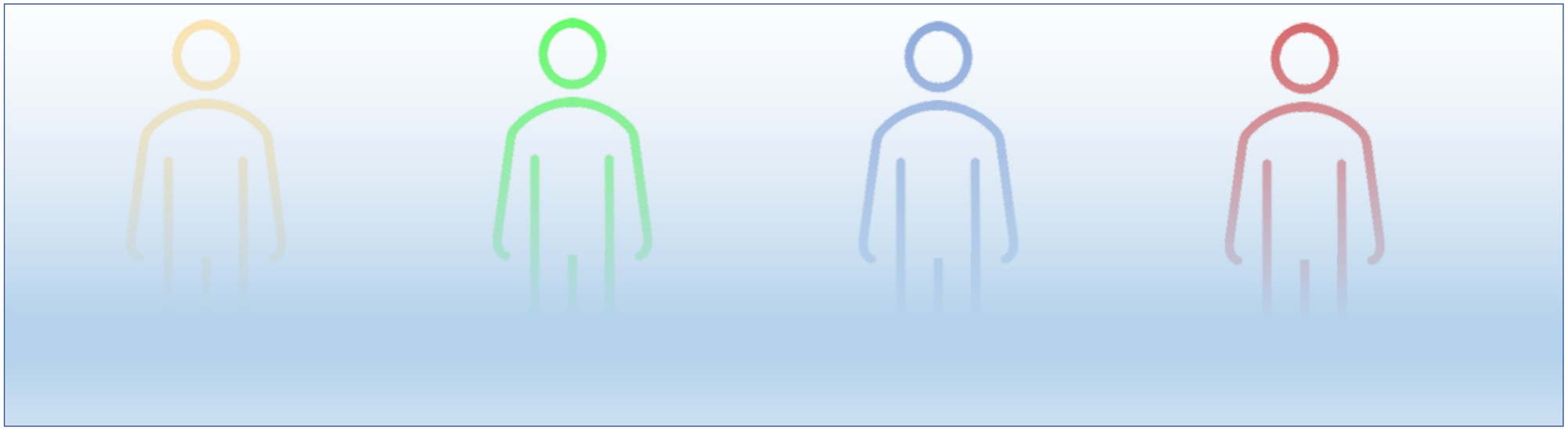
- Overview of less common subtypes of TNBC
- Molecular/clinical features and treatment of special subtypes
- **Newer tools for disease management**
  - **Possible Molecular Approaches**
  - **pCR**
  - **ctDNA**
- Harnessing contemporary research tools to further disease-specific understanding

Developing Precision Therapy for Breast Cancer

Therapy De-escalation

Therapy Escalation

Special Subtypes of TNBC



Local therapy Only

Target therapy only

Cytotoxic therapy +/- targeted therapy

Resistant disease

Possible Molecular Approaches

	Higher Risk (Escalation)	Lower Risk (De-escalation)	Possible Molecular Targets/Options	Possible Subtype-Agnostic Targets
Invasive carcinomas of the breast				 • High Tumor Mutational Burden • Deleterious BRCA mutation 
TN Invasive Lobular Carcinoma	✓		AR, HER2	
Carcinoma with apocrine differentiation	?	?	AR	
Metaplastic carcinoma	✓		IO, DNA Repair, PIK3, MEK, wNT, other..	
Salivary gland-type breast tumors				
Adenoid cystic carcinoma		✓		
Secretory carcinoma		✓	NTRK	
Neuroendocrine breast neoplasms				
Neuroendocrine carcinoma	✓		IO, small cell trials	

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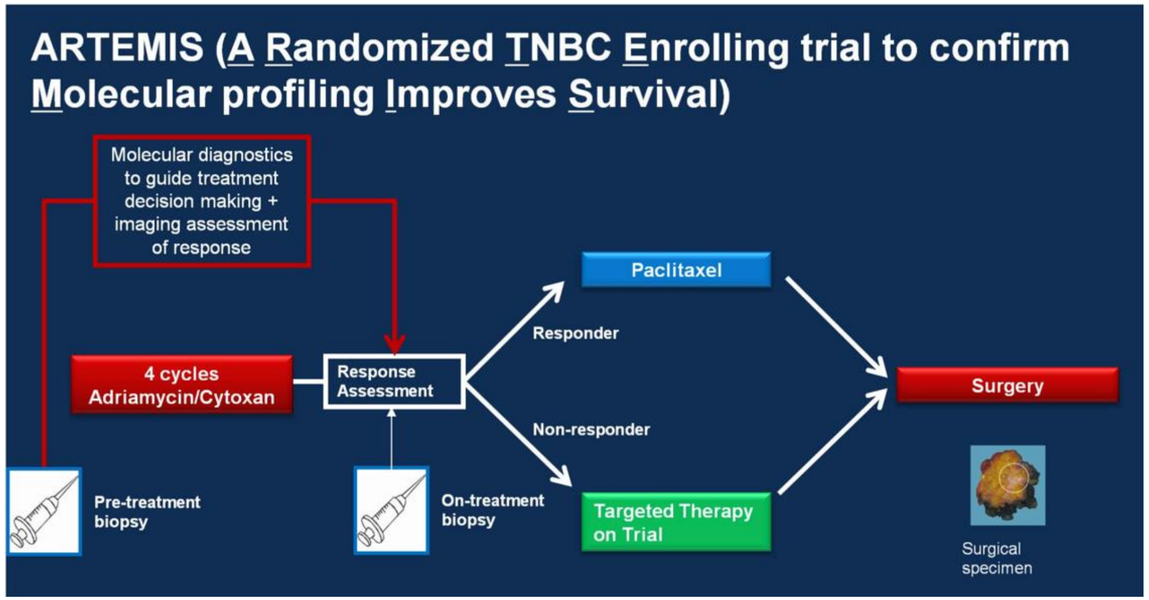
Neoadjuvant Space for Biomarker-guided therapy: The ARTEMIS Trial

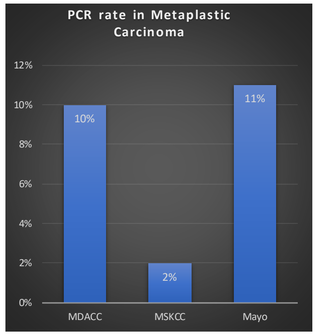


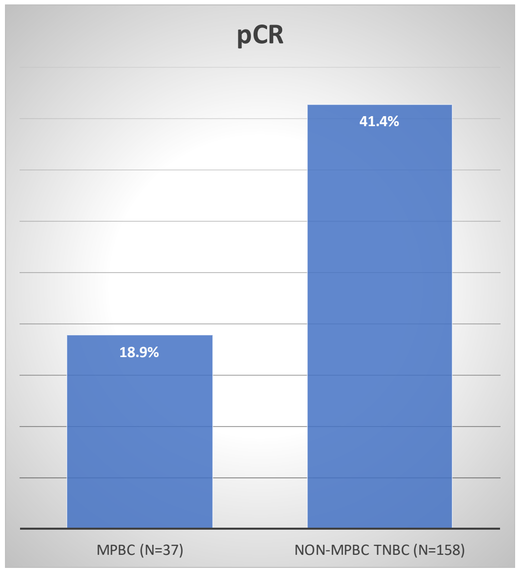
	MPBC	Non-MPBC	p
Targeted therapy			
No – N (%)	13 (62)	115 (77)	0.17
Yes – N (%)	8 (38)	34 (23)	
Progression on AC			
No – N (%)	16 (76)	137 (92)	**0.04**
Yes – N (%)	5 (24)	12 (8)	
RCB Index			
pCR-RCB1 – N(%)	7 (33)	87 (58)	**0.04**
RCB II/III – N(%)	14 (67)	62 (42)	

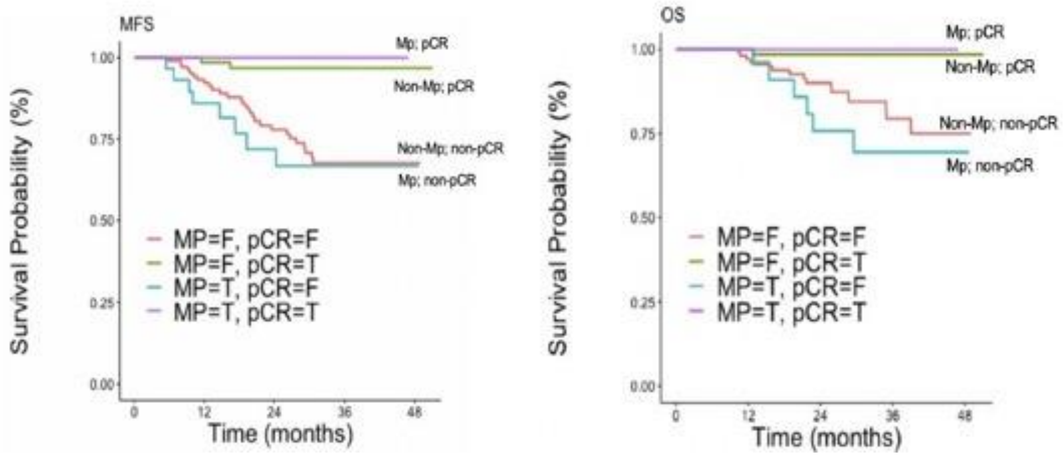
- Patients with MPBC have higher rates of disease progression on AC
- More likely to have residual disease after neoadjuvant therapy

Moulder S, et al. ASCO 2017; Yam C, et al, ASCO 2018

Neoadjuvant Space for Biomarker-guided therapy: Lessons from the ARTEMIS Trial





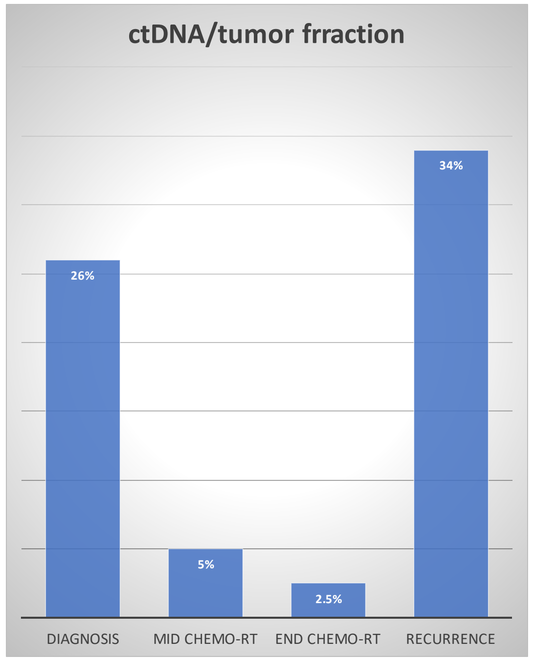


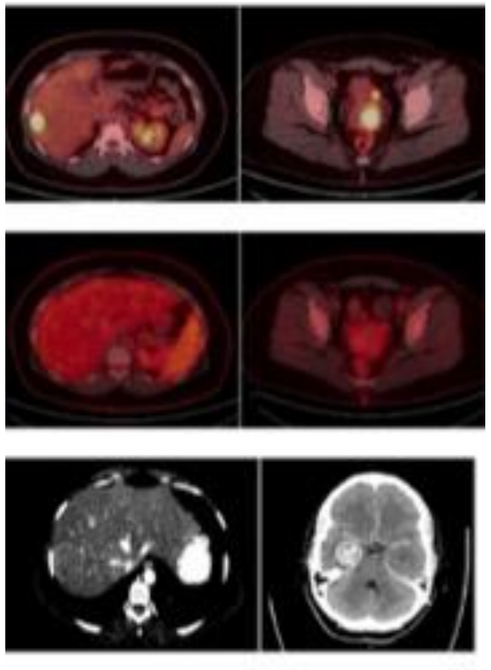
- pCR rates can be improved above historical levels, but remain below that of non-MPBC TNBC
- As in TNBC NST, pCR correlates with survival in MPBC
- An intermediate US can be a good surrogate marker for efficacy of neo-adjuvant therapy in MPBC

Abuhadra N et al, SABCS 2020; Wong W, et al, *NPJ Breast* 2021; Hennessy BT , et al, *Ann Oncol* 2006; ; Al-Hilli Z, et al, *Breast Cancer Res and Treat* 2019

Circulating Biomarkers

Small Cell Carcinoma of the Cervix



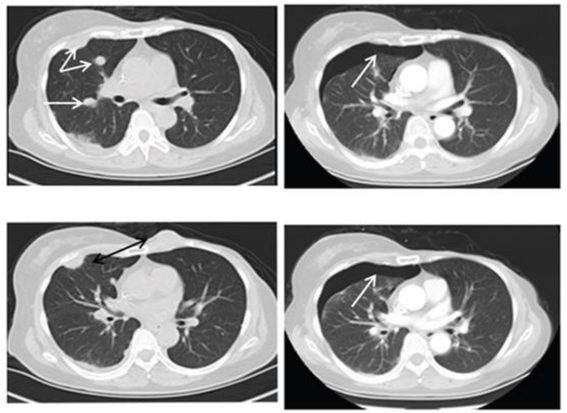


Abbas A, et al, *Frontiers in Oncology*, 2021

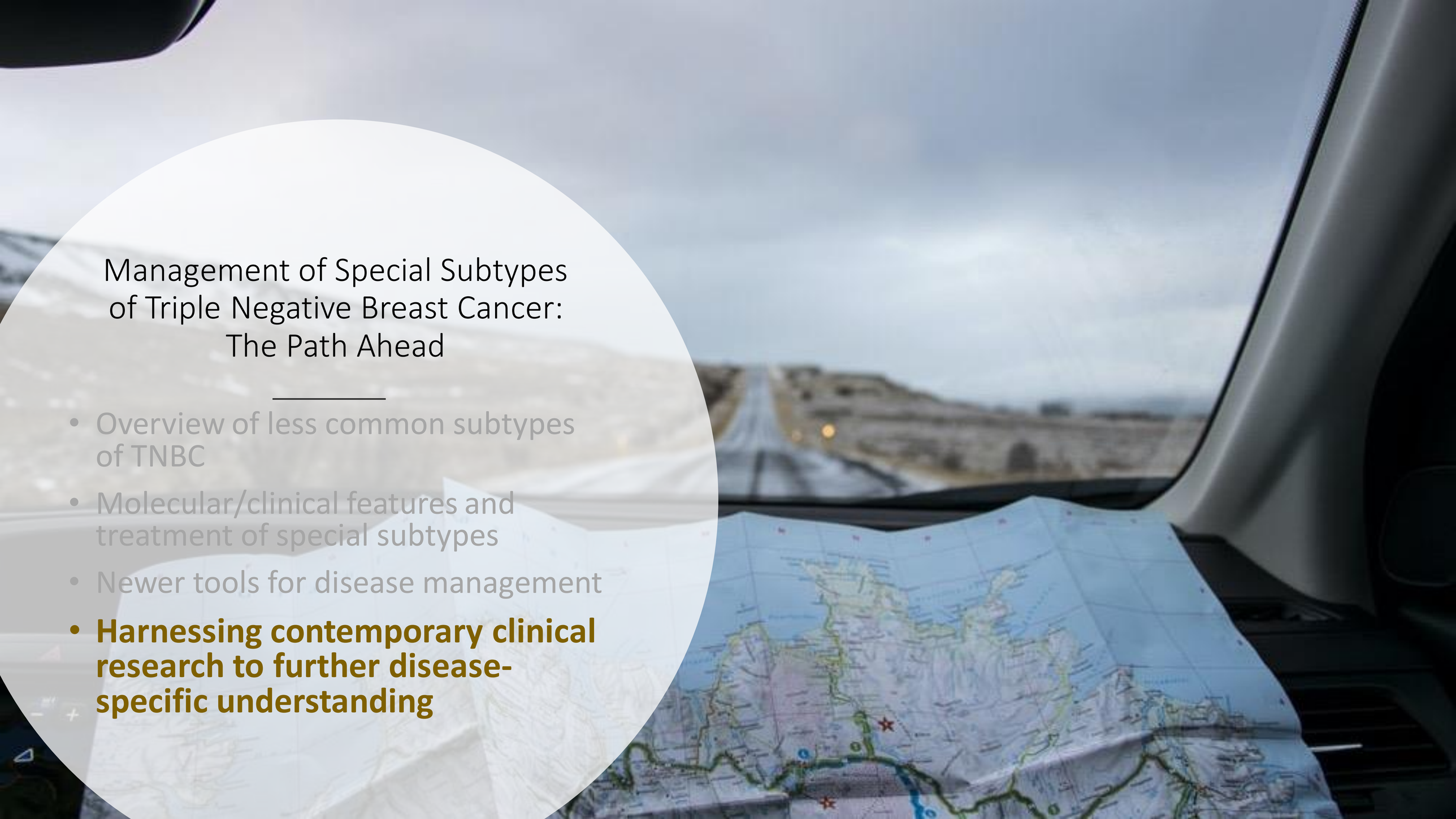
MPBC: Spindle Cell Breast Carcinoma

- Case report of 51 yo with MPBC spindle refractory to chemotherapy and bevacizumab
- Marked clinical and radiographic response to apatinib
- Tumor mutational profile at T0 and T2 months demonstrated marked decrease in the number of mutated genes

Pre-apatinib 2 MO apatinib



Zhou N, et al, *Oncotarget*, 2016



Management of Special Subtypes of Triple Negative Breast Cancer: The Path Ahead

- Overview of less common subtypes of TNBC
- Molecular/clinical features and treatment of special subtypes
- Newer tools for disease management
- **Harnessing contemporary clinical research to further disease-specific understanding**

Where are we getting our information from?

- Retrospective reviews
  - Large databases: US and other global registries
    - Definitions of rare cancers can vary by series
    - Highly variable pathology review
- Small case series
- Individual case reports

Can We Conduct Disease-specific Trials?

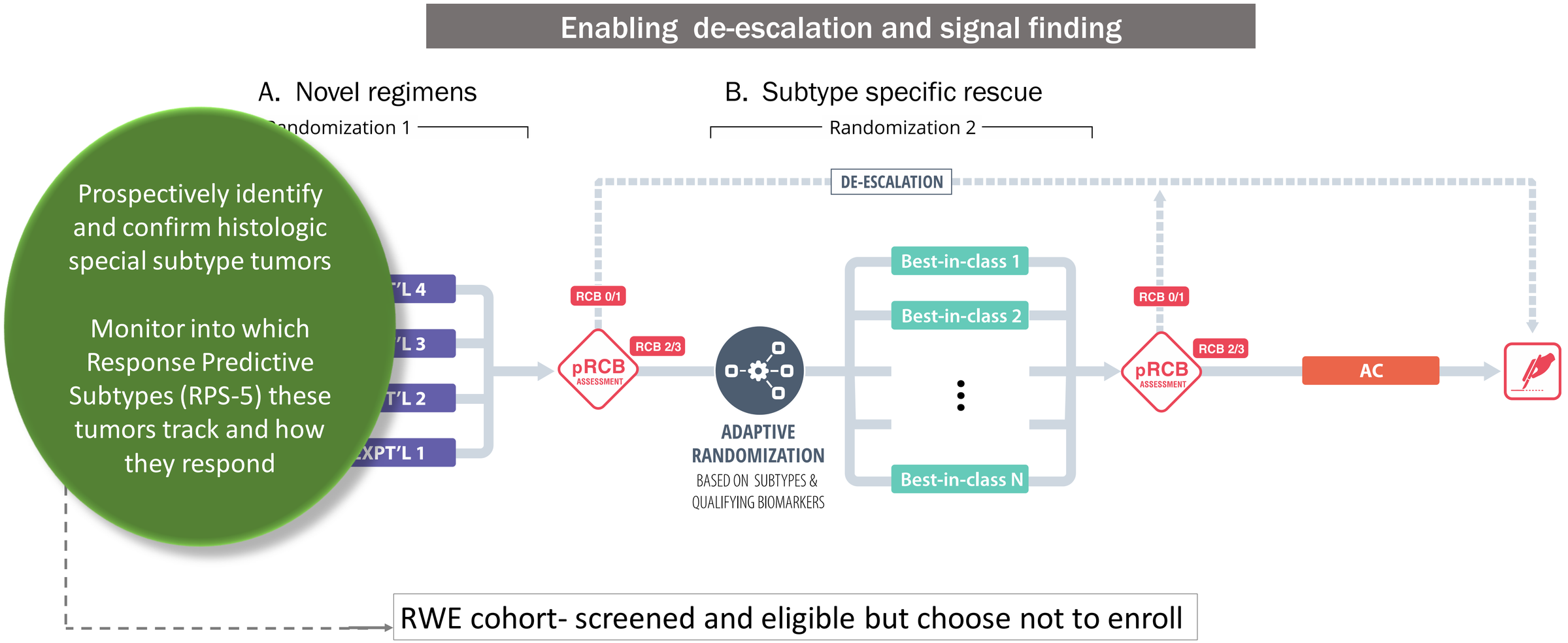
- Smaller N
  - Unlikely to be run by industry
  - Value of randomized result makes a large N ideal, but this may be impractical
  - Statistical design issues: need to accept larger α, β error
  - *Will centers open?*
- NRG (GOG legacy) has conducted NCTN trials in this space, most of which were single arm non-randomized
- *Are international efforts needed?*

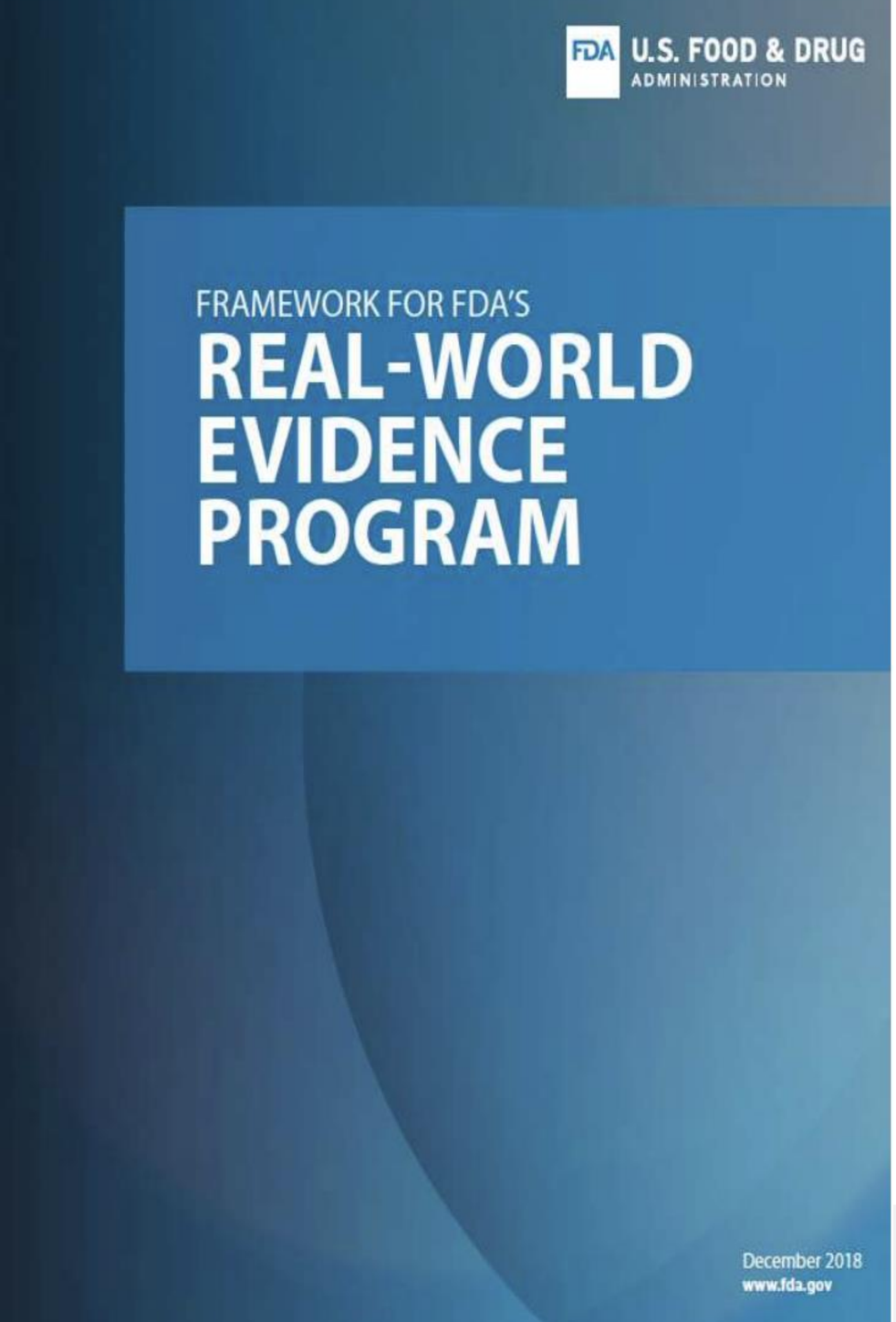
How else might we get disease specific answers?

- Embed in umbrella trials of rare tumors
  - DART
- Retrospective review of contemporary trials
  - I-SPY2
- Prospective identification of subjects with special subtype tumors
  - ARTEMIS
  - I-SPY2.2
- Big data

Can we further harness technology, virtual pathology, to facilitate identification and validity?

I-SPY 2.2





Real World Evidence in Rare Breast Cancers

- Real world data can have applications in rare diseases, when clinical trials are not feasible.
- FDA included this in RWE guidance (Available for download.)
- Flatiron data have helped address questions in less common breast cancer populations:
  - Post-authorization safety study for TDM-1 in patients with low ejection fraction
  - RWD to provide evidence to support a label expansion for palbociclib in men

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Take Home Messages

- We have some, albeit limited disease-specific information on how to treat special subtypes of triple negative breast cancer
- As biologic principals applied to breast cancer NST extend to less common subtypes we can improve our understanding of these tumors
- We may need to think beyond the randomized trial to further our knowledge in this space

Thank you!

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Back-Up Slides