Management of stage I TNBC

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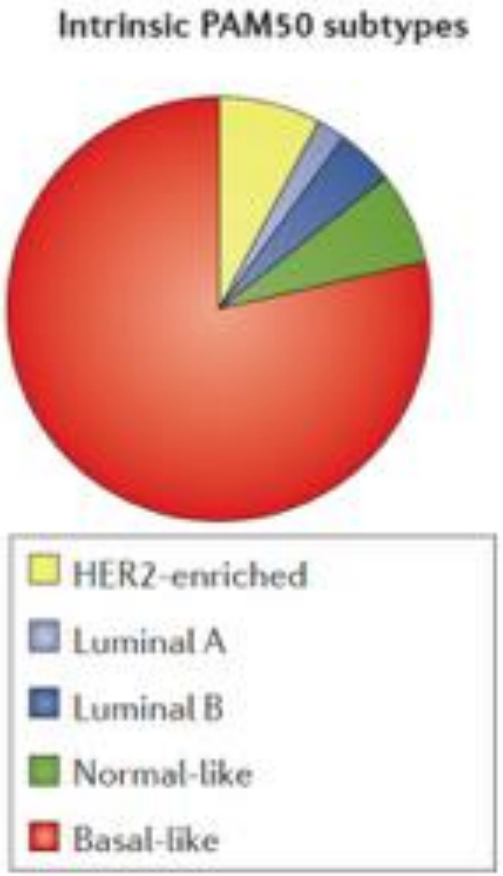
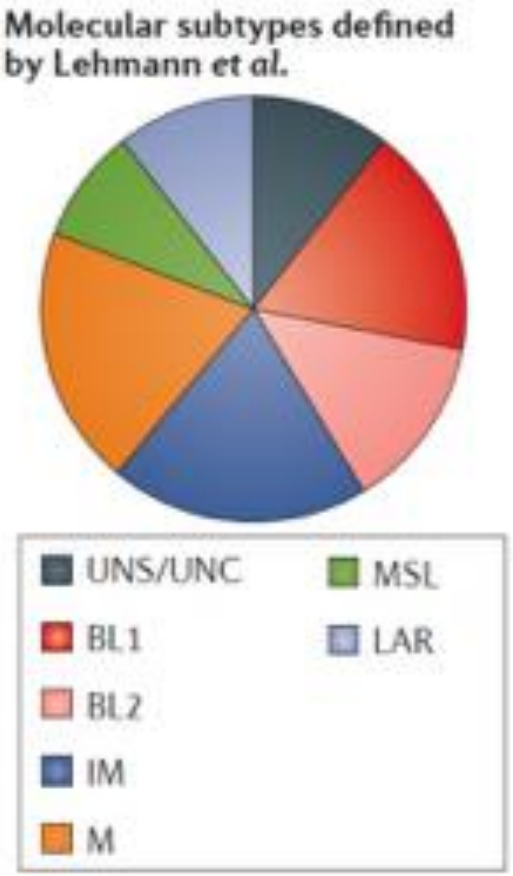
TNBC: definition

The term TNBC was first used in 2005 to refer to a subset of patients with breast cancer (10-15%) for whom **chemotherapy was the only treatment available**, given the **lack ER/PR expression and HER2 overexpression**.

It is a heterogenous biologic entity, generally associated with early relapse, visceral involvement and poor prognosis.

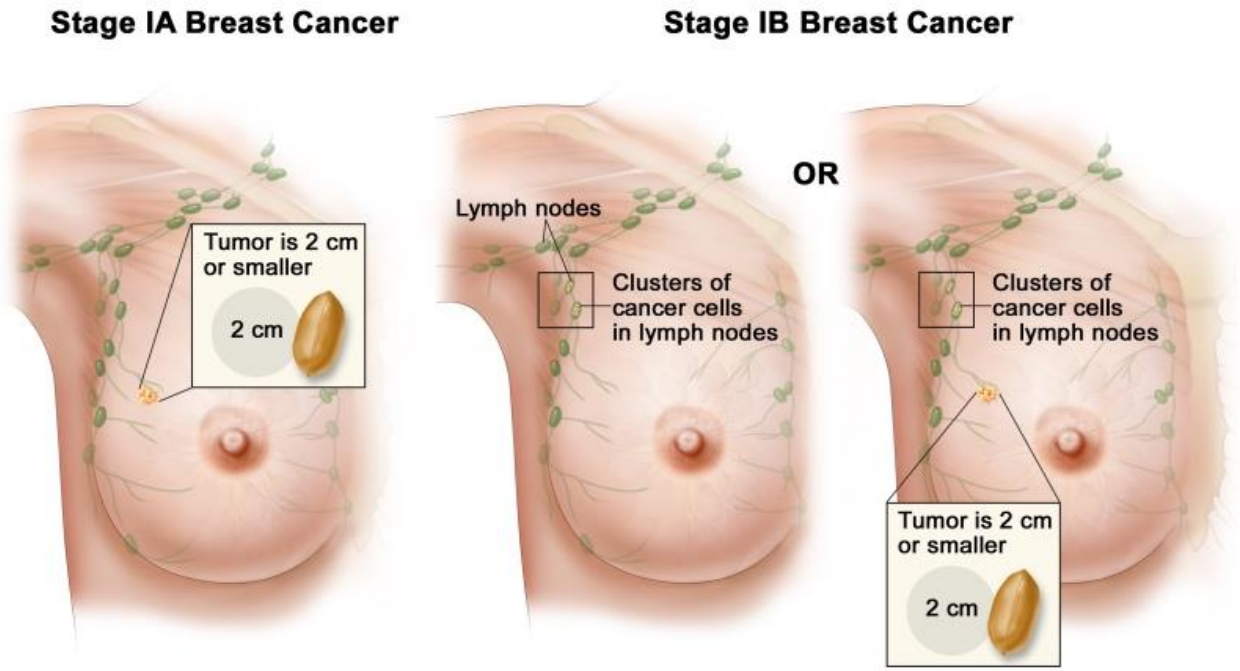


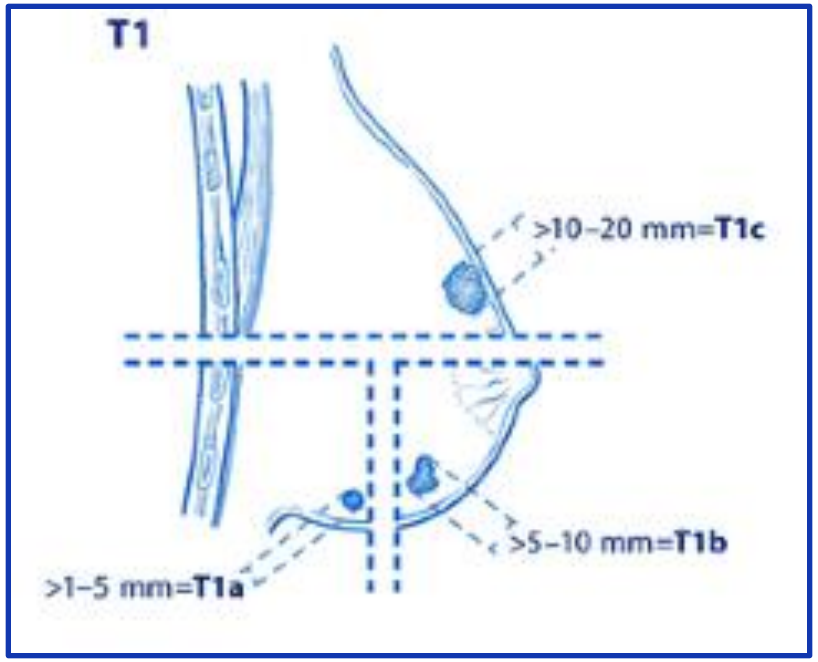


Brenton et al. J. Clin. Oncol. 2005, Bianchini et al. Nat Rev Clin Onc 2016

Stage I TNBC: definition and incidence

One third of all TNBCs are diagnosed as **stage I tumors**





JP Leone et al. Am J Clin Onc 2019

WHAT TYPES OF TREATMENTS ARE RECOMMENDED FOR STAGE I TNBC?

St. Gallen Guidelines

Table 3. Systemic therapy for HER2-positive or triple-negative breast cancers

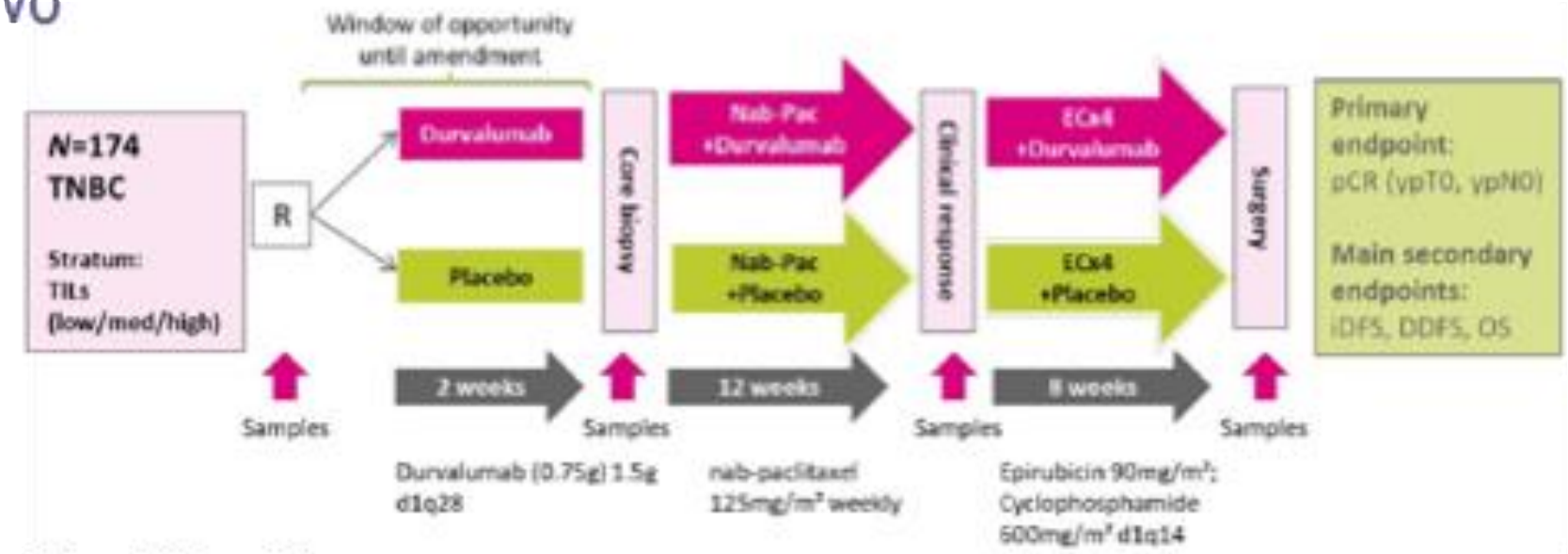
Anatomic stage		Tumor subtype HER2+	TNBC
Stage I Typically as adjuvant therapy	T1a T1b T1c	TH—case by case TH TH	Chemotherapy—case by case TC chemotherapy AC/T chemotherapy
Stage II Neoadjuvant therapy preferred		AC/TH or TCH, with addition of P if neoadjuvant and/or node-positive	AC/T chemotherapy[b]
Stage III Neoadjuvant therapy preferred		AC/THP or TCHP[a]	AC/T chemotherapy[b]
Residual invasive cancer after neoadjuvant therapy		Trastuzumab emtansine	Capecitabine

- **Non-anthracycline, taxane-based regimens are alternatives for low/int risk (eg. Stage 1)**

St. Gallen Consensus Guidelines 2021 - Burstein HJ et al. Ann Onc 2021

Clinical trial evidence

GeparNuevo

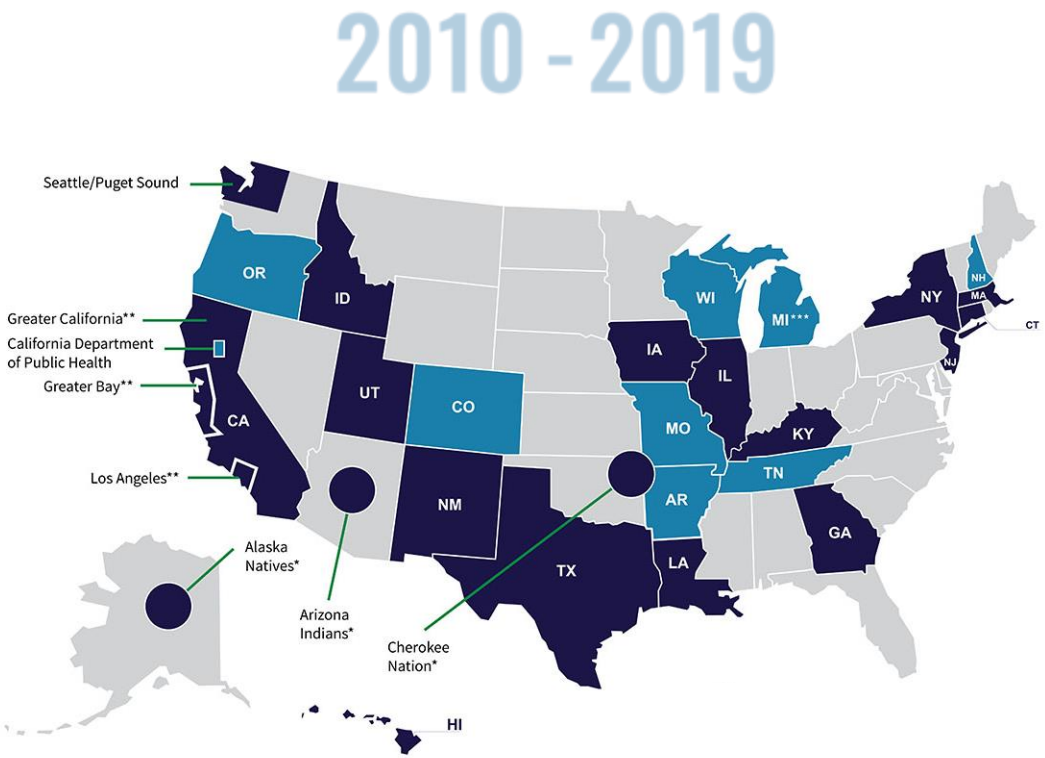


Outcomes in Combined Arms:

Stage 1, n=64	Stage 2+, n=113
pCR rate = 52.5%	pCR rate = 46.9%
DDFS = 95.1 %	DDFS = 78.8 %

Loibl S. et al. Ann Onc 2022

Outcomes and chemo use for stage I TNBC in SEER



- Women with Stage IA TNBC from SEER
- Diagnosed 2010-2019
- One primary malignancy
- Known treatment history vital status, and cause of death

N=10,048

Study Population N=8,601

- No surgery: n=314
- Received neoadjuvant chemo: n=1,116
- Received neoadjuvant radiation treatment: n=17

Patients Characteristics

		Chemotherapy				
		No / Unknown		Yes		
		N	%	N	%	p value
All patients		3306	**38.4%**	5295	**61.6%**	
Age at diagnosis	<50	323	9.8%	1200	22.7%	**<0.001**
	50-64	992	30.0%	2486	46.9%	
	>64	1991	60.2%	1609	30.4%	
T	T1mi (*≤1 mm*)	210	6.4%	22	0.4%	**<0.001**
	T1a (*1-5 mm*)	744	22.5%	216	4.1%	
	T1b (*6-10 mm*)	863	26.1%	1312	24.8%	
	T1c (*11-20 mm*)	1489	45.0%	3745	70.7%	
Histology	Ductal	2987	90.4%	4994	94.3%	**<0.001**
	Lobular	43	1.3%	33	0.6%	
	Ductal and lobular	22	0.7%	40	0.8%	
	Other	254	7.7%	228	4.3%	
Grade	I	256	7.7%	89	1.7%	**<0.001**
	II	1041	31.5%	980	18.5%	
	III/IV	1875	56.7%	4158	78.5%	
	Unknown	134	4.1%	68	1.3%	
Surgery	Partial mastectomy	2367	71.6%	3820	72.1%	0.583
	Mastectomy	939	28.4%	1475	27.9%	
Radiation	No / Unknown	1643	49.7%	2024	38.2%	**<0.001**
	Yes	1663	50.3%	3271	61.8%	

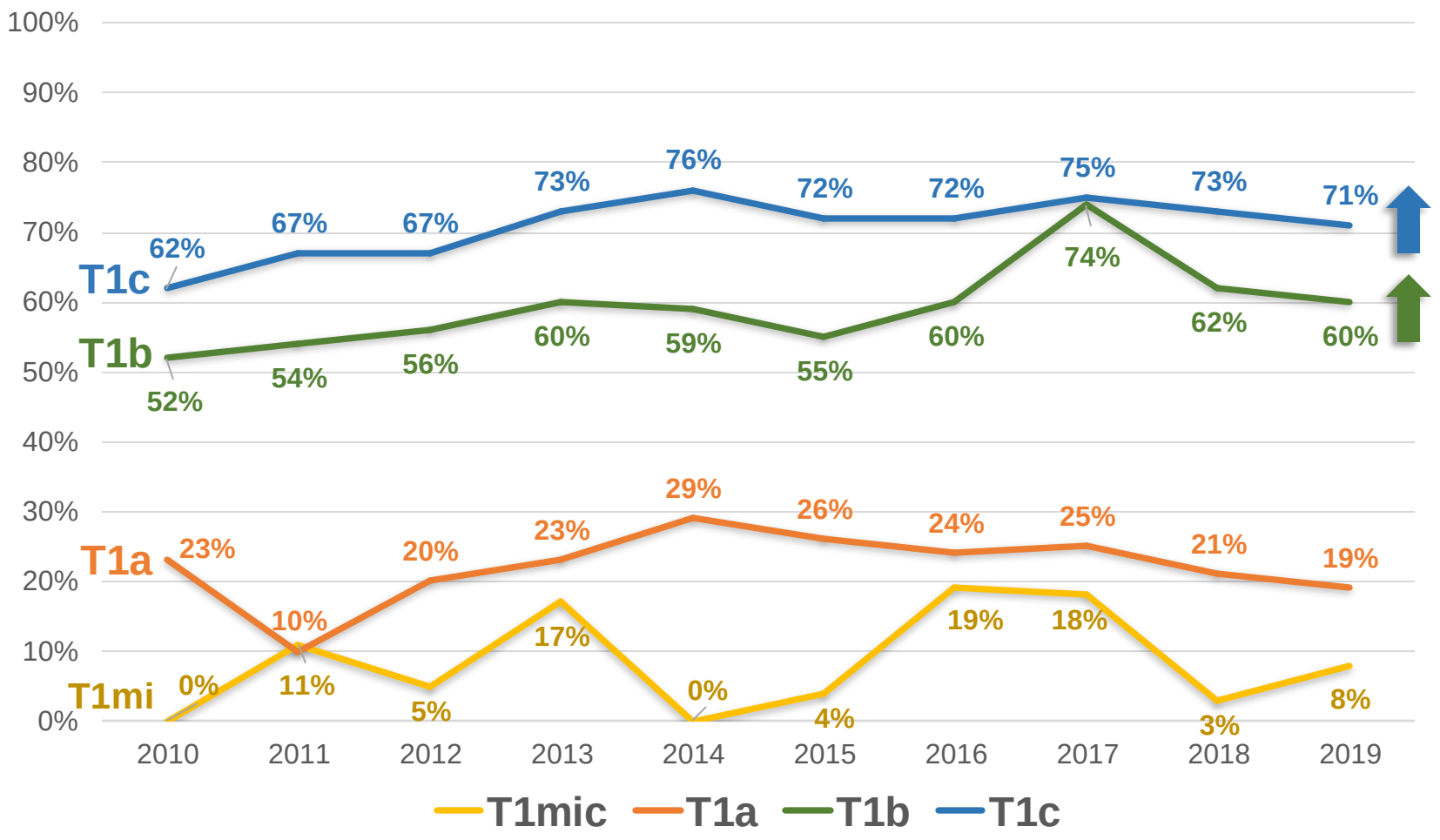
Predictors of Chemotherapy Use

Variables **significantly associated** (all p<0.02) with the use of chemotherapy at multivariate logistic regression were:

- **Younger age** (<50 vs. >64, **OR=5.19**)
- **Married status** (vs. Single, **OR=1.28**)
- **Ductal histology** (vs. Other, **OR=2.05**)
- **High tumor grade** (vs. low grade, **OR=4.89**)
- **Larger tumors** (Reference T1mic, T1a **OR=2.91**, T1b **OR=19.16**, T1c **OR=31.49**)

Use of Chemotherapy Over Time

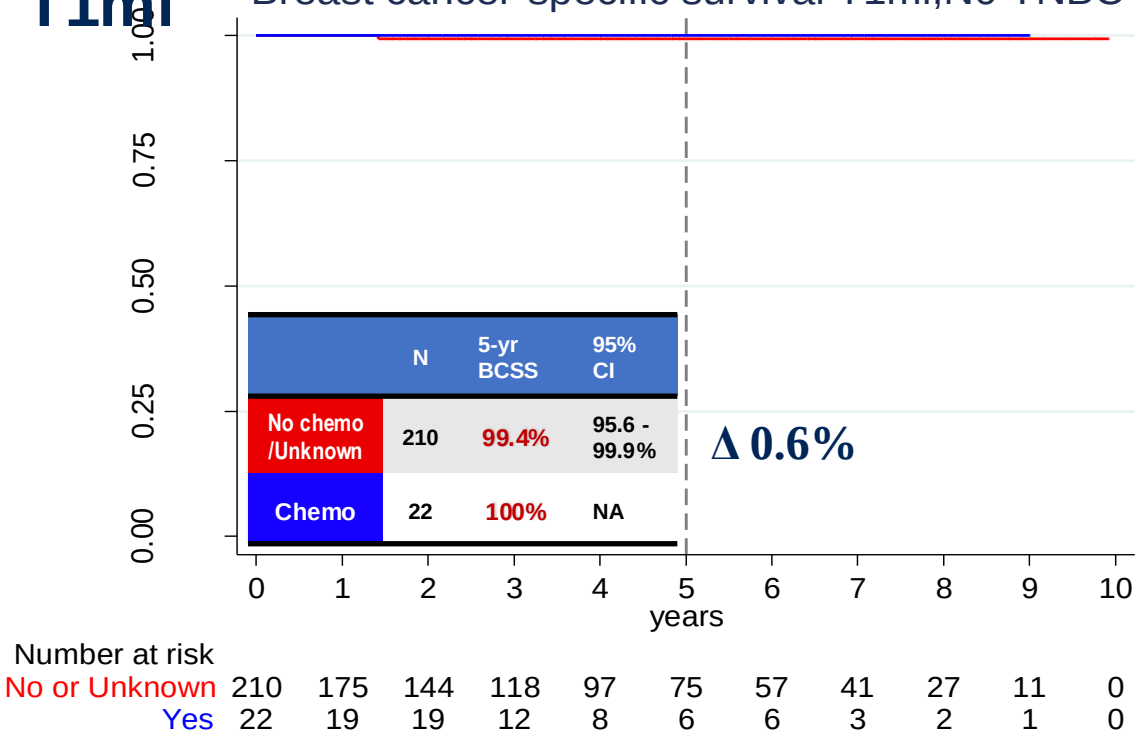
- An increase of the use of chemotherapy was observed with increasing tumor size.
- Additionally, the use of chemo significantly increased during 2010-2019 for both T1b and T1c tumors (p for trend <0.01).



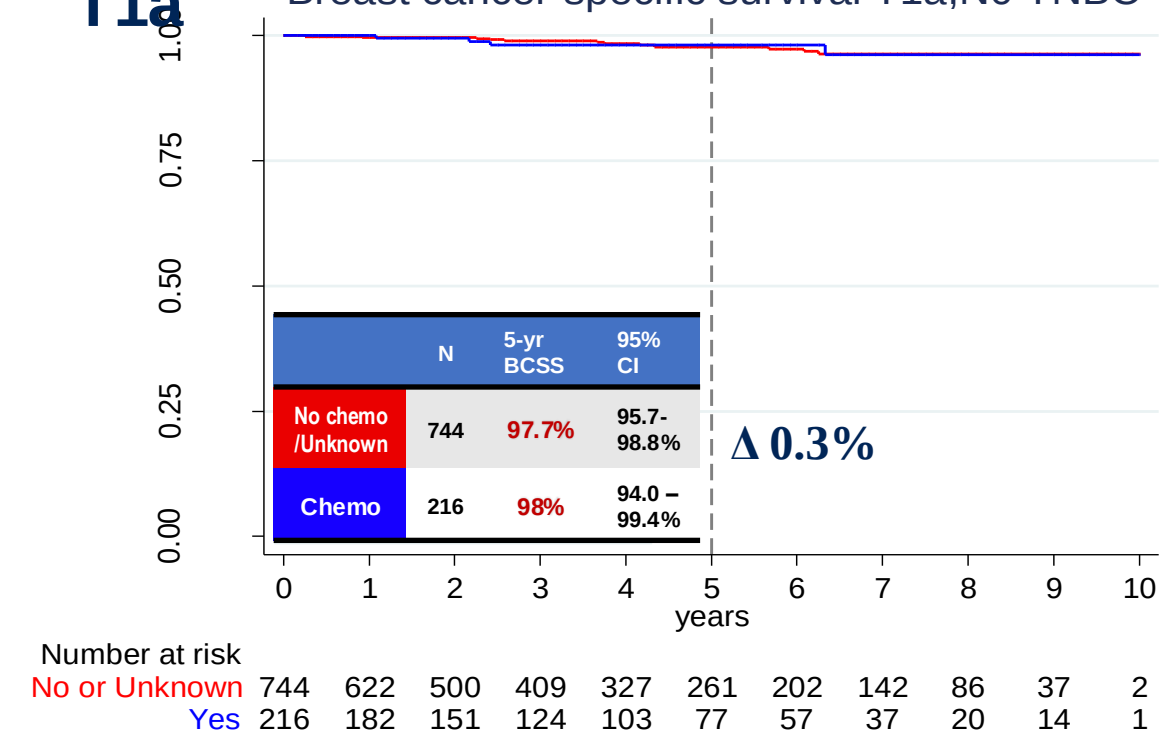
BCSS in Patients With T1mi & T1a TNBC

- Marginal differences in **5-year BCSS** for **T1mi** and **T1a** TNBC depending on the use of chemotherapy.

T1mi



T1a



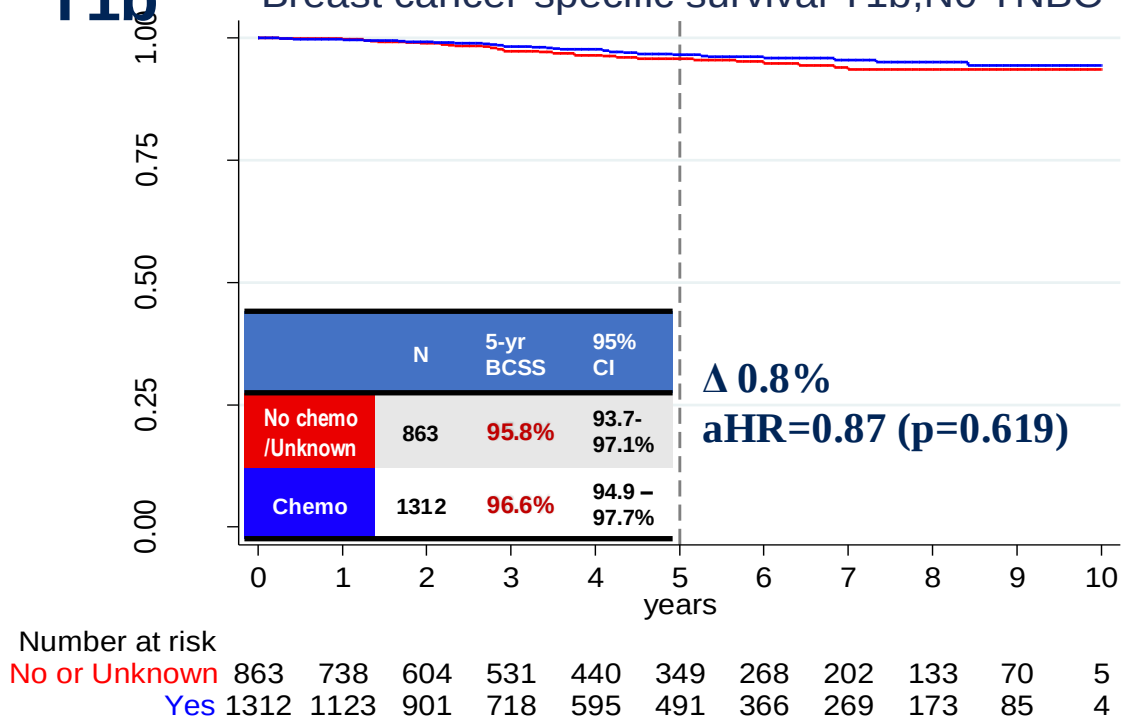
Median follow up: 48 months (IQR: 20 – 83)

No adjusted analysis could be performed due to low event rate.

BCSS in Patients With T1b & T1c TNBC

- No BCSS improvement in **T1b** TNBC (adjusted HR=0.87; p=0.619)
- Significant BCSS improvement in **T1c** TNBC (adjusted HR=0.64; **p=0.002**)

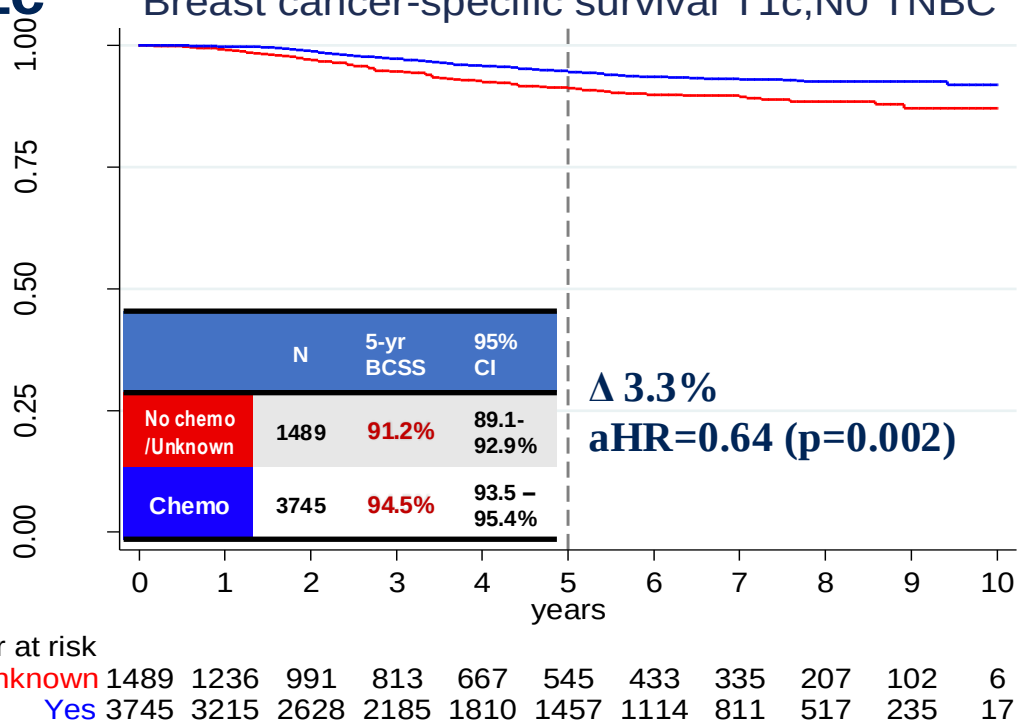
T1b



Number at risk

No or Unknown	863	738	604	531	440	349	268	202	133	70	5
Yes	1312	1123	901	718	595	491	366	269	173	85	4

T1c



Number at risk

No or Unknown	1489	1236	991	813	667	545	433	335	207	102	6
Yes	3745	3215	2628	2185	1810	1457	1114	811	517	235	17

Multivariable cox models adjusted for: age at diagnosis, race, tumor grade, histology, radiation, marital status, income, and rurality.

Neoadjuvant or adjuvant chemotherapy?

5-10% of patients with cT1a/b TNBC and 10-15% of patients with cT1c TNBC undergoing upfront surgery are found to have occult node-positive disease

Clinical T Category	Dana-Farber Brigham Cancer Center (*n* = 343)		National Cancer Database (*n* = 46,015)	
	N	Number of pathologic node positive (%)	*N*	Number of pathologic node positive (%)
cT1a/b	96	9 (9.4%)	8171	399 (4.9%)
cT1c	175	26 (14.9%)	18,608	2121 (11.4%)
cT2	72	15 (20.8%)	19,236	3784 (19.7%)

US of the axilla + FNAB of suspicious noted upstaged 7.5% of cT1c N0 cases to N1

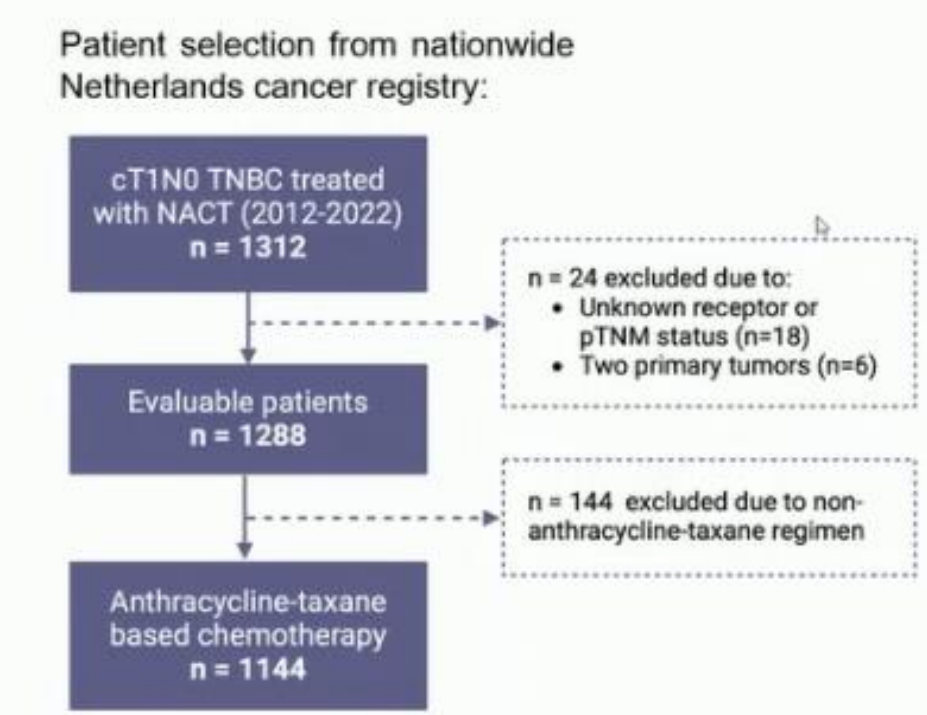
→ Before upfront surgery for stage I TNBC, axillary US is highly recommended (particularly for cT1c!)

Mittendorf EA, Ann Surg Onc 2023

Outcomes with NACT for stage I TNBC (ESMO24)

A registry analysis of **1144 patients with cT1 N0 TNBC receiving NACT** was conducted (**94% cT1c**)

All received neoadjuvant anthracyclines/taxanes, 40% also received platinum, 25% received adjuvant capecitabine

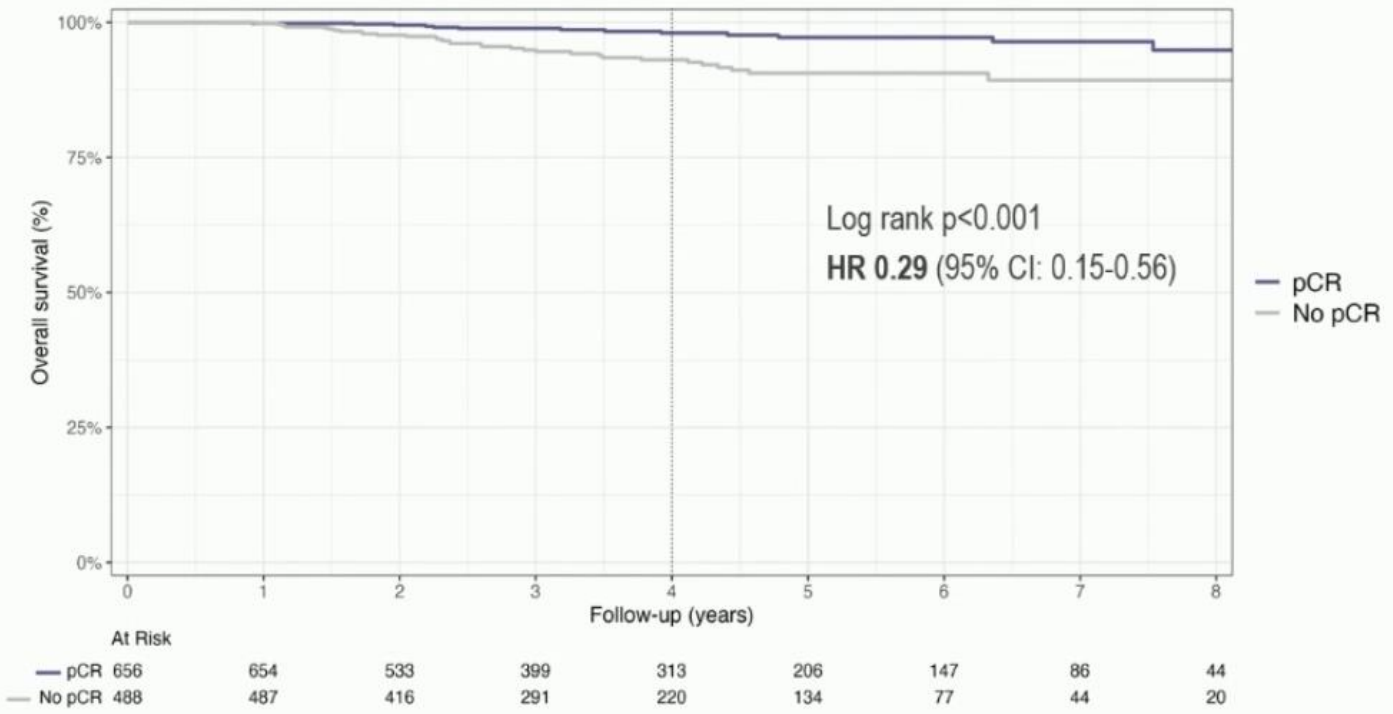


	All patients (N=1144)
Age (years)	
Median [Min, Max]	50.0 [22.0, 77.0]
cT stage	
1a/b	67 (5.9%)
1c	1077 (94.1%)
Tumor grade	
Grade 1/2	274 (24.0%)
Grade 3	777 (67.9%)
Missing	93 (8.1%)
Histological subtype	
Ductal carcinoma	1034 (90.4%)
Lobular carcinoma	16 (1.4%)
Other	94 (8.2%)
Neoadjuvant regimen	
With platinum	472 (41.3%)
Without platinum	672 (58.7%)
Type of surgery	
Lumpectomy	818 (71.5%)
Mastectomy	324 (28.3%)
Missing	2 (0.2%)
Adjuvant capecitabine	
Yes	282 (24.7%)
No	858 (75.0%)
Unknown	4 (0.3%)

De Graaf M. ESMO 2024

Overall survival in patients with pCR vs RD

pCR rate: 57%, similar for platinum vs. no platinum.



	N	4-year OS (95% CI)
pCR	656	98% (97% - 99%)
Residual disease	488	93% (90% - 96%)

Δ 5%

Median follow-up 3.8 years (IQR 2.4-5.6 years)

Total no. events = 39 (3.4%)

→ Supports consideration of neoadjuvant anthracyclines/taxanes for patients with cT1c disease

De Graaf M. ESMO 2024

cT1c is heterogenous

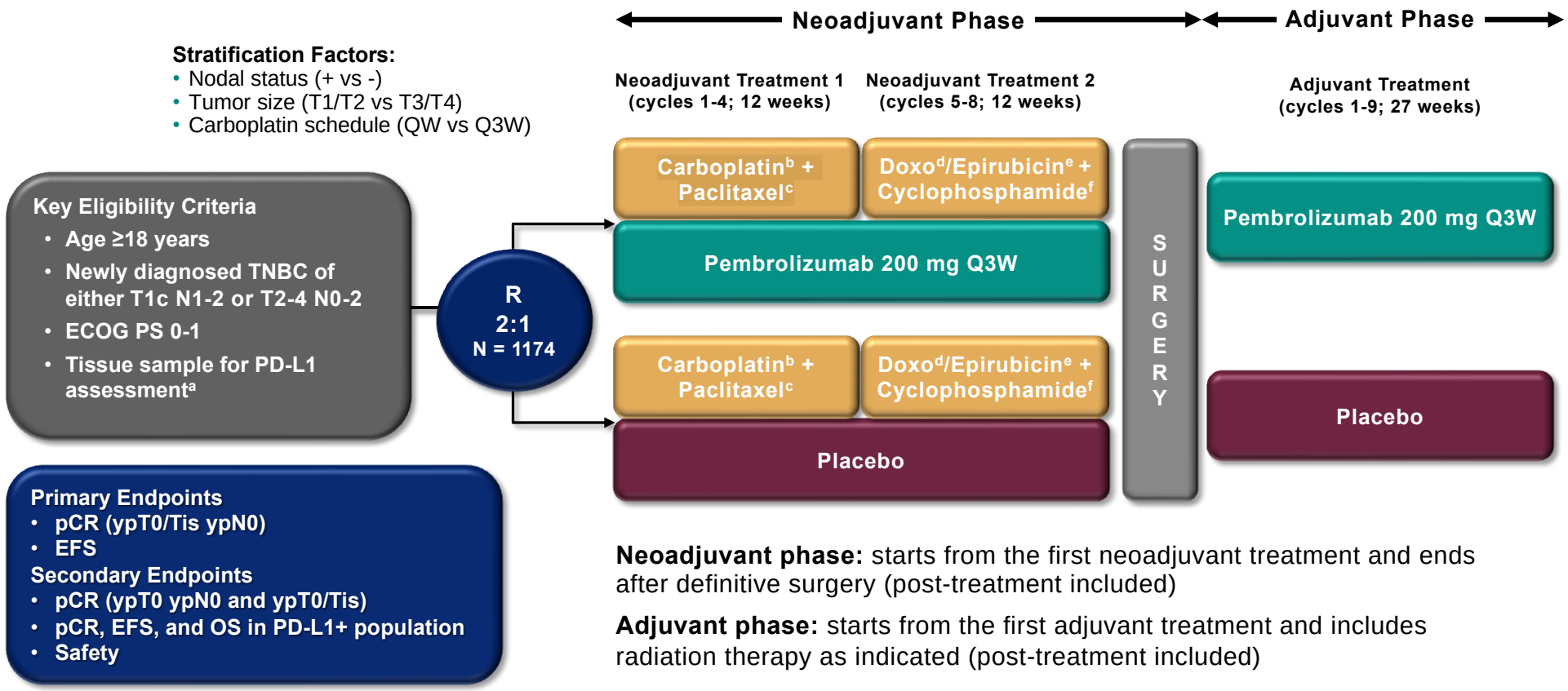
Smaller sizes (<15 mm) may warrant upfront surgery and less chemotherapy (e.g. TC)

Larger sizes (≥15 mm) may warrant NACT with inclusion of anthracyclines (unclear role of carbo)

→ Remains a case-by-case scenario, requiring the inclusion of additional clinico-pathologic factors (age, comorbidities, grade, LVI, Ki67) and patient preference

What about borderline stage I / stage II?

Patients with stage I TNBC were excluded from KEYNOTE-522, but **T2N0 were included**

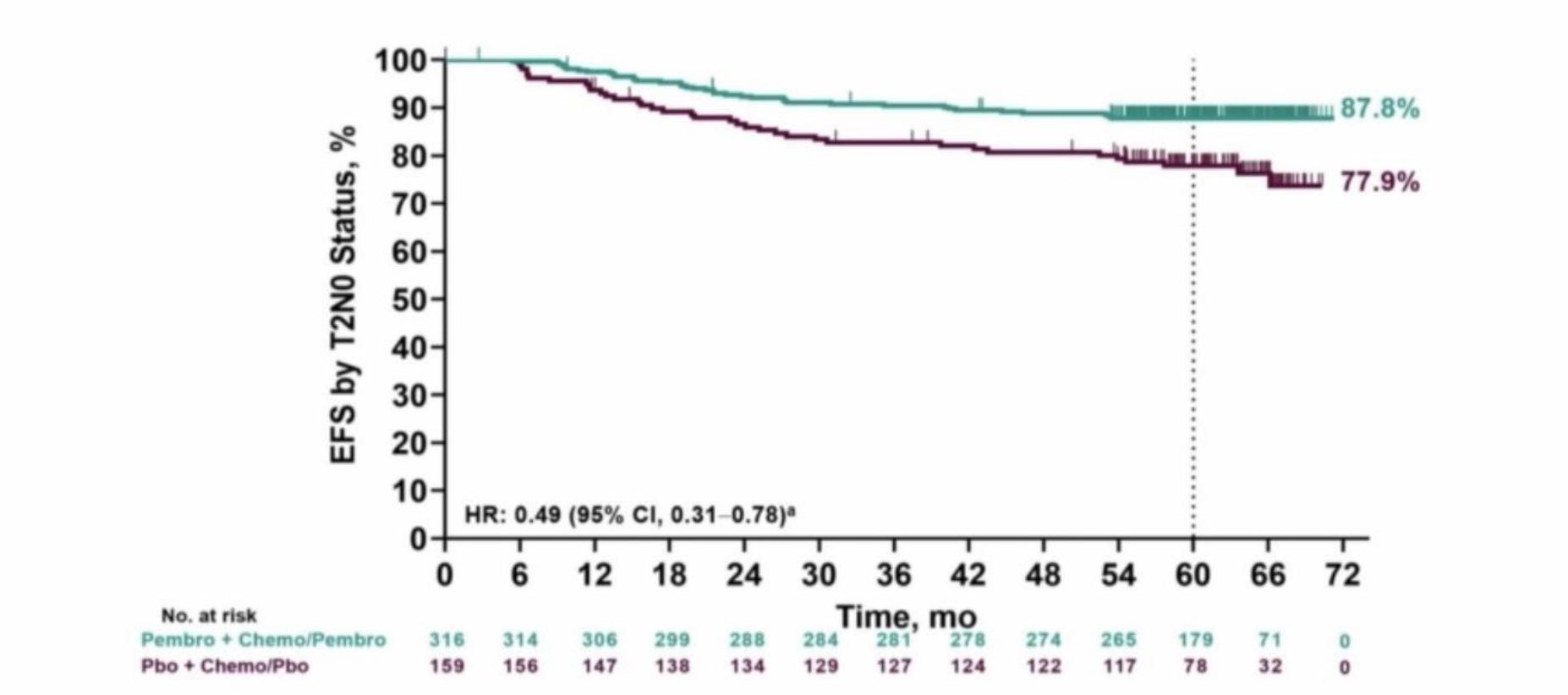


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

EFS with the KN522 regimen in T2N0

Relevant EFS benefit warrants the use of **neoadjuvant chemo + pembro for patients with TNBC of ≥ 2 cm** (in the absence of contraindications or relevant comorbidities)



Schmid P, SABCS 2023

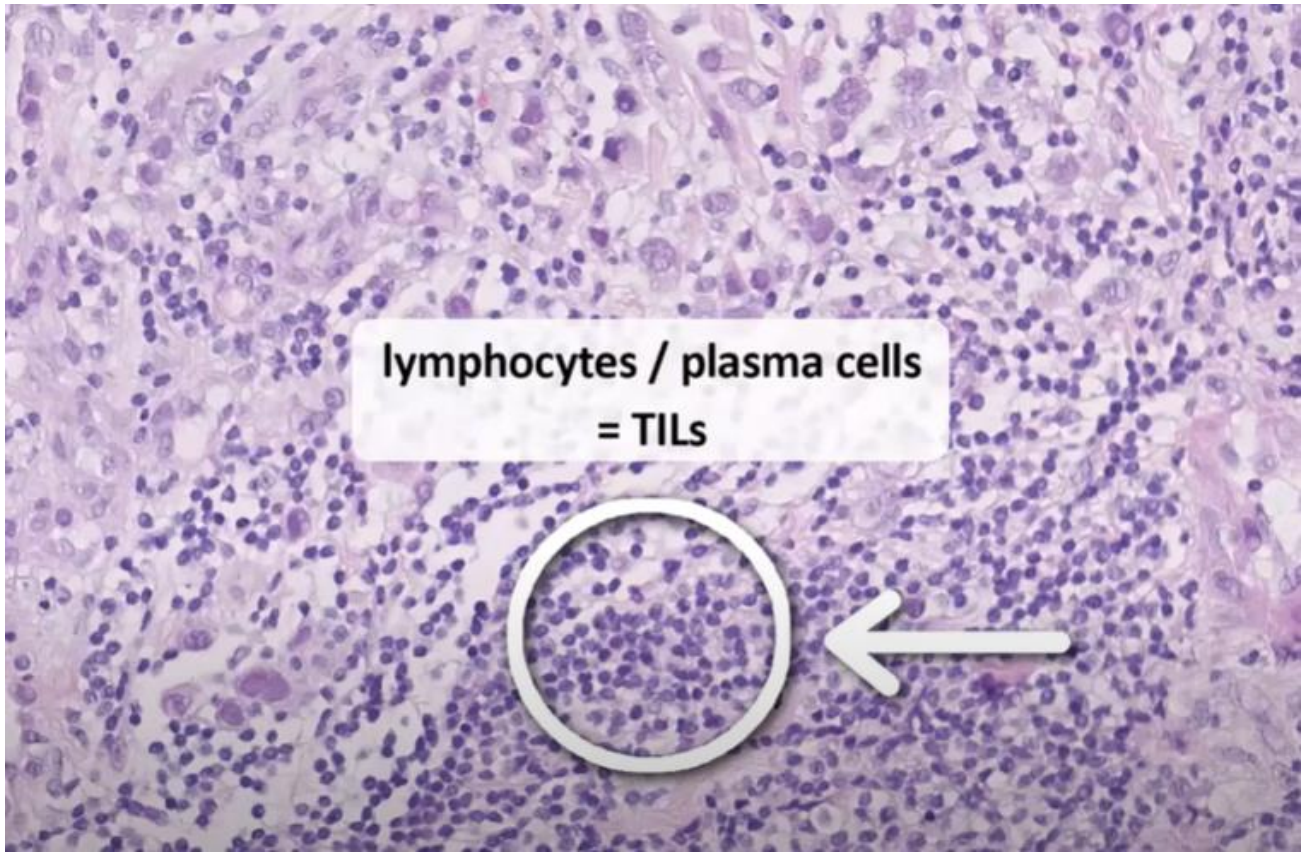
WHAT BIOMARKERS MAY AID TREATMENT DECISIONS FOR STAGE I TNBC?

TILs

IGG signature

ctDNA

Biomarkers: TILs

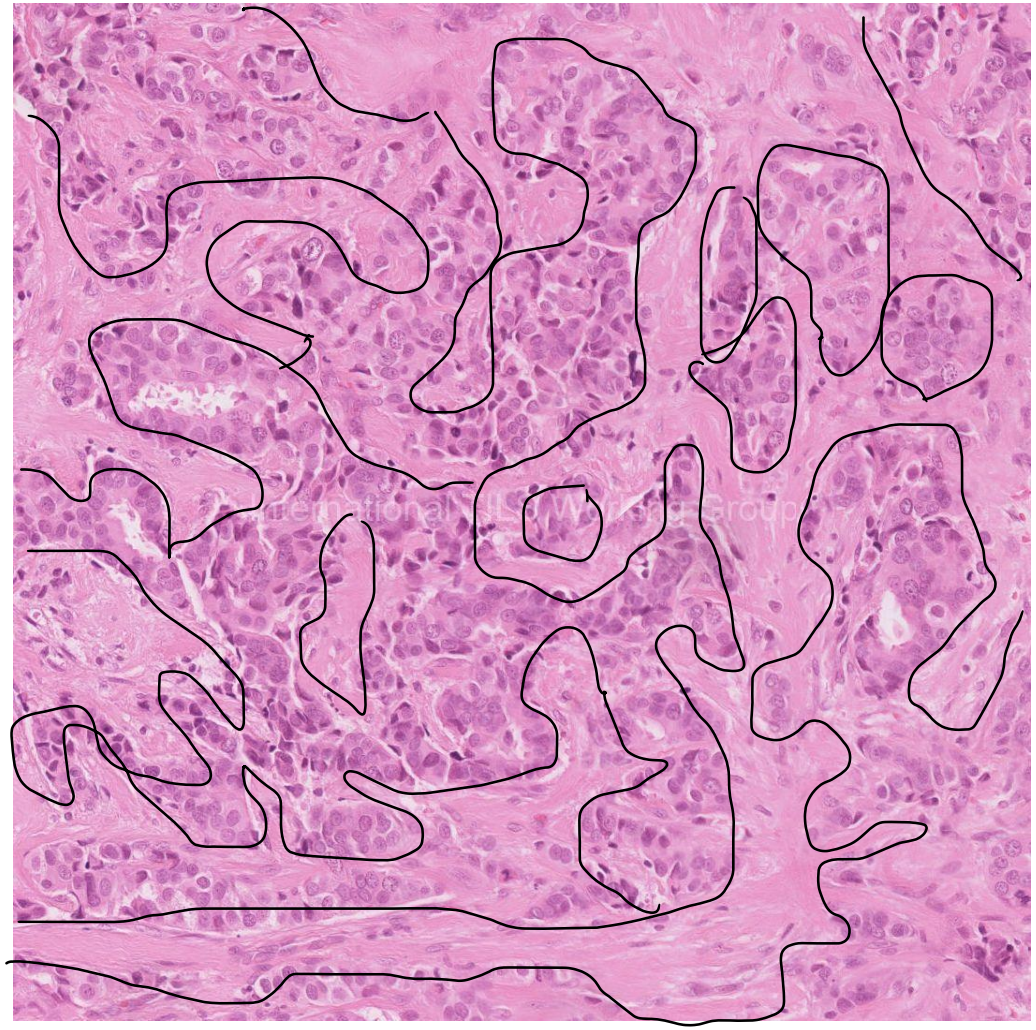


Stromal TILs (sTILs) = **% of stromal area** occupied by **mononuclear inflammatory** cells over the total stromal area within the tumor (i.e., not the % of cells in the stroma that are lymphocytes)

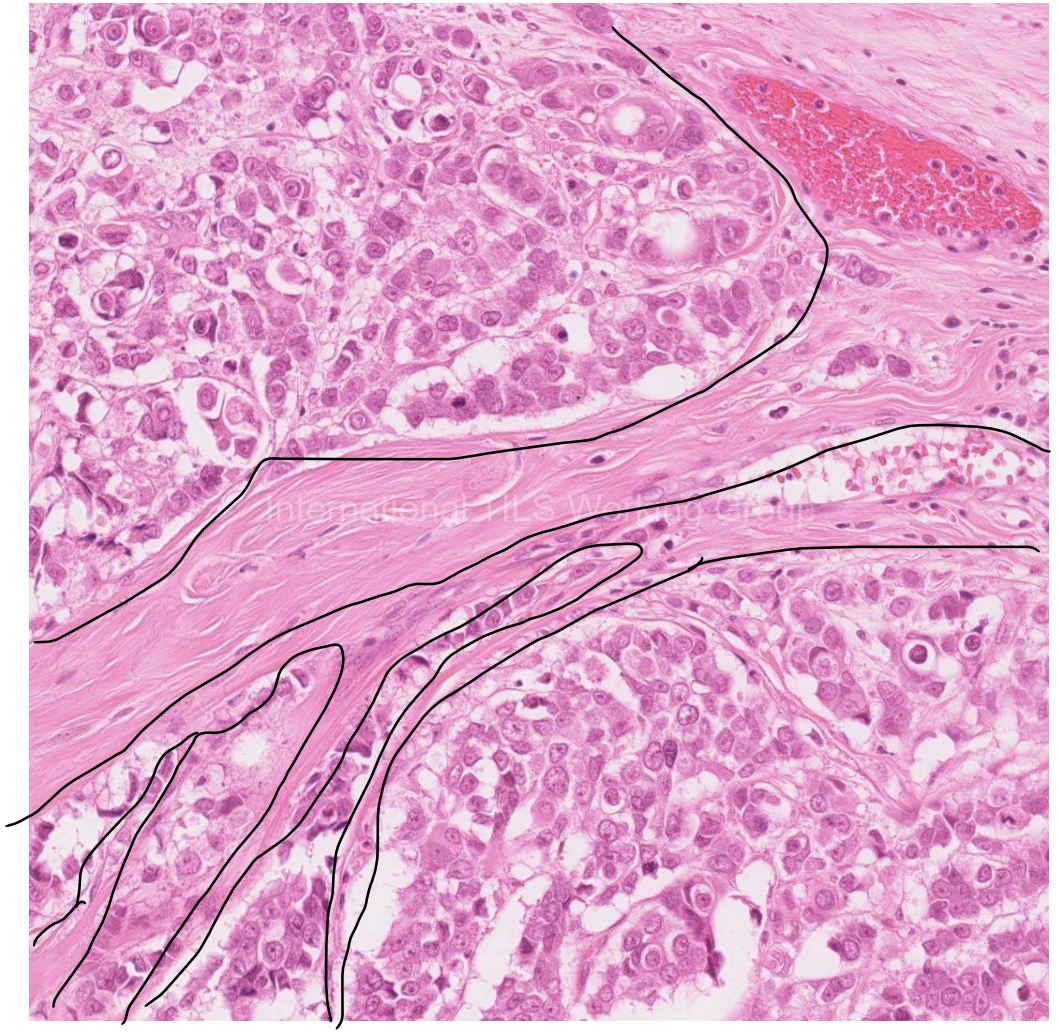
Salgado R. Webinar 2022. https://www.youtube.com/watch?v=dCI9sYePWfc

Biomarkers: TILs

<1% TILs

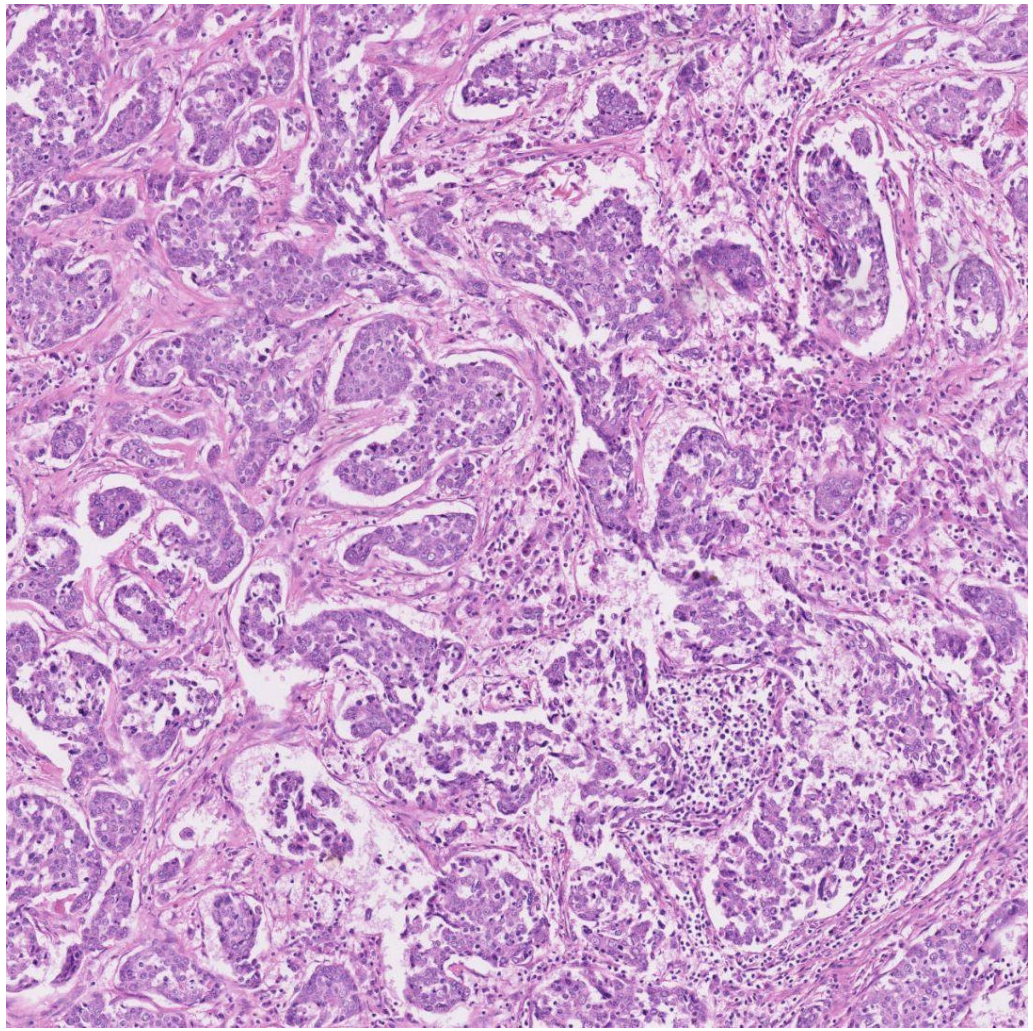


<1% TILs

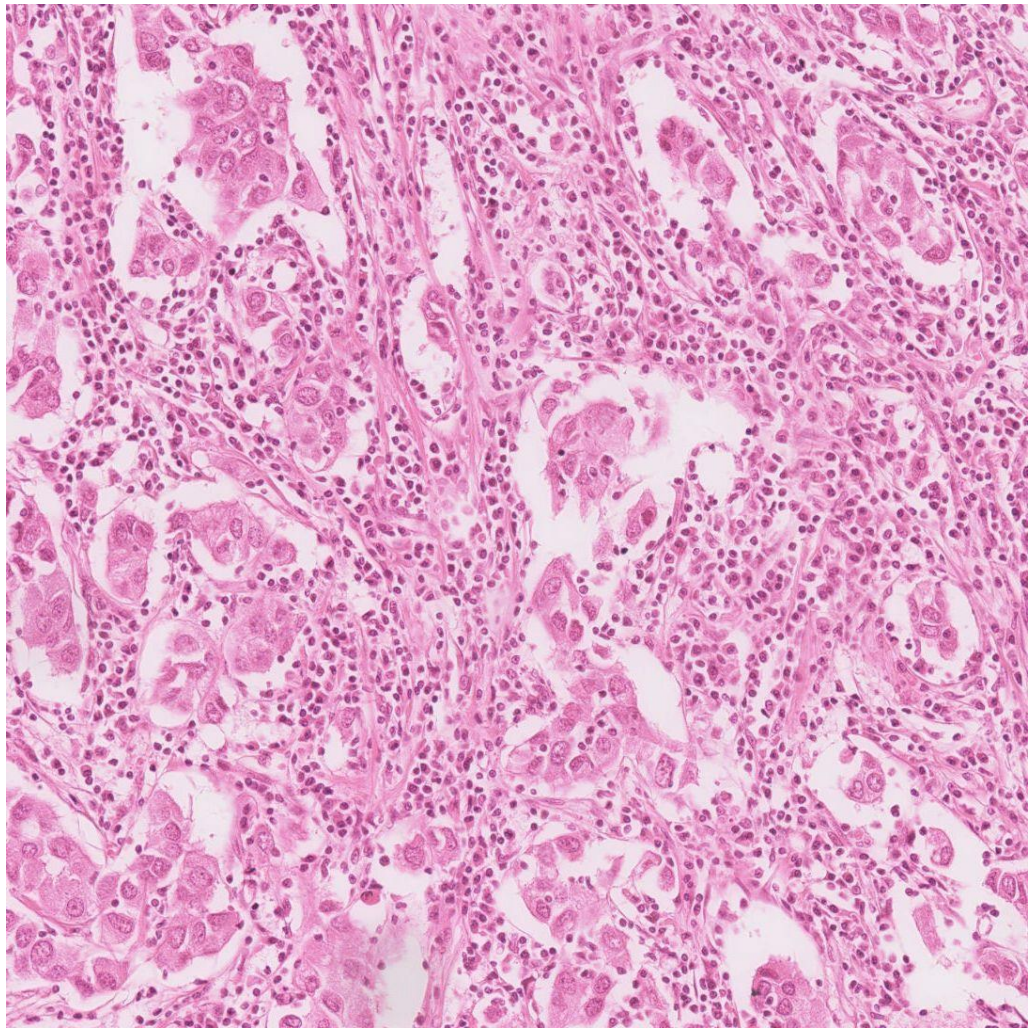


Biomarkers: TILs

50% TILs



90% TILs

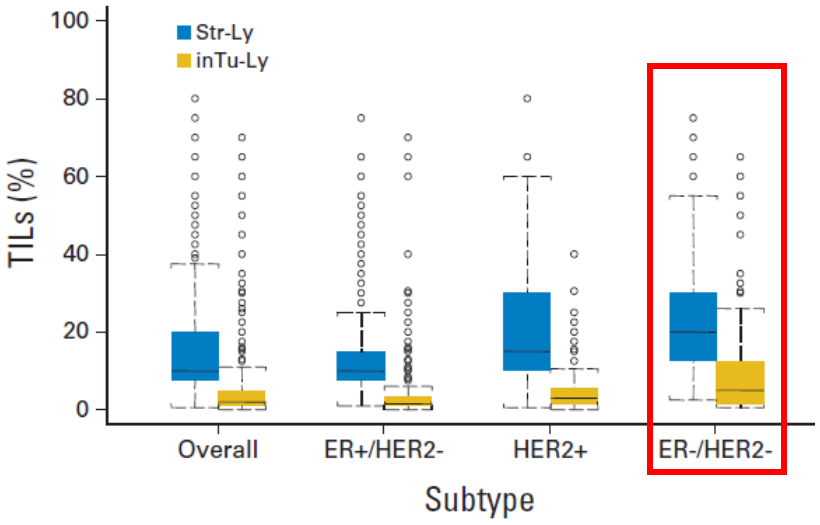


www.tilsinbreastcancer.org

Distribution of TILs

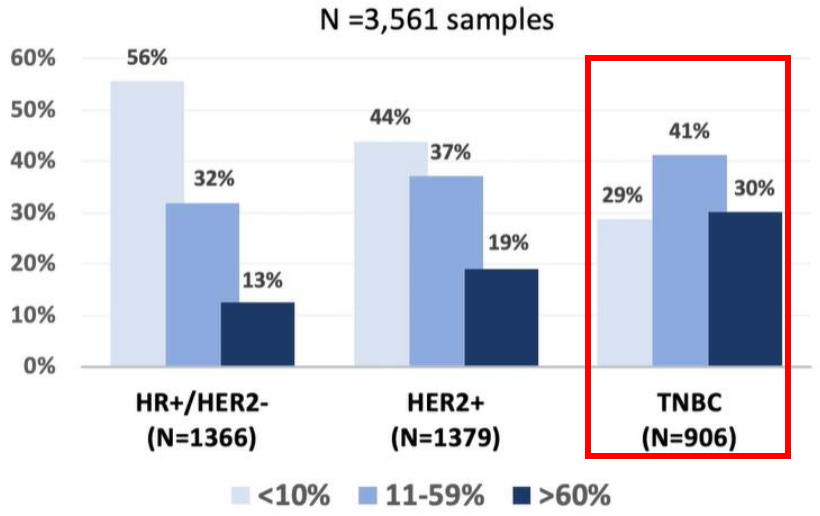
Approximately 20-30% of TNBCs show ≥50% TILs

N = 2,009



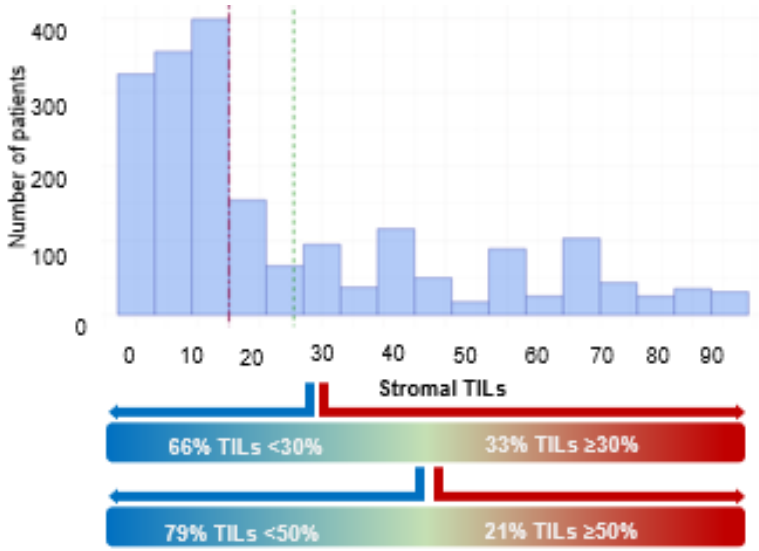
	Overall		ER+/HER2-		HER2+		ER-/HER2-	
n	2,009	2,009	1,079	1,079	297	297	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	7.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65

Loi S. JCO. 2013



Denkert C. Lancet Oncol. 2018

TNBC
N = 1,966



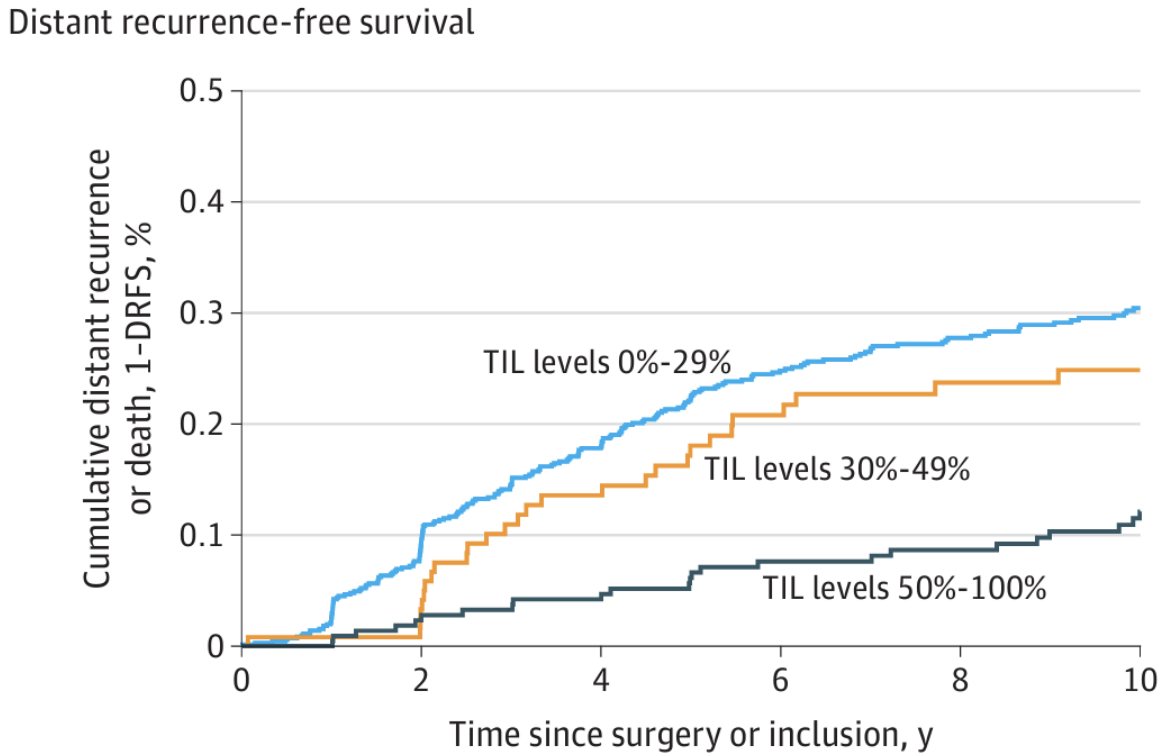
León-Ferre R. SABCS. 2022

Biomarkers: TILs

The presence of sTILs represents a strong prognostic factor

Much higher rates of distant recurrence (approaching 30%) for **untreated** stage I TNBC patients with <50% sTILs, compared with those having ≥50% sTILs

Personal opinion: the solidity of the retrospective data available warrants routine reporting of TILs and inclusion in decision making for borderline cases (suggested threshold: >50% TILs)



No. at risk by TIL level

0%-29%	728	632	545	457	384	307
30%-49%	127	115	99	86	71	63
50%-100%	226	207	201	186	168	147

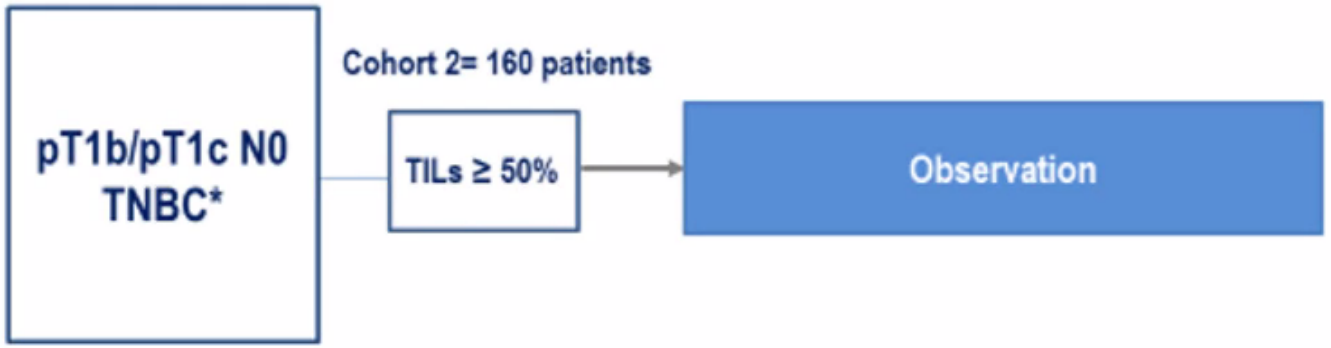
Leon-Ferre R. et al, JAMA 2024

Prospective trial planned: ETNA

ETNA-cohort 2 study design

PI: Dr. Barbaba Pistilli (Gustave Roussy Cancer Center)

Open label, multicentric, phase II, single-arm biomarker driven trial



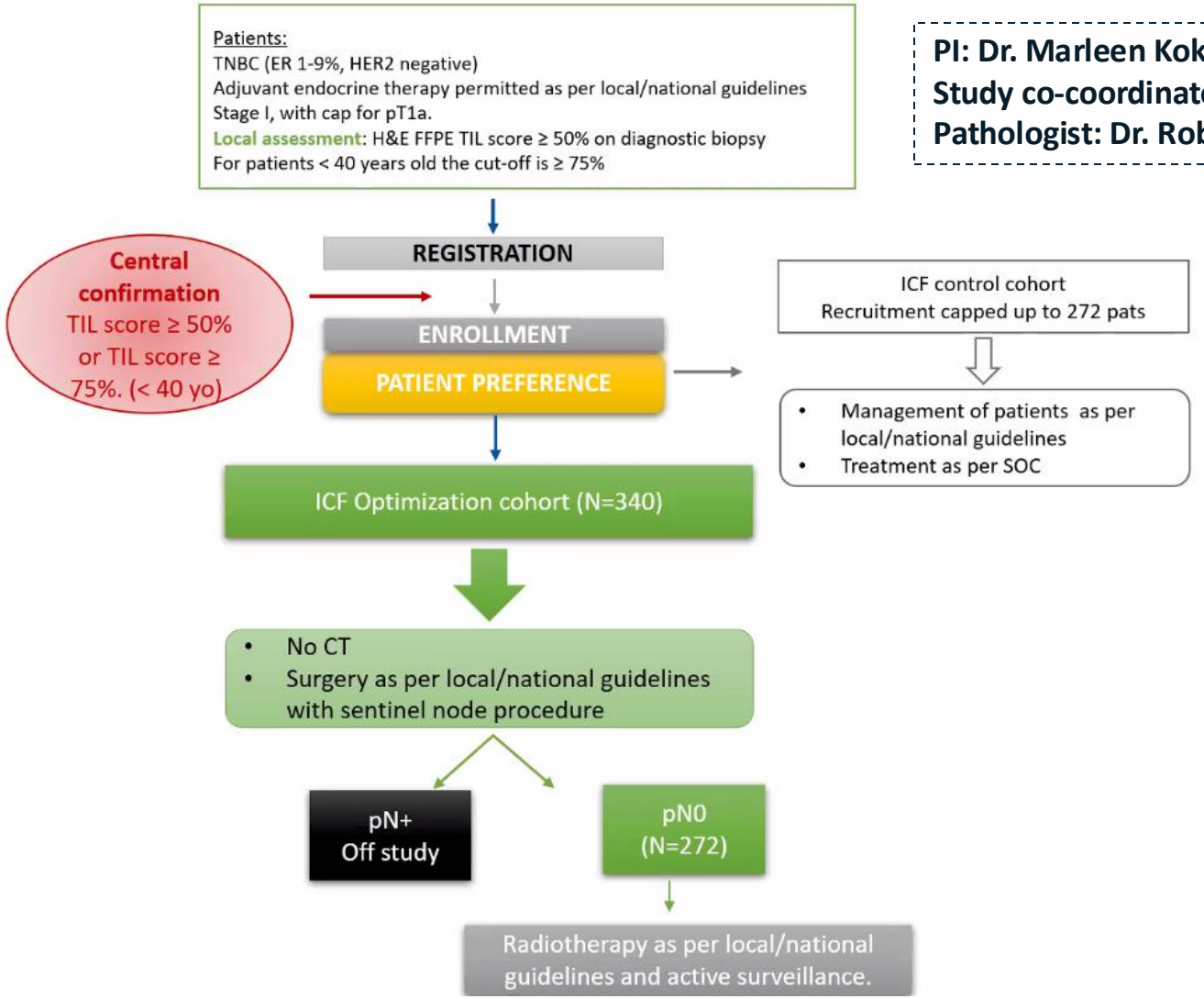
Primary Objective:
- 3-year iDFS

Secondary Objectives:
- 3-year OS
- 3-year DDFS
- QOL
- Cost effectiveness

Screening	Follow-up: Every 6 months for 3 years
Blood test, medical history Tumor samples (biopsy + surgery)	QoL, standard work-up (WeSHARE plateform)

*screening 1000 patients, assuming an expected proportion of TILS ≥ 50%: 16% (Loi et al JCO 2019; unpublished data)

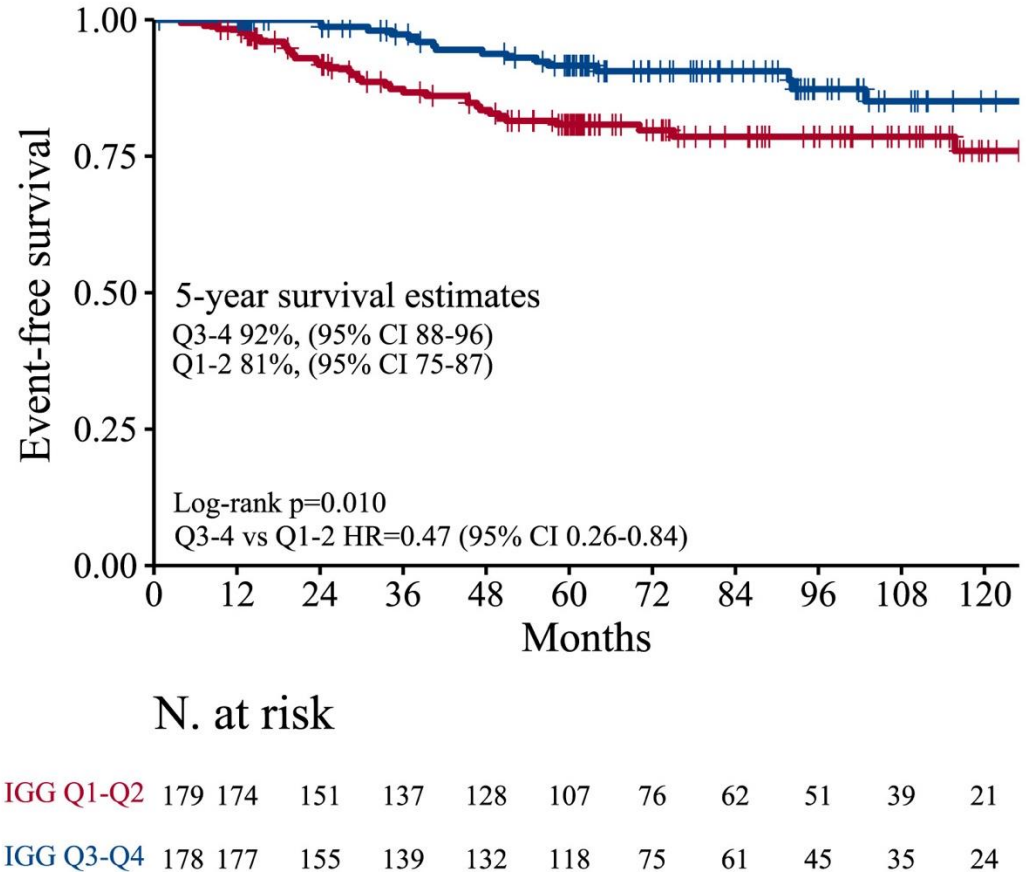
Prospective trial planned: OPTImisation of treatMent for pAtients with low stage triple-negative breast cancer patients with high sTIL (OPTImaL)



PI: Dr. Marleen Kok, The Netherlands (NKI)
Study co-coordinator: Prof. Dr. Sabine Linn (NKI)
Pathologist: Dr. Roberto Salgado

B-cell/immunoglobulin signature (IGG) in the context of stage I TNBC

A 14-gene immunoglobulin B-cell signature was found to be significantly associated with outcomes in a pooled analysis of 7 clinical trials, including a total of 357 patients with stage I TNBC

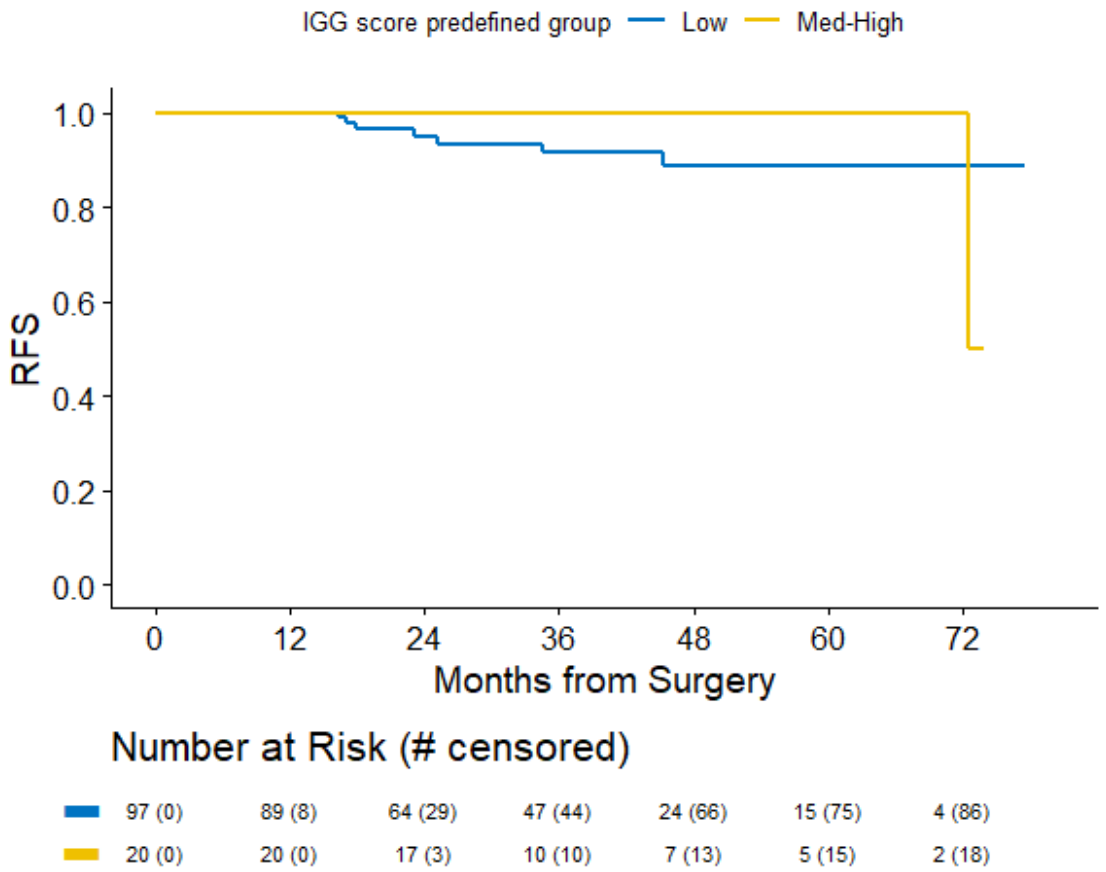


Conte B. et al eBioMedicine 2024

B-cell/immunoglobulin signature (IGG) in the context of stage I TNBC

Retrospective analysis among 117 patients with stage I TNBC treated at Dana-Farber Cancer Institute

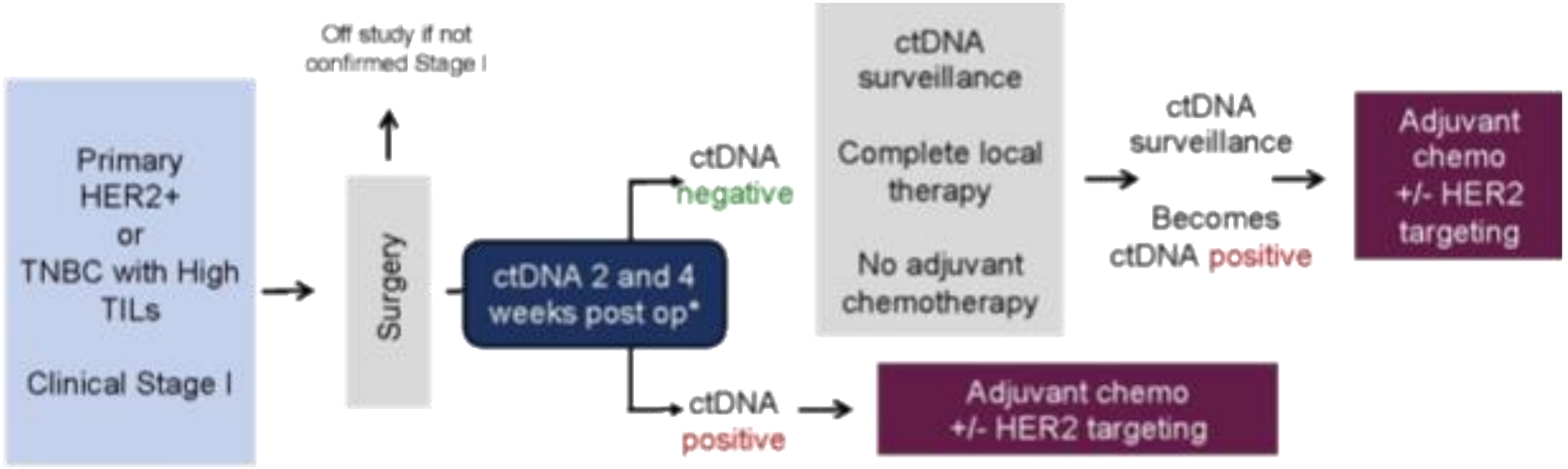
Trend in worse outcomes among patients with low IGG score, with 3-year RFS of 91% (vs 100%), HR 0.52, p=0.54



ctDNA to tailor treatment in stage I TNBC

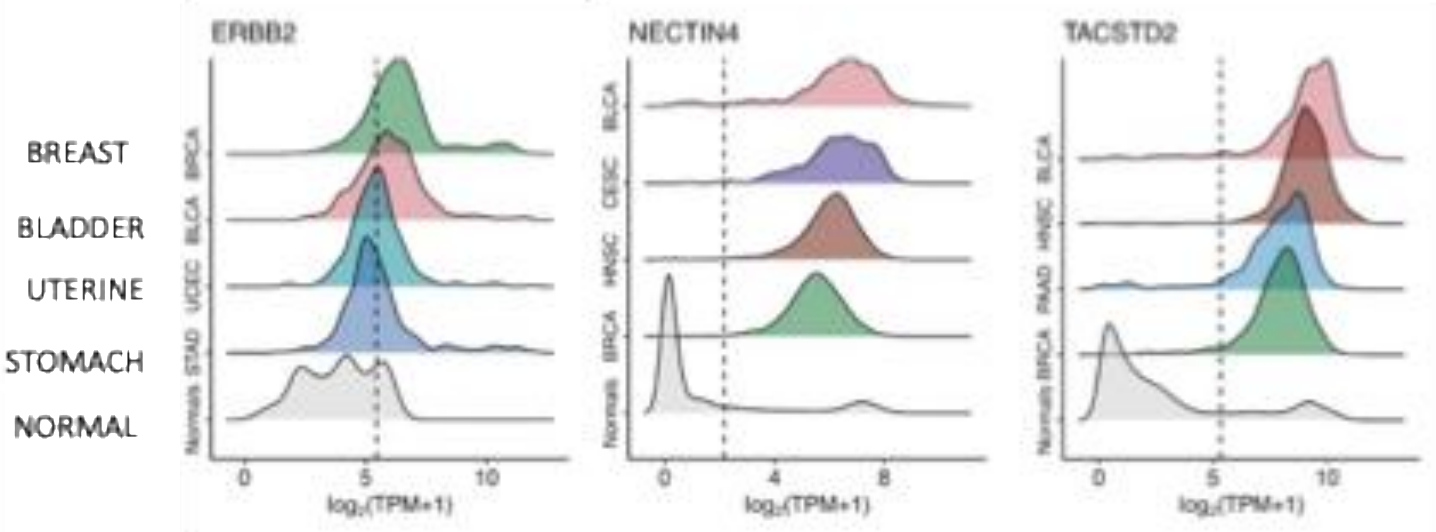
Chemotherapy De-escalation Study in Stage 1 TNBC: SAFE-DE

PI: N. Turner, NCT05058183



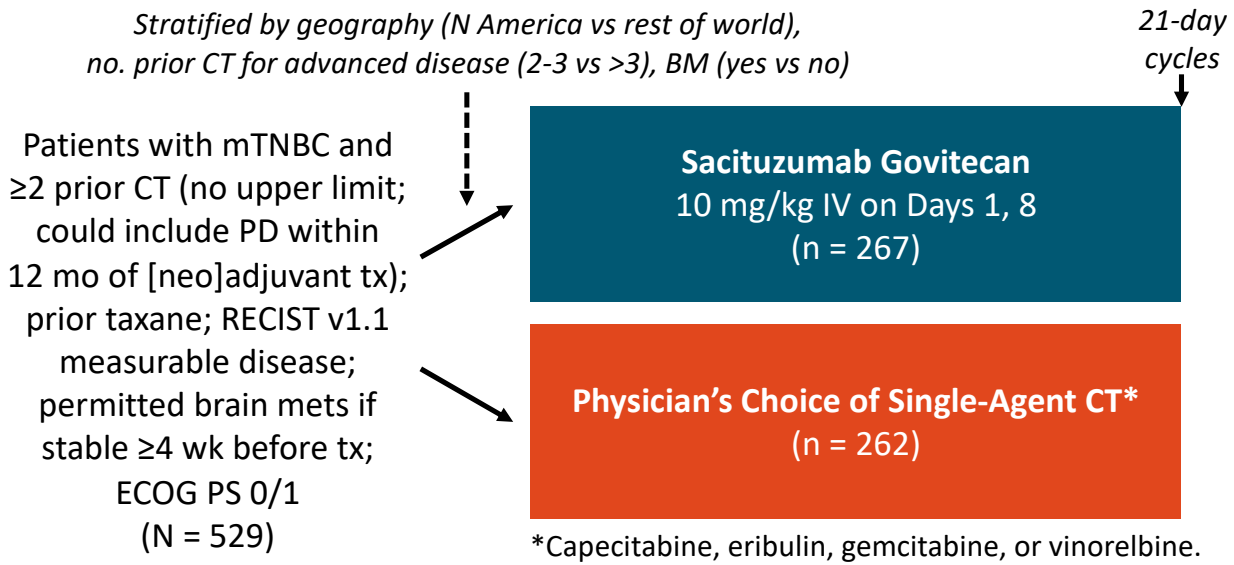
Multiple ADC targets expressed by TNBC

Preference for targets that are **expressed on the cell surface**, undergo **internalization** and have a **differential expression** in tumor vs normal tissue

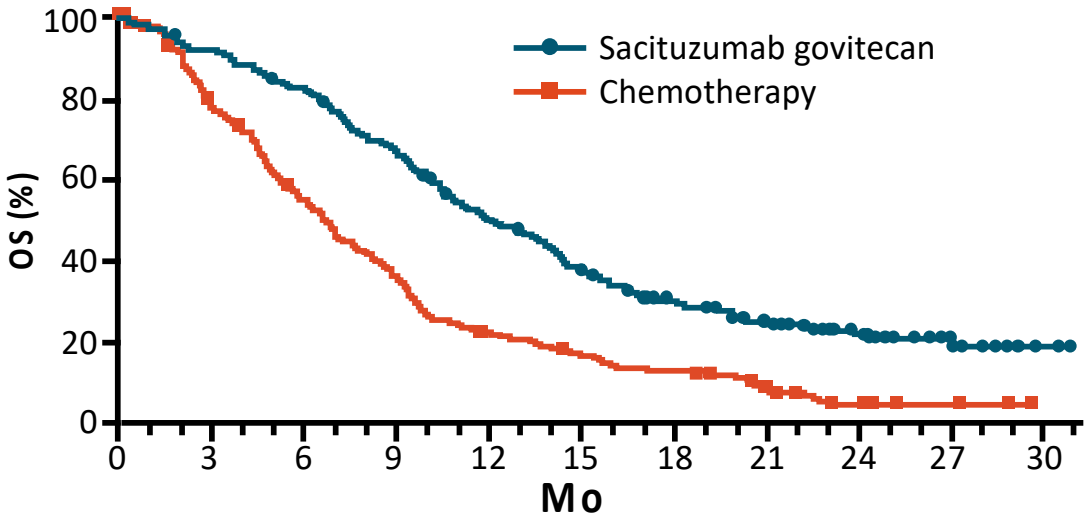


Bosi C. et al Eur J Cancer 2023

SG for metastatic TNBC



OS Analysis	SG (n = 235)	CT (n = 233)
Events	173	199
Median OS, mo	**12.1**	**6.7**
HR	**0.48 (95% CI: 0.39-0.59; *P* <.0001)**	

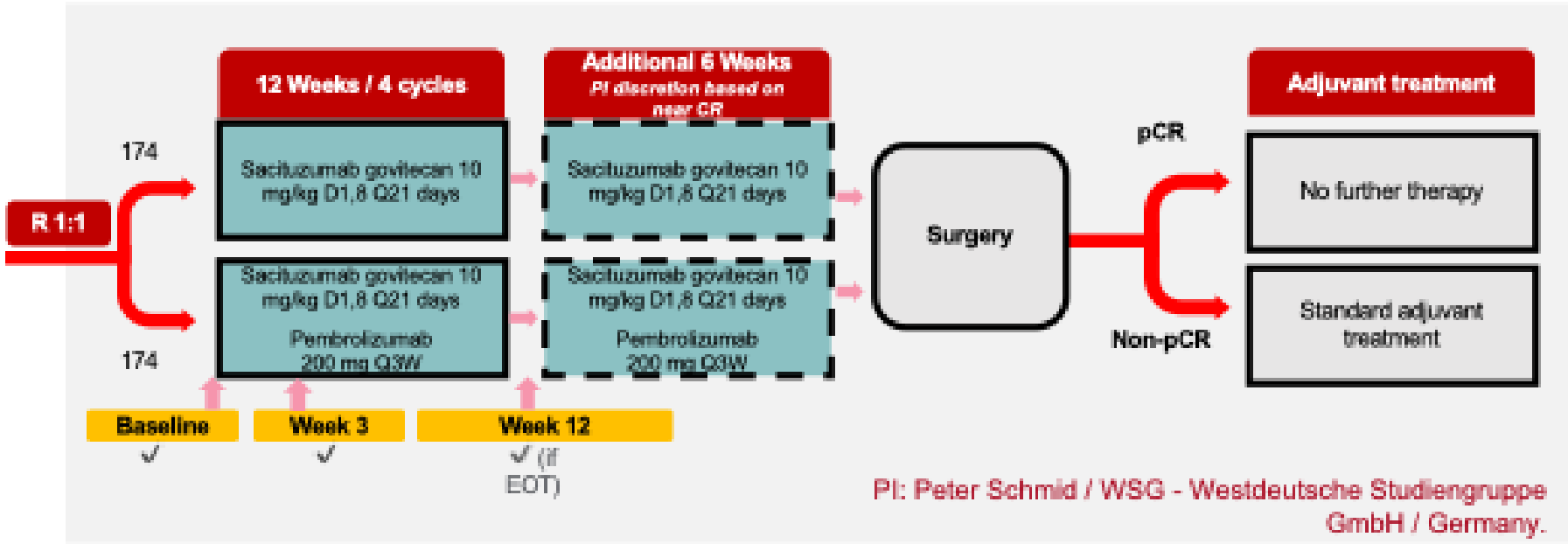


Bardia A. et al. NEJM 2021

ADAPT-TN-III: Sacituzumab Govitecan (+/- Pembrolizumab)

Randomized, open-label, neoadjuvant, phase-II-trial in low-risk early TNBC

Clinical stage 1 TNBC
or patients not suitable for poly-chemotherapy + pembrolizumab
N=348



Blood sample

NCT06081244

PRIMARY ENDPOINTS: pCR (at surgery), iDFS (after 3 years)

SECONDARY ENDPOINTS: OS, dDFS, dDFI, RFS, HRQoL, BCFI

Take-Home Messages

- Stage I TNBC is common, accounting for **about one third of all TNBC diagnoses**, and associated with up to 30% risk of recurrence if left untreated
- **Chemotherapy is recommended for most stage I TNBCs, with a case-by-case discussion for T1a tumors**
- Both the **neoadjuvant** and **adjuvant** approaches are reasonable, always remembering to adequately stage the axilla (US highly recommended)
- There is sufficient evidence to routinely evaluate **TILs** and include them in the decision-making process for borderline cases
- Novel biomarkers (e.g. TNBC-DX, ctDNA) and treatments (e.g. ADCs) will hopefully further refine treatment for this highly prevalent disease in the coming years

Thank you for your attention!

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