

Small triple-negative breast cancer: biomarkers and management

Romualdo Barroso-Sousa

Oncologista Clínico, Head de Pesquisa em Oncologia e
Líder Nacional de Câncer de Mama - DASA Oncologia

DASA
oncologia

Conflito de Interesses

De acordo com a Resolução 1931/2009 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro que:

PALESTRAS: ASTRAZENECA, DAICHI-SANCHIO, GILEAD, ELI LILLY, LIBBS, NOVARTIS, PFIZER, ROCHE, MSD

ADVISORY BOARD: ASTRAZENECA/DAICHI-SANCHIO, ELI LILLY, LIBBS, NOVARTIS, ROCHE

APOIO PARA CONGRESSOS/EVENTOS DE EDUCAÇÃO MÉDICA: ROCHE, ELI LILLY, DAICHI-SANCHIO, MSD

APOIO PARA PESQUISA (VIA INSTITUIÇÃO): ASTRAZENECA

Não possuo ações de qualquer empresa da indústria farmacêutica ou de diagnóstico

Small TNBC: Facts



- One third of all triple-negative breast cancers (**TNBC**) are diagnosed as **stage I tumors**



- Outcomes for **stage I TNBC** remain poorly defined, given the common exclusion from clinical trials



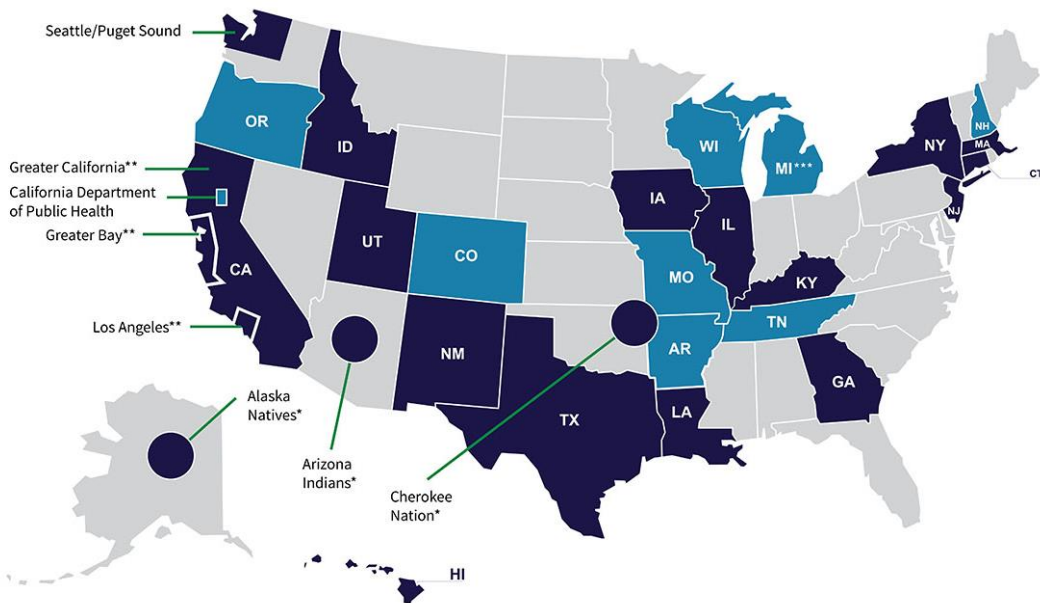
- Systemic treatment for stage I TNBC is limited to **chemotherapy**, although its benefit and utilization remain currently unclear

Survival Outcomes T1abN0 TNBC

	T1a				T1b			
	No Chemotherapy (N=74)		With chemotherapy (N=25)		No Chemotherapy (N=94)		With chemotherapy (N=170)	
	5y estimate (%)	95% CI	5y estimate (%)	95% CI	5y estimate (%)	95% CI	5y estimate (%)	95% CI
OS	94	85 to 98	100		91	82 to 95	96	91 to 98
BSCC	95	86 to 99	100		95	88 to 98	98	94 to 99
IDFS	86	75 to 92	91	68 to 98	81	71 to 88	88	81 to 92
DRFS	93	84 to 97	100		90	81 to 95	96	90 to 98

Study Population

2010 - 2019



- 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

Methods

PRIMARY OUTCOME

- Breast cancer-specific survival: evaluated using multivariable Cox models

SECONDARY OUTCOMES

- Predictors of chemotherapy use: evaluated by multivariable logistic regression
- Trends in use of chemotherapy over time



Patients Characteristics

		Chemotherapy				p value
		No / Unknown		Yes		
		N	%	N	%	
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%	

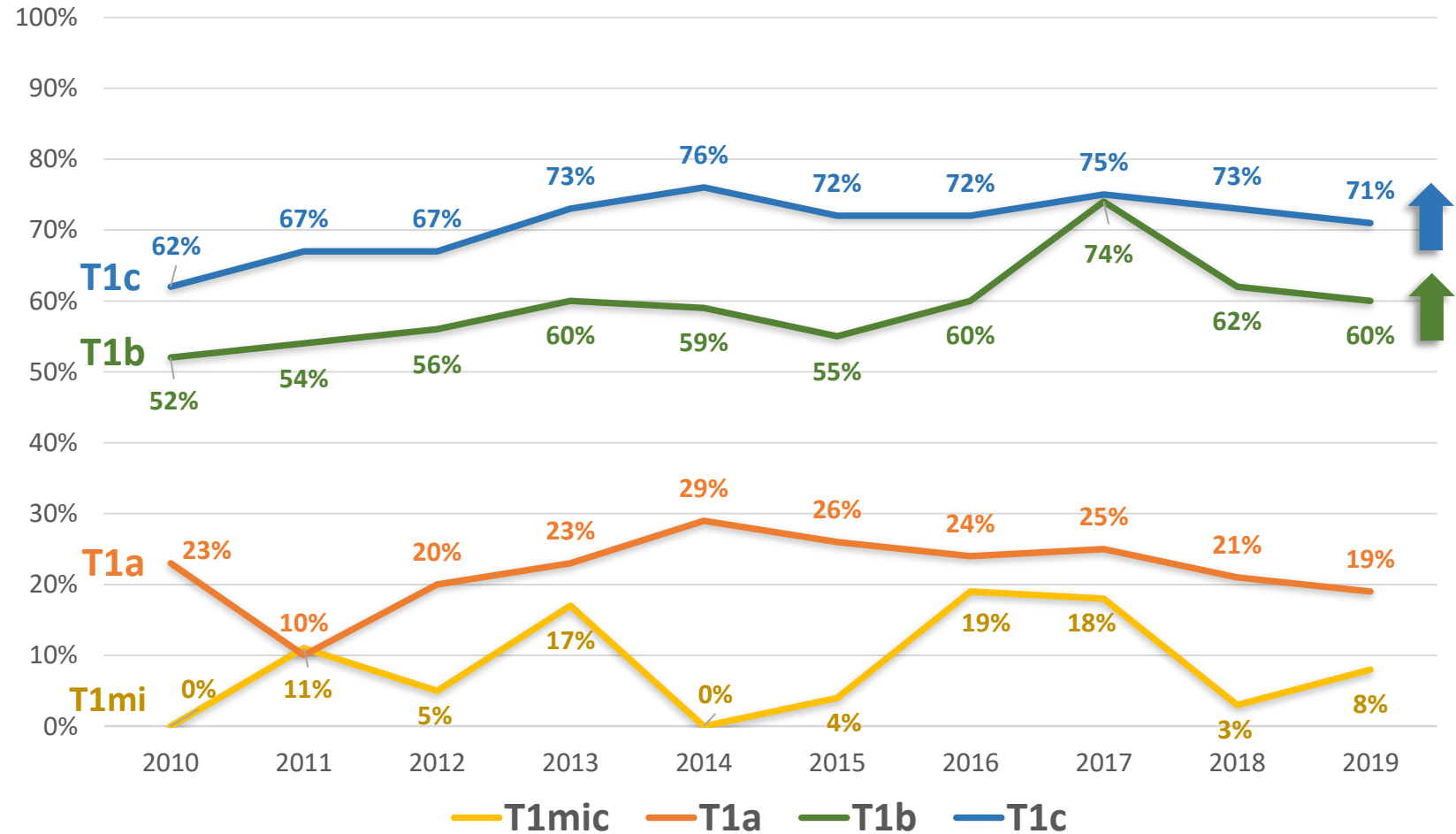
Predictors of Chemotherapy Use

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**)

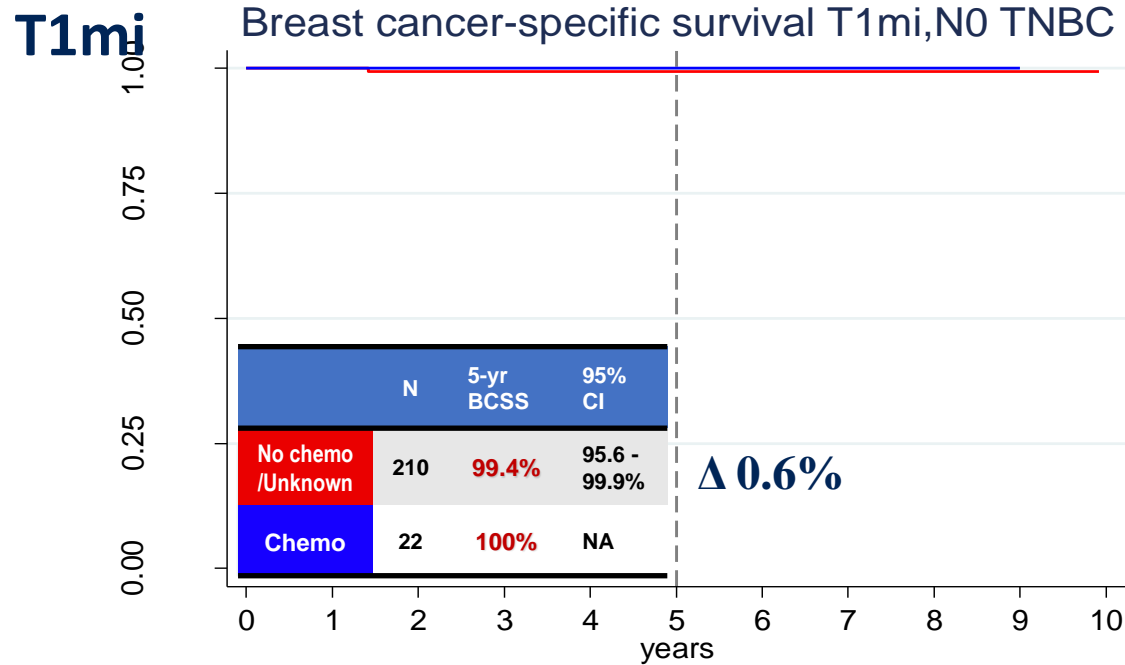
Use of Chemotherapy Over Time

- 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).

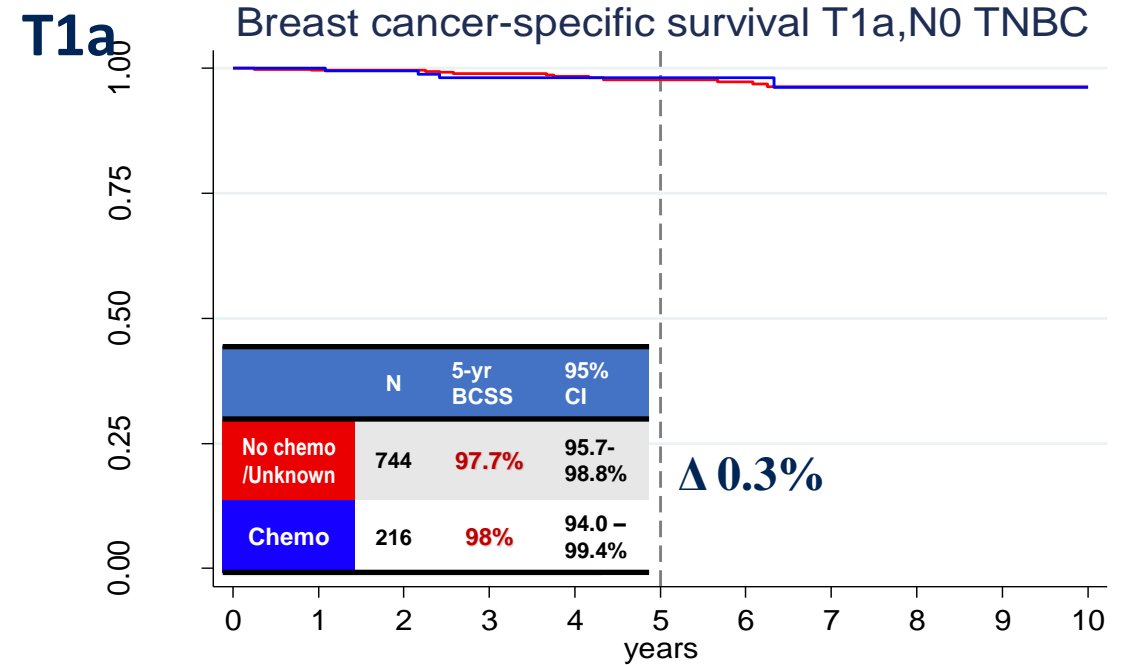


BCSS in Patients With T1mi & T1a TNBC

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



Number at risk	0	1	2	3	4	5	6	7	8	9	10
No or Unknown	210	175	144	118	97	75	57	41	27	11	0
Yes	22	19	19	12	8	6	6	3	2	1	0



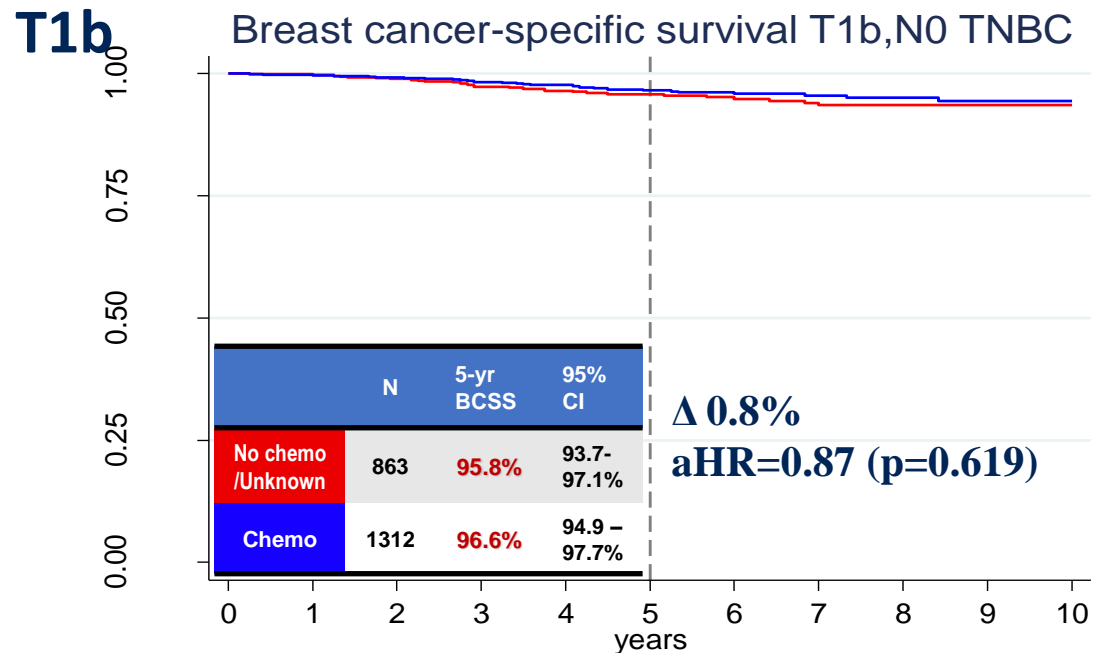
Number at risk	0	1	2	3	4	5	6	7	8	9	10
No or Unknown	744	622	500	409	327	261	202	142	86	37	2
Yes	216	182	151	124	103	77	57	37	20	14	1

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

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

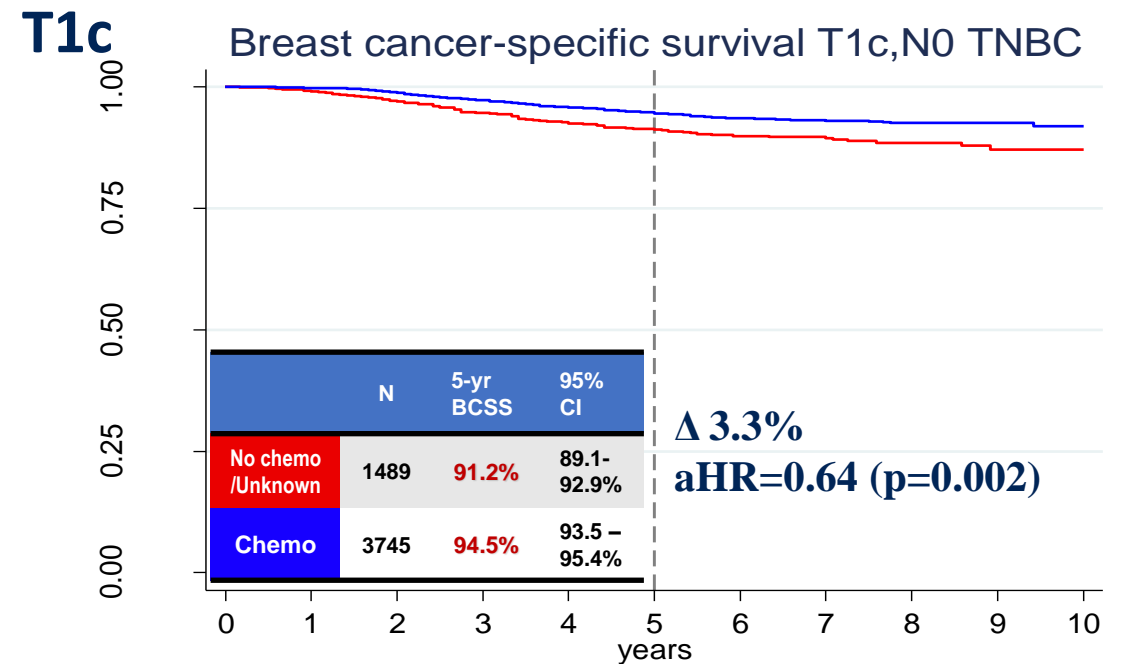
BCSS in Patients With T1b & T1c TNBC

- ✓ 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**)



Number at risk

	0	1	2	3	4	5	6	7	8	9	10
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



Number at risk

	0	1	2	3	4	5	6	7	8	9	10
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.

Manejo



T1a/b

Surgery followed by CT (SIZE, age and grade)

- Carboplatin and Taxanes
- AC-T



T1c

Neoadjuvant CT

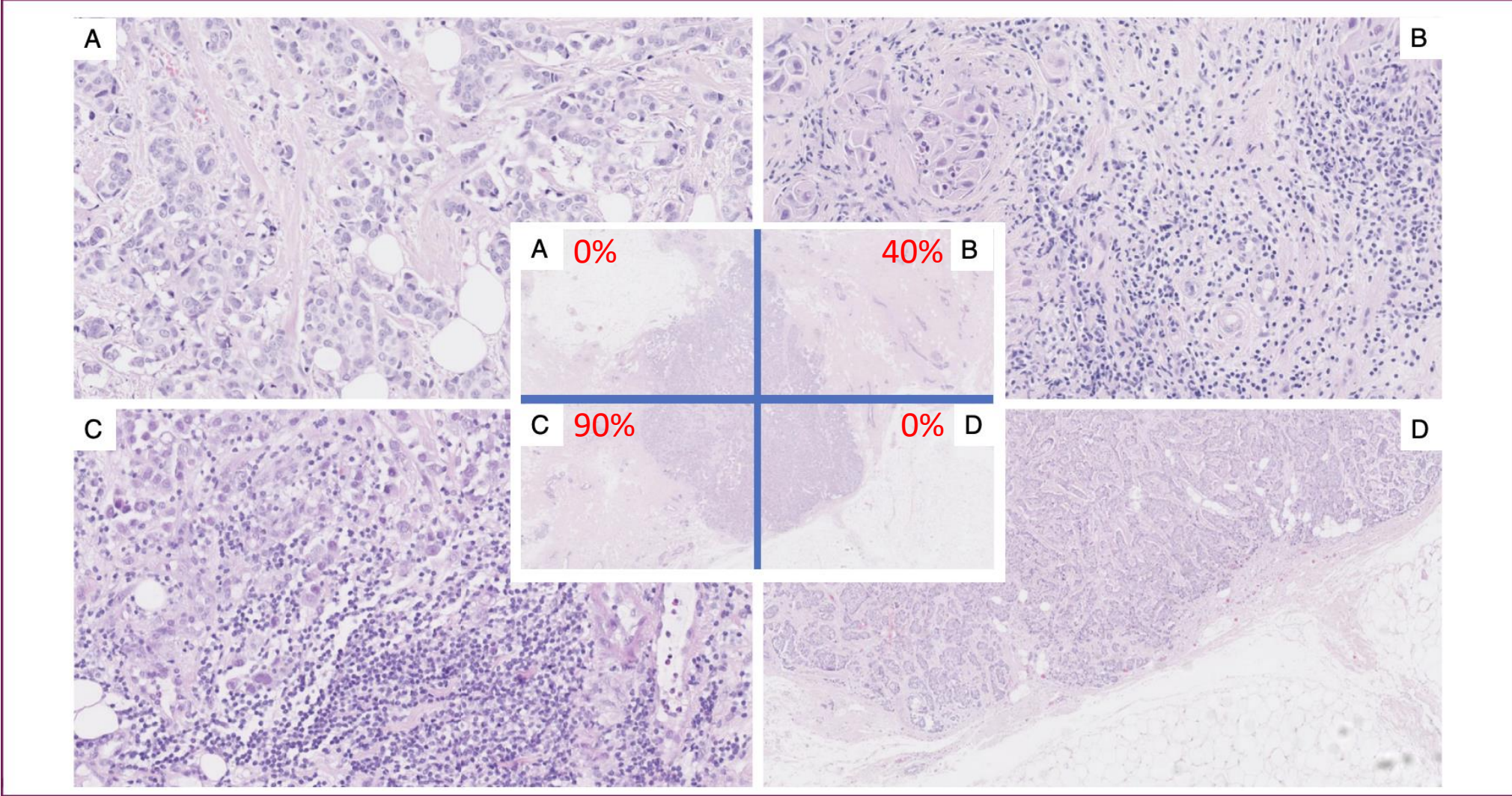
- AC-T
- Carboplatin and Taxane

How to select patients for chemotherapy?



Now

Tumor-infiltrating lymphocytes

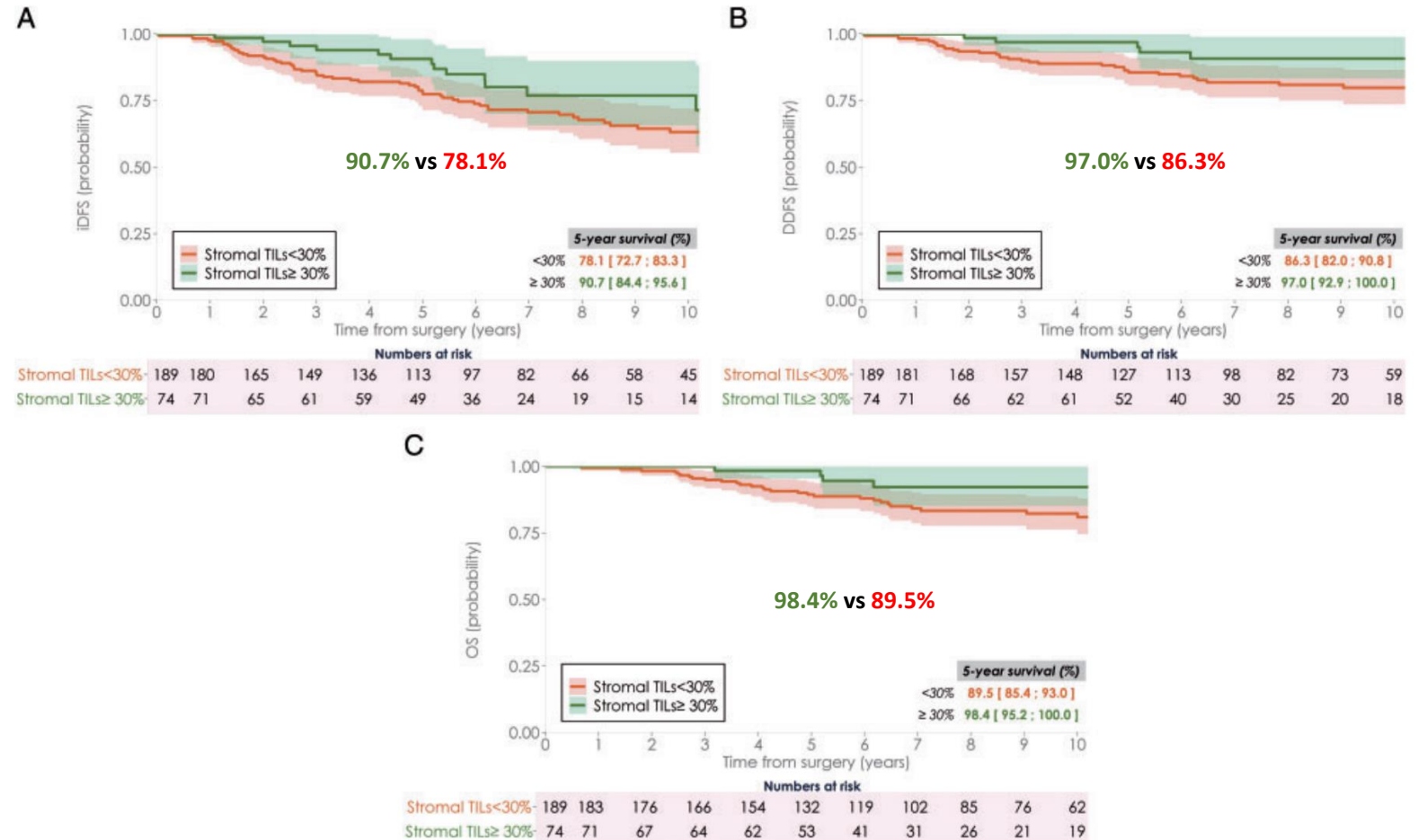


ORIGINAL ARTICLE

Prognostic value of tumor-infiltrating lymphocytes in patients with early-stage triple-negative breast cancers (TNBC) who did not receive adjuvant chemotherapy

J. H. Park^{1,2†}, S. F. Jonas^{3,4†}, G. Bataillon^{5†}, C. Criscitiello^{6†}, R. Salgado^{7,8}, S. Loi⁸, G. Viale⁹, H. J. Lee¹⁰, M. V. Dieci^{11,12}, S.-B. Kim¹, A. Vincent-Salomon^{5,13}, G. Curigliano^{6,14‡}, F. André^{15,16‡} & S. Michiels^{3,4*‡}

- Overall, 476 patients were included in the analysis from the 4 centers: GR (95), Curie (150), IEO (159), and Asan (72).
- Average age was 64 years (range 24-96 years), and 83% of patients were node-negative.



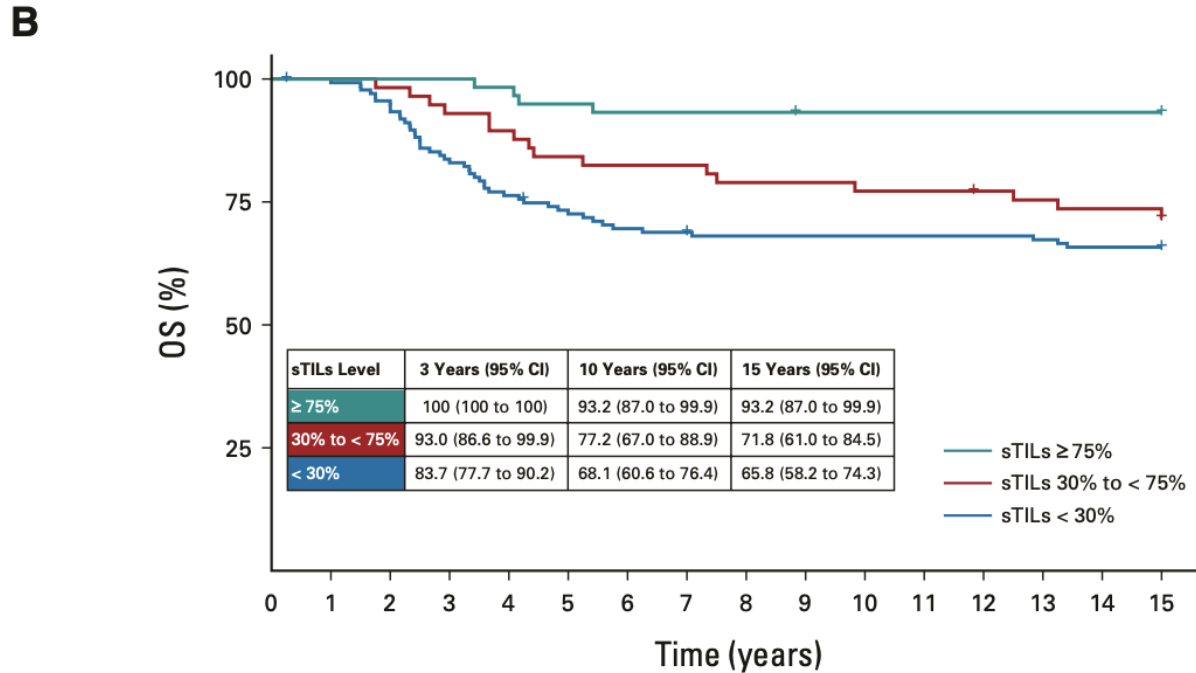
Prognostic Value of Stromal Tumor-Infiltrating Lymphocytes in Young, Node-Negative, Triple-Negative Breast Cancer Patients Who Did Not Receive (neo)Adjuvant Systemic Therapy

Vincent M.T. de Jong, MD¹; Yuwei Wang, MSc¹; Natalie D. ter Hoeve, BSc²; Mark Opdam, BSc¹; Nikolas Stathonikos, MSc²; Katarzyna Józwiak, PhD³; Michael Hauptmann, PhD³; Sten Cornelissen, BSc⁴; Willem Vreuls, MD⁵; Efraim H. Rosenberg, PhD⁶; Esther A. Koop, MD⁷; Zsuzsanna Varga, MD⁸; Carolien H.M. van Deurzen, MD⁹; Antien L. Mooyaart, MD⁹; Alicia Córdoba, MD¹⁰; Emma J. Groen, MD⁶; Joost Bart, MD¹¹; Stefan M. Willems, MD¹¹; Vasiliki Zolota, MD¹²; Jelle Wesseling, MD^{1,6,13}; Anna Sapino, MD^{14,15}; Ewa Chmielik, MD¹⁶; Ales Ryska, MD¹⁷; Annegien Broeks, PhD⁴; Adri C. Voogd, PhD^{18,19}; Sherene Loi, MD²⁰; Stefan Michiels, PhD²¹; Gabe S. Sonke, MD²²; Elsken van der Wall, MD²³; Sabine Siesling, PhD^{20,24}; Paul J. van Diest, MD²; Marjanka K. Schmidt, PhD^{1,25}; Marleen Kok, MD²²; Gwen M.H.E. Dackus, MD^{1,2}; Roberto Salgado, MD^{20,26}; and Sabine C. Linn, MD^{1,2,22}

TABLE 1. Characteristics of 441 Young, Systemically Untreated Triple-Negative Breast Cancer Patients According to the sTILs Percentage

Characteristic	Overall N = 441 (100%)	sTIL Percentage		
		< 30% n = 230 (52.2%)	30% to < 75% n = 117 (26.5%)	≥ 75% n = 94 (21.3%)
Age, years, median (IQR)	35 (32-38)	35 (32-38)	35 (32-38)	36 (33-38)
sTILs, median % (IQR)	20 (5-70)	NA	NA	NA
T stage, No. (%) ^a				
1 ^b	4 (0.9)	2 (0.9)	2 (1.7)	0 (0.0)
1a	2 (0.5)	1 (0.4)	1 (0.9)	0 (0.0)
1b	32 (7.2)	16 (7.0)	7 (6.0)	9 (9.6)
1c	218 (49.4)	119 (51.7)	49 (41.9)	50 (53.2)
2	175 (39.7)	89 (38.7)	52 (44.4)	34 (36.2)
3	10 (2.3)	3 (1.3)	6 (5.1)	1 (1.0)
Tumor grade, No. (%) ^c				
1	3 (0.7)	3 (1.3)	0 (0.0)	0 (0.0)
2	59 (13.4)	38 (16.5)	12 (10.3)	9 (9.6)
3	379 (85.9)	189 (82.2)	105 (89.7)	85 (90.4)
Histologic subtype, No. (%)				
Carcinoma NST	404 (91.6)	204 (88.7)	113 (96.6)	87 (92.6)
Metaplastic carcinoma	24 (5.4)	17 (7.4)	4 (3.4)	3 (3.2)
Others ^d	13 (3.0)	9 (3.9)	0 (0.0)	4 (4.2)
Lymphovascular invasion, No. (%)				
Absent	388 (88.0)	196 (85.2)	107 (91.5)	85 (90.4)
Present	53 (12.0)	34 (14.8)	10 (8.5)	9 (9.6)
Tumor <i>BRCA1</i> status, No. (%)				
Wild-type	277 (62.8)	143 (62.2)	76 (65.0)	58 (61.7)
Mutated	103 (23.4)	52 (22.6)	25 (21.3)	26 (27.7)
Not evaluable	61 (13.8)	35 (15.2)	16 (13.7)	10 (10.6)

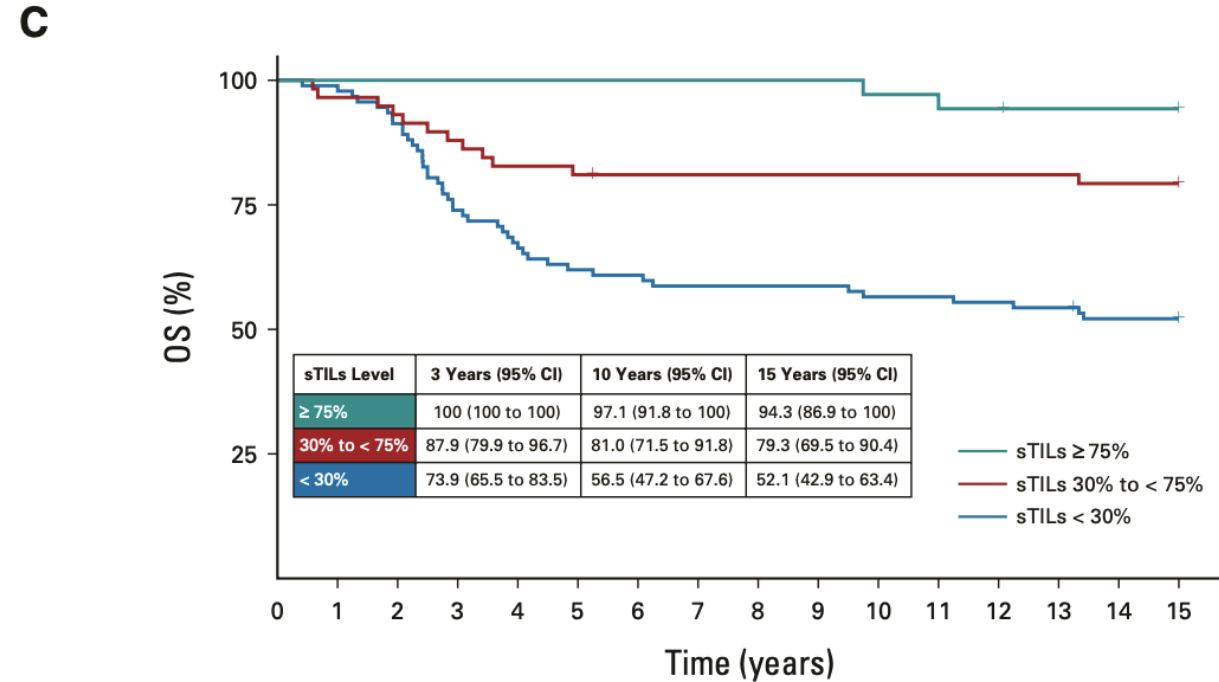
Kaplan-Meier curves for OS according to sTILs categories and T stage:



No. at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
sTILs < 30%	136	134	128	113	103	97	93	92	90	90	90	90	90	89	87	87
sTILs 30% to < 75%	57	57	56	53	51	48	47	47	45	45	44	44	43	42	41	40
sTILs ≥ 75%	59	59	59	59	58	56	55	55	55	54	54	54	54	54	54	54

Stage I

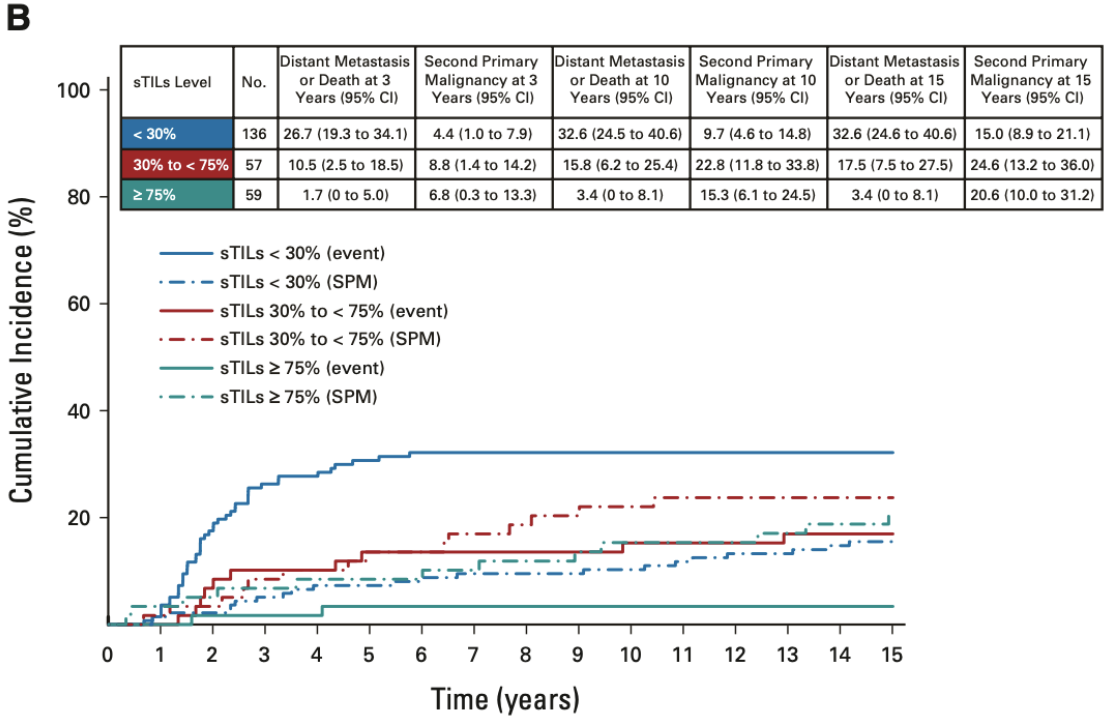


No. at risk:

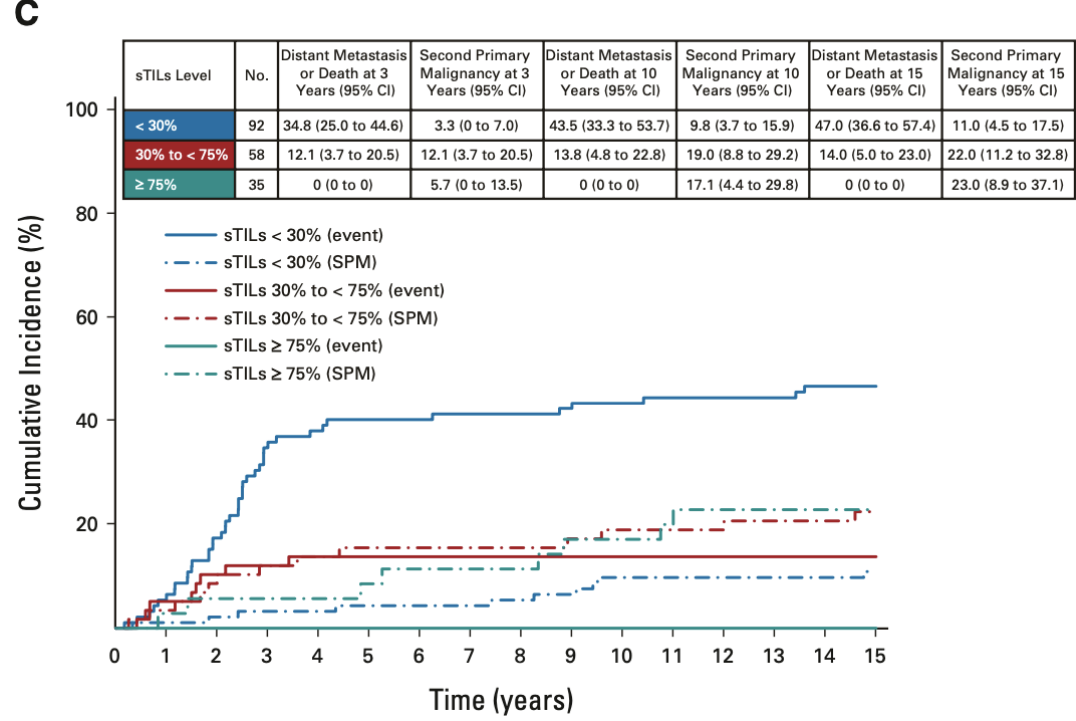
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
sTILs < 30%	92	91	84	68	62	57	56	54	54	54	52	52	51	50	47	47
sTILs 30% to < 75%	58	56	54	51	48	47	46	46	46	46	46	46	46	46	45	45
sTILs ≥ 75%	35	35	35	35	35	35	35	35	35	35	34	34	33	32	32	32

Stage II

Cumulative incidence functions for distant metastasis or death and second primary malignancy according to sTILs categories and T stage

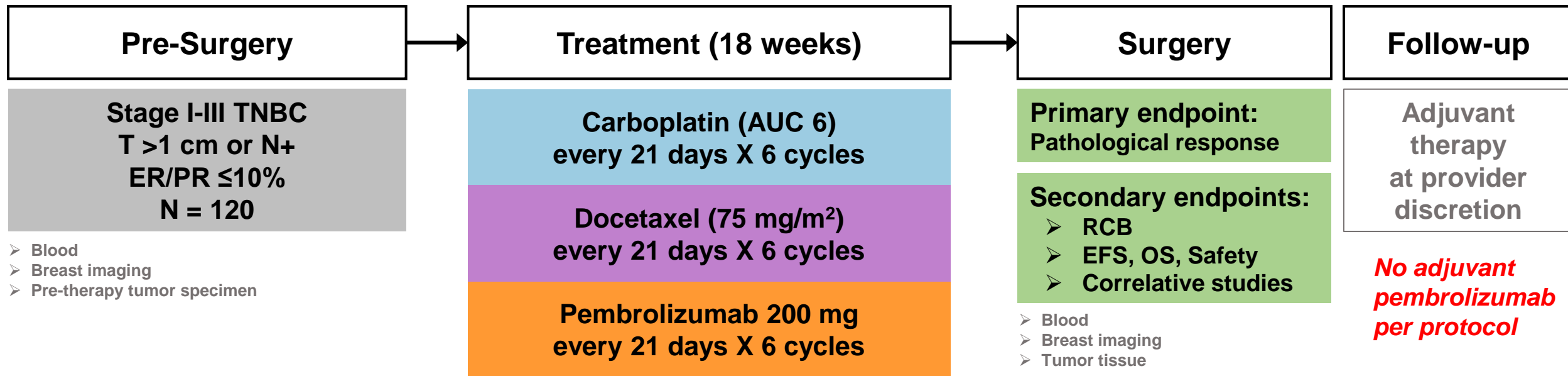


Stage I



Stage II

Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)

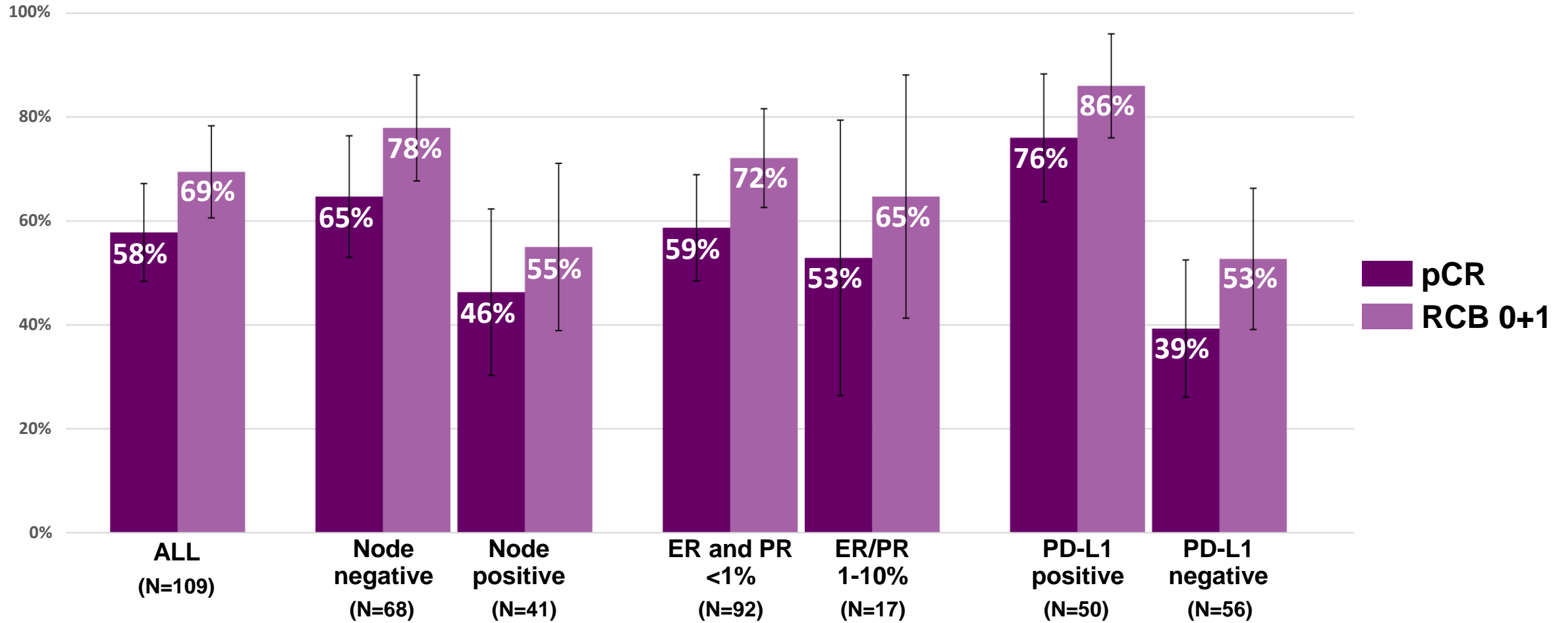


Sites: University of Kansas and Baylor University Medical Center



THE UNIVERSITY OF KANSAS
CANCER CENTER

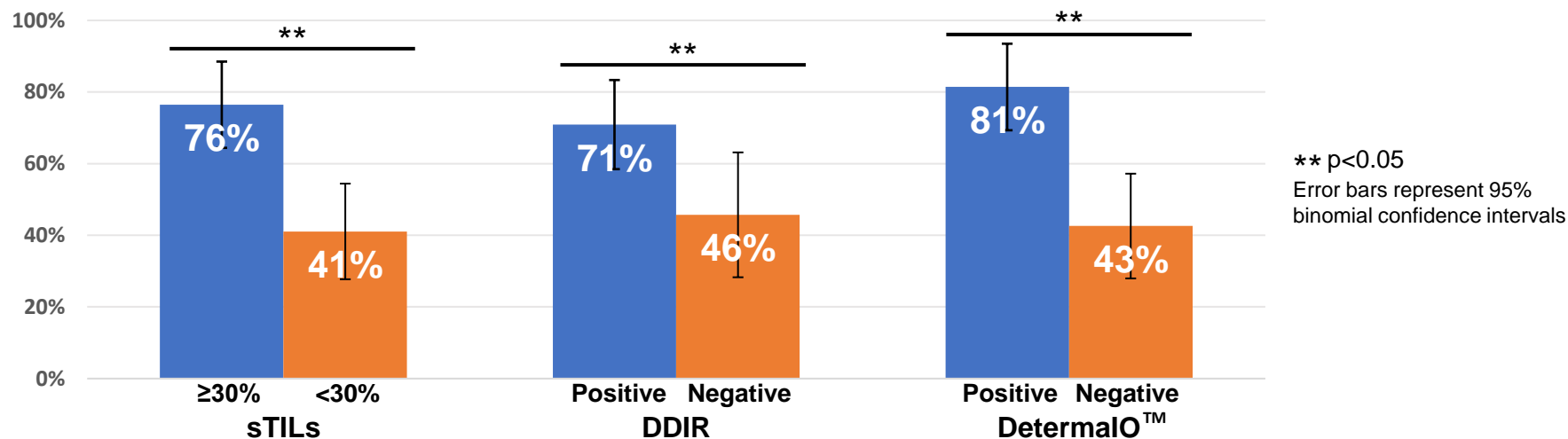
RESULTS: Pathologic response



- Among patients with stage II-III disease and ER & PR IHC <1%, pCR and RCB 0+1 rates were 59% and 69%, respectively.
- pCR in TNM stage I, II, and III disease was 69%, 59%, and 43%, respectively.

Error bars represent 95% binomial confidence intervals

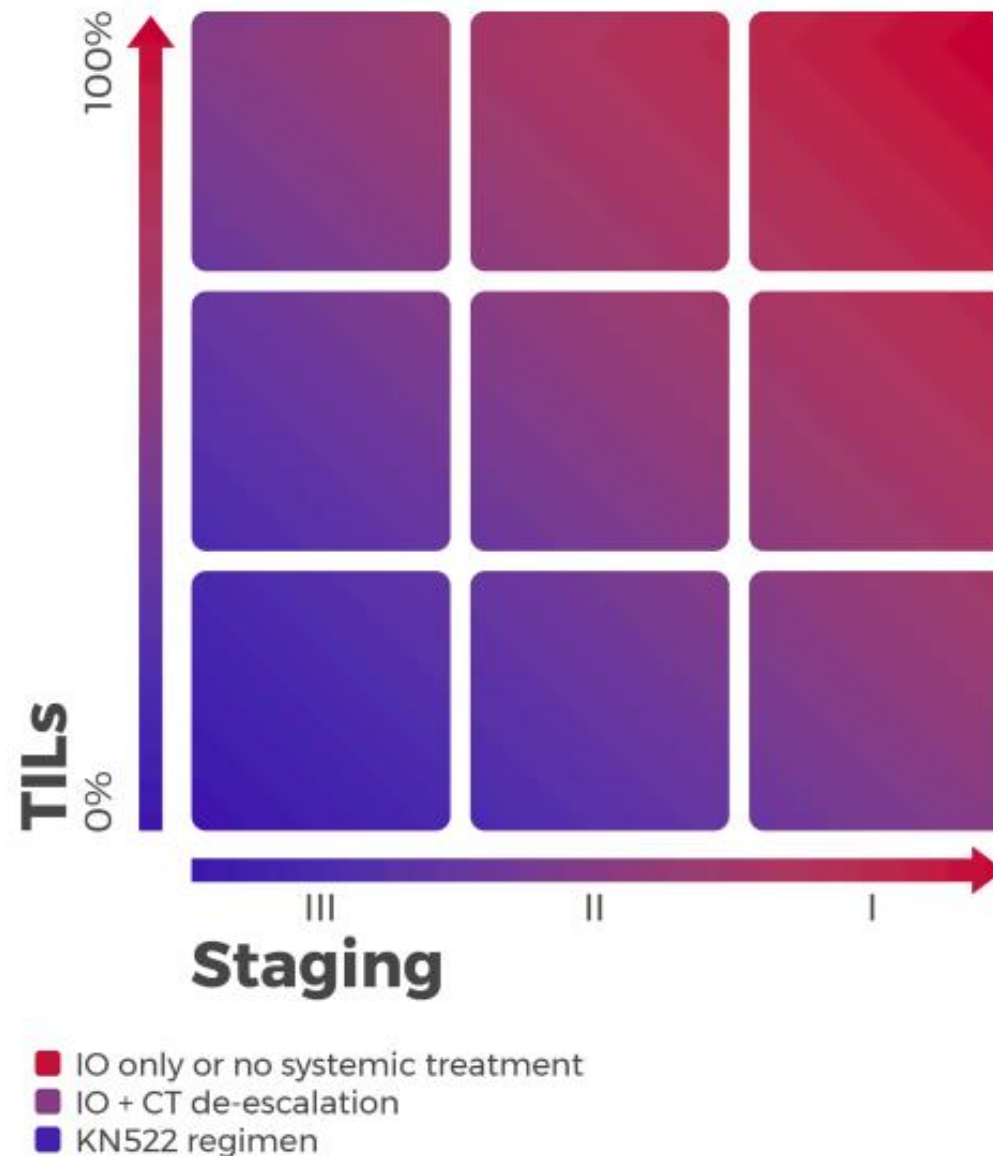
Pathologic response by immune markers



Univariable analysis								
Variable ^a			pCR			RCB 0+1 ^b		
			Frequency	OR (95% CI)	p	Frequency	OR (95% CI)	p
sTILs	≥ 30%	51/107 (48%)	39/51 (76%)	4.66 (2.02-10.78)	<0.001	41/51 (80%)	2.73 (1.14-6.57)	0.025
	< 30%	56/107 (52%)	23/56 (41%)	1		33/55 (60%)	1	
	Every 10% absolute increase		–	1.28 (1.12-1.47)	<0.001	–	1.19 (1.03-1.37)	0.017
DDIR	Positive	55/90 (61%)	39/55 (71%)	2.90 (1.20-7.00)	0.018	44/55 (80%)	2.80 (1.08-7.24)	0.034
	Negative	35/90 (39%)	16/35 (46%)	1		20/34 (58%)	1	
	Every 0.10 absolute increase		–	1.30 (1.09-1.55)	0.003	–	1.29 (1.07-1.55)	0.007
DetermalO™	Positive	43/90 (48%)	35/43 (81%)	5.91 (2.26-15.45)	<0.001	37/43 (86%)	4.34 (1.53-12.32)	0.006
	Negative	47/90 (52%)	20/47 (43%)	1		27/46 (59%)	1	
	Every 0.20 absolute increase		–	1.46 (1.18-1.80)	0.001	–	1.38 (1.10-1.73)	0.005

^a sTILs data available for n=107. DDIR and DetermalO™ data available for n=90. ^b RCB 0+1 data available for n=108.

How to use
TIL in clinical
practice?



EORTC 2257: OPTimisation of treatMent for pAtients with low stage triple-negative breast cancer patients with high sTIL (OPTimal)

PI: Marleen Kok, NKI, Netherlands
Key-pathologist: Roberto Salgado

Primary endpoint

DRFS (97% at 3-yrs considered a success)

Status

- Synopsis approved by EORTC
- Funding in place to start in the Netherlands
- Under consideration by ECOG
- Grant writing ongoing for European countries (interest from Belgium, Germany, Italy, Ireland)
- Also interest: Australia, Japan

Registration before surgery

- TNBC (ER 0-9%, HER2-negative)
- cT1abcN0
- sTIL \geq 50% on diagnostic biopsy (sTIL \geq 75% for age below 40) – local pathologist

Central confirmation of sTIL on biopsy

surgery

pT1abc

Off-study: pT2, pN1

Central confirmation of sTIL on resection material

Patient preference

Optimisation cohort, n=272

Control cohort, capped at n=272

Radiotherapy and surveillance

Radiotherapy and chemotherapy as per local standard

Alternative registration after surgery

- TNBC (ER 0-9%, HER2-negative)
- pT1abcN0
- sTIL \geq 50% on resection (sTIL \geq 75% for age below 40) – local pathologist

Other possible designs for de-escalation in small TNBC

- Less chemotherapy (< 6 cycles)
- Less CT plus IO
- ADCs instead of CT (de-escalation?)
- PARP inhibitors for BRCA mutated patients

How to select patients for chemotherapy?



Obrigado

Romualdo.sousa.ext@dasa.com.br



@DR.ROMUALDOBARROSO



Romualdo Barroso

MD, PhD Medical Oncologist at
DASA Oncology

