AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino
SC FORMAZIONE PERMANENTE
E RAPPORTI CON L'UNIVERSITÀ

CPO
Centro di Riferimento per l'Epidemiologia
e la Prevenzione Oncologica in Piemonte

rete oncologica

PREVENZIONE PIEMONTE

REGIONE PIEMONTE

EVENTO FORMATIVO RESIDENZIALE

WORKSHOP

14 DICEMBRE 2023

ORE 8.30 - 16.30

AULA MAGNA DOGLIOTTI
CORSO BRAMANTE, 88/90 - TORINO

CRPT - PROGRAMMA REGIONALE DI SCREENING PER IL TUMORE DELLA MAMMELLA

PREVENZIONE SERENA

LO SCREENING PER LA MAMMELLA

ore 11.30 DISCUSSIONE **Franca Artuso, Annalisa Castella**

3ˆ SESSIONE "DAI PIÙ BUONI ... AI PIÙ CATTIVI"
Moderano: **Corrado De Sanctis, Francesca Pietribiasi**

ore 11.40 **Aspetti epidemiologici**
Stefano Rousset

ore 11.55 **Dalla parte dell'anatomo-patologo**
Isabella Castellano

ore 12.10 **Dalla parte dell'oncologo**
Anna Vandone

ore 12.25 **Dalla parte del chirurgo**
Maria Grazia Baù

ore 12.40 **Dalla parte delle associazioni**
Valeria Martano

ore 12.55 DISCUSSIONE **Corrado De Sanctis, Francesca Pietribiasi**

Dalla parte del chirurgo….

Modulazione chirurgica in base al grado di «malvagità» ?

- Cosa intendiamo per bontà o malvagità di una neoplasia mammaria ?
- Contesto di tumori screening- detected
- I tumori della mammella *screen-detected* mostrano una prognosi più favorevole, in media, rispetto ai cancri sintomatici, grazie a uno stadio più precoce alla diagnosi e a un *grading* più differenziato . I cancri intervallo hanno più probabilità di essere di alto grado o di avere i recettori per gli estrogeni negativi rispetto ai tumori individuati con lo screening

Paci E, Ponti A, Zappa M, et al. Early diagnosis, not differential treatment, explains better survival in service screening. *Eur J Cancer* 2005;41(17):2728-34.

- Lo stadio, come atteso, mostra una distribuzione nettamente più favorevole nelle donne che partecipano allo screening, le quali hanno cancri in stadi più precoci; tuttavia l'anticipazione diagnostica non sembra modificare l'immunofenotipo, almeno per quanto la potenza statistica di questo campione permetta di valutare.

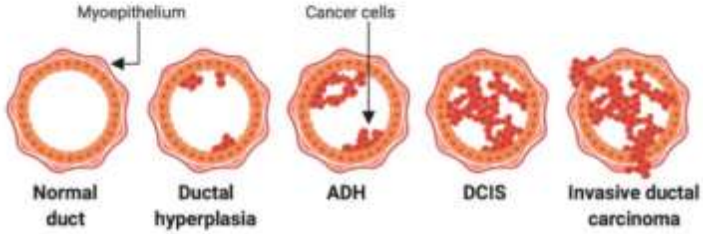
(Studio screening Emilia Romagna)

«grado di bontà e cattiveria, bruttezza?»

Current risk categories

Histologic groups based on future invasive cancer risk (Tice et al JNCI, 2013):

1. Non-proliferative lesions
2. Proliferative changes without atypia
   - Papilloma or papillomatosis
   - Usual ductal hyperplasia
   - Radial scar
   - Columnar cell hyperplasia
   - Hyperplasia NOS, complex fibroadenoma, flat epithelial atypia, blunt duct adenosis
3. Proliferative changes with atypia
   - Atypical ductal and lobular hyperplasia
   - Atypical hyperplasia, NOS
   - Intraductal papilloma with atypia
4. Lobular Carcinoma *In Situ*



CLIS, iperplasia atipica et al.

- Iniziamo con i più, più buoni
- CLIS (fattore di prognosi), iperplasia atipica

Che spazio ha la chirurgia ? ridotto

Ruolo della farmaco prevenzione (Karisma Trial, Anastrozolo tre volte la settimana)

Il carcinoma lobulare in situ (CLIS) è responsabile di circa un quarto delle forme di lesioni preinvasive della mammella. Non dà sintomi e non si vede alla mammografia; perciò, la sua diagnosi è sempre occasionale, quando si associa ad altre patologie mammarie che richiedono un intervento chirurgico

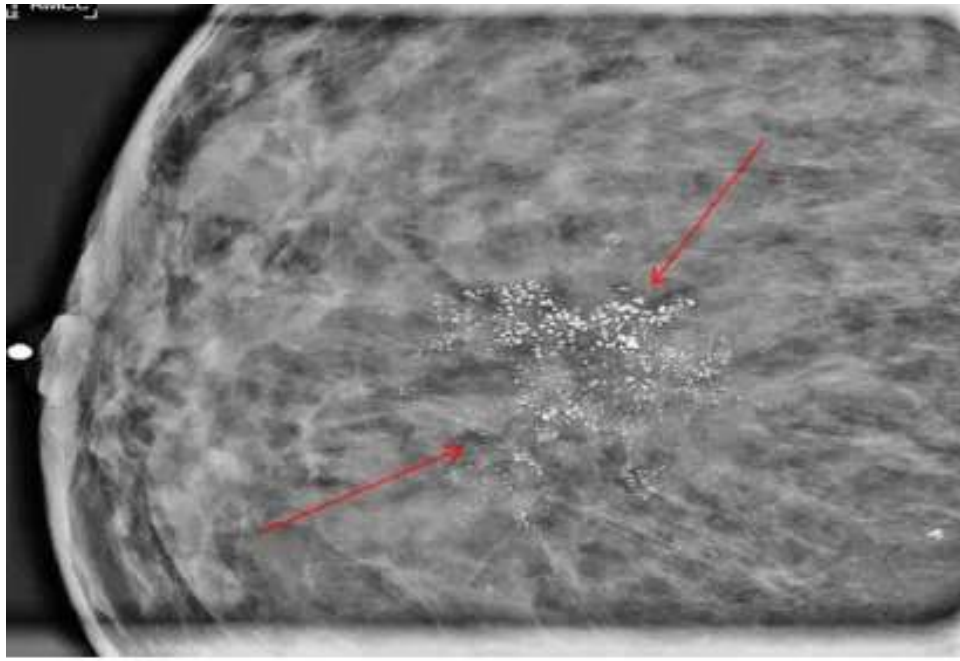
richiede approfondimento con RMN, non necessita quasi mai di asportazione chirurgica, però la letteratura concorda: va rimosso se c'è un nodo, un'area di distorsione, una lesione all'imaging

CDIS

Indicazione chirurgica

Sono in corso 2 trials sull'astensione dal trattamento chirurgico

Trial LORD e LORIS



mammografia - microcalcificazioni (CDIS)

Background: The Surgery Versus Active Monitoring for Low-Risk DCIS (LORIS) trial is studying the safety of monitoring core-biopsy diagnosed low-risk ductal carcinoma in situ (DCIS) without excision. We sought to determine the incidence and characteristics of synchronous invasive carcinoma found in LORIS-eligible women who underwent excision, as this knowledge is essential in assessing the safety of observation alone.
Methods: Women meeting LORIS eligibility criteria (age ≥46 years, screen-detected calcifications, non-high-grade DCIS diagnosed by core biopsy, absence of nipple discharge, or strong family history of breast cancer) who underwent surgical excision from 2009 to 2012 were identified. Histologic findings of excision specimens were reviewed.
Results: Overall, 296 LORIS-eligible cases were identified; 58 (20 %) had invasive carcinoma on final pathology (90 % invasive ductal, 78 % >1 mm in size, 21 % high grade, 3 % triple negative, 9 % HER2 amplified). Of these, 18 (31 %) were pT1b or larger and 3 (5 %) were pN1. Among eligible upgraded cases, 90 % received radiation, 89 % received endocrine therapy, and 18 % were recommended chemotherapy. Women upgraded to invasive carcinoma were more likely to have intermediate-grade DCIS on core biopsy and to have undergone mastectomy.
Conclusions: Among LORIS-eligible women, 20 % had invasive carcinoma at surgical excision that was heterogeneous in grade, size, and receptor status. Information gained from surgical excision influenced receipt of adjuvant radiation and endocrine therapy in most patients, and indicated benefit from chemotherapy in 18 % of patients. Surgical excision is warranted until additional risk stratification is available to identify a cohort of DCIS patients at lower risk for clinically significant synchronous invasive carcinoma.
M. Morrow Ann. Surg. Oncology 2016 Oct. 23(11) 3487-3493

- Anche tra le forme invasive esiste una gradualità

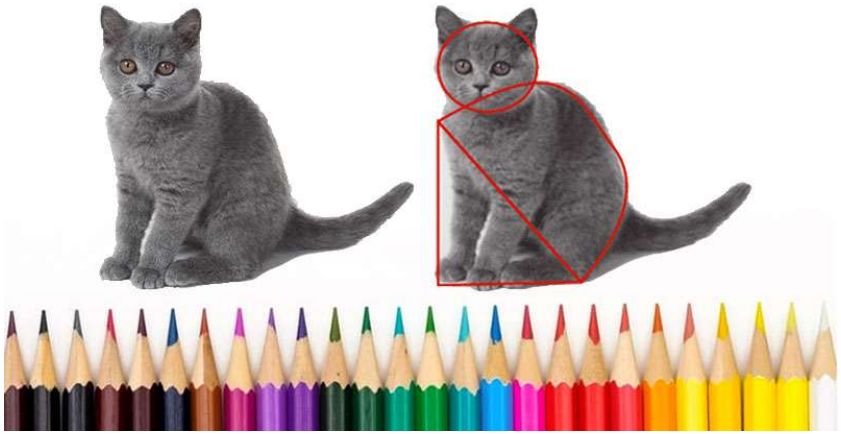
- I « buoni»:
- Tumori Tubulari e tumori adenoideo cistico, midollare e mucinoso: omissione del linfonodo sentinella

Mediamente buoni

- Luminal A e B

Dalla parte del chirurgo: tipologia di trattamento cosa può fare il chirurgo-> Modulare la chirurgia

Strumenti del chirurgo



- Ampia resezione: indipendente dai fattori prognostici
- Mastectomia: dimensione- dipendente
- chirurgia dell'ascella (axillary staging): Oggetto di dibattito più recente

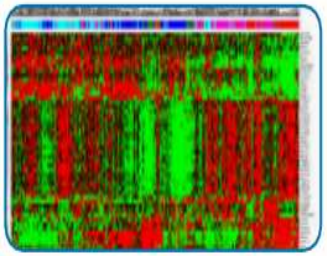
Why Do We Stage the Axilla?

- Improve Survival
- Necessary for Local Control
- Inform adjuvant therapy

No
No in cN0
Sometimes

Study	FNR/Nodes Left Behind	Nodal Recurrence	OS
NSABP B32	10%	0.7%	NS
Milan	9%	0	NS
ACOSOG Z0011	27%	1.1%	NS
AMAROS	33%	1.6%	NS

Fisher B, N Engl J Med 20
Krag D, Lancet Oncol 201
Veronesi U, N Engl J Med
Giuliano A, Ann Surg 2016
Bartels S, J Clin Oncol 20



Decisions for systemic therapy increasingly based on receptor subtype

- Nodal status less important in determining systemic therapy recommendations, particularly in HR+/HER2- breast cancer

	McCartan	Lee
# patients	5362	3363
T size	T1-3	T1-2
Menopausal status	Any	Post
Macrometastases	19%	23%
pN2/3	6%*	3.6%

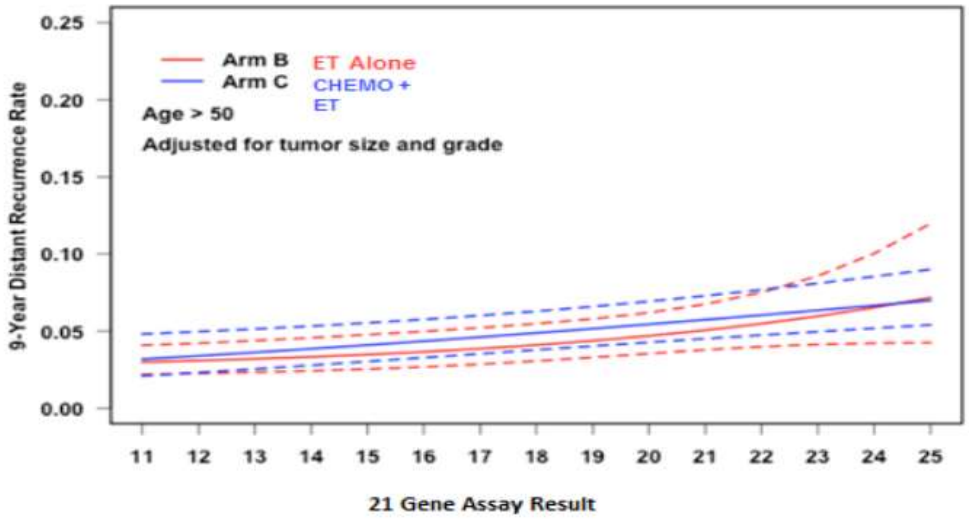
*> 2+ nodes

McCartan D, Ann Surg Oncol 2016;25:3324 Lee M, Ann Surg Oncol 2023;30:92

Nodal Status Not the Primary Determinant of Therapy Postmenopausal HR+/HER2-

TAILORx

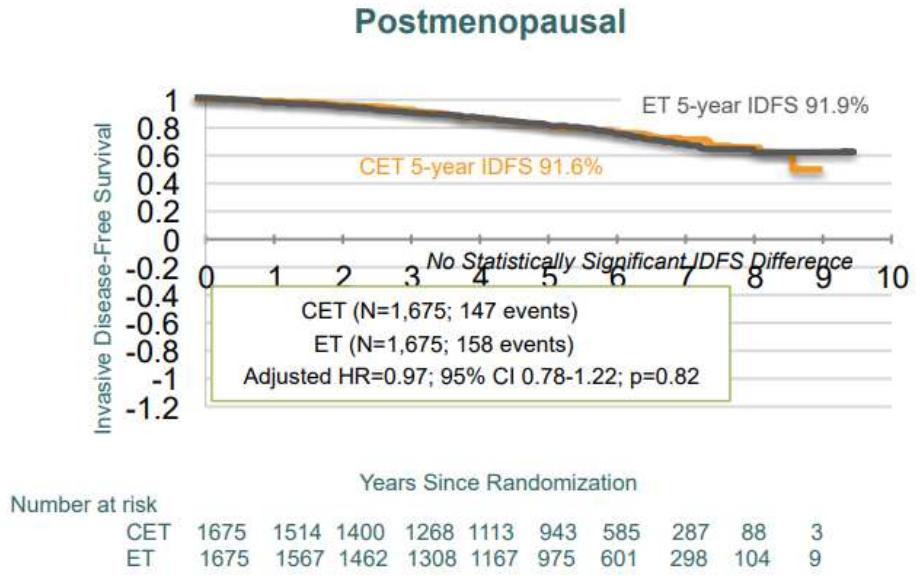
RS 11-25



Sparano J, N Engl J Med 2018;379:111

RxPONDER

RS 0-25



Kalinsky K, N Engl J Med 2021;385:2336

Omettere la BLS > 70 aa (Studio SOUND)

	n	Age	Eligibility	Median f/u (years)	Nodal recurrence
CALBG 9343	200	≥ 70	cT1N0	12.6	3%
IBCSG 10-93	239	≥ 60	cN0	6.6	3%
Milan	110	≥ 65	cT1N0	5	1.8%

SSO Choosing Wisely	NCCN
Avoid SLNB	SLNB “optional”

Hughes K, J Clin Oncol 2013;31:2382 Rudenstam C, J Clin Oncol 2006;24:337 Martelli G, Ann Surg 2005;242:1

Il brutto e cattivo: tumore triplo negativo ed Herb2 +

La gestione del cancro al seno triplo negativo (TN) e HER2-positivo (HER2+) in stadio iniziale si è evoluta in modo significativo con il continuo miglioramento delle terapie sistemiche. L'uso della chemioterapia neoadiuvante (NAC) è diventato lo standard per la malattia in stadio II, sia per il downstaging chirurgico che per la valutazione della risposta al trattamento, consentendo la personalizzazione della terapia sistemica nel contesto adiuvante. Tuttavia, l'approccio terapeutico ottimale per la malattia TN e HER2+ in stadio I rimane controverso, dato il carico limitato di malattia alla presentazione, con la maggior parte dei pazienti considerati candidati per un intervento chirurgico limitato, e gli eccellenti risultati complessivi con regimi terapeutici sistemici ridotti nel contesto adiuvante.

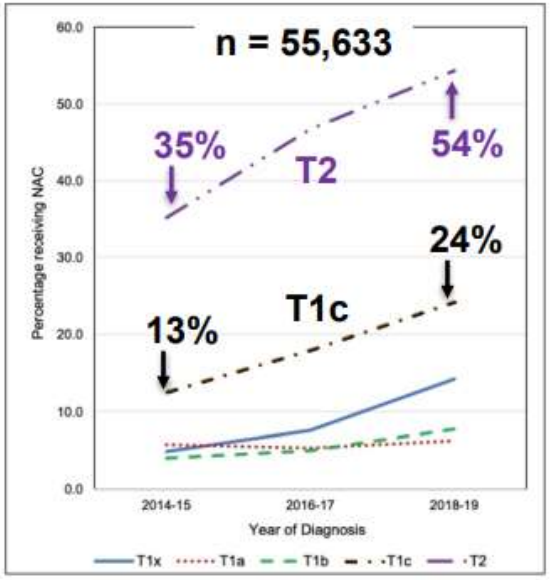
Un dilemma terapeutico moderno !

La chemioterapia neoadiuvante (NAC) è sempre più utilizzata nella TN e nella fase iniziale Malattia HER2+

- Studi randomizzati supportano l'uso della NAC nella malattia in stadio II:
  - Alti tassi di pCR
  - Miglioramenti in DFS/OS con la personalizzazione delle terapie adiuvanti se non pCR
- I pazienti allo stadio I costituiscono una piccolissima minoranza

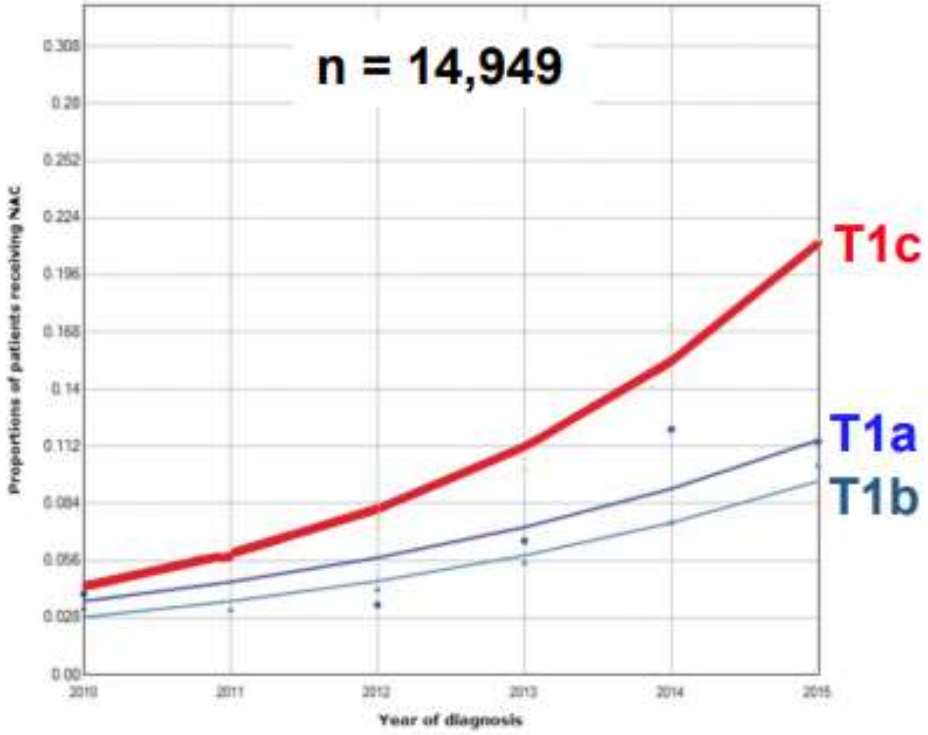
Use of NAC in Stage 1 and 2 TN Breast Cancer: NCDB

- Increasing use of NAC observed among **stage I** patients
- Rate of NAC:
  - 2014: 19.5%
  - 2019: 33.6%



Use of NAC in Stage 1 and 2 HER2+ Breast Cancer: NCDB

- Increasing use of NAC observed among **stage I** patients:
- Rate of NAC:
  - 2010: 4%
  - 2015: 17%
- Greatest annual percent change of **37.8%** among T1c subset



Leidman M, Breast Cancer Res Treat 2021

- Perché il dibattito?
- I regimi NAC possono comportare rischi di tossicità associata alla chemioterapia e all'immunoterapia senza benefici dimostrati dal passaggio alla terapia adiuvante pazienti in stadio I senza pCR
- • I regimi adiuvanti «descalated» hanno risultati eccellenti nello stadio patologico I malattia
- • Il downstaging chirurgico spinge a prendere in considerazione la NAC , ma la chirurgia del seno è raramente modificata
- Trattamento della malattia ascellare occulta?

Overview

- Data supporting NAC in **early-stage** TN and HER2+ disease
- De-escalation opportunities in **stage I** disease
- **Nodal disease burden** among cT1N0 patients
- **Need for ALND** in the cT1N0 TN and HER2+ population

NAC in Early-Stage TN and HER2+ Disease

- Stage II disease: improvements in pCR rates and a benefit from chemotherapy switch if non-pCR; data is lacking in stage I

- • TN subset: – CREATE-X – I-SPY2, KEYNOTE-522
- • HER2+ subset: – NEOSPHERE, TRYPHAENA, BERENICE, TRAIN-2 – KATHERINE

CREATE-X Trial

Stage I-III HER2– patients with non-PCR after NAC

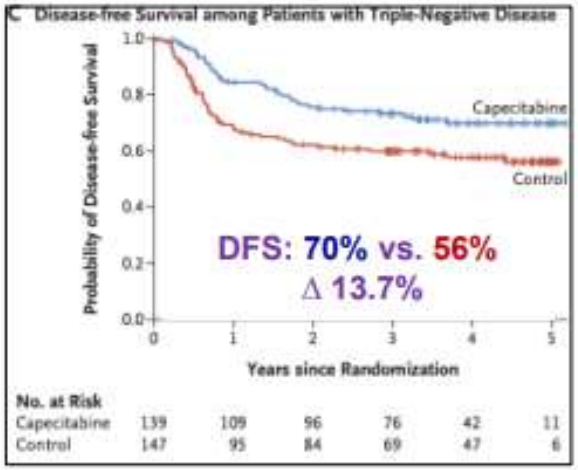
2007 - 2012

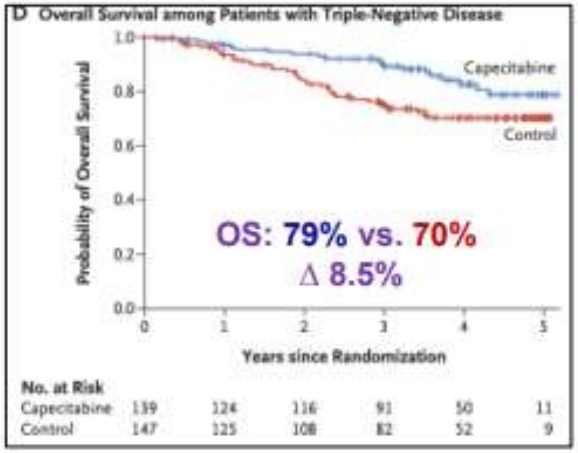
n = 887

→ Capecitabine x 6-8 cycles **n = 443**

→ Control **n = 444**

- 32% (n = 286) patients were TN
- Significant improvement in DFS and OS in TN subset **with capecitabine**
- **n = 38 (4.1%)** stage I patients included
- Validated in a meta-analysis of 12 RCTs including n = 15,457 patients



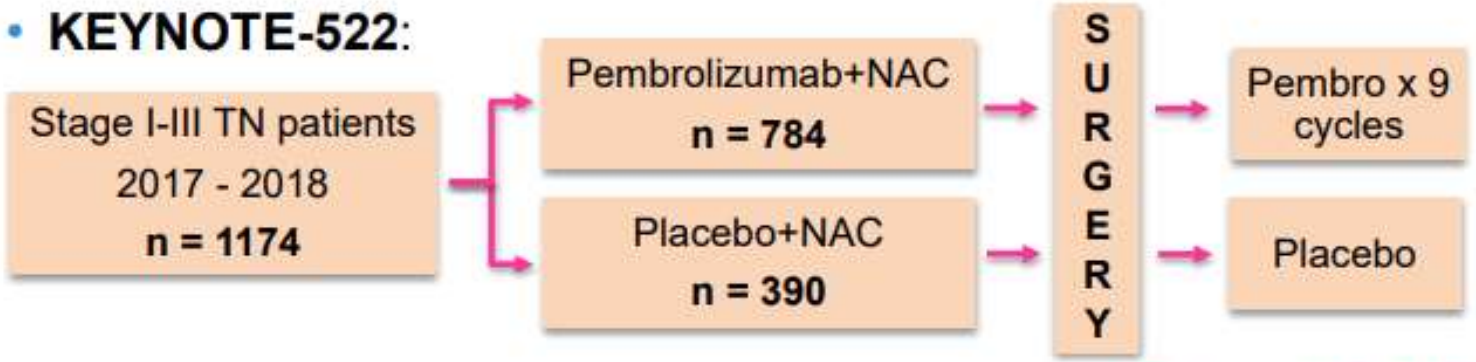


Masuda N, NEJM 2017
van Mackelenbergh, Eur J Cancer 2022

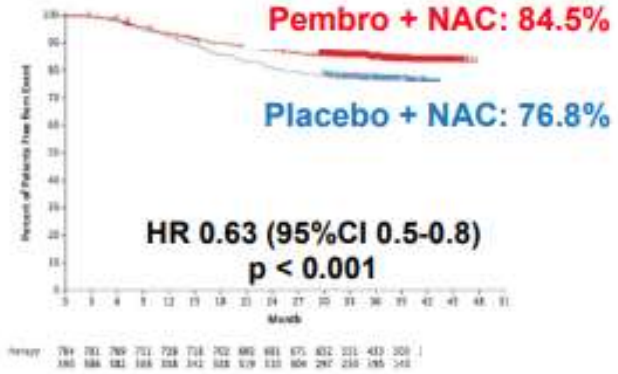
I-SPY2 and KEYNOTE-522 Trials

- **I-SPY2**: addition of pembrolizumab to standard NAC improved rates of pCR in TN patients, from **22% to 60%**

- **KEYNOTE-522**:



- **Improvement in 3-year EFS**
- Greatest benefit among **N+** patients (HR 0.65)
- **n = 1** stage I patient included



Nanda R, JAMA Oncol 2020
Schmid P, NEJM 2020 & 2022

Trials of Dual HER2-Blockade

- Early studies established neoadjuvant chemotherapy + trastuzumab in stage II-III HER2+ disease, and the prognostic value of pCR

Trial	n	Neoadjuvant Regimen	% pCR	% stage I
NEOSPHERE	417	Docetaxel+H Docetaxel + H + P H + P Docetaxel + P	29% **46%** 17% 24%	**0%**
TRYPHAENA	225	FEC + H + P → docetaxel + H + P FEC → docetaxel + H + P Docetaxel + carboplatin + H + P	**62%** **57%** **66%**	**0%**
BERENICE	400	ddAC → paclitaxel + H + P FEC → docetaxel + H + P	**62%** **61%**	**0%**

- Pertuzumab subsequently approved in 2013, and dual blockade has been standard for neoadjuvant HER2+ regimens
- **No evidence** to recommend neoadjuvant treatment with pertuzumab in **cT1N0** disease

Gianni, Lancet Oncol 2012
Schneeweiss, Ann Oncol 2013
Swan, Ann Oncol 2018
NCCN 2023: Gradishar W, J Natl Compr Canc Netw

KATHERINE Trial

Stage I-III HER2+ patients with non-PCR after NAC

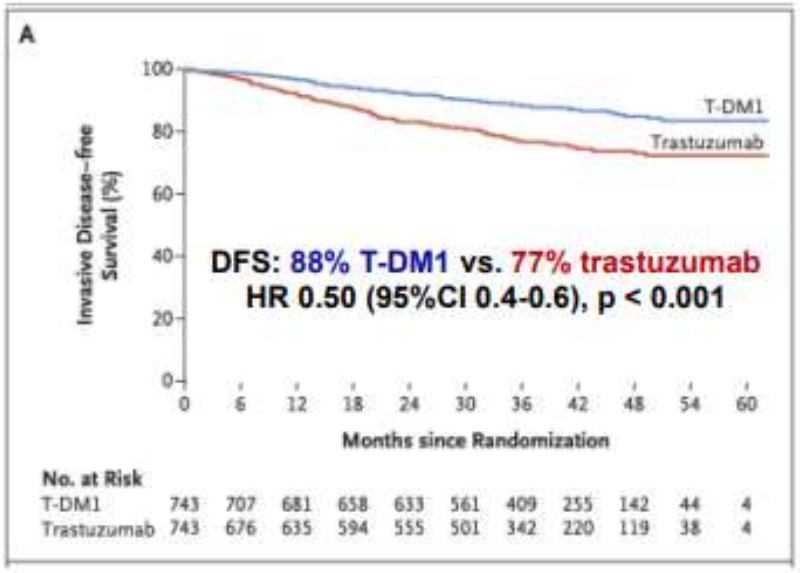
2013 - 2015

n = 1486

→ Trastuzumab x 14 cycles **n = 743**

→ T-DM1 x 14 cycles **n = 743**

- NAC regimens: chemotherapy including taxane + H +/- P
- Significant improvement in 3-year DFS with **switch to T-DM1**
- **n = 67 (< 5%)** stage I patients included



von Minckwitz G, NEJM 2019

Few Stage I Patients in NAC Trials

Trial	N	Design & Primary Finding	% of stage I patients
CREATE-X 2007-2012	887	RCT of stage I-III HER2- patients with non-pCR to NAC: improved OS/DFS in TN with **capecitabine** (vs placebo)	**4.1%** (n = 38)
KEYNOTE-522 2017-2018	1174	RCT of stage II-III TN patients: improved EFS with **pembrolizumab** + NAC > adjuvant pembro compared to NAC alone	**0.1%** (n = 1)
KATHERINE 2013-2015	1486	RCT of stage I-III HER2+ patients with non-pCR to NAC: improved DFS with receipt of **T-DM1** (vs HP)	**1.3%** cT1 (n = 19) **3.2%** cN0 (n = 48)

Masuda N, NEJM 2017
Schmid P, NEJM 2022
Von Minckwitz G, NEJM 2019

De-Escalation in Stage I: TN

CREATE-X Subset Analyses

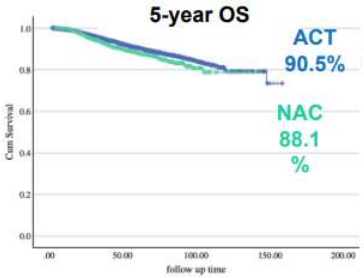
Subgroup	DFS	OS
cT1 at presentation (n = 129) n = 68 capecitabine vs. n = 61 control	HR 0.65 (CI 0.3-1.4, p = 0.8)	HR 0.63 (CI 0.1-2.8, p = 0.9)
Node-negative (n = 347) n = 176 capecitabine vs. n = 171 control	HR 0.87 (CI 0.5-1.6, p = 0.3)	HR 0.56 (CI 0.2-1.6, p = 0.2)

No benefit from capecitabine in cT1 or pN0 TN tumors

Survival Outcome of NAC vs Adjuvant Chemotherapy in cT1N0 TN

NCDB Analysis

- n = 48,329 patients treated from 2006 to 2016
  - Compared NAC (n = 3,455) vs. adjuvant ACT (n = 32,066)
- Similar 5-year OS with adjuvant ACT vs. NAC
  - T1a, T1b, T1c subsets
- Upfront surgery permits a nuanced approach to adjuvant therapy without compromise in outcomes



Huang K, Ann Surg Oncol 2023

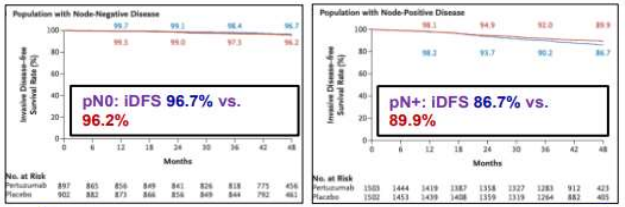
De-Escalation in Stage I: HER2+

APHINITY Trial: Adjuvant Pertuzumab and Trastuzumab

Operable HER2+
n = 4805

- Adjuvant chemo + 1 year trastuzumab
  n = 2405
- Adjuvant chemo + 1 year trastuzumab + pertuzumab
  n = 2400

- Median follow-up of 8.4 years



No benefit from dual-agent therapy in the pN0 subset

Von Minckwitz G, NEJM 2017

- Dati a supporto della NAC nella malattia TN e HER2+ in stadio iniziale …
- Opportunità di de-escalation nella malattia in stadio I…

- **Nodal disease burden** among cT1N0 patients
- **Need for ALND** in the cT1N0 TN and HER2+ population

Nodal Burden in cN0 TN and HER2+

- Contemporary series of nodal burden at upfront surgery:

Study	Design	Finding
Lee et al 2006-2011	**T1-T2**, cN0, postmenopausal n = 402 TN n = 297 HER2+	Rate of pN2-3 disease similar among subtypes: **3.5% in TN and 4.4% in HER2+**
Mamtani et al 2020-2022	**T1**, cN0 n = 218 TN n = 288 HER2+	Rate of pN1 disease: 9.5% **Rate of pN2-3 disease: 1.5%**
Mittendorf et al (DFCI) 2016-2021	**T1-T2**, cN0 n = 343 TN	**Any positive nodes:** **cT1a/b: 9%** **cT1c: 16%** cT2: 21%
Mittendorf et al (NCDB) 2016-2021	**T1-T2**, cN0 n = 46,015 TN	**Any positive nodes:** **cT1a/b: 5%** **cT1c: 11%** cT2: 20%

Lee M, Ann Surg Oncol 2023
Mittendorf E, Ann Surg Oncol 2023
Mamtani A, manuscript under review 2023

Decreasing Use of ALND in cN0 Disease

- ACOSOG Z0011 trial: established **safe omission of ALND** in cT1-2N0 patients with 1-2 +SLN having BCT
  - No difference in 10-year DFS and OS
  - < 2% regional recurrence after SLNB only
- Subsequently validated in the mastectomy setting (AMAROS, OTOASOAR)
- Omission of ALND among cN0 patients with limited nodal disease at upfront surgery has significantly reduced surgical morbidity

Value in Identifying TN Nodal Disease *Mittendorf E*

KEYNOTE-522: greatest benefit of NAC + pembrolizumab among node-positive TNBC

• Mittendorf et al sub-analysis:

– cT1-2N0 TN with negative clinical examination, n = 499

– Axillary US performed at physician discretion: n = 170 (34%)

– Rate of detection of occult nodal disease: cT1c: 7.5%, cT2: 9%

– Rate of detection among n = 19 cT1c with routine US: 5.3%

• Must also weigh operator variability, false-positives

• Value in risk stratification and identification of those that may benefit from immunotherapy

Rates of ALND in cN0 TN and HER2+

- Limited data in the T1N0 subset

Study	Design	% ALND
Mamtani et al 2010-2015	c**T1-2**N0 patients having upfront BCT with +SLN High-risk (**TN, HER2+, age < 50**) subset: N = 242	**15%**
Morrow et al 2010-2016	cT1-2N0 patients having upfront BCT with +SLN Dedicated axillary imaging not routine TN or HER2+ subset: N = 125	**16%**

- Increasing (T2) tumor size is associated with higher nodal burden

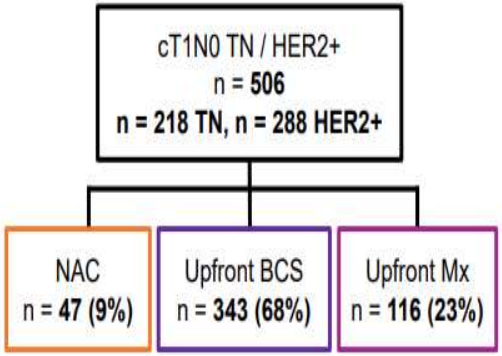
- Low rates of ALND in the early-stage cN0 TN and HER2+ subset

mtani A. Ann Surg Oncol 2016

Which Approach Minimizes ALND?

MSKCC Experience

Consecutive cT1N0 TN and HER2+ patients
Treated Jan 2020 – Dec 2022



Indications for ALND: Any +SLN after NAC, for ≥ 3 +SLN at upfront surgery, or 1-2 +SLN at upfront mastectomy not requiring PMRT

Mamtani A, manuscript under review 2023

Which Approach Minimizes ALND?

MSKCC Experience

+SLN	NAC n = 47	Upfront BCS n = 343	Upfront Mx n = 116	P
0	**93%**	**89%**	**85%**	0.5
Micromet only	4%	2%	4%	
1–2	2%	8%	10%	
≥ 3	0%	2%	1%	

Rates of ALND:
6% after NAC
1.7% upfront BCS
1.7% upfront mastectomy
(p = 0.1)

- No factors predictive of ALND:
  - T stage (T1a-b: ref; T1c: OR 2.9 [0.8-2.0], p = 0.1)
  - Subtype (TN: ref; HER2+: OR 2.1 [0.6-9.4], p = 0.3)
  - Approach (NAC: ref; upfront BCS OR 0.26 [0.07-1.3]; upfront mastectomy OR 0.26 [0.03-1.6], p = 0.2)

Feature	NAC n = 47	Upfront BCS n = 343	Upfront Mx n = 116	P
Age, years, median	**46**	**59**	**50**	**< 0.001**
cT stage 1a-1b 1c	 0% **100%**	 39% **61%**	 58% **42%**	**< 0.001**
Pathologic size, cm, median	0.1	1.2	0.8	< 0.001
Ductal histology	100%	90%	95%	0.2
Poorly differentiated	75%	74%	70%	0.9
Subtype TN HER2+	 49% 51%	 46% 54%	 33% 67%	0.04
Axillary US performed	23%	26%	33%	0.3

Which Approach Minimizes ALND?

MSKCC Experience

- **De-escalation in systemic therapy** seen after upfront surgery

TN subset:

Regimen	NAC	Upfront Surgery
ACT	**100%**	**47%**
TC or CMF	-	**36%**
None (pT1aN0)	-	**10%**
Declined	-	7%

HER2+ subset:

Regimen	NAC	Upfront Surgery
Polychemotherapy + HP	**100%**	**19%**
TH	-	**66%**
None (pT1aN0)	-	**13%**
Declined	-	2%

ntani A, manuscript under review 2023

Conclusioni!

ALND richiesto da < 2% dei pazienti cT1N0 TN e HER2+ sottoposti a intervento chirurgico up- front

- Nessun vantaggio della NAC nel ridurre ulteriormente il rischio di ALND
- Potenziale di riduzione del regime terapeutico sistemico nelle pazienti con linfonodi negativi

- Mancano prove di benefici derivanti dalla NAC nella malattia in stadio I
- Il carico pesante di malattia linfonodale è raro e l'ALND è poco frequente in pazienti TN e HER2+ trattati con chirurgia up front
- Il solo downstaging ascellare non è un'indicazione per la NAC
- I regimi terapeutici sistemici «ridotti» offrono risultati eccellenti nello stadio I malattia, in particolare HER2+
- Il continuo perfezionamento delle strategie di trattamento è fondamentale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e la Prevenzione Oncologica in Piemonte
rete oncologica
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REGIONE PIEMONTE
14 DICEMBRE 2023
ORE 8.30 - 16.30
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PER IL TUMORE DELLA MAMMELLA
PREVENZIONE SERENA
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Grazie!