LABORATUVARDAN KLİNİĞE: CERRAHİDE GELİŞMELER

PROF. DR. NESLİHAN CABIOĞLU

İ.Ü. İstanbul Tıp Fakültesi,

Genel Cerrahi Anabilim Dalı

MEME KANSERİNDE LABORATUVARDAN CERRAHİYE YANSIYAN NE DEĞİŞİKLİKLER OLDU?

- BİYOLOJİK AJANLARIN KULLANIMI İLE CERRAHİ GİRİŞİMLERDE KONSERVATİF YAKLAŞIM
- YAN ETKİLERDE AZALMA VE HAYAT KALİTESİNDE ARTIŞ
- HEDEFE YÖNELİK VE KİŞİYE ÖZEL TEDAVİLER

MEME KANSERİ BİYOLOJİSİNDE DEĞİŞEN HİPOTEZLER

HALSTED HİPOTEZİ
LOKO-REJYONEL HASTALIK (1870s-1970s)
RADİKAL MASTEKTOMİ

DR.WILLIAM STEWART HALSTED (1852–1922)

FISHER HİPOTEZİ
SİSTEMİK HASTALIK (1970s – 1990s)
SİSTEMİK TEDAVİ + MKC + HT

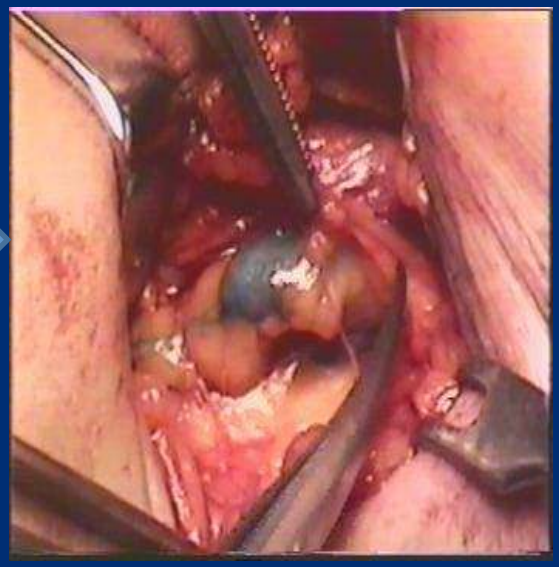
DR.BERNARD FISHER (1918-)

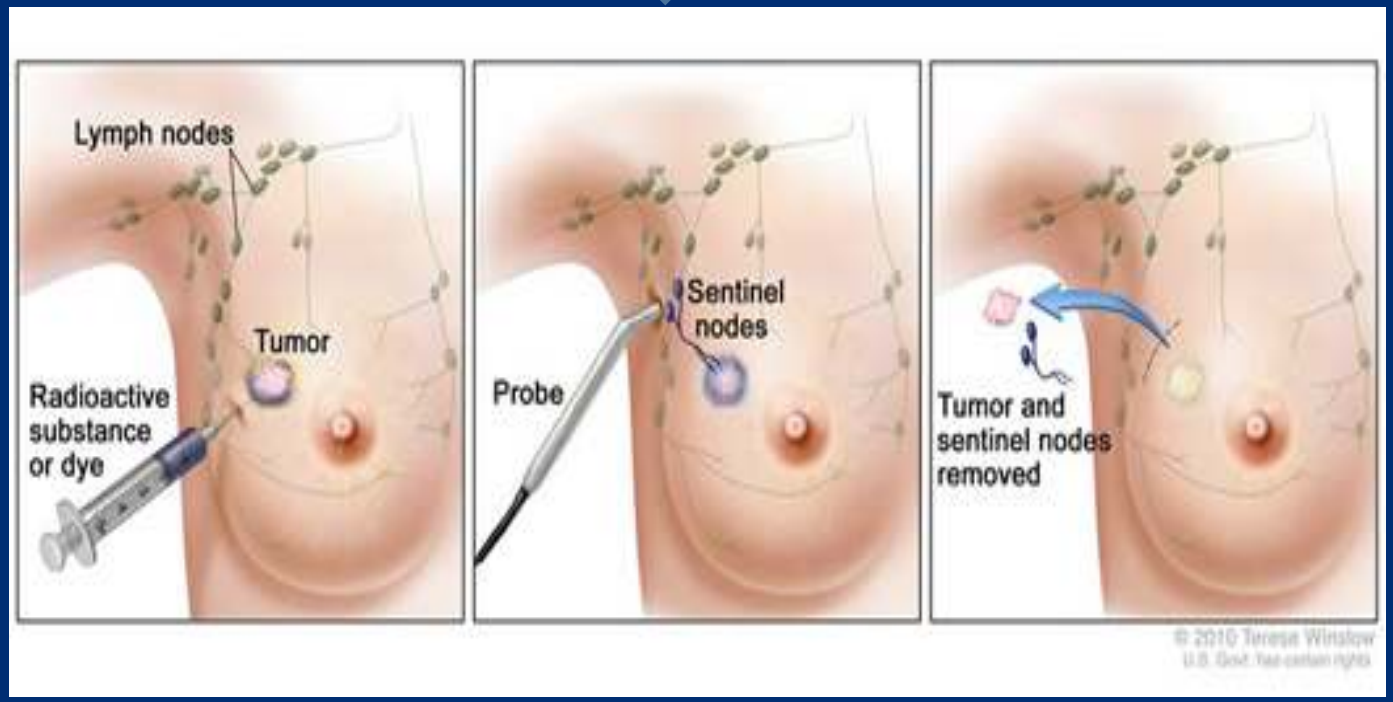
INTERMEDIATE HİPOTEZ
HETEROJEN HASTALIK (1990s – 2010s)
KİŞİYE ÖZEL TEDAVİ

ONE SIZE FITS ALL

ALND

SLNB




Lymph nodes
Tumor
Radioactive substance or dye
Probe
Sentinel nodes
Tumor and sentinel nodes removed

KİŞİYE ÖZEL (RISK-BASED) TARAMA

✓ **WISDOM PROSPEKTİF RANDOMİZE KLİNİK ÇALIŞMASI (UCSF)**

(Women Informed to Screen Depending on Measures of Risk)

I. GRUP-NORMAL TARAMA (40 – 74 YAŞ YILDA BİR MMG)

II. GRUP-KİŞİYE ÖZEL TARAMA

- **-MEDİKAL ÖZGEÇMİŞ**
- **-AİLE ANAMNEZİ**
- **-YAŞAM TARZI**
- **-GENETİK PROFİL (TÜKRÜKTEN 9 GEN ANALİZİ)**

DÜŞÜK RİSK
50 YAŞ, 2 YILDA BİR MMG

YÜKSEK RİSK
40 YAŞ, MMG 6 AY SONRA EMAR,
6 AY SONRA MMG-SONRA MRG

Wisdom: About the study (online). 2015. https://wisdom.secure.force.com/portal/WsdSiteStudy. Accessed June 9, 2016. Published 2015.

Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ – The LORD study

Lotte E. Elshof[a,b,c], Konstantinos Tryfonidis[d], Leen Slaets[e], A. Elise van Leeuwen-Stok[f], Victoria P. Skinner[a], Nicolas Dif[g], Ruud M. Pijnappel[h], Nina Bijker[i], Emiel J.Th. Rutgers[a], Jelle Wesseling[b,j,*]

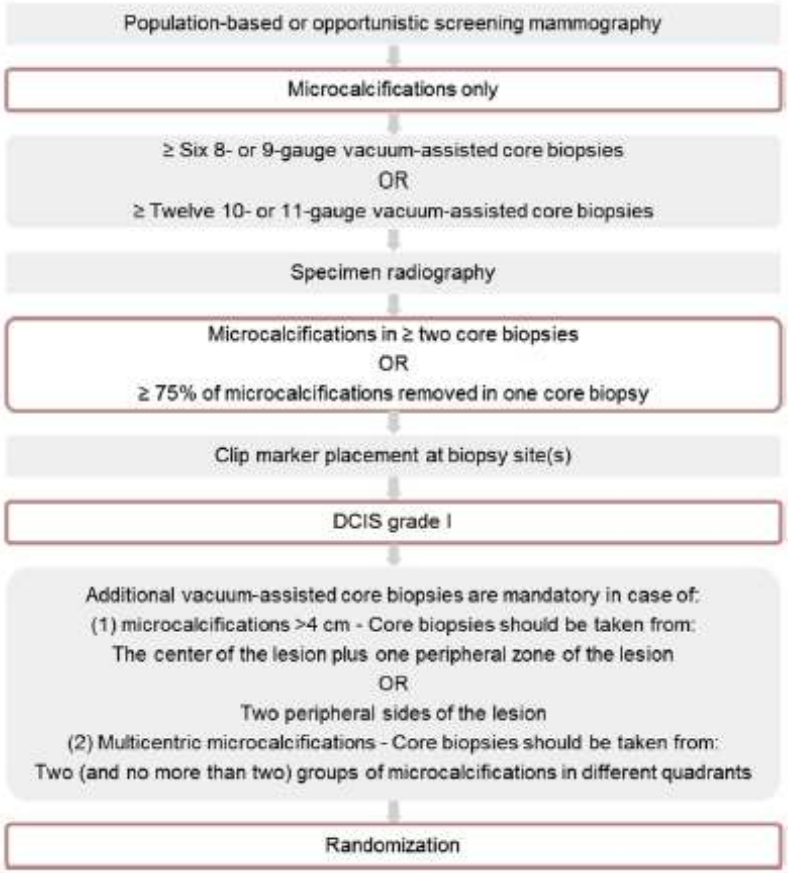


Fig. 1. Flow chart of diagnostic workup prior to randomisation.

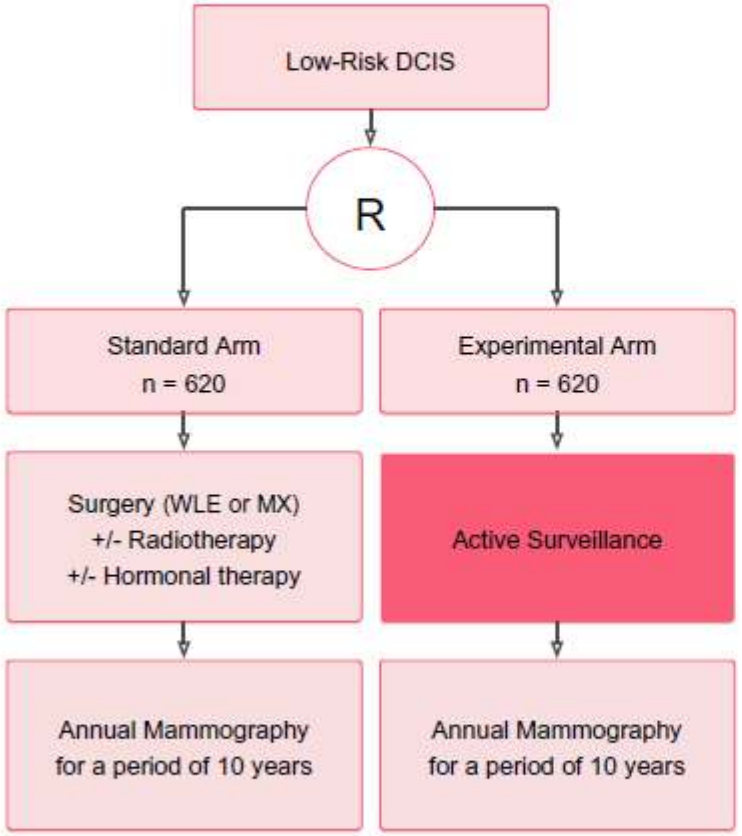
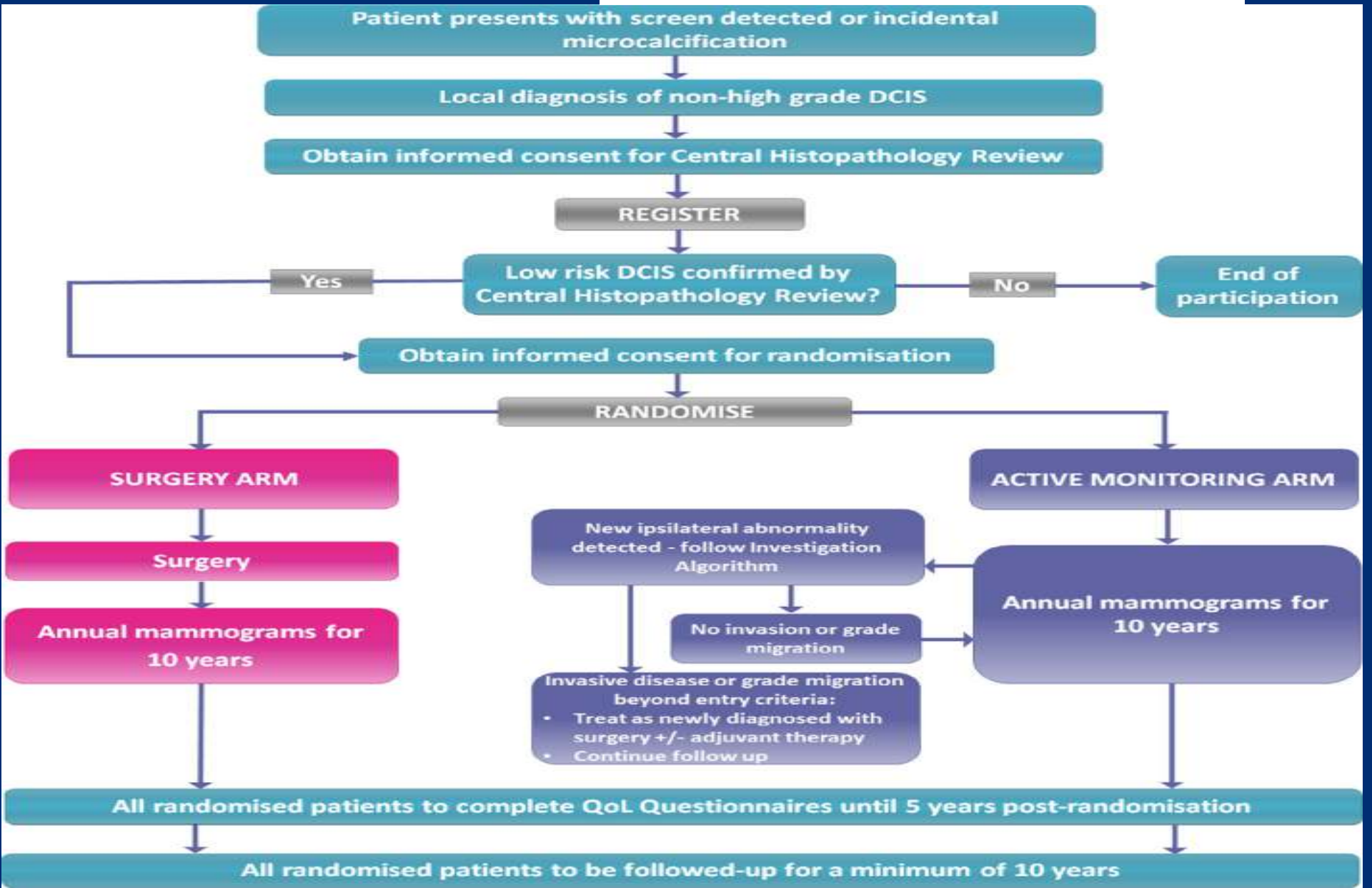


Fig. 2. Flow chart of study design. R = randomisation. WLE = wide local excision. MX = mastectomy.

Addressing overtreatment of screen detected DCIS; the LORIS trial

A. Francis et al / European Journal of Cancer 51 (2015) 2296–2303



Ann Surg Oncol (2017) 24:3534–3540
DOI 10.1245/s10434-017-6018-9

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

ORIGINAL ARTICLE – BREAST ONCOLOGY

Surgical Upstaging Rates for Vacuum Assisted Biopsy Proven DCIS: Implications for Active Surveillance Trials

Lars J. Grimm, MD, MHS[1], Marc D. Ryser, PhD[2], Ann H. Partridge, MD, MPH[3], Alastair M. Thompson, MD[4], Jeremy S. Thomas, MBBS[5], Jelle Wesseling, MD, PhD[6], and E. Shelley Hwang, MD, MPH[7]

[1]Department of Radiology, Duke University, Durham, NC; [2]Department of Mathematics, Duke University, Durham, NC; [3]Division of Oncology, Department of Medicine, Harvard Medical School, Boston, MA; [4]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; [5]Department of Pathology, Western General Hospital, Edinburgh, UK; [6]Department of Pathology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [7]Department of Surgery, Duke University Comprehensive Cancer Center, Durham, NC

COMET ÇALIŞMASI:
Comparison of Operative to Monitoring to Endocrine Therapy in Low Risk DCIS (USA)

	COMET	LORIS[9]	LORD
Inclusion criteria			
Age (year)	≥40	≥46	≥45
Nuclear grade	Low and intermediate	Low and intermediate	Low
Morphology	Calcifications only	Calcifications only	Calcifications only
Hormone receptor status	ER and/or PR positive, plus HER2 negative if performed	N/A	N/A
Biopsy technique	VACB and/or surgical biopsy	At least 12 gauge VACB and/or surgical biopsy	6 samples with 8–9 gauge or 12 samples with 10–11 gauge VACB
Exclusion criteria			
History of cancer	Exclude if invasive breast cancer	Exclude if invasive breast cancer or ipsilateral DCIS	Exclude if any cancer except in situ of the cervix or basal carcinoma of the skin
Symptomatic	Exclude	Exclude	Exclude
Comedonecrosis	Exclude	Exclude	N/A
Synchronous invasive cancer	Exclude	Exclude	Exclude
Bilateral DCIS at presentation	Include	Include	Exclude
High risk	Include	Exclude if high risk per NICE guidelines[23]	Exclude if family with BRCA 1/2 mutation
History of chemoprevention	Exclude	N/A	N/A

Topical 4-OHT vs. oral TAM in women planning surgery for DCIS

DCIS diagnosed by core needle bx

↓

Stratification

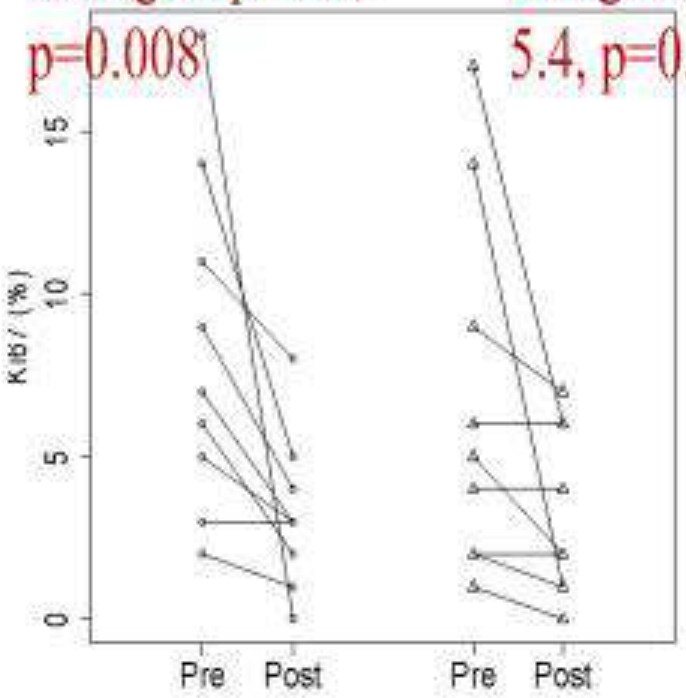
menopausal status

4-OHT gel 2 mg per breast + oral placebo (n=14)

Oral Tamoxifen 20 mg qd + gel placebo (n=12)

Oral group -5.4, p=0.008

Gel group -5.4, p=0.03

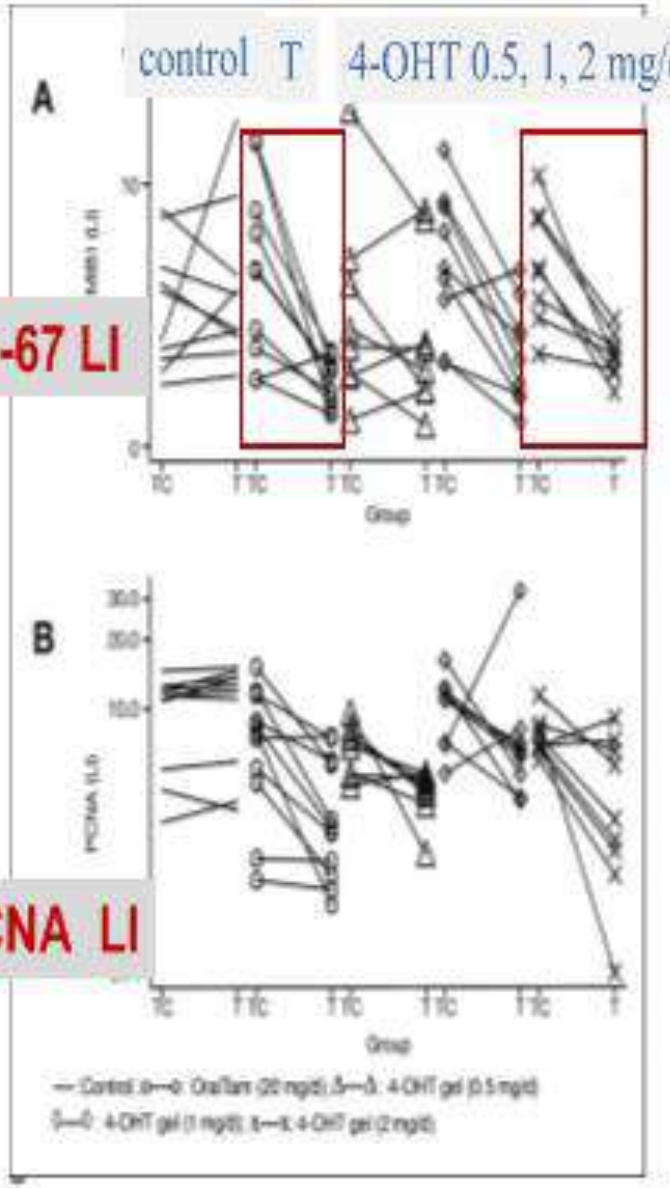


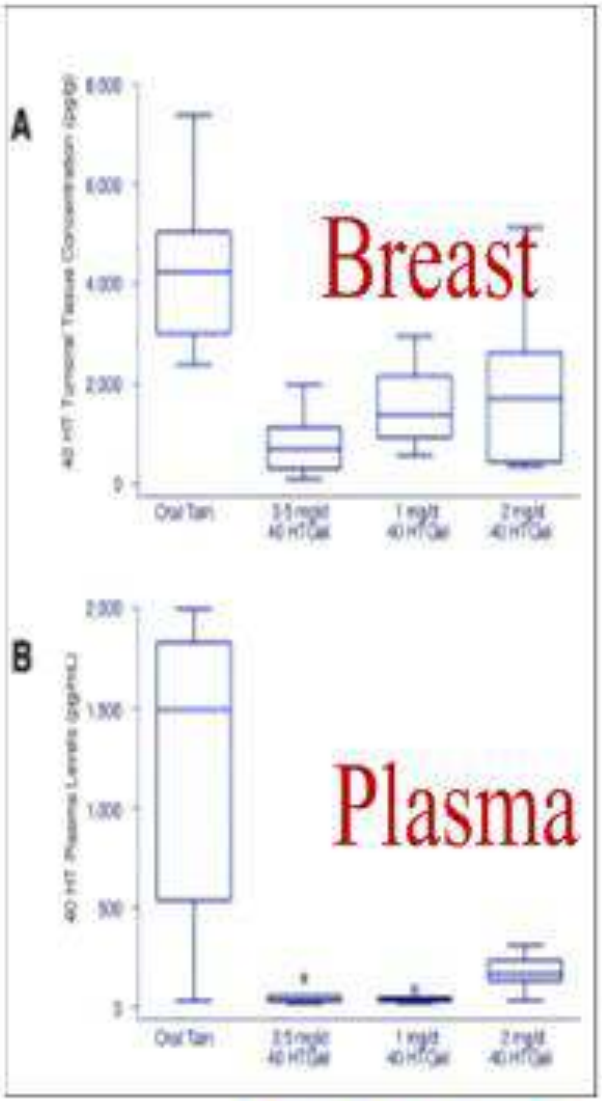
Between group difference, p=0.9

Lee O et. al., Clinical Can Res 2014

Window trial of oral tamoxifen and 3 doses of 4-OHT gel applied to the breast.

~10 women per group, therapy for 15-22 days

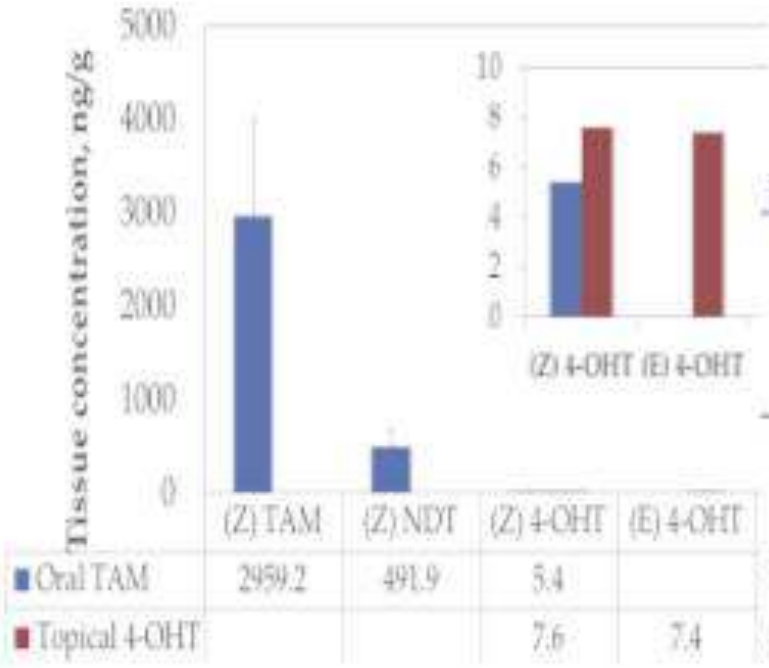




Rouanet P et al. JCO 2005;23:2980-2987

JOURNAL OF CLINICAL ONCOLOGY

Oral tamoxifen vs. 4-OHT gel in women with DCIS



Serum concentrations of 4-OHT 5x higher than gel group

Breast adipose tissue concentrations equivalent

Coagulation proteins not increased in gel group

Markers of estrogenicity in serum unchanged

	Tamoxifen (20mg/day) (N=13)		4-OHT gel (4mg/day) (N=10)	
	Mean ± SD	P*	Mean ± SD	P*
IGF-1 (ng/mL)	-8.7 ± 8.3	0.003	-5.2 ± 9.5	0.12
SHBG (ng/mL)	45.5 ± 40.2	0.002	10.3 ± 74.4	0.67
vWF	51.2 ± 71.0	0.02	-2.6 ± 52.3	0.88
Factor VIII	11.6 ± 17.3	0.03	8.7 ± 18.5	0.17
Factor IX	51.2 ± 71.0	0.02	-2.6 ± 52.3	0.88
Total Protein S	-2.7 ± 9.3	0.32	-1.6 ± 6.5	0.46

Lee O et. al., Clinical Can Res 2014

ONCOTYPE DX DCIS MULTİGEN (12 GEN) TESTİ:

•sadece MKC (RT siz) DCIS veya invasif kanser nüks riskini belirliyor. (7 kanser, 5 referans gen):

düşük, orta, yüksek diye 3 grup.

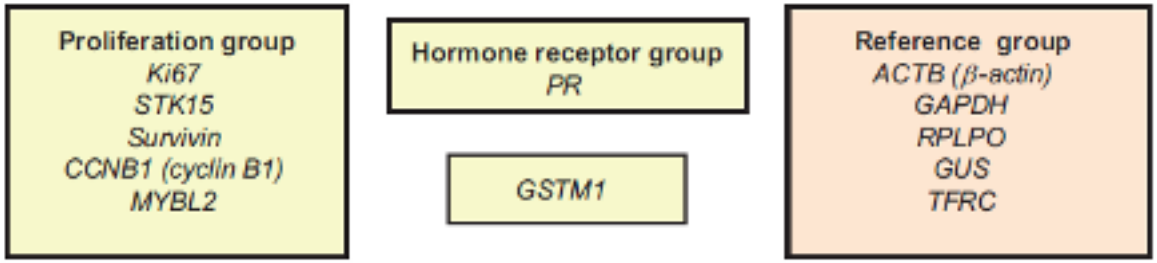


Figure 1. Panel of 12 genes included in the DCIS Score. Seven cancer-related genes: *Ki67* = MKI67; *STK15* = aurora kinase A; *survivin* = BIRC5; *CCNB1* = cyclin B1; *MYBL2* = v-myb myeloblastosis viral oncogene homolog (avian)-like 2; *PR* = progesterone receptor; and *GSTM1* = glutathione S-transferase M1. Five reference genes: *ACTB* = beta-actin; *GAPDH* = glyceraldehyde-3-phosphate dehydrogenase; *RPLPO* = large ribosomal protein; *GUS* = beta-glucuronidase; and *TFRC* = transferrin receptor.

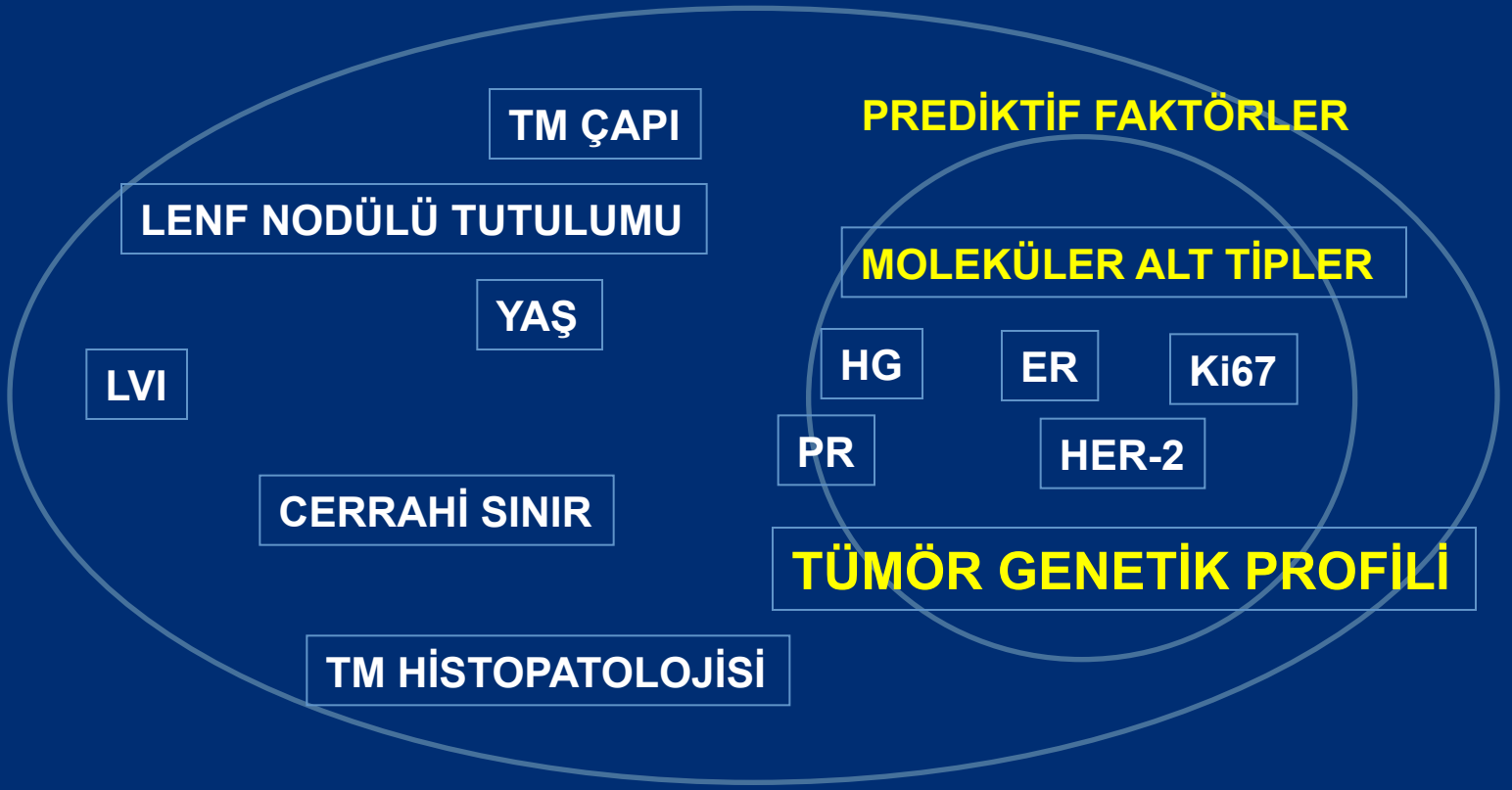
J Clin Oncol. 2016 Sep 12. pii: JCO678532. [Epub ahead of print]

Cost Effectiveness of the Oncotype DX DCIS Score for Guiding Treatment of Patients With Ductal Carcinoma In Situ.

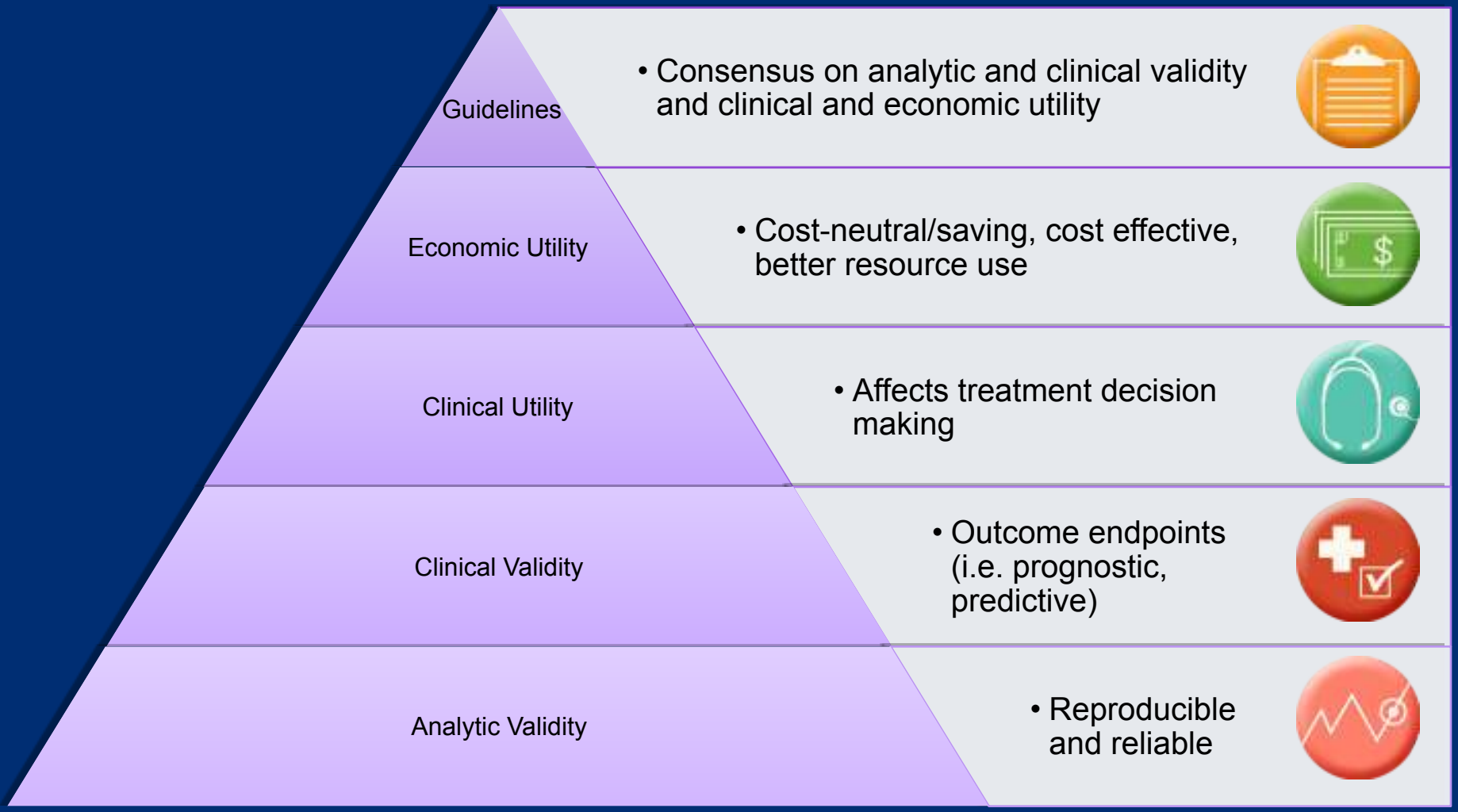
Raldow AC[1], Sher D[1], Chen AB[1], Recht A[1], Punglia RS[2].

Ekonomik bulunmadı!

MEME KANSERİNDE PROGNOSTİK VE PREDİKTİF FAKTÖRLER



KLİNİK OLARAK FAYDALI BİR GENETİK TEST:



Adapted from Simon et al. *J Clin Onc*. 2005. Hayes et al. *Breast*. 2003.

MEME KANSERİ İÇİN KULLANILAN GENOMİK BİYOMARKER TESTLER

- 21-GEN — ONCOTYPE DX RS*
- 12-GEN — ENDOPREDICT*
- 50-GEN — PAM50-ROR/PROSIGNA*
- 2-GEN — BREAST CANCER INDEX*
- 70-GEN — MAMMAPRINT*

MEME KANSERİ İÇİN KULLANILAN NON-GENOMIC TESTLER

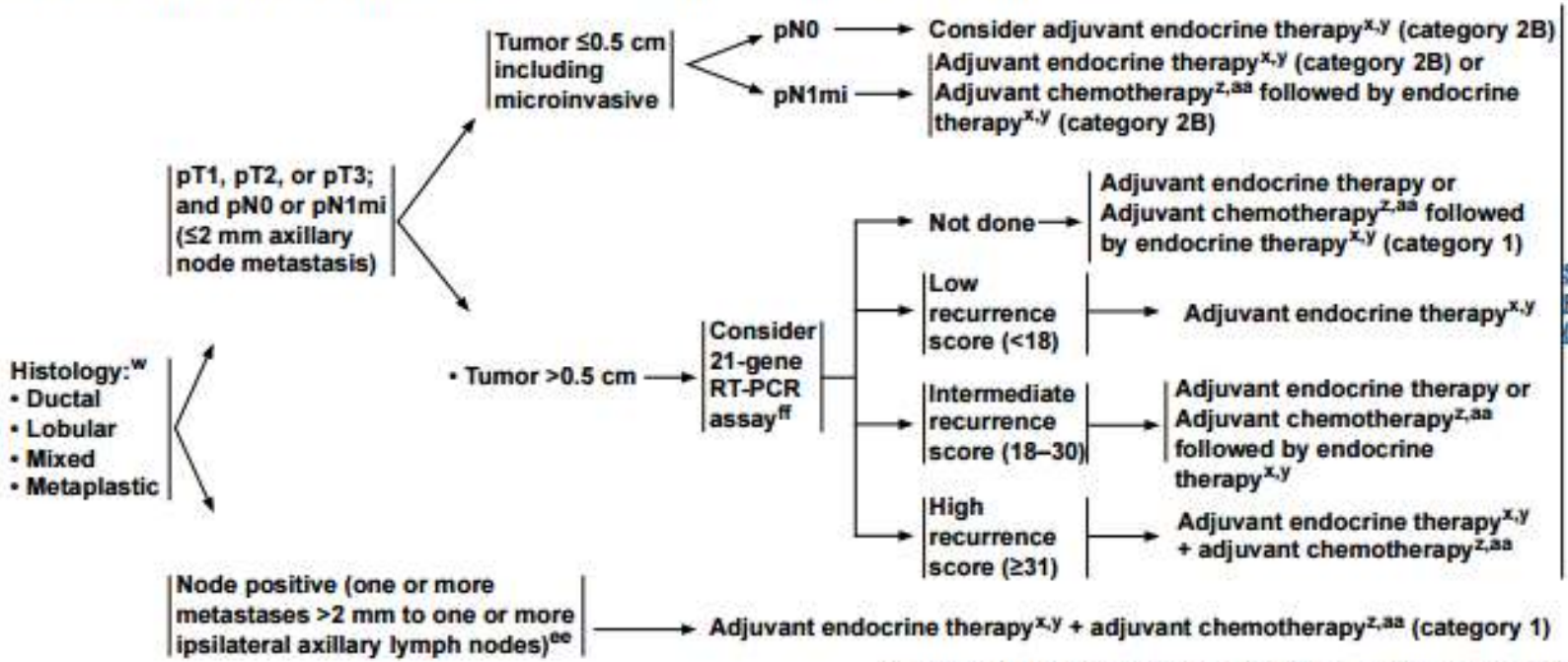
- IHC4
- MAMMOSTRAT
- UPA/PA-1
- DİĞERLERİ

* ASCO TM MARKER GUIDELINES FOR PROGNOSIS IN ER+, pN-, HER-2 – BREAST CANCER

Harris l, et al. JCO 2016

Cardoso F, et al. N Eng J Med 2017

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE[b]



[z]Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant

[b]See Principles of HER2 Testing (BINV-A).

[ee]The 21-gene RT-PCR assay recurrence score can be considered in select patients with 1–3 involved ipsilateral axillary lymph nodes to guide the addition of combination chemotherapy to standard hormone therapy. A retrospective analysis of a prospective randomized trial suggests that the test is predictive in this group similar to its performance in node-negative disease.

Oncotype DX® RECURRENCE SCORE (RS) CALCULATED FROM 21 DIFFERENT GENES

16 CANCER RELATED GENES

Estrogen	Proliferation	HER2	Invasion	Others
ER PR Bcl2 SCUBE2	Ki-67 STK15 Survivin Cyclin B1 MYBL2	GRB7 HER2	Stromelysin 3 Cathepsin L2	CD68 GSTM1 BAG1

5 REFERENCE GENES

Beta-actin	GAPDH	RPLPO	GUS	TFRC

Paik et al. N Engl J Med. 2004

Oncotype DX® RECURRENCE SCORE (RS) CALCULATION AND RISK CATEGORIES

Recurrence Score =

+ 0.47 x HER2 Group Score
- 0.34 x Estrogen Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Risk Group	*Recurrence Score*
Low risk	<18
Intermediate risk	18 - 30
High risk	≥31

Paik et al. N Engl J Med. 2004

The Journal of Breast Health

J Breast Health (2013). 2016 Jul; 12(3): 107–111.
Published online 2016 Jul 1. doi: 10.5152/tjbh.2016.2874

PMCID: PMC5351479

Correlations Between Oncotype DX Recurrence Score and Classic Risk Factors in Early Breast Cancer: Results of A Prospective Multicenter Study in Turkey

Vahit Özmen,[1] Ajlan Atasoy,[2] Erhan Gökmen,[3] Mustafa Özdoğan,[4,12] Nilufer Güler,[5] Cihan Uras,[6] Engin Ok,[7] Orhan Demircan,[8,12] Abdurrahman Işıkkdoğan,[9] Neslihan Cabioğlu,[1] Fatma Şen,[10] and Pınar Saip[10]

Cureus

Open Access Original Article

DOI: 10.7759/cureus.522

Impact of Oncotype DX Recurrence Score on Treatment Decisions: Results of a Prospective Multicenter Study in Turkey

Vahit Ozmen [1], Ajlan Atasoy [2], Erhan Gokmen [3], Mustafa Ozdogan [4], Nilufer Guler [5], Cihan Uras [6], Engin Ok [7], Orhan Demircan [8], Abdurrahman Isikdogan [9], Pinar Saip [10]

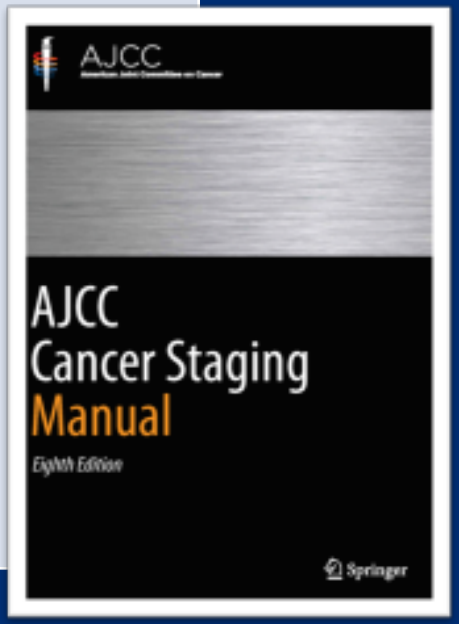
KİŞİYE ÖZEL SİSTEMİK TEDAVİ

- RETROSPEKTİF KLİNİK ÇALIŞMALAR ERKEN EVRE MEME KANSERİ TANISI ALAN HASTALARIN (pT1-3 N0-1mic M0) %30-50'SİNDE GEREKSİZ SİSTEMİK TEDAVİ UYGULANDIĞINI GÖSTERMEKTEDİR.
- YENİ MOLEKÜLER TESTLER HASTALARIN %30-40'INDA SİSTEMİK TEDAVİ KARARINI DEĞİŞTİRMEKTEDİR.
- TÜRKİYE ONKOTYPE DX ÇALIŞMASI: %30 SİSTEMİK TEDAVİDE DEĞİŞİKLİK

Gotzsche PC, Jørgensen KJ. Cochrane Database Syst Rev. 2013
Drukker CA et al. Breast Cancer Res Treat 2014
Katz SJ, Monica Morrow. Cancer 2013
Ozmen V, et al. Cureus 2016
Ozmen V, et al. The European Journal of Breast Health 2016

TNM EVRELEMESİ 2018

CHANGE	DETAILS OF CHANGE	LEVEL OF EVİDENCE
AJCC **Anatomic** and **Prognostic Stage Groups**	There are two stage group tables presented in this chapter: l. **Anatomic Stage Group** table based solely on anatomic extent of cancer as defined by the **T, N, and M** categories. 2**. Prognostic Stage Group** table based on populations of persons with breast cancer that have been offered ---and mostly treated with -- appropriate endocrine and/or systemic chemotherapy, which includes anatomic T, N, and M plus tumor grade and the status of the biomarkers human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR).	II



TNM EVRELEMESİ 2018

Change	Details of Change	Level of Evidence
Inclusion of Multigene Panels (when available) as Stage Modifiers – 21 Gene Recurrence Score (**Oncotype Dx®**)	For patients with **hormone receptor-positive, HER2-negative, and lymph node-negative tumors,** a **21-gene (Oncotype Dx®) recurrence score < 11**, **regardless of T size**, places the tumor into the same **prognostic category as T1a—T1bN0M0** and staged using the AJCC Prognostic Stage table as Stage I	I

TNM EVRELEMESİ 2018

Change	Details of Change	Level of Evidence
Inclusion of Multigene Panels (when available) as Stage Modifiers - **Mammaprint**	For patients with **hormone receptor-positive, HER2-negative, and lymph node-negative tumors,** a **Mammaprint low-risk score**, **regardless of T size**, places the tumor into the same prognostic category as **T1a—T1bN0M0.**	II

TNM EVRELEMESİ 2018

Change	Details of Change	Level of Evidence
Inclusion of Multigene Panels (when available) as Stage Modifiers – **EndoPredict**	For patients with **hormone receptor-positive,** **HER2-negative, and** **lymph node-negative tumors,** a **12-gene (EndoPredict) low-risk score,** **regardless of T size,** places the tumor into the same prognostic category as **T1a—T1bN0M0**.	II

TNM EVRELEMESİ 2018

Change	Details of Change	Level of Evidence
Inclusion of Multigene Panels (when available) as Stage Modifiers — PAM 50 (Prosigna)	For patients with **hormone receptor-positive, HER2-negative, and lymph node-negative tumors,** **a PAM50 risk of recurrence (ROR) score in the low range, regardless of T size, places the** tumor into the same prognostic category as **T1a-T1bN0 M0**.	II

TNM EVRELEMESİ 2018

Change	Details of Change	Level of Evidence
Inclusion of Multigene Panels (when available) as Stage Modifiers — **Breast Cancer Index**	For patients with **hormone receptor-positive, HER2-negative, and lymph node-negative tumors** a **Breast Cancer Index in the low-risk range**, **regardless of T size**, places the tumor into the same prognostic category as **T1a-T1bN0M0**.	II

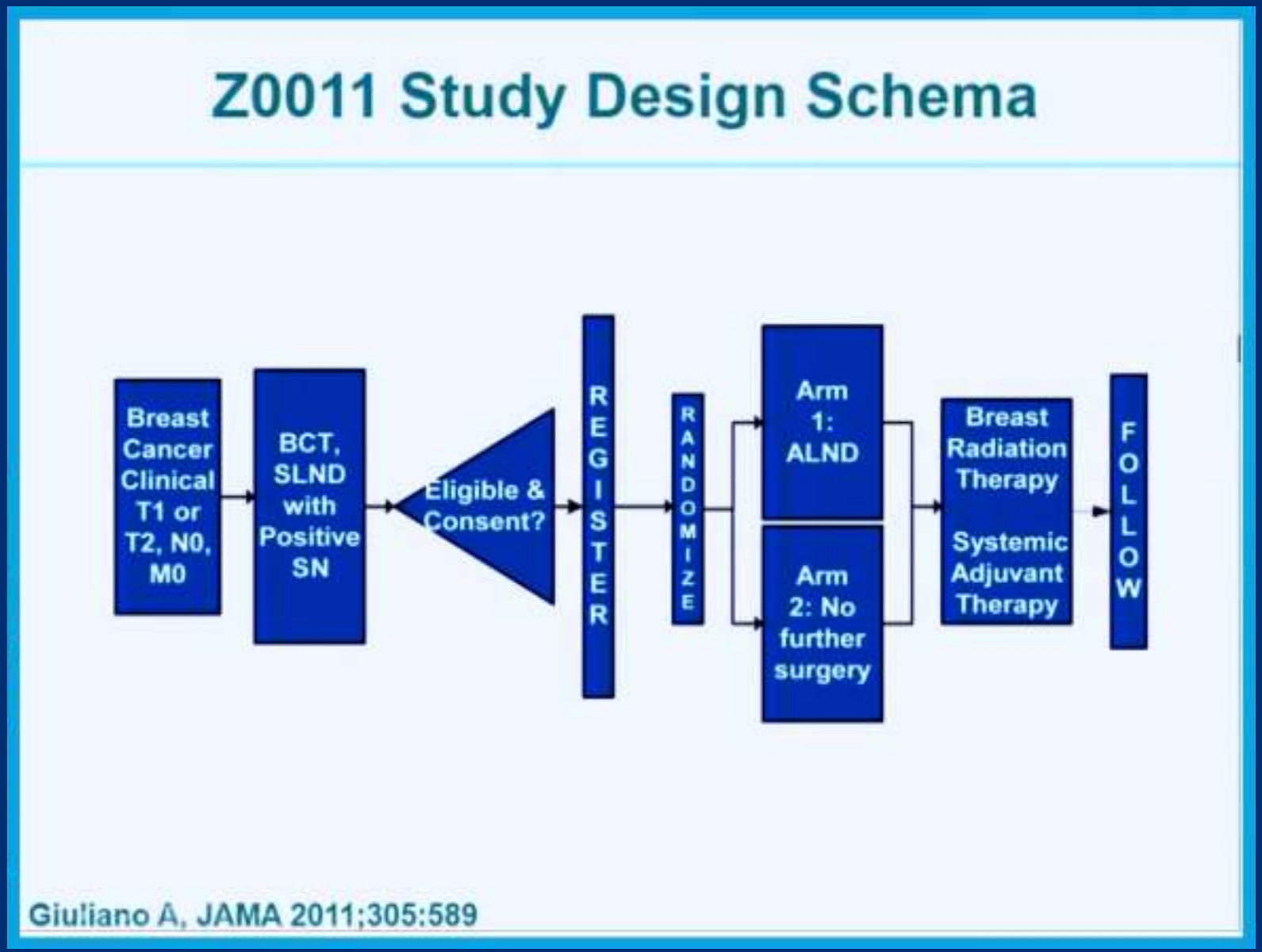
Prognostik Evreleme (TNM 2018)

When T is...	And N is...	And M is...	And G is...	And HER2 Status* is...	And ER Status is...	And PR Status is...	Then the Prognostic Stage Group is...
T3	N1-2	M0	1	Positive	Positive	Positive	IB***
T3	N1-2	M0	2	Positive	Positive	Positive	IB***
T1	N0	M0	1	Negative	Negative	Negative	IIA***
T1	N0	M0	2	Negative	Negative	Negative	IIA***
T1	N0	M0	3	Negative	Positive	Negative	IIA***
T1	N0	M0	3	Negative	Negative	Positive	IIA***
T1	N0	M0	3	Negative	Negative	Negative	IIA***
T0-1	N1mi	M0	1	Negative	Negative	Negative	IIA
T0-1	N1mi	M0	2	Negative	Negative	Negative	IIA
T0-1	N1mi	M0	3	Negative	Positive	Negative	IIA
T0-1	N1mi	M0	3	Negative	Negative	Positive	IIA
T0-1	N1mi	M0	3	Negative	Negative	Negative	IIA
T0-1	N1	M0	1	Positive	Positive	Negative	IIA
T0-1	N1	M0	1 - 2	Positive	Negative	Any	IIA
T0-1	N1	M0	1	Negative	Positive	Negative	IIA
T0-1	N1	M0	1	Negative	Negative	Positive	IIA
T0-1	N1	M0	3	Negative	Positive	Positive	IIA
T2	N0	M0	1	Positive	Positive	Negative	IIA
T2	N0	M0	1 - 2	Positive	Negative	Any	IIA
T2	N0	M0	1	Negative	Positive	Negative	IIA
T2	N0	M0	1	Negative	Negative	Positive	IIA
T2	N0	M0	3	Negative	Positive	Positive	IIA
T0-2	N2	M0	1	Negative	Positive	Positive	IIA***
T3	N1-2	M0	1	Negative	Positive	Positive	IIA

AJCC Anatomic Stage Groups

T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA

KİŞİYE ÖZEL CERRAHİ TEDAVİ (AKSİLLAYA YAKLAŞIM)



ACOSOG Z0011 Update

Nodal Recurrence

Median f/u 6.3 yrs		Median f/u 9.25 yrs	
ALND	**SN**	**ALND**	**SN**
0.5%	0.9%	0.5%	1.1%
p = 0.45		p = 0.45	

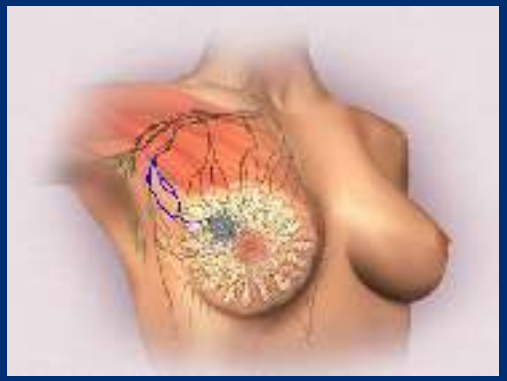
Overall Survival

5 year		10 year	
ALND	**SN**	**ALND**	**SN**
92%	93%	84%	86%
p = 0.14		p = 0.40	

Giuliano A, JAMA 2011;305:589

Giuliano A, Ann Surg 2016;264:413

KİŞİYE ÖZEL AKSİLLA CERRAHİSİ (cN0)



10 YILLIK TAKİPLERDE ALND İLE SLNB ARASINDA LRR, DFS VEYA OS BAKIMINDAN FARK OLMADIĞI GÖRÜLMÜŞTÜR.

SLNB, cN0 HASTALARDA STANDART BİR CERRAHİ GİRİŞİM OLMUŞTUR.

cN0 HASTALARIN ÖNEMLİ BİR KISMINDA ALND GEREKSİNİMİ ORTADAN KALKMIŞTIR.

KİŞİYE ÖZEL AKSİLLA CERRAHİSİ (cN+)

NEOADJUVAN KEMOTERAPİ (NAK) SONRASI NODAL TAM CEVAP (pCR=patolojik complete response)

ÇALIŞMA	SAYI	NODAL pCR
ACOSOG Z1071	694	%41
SN FNAC	145	%35
Mamtani et al.	195	%49

Boughey J, et al. JAMA 2013
Boileau J, et al. J Clin Oncol 2105
Mamtani A, et al. Ann Surg Oncol 2016

cN+ HASTALARDA NAK SONRA SLNB

3 PROSPEKTİF KLİNİK ÇALIŞMADA NAK SONRASI YANLIŞ NEGATİFLİK ORANI (FNR=FALSE NEGATIVE RATE)

ÖZELLİKLER	ACOSOG Z 1071	SN FNAC	SENTINA
SAYI	694	145	592
cTN	cT0-4-N1/2	cT0-3 N1/2	Ct0-4 N1/2
FNR	%12.6	%8.4	%14.2

Boughey J, et al. Ann Surg 2014
Boileau J, et al. J Clin Oncol 2105
Kuehn T, et al. Lancet Oncol 2013

ACOSOG Z1071 – cN1 patients

How do we translate these findings in clinical practice ???

FNR by Number of SN

# SN Removed	1	2	≥ 3	
% of Cases	12%	24%	57%	
False Negative Rate	32%	21.1%	9.1%	p=.007

Bougney JC, JAMA 2013

SLN Biopsy After Neoadjuvant Therapy cN1 convert cN0

	ACOSOG Z1071	SENTINA	SN FNAC
N	649	592(cN+)*	153
Mapping	Dual tracer recommended (79%)	Technetium required	Technetium required, IHC
Pre-op biopsy?	Yes	Not required (biopsy =25%)	Yes
Nodal pCR	41%	52% ypN0 (?)	35%
IR	92.7%	80.1%	87.6%
FNR (Overall)	12.6%	14.2%	8.4%
1 SLN	31.5%	24.3%	18.2%
2 SLN	21.1%	18.5%	4.9%
≥3SLN	9.1%	7.3%	

*1737 patients enrolled in 4 arm multicenter trial. 592 ARM C were cN+ to cN0

MDACC Experience

Clipping the node for SLN after NAC

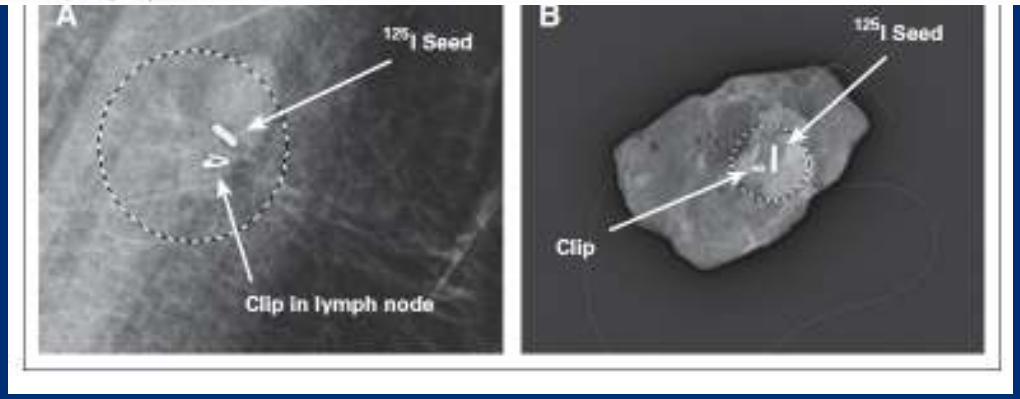
- Clipped node +/- SLN to reflect the status of the nodal basin in all-comers undergoing NAC

	N	Node +	pCR (%)	FNR (%)
Clipped node	191	120	37%	4.2% (95%CI 1.4-9.5)
SLN	118	74	37%	10.1% (95%CI 4.2-19.8)
SLN + clipped node	118	74	37%	1.4% (95%CI 0.03-7.3)

Also noted clipped node was not a SLN in ~ 20% pts

⟶ *"Targeted Axillary Dissection"*

Caudle AS et al JCO 2016;34(10):1072-8

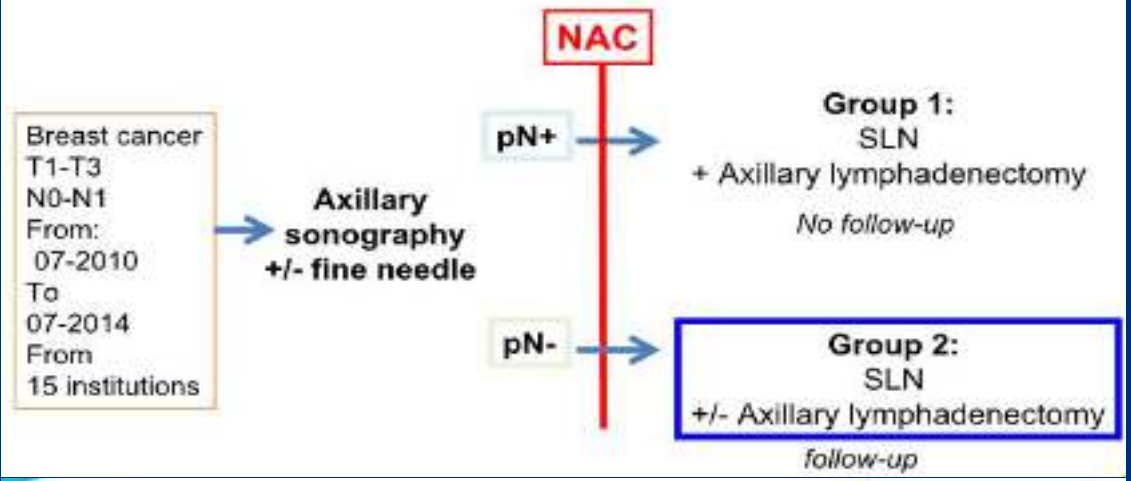


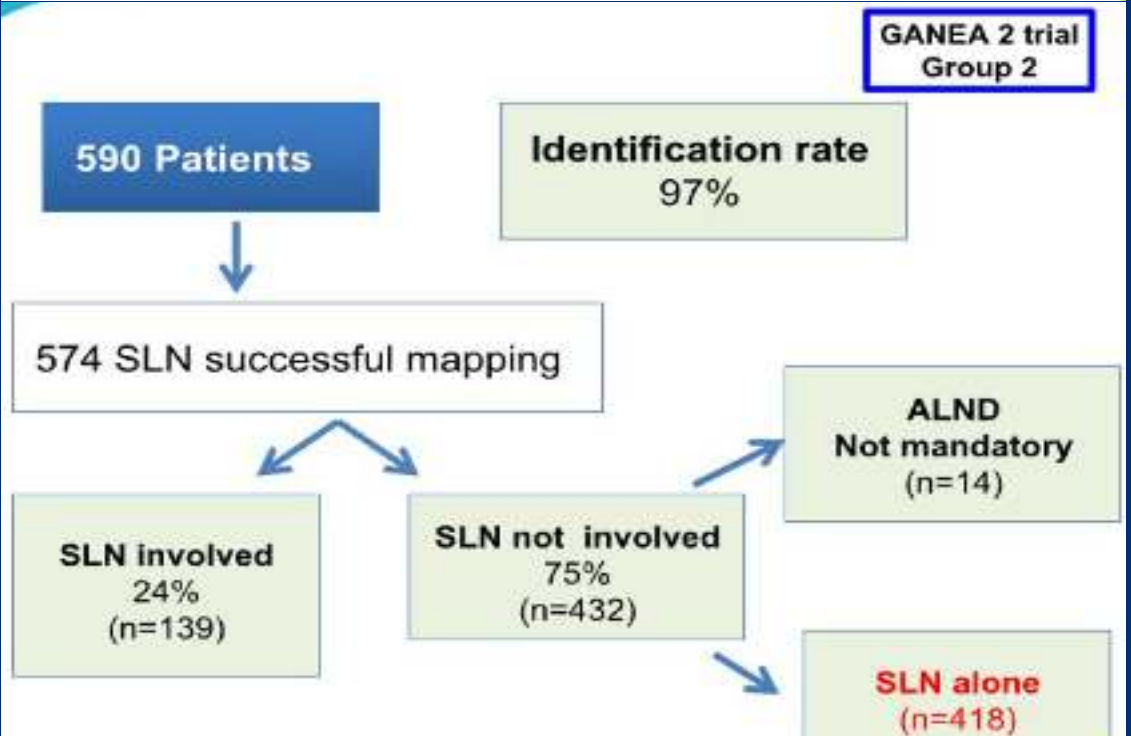
Sentinel node detection after neoadjuvant chemotherapy
(GANEA 2 trial):
Follow-up of a prospective multi-institutional cohort

Pr Jean-Marc Classe, MD. PhD
Institut de Cancérologie de l'Ouest – Centre Gauducheau – Nantes - France

GANEA 2 trial

Prospective Multi-institutional French Cohort





GANEA 2 trial
Group 2

Follow-up organization:

Clinical visit / 6 months:
Clinical breast and axillary assessment
+/- axillary sonography if necessary
AND **Mammography/ year**

3 years survival	N= 418 (SLN alone)
Overall survival	**97.8%** [94.9-99.1]
Disease free survival	**94.8%** [91.0-97.1%]

GANEA 2 trial
Group 2

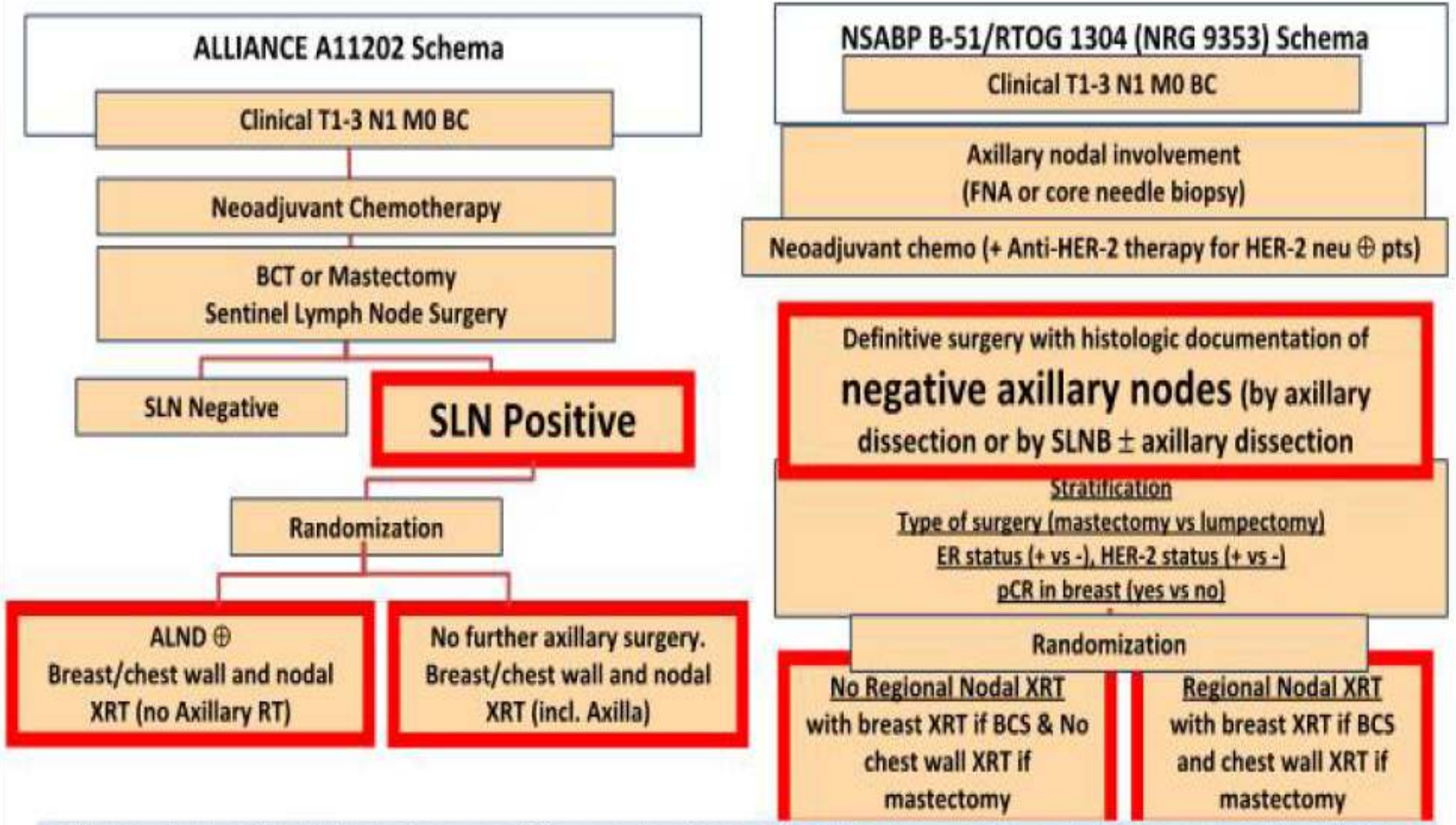
Events

418 Patients SLN alone without ALND
Median Follow-up =36 months

Relapse	N=10
Metastasis	**3**
Breast relapse	**3 homo L** **3 contra L**
Axillary relapse	1 (0.2%)

San Antonio Breast Cancer Symposium, December 6-10, 2016

Post NAC Trials of Axillary Management



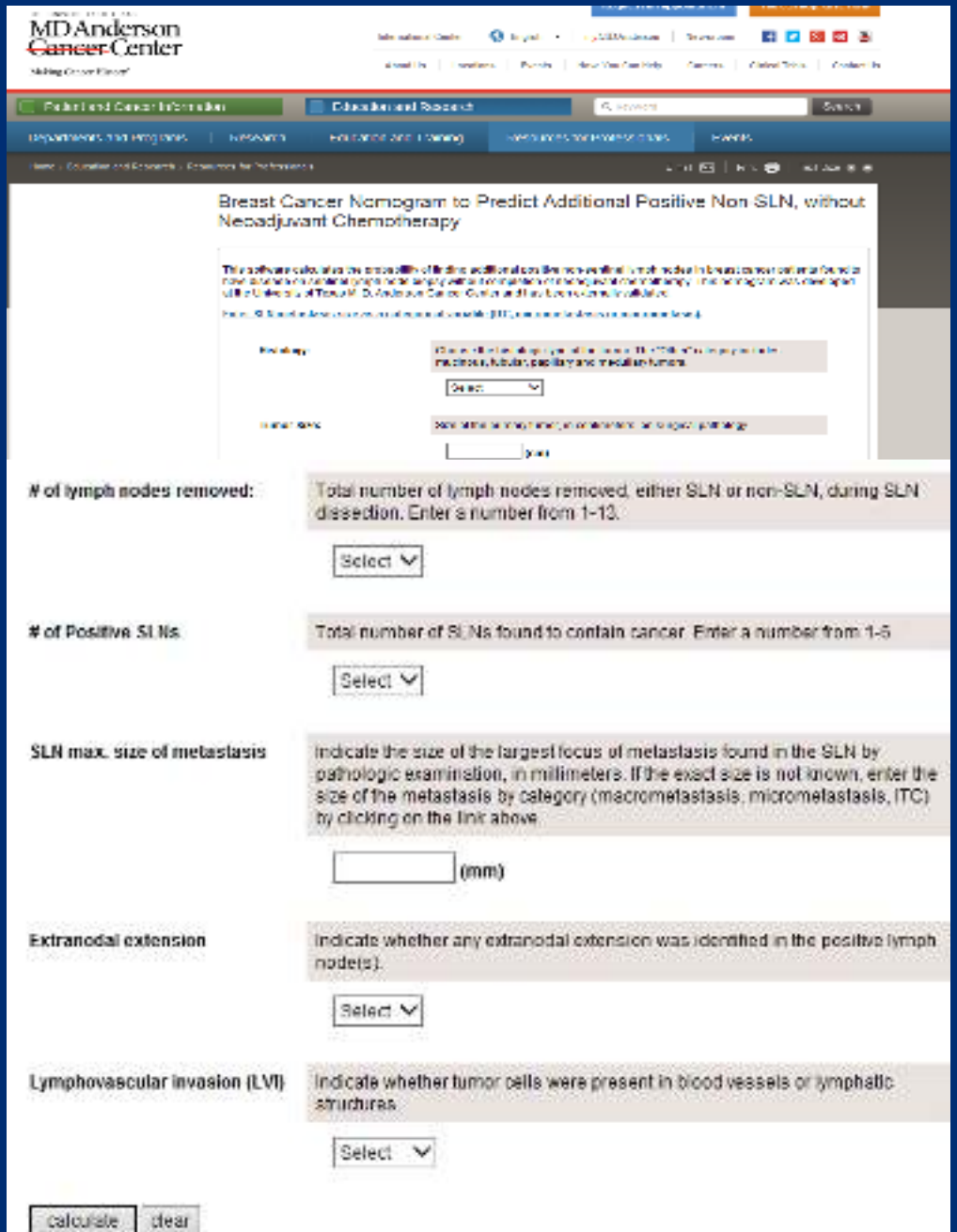
AKSİLLER RT ALND YERİNİ TUTABİLİR Mİ?

NAK CEVABI TAM HASTALARA POSTMASTEKTOMİ RT VERİLMEYEBİLİR Mİ?

AKSİLLER DİSSEKSİYONDAN KAÇINMA STRATEJİLERİ

- cN- HASTALARDA ÖNCELİKLE SLNB YAPILMALIDIR.
- cN + HASTALARDA ÖNCELİKLE NEOADJUVAN KEMOTERAPİ (NAK) UYGULANABİLİR . (LUMİNAL A?)
- cN + HASTALARDA SLNB DE EN AZ 3 SLN ÇIKARILMALI.
- ŞÜPHELİ LENF NODUNA NAK ÖNCESİ KLİPS İDEAL VE SLN&KLİPSLİ LN ÇIKMALI.
- NAK SONRASI SLNB (-) İSE ALND GEREKMEYEBİLİR (EN AZ 3 SLN ÇIKMIŞ OLMALI).
- NAK SONRASI SLNB (+) İSE STANDART TEDAVİ ALND. (RANDOMİZE ÇALIŞMALAR DEVAM EDİYOR)

NONSENTİNEL LENF NODU POZİTİFLİĞİNİ BELİRLEYEN NOMOGRAMLAR



SENTİNEL LENF NODU POZİTİFLİĞİNİ BELİRLEYEN NOMOGRAMLAR

T1 MEME KANSERİNDE CXCR4/CCR7 KEMOKİN RESEPTÖRLERİNİN EKSPRESYONUNUN LENF NODU METASTAZIYLA İLİŞKİSİ

- **CCR7 ligandı CCL21 lenf nodlarında yüksek oranda**

- **Primer tümörde artmış CCR7 ekspresyonu lenf nodu metastazlı AC, özafagus ve mide kanserleri ile ilişkili**

- **T1 lenf nodu pozitif ve negatif meme kanserli hastaların primer tümörlerinde CXCR4, HER2-neu, and CCR7 ekspresyonunun aksiller lenf nodu metastazıyla ilişkisini araştırdık.**

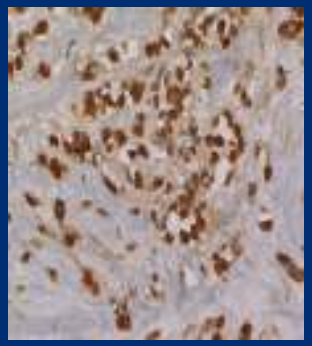
Cabioglu, N., M.S. Yazici, B. Arun, K.R. Broglio, G.N. Hortobagyi, J.E. Price, A.A. Sahin, "CCR7 and CXCR4 as novel biomarkers predicting axillary lymph node metastasis in T1 breast cancer," Clin Cancer Research., 11, 5686-5693 (2005).

MATERYAL VE METOD

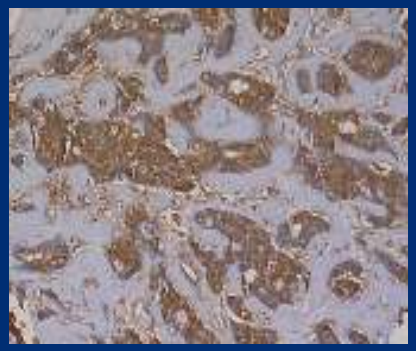
- **T1 (≤2 cm) lenf nod-negatif (n = 99) ve**
- **and lenf-nod pozitif (n = 98) meme kanseri parafin blok kesitleri.**

İmmünohistokimya: (Avidin-biotin kompleks metodu)

- CXCR4, CCR7, HER2-neu ab



Nükleer CXCR4(+)



Sitoplasmik CXCR4(+)

HER2-NEU(+)

CCR7(+)

Tümör karakteristikleri	Lenf nod (LN) pozitif	LN negatif	*P değeri*
Sitoplasmik CXCR4	11.2%	5.1%	0.113
Sitoplasmik CCR7	21.5%	8.5%	0.013
HER2 ⇑	21.5%	9.3%	0.019
	LNLN ≥4 (+)	LN <4 (+)	
CXCR4⇑/HER2⇑	16.7% (2/12)	1.2% (1/82)	0.04

- Multivariate logistik regresyon analizinde:
- yaygın kuv. sitoplasmik CCR7 (OR=2.6, 95% CI, 1.1 - 6.6, *P* = 0.037) ve HER2-neu (OR=2.4, 95% CI, 1.0 to 5.6, *P* = 0.05) ekspresyonları lenf nodu metastazının prediktörleri.

SONUÇLAR

- **Kemokin reseptörü CCR7 meme kanseri lenf nodu metastazlarında yeni bir biyomarkerdır.**

- **CXCR4/ HER2-neu koekspresyonu ekstensif lenf nodu tutulumu ilişkilidir. (SDF-CXCR4 etkileşimi HER2 aktivasyonunu artırmaktır.)**

- **Bu biyomarkerlar sentinel ve nonsentinel lenf nodunun pozitifliğini predikte etmek için nomogram çalışmalarında kullanılabilir.**

Cabioglu, N., J. Summy, C. Miller, N. Parikh, A. Sahin, S. Tuzlali, K. Pumiglia, G.E. Gallick, J.E. Price, "CXCL-12/stromal cell-derived factor-1 alpha transactivates HER2-neu in breast cancer cells by a novel pathway involving Src kinase activation," Cancer Res., 65, (6493-6497), 2005.

NAK SONRASI MOLEKÜLER TİPLERE GÖRE PATOLOJİK TAM CEVAP

MOLEKÜLER ALT TİP	NODAL pCR(%)	MEME pCR (%)	p
TÜM HASTALAR	%48	%37	<0.0001
LUMİNAL A (ÖR+/HER-2-)	%21	%10	0.0003
LUMİNAL B (ÖR+/HER-2+)	%70	%59	0.3
HER-2 + (ÖR-/HER-2+)	%97	%70	0.3
TRIPLE NEGATİF (ÖR-/HER-2-)	%47	%40	<0.0001

Mamtani A, et al. Ann Surg Oncol 2016

NAK SONRASI MOLEKÜLER TİPLERE GÖRE PATOLOJİK TAM CEVAP: İ.Ü. İSTANBUL TIP FAKÜLTESİ GENEL CERRAHİ ANABİLİM DALI DENEYİMİ

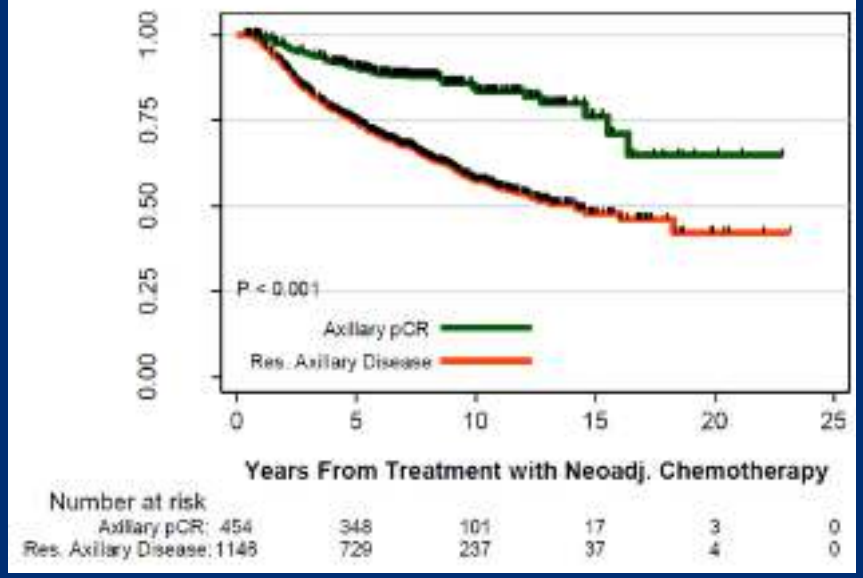
Tümör Özellikleri	Patolojik Tam Cevap Oranı (%)	P Değeri
Tedavi (2007 sonrası)	23,9	0.0001
Tedavi (2007 öncesi)	6,8	
Nonluminal HER2	46,4	
Triple Negatif	37,7	
Luminal	20,8	
HER2(+) Luminal	39,1	
HER2(-) Luminal	16,4	

Ocak 1993-Ocak 2017 arasında 509 lokal ileri meme kanserli hasta

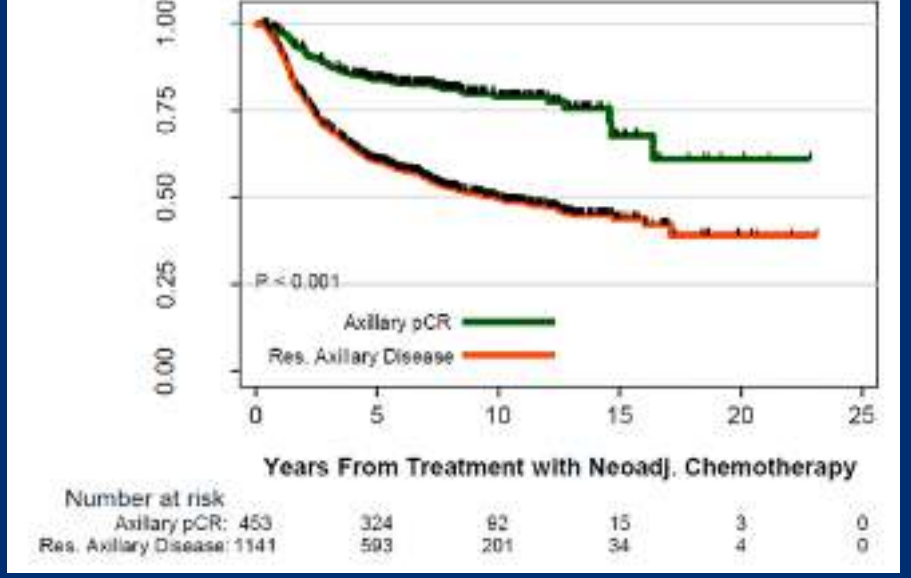
Published in final edited form as:
JAMA Oncol. 2016 April 1; 2(4): 508–516. doi:10.1001/jamaoncol.2015.4935.

10-year Outcomes of Breast Cancer Patients with Cytologically Confirmed Axillary Lymph Node Metastases and Pathologic Complete Response after Primary Systemic Chemotherapy

a OS in all patients by pathologic lymph nodes.



b RFS in all patients by pathologic lymph nodes.



NEOADJUVAN KT SONRASI PATOLOJİK TAM CEVAP VE PROGNOSTİK ÖNEMİ?

pCR tanımı: NAK sonrası hem in situ hem invazif tümör yok olması

pCR hastalarda DFS :

- luminal B/(HER2) (-) (P = .005),
- HER2(+)/nonluminal (P < .001), ve
- triple-negatif (P < .001) tümörlü hastalarda daha iyi .
- luminal A (P = .39) veya luminal B/HER2-pozitif grupta anlamsız .

von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012; 30: 1796-804.

NEOADJUVAN KEMOTERAPİ SONRASI CERRAHİSİZ İZLEYEBİLECEĞİMİZ BİR GRUP VAR MI?

Ann Surg Oncol (2017) 24:2855–2862
DOI 10.1245/s10434-017-5926-z

Annals of SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Nonoperative Management for Invasive Breast Cancer After Neoadjuvant Systemic Therapy: Conceptual Basis and Fundamental International Feasibility Clinical Trials

Henry M. Kuerer, MD, PhD[1], Marie-Jeanne T. F. D. Vrancken Peeters, MD, PhD[2], Daniel W. Rea, MBBS, PhD[3], Mark Basik, MD[4,5], Jennifer De Los Santos, MD[6], and Joerg Heil, MD[7]

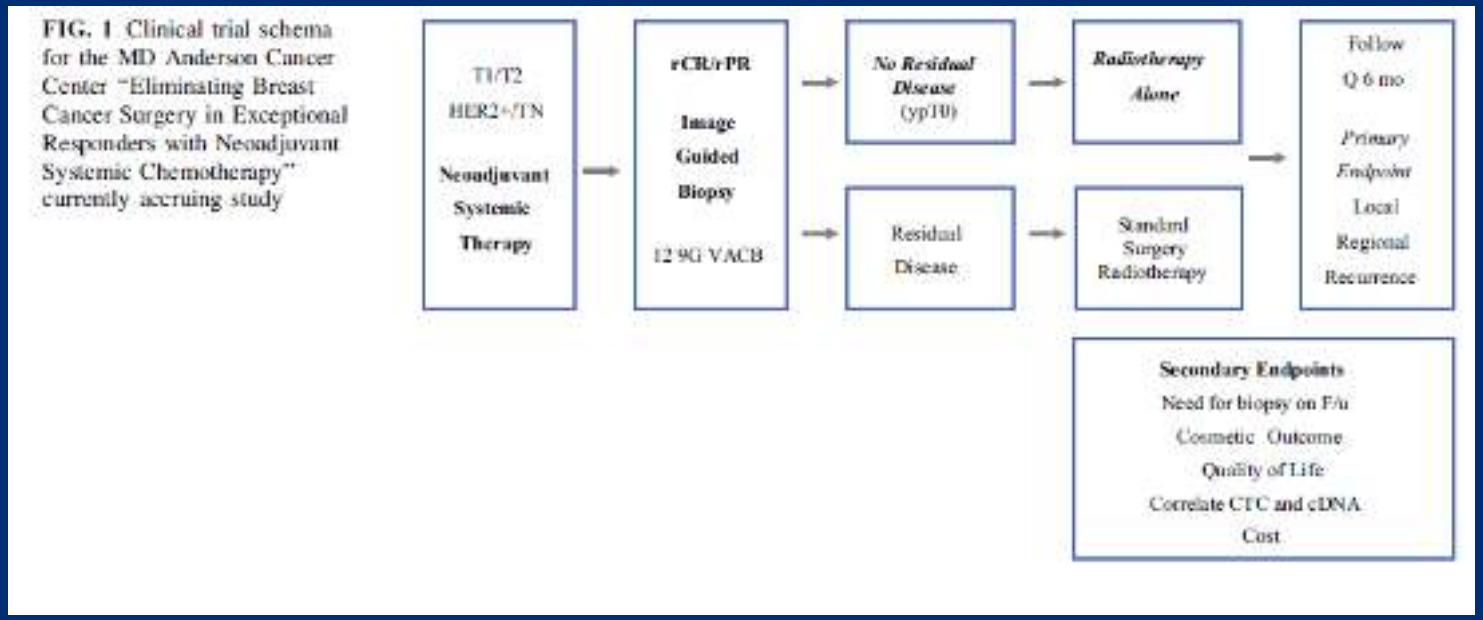


FIG. 1 Clinical trial schema for the MD Anderson Cancer Center "Eliminating Breast Cancer Surgery in Exceptional Responders with Neoadjuvant Systemic Chemotherapy" currently accruing study

Ann Surg. 2017 May 25. doi: 10.1097/SLA.0000000000002313. [Epub ahead of print]

A Clinical Feasibility Trial for Identification of Exceptional Responders in Whom Breast Cancer Surgery Can Be Eliminated Following Neoadjuvant Systemic Therapy.

Kuerer HM[1], Rauch GM, Krishnamurthy S, Adrada BE, Caudle AS, DeSnyder SM, Black DM, Santiago L, Hobbs BP, Lucci A Jr, Gilcrease M, Hwang RF, Candelaria RP, Chavez-MacGregor M, Smith BD, Arribas E, Moseley T, Teshome M, Miggins MV, Valero V, Hunt KK, Yang WT.

METHODS: Forty patients with T1-3N0-3 triple-negative or HER2-positive cancer receiving NST were enrolled in this single-center prospective trial. Patients underwent ultrasound-guided or mammography-guided FNA and VACB of the initial breast tumor region before surgery. Findings were compared with findings on pathologic evaluation of surgical specimens to determine the performance of biopsy in predicting residual breast disease after NST.

RESULTS: Median initial clinical tumor size was 3.3 cm (range, 1.2-7.0 cm); 16 patients (40%) had biopsy-proven nodal metastases. After NST, median clinical tumor size was 1.1 cm (range, 0-4.2 cm). Nineteen patients (47.5%) had a breast pCR and were concordant with pathologic nodal status in 97.5%. Combined FNA/VACB demonstrated an accuracy of 98% (95% CI, 87%-100%), false-negative rate of 5% (95% CI, 0%-24%), and negative predictive value of 95% (95% CI, 75%-100%) in predicting residual breast cancer. VACB alone was more accurate than FNA alone (P = 0.011).

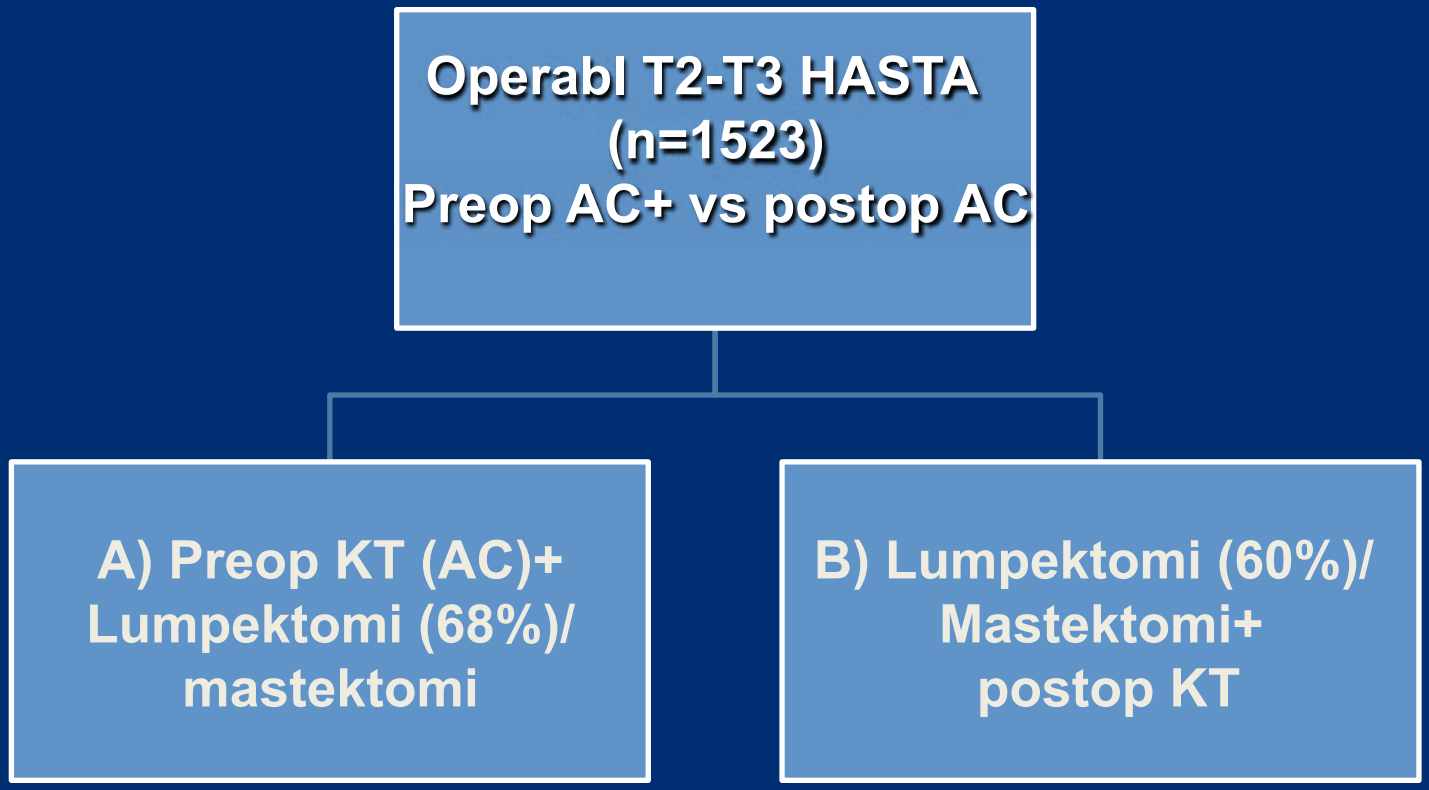
JAMA Surgery | Original Investigation

Identification of Patients With Documented Pathologic Complete Response in the Breast After Neoadjuvant Chemotherapy for Omission of Axillary Surgery

Andrea B. Tadros, MD; Wei T. Yang, MD; Savitri Krishnamurthy, MD; Gaiane M. Rauch, MD, PhD; Benjamin D. Smith, MD; Vicente Valero, MD; Dalliah M. Black, MD; Anthony Lucci Jr, MD; Abigail S. Caudle, MD; Sarah M. DeSnyder, MD; Medget Teshome, MD; Carlos H. Barcenas, MD; Makesha Miggins, MD; Beatriz E. Adrada, MD; Tanya Moseley, MD; Rosa F. Hwang, MD; Kelly K. Hunt, MD; Henry M. Kuerer, MD, PhD

RESULTS The analysis included 527 patients (median age, 51 [range, 23-84] years). Among 290 patients with initial nodal ultrasonography showing N0 disease, 116 (40.4%) had a breast pCR and 100% had no evidence of axillary lymph node metastases after NCT. Among 237 patients with initial biopsy-proved N1 disease, 69 of 77 (89.6%) with and 68 of 160 (42.5%) without a breast pCR had no evidence of residual nodal disease ($P < .01$). Patients without a breast pCR had a relative risk for positive nodal metastases of 7.4 (95% CI, 3.7-14.8; $P < .001$) compared with those with a breast pCR.

NSABP-18 STUDY



Lumpektomi sonrası: lokal nüks oranı (9-yıl takip):
10.7% (A) vs 7.6 (B) p=0.12

OS; fark yok!

NEOADJUVAN KT SONRASI NE ZAMAN CERRAHİ

- **NAK sonrası MKC: updates of NationalSurgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27.** J Clin Oncol. 2008; 26(5): 778-85. Rastogi et al.
- B-18: 751 hasta preop AC, ve 742 hasta postopAC.
- B-27: 784 hasta preop AC + cerrahi, 783 hasta: AC + T ve cerrahi ve 777 hasta AC + cerrahi+ T.

NEOADJUVAN KT SONRASI NE ZAMAN CERRAHİ?

- B-18 : DFS ve OS açısından 2 grup arasında fark yok.
- DFS ve OS açısından <50 yaş kadınlarda preop KT lehine (hazard ratio [HR] = 0.85, P = .09 for DFS; HR = 0.81, P = .06 for OS).

- B-27: AC ye T eklenmesi DFS veya OS değiştirmedi.
- Ancak patolojik tam cevap arttı: (26% v 13%, respectively; P < .0001).
- İki çalışmada da pCR hastalarda OS ve DFS daha iyi.

NEOADJUVAN KT SONRASI MKC

Chen AM et al. ***Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience.*** *J Clin Oncol.2004 Jun 15;22(12):2303-12.*

- 1987- 2000: 340 hasta NAK, KC ve RT
- Klinik evre: evre I : %4, evre II %58, evre III: %38
- 5 yıllık IBTR ve lokal nükssüz sağkalım sırasıyla: %95 ve % 91.

NEOADJUVAN KT SONRASI MKC YAPILABİLİR Mİ?

- M. D. Anderson Prognostic Index (MDAPI):
- LVI, residüel tm >2cm, residüel tm multifokal, klinik N2&N3,
- 0 (iyi prognostik faktör) veya 1 (kötü prognostik) : toplam skor 4
- 5-yıllık IBTR-siz sürvi oranları :

  düşük risk grubu : % 97

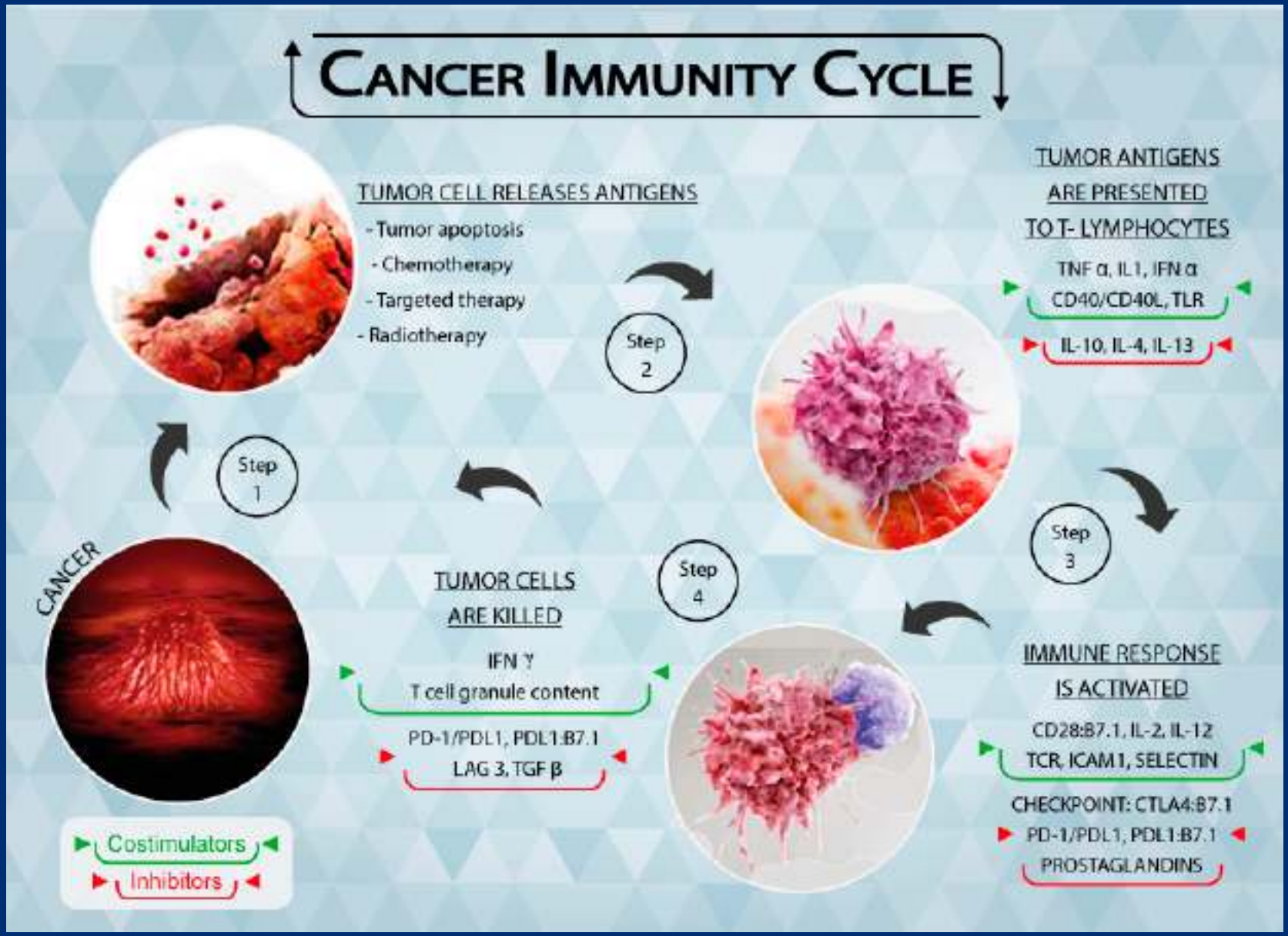
  Orta risk grubu : %88

  Yüksek risk grubu : %82
- Bu Prognostik Indeks içine ek biyomarkerlar alınabilir mi?

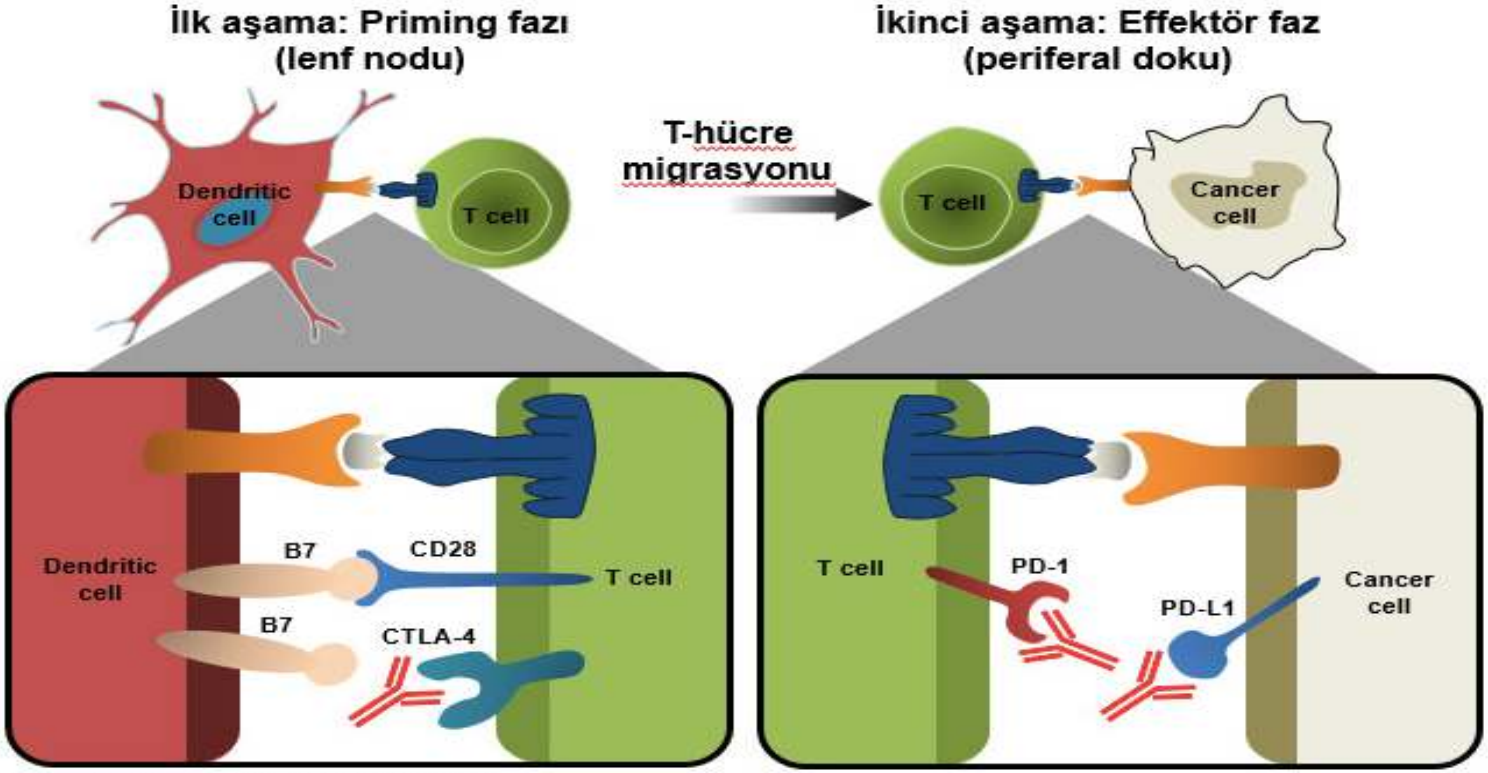
LABORATUVARDA SON YILLARDA YILDIZI YENİDEN PARLAYAN NE VAR?

İMMUNOTERAPİ

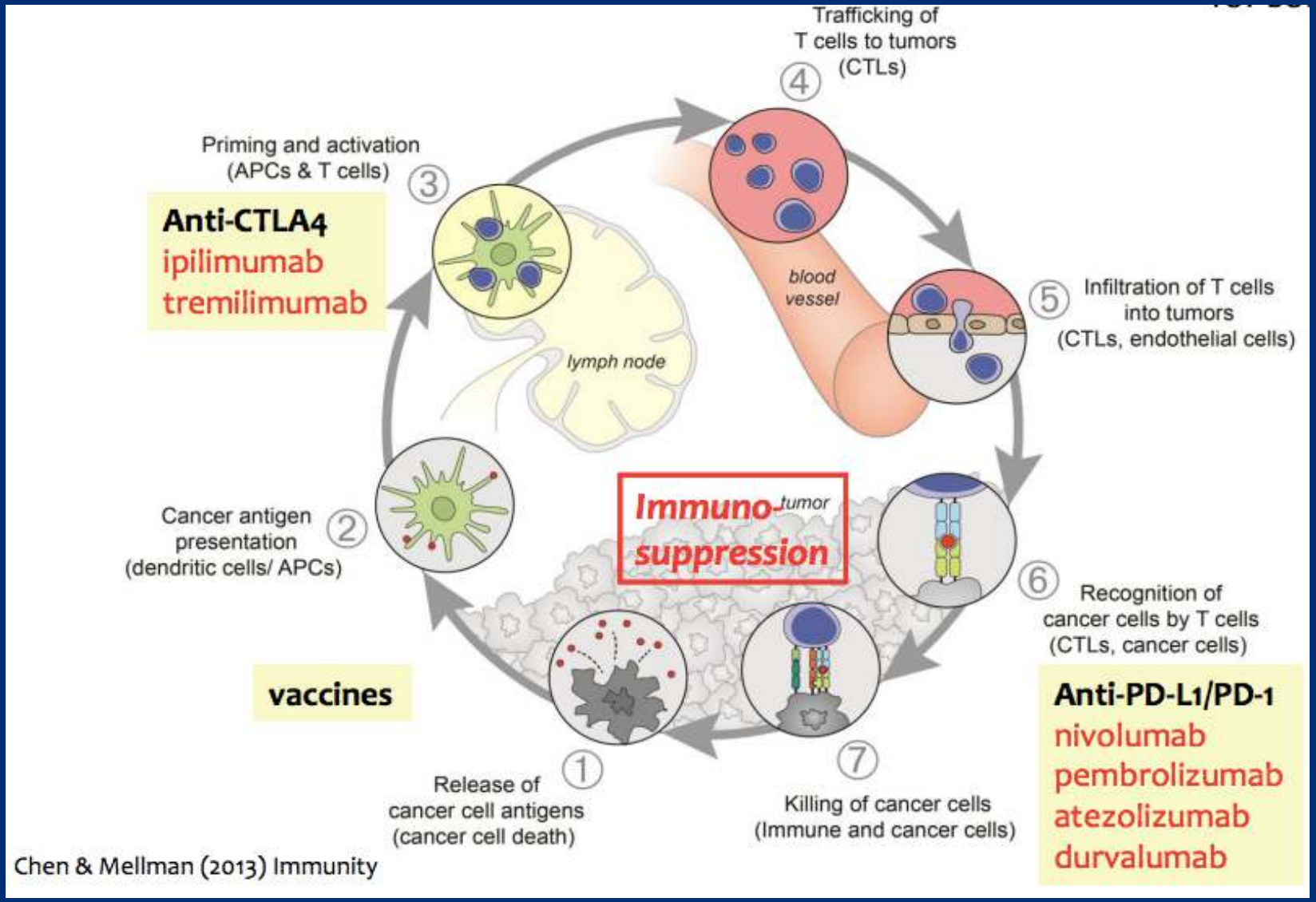
TÜMÖR İMMÜNOLOJİSİ



CTLA-4 & PD-1/L1
Kontrol noktası (Checkpoint) Blokajı



Ribas A. N Engl J Med. 2012;366:2517-2519.



Chen & Mellman (2013) Immunity

Table 1. Prognostic significance of PD-1 expression in human tumor-infiltrating lymphocytes

Tumor	Clinical correlation	Refs
Breast	High tumor-infiltrating PD-1$^+$ cell counts decreased patient survival	[54]
Breast	PD-1$^+$ TILs associated with tumor size, grade, LN status, and worse overall survival	[55]
Prostate	CD8$^+$ TILs expressed high levels of PD-1 and had restricted TCR Vbeta gene usage	[56]
Thyroid	PD-1$^+$ T cells in LNs were indicative of recurrent disease and correlated with Treg frequency	[57]
Melanoma	PD-1$^+$ TILs expressed CTLA-4, displayed an exhausted phenotype, and were functionally impaired compared with PD-1$^-$ TILs	[58]
Melanoma	PD-1 expression on CD4$^+$/CD8$^+$ T cells was found in primary tumor, with greater expression in distant metastases	[59]
Ovarian	CD8$^+$PD-1$^+$ T cells were impaired in IFN-γ/TNF-α secretion compared with CD8$^+$PD-1$^-$ T cells	[60]
RCC	Presence of PD-1$^+$ intratumoral immune cells associated with advanced stage and significant risk for cancer-specific death compared with PD-1$^-$ patients	[61]
NSCLC	CD8$^+$ TILs increased PD-1 expression resulting in reduced cytokine production and capacity to proliferate	[62]
HCC	CD8$^+$PD-1$^+$ TILs predicted disease progression and tumor recurrence	[63]

Table 2. Prognostic significance and pathological associations of PD-L1 and PD-L2 on human tumor cells

Tumor	Clinical correlation	Refs
Colon	PD-L1 expression was associated with TNM stage and predicted prognosis	[64]
Cervical	PD-L1 was expressed in only a minority of samples and influences patient survival	[65]
Pancreatic	PD-L1-positive patients had poorer prognosis than PD-L1-negative patients and PD-L1 was inversely correlated with $CD8^+$ TILs; PD-L2 showed no significant correlation with patient survival	[66]
Breast	PD-L1 expression was correlated with tumor size, grade, LN status, and significantly worse overall survival	[67]
Ovarian	PD-L1 expression on monocytes in ascites and blood from patients with malignant ovarian carcinoma was greater than in those with borderline/benign disease; PD-L1 expression led to poorer prognosis and was inversely correlated with intraepithelial $CD8^+$ T cells, while PD-L2 showed poorer prognosis but not a significant difference	[68,69]
RCC	Soluble PD-L1 was associated with larger tumors, worse stage, grade, and necrosis, and increased risk of death; PD-L1 was associated with poor prognosis	[70,71]
HCC	PD-L1 expression on hematoma cells enriched apoptotic $CD8^+$ T cells; greater expression of PD-L1 was associated with significantly poorer prognosis and was an independent predictor for recurrence, while PD-L2 expression correlated with poorer survival but not recurrence	[63,72]
NSCLC	PD-L1 was associated with EGFR[a] mutations and was a negative prognostic factor	[73]
Melanoma	Greater PD-L1 expression correlated with significantly lower overall survival and vertical growth of primary tumors; PD-L1 marks a subset of melanomas with shorter overall patient survival	[74,75]
Esophageal	PD-L1 and PD-L2 expression led to significantly poorer prognosis while only PD-L2 expression was inversely correlated with $CD8^+$ TILs	[76]

[a]Epidermal growth factor receptor.

Table 3. Biological agents targeting PD-1 or PD-L1 in cancer clinical trials

Biological agent	Class	Target	Company
CT-011 (pidilizumab)	Humanized IgG1	PD-1	CureTech
MK-3475 (lambrolizumab, pembrolizumab)	Humanized IgG4	PD-1	Merck
BMS-936558 (nivolumab)	Human IgG4	PD-1	Bristol–Meyers Squibb
AMP-224	PD-L2 IgG2a fusion protein	PD-1	Amplimmune/GlaxoSmithKline
BMS-936559	Human IgG4	PD-L1	Bristol–Meyers Squibb
MEDI4736	Humanized IgG	PD-L1	MedImmune
MPDL3280A	Human IgG	PD-L1	Roche
MSB0010718C	Human IgG1	PD-L1	Merck

PDL-1 VE PD1 LİGANDLARINI HEDEFLEYEN MONOKLONAL ANTİKORLARLA İLGİLİ YAYINLANAN MONOTERAPİ VEYA KOMBİNASYON TEDAVİSİ ÇALIŞMALARI

Antibody	Dose	Phase	Cancer	NCT* Number
Monotherapy				
Pidilizumab	0.2–6 mg/kg	I	AML, CLL, NHL, HL, MM	N/A
Pidilizumab	1.5 or 6 mg/kg	II	Malignant melanoma	NCT01435369
Pembrolizumab	1–10 mg/kg	I	Advanced solid tumors	NCT01295827
Nivolumab	0.3–10 mg/kg	I	Advanced solid tumors	NCT00441337
Nivolumab	1–10 mg/kg	I	Advanced solid tumors	NCT00730639
Nivolumab	1–20 mg/kg	I	Advanced solid tumors	N/A
Nivolumab	0.3–10 mg/kg	II	RCC	NCT01354431
Nivolumab	1 or 3 mg/kg	II	Platinum-resistant ovarian cancer	N/A
BMS-936559	0.3–10 mg/kg	I	Advanced solid tumors	NCT00729664
MPDL3280A	1–20 mg/kg	I	Advanced solid tumors and disease-specific cohorts	NCT01375842
MEDI4736	0.1–15 mg/kg	I	Advanced solid tumors	NCT01693562
MSB0010718C	1–20 mg/kg	I	Refractory malignancies	NCT01772004
Combination therapy				
Pidilizumab after ASCT	1.5 mg/kg	II	NHL	NCT00532259
Pidilizumab + rituximab	3 mg/kg	II	Follicular lymphoma	NCT00904722
Nivolumab + ipilimumab	1 mg/kg + 3 mg/kg	I	Malignant melanoma	NCT01024231
Nivolumab + platinum and nivolumab + ipilimumab	10 mg/kg and 1 mg/kg + 3 mg/kg	I	NSCLC	NCT01454102
Nivolumab + ipilimumab	3 mg/kg + 1 mg/kg	I	RCC	NCT01472081
Nivolumab + multipeptide vaccine	1–10 mg/kg	I/II	Malignant melanoma	NCT01176461

MİKROSATELLİT İNSTABİLİTELİ KOLOREKTAL KANSERDE İMMUNOTERAPİ

Table 1. Ongoing phase II and III clinical trials on immune checkpoint inhibitors in mCRC.

ClinicalTrials.gov Identifier	Agent	Trial	Patient Population	Phase	Primary Endpoint
NCT02860546	Nivolumab	A study evaluating TAS-102 plus nivolumab in patients with MSS CRC	mCRC	2	irORR
NCT02060188	Nivolumab	An investigational immunotherapy study of nivolumab and nivolumab in combination with other anti-cancer drugs in colon cancer that returned or spread (CheckMate142)	MSI/MSS mCRC	2	ORR
NCT02981524	Pembrolizumab	Phase 2 Study of GVAX (With CY) and pembrolizumab in pMMR advanced colorectal cancer	MMR-p mCRC	2	ORR
NCT02437071	Pembrolizumab	Assessment of the efficacy of pembrolizumab plus radiotherapy or ablation in metastatic colorectal cancer patients	mCRC	2	ORR
NCT02563002	Pembrolizumab	Study of pembrolizumab (MK-3475) vs. standard therapy in patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) stage IV colorectal carcinoma (MK-3475-177/KEYNOTE-177)	mCRC	3	PFS
NCT01876511	Pembrolizumab	Phase 2 Study of MK-3475 in patients with microsatellite instability (MSI) tumors	MSI/MSS mCRC	2	irORR/irPFS
NCT02788279	Atezolizumab	A study to investigate efficacy and safety of cobimetinib plus atezolizumab and atezolizumab monotherapy vs. regorafenib in patients with metastatic colorectal adenocarcinoma	mCRC	3	OS
NCT02291289	Atezolizumab	A multi-center study of biomarker-driven therapy in metastatic colorectal cancer	mCRC	2	PFS
NCT02992912	Atezolizumab	Atezolizumab with stereotactic ablative radiotherapy in patients with metastatic tumors (SABR-PD-L1)	Metastatic tumors	2	PFS
NCT03050814	Avelumab	Standard of care alone or in combination with Ad-CEA vaccine and avelumab in patients with previously untreated metastatic colorectal cancer (QUILT-2.004)	mCRC	2	18mPD
NCT02870920	Tremelimumab	Durvalumab and tremelimumab and best supportive care vs. best supportive care alone in patients with advanced colorectal adenocarcinoma refractory to standard therapies	mCRC	2	OS
NCT02227667	MEDI4736	Evaluation of the efficacy of MEDI4736 in immunological subsets of advanced colorectal cancer	mCRC	2	BRR

mCRC, metastatic colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stability; MMR-p, mismatch repair proficient; ORR, objective response rate; irORR, immune-related ORR; PFS, progression-free survival; irPFS, immune-related PFS; OS, overall survival; 18mPD, progressive disease at 18 months; BRR, best response rate. Details available at: www.clinicaltrials.gov.

SEPSİSTE İMMUNOTERAPİ

Arch Surg. 2002 Sep;137(9):1037-43; discussion 1043.

Decreased cytokine expression in peripheral blood leukocytes of patients with severe sepsis.

Cabioglu N[1], Bilgic S, Deniz G, Aktas E, Seyhun Y, Turna A, Gunay K, Esen F.

RESULTS: Higher serum IL-6, IL-8, C-reactive protein, and procalcitonin levels were found in patients with high multiple organ dysfunction and sepsis-related organ failure assessment scores (greater than or equal to the median values [8 and 11, respectively]), in contrast to decreased T-lymphocyte-associated IL-6 and TNF-alpha and monocyte-associated IL-10 and IL-12 proportions. Furthermore, in 28-day all-cause mortality analysis, there were higher levels of C-reactive protein and procalcitonin in nonsurvivors (n = 9) than in survivors (n = 7), while T-lymphocyte-associated IL-2, IL-6, IL-10, and TNF-alpha and monocyte-associated IL-10 and TNF-alpha proportions decreased in the nonsurvivors.

SEPSİSTE İMMUNOTERAPİ

STAT5 phosphorylation in T cell subsets from septic patients in response to recombinant human interleukin-7: a pilot study

Julie Demaret,[*,†,1] *Guillaume Dupont,*[*,†,1] *Fabienne Venet,*[*,†] *Arnaud Friggeri,*[§] *Alain Lepape,*[§] *Thomas Rimmelé,*[¶] *Jérôme Morel,*[‡] *and Guillaume Monneret*[*,†,2]

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- 13 Septik şoklu hasta lökositleri ex vivo ortamda düşük doz IL-7 etkisiyle T eff vs T reg artar
- Ex olan hastalarda STAT 5 eksikliği mevcut (STAT5 IL7 için anahtar signal molekülü).

IL-7 Restores Lymphocyte Functions in Septic Patients

Fabienne Venet,*[,†] Anne-Perrine Foray,* Astrid Villars-Méchin,* Christophe Malcus,* Françoise Poitevin-Later,* Alain Lepape,[†,‡] and Guillaume Monneret*[,†]

70 septik şok hastası: ex vivo IL7 ile uyarılaması:
Lökositlerden IFNgamma sekresyounu artırır.
STAT 5 fosforilizasyonu, T4 ve T8 proliferasyonları artar.

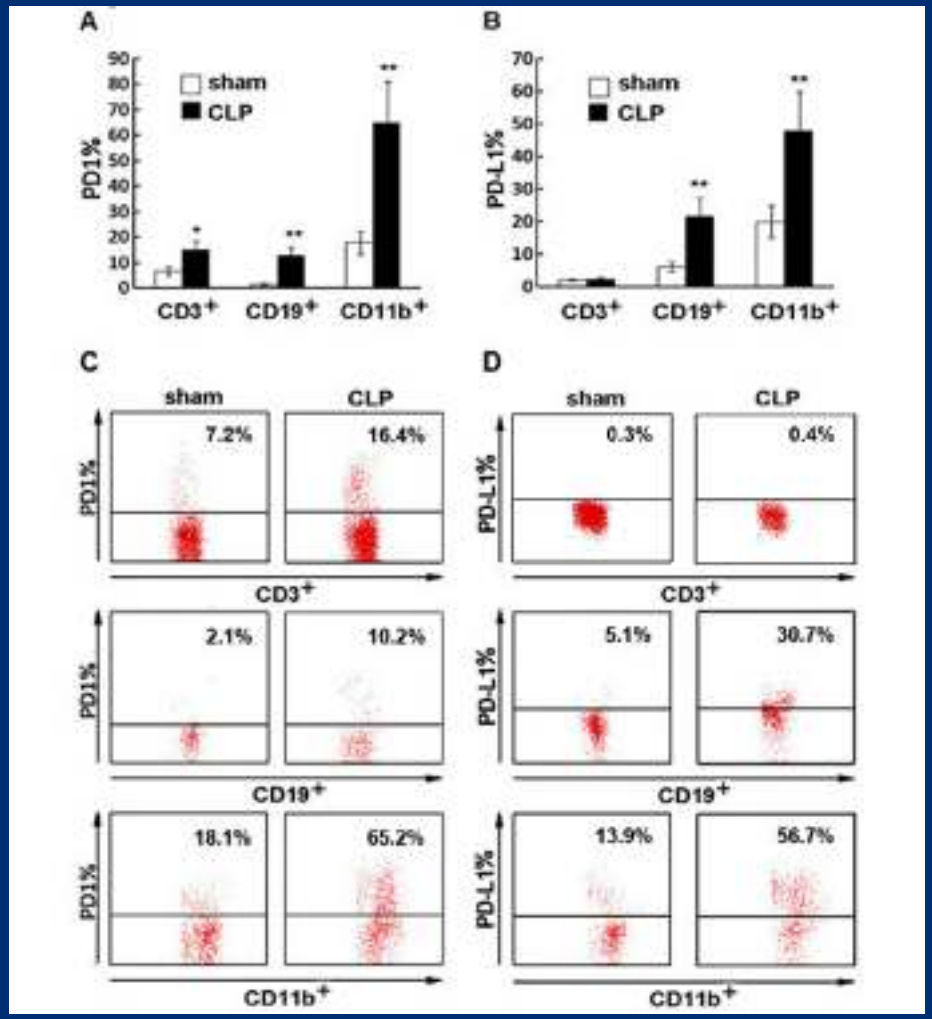
Zhang et al. Critical Care 2010, 14:R220
http://ccforum.com/content/14/6/R220

CRITICAL CARE

RESEARCH Open Access

PD-L1 blockade improves survival in experimental sepsis by inhibiting lymphocyte apoptosis and reversing monocyte dysfunction

Yan Zheng[†], Ying Zhou[†], Jingsheng Lou[†], Jinbao Li[†], Lulong Bo[†], Kerning Zhu[†], Xiaojun Wan[†], Xiaoming Deng[*], Zalong Cai[*]



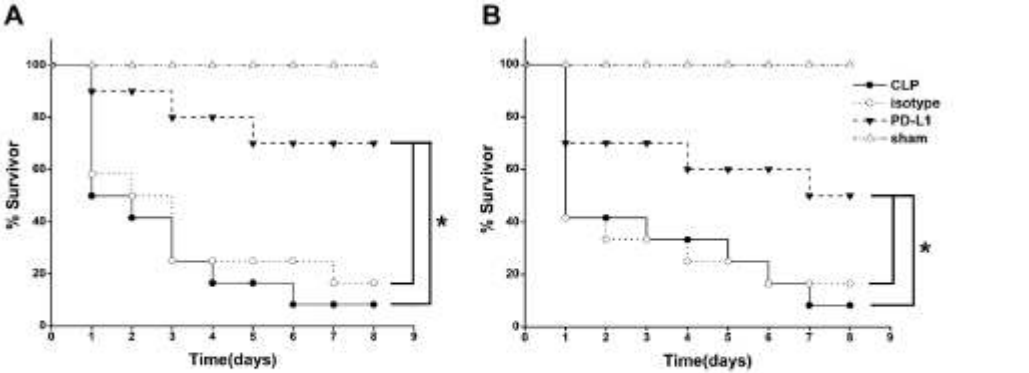


Figure 2 Anti-PD-L1 antibody administration protects mice from sepsis-induced lethality. **(A)** Anti-PD-L1 antibody pretreatment protected mice from CLP. CLP mice were given 50 μg anti-PD-L1 antibody (n = 18), 50 μg isotype control antibody (n = 12) or 0.2 mL saline intraperitoneally 24 h before CLP surgery. **(B)** Effect of intraperitoneal anti-PD-L1 antibody treatment given 3 h after CLP. CLP mice were given 50 μg anti-PD-L1 antibody (n = 18), 50 μg isotype control antibody (n = 12) or 0.2 mL saline (n = 12) intraperitoneally 3 h after CLP. Survival was monitored for eight days. Data are shown as the survival percent of animals. *P <0.05.

AntiPDL1: Mortalite azalır.
Sürvi artar.

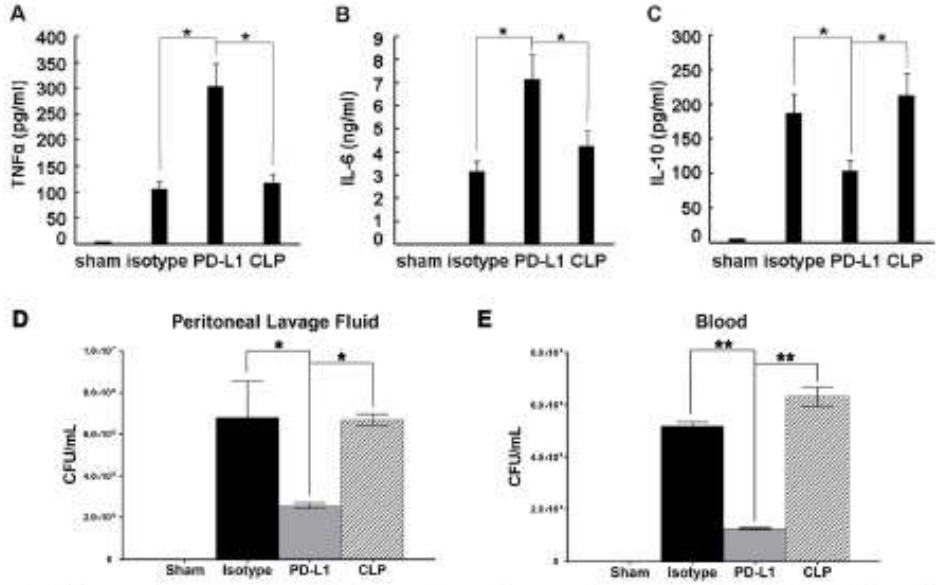


Figure 6 Levels of plasma cytokines and bacterial clearance. Mice underwent a sham procedure, CLP, CLP plus anti-PD-L1 administration, or CLP plus isotype control administration (n = 5 for each group). Levels of TNF-α **(A)**, IL-6 **(B)** and IL-10 **(C)** were measured 24 h after surgery. Treatment with anti-PDL1 antibody improves bacterial clearance in septic mice. Mice that received anti-PD-L1 antibody exhibited a deceased bacterial burden in peritoneal lavage fluid in comparison with mice that received isotype antibody or saline **(D)**. Mice that received anti-PD-L1 antibody exhibited a deceased bacterial burden in blood in comparison with mice that received isotype antibody or saline **(E)**. * $P < 0.05$, ** $P < 0.01$.

AntiPDL1: TNFα ve IL6 artar,
IL-10 azalır.

LABORATUVARDAN KLİNİĞE YENİ BULUŞLARI NASIL TAŞIYALIM?

- Bu çalışmaları kimler yapmalı?
- Temel bilimciler: yani moleküler biyologlar mı, genetikçiler, immunologlar mı
- Yoksa klinisyenler: cerrahlar mı, onkologlar mı?
- ALT Yapı Eğitim nasıl olmalı?

GELİŞMİŞ ÜLKELERDE SİSTEM NASIL?

- ABD: Cerrahi asistanlığı içinde 1 yıl araştırma
- 3 yıllık Surgical Oncology Fellowship programları içinde 1 yıl laboratuvarda araştırma (MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center vs)

AMAÇ: LABORATUVAR VE KLİNİĞE HAKİM AKADEMİSYENLER YETİŞTİRMEK

- Öğretim üyeleri hem Surgical Oncology de hem Cancer Biology de öğretim üyesi olup master ve doktora programları yürütebiliyorlar.
- Öğretim üyelerinin bazıları en az %50 zamanını laboratuvar araştırmalarına ayırmak zorunda.
- Kendi laboratuvarı ve büyük grantları (NIH. NCI) olanlar mevcut
- Ya da çoğu Kanser Merkezi içindeki laboratuvarlarla ortak çalışmalar yürütüyor, laboratuvarları temel bilim hocalarıyla paylaşıyor.

TÜRKİYEDE SİSTEM NASIL?

- Türkiyede ise bizler temel bilim hocalarımızla işbirliği içinde çalışıyoruz.
- Ek doktora yapmış akademisyenler var ama son derece az.
- Genelde temel bilimci hocalarımızla beraber işbirliği içinde proje yürütümü

SONUÇLAR

- Laboratuvar çalışmalarında yeni prognostik ve prediktif markerların bulunmasıyla beraber özellikle meme kanserinde ve diğer bazı kanser türlerinde bugün tanı ve tedavide **KİŞİYE ÖZEL** ve **HEDEFE YÖNELİK** yaklaşım söz konusudur.

- Günümüz tedavilerindeki gelişmeler cerrahinin gittikçe daha **KONSERVATİF** olmasına yol açmakta, yan etkiler azalmakta ve yaşam kalitesi artmaktadır.

- İmmunoterapideki gelişmeler gerek kanserde gerek sepsiste cerrahinin önümüzdeki 10 yılda parlayan yıldızı olacaktır.

- Translasyonel çalışmaların gelişmesi gerek klinik gerek laboratuvara hakim bilim adamlarının artmasıyla ivme kazanacaktır.

TEŞEKKÜRLER

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MD Anderson Cancer Center
Making Cancer History®

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