KONGRELERDEN ESİNTİLER

Dr. Serap Akyürek

Ankara Üniversitesi Tıp Fakültesi Radyasyon Onkolojisi Anabilimdalı

Plan

- Akselere parsiyel meme ışınlaması (APBI) 2016 guideline
- LN (+) meme kanserinde neoadj KT ve mastektomi veya MKC sonrası RT'nin lokal-bölgesel kontrole etkisi (ACOSOG Z1071 Alliance)
- DCIS da MKC sonrası tüm meme RT (WBRT) ± boost

Accelerated Partial Breast Irradiation(APBI) An Update of an ASTRO Evidence-Based Consensus Statement

Alphonse Taghian, MD, PhD
Massachusetts General Hospital, Boston, MA

On behalf of the ASTRO APBI Guideline Update Task Force

- Akselere parsiyel meme RT (APBI) → erken evre meme kanserinde lumpektomi sonrası tümör yatağına yüksek doz RT verilmesi

- **Teknikler**
  - **Brakiterapi**
    - Multikateter intertisyel brt
    - İntrakaviter brt (balon ve hibrid aplikator)
  - **Eksternal RT**
    - 3D konformal RT
    - IMRT
  - **İntraoperatif RT**
    - İntrabeam (Kv foton)
    - Mobetron (elektron)
    - Novac7 (elektron)

Hasta seçim kriterleri

Organization	Age	Tumor size	Margin	Histology	LN status
American Brachytherapy Society[64]	> 50	< 3 cm	Negative (at inked margin)	Invasive ductal carcinoma	pN0; by SLN or axillary dissection
American Society of Breast Surgeons[56]	> 45	< 2 cm	Negative (> 2 mm)	Invasive ductal carcinoma or DCIS	pN0; by SLN or axillary dissection
ASTRO[52]	> 60	< 2 cm	Negative (> 2 mm)	Invasive ductal or other favorable subtypes (mucinous, tubular, and colloid)	pN0; by SLN or axillary dissection

APBI ASTRO Guideline-2016

- İlk konsensus 2009 da yayınlanmıştı
- Bu konsensus da güncelleme yapılmış ve 2 anahtar soru üzerinde durulmuştur

1. Hangi hastalar APBI için alınabilir (klinik çalışma dışı)

- Uygun grup
- Dikkatli yaklaşım gereken grup
- Uygun olmayan grup

Özellikle yaş, marjin ve DCIS

2. Hangi hastalar intraop PBI için uygun olabilir

APBI ASTRO Guideline-2016

- Medline/PubMed 30.5.2008-15.3.2016 tarama
  - Yaş>18
  - Stg I-II
  - MKC sonrası APBI
  - OS; PFS,RR, toksite, QOL

- 419 abstrakt → 45 makale alınmış

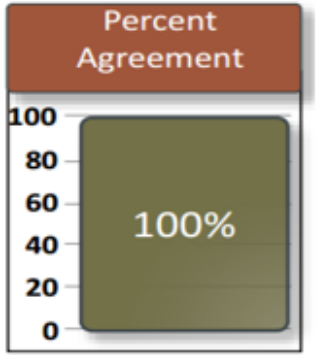
KQ1: Which patients may be considered for APBI outside of a clinical trial?

Age

A. Include age ≥50 years in the "suitable" group.

B. Patients who are aged 40-49 years and who meet all other elements of suitability are considered cautionary.

C. Retain patients with age less than 40 years or those who are 40 – 49 years without meeting other elements of suitable in the "unsuitable" group.



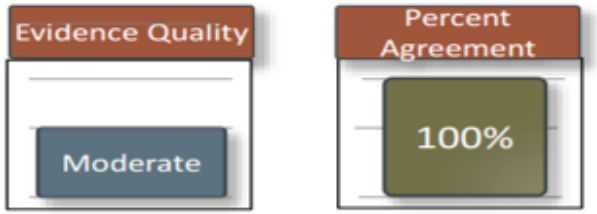
KQ1: Which patients may be considered for APBI outside of a clinical trial?

Margins

A. Maintain the current selection criteria for "suitable", "cautionary" and "unsuitable" patients based on margin status.

DCIS

A. Include patients with low-risk DCIS as per RTOG 9804 criteria (i.e. screen-detected, low to intermediate nuclear grade, ≤ 2.5 cm size, resected with margins negative at ≥ 3 mm), in the "suitable" group.



KQ1: Which patients may be considered for APBI outside of a clinical trial?

Patient Group	Risk Factor	Original	Update
Suitable	Age	≥ 60 years	≥ 50 years
	Margins	Negative by at least ≥2 mm	No change
	T stage	T1	Tis or T1
	DCIS	Not allowed	If all of the below: • Screen-detected • Low to intermediate nuclear grade • Size ≤ 2.5 cm • Resected with margins negative at ≥ 3 mm

KQ1: Which patients may be considered for APBI outside of a clinical trial?

Patient Group	Risk Factor	Original	Update
Cautionary	Age	50 – 59 years	• 40-49 years if all other criteria for "suitable" are met • ≥ 50 if patient has at least one of the pathologic factors below and does not have any "unsuitable" factors. ***Pathologic factors*:** • Size 2.1-3.0 cm* • T2 • Close margins (<2 mm) • Limited/focal LVSI • ER negative • Clinically unifocal with total size 2.1-3.0 cm† • Invasive lobular histology • Pure DCIS ≤3 cm if not in "suitable" group • EIC ≤3 cm
	Margins	Close (<2 mm)	No change
	DCIS	≤3 cm	≤3 cm and not in “suitable” group

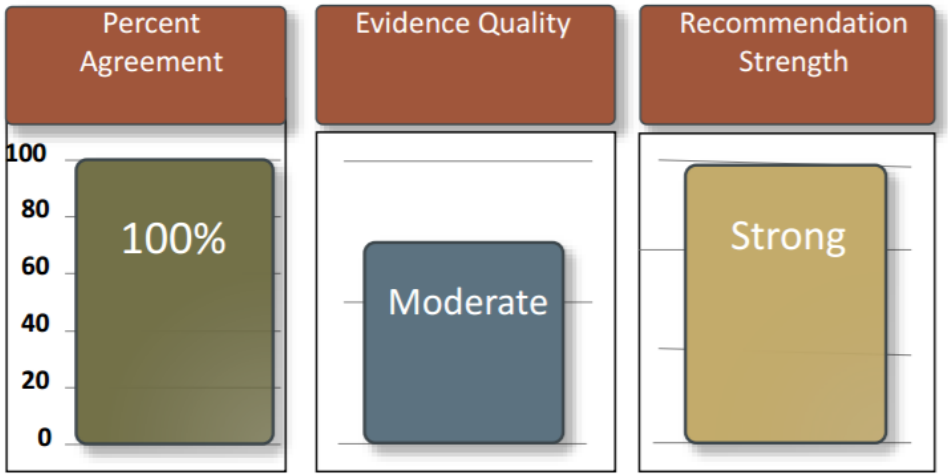
* The size of the invasive tumor component;† Microscopic multifocality allowed, provided the lesion is clinically unifocal (a single discrete lesions by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) falls between 2.1 and 3.0 cm.

KQ1: Which patients may be considered for APBI outside of a clinical trial?

Patient Group	Risk Factor	Original	Update
Unsuitable	Age	<50 years	• <40 years • 40 – 49 years and do not meet the criteria for "cautionary"
	Margins	Positive	No change
	DCIS	>3 cm	No change

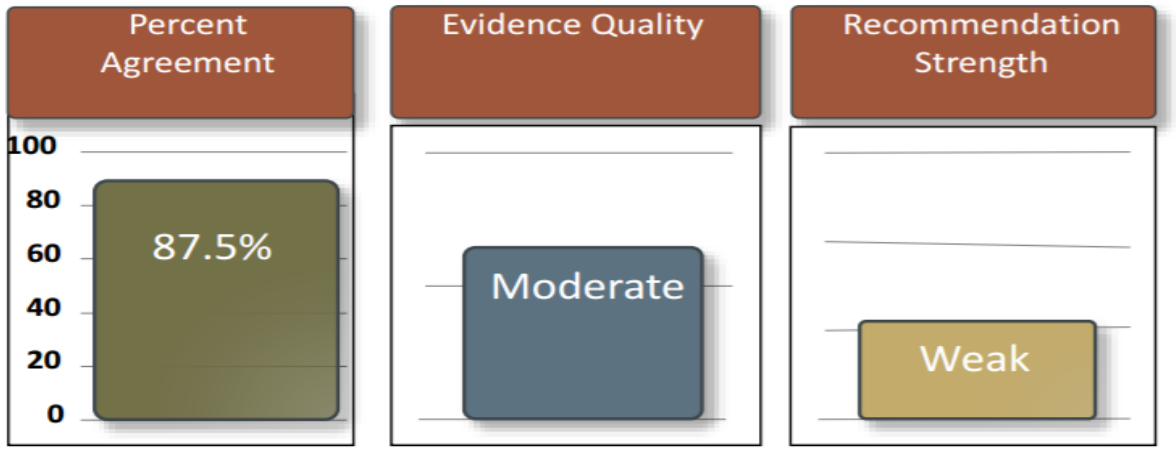
KQ2: Which patients may be considered for intraoperative partial breast irradiation?

B. Electron beam IORT should be restricted to women with invasive cancer considered "suitable" for partial breast irradiation (Table 1) based on the results of a multivariate analysis with median follow up of 5.8 years.



KQ2: Which patients may be considered for intraoperative partial breast irradiation?

C. Clinical outcome data from low-energy x-ray IORT as a treatment modality for PBI are limited by the short median follow up (2.4 years) from an early stage breast cancer phase III trial and a paucity of other prospective data with longer follow up. Therefore, low-energy x-ray IORT for PBI should be used within the context of a prospective registry or clinical trial. When low-energy x-ray IORT is used, its use should be restricted to women with invasive cancer considered "suitable" for partial breast irradiation.



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Special Article

Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement

Candace Correa MD [a], Eleanor E. Harris MD [b], Maria Cristina Leonardi MD [c], Benjamin D. Smith MD [d], Alphonse G. Taghian MD PhD [e], Alastair M. Thompson MD [f], Julia White MD [g], Jay R. Harris MD [h,*]

RUTGERS
Cancer Institute
of New Jersey

Impact of radiation on Local regional control in women with node positive breast cancer treated with neoadjuvant chemotherapy and axillary lymph node dissection: results from ACOSOG Z1071 (Alliance)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Bruce G. Haffty, MD

Linda M. McCall, Karla V. Ballman, Kelly K. Hunt, and Judy C. Boughey

ACOSOG Z1071 (ALLİANCE)

Clinical Investigation

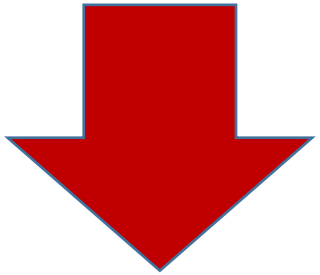
Patterns of Local-Regional Management Following Neoadjuvant Chemotherapy in Breast Cancer: Results From ACOSOG Z1071 (Alliance)

Bruce G. Haffty, MD,* Linda M. McCall, MS,† Karla V. Ballman, PhD,‡ Sarah McLaughlin, MD,§ Reshma Jagsi, MD,‖ David W. Ollila, MD,¶ Kelly K. Hunt, MD,# Thomas A. Buchholz, MD,** and Judy C. Boughey, MD††

2016 Mart, Int J Radiat Oncol Biol Phys

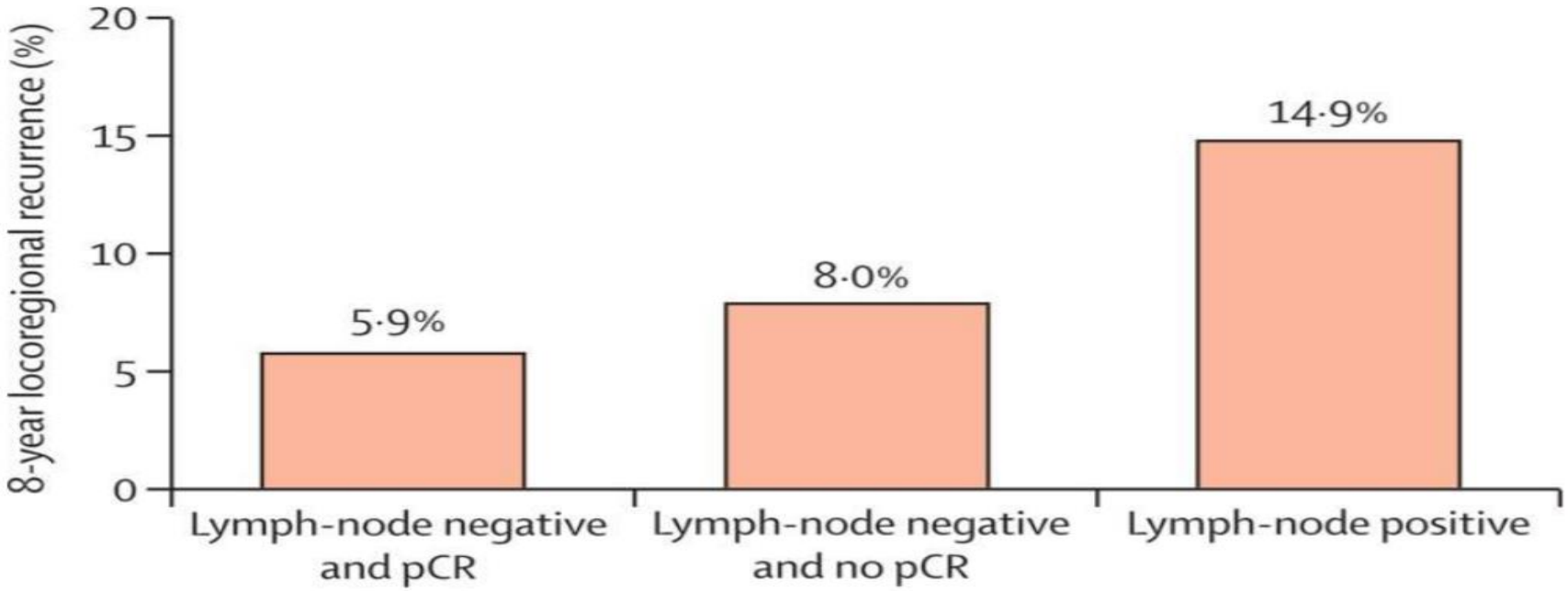
ACOSOG Z1071 (ALLİANCE)

ASTRO 2016



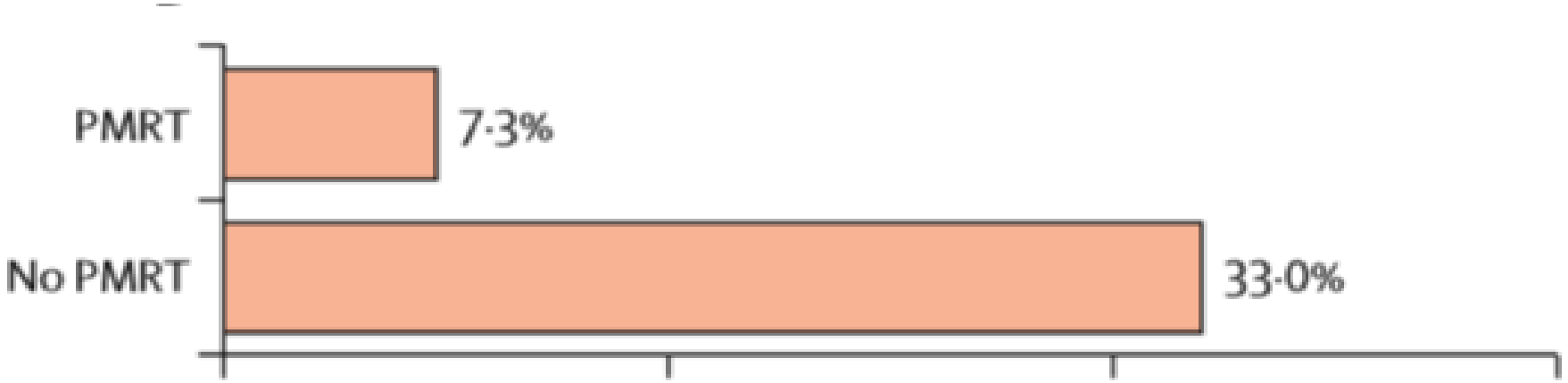
LN(+), NAC ve cerrahi (mastektomi veya MKC) sonrası adj RT'nin lokal-bölgesel kontrol de ki etkisi??

NSABP B-18 ve B-27 NAC, mastektomi (+), post-mastektomi RT (-) olgular da LRR



Hoffman, Lancet Oncol 2012

- MDACC → NAC sonrası pCR olan evre III hastalarda 10Y LRR



P=0.04

Hoffman, Lancet Oncol 2012

ACOSOG Z1071 (ALLİANCE)

- 2009-2011
- Faz II, çok merkezli çalışma
- 701 inv meme ca T1-3, N1-2
- NAC sonrası tüm hastalar SLND → ALND
- MKC veya mastektomi sonrası ± adj RT

ACOSOG Z1071 (ALLİANCE)

Sonuçlar

- **Cerrahi**
  - Mastektomi 422 **(%60.4)**
  - MKC 277 (%39.6)
- **Lenf nodu**
  - 506 **(%72.2)** patolojik **LN (+)**
  - 195 (%27.8) patolojik LN (-)
- **Radyoterapi**
  - 591 **(%85.3)** adj **RT (+)**
  - 102 (%14.7) adj RT (-)

ACOSOG Z1071 (ALLİANCE)

- Median takip **4 yıl** (3ay-6.2 yıl)
- Lokal-Bölgesel Rekurrens (LRR) - **40 hasta**
  - 24 lokal, 9 bölgesel, 6 lokal-bölgesel
- Uzak met – 118, ex-96 hasta

ACOSOG Z1071 (ALLİANCE)

- Patolojik **tam yanıt**(pCR), **rezidü hastalık** varlığı ile karşılaştırıldığında

  - LRR siz sağkalım……HR 0.23, p=0.003
  - Hastalıksız sağkalım……HR 0.40, p=0.002
  - Meme ca spesifik sağkalım……HR 0.27, p=0.0007
  - Genel sağkalım……HR 0.33, p=0.001

ACOSOG Z1071 (ALLİANCE)

- RT alan ve almayan hastalar karşılaştırıldığında

  - Hastalıksız sağkalım
  - Meme ca spesifik sağkalım
  - Genel sağkalım

  } Fark yok

- LRR siz sağkalım
  - Patolojik **N (-)** **RT (+)** **%95** vs RT (-) **%70** p=0.15
  - Patolojik **N (+)** **RT (+)** **%92** vs RT (-) **%72** p=0.11

LRR için Risk Faktörleri

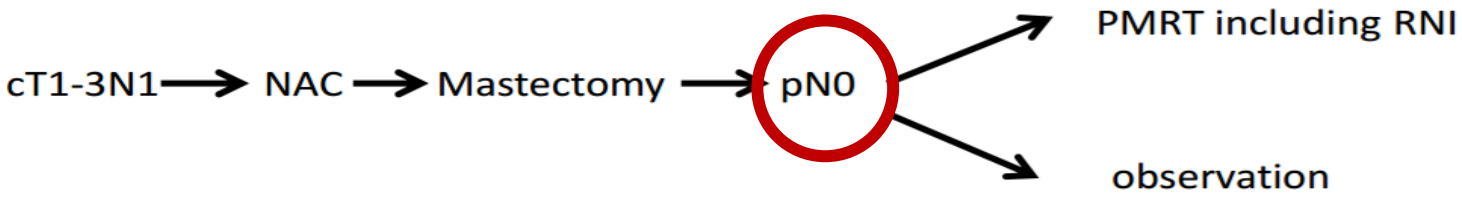
Univaryan analiz

		HR (%95 CI)	P değeri
T evre	T0-2	1.00 (ref)	0.34
	T3-4	1.38 (0.72-2.65)	
Pat. CR meme	(-)	1.00 (ref)	0.019
	(+)	0.35 (0.15-0.84)	
Pat. CR aksilla	(-)	1.00 (ref)	0.064
	(+)	0.51 (0.25-1.04)	
Yaş	<50	1.00 (ref)	0.42
	≥50	1.30 (0.69-2.45)	
Tm biyoloji	Her2 (-)	1.00 (ref)	0.002
	Her2 (+)	1.49 (0.65-3.45)	
	Triple (-)	3.59 (1.68-7.68)	
MKC		1.00 (ref)	0.067
Mastektomi		0.55 (0.29-1.04)	
Radyoterapi	(+)	1.00 (ref)	0.033
	(-)	2.18 (1.06-4.48)	

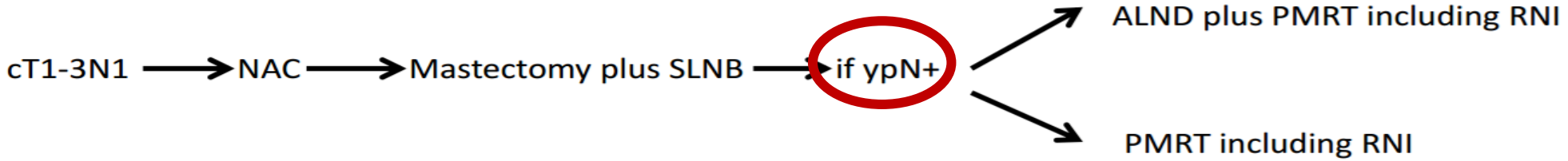
Sonuç

- NAC sonrası Adj RT alan ve almayan hastalarda OS, DFS ve DMFS farklılık göstermemiştir
- Adj RT LRR' i yaklaşık 2 kat azaltmaktadır!
- Adj RT hem patolojik LN (+) hem de LN (-) hastalarda lokal-bölgesel kontrolü iyileştimede etkili görünmektedir (trend mevcut)
- Tümör biyolojisi (triple negatif ve Her2+) LRR de önemli bir etkiye sahip
- Randomize bir çalışma değil, RT kararı ve planı tedavi eden Dr yetkisinde ve RT kalite kontrolü yok!

NSABP B51/RTOG 1304 Phase III Trial



Alliance A011202 Phase III trial



Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control: Collaborative Analysis of Patients Treated at Ten Academic Institutions

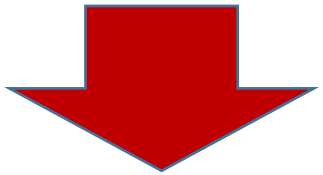
Meena S. Moran, MD
Professor, Therapeutic Radiology
Yale University School of Medicine

ASTRO-2016

- DCIS olgularda tüm meme RT (WBRT) sonrası tm yatağına ‘boost’ uygulamasının bir katkısı var mı?

- DCIS-boost verilmesinin ipsilateral meme tümör rekürrens (IBTR) de bir etkisi var mıdır?

- MKC sonrası WBRT ile yaklaşık %50 IBTR riski azalmakta
  - Bu katkı tüm subgruplar için geçerli
- IBTR en fazla olduğu bölge tm yatağı → tümör yatağına boost ile RT doz artımına olanak sağlamakta
- İnvaziv tümörlerde WBRT sonrası boost RT ne öğrendik



Boost vs. No Boost Invasiv Tm

	Lyon [1]	Budapest[2]	EORTC [3]
Median F/U	3.3 yrs	5.3	20 yrs
#patients	1024	207	5138
Fractionation	50 Gy/ 2.5 Gy ± 10 Gy	50 Gy/2 Gy ±12-16 Gy	50 Gy /2Gy ± 16 Gy
LR(Boost vs. no Boost)	3.6% vs 4.5%	15.5% vs 6.7%	12% vs 16%
p value	0.044	0.049	<0.0001

LR risk azalması tüm yaş gruplarında geçerli!

DCIS Boost vs No Boost

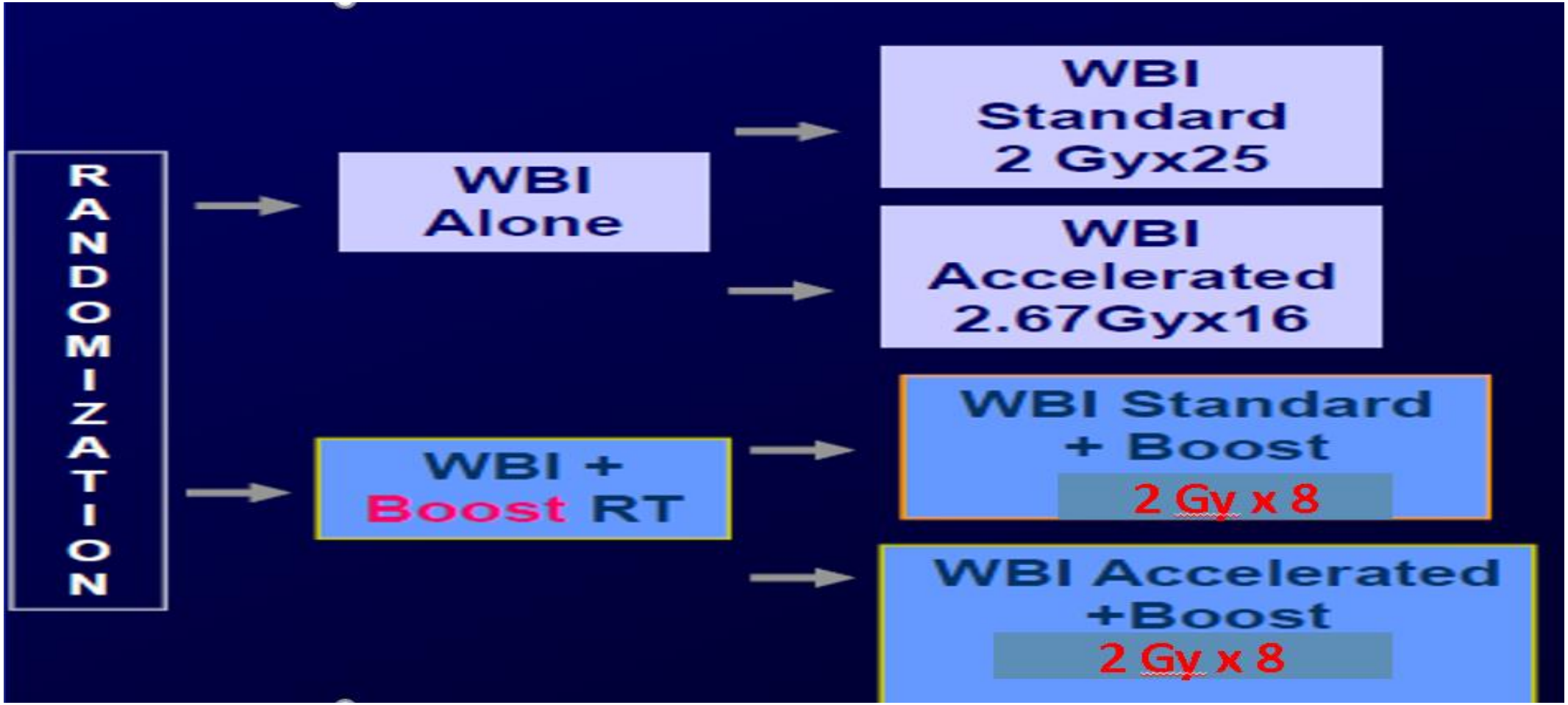
Study	Year published	Total # Patients	% Boosted	Median F/U	Effect of Boost for DCIS
Vargas	2005	313	95.0%	7 yrs	No
Omlin	2006	316*	52.0%	6 yrs	Yes
Yerushalmi	2006	75	25.0%	6.8 yrs	No
Jiveliouk	2009	107	37.3%	4 yrs	No
Monteau	2009	208**	71%	7.4 yrs	Yes
Wai	2011	482	29.8%	9.3 yrs	No
Rakovitch	2013	1895	29.6%	10 yrs	No
Meattini	2013	389	48.8%	7.7 yrs	Yes
Wong	2012	220	36%	3.8 yrs	Yes
Kim	2014	728	31.9%	6.7 yrs	No
Current Study, Moran	2015	4,131	64.4%	9 yrs	Yes

DCIS Boost vs No Boost

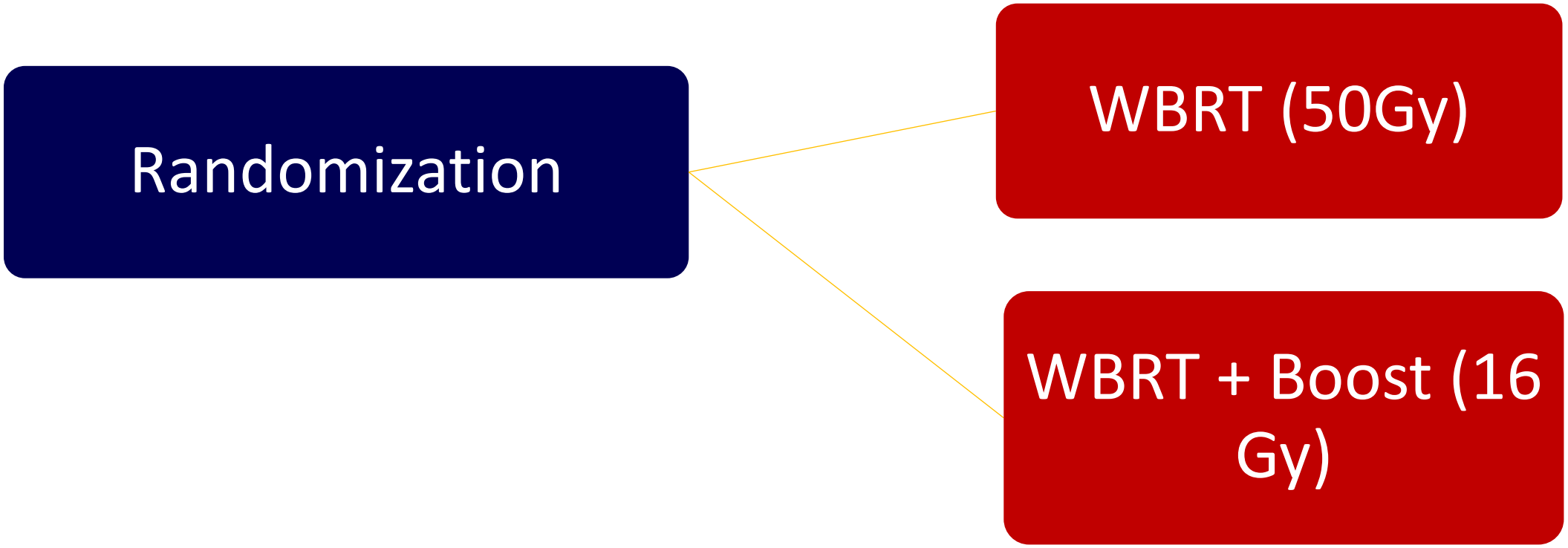
- DCIS boost yararını göstermek çok zor!!!!
  - WBRT sonrası IBTR zaten çok az!!!
  - Çok uzun takip gerekli

- Faz III yayınlanmış çalışma yok!!

PIII-Boost for DCIS TROG 07.01/BIG 3-07



PIII Boost for DCIC: BONBIS Trial



Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control: Collaborative Analysis of Patients Treated at Ten Academic Institutions

- 10 merkez, USA, Kanada ve Fransa (tecrübeli akademik merkez)
- Hastalar
  - Pür DCIS
  - RT…..WBRT (APBI olmayacak)
  - Boost **foton** veya **elektron** demetleri (brt dahil değil)
  - Min 5 yıl takip

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control: Collaborative Analysis of Patients Treated at Ten Academic Institutions

- **Sonuçlar**
  - Toplam n= **4131**
    - Boost (-) 1470 **(%35.6**)
    - Boost (+) 2661 **(%64.4**)
  - Median yaş**: 56**
  - Median takip: **9 yıl**
  - Marjin (+) n=168 **(%4**)
  - Grade 2-3 komponent n=2817 **(%68**)
  - ER durum bilinen n=1538 **(%37**)

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control: Collaborative Analysis of Patients Treated at Ten Academic Institutions

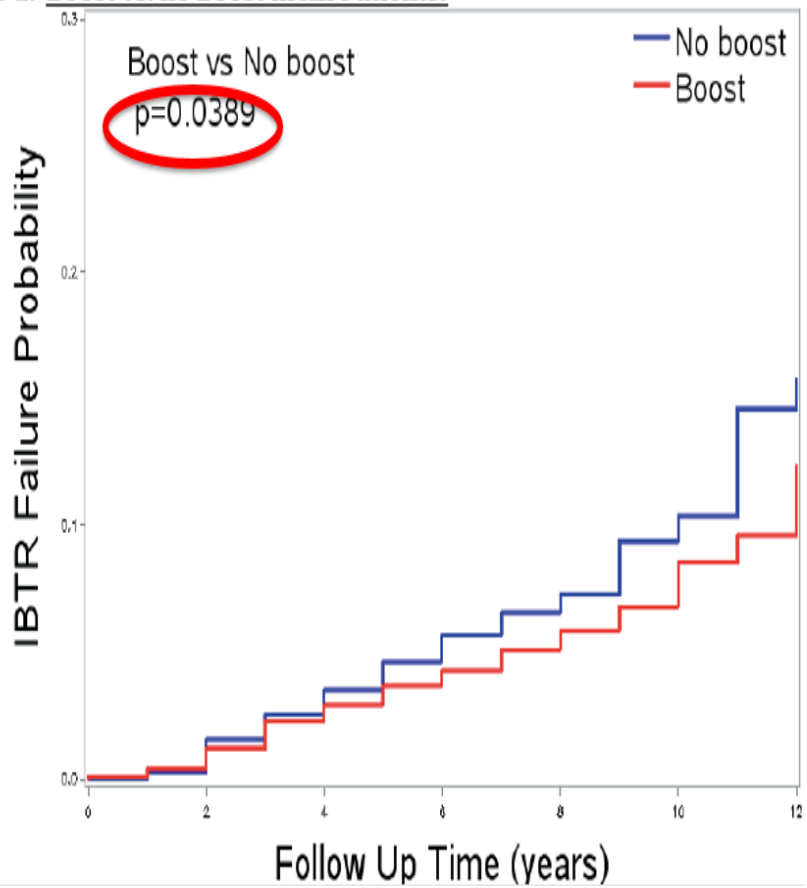
- Tüm grup için
  - 253 **(%6.1)** IBTR
    - İnvaziv rekr n=118 **(%47**)
    - DCIS rekr n=135 **(%53**)

  - IBTR-free OS
    - 5Y %96.8
    - 10Y %93.6
    - 15Y %90.4

Boost vs No Boost n=4131

Yıllar	**Boost % (95% CI)**	**No-boost % (95% CI)**	**p=0.0389**
5	97.1% (0.96-0.98)	96.3% (0.95-0.97)	
10	94.1% (0.93-0.95)	92.5% (0.91-0.94)	
15	91.6% (0.90-0.93)	88.0% (0.85-0.91)	

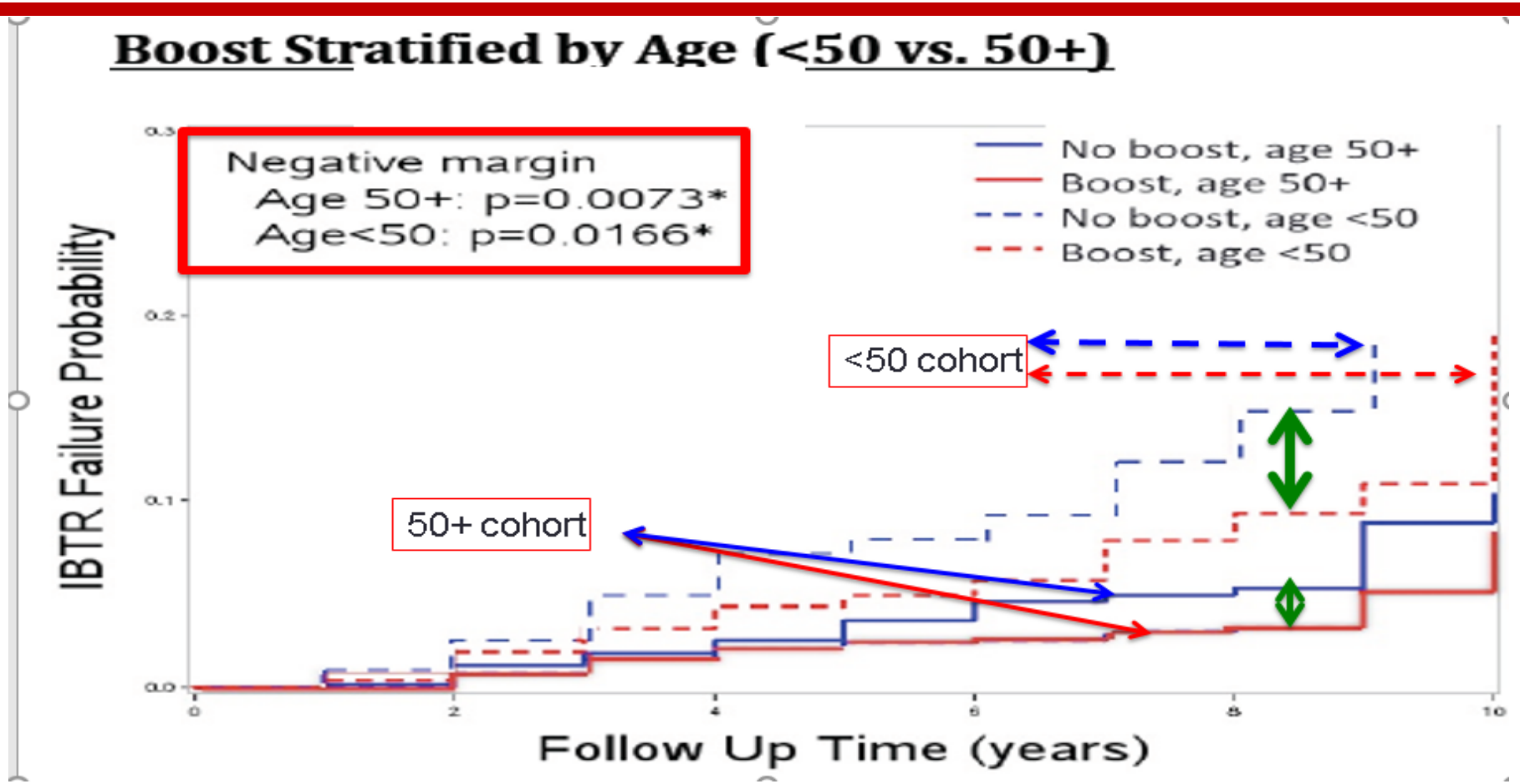
Figure 1. Boost vs. no Boost in All Patients:



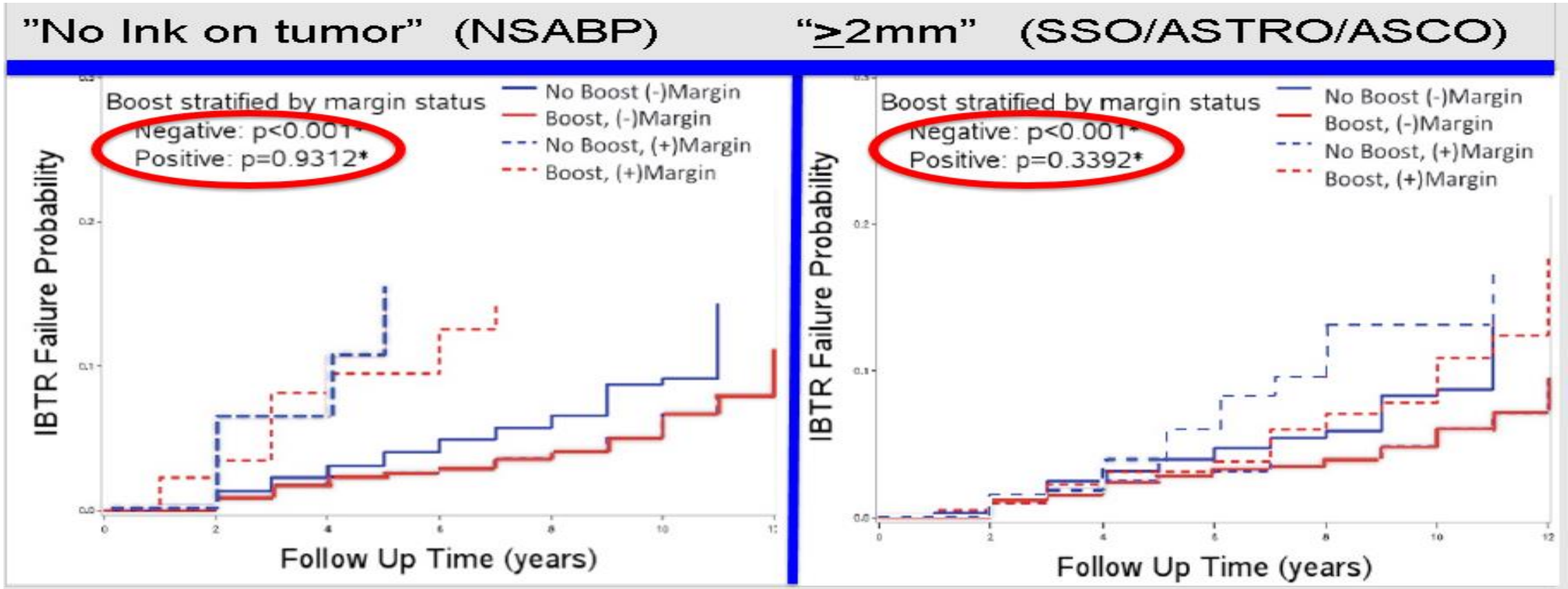
Multivaryan Analiz- Boost vs No Boost

Characteristics		HR	P-value
Boost	no	1.0	-
	yes	0.69(0.53-0.91)	<0.010
Grade	I	1.0	-
	II/III	1.62 (1.06-2.47)	0.020
Comedo	no	1.0	-
	yes	1.13 (0.81-1.57)	0.470
Tamoxifen	no	1.0	-
	yes	0.60 (0.42-0.95)	0.030
Margin	neg	1.0	-
	positive	1.79(1.05-3.05)	0.030
Age	<50	1.0	-
	⩾50	0.57 (0.45-0.74)	0.010

DCIC-Boost vs No Boost
Yaşa göre değerlendirilmesi



DCIC-Boost vs No Boost
Marjin tanımına göre değerlendirilmesi



Sonuç

- Bu çalışma DCIS - boost araştıran en fazla hasta sayılı çalışma!!!
- DCIS boost, invaziv kanserlerde olduğu gibi uzun dönem IBTR'i önlemede küçük ancak anlamlı katkı sağlamakta!!!
- Bu katkı
  - tamoksifen kullanımı veya
  - (-) sınırdan bağımsız
- DCIS boost eklenmesi, özellikle yaşam beklentisi 10 yılın üzerinde olan hastalarda göz önünde bulundurulmalı

RT yaklaşımlarına göre LRR

	LRR (5 YR)	HR(p)
Mastectomy		
Residual Node Positive		
PMRT	93.7%	2.24 (.17)
No PMRT	59.8%	
Residual Node Negative		
PMRT	100%	
No PMRT	95.4%	
Breast Conserving Surgery		
Residual Node Positive		
Regional Nodal RT	88.5%	1.01 (.99)
No Regional Nodal RT	90.5%	
Residual Node Negative		
Regional Nodal RT	90.3%	1.59 (.54)
No Regional Nodal RT	93.8 %	

Abstract 323: ART and loco-regional control for N+ treated with neo-adjuvant chemotherapy and ALND (ACOSOG Z1071)

Multivariate Analysis

Molecular Phenotype	Hazard Ratio	P value
HR pos/Her2-	1.00	
Her2+	2.11	
Triple negative	5.53	< 0.0001

LRR için Risk Faktörleri

Multivariate Analysis

Molecular Phenotype	Hazard Ratio	P value
HR pos/Her2-	1.00	
Her2+	2.11	
Triple negative	5.53	< 0.0001

Triple negative patients

LRR-free survival

	No XRT	XRT	P value
Mastectomy	75.8%	90%	NS
BCT (nodal)	85.7%	95.2%	NS

KQ2: Which patients may be considered for intraoperative partial breast irradiation?

A. Patients interested in cancer control equivalent to that achieved with whole breast irradiation post lumpectomy for breast conservation should be counseled that in two clinical trials the risk of IBTR was higher with IORT.

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control: Collaborative Analysis of Patients Treated at Ten Academic Institutions

		N (%)	N (%)	squared
Number of patients	4131	1470 (35.6)	2661(64.4)	**p value**
Age (median)	56.1	56.2	56.0	NS
Standard Deviation	10.9	10.7	11.0	
Age (years)				0.1245
<50	1301(31.5)	441(30)	860 (32.3)	
≥50	2830(68.5)	1029 (70)	1801(67.7)	
DCIS Grade				0.4846
I	694(16.8)	250(17)	444(16.7)	
II /III	2817(68.2)	975(66.3)	1842(69.2)	
Unknown	620(15)	245(16.7)	375(14.1)	
Tumor size				0.0808
≤1.0cm	1659(40.2)	608(41.4)	1051(39.5)	
>1.0cm	1680(40.7)	665(45.2)	1015(38.1)	
unknown	792(19.2)	197(13.4)	595(22.4)	
Margin status				<0.001
(Positive-0mm)	168(4.1)	44(3.0)	124(4.7)	
(Negative>0mm)	3611(87.4)	1285(87.4)	2326(87.4)	
Unknown	352(8.5)	141(9.6)	211(7.9)	
Comedo necrosis				0.0266
Absent	1066(25.8)	262(17.8)	804(30.2)	
Present	1301(31.5)	270(18.4)	1031(38.7)	
Unknown	1764(42.7)	938(63.8)	826(31)	
Estrogen receptor status				0.0429
negative	296(7.2)	85(5.8)	211(7.9)	
positive	1242(30.1)	287(19.5)	955(35.9)	
unknown	2593(62.8)	1098(74.7)	1495(56.2)	