San Antonio Meme Kanseri Sempozyumu

10-14 Aralık 2019

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Tıbbi Onkoloji Kliniği

Ankara Meme Hastalıkları Derneği
16 Ocak 2020, Ankara

SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM
December 10-14, 2019
Henry B. Gonzalez Convention Center, San Antonio, Texas, USA

- 1977'den beri yapılmakta
  - 1 gün→5 gün, 90 ülke
- 2007'de isim değişikliği CTRC Cancer Therapy and Research Center in UT Health Science Center -AACR San Antonio Breast Cancer Symposium
- 1990- 13.SanAntonio 526 katılımcı-201 yazı-24 ülke
- ……
- 2018-41.SanAntonio 7749 katılımcı-1596 yazı-88 ülke

Klinik Çalışmalar

- Metastatik Evre (6 sunum)
- Erken ve Lokal İleri Evre
  - Neoadjuvan (5 sunum)
  - Adjuvan (2 sunum)

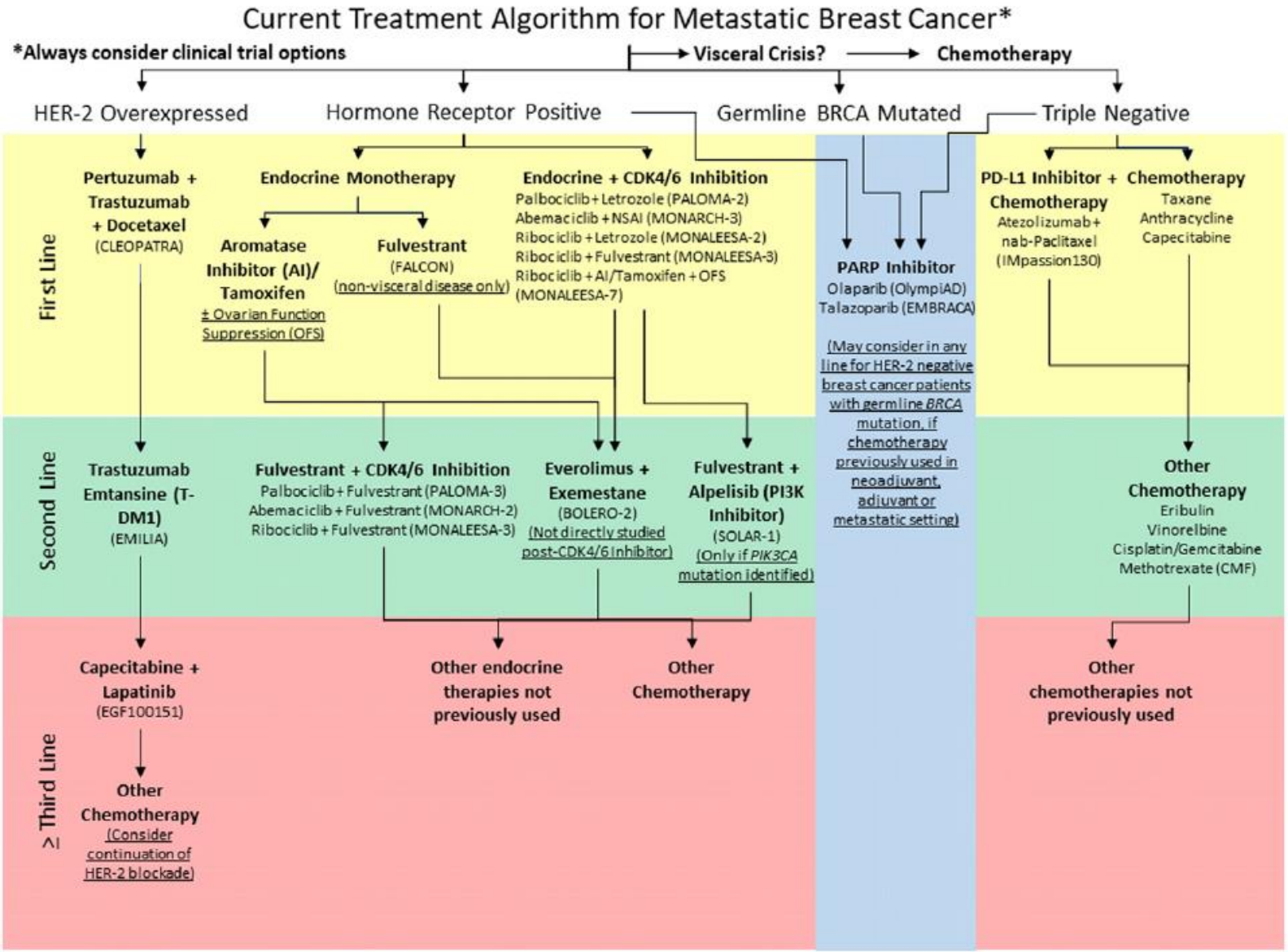


FIGURE 1. Current Treatment Algorithm for MBC

Abbreviation: MBC, metastatic breast cancer.

San Antonio Breast Cancer Symposium Dec 10-14, 2019

CDK4/6 Inhibitors + Endocrine Therapy Improve PFS in the 1st/2nd line MBC Setting

Study/Arms	[1]Paloma 1	[2]Paloma 2	[3]Monaleesa 2	[4]Monarch 3	[5]Monaleesa 7	[6]Paloma 3	[7]Monarch 2	[8]Monaleesa 3
Phase	2	3	3	3	3	3	3	3
CDK4/6i ET partner	Palbo AI	Palbo AI	Ribo AI	Abema AI	Ribo AI/Tam + OS	Palbo Fulvestrant	Abema Fulvestrant	Ribo Fulvestrant
N	165	666	668	493	642	521	669	726
Median PFS (months) Placebo	10.2	14.5	16	14.7	13.0	4.6	9.3	12.8
Median PFS (months) CDK 4/6i	20.2	27.6	25.3	28.1	23.8	11.2	16.4	20.5
HR 95% CI	0.48 0.31-0.74	0.56 0.46-0.69	0.54 0.41-0.69	0.55 0.44-0.69	0.55 0.44-0.69	0.50 0.40-0.62	0.553 0.45-0.68	0.593 0.480-0.732
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

[1]Finn R, et al. Lancet Oncol. 2015; 16:25-35; [2]Rugo H, et al, et al. SABCS. 2017; [3]Hortobagyi GN, et al. ASCO; [4]Goetz MP, et al. J Clin Oncol. 2017 Nov 10;35(32):3638-3646; [5]Tripathy D, et al. Lancet Oncol. 2018 Jul;19(7):904-915. [6]Turner NC, et al. N Engl J Med. 2015;373:209-219; [7]Sledge GW, et al. JCO. 2017;35:2875-2884; [8]Slamon DJ, et al. J Clin Oncol. 2018 Aug 20;36(24):2465-2472.

CDK4/6 Inhibitors + Endocrine Therapy Improve OS in the 1st/2nd line MBC Setting

Study/Arms	[1]Monaleesa 7	[2]Paloma 3	[3]Monarch 2	[4]Monaleesa 3
Phase	3	3	3	3
CDK4/6i ET partner	Ribo AI/Tam + OS	Palbo Fulvestrant	Abema Fulvestrant	Ribo Fulvestrant
N	642	521	669	726
ITT Median OS (mo) Placebo	40.9	28.0	37.3	40.0
ITT Median OS (mo) CDK 4/6i	NE	34.9	46.7	NR
HR 95% CI, P value	0.71 0.54-0.95; p=0.00973	0.81 0.64-1.03, p=0.09	0.757 0.606-0.945, p=0.01	0.724 0.568-0.924, p=0.00455
OS: Primary resistance, early relapse, 2L		20.2 vs 26.2 HR 1.14, NS	38.7 vs 31.5 HR 0.686, 0.451-1.043	40.2 vs 32.5 HR 0.730, 0.530-1.004
OS: Secondary Resistance, sensitivity to prior therapy, 1L		39.7 vs 29.7 HR 0.72, 0.55-0.94	48.8 vs 40.7 HR 0.787, 0.606-1.021	NR vs 45.1 mo HR 0.700, 0.479-1.021
HR Time to chemotherapy	0.60, 0.46-0.77	0.58, 0.47-0.73, p>0.001	0.638, 0.527-0.773	NR

Fark: 9.4 ay

[1]Im et al, NEJM 2019; [2]Turner et al, NEJM 2018; [3]Sledge et al, JAMA Oncol 2019; [4]Slamon et al, ESMO 2019

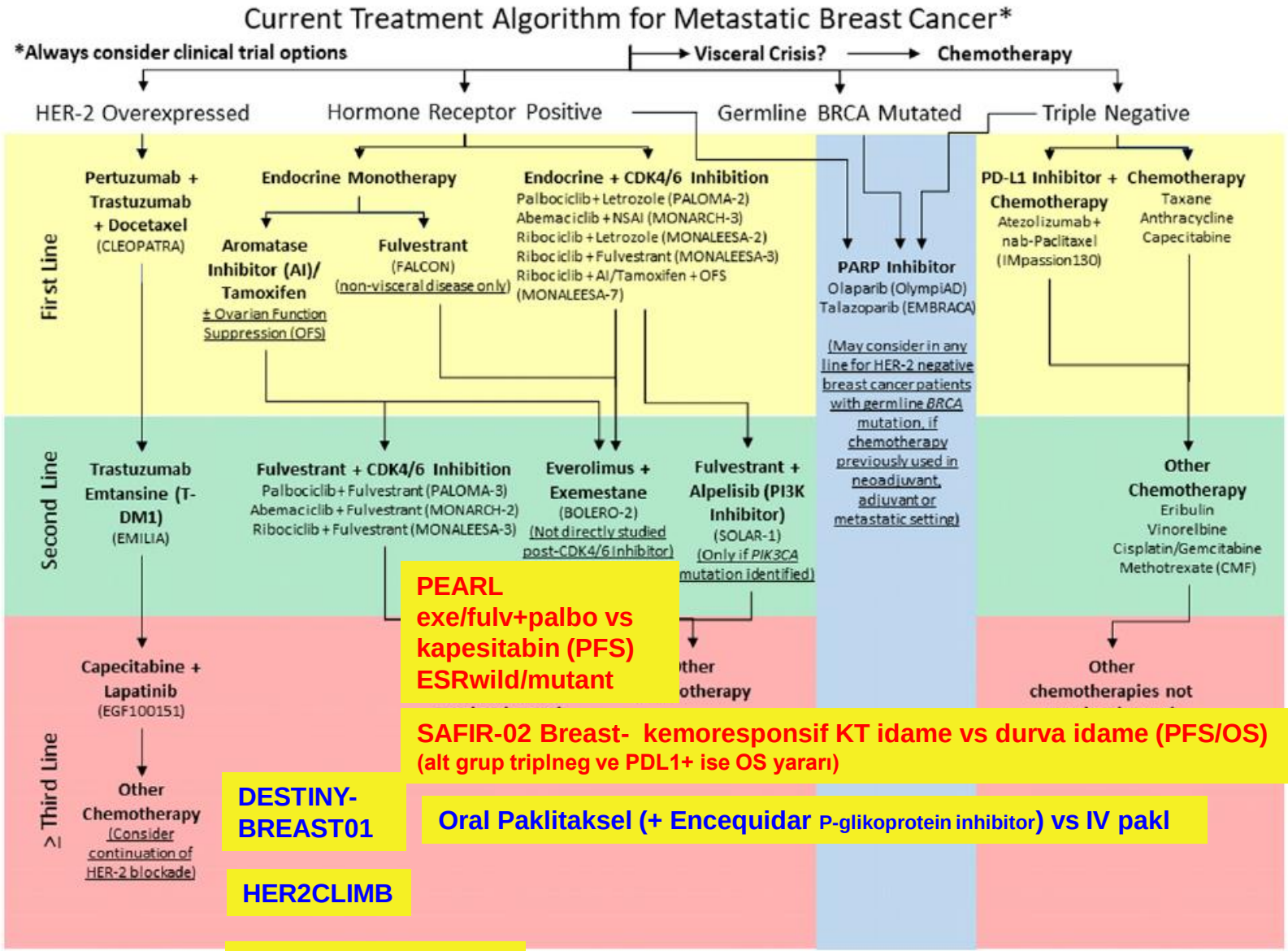


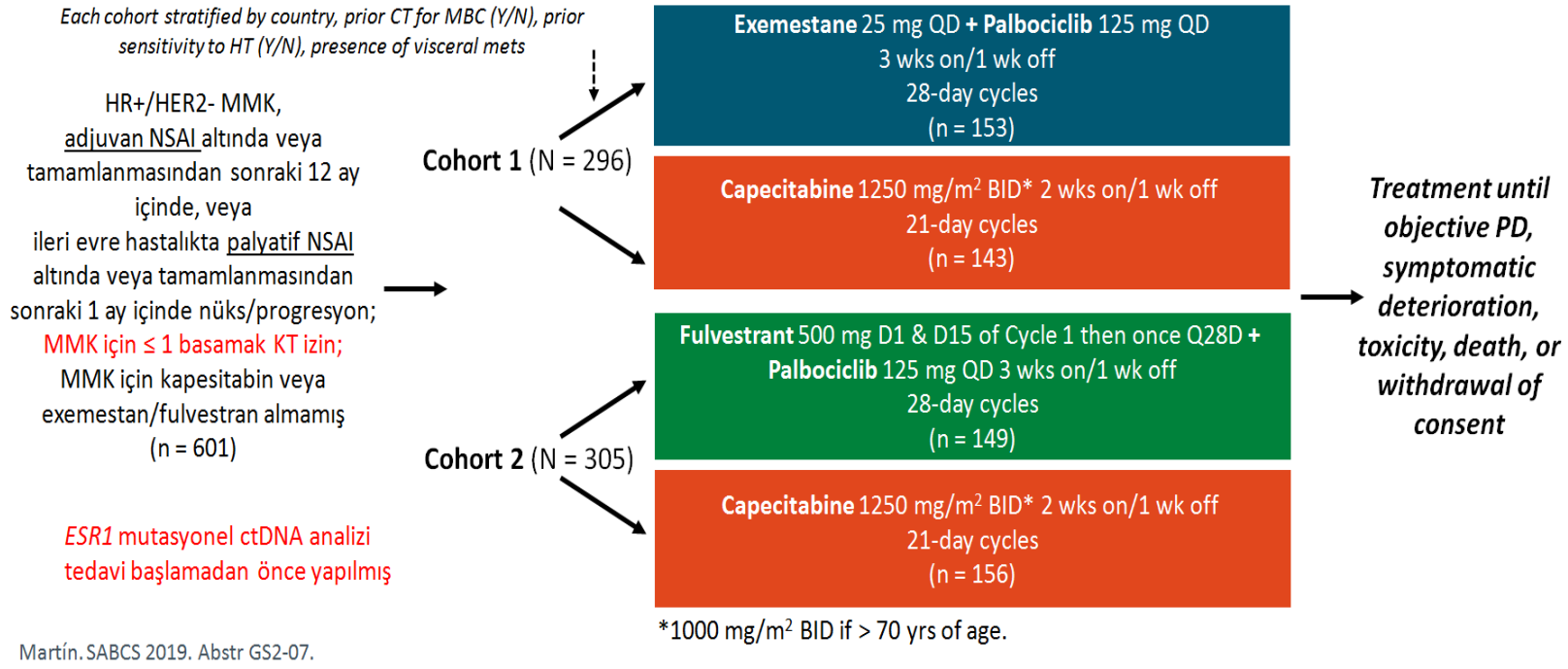
FIGURE 1. Current Treatm

Abbreviation: MBC, metas

PEARL: Palbociclib + Endocrine Therapy vs Capecitabine in Postmenopausal Women With HR+/HER- MBC and Previous AI Therapy

- Phase III, international, randomized study with 2 cohorts; 4 countries, 37 sites (GEICAM-İspanyol, CECOG-orta Avrupa-Avusturya, Macaristan, İsrail)

İkinci kohort eklendi çünkü *MMK.de ESR1* mutasyonları AI direnci mekanizmalarından ve SERD fulvestrant *ESR1* mutasyon + tm.de etkin olabilir



Martín. SABCS 2019. Abstr GS2-07.

Viseral hast %67, ESR1 wild type %68, önceki hormonal tedaviye hassasiyet % 70-78, önceden met.ik için 1 basamak KT %68-70

PEARL: PFS

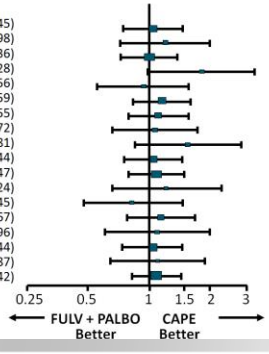
Objective	Comparison	Median F/U, mos	Median PFS, Mos (95% CI)	HR (95% CI)	*P* Value
Coprimary objective 1: Cohort 2 (n = 305)	FULV + PALBO (n = 149) vs CAPE (n = 156)	13.47	7.5 (5.7-10.9) vs 10.0 (6.3-12.9)	1.09 (0.83-1.44)	.537
Coprimary objective 2: *ESR1* WT (n = 393)	ET + PALBO (n = 206) vs CAPE (n = 187)	18.89	8.0 (6.5-10.9) vs 10.6 (7.4-13.0)	1.08 (0.85-1.36)	.526
Secondary objective: Cohort 1 & 2 (n = 601)	ET + PALBO (n = 302) vs CAPE (n = 299)	17.64	7.4 (5.9-9.3) vs 9.4 (7.5-11.3)	1.09 (0.90-1.31)	.380

- 2 coprimary endpoints not met
  - PFS with PALBO + FULV not superior to CAPE in patients with MBC resistant to AIs
  - PFS with PALBO + ET not superior to CAPE in patients with *ESR1* WT tumors

Martín. SABCS 2019. Abstr GS2-07.

PEARL: PFS by Subgroup for Cohort 2 (n = 305)

Subgroup	FULV + PALBO Events/N (%)	CAPE Events/N (%)	HR (95% CI)	*P* Value*
Visceral	72/97 (74.2)	68/102 (66.7)	1.04 (0.75-1.45)	0.811
Nonvisceral	36/52 (69.2)	26/54 (48.1)	1.19 (0.72-1.98)	0.497
Yes prior sensitivity to HT	84/119 (70.6)	72/122 (59.0)	0.99 (0.73-1.36)	0.974
No prior sensitivity to HT	24/30 (80.0)	22/34 (64.7)	1.79 (0.98-3.28)	0.057
Yes prior CT for MBC	31/41 (75.6)	28/41 (68.3)	0.93 (0.55-1.56)	0.784
No prior CT for MBC	77/108 (71.3)	66/115 (57.4)	1.15 (0.82-1.59)	0.419
Age < 65 yrs	73/93 (78.5)	63/103 (61.2)	1.10 (0.79-1.55)	0.566
Age ≥ 65 yrs	35/56 (62.5)	31/53 (58.5)	1.06 (0.65-1.72)	0.814
One site	38/56 (67.9)	15/35 (42.9)	1.54 (0.85-2.81)	0.155
Multiple sites	70/93 (75.3)	79/121 (65.3)	1.05 (0.76-1.44)	0.786
Measurable lesions	81/116 (69.8)	78/126 (61.9)	1.08 (0.79-1.47)	0.630
Nonmeasurable lesions	27/33 (81.8)	16/30 (53.3)	1.20 (0.65-2.24)	0.558
Treatment line: 1st	26/38 (68.4)	25/42 (59.5)	0.83 (0.47-1.45)	0.503
Treatment line: 2nd	54/76 (71.1)	50/78 (64.1)	1.14 (0.77-1.67)	0.515
Treatment line: ≥ 3rd	28/35 (80.0)	19/32 (59.4)	1.09 (0.60-1.96)	0.786
ESR1: WT	76/102 (74.5)	60/98 (61.2)	1.03 (0.73-1.44)	0.880
ESR1: Mutated	25/38 (65.8)	30/48 (62.5)	1.10 (0.64-1.87)	0.734
All	108/149 (72.5)	94/156 (60.3)	1.08 (0.82-1.42)	0.599



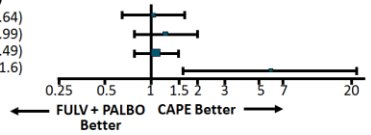
*Unadjusted Cox *P*-value comparing FULV + PALBO vs CAPE in each subgroup.

PEARL: PFS by Intrinsic Breast Cancer Subtype

Cohort 2

Subgroup	FULV + PALBO Events/N (%)	CAPE Events/N (%)	HR (95% CI)	*P* Value*
Luminal A	42/58 (72.4)	31/52 (59.6)	1.03 (0.64-1.64)	.914
Luminal B	33/43 (76.7)	37/58 (63.8)	1.25 (0.78-1.99)	.359
Luminal A+B	75/101 (74.3)	68/110 (61.8)	1.07 (0.77-1.49)	.681
Nonluminal	11/11 (100)	4/9 (44.4)	5.87 (1.60-21.6)	.008

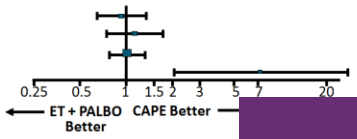
*Unadjusted Cox *P*-value comparing FULV + PALBO vs CAPE in each subgroup.



ESR1 WT

Subgroup	ET + PALBO Events/N (%)	CAPE Events/N (%)	HR (95% CI)	*P* Value*
Luminal A	71/97 (78.0)	49/70 (70.0)	0.94 (0.65-1.35)	.731
Luminal B	45/59 (76.3)	48/68 (70.6)	1.14 (0.76-1.72)	.519
Luminal A+B	116/150 (77.3)	97/138 (70.3)	1.01 (0.77-1.33)	.930
Nonluminal	17/17 (100)	4/8 (50.0)	7.36 (2.05-26.4)	.002

*Unadjusted Cox *P*-value comparing ET + PALBO vs CAPE in each subgroup.



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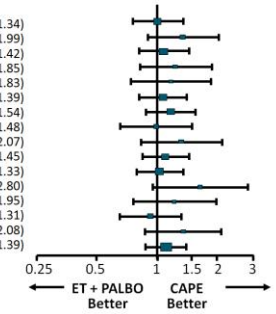
PEARL: PFS by Subgroup for *ESR1* WT (n = 393)

up	ET + PALBO Events/N (%)	CAPE Events/N (%)	HR (95% CI)	*P* Value*
	108/137 (78.8)	81/115 (70.4)	1.00 (0.75-1.34)	.996
eral	53/69 (76.8)	45/71 (63.4)	1.33 (0.89-1.99)	.165
sensitivity to HT	111/148 (75.0)	84/132 (63.6)	1.07 (0.81-1.42)	.634
sensitivity to HT	50/58 (86.2)	42/55 (76.4)	1.22 (0.81-1.85)	.335
CT for MBC	44/57 (77.2)	33/46 (71.7)	1.16 (0.74-1.83)	.516
CT for MBC	117/149 (78.5)	93/141 (66.0)	1.06 (0.81-1.39)	.678
yrs	111/130 (85.4)	84/125 (67.2)	1.16 (0.87-1.54)	.302
yrs	50/76 (65.8)	42/62 (67.7)	0.98 (0.65-1.48)	.927
	54/74 (73.0)	29/45 (64.4)	1.30 (0.82-2.07)	.260
sites	107/132 (81.1)	97/141 (68.8)	1.10 (0.83-1.45)	.514
able lesions	128/169 (75.7)	102/149 (68.5)	1.02 (0.79-1.33)	.878
surable lesions	33/37 (89.2)	24/37 (64.9)	1.63 (0.95-2.80)	.078
nt line: 1st	37/49 (75.5)	36/57 (63.2)	1.21 (0.76-1.95)	.423
nt line: 2nd	77/96 (80.2)	55/74 (74.3)	0.92 (0.65-1.31)	.652
nt line: ≥ 3rd	47/60 (78.3)	35/54 (64.8)	1.34 (0.86-2.08)	.191
	161/206 (78.2)	126/187 (67.4)	1.10 (0.87-1.39)	.425



justed Cox *P*-value comparing ET + PALBO vs CAPE in each subgroup.

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Response, %	Cohort 2 FULV + PALBO (n = 149)	Cohort 2 CAPE (n = 156)	Cohort 2 Odds Ratio (95% CI)	*ESR1* WT ET + PALBO (n = 206)	*ESR1* WT CAPE (n = 187)	*ESR1* WT Odds Ratio (95% CI)
ORR (CR + PR)	27	33	0.73 (0.42-1.27)	28	37	0.67 (0.42-1.08)
CBR	49.0	48.1	1.06 (0.67-1.66)	50.5	50.3	1.03 (0.69-1.53)

PEARL: Safety

Adverse Events, n (%)	EXE + PALBO (n = 150)	FULV + PALBO (n = 149)	CAPE (n = 289)
Any AE	147 (98.0)	148 (99.3)	286 (99.0)
▪ Related	133 (88.7)	128 (85.9)	275 (95.2)
▪ Leading to discontinuation	3 (2.0)	8 (5.4)	37 (12.8)
Serious AEs, %	24 (16.0)	19 (12.8)	63 (21.8)
▪ Related	6 (4.0)	5 (3.4)	30 (10.4)
▪ Leading to discontinuation	5 (3.3)	2 (1.3)	12 (4.2)
On study treatment deaths w/n 30 days of last dose	2 (1.3)	5 (3.4)	5 (1.7)
▪ Related	0	0	3 (1.0)
Most common grade ≥ 3 AEs, %			
▪ Decreased neutrophil count	86 (57.3)	83 (55.7)	16 (5.5)
▪ Febrile neutropenia	2 (1.3)	1 (0.7)	4 (1.4)
▪ Palmar-plantar erythrodyesthesia syndrome	0	0	68 (23.5)
▪ Diarrhea	2 (1.3)	2 (1.3)	22 (7.6)
▪ Fatigue	2 (1.3)	1 (0.7)	16 (5.5)
▪ Anemia	1 (0.7)	3 (2.0)	10 (3.5)

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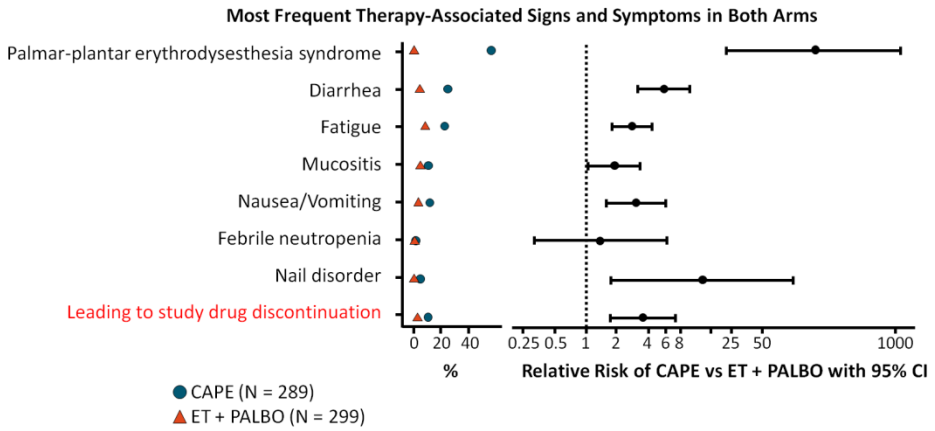
PEARL: Grade ≥ 2 AEs per Patient



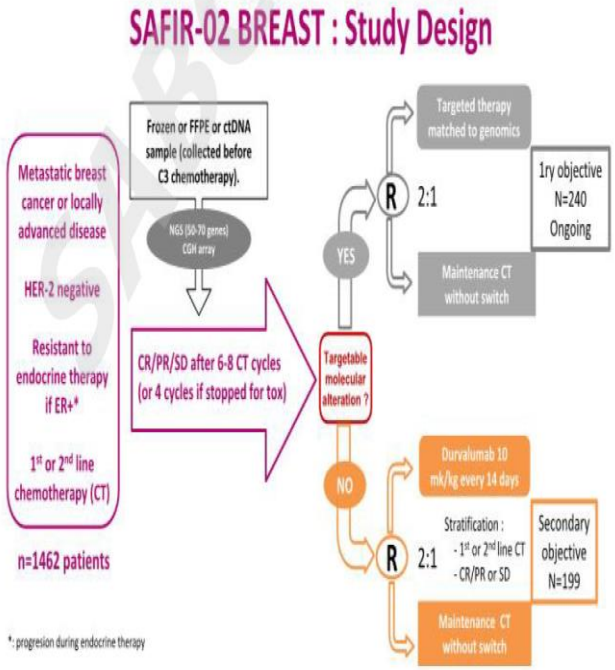
Palbociclib + fulvestrant demonstrated similar PFS vs capecitabine in women with MBC resistant to AIs

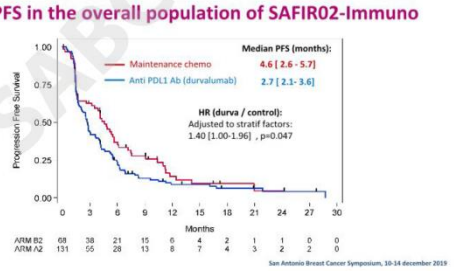
Palbociclib + endocrine therapy demonstrated similar PFS vs capecitabine in women with *ESR1* WT tumors

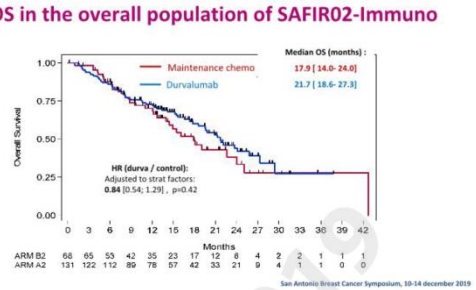
No differences in efficacy comparisons in subgroup analyses including patients with luminal breast cancer

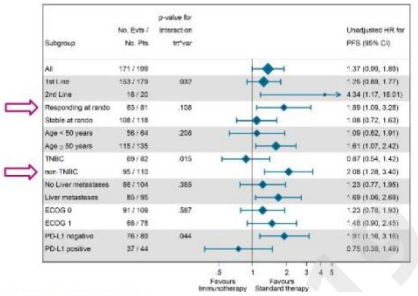
Improved safety profile with palbociclib with endocrine therapy vs capecitabine, including fewer treatment discontinuations 3.7% vs 12.8%) and fewer treatment-related serious AEs (3.7% vs 10.4%)

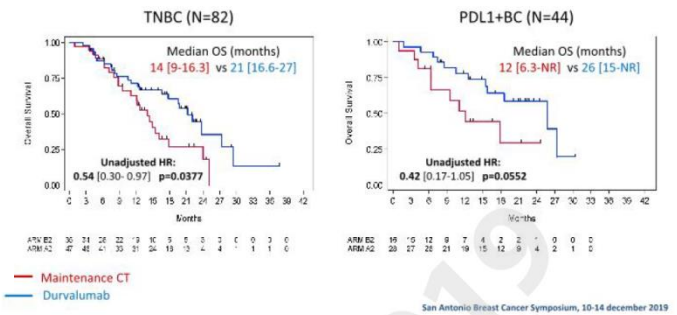
HER2(-) MMK Durvalumab vs İdame KT: randomize faz II











IHC subtypes defined on primary tumor (n=192)		
TNBC	47 (37.6%)	35 (52.2%)
HR+/HER2-	76 (60.8%)	32 (47.8%)
HER2+	2 (1.6%)	0 (0.0%)
PDL1 expression (≥ 1% IC, SP142) (n=133)	28 (32.6%)	16 (34.0%)
1st Line CT	118 (90.1%)	61 (89.7%)

	PDL1+	PDL1-
TNBC n=61	32 (52.4%)	29 (47.6%)
Non-TNBC n=67	10 (14.9%)	57 (85.1%)

PDL1 status was assessed by IHC using SP142 antibody, on a metastatic tumor sample and on tumor-infiltrating immune cells as a percentage of tumor area (≥ 1% [PDL1-positive]

For N=5 tumors. we don't have the HR status

- Tüm grupta durvalumab idame KT den üstün değil (PFS, OS)
- Esplaratuar analiz; üçlü neg veya PDL1 pozitif altgrupta OS yararı
- Sonuç: idame KT > durva monotx (PFS)

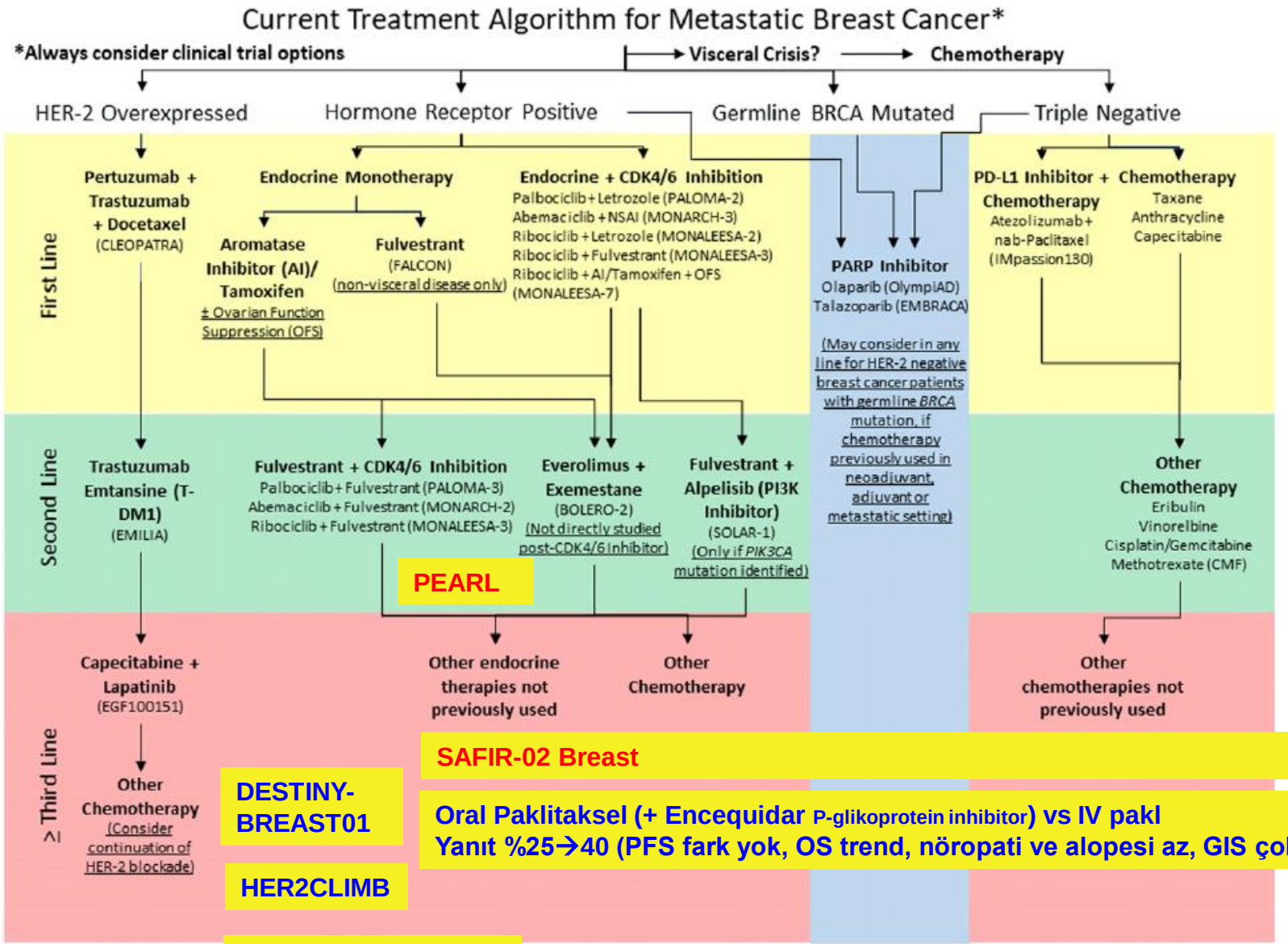
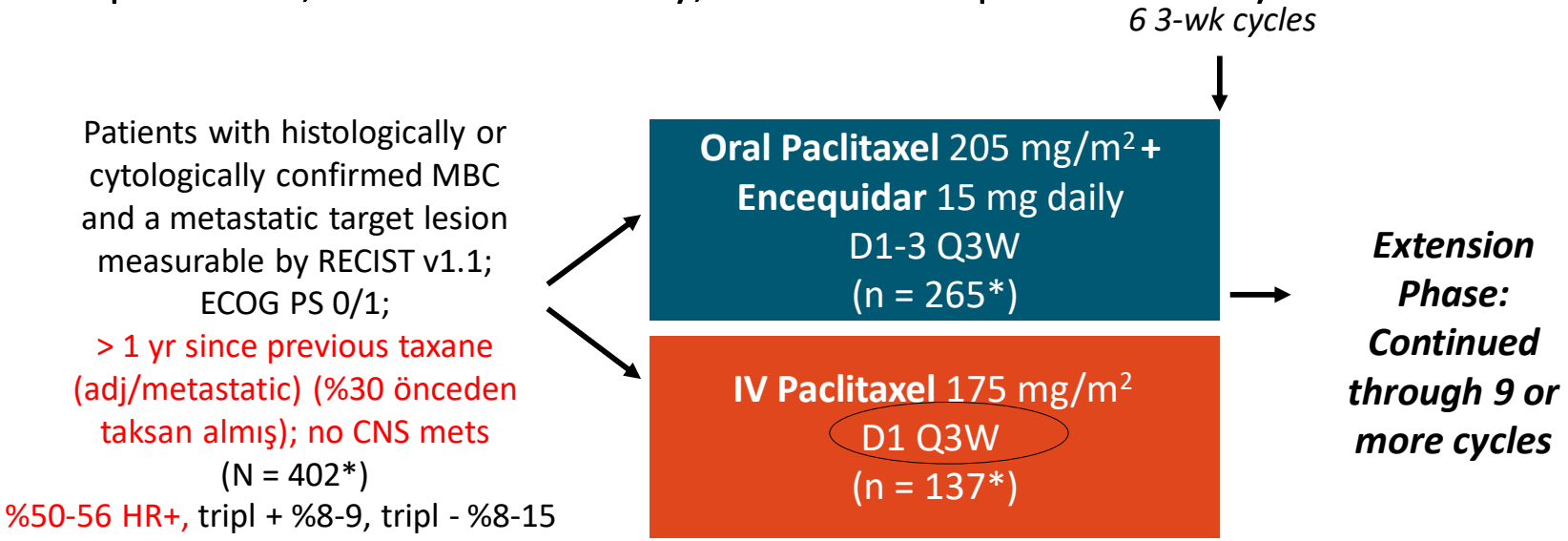


FIGURE 1. Current Treatm

Abbreviation: MBC, metastatic breast cancer.

Oral Paclitaxel With P-Glycoprotein Pump Inhibitor Encequidar vs Intravenous Paclitaxel in Metastatic Breast Cancer

- Open-label, multicenter study, randomized phase III study



- Primary endpoints: confirmed tumor response by Wk 19 (mITT) identified as 2 consecutive scans of PR/CR (RECIST v1.1) by blinded, adjudicated central independent review; safety/tolerability
- Secondary endpoints: PFS and OS

Umanzor. SABCS 2019. Abstract GS6-01

Oral Paclitaxel in MBC: Response (mITT; Primary Endpoint)

Outcome, %	OPE (n = 235)	IV Paclitaxel (n = 125)	Treatment Difference, % (*P* value)
Confirmed response rate	40.4	25.6	14.8 (*P* = .005)
▪ PR	39.1	24.8	
▪ CR	1.3	0.8	
SD	23.8	39.2	--
PD	16.2	21.6	--

- Primary endpoint also significant for ITT analysis
- Responses favored oral formulation across most patient groups evaluated, including age (< 65 vs ≥ 65 yrs of age), ECOG PS (0 vs 1), HR status (HR+/HER2- vs HR+/HER2+ vs triple negative vs HR/HER2 unknown), and prior CT (taxane vs anthracycline)

Umanzor. SABCS 2019. Abstract GS6-01

Oral Paclitaxel in MBC: Ongoing Survival Analyses (mITT)

Outcome	OPE (n = 235)	IV Paclitaxel (n = 125)	HR (95% CI)	*P* Value
Median estimated PFS, mos	9.3	8.3	0.760 (0.551-1.049)	.0773
▪ Censored summary, %	58.3	48.0		
▪ Patients with event, %	41.7	52.0		
▪ Patients d/c with no event (censored), %	40.4	36.8		
▪ Ongoing patients with no event (censored), %	17.9	11.2		
Median estimated OS, mos	27.9	16.9	0.684 (0.475-0.985)	.0353
▪ Censored summary, %	68.9	58.4		
▪ Patients with event, %	31.1	41.6		
▪ Patients d/c with no event (censored), %	17.9	18.4		
▪ Ongoing patients with no event (censored), %	51.1	40.0		

- Median estimated OS for ITT: 27.7 mos with OPE vs 16.9 mos with IV paclitaxel; HR: 0.762 (95% CI: 0.540-1.077; *P* = .114)

Umanzor. SABCS 2019. Abstract GS6-01

Oral Paclitaxel in MBC: Investigator Conclusions

- Improved ORR confirmed with oral paclitaxel and encequidar vs IV paclitaxel in MBC
  - Centrally confirmed ORR in mITT: 40.4% with OPE vs 25.6% with IV paclitaxel (*P* = .005)
  - Responses with oral formulation were durable, reaching past 200 days in 33.7% of patients
- Similar PFS, but extended OS with oral formulation in mITT
- Neuropathy and alopecia reduced, but low-grade GI effects increased with OPE vs IV paclitaxel
- Investigators concluded that OPE represents a meaningful clinical improvement in paclitaxel clinical profile and provides an important oral therapeutic option for patients with MBC

Umanzor. SABCS 2019. Abstract GS6-01

SOPHIA: Second Interim OS Analysis of Margetuximab + CT vs Trastuzumab + CT for HER2+ MBC After Previous HER2 Therapy

- Trastuzumab and pertuzumab + CT and T-DM1 are current SoC for first-line and second-line treatment of HER2+ MBC, respectively[1,2]
  - No established SoC beyond second-line therapy
- Margetuximab: HER2-binding antibody with Fc portion engineered to have increased affinity for activating Fcγ receptor RIIIA (CD16A) and decreased affinity for inhibitory Fcγ receptor RIIB (CD32B) compared with trastuzumab[3]
  - Intent is to enhance innate and adaptive immunity, respectively[3,4]
- Phase III SOPHIA trial designed to evaluate efficacy and safety of margetuximab + CT vs trastuzumab + CT in patients with advanced or metastatic BC who received ≥ 2 previous lines of anti-HER2 therapy[5]
  - First interim analysis reported improved PFS and response rates with margetuximab + CT[6] ASCO2019

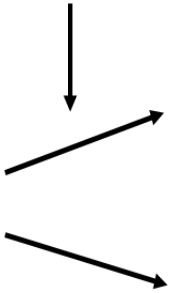
1. Swain Lancet Oncol. 2013;14:461. 2. Dieras. Lancet Oncol. 2017;18:732. 3. Nordstrom. Breast Cancer Res. 2011;13:R123. 4. Clynes. Nat Med. 2000;6:443. 5. Rugo. SABCS 2019. Abstr GS1-02. 6. Rugo. ASCO 2019. Abstr 1000.

SOPHIA Second Interim Survival Analysis: Study Design

- Randomized, open-label phase III trial (data cutoff: September 30, 2019)

Stratified by CT, no. of prior lines of tx (> 2 vs ≤ 2), no. of metastatic sites (> 2 vs ≤ 2)

Patients with HER2+ advanced BC with
≥ 2 previous anti-HER2 therapies, including pertuzumab;
1-3 prior lines of tx for metastatic disease;
prior brain metastasis allowed if treated/stable
(n = 536)
%62 HR(+)



Margetuximab 15 mg/kg Q3W **+ CT***
in 3 wk cycles
(n = 266)

Trastuzumab 8 mg/kg loading → 6 mg/kg Q3W **+**
+ monoterapi CT* in 3 wk cycles
(n = 270)

*Investigators choice of CT: capecitabine, eribulin, gemcitabine, or vinorelbine.

- Sequential primary endpoint: PFS, OS
- Secondary endpoints: ORR by central blinded analysis, investigator-assessed PFS
- Tertiary and exploratory endpoints: investigator-assessed CBR, DoR, safety, and effect of CD16A, CD32A, and CD32B alleles on margetuximab efficacy

Rugo. SABCS 2019. Abstr GS1-02.

SOPHIA Second Interim Survival Analysis: Patient Population

Characteristic	Margetuximab + CT (n = 266)	Trastuzumab + CT (n = 270)
Median age, yrs	55	56
Female, n (%)	266 (100)	267 (98.9)
ECOG PS 0/1, n (%)	149 (56)/117 (44)	161 (60)/109 (40)
Metastatic/locally advanced unresectable, n (%)	260 (98)/6 (2)	264 (98)/6 (2)
Patients with measurable disease by CBA, n (%)	262 (99)	262 (97)
Number of metastatic sites, n (%)		
▪ Patients with ≤ 2	138 (52)	144 (53)
▪ Patients with > 2	128 (48)	126 (47)
Hormone receptor positive/negative, n (%)	164 (62)/102 (38)	170 (63)/98 (36)
Backbone chemotherapy, n (%)		
▪ Capecitabine	71 (27)	72 (27)
▪ Eribulin	66 (25)	70 (26)
▪ Gemcitabine	33 (12)	33 (12)
▪ Vinorelbine	96 (36)	95 (35)

Rugo. SABCS 2019. Abstr GS1-02.

SOPHIA Second Interim Survival Analysis: Previous Therapy

Characteristic, n (%)	Margetuximab + CT (n = 266)	Trastuzumab + CT (n = 270)
Settings of previous therapy		
▪ Adjuvant and/or neoadjuvant	158 (59)	145 (54)
▪ Metastatic only	108 (41)	125 (46)
Previous metastatic lines of therapy		
▪ ≤ 2 lines	175 (66)	180 (67)
▪ > 2 lines	91 (34)	90 (33)
Type of previous anti-HER2 therapy		
▪ Trastuzumab	266 (100)	270 (100)
▪ Pertuzumab	266 (100)	269 (100)
▪ T-DM1	242 (91)	247 (92)
▪ Lapatinib/other anti-HER2 therapy	41 (15)/6 (2)	39 (14)/6 (2)
Previous chemotherapy		
▪ Taxane	252 (95)	249 (92)
▪ Anthracycline	118 (44)	110 (41)
▪ Platinum	34 (13)	40 (15)
Previous endocrine therapy	126 (47)	133 (49)

Rugo. SABCS 2019. Abstr GS1-02.

SOPHIA Second Interim Survival Analysis: PFS

Outcome	Margetuximab + CT (n = 266)	Trastuzumab + CT (n = 270)	HR (95% CI)	*P* Value
PFS: primary analysis by Central Blinded Analysis* ▪ No. of events, n ▪ Median PFS, mos (95% CI)	130 5.8 (5.52-6.97)	135 4.9 (4.17-5.59)	0.76 (0.59-0.98)	.033
PFS: primary analysis by investigator assessment* ▪ No. of events, n ▪ Median, mos (95% CI)	160 5.6 (5.06-6.67)	177 4.2 (3.98-5.39)	0.70 (0.56-0.87)	.001
PFS: 2nd interim analysis by investigator assessment† ▪ No. of events, n ▪ Median , mos (95% CI)	208 5.7 (5.22-6.97)	222 4.4 (4.14-5.45)	0.71 (0.58-0.86)	.006

*Data cutoff: October 2018, after 265 PFS events. †Data cutoff: September 2019, after 430 PFS events.

PFS her analizde Margetuximab kolu lehine anlamlı

Rugo. SABCS 2019. Abstr GS1-02.

SOPHIA Second Interim Survival Analysis: Response (ITT)

Outcome	Margetuximab + CT (n = 266)	Trastuzumab + CT (n = 270)	Nominal *P* Value
ORR*, n (%; 95% CI)	67 (25.2; 20.1-30.9)	37 (13.7; 9.8-18.4)	.0006
CBR†, n (%; 95% CI)	128 (48.1; 42.0-54.3)	96 (35.6; 29.9-41.6)	.0025
Best overall response, n (%)			
▪ CR	5 (1.9)	4 (1.5)	--
▪ PR	62 (23.3)	33 (12.2)	--
▪ SD	143 (53.8)	158 (58.5)	--
▪ PD	40 (15.0)	57 (21.1)	--
▪ Not evaluable/available	16 (6.0)	18 (6.7)	--
Median DoR, mos (95% CI)	6.9 (5.45-7.49)	7.0 (5.55-8.15)	.7400

*CR + PR. †CR + PR + SD > 6 mos.
Data cutoff: September 2019.

Rugo. SABCS 2019. Abstr GS1-02.

SOPHIA Second Interim Survival Analysis: OS

Outcome	Margetuximab + CT (n = 266)	Trastuzumab + CT (n = 270)	Median Difference, mos	HR (95% CI)	*P* Value
OS: 1st interim analysis*					
▪ No. of events, n	78	80			
▪ Median OS, mos (95% CI)	18.9 (16.16-25.07)	17.2 (15.80-33.31)	1.7	0.95 (0.69-1.31)	.758
OS: 2nd interim analysis†					
▪ No. of events, n	131	139			
▪ Median OS, mos (95% CI)	21.6 (18.86-24.05)	19.8 (17.54-22.28)	1.8	0.89 (0.69-1.13)	.326
OS in CD16A-185 F carrier: 2nd interim analysis†					
▪ No. of events, n/N	103/221	114/216			
▪ Median OS, mos (95% CI)	23.7 (18.89-28.32)	19.4 (16.65-22.28)	4.3	0.79 (0.61-1.04)	.087

*Data cutoff: October 2018, after 158 (41%) of 385 events need for final OS analysis occurred. Median follow-up: 9.2 mos.
†Data cutoff: September 2019, after 270 (70%) of 385 events need for final OS analysis occurred. Median follow-up: 15.6 mos.

- No real differences among groups observed in OS subgroup analyses, with the exception of HER2 IHC3+ (HR: 0.71; 95% CI: 0.51-1.00)

SOPHIA Second Interim OS Analysis: Investigator Conclusions

- In patients with HER2+ MBC after prior anti-HER2 therapy, margetuximab + CT improved PFS compared to trastuzumab + CT
  - 24% reduction in risk of PFS in primary analysis by central blinded analysis (HR: 0.76; *P* = .033)
  - 29% reduction in risk of PFS in second interim analysis by investigator assessment (HR: 0.71; nominal *P* = .0006)
- Second interim OS not significantly different between arms
  - Trend toward improved OS with margetuximab + CT in overall population (median OS: 21.6 vs 19.8 mos; HR: 0.89; *P* = .326) and in patients with CD16A-F genotype (median OS: 23.7 vs 19.4 mos; HR: 0.79; nominal *P* = .087 for this exploratory endpoint)
- Overall safety of margetuximab and trastuzumab arms comparable
  - Higher IRR rate with margetuximab (13.3% vs 3.4%); mostly low grade, on first infusion only
- Final OS analysis (after 385 events) anticipated in 2020

Rugo. SABCS 2019. Abstr GS1-02.

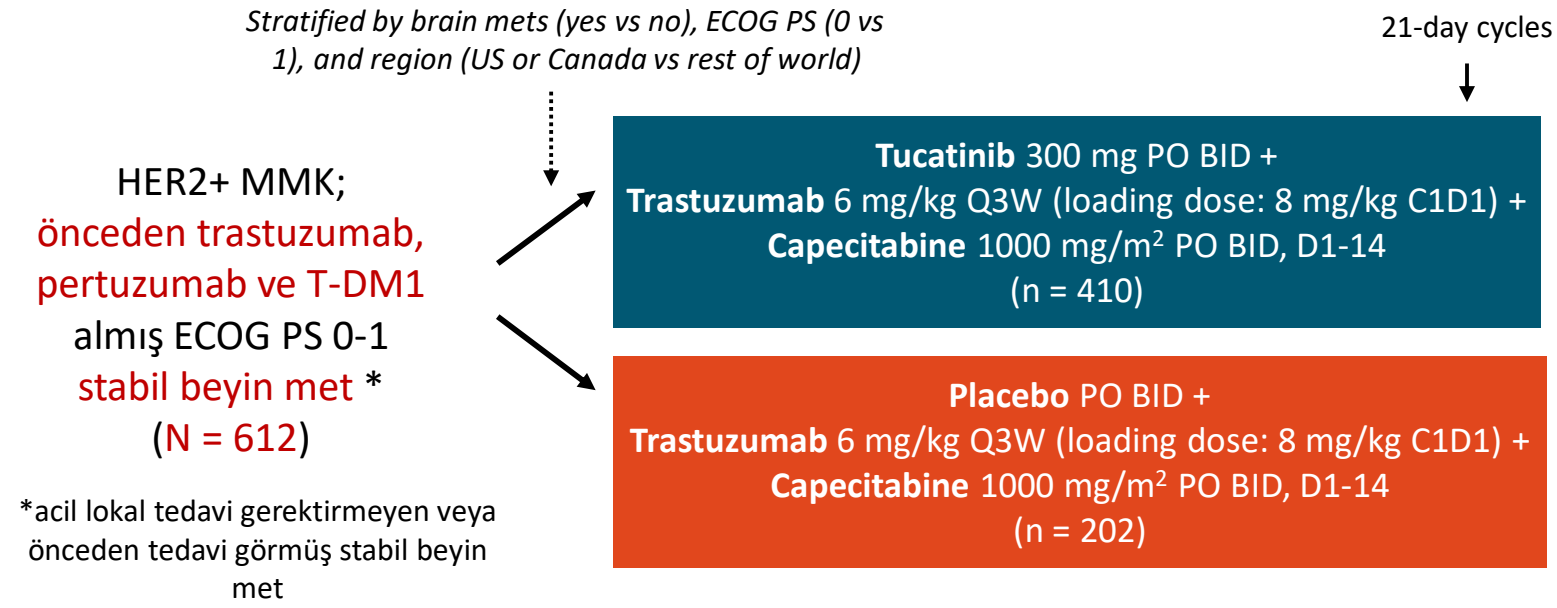
HER2CLIMB: önceden tedavi almış HER2+ MMK (beyin met dahil) Trastuzumab ve Kapesitabin +/- Tukatinib (Faz III)

- A standard of care regimen for patients with HER2+ MBC previously treated with trastuzumab, pertuzumab, and T-DM1 remains undefined[1,2]
- Up to 50% of patients with HER2+ MBC may develop brain metastases, which remain challenging to treat; new options are needed[3]
- Tucatinib: investigational, oral TKI selective for HER2 with minimal inhibition of EGFR[4,5]
  - In vitro, tucatinib showed > 1000-fold sensitivity for HER2 relative to EGFR[6]
  - Selectivity results in fewer EGFR-related toxicities than many other HER2-targeted TKIs[7]
- In phase Ib, tucatinib with capecitabine and trastuzumab achieved an ORR of 61% and PFS of 7.8 mos in patients with HER2+ MBC previously treated with SoC HER2-targeted agents[8]
- Current primary analysis evaluated efficacy, safety of tucatinib plus trastuzumab and capecitabine in HER2+ MBC, with or without brain mets, refractory to SoC therapies[9,10]

1. Giordano. J Oncol Pract. 2018;14:501. 2. Cardoso. Ann Oncol. 2018;29:1634. 3. Brufsky. Clin Cancer Res. 2011;17:4834. 4. Moulder. Clin Cancer Res. 2017;23:3529. 5. Pheneger. Cancer Research. 2009;69:1795. 6. Kulukian. SABCS 2019. Abstract P1-18-09. 7. Pernas. Ther Adv Med Oncol. 2019;11:1-16. 8. Murthy. Lancet Oncol. 2018;19:880. 9. Murthy. SABCS 2019. Abstr GS1-01. 10. Murthy. N Engl J Med. 2019;[E-pub].

HER2CLIMB: önceden tedavi almış HER2+ MMK (beyin met dahil) Trastuzumab ve Kapesitabin +/- Tukatinib (Faz III)

- Randomized, double-blind, placebo-controlled, active comparator phase III trial at 155 sites in 15 countries (February 2016 to May 2019); data cutoff: September 4, 2019; median f/u: 14.0 mos



- Birincil Sonlanım: PFS

(RECIST v 1.1 by BICR) among first 480 randomized patients (90% power with 288 events at α = 5%, HR: 0.67)

- İkincil Sonlanım (total population): OS, PFS in patients w/ brain mets, ORR in patients w/ measurable disease, safety in patients who received ≥ 1 dose of study tx

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;[E-pub].

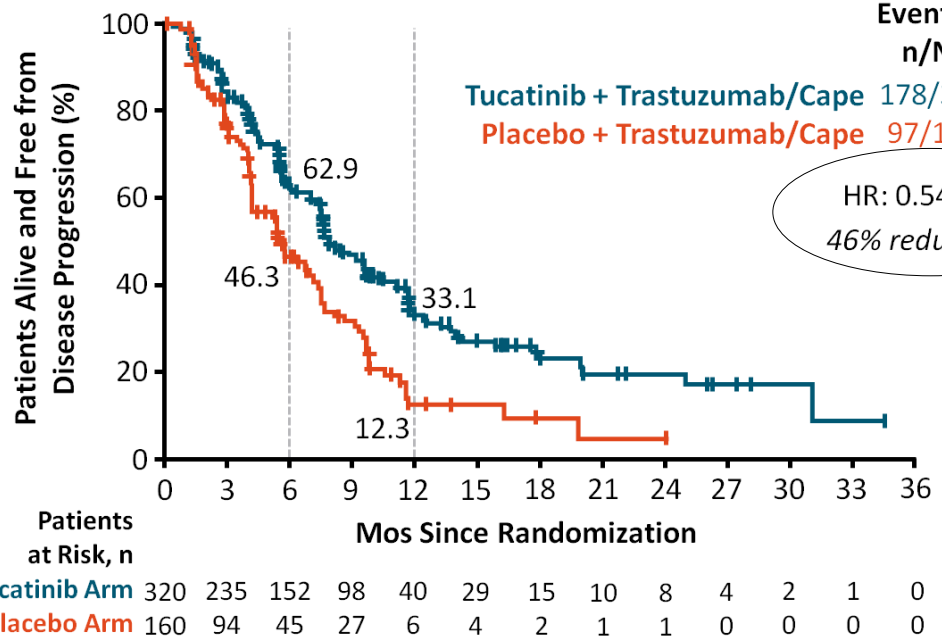
HER2CLIMB: önceden tedavi almış HER2+ MMK (beyin met dahil) Trastuzumab ve Kapesitabin +/- Tukatinib

Characteristic	Tucatinib + Trastuzumab/Capecitabine (n = 410)	Placebo + Trastuzumab/Capecitabine (n = 202)
Female, n (%)	407 (99)	200 (99)
Median age, yrs (range)	55.0 (22-80)	54.0 (25-82)
ECOG PS 0/1, n (%)	204 (50)/206 (50)	94 (47)/108 (54)
Stage IV at initial diagnosis, n (%)	143 (35)	77 (39)
Hormone receptor status, n (%)		
▪ ER and/or PR positive	243 (60)	127 (63)
▪ ER and PR negative	161 (40)	75 (37)
Median prior lines of therapy, n (range)		
▪ Overall	4.0 (2-14)	4.0 (2-17)
▪ Metastatic setting	3.0 (1-14)	3.0 (1-13)
Presence or history of brain metastases, n (%)	198 (48)	93 (46)
▪ Treated, stable	118 (59.6)	55 (59.1)
▪ Untreated	44 (22.2)	22 (23.7)
▪ Treated, progressing	36 (18.2)	16 (17.2)

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;[E-pub].

HER2CLIMB: önceden tedavi almış HER2+ MMK (beyin met dahil) Trastuzumab ve Kapesitabin +/- Tukatinib :PFS

HER2CLIMB: PFS (Primary Endpoint Population)



	Events, n/N	Median PFS, Mos (95% CI)	1-Yr PFS, % (95% CI)
Tucatinib + Trastuzumab/Cape	178/320	7.8 (7.5-9.6)	33 (27-40)
Placebo + Trastuzumab/Cape	97/160	5.6 (4.2-7.1)	12 (8-21)

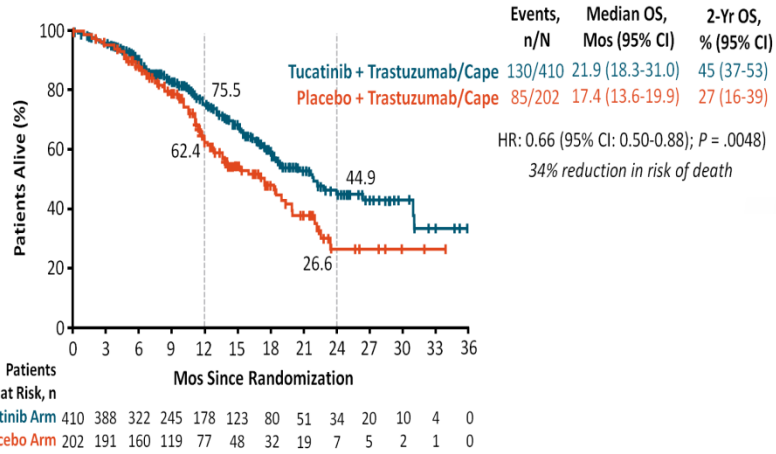
HR: 0.54 (95% CI: 0.42-0.71; $P < .00001$)

46% reduction in risk of disease progression

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;[E-pub].

HER2CLIMB: önceden tedavi almış HER2+ MMK (beyin met dahil) Trastuzumab ve Kapesitabin +/- Tukatinib: OS ve Altgrup Analizi

HER2CLIMB: OS (Total Population)



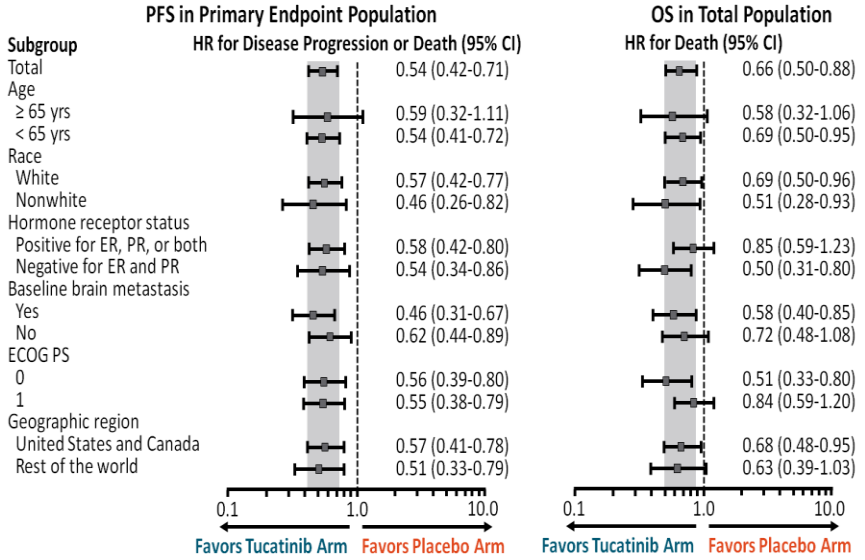
	Events, n/N	Median OS, Mos (95% CI)	2-Yr OS, % (95% CI)
Tucatinib + Trastuzumab/Cape	130/410	21.9 (18.3-31.0)	45 (37-53)
Placebo + Trastuzumab/Cape	85/202	17.4 (13.6-19.9)	27 (16-39)

HR: 0.66 (95% CI: 0.50-0.88); *P* = .0048)

34% reduction in risk of death

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;[E-pub].

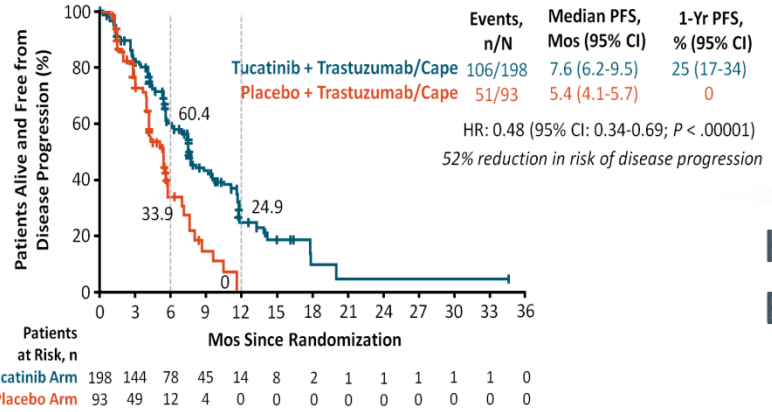
HER2CLIMB: PFS and OS Subgroup Analyses



Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;[E-pub].

HER2CLIMB: önceden tedavi almış HER2+ MMK (beyin met dahil) Trastuzumab ve Kapesitabin +/- Tukatinib (Beyin met PFS ve Altgrup)

HER2CLIMB: PFS in Patients With Brain Metastases (Total Population)



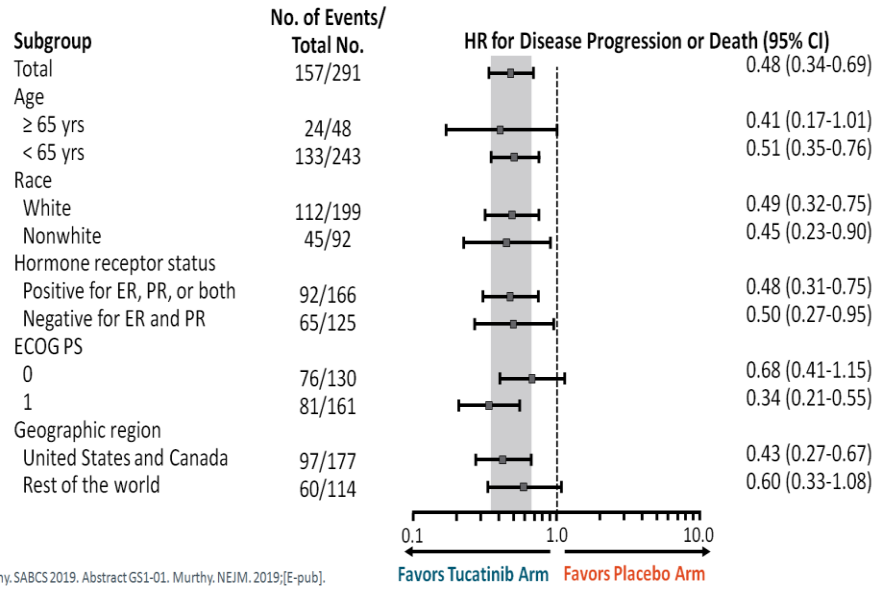
	Events, n/N	Median PFS, Mos (95% CI)	1-Yr PFS, % (95% CI)
Tucatinib + Trastuzumab/Cape	106/198	7.6 (6.2-9.5)	25 (17-34)
Placebo + Trastuzumab/Cape	51/93	5.4 (4.1-5.7)	0

HR: 0.48 (95% CI: 0.34-0.69; $P < .00001$)

52% reduction in risk of disease progression

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;[E-pub].

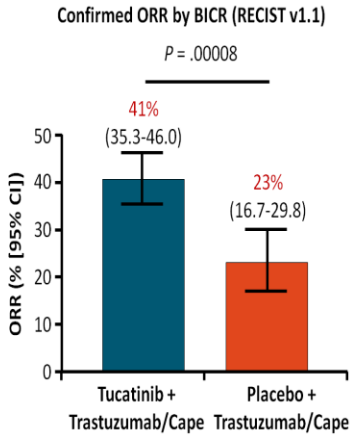
HER2CLIMB: PFS Subgroup Analysis in Patients With Brain Metastases (Total Population)



Murthy. SABCS 2019. Abstract GS1-01. Murthy. NEJM. 2019;[E-pub].

HER2CLIMB: önceden tedavi almış HER2+ MMK (beyin met dahil) Trastuzumab ve Kapesitabin +/- Tukatinib (Yanıt ve Güvenlik)

HER2CLIMB: Responses (Total Population)



Stratified Cochran-Mantel-Haenszel *P* value for ORR.

Response, n (%)	Patients with Measurable Disease by BICR	
	Tucatinib Arm (n = 340)	Control Arm (n = 171)
Best Overall Response*		
▪ CR	3 (1)	2 (1)
▪ PR	135 (40)	37 (22)
▪ SD	155 (46)	100 (59)
▪ PD	27 (8)	24 (14)
▪ NE	0	1 (1)
▪ Not available†	20 (6)	7 (4)

*Per RECIST v1.1. †Patients without post-baseline assessments.

Murthy. SABCS 2019. Abstr GS1-01. Reproduced with permission.

HER2CLIMB: Safety Summary

AE, n (%)	Tucatinib + Trastuzumab/Cape (n = 404)	Placebo + Trastuzumab/Cape (n = 197)
Any grade AE	401 (99)	191 (97)
Grade ≥ 3 AE	223 (55)	96 (49)
AEs leading to tucatinib or placebo discontinuation	23 (6)	6 (3)
AEs leading to trastuzumab discontinuation	17 (4)	5 (3)
AEs leading to capecitabine discontinuation	41 (10)	18 (9)
Deaths due to AEs	6 (2)	5 (3)
Median duration of exposure, mos	**Tucatinib**	**Placebo**
Primary endpoint population	7.3	4.4
Total population*	5.8	4.4

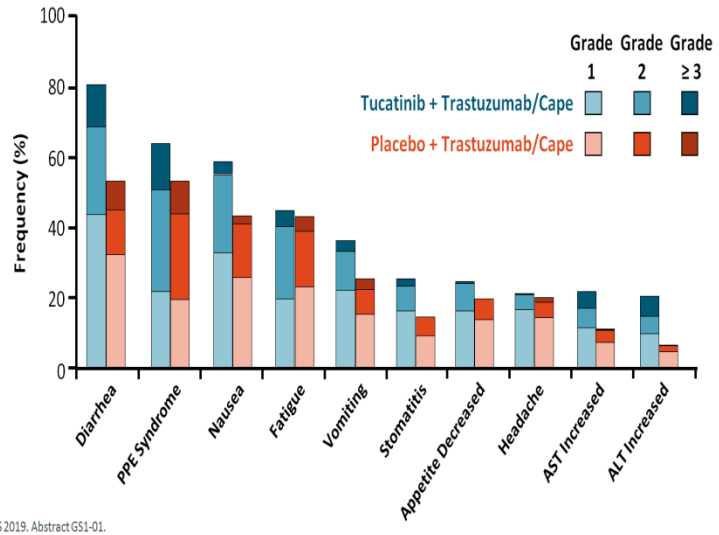
*Shorter exposure resulting from shorter follow up in patients enrolled beyond the primary endpoint population.

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;[E-pub].

Geç basamakta yüksek yanıt

HER2CLIMB: önceden tedavi almış HER2+ MMK (beyin met dahil) Trastuzumab ve Kapesitabin +/- Tukatinib (Yan Etki)

HER2CLIMB: Most Common Adverse Events



Murthy. SABCS 2019. Abstract GS1-01.

HER2CLIMB: Key Safety Events

- Diarrhea: most common AE in both arms
  - All grade: 81% w/ tucatinib vs 53%; grade ≥ 3: 13% w/ tucatinib vs 9%
  - Antidiarrheal used in fewer than one half of all cycles with reported diarrhea; when used, duration of antidiarrheal treatment was short (median: 3 days/cycles) and same in both arms
- Hand-foot syndrome (PPE): common in both arms
  - All grade: 63% w/ tucatinib vs 53%; grade ≥ 3: 13% w/ tucatinib vs 9%
  - PPE is an expected capecitabine side effect; difference in rates between arms due in part to longer duration of exposure in tucatinib arm
- LFT elevations: seen in both arms
  - Low-grade, transient, reversible

LFT Elevation, %	Tucatinib + Trastuzumab/ Capecitabine	Placebo + Trastuzumab/ Capecitabine
All-grade		
▪ AST	21	11
▪ ALT	20	7
Grade ≥ 3		
▪ AST	4.5	0.5
▪ ALT	5.4	0.5
Drug d/c due to elevation		
▪ AST	0.7	0.5
▪ ALT	1.0	0.5

Murthy. SABCS 2019. Abstract GS1-01. Murthy. NEJM. 2019;[E-pub].

HER2CLIMB: Investigator Conclusions

- In patients with HER2+ MBC previously treated with trastuzumab, pertuzumab, and T-DM1, the addition of tucatinib to trastuzumab/capecitabine improved outcomes and response rates compared with trastuzumab/capecitabine alone
  - Reduced risk of death by 33% in total population (HR: 0.66)
  - Reduced risk of disease progression or death by approximately 50% in all patients (HR: 0.54) and in patients with brain metastases (HR: 0.48)
  - Nearly doubled confirmed ORR (41% vs 23%)
  - PFS and OS benefit from tucatinib consistent across subgroups
- Tucatinib + trastuzumab/capecitabine was well tolerated with mostly low-grade AEs and few d/c
  - Risk of diarrhea and elevated ALT/AST higher with tucatinib, but transient/reversible
- Investigators concluded that tucatinib + trastuzumab/capecitabine has the potential to become SoC in heavily pretreated HER2+ MBC

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;[E-pub].

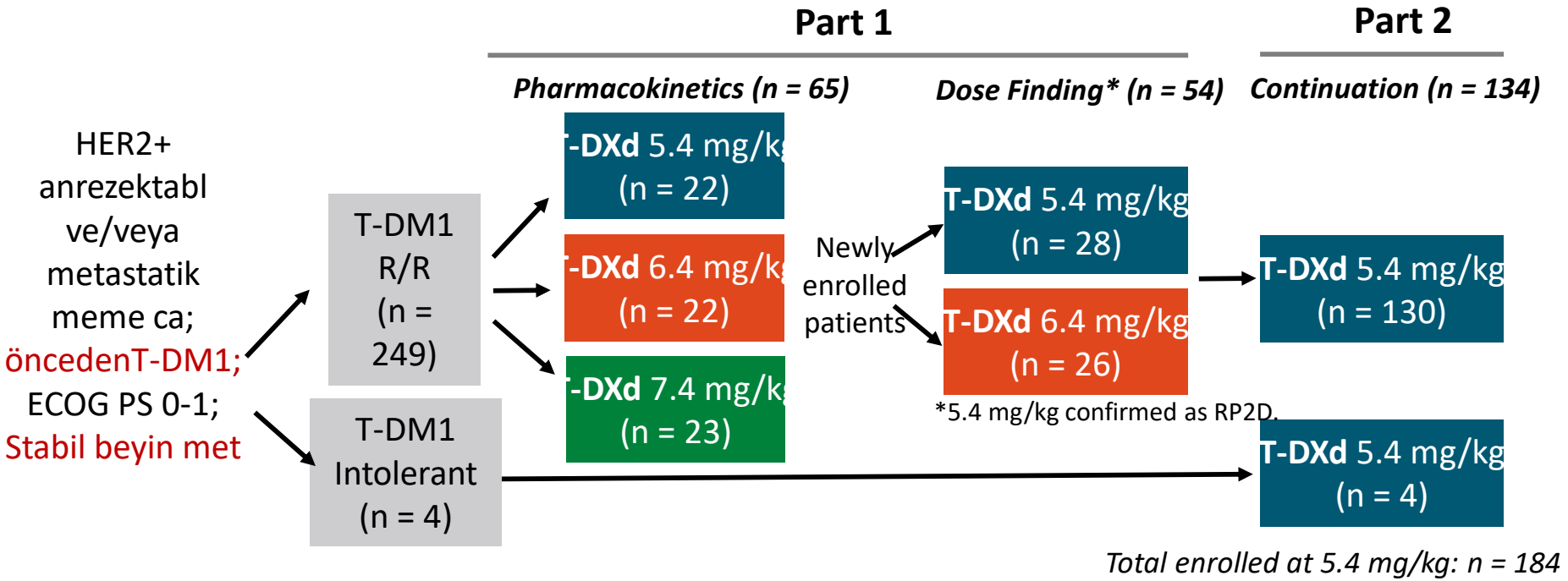
DESTINY-Breast01 Faz II önceden T-DM1 almış HER2+MMK.de Trastuzumab Deruxtecan (DS-8201a)

- Trastuzumab deruxtecan (DS-8201a): ADC comprising a humanized HER2-targeted mAb with a tumor-selective cleavable tetrapeptide linker and a topoisomerase I inhibitor "payload"
  - High drug-to-antibody ratio: ~ 8:1
  - High potency payload that is membrane permeable, allowing targeting of nearby cells in tumor regardless of HER2 expression ("bystander antitumor effect")
- In phase I dose-expansion study, T-DXd showed antitumor activity and tolerable safety in HER2-positive advanced BC previously treated with T-DM1[1]
  - ORR: 59.5% (95% CI: 49.7 to 68.7)
  - Most common TEAEs: GI, hematologic (mostly low grade); key risk identified: ILD
- Current phase II study designed to confirm outcomes of phase I T-DXd study, establish a final recommended dose, and evaluate efficacy, safety of recommended dose[2]

1. Tamura. Lancet Oncol. 2019;20:816. 2. Krop. SABCS 2019. Abstr GS1-03. 5. Modi. NEJM. 2019:[Epub].

DESTINY-Breast01: önceden T-DM1 almış HER2+MMK.de Trastuzumab Deruxtecan (DS-8201a) Faz II

- Açık etiketli, çokmerkezli, randomize, 2-bölümlü faz II



- Birincil sonlanım : ORR ICR (RECIST v1.1) (*ICR: independent central review*)
- İkincil sonlanım: investigator-assessed ORR, DCR, DoR, CBR, PFS, OS, PK, safety

%52 HR(+), %92 viseral met, beyin met %13, IHK3+ %84

önceden %100 trastuzumab ve TDM-1, %68 pertuzumab

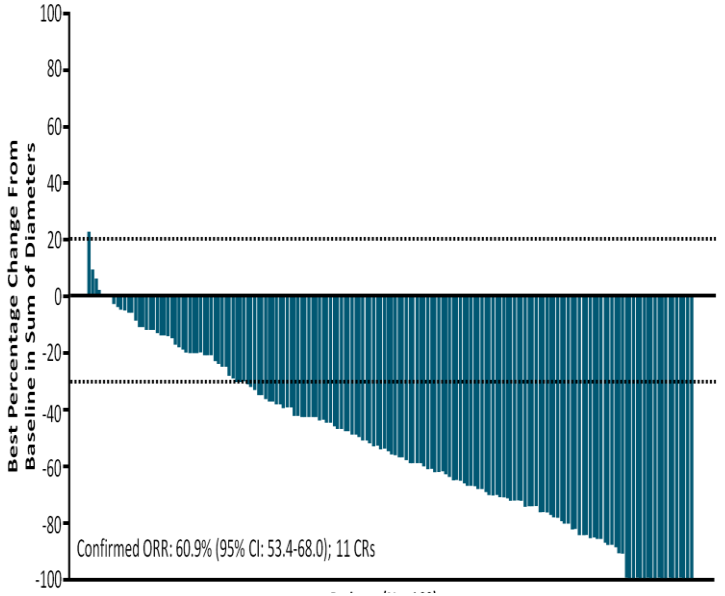
diğer anti-her2 %54

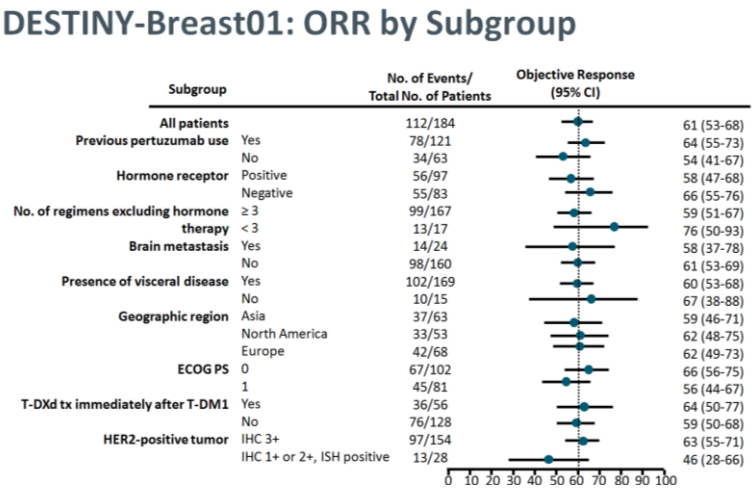
Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2019:[Epub].

DESTINY-Breast01: önceden T-DM1 almış HER2+MMK.de Trastuzumab Deruxtecan (DS-8201a) Faz II : Yanıt Oranı

Response (ITT)	T-DXd 5.4 mg/kg (N = 184)
ORR* (by ICR; n = 112), % (95% CI)	% 60.9 (53.4-68.0)
▪ CR (n = 11)	6.0
▪ PR (n = 101)	54.9
▪ SD (n = 67)	36.4
▪ PD (n = 3)	1.6
▪ Not evaluable (n = 2)	1.1
DCR, % (95% CI)	97.3 (93.8-99.1)
6-mo CBR, % (95% CI)	76.1 (69.3-82.1)
Median DoR, mos (95% CI)	14.8 (13.8-16.9)
Median time to response, mos (95% CI)	1.6 (1.4-2.6)

*Primary endpoint.

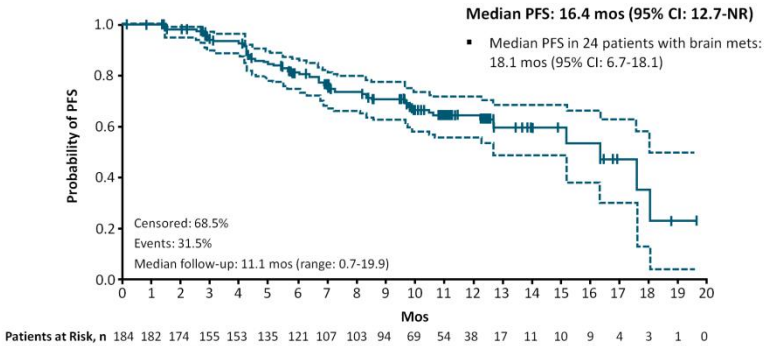




Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2019:[Epub].

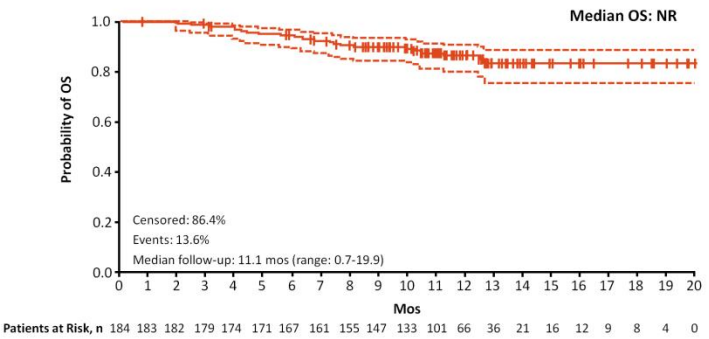
DESTINY-Breast01: önceden T-DM1 almış HER2+MMK.de Trastuzumab Deruxtecan (DS-8201a) Faz II (PFS, OS, Safety)

DESTINY-Breast01: PFS



Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2019:[Epub].

DESTINY-Breast01: OS



Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2019:[Epub].

DESTINY-Breast01: AEs in Overall Population

AE, n (%)	T-DXd 5.4 mg/kg (N = 184)		
	Any Grade	Grade 3	Grade 4
Any AE	183 (99.5)	89 (48.4)	7 (3.8)
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Neutropenia	64 (34.8)	36 (19.6)	2 (1.1)
Decreased appetite	57 (31.0)	3 (1.6)	0

AE, n (%)	T-DXd 5.4 mg/kg (N = 184)		
	Any Grade	Grade 3	Grade 4
Anemia	55 (29.9)	15 (8.2)	1 (0.5)
Diarrhea	54 (29.3)	5 (2.7)	0
Decreased WBC	39 (21.2)	11 (6.0)	1 (0.5)
Thrombocytopenia	39 (21.2)	7 (3.8)	1 (0.5)
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain	31 (16.8)	2 (1.1)	0
Decreased lymphocytes	26 (14.1)	11 (6.0)	1 (0.5)

Ortanca tedavi süresi: 10.0 ay (aralık: 0.7-20.5)
İlaç ilişkili doz azaltımı %21, kesilmesi %14 (pnömonit ve interstisyel akc hast)

Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2019:[Epub].

DESTINY-Breast01: AEs of Special Interest

AE, n (%)	T-DXd 5.4 mg/kg (N = 184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
İnterstisyel akc hastalığı	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	25 (13.6)
Cardiac failure	1 (0.5)	0	0	0	0	1 (0.5)
Cardiac failure (congestive)	0	1 (0.5)	0	0	0	1 (0.5)
Ejection fraction decrease	0	2 (1.1)	1 (0.5)	0	0	3 (1.6)

- Median time to investig-report ILD onset: 193 days (range: 42-535)
- 13/20 patients with grade ≥ 2 ILD received corticosteroids
- 7 patients recovered, 2 were recovering, 12 unknown or not followed to ILD resolution
- 4 fatal cases of ILD with onset from 63-148 days and death 9-60 days after ILD diagnosis (3 received steroids)
- No patients with cardiac failure and LVEF decline were reported
- No patients with LVEF < 40% or a decrease of ≥ 20% at any timepoint
- 4/5 patients with cardiac AEs continued treatment for 2-18 cycles

Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2019:[Epub].

DESTINY-Breast01: Conclusions

- In heavily pretreated patients with HER2+ unresectable or metastatic BC, T-DXd achieved strong, durable benefit
  - ORR: 60.9%, with consistent responses across subgroups
  - Median DoR: 14.8 mos
  - Median PFS: 16.4 mos
- Safety consistent with phase I study
  - Most common AEs: low-grade GI and hematologic toxicities
  - Identified ILD as a key risk with T-DXd; investigators recommend close monitoring for symptoms, and if ILD suspected, to hold T-DXd, start steroids
- Investigators suggest T-DXd may become new SoC for advanced HER2+ BC
- Ongoing phase III studies of T-DXd in BC: DESTINY-Breast02 (vs SoC after T-DM1 in HER2+ BC), DESTINY-Breast 03 (vs T-DM1 in HER2+ BC), DESTINY-Breast04 (vs CT in HER2 low* BC)

*IHC 2+/ISH- or IHC 1+.

Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2019:[Epub].

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

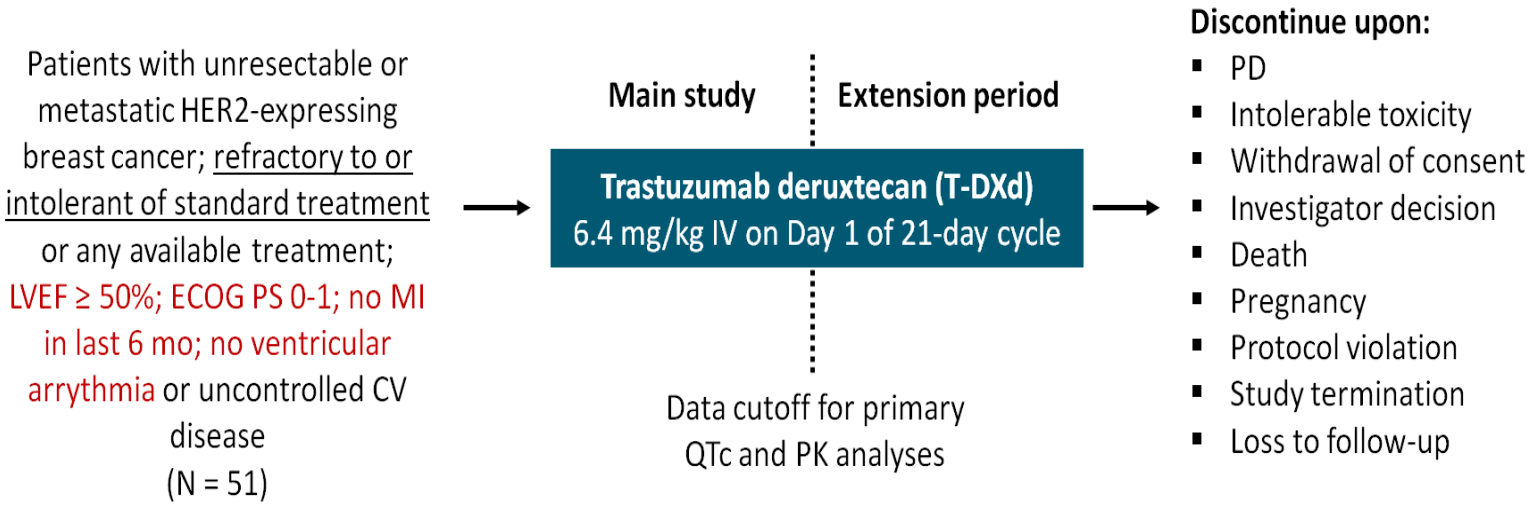
ENHERTU® – FDA onayı Ocak 2020

This article was published on December 11, 2019, at NEJM.org.

DOI: 10.1056/NEJMoa1914510

Phase I Study to Assess the Effect of Trastuzumab Deruxtecan on QTc Interval and Pharmacokinetics in HER2-Expressing Metastatic or Unresectable Breast Cancer

- Open-label, multicenter, single-arm phase I trial conducted at 7 sites in Japan



- Primary endpoints: QTc interval and PK parameters
- Secondary endpoints: safety and efficacy
- %75 ER (+), prior therapy for met.ic br. ca, hormonotx %84, CDK4/6 inhib %22, trast %24, pertuz %16, TDM1 %16, ≥ 5 prior regimen % 78

Yamashita. SABCS 2019. Abstr P1-18-12.

T-DXd Effect on QTc and PK: Investigator Conclusions

- In patients with HER2-expressing breast cancer, T-DXd 6.4 mg/kg is not associated with clinically meaningful prolongation of QTc interval
- Accumulation of T-DXd from Cycle 1 to Cycle 3 was consistent with terminal elimination half-life and steady state reached in Cycle 3
  - Little or no accumulation seen for DXd
- T-DXd associated with manageable safety profile and antitumor activity
- Phase III studies ongoing with lower dose (5.4 mg/kg) of T-DXd in HER2+ and HER2-low patients with breast cancer
  - DESTINY-Breast02 (NCT03523585), DESTINY-Breast03 (NCT03529110), DESTINY-Breast04 (NCT03734029)

Yamashita. SABCS 2019. Abstr P1-18-12.

Özet-MMK

- PEARL önceden Aİ almış postmenap HR+HER2- MMK palbo+hormonal tx, monoterapi kapesitabine üstün değil (PFS)
- SAFIR kemoresponsif MMK.de idame durvalumab idame KT den üstün değil (PFS, OS) ama altgrup analizinde üçlü neg veya PDL1+ altgruplarda OS yararı
- Oral paklitaksel (+encequidar) > 3hf.da bir IV paklitaksel (RR) ve daha az nöropati-alopesi (GIS yan etkiler)

- SOPHIA önceden trast ve pert almış her2+ MMK.de margetuximab+KT vs trastuzumab+KT –PFS ve OS yararı var ancak anlamlı OS yararı yok
- HER2 CLIMB önceden yoğun tedavi almış her2+ MMK (beyin met dahil) trastuzumab+kapesitabin +/- tukatinib PFS (RR ve OS) yararı
- DESTINY Breast01 faz II önceden yoğun tedavi almış (TDM1 dahil) her2+ MMK monoterapi trast deruxtecan ile RR yüksek (PFS, OS yararı) -SoC

Erken Evre ve Lokal İleri Evre

- Neoadjuvan Çalışmalar
- **Neoadjuvan Kemoterapi**
  - **Germline BRCA mutasyonu olanlarda neoadjuvan tedavi: Cisplatin vs. AC (INFORM)**
  - **GeparX: İdeal nab-paklitaxel şeması ne olmalı? Kemoterapiye denosumab eklenmesi PCR'ı artırır mı?**
- **Triple negatif meme kanserinde Neoadjuvan İmmunoterapi**
  - **Neoadjuvan kemoterapiye pembrolizumab eklenmesi (KEYNOTE-522)**
  - **Neoadjuvan kemoterapiye atezolizumab eklenmesi (NeoTRIPaPDL1 Michelangelo)**
- **Neodjuvan Endokrin tedavi**
  - **Luminal B MK: Neoadjuvan ribociclib+letrozole vs. Kemoterapi (SOLTI-1402/CORALLEEN)**
- Adjuvan Çalışmalar

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- Adjuvan Çalışmalar

Erken Evre ve Lokal İleri Evre: Özet

- Neoadjuvan Çalışmalar
- Neoadjuvan Kemoterapi
  - Germline BRCA mutasyonu olanlarda neoadjuvan sisplatin, AC den üstün değil (INFORM) erken sonlanmış (-) çalışma
  - GeparX: İdeal nab-paklitaxel şeması: haftalık nab-paklitaksel > 3 haftada 2 hf nab-pakl (pCR farkı %6)
- Triple negatif meme kanserinde Neoadjuvan İmmunoterapi
  - Neoadjuvan kemoterapiye pembrolizumab eklenmesi (KEYNOTE-522)
  - Neoadjuvan kemoterapiye (nabpakl-karbop) atezo eklenmesi (NeoTRIPaPDL1 Michelangelo)
- Neodjuvan Endokrin tedavi
  - Luminal B MK: neoadjuvan ribociclib+letrozole vs. kemoterapi (SOLTI-1402/CORALLEEN)- preop düşük ROR skorları benzer oranda
- Adjuvan Çalışmalar

Triple negatif meme kanserinde platin ile ilgili ne biliyoruz?

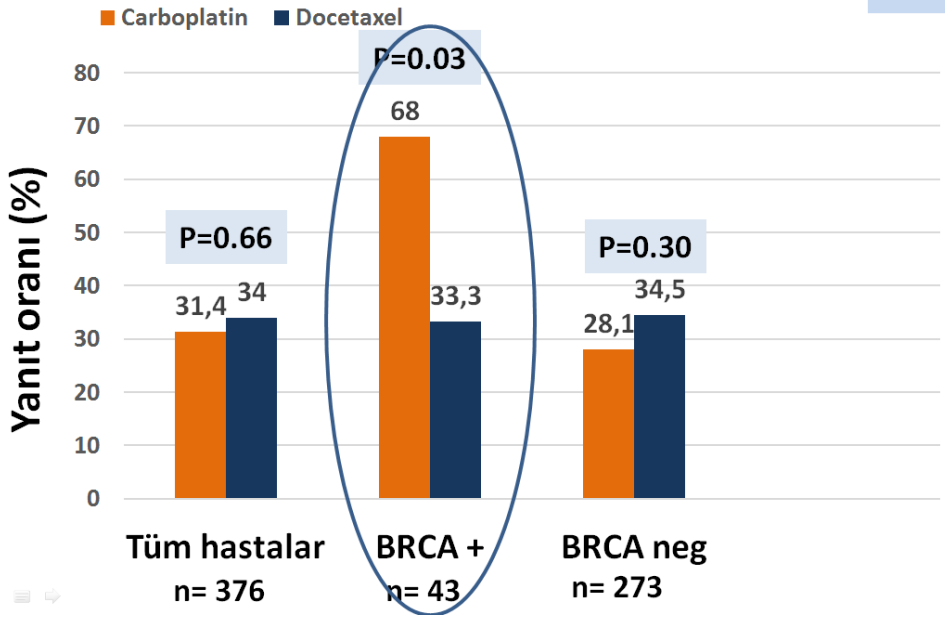
METASTATİK TNMK

TNT çalışması

Triple negatif veya *BRCA1/2+* metastatik veya reküren lokal ileri MK (N = 376)

- **Carboplatin** AUC6 Q3W x 6 cycles (n = 188)
- **Docetaxel** 100 mg/m^2 Q3W x 6 cycles (n = 188)

Her iki kolda da progresyonda çapraz geçiş izni var



43 BRCA mutas+: 32 TNMK, 11 ER+

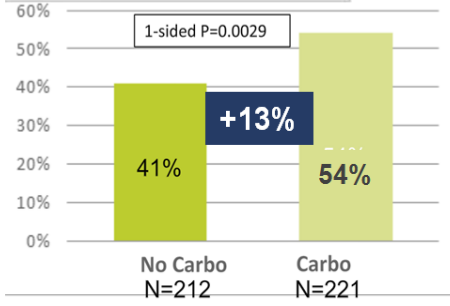
BRCA mutas+: Carboplatin ile daha iyi yanıt ve PFS

BRCA mutas - ise: Docetaxel ve Carboplatin benzer

Tutt A, et al. Nat Med 2018: 24: 628-37

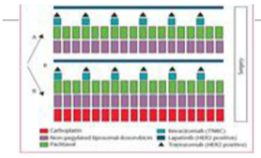
TNMK: Neoadjuvan tedaviye platin eklenmesi

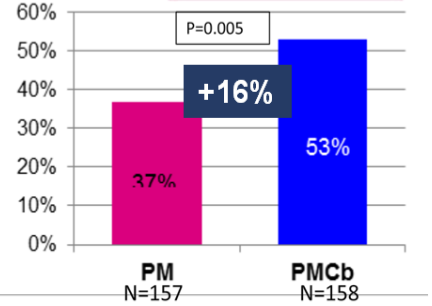
CALGB 40603



Sikov W, et al. J Clin Oncol 2014

GEPARSIXTO

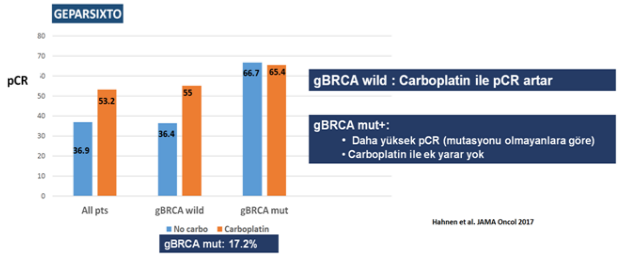




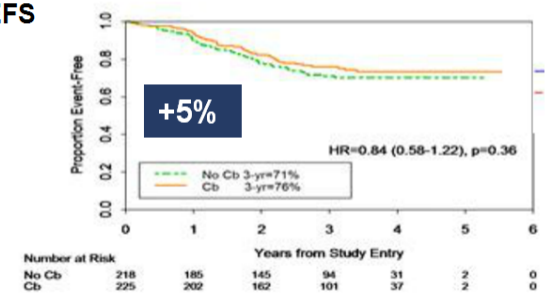
von Minckwitz G, et al. Lancet Oncol 2014

pCR'da artış: Net +13-16%

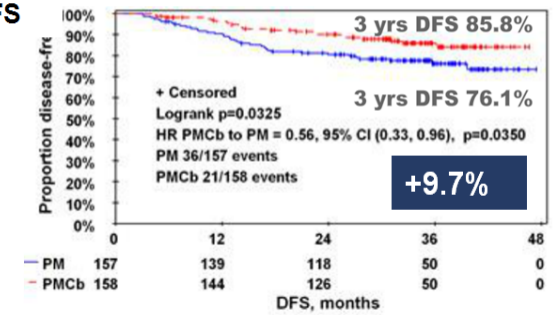
Neoadjuvan platin: Kim fayda görüyor?



EFS



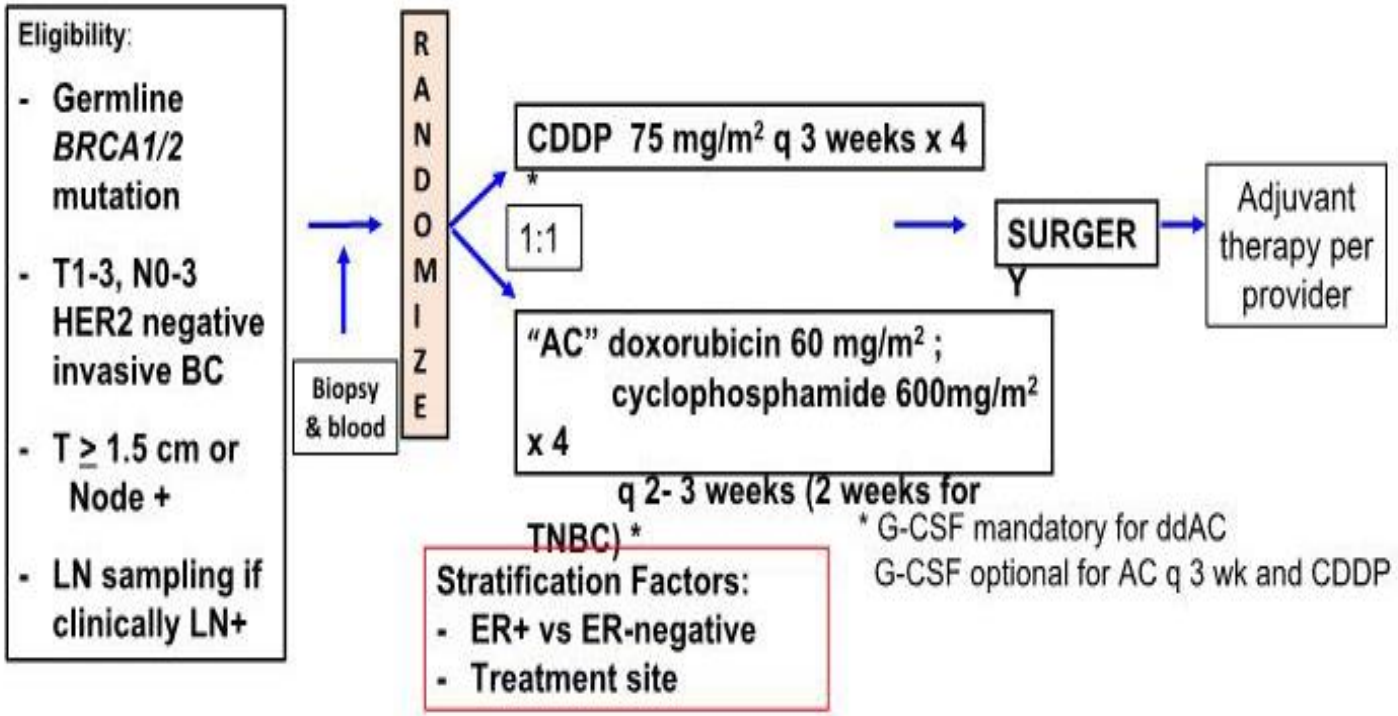
DFS



Gianni L. Lancet Oncol. 2012 Jan;13:25, Gianni ASCO 2015

Metaanaliz: 2018 Ann Oncol Poggio F
9 Randomized trials (n:2109)
pCR: increased with platinum (37%→ 52.1%)
Higher risk of grade ¾ hematological AE
2 trials with survival data: No significant difference in EFS and OS

Faz II TBCRC 031 (INFORM): gBRCA^{+} meme kanserinde neoadjuvan Cisplatin vs AC

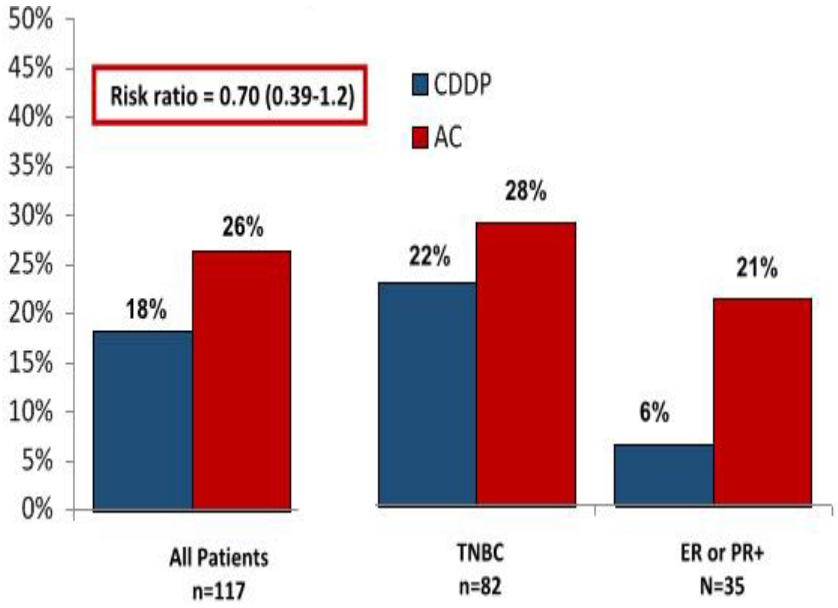


- **Hedef: 170 hasta**
- **Gerçekleşen: 118 hasta (yavaş hasta alımı sebebiyle erken sonlandırılmış)**

BRCA1 %69, BRCA2 %30
Tripl neg %70, HR+ %30

Tung et al. SABCS GS6-03

pCR (Cisplatin vs. AC)



INFORM çalışması: (Yalnız BRCA mut+)

Pratiğimizi değiştirir mi ? HAYIR

Bildiklerimizi doğruladı

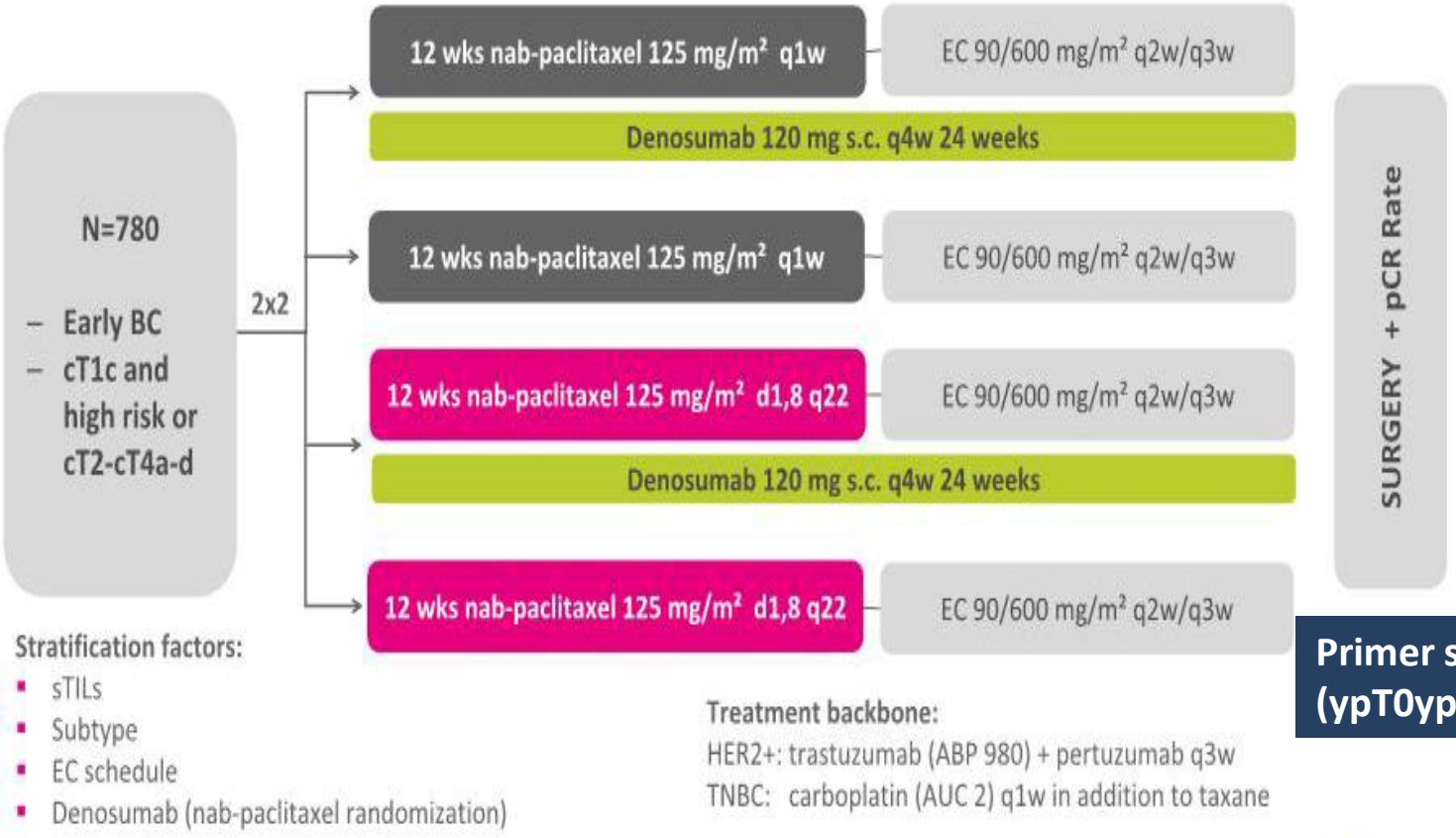
BRCA mutasyonu olanlar DNA hasarı yapan tedavilere duyarlı (AC, platin vb)

Ancak platin, AC'nin yerini tutmaz

- **gBRCA taşıyıcılarında: pCR açısından Cisplatin, AC'ye üstün değil**
  - **Hem triple negatif hem de ER/PR+ olanlar için**
- **Daha önceki çalışmalara göre cisplatin ile elde edilen pCR düşük → hasta özellikleri farklı (%30 ER+)**
- **Sonuçlar Geparsixto ve Brightness çalışmaları ile uyumlu**
  - **gBRCA mut (+)→ Carboplatin eklenmesi pCR'ı artırmaz**
  - **gBRCA+: DNA-hasarı yapan ilaçlara mutasyon olmayanlardan daha hassas (Sis veya AC)**

Tung et al. SABCS GS6-03

GeparX çalışması: 2x2 çalışma dizaynı

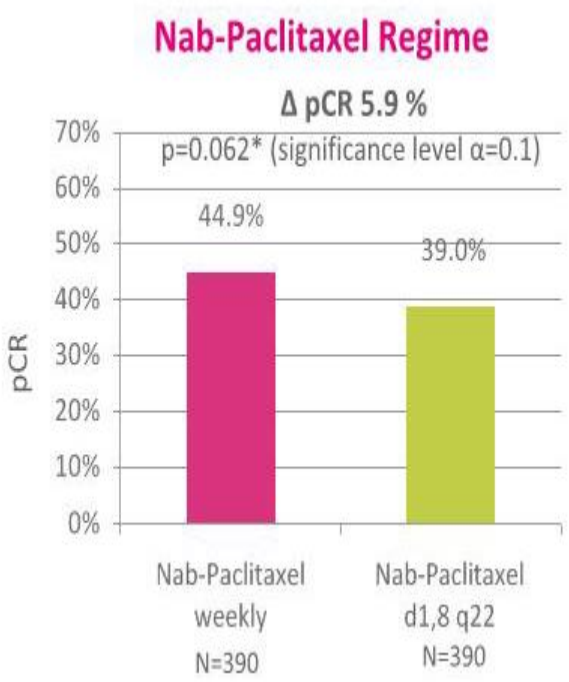


Primer sonlanım: pCR (ypT0ypN0)

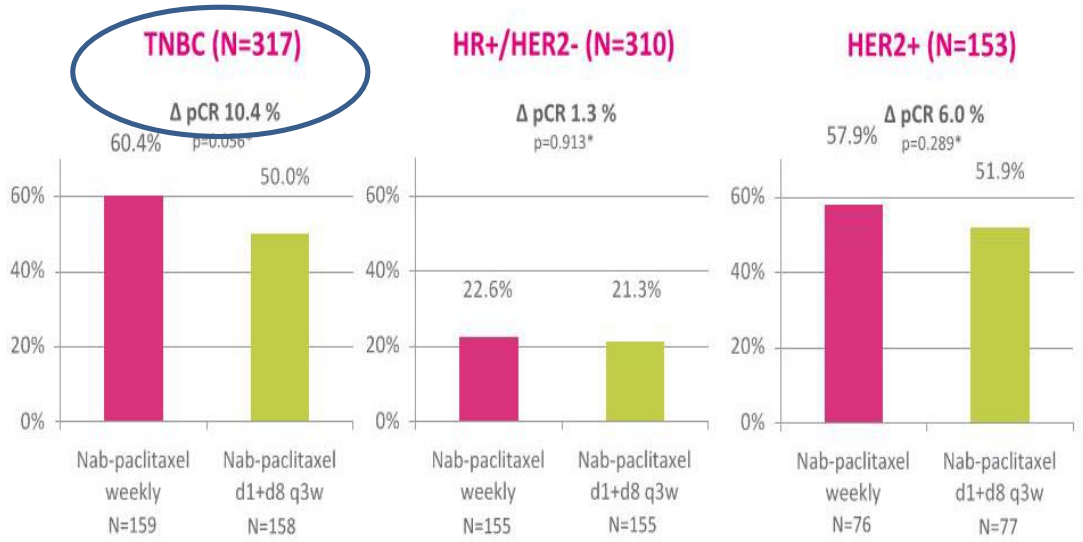
- **İdeal nab-paklitaxel şeması ne olmalı?** **Haftalık** **vs.** **1 ve 8. gün, 22 günde bir**
- **Neoadjuvan kemoterapiye denosumab eklenmesi pCR'ı artırır mı?**

Blohmer et al. SABCS GS2-06

Haftalık nab-paklitaxel ile pCR (ypT0ypN0) daha yüksek



Moleküler alttiplere göre pCR



pCR: %44.9 vs. %39
P: 0.062 (significance level α=0.1)
Net fark: %5.9

Haftalık nab-paklitaxel ile:
Artmış ciddi advers olay (%31.5 vs %24.4)
Artmış advers olaya bağlı tedavi kesilmesi (%17.5 vs. %3.7)

Blohmer et al. SABCS GS2-06

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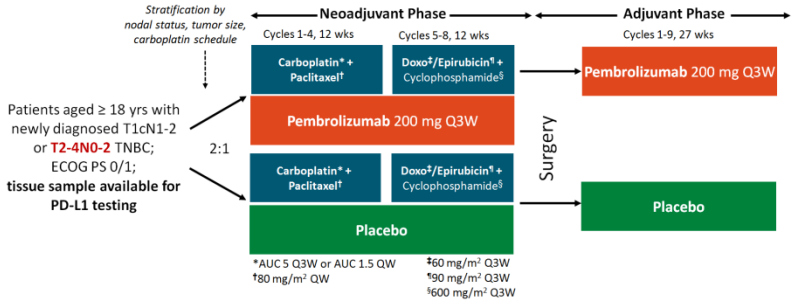
- Adjuvan Çalışmalar

Erken Evre Üçlü Negatif Meme Kanserinde
Neoadj platin temelli KT+/-Pembro →Adj Pembro/Plasebo
KEYNOTE-522 ESMO 2019 LBA9

Pembrolizumab in the Neoadjuvant/Adjuvant Setting for Early TNBC (KEYNOTE-522): Phase III Study Design



- Primary endpoints: **pCR** (ypT0/Tis ypN0) by local review, **EFS** by local review
- Secondary endpoints: pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS, AE

KEYNOTE-522: pCR

ypT0/Tis ypN0 (Primary Endpoint)	Pembro + Chemo	Placebo + Chemo
Events, n/N	260/401	103/201
pCR, %	64.8	51.2
Estimated treatment difference	FARK: 13.6 (5.4-21.8); *P* = .00055	
ypT0 ypN0	**Pembro + Chemo**	**Placebo + Chemo**
Events, n/N	240/401	91/201
pCR, %	59.9	45.3
Estimated treatment difference	14.5 (6.2-22.7)	
ypT0/Tis	**Pembro + Chemo**	**Placebo + Chemo**
Events, n/N	275/401	108/201
pCR, %	68.6	53.7
Estimated treatment difference	14.8 (6.8-23.0)	

T1-2 %73 ve %53 LN +, %58 karbo 3 hf.da bir

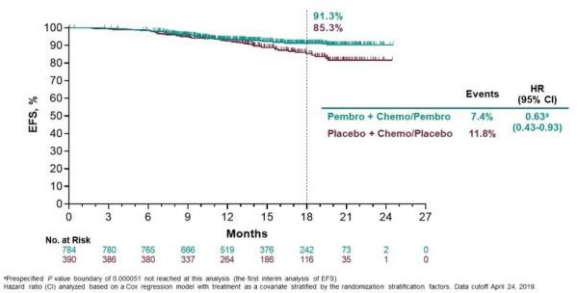
KEYNOTE-522: EFS (Interim Analysis)

	Pembro + Chemo (n = 784)	Placebo + Chemo (n = 390)
Events, %	7.4	11.8
18-mo EFS, %	91.3	85.3
HR (95% CI)	0.63* (0.43-0.93)	

*Prespecified *P* valu

Schmid KN522 ESMO 2019

Event-Free Survival at IA2



*Prespecified *P* value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS).
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff April 24, 2019.

pCR artışı

Pembro ile pCR (ypT0/Tis; ypN0): %64.8 (vs % 51.2 plasebo) (*P* = .00055)

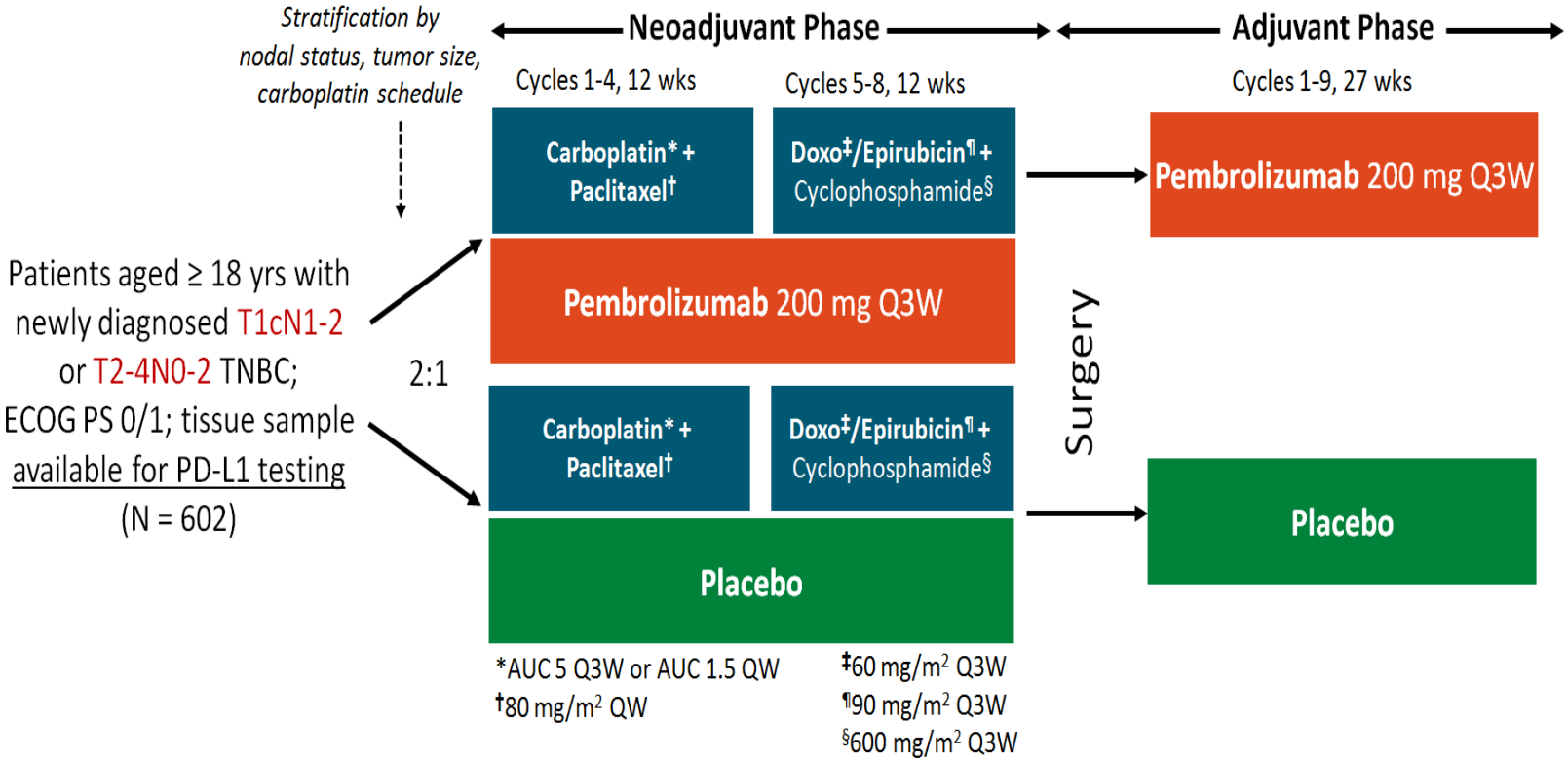
Erken veri pembro eklenmesiyle EFS yararı trendi (HR: 0.63)

PD-L1 positive,* n (%) 656 (83.7) vs 317 (81.3)

*CPS (number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100)

ICH 22C3 pharmDx assay; PD-L1 positive = CPS ≥ 1

KEYNOTE-522 Study of Neoadjuvant Pembrolizumab vs Placebo in Combination With Chemotherapy for Early-Stage TNBC: Subgroup Analysis of pCR



- Primary endpoints: pCR (ypT0/Tis ypN0) by local review, EFS by local review
- Secondary endpoints: pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS, AE
- Exploratory endpoints: RCB, pCR by subgroups, EFS by pCR

Schmid. SABCS 2019. Abstr GS3-03.

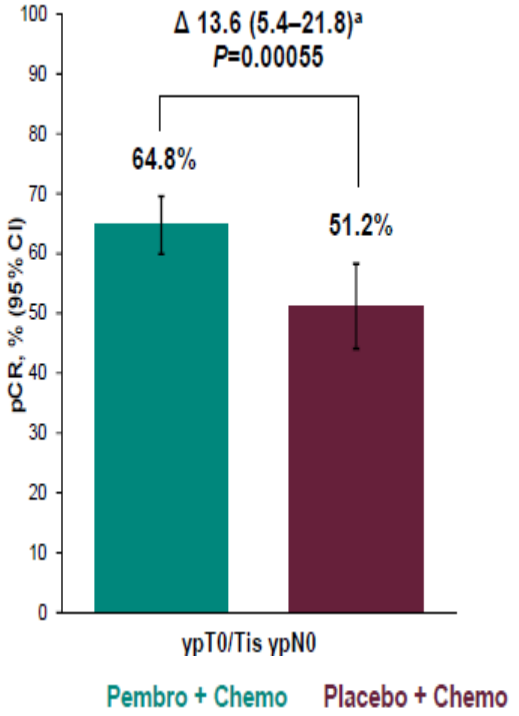
KEYNOTE-522: pCR by Key Patient Subgroups

pCR, % (n/N)		Pembrolizumab + Chemotherapy (n = 401)	Placebo + Chemotherapy (n = 201)	Δ (95% CI)
Disease stage	▪ IIA	73.1 (133/182)	62.1 (54/87)	11.0 (-0.7 to 23.2)
	▪ IIB	56.2 (68/121)	48.4 (30/62)	7.8 (-7.4 to 22.8)
	▪ IIIA	66.7 (40/60)	42.1 (16/38)	24.6 (4.3 to 43.1)
	▪ IIIB	48.6 (18/37)	23.1 (3/13)	25.6 (-6.1 to 48.9)
Lymph node involvement	▪ Negative	64.9 (124/191)	58.6 (58/99)	6.3 (-5.3 to 18.2)
	▪ Positive	64.8 (136/210)	44.1 (45/102)	20.6 (8.9 to 39.1)
PD-L1 expression	▪ CPS < 1	45.3 (29/64)	30.3 (10.33)	18.3 (-3.3 to 36.8)
	▪ CPS ≥ 1	68.9 (230/334)	54.9 (90/164)	14.2 (5.3 to 23.1)
	▪ CPS ≥ 10	77.9 (162/208)	59.8 (55/92)	17.5 (6.2 to 29.1)
	▪ CPS ≥ 20	81.7 (103/126)	62.5 (40/64)	18.5 (5.0 to 32.7)
Chemotherapy exposure*	▪ Full exposure	69.7 (314/307)	55.3 (88/159)	14.4 (5.1 to 3.6)
	▪ < Full exposure	51.1 (46/90)	35.7 (15/42)	15.4 (-3.0 to 32.1)

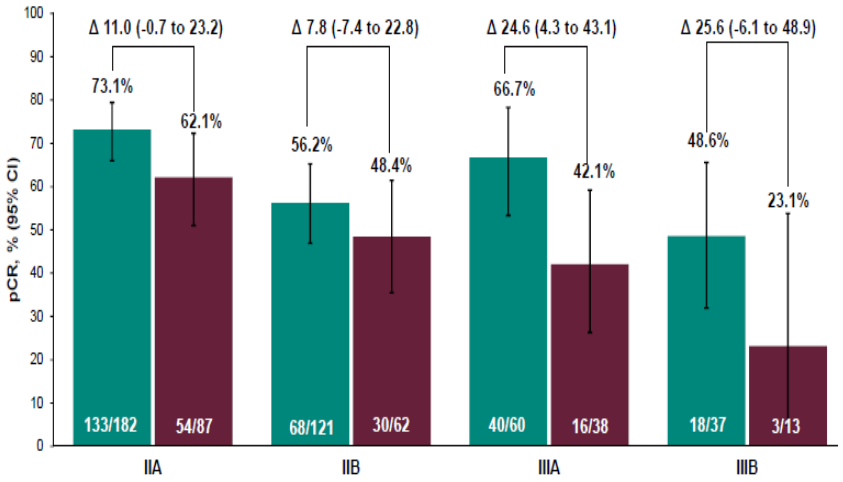
*Full exposure comprised paclitaxel weekly 10-12 doses, carboplatin weekly 10-12 doses or Q3W 4 doses, doxorubicin or epirubicin Q3W 4 doses, and cyclophosphamide Q3W 4 doses, regardless of exposure to pembrolizumab.

Schmid. SABCS 2019. Abstr GS3-03.

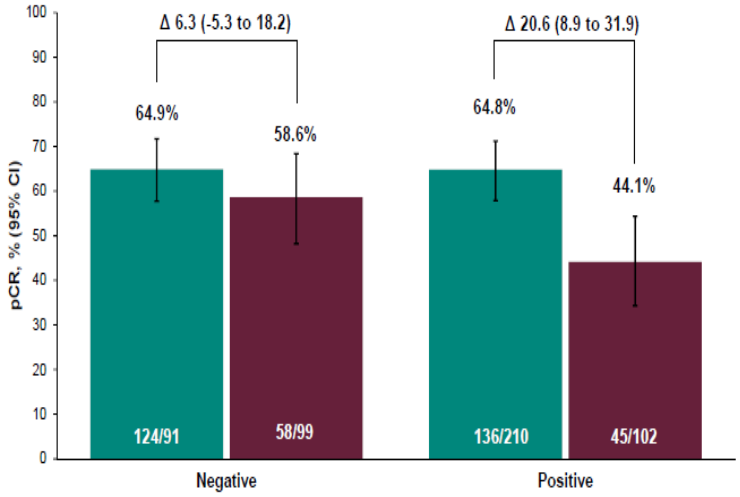
Pembrolizumab ile pCR'da anlamlı artış



Evreye göre pCR



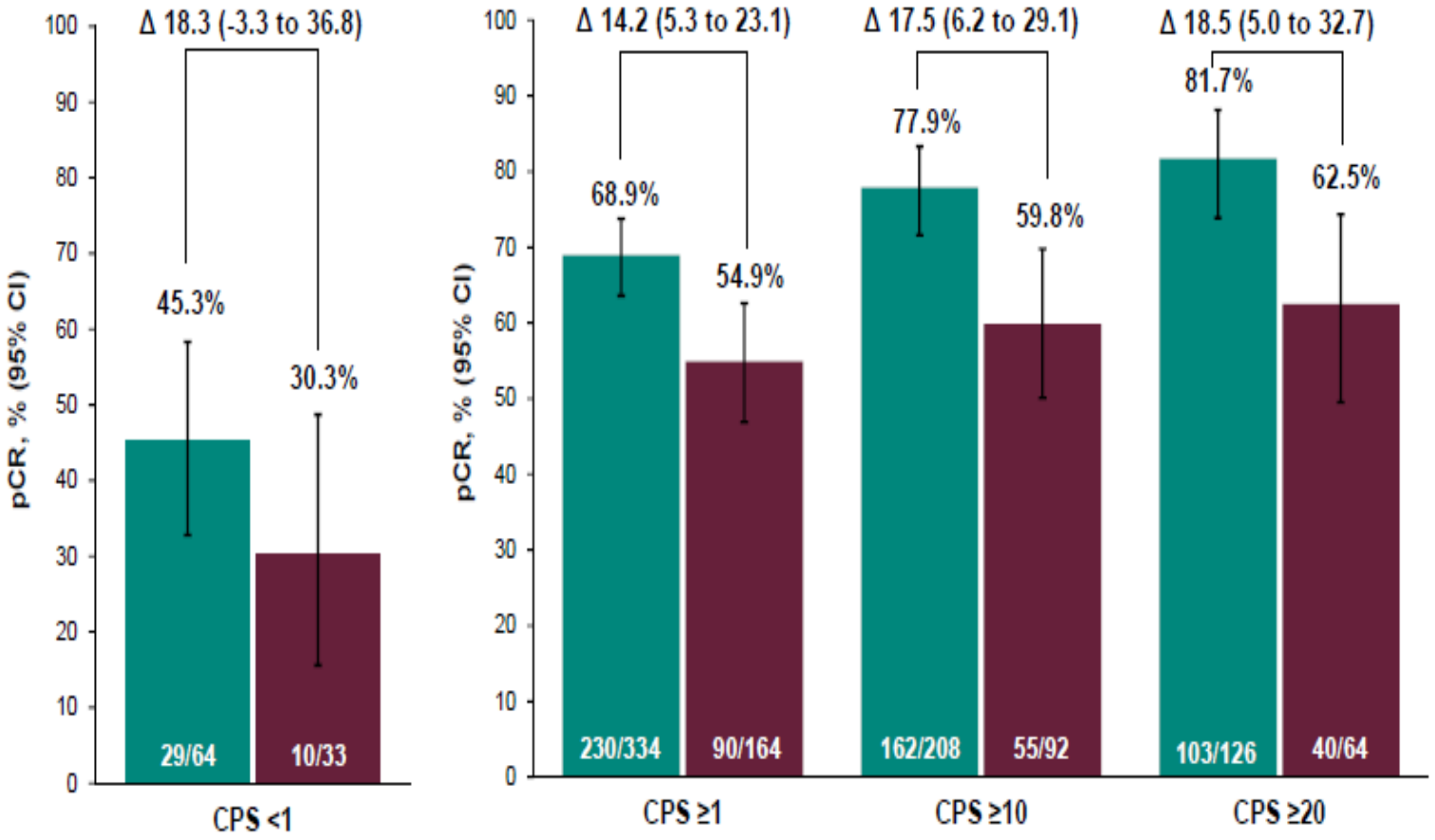
LN tutulumuna göre pCR



Evre III veya LN (+) lerde daha fazla pCR (pembro yararı)

Peter Schmid et al. SABCS 2019, GS03-03

pCR'daki artış PD-L1 düzeyinden bağımsız



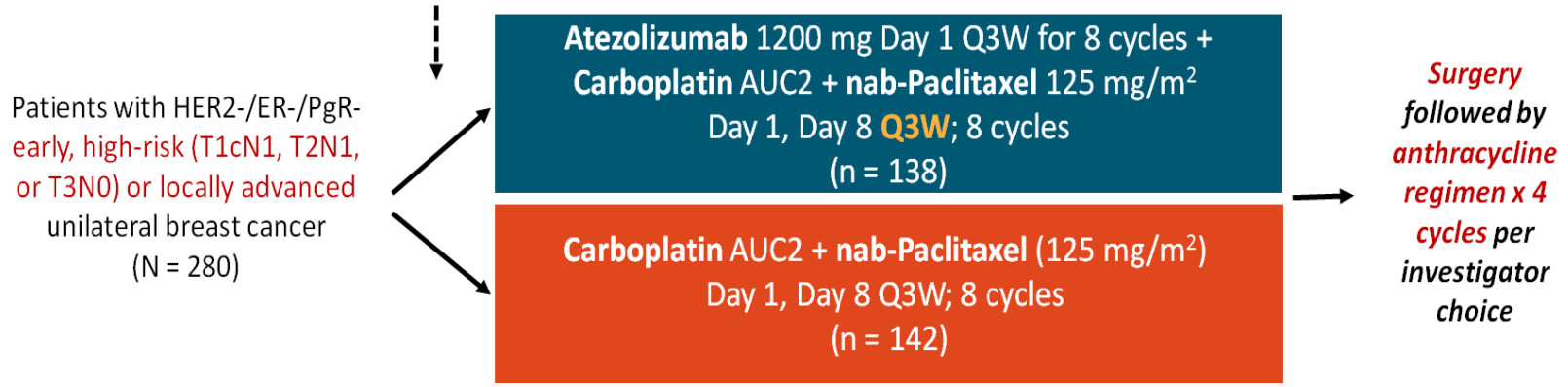
Pre-specified analysis. PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Estimated treatment difference based on Miettinen & Nurminen method stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs QW). Data cutoff date: September 24, 2018.

Peter Schmid et al. SABCS 2019, GS03-03

NeoTRIPaPDL1 Michelangelo: Neoadjuvant Chemotherapy ± Atezolizumab in Early, High-Risk and Locally Advanced TNBC

- Open-label, randomized phase III trial

Stratified by geographical area, disease stage (early, high risk vs locally advanced), PD-L1 expression (positive IC vs negative)

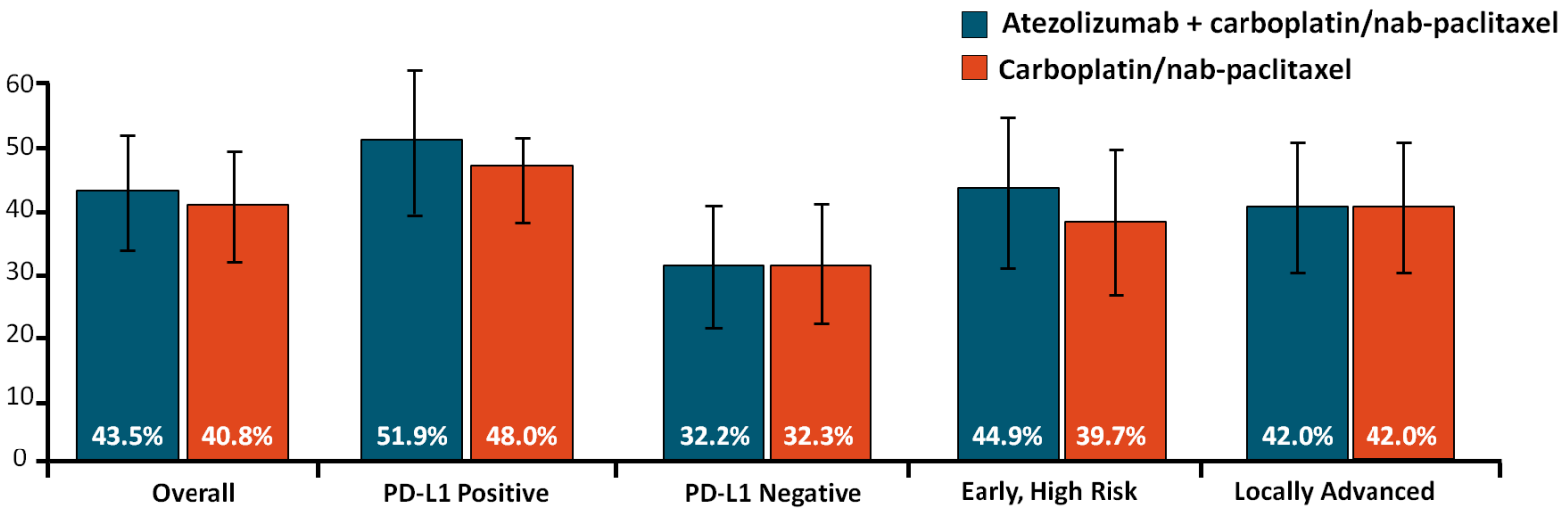


- Primary endpoint: EFS at 5 yrs after randomization of last patient
- Key secondary endpoint: pCR rate (defined as absence of invasive cells in breast and lymph nodes)
- Other secondary endpoints: tolerability; predictive biomarkers of benefit and/or resistance

LN (-) %13, riskli erken evre %50, PDL1 + %43,

Gianni. SABCS 2019. Abstr GS3-04.

NeoTRIPaPDL1: pCR Rate (ITT)



- Overall pCR rate difference: 2.63%; odds ratio: 1.11 (95% CI: 0.69-1.79); *P* = .66

Gianni. SABCS 2019. Abstr GS3-04. Reproduced wit permission.

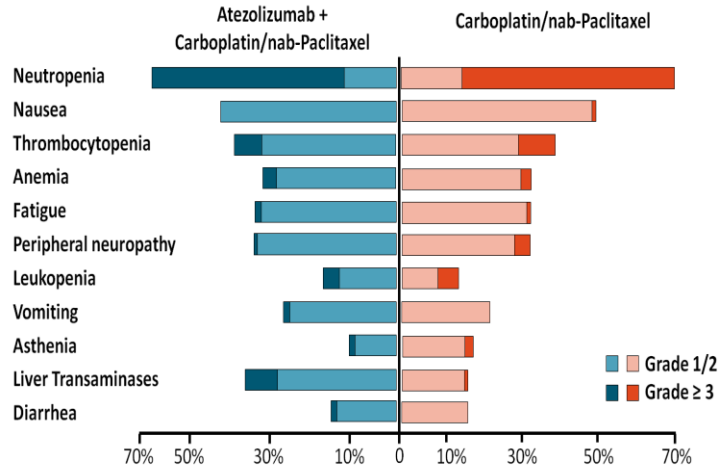
Neoadj atezolizumab eklemekle pCR artışı yok

NeoTRIPaPDL1: Multivariate Analysis of Factors Associated With pCR

Variable	Odds Ratio (95% CI)	*P* Value
Treatment: with atezolizumab vs without	1.11 (0.88-1.40)	.39
PD-L1 expression: positive vs negative	2.08 (1.64-2.65)	< .0001
Disease stage: early, high risk vs locally advanced	0.84 (0.66-1.06)	.15

pCR için, çok değişkenli analizde tek anlamlı etken: PD-L1 durumu

NeoTRIPaPDL1: Treatment-Related AEs in ≥ 15% of Patients



Gianni. SABCS 2019. Abstr GS3-04.

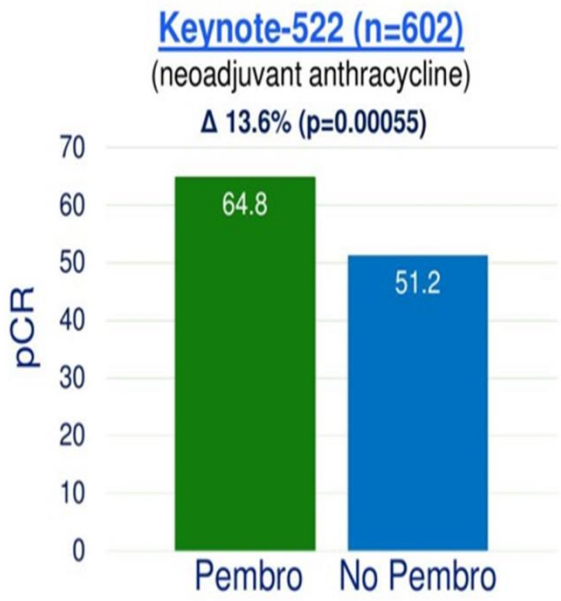
Güvenlik: Tedavi ilişkili advers olaylar benzer ama atezolizumab ile daha fazla ciddi advers olay ve KCFT yüksekliği

Neoadjuvan Kemoterapi+İmmunoterapi: 2 benzer design 2 farklı sonuç

Pembrolizumab:

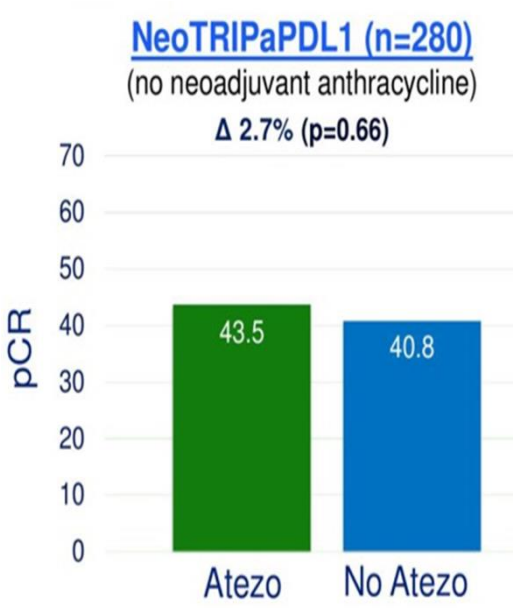
- **pCR'da artış**

  (özellikle evre 3 ve LN +)



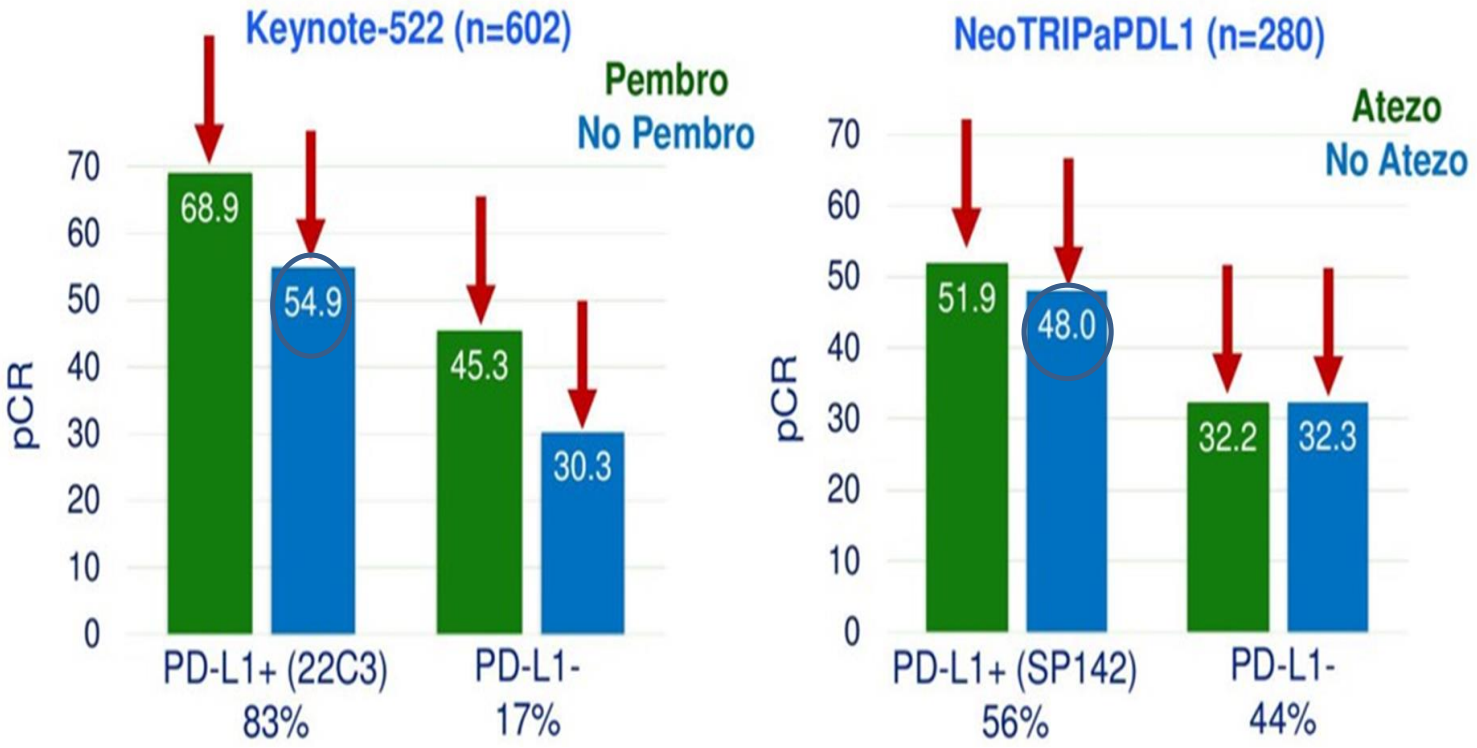
Atezolizumab:

- **pCR'da artış yok**



Peter Schmid et al. SABCS 2019, GS03-03, Gianni L et al. SABCS 2019, GS03-04

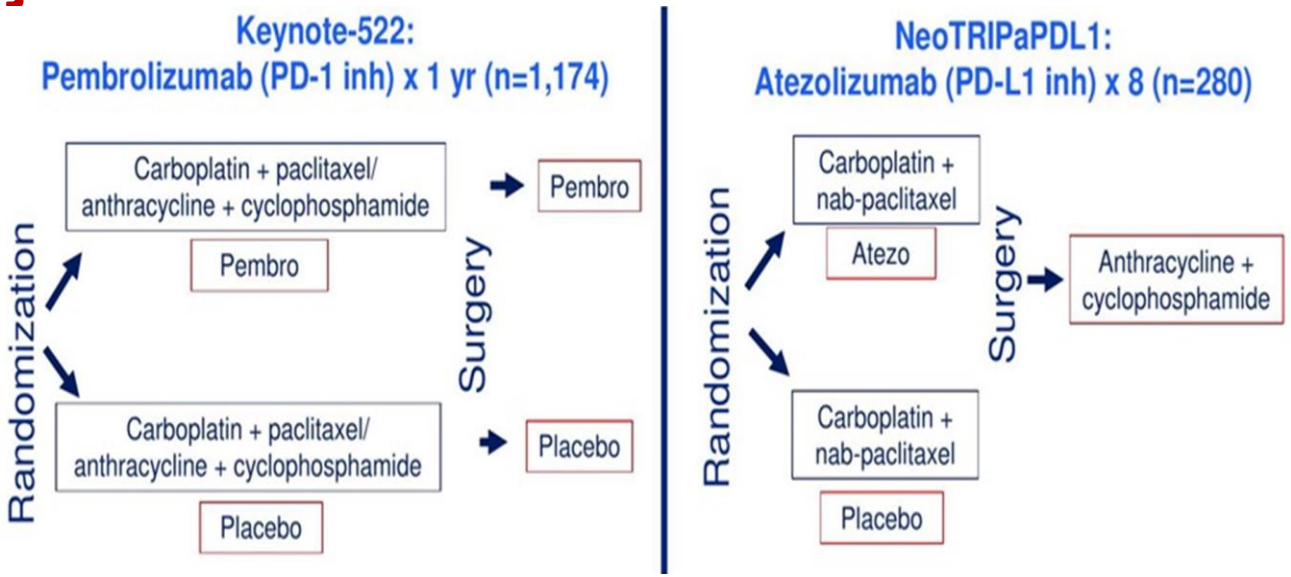
PD-L1+ liği: Neoadjuvan kemoterapi ile yüksek pCR'i predikte ediyor, ANCAK kimin immunoterapiden yarar sağlayacağını göstermiyor.



Peter Schmid et al. SABCS 2019, GS03-03, Gianni L et al. SABCS 2019, GS03-04

2 çalışma arasında farklılıklar

1. Tedavi şeması



	KEYNOTE-522	NeoTRIPaPDL1
Neoadj. kemoterapi	Pac+carbo→ AC	Carbo+nab-pakitaxel x8 Postop 4 AC
İmmunoterapi	Pembrolizumab (Anti-PD1)	Atezolizumab (Anti-PD-L1)
İmmunoterapi süresi	8 kür→ 1 yıla tamamlama	8 kür

2 çalışma arasında farklılıklar

2. Klinikopatolojik özellikler

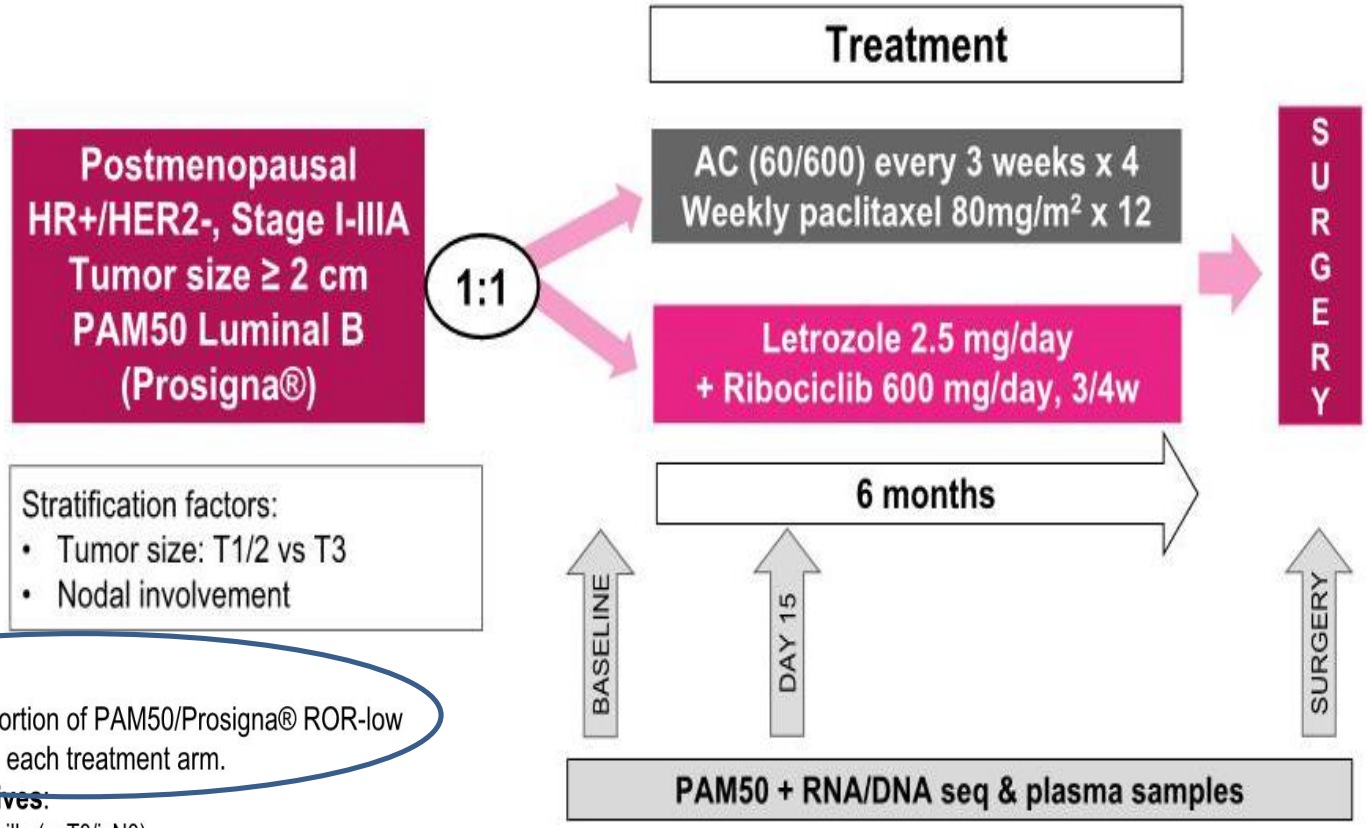
	KEYNOTE-522	NeoTRIPaPDL1
PD-L1 pozitifliği	%83 (22C3)	%56 (SP142)
T1, T2	%74	%56
Nod+	%51	%87
Evre IIA/IIB	%75	%51
Evre IIIA/IIIB	%25	%49 (%15 N3)

Peter Schmid et al. SABCS 2019, GS03-03, Gianni L et al. SABCS 2019, GS03-04

Erken Evre ve Lokal İleri Evre

- Neoadjuvan Çalışmalar
- **Neoadjuvan Kemoterapi**
  - **Germline BRCA mutasyonu olanlarda neoadjuvan tedavi: Cisplatin vs. AC (INFORM)**
  - **GeparX: İdeal nab-paklitaxel şeması ne olmalı? Kemoterapiye denosumab eklenmesi PCR'ı artırır mı?**
- **Triple negatif meme kanserinde Neoadjuvan İmmunoterapi**
  - **Neoadjuvan kemoterapiye pembrolizumab eklenmesi (KEYNOTE-522)**
  - **Neoadjuvan kemoterapiye atezolizumab eklenmesi (NeoTRIPaPDL1 Michelangelo)**
- **Neodjuvan Endokrin tedavi**
  - **Luminal B MK: Neoadjuvan ribociclib+letrozole vs. kemoterapi (SOLTI-1402/CORALLEEN)**
- Adjuvan Çalışmalar

CORALEEN Çalışma dizaynı



Primary objective:

- To evaluate the proportion of PAM50/Prosigna® ROR-low disease at surgery in each treatment arm.

Key secondary objectives:

- pCR in the breast and axilla (ypT0/isN0).
- RCB and PEPI score.
- Changes in PAM50 intrinsic subtype, ROR score and Ki67 across the 3 time-points.
- Safety.
- ORR by MRI and Physical examination.
- Rate of breast conserving surgery.
- Quality of life.
- Biomarkers of response.

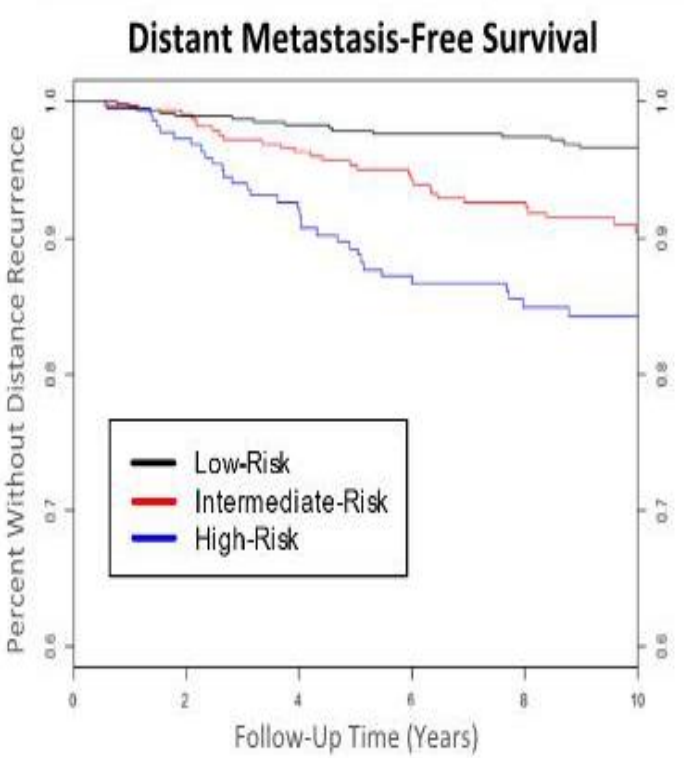
Gavilla J et al. SABCS 20019; GS2-05

PAM50/Prosigna-ROR (risk of recurrence) skoru

ROR score (0-100) = subtype + proliferation + tumor size

Definition of ROR-low/med/high disease

	Node-negative	Node+ 1-3	Node+ >3
ROR-low	0-40	0-15	-
ROR-intermediate	>40-60	>15-40	-
ROR-high	>60-100	>40-100	High



Walden et al. BMC Cancer 2015 Prat et al. Ann Oncol 2012; Prat et al. J Clin Oncol 2013. Prat et al. Clin Cancer Res 2015.

Hasta Özellikleri

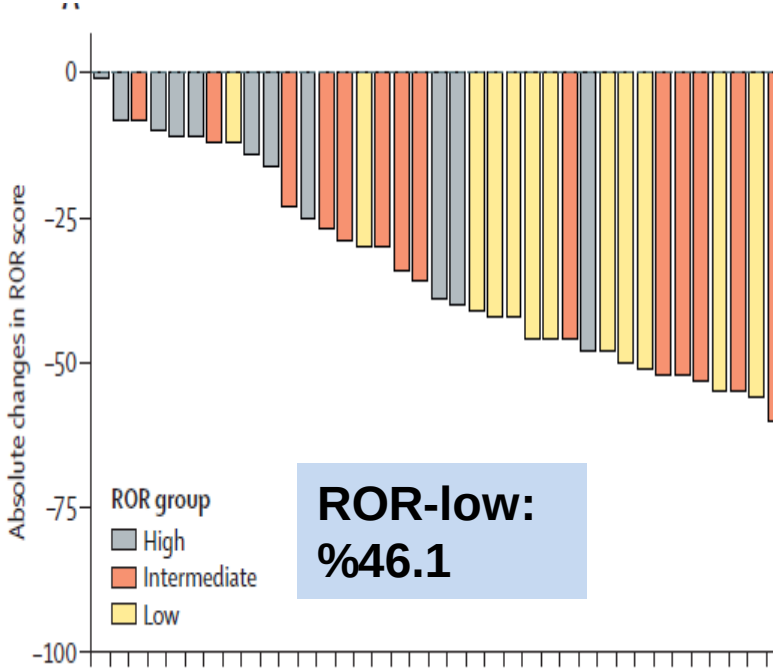
Characteristic, n (%)	Randomized population	
	Chemotherapy n=54	Ribociclib + letrozole n=52
Median age (IQR)	64 (58.3-71.8)	63 (56.5-70.3)
Clinical Tumor size		
T1	3 (5.5%)	3 (5.8%)
T2	43 (79.6%)	40 (76.9%)
T3	8 (14.8%)	9 (17.3%)
Clinical Axillary Nodes		
N0	31 (57.4%)	31 (59.6%)
N1	22 (40.8%)	19 (36.6%)
N2	1 (1.8%)	2 (3.8%)
Ki67 expression (local)		
Ki67 median (IQR)	35 (27.0-40.0)	30 (21.8-40.0)
PROSIGNA		
Median ROR score (IQR)	77 (66.6-82.0)	70 (64.6-80.3)
ROR risk class		
Intermediate	6 (11.1%)	8 (15.4%)
High	48 (88.9%)	44 (84.6%)

Gavilla J et al. SABCS 20019; GS2-05

ROR skorunda net değişim

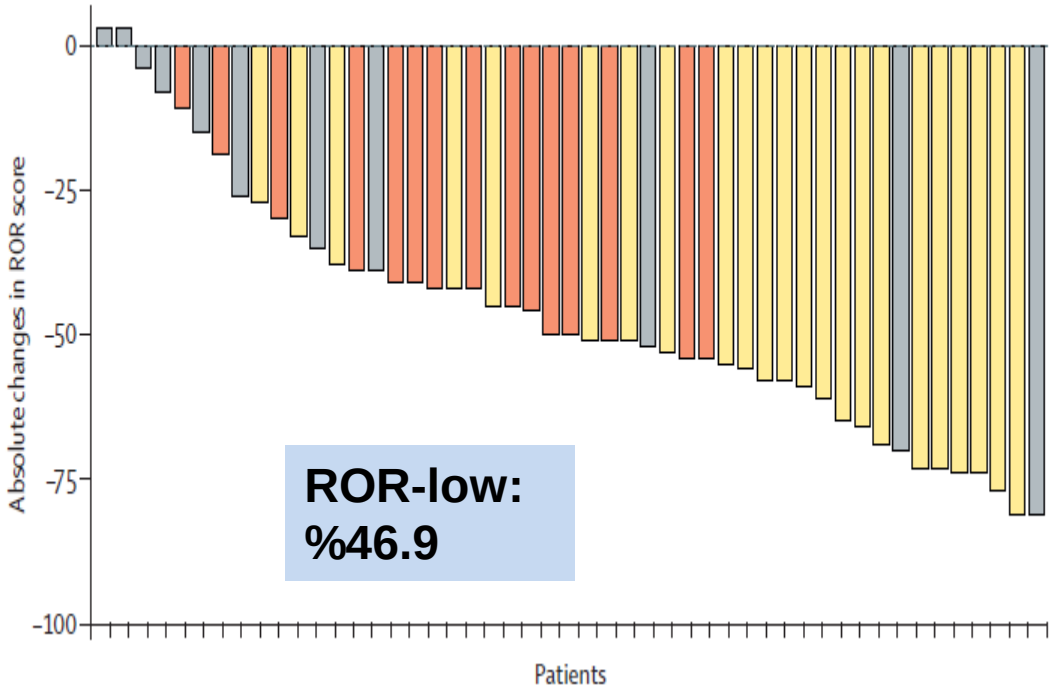
Δ ROR change = ROR score at surgery – ROR at baseline

Kemoterapi



ROR-low: %46.1

Ribociclib+letrozole



ROR-low: %46.9

Gavilla J et al. SABCS 20019; GS2-05

Cerrahi sonuçları

- **Yanıt oranı:**
  - **Kemoterapi: %78.8 vs. Ribo+letrozole: %57.1**

		Chemotherapy n= 52		Ribociclib + letrozole n= 49	
		N (%)	95% IC	N (%)	95% IC
ROR score median (IQR)		25 (12.0-45.0)		18 (12.0-35.0)	
Central Ki67 IHC median (IQR)		10 (3.0-20.0)		3 (1.0-8.0)	
RCB 0-1 rate		6 (11.8%)	4.5-27.8	3 (6.1%)	1.3-16.8
pCR rate		3 (5.8%)	1.4-16.6	0 (0%)	0-7.2
PEPI	0	9 (17.3%)	8.6-31.4	11 (22.4%)	11.7-36.6
	1-3	24 (46.1%)	33.6-62.6	25 (51.0%)	36.3-65.6
	≥4	17 (32.7%)	21.2-48.7	13 (26.6%)	15.0-41.2
	Missing	2 (3.9%)		0	

preoperative endocrine prognostic index score (PEPI)
PEPI skor 0: düşük relaps riski ve adjuvan tedavi faydasız

Gavilla J et al. SABCS 20019; GS2-05

Sonuç

Yüksek riskli luminal B hastada:

- **Neoadjuvan ribocicilib+letrozole: Cerrahide yüksek oranda ROR-low hastalık sağlıyor**
- **Kemoterapi: Benzer oranda cerrahide yüksek oranda ROR-low hastalık sağlıyor, ancak daha toksik**

- **Kemoterapisiz bir neoadjuvan tedavi stratejisi mümkün gözüküyor → Çalışma yapılmalı**

Peter Schmid et al. SABCS 2019, GS03-03

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Erken Evre ve Lokal İleri Evre

- Neoadjuvan Çalışmalar
- Adjuvan Çalışmalar
- De-eskalasyon- Evre I HER2+ meme ca TDM1 vs Trast + Pakl ATEMPT
- Eskalasyon- HER2+ meme ca adjuvan taksan + trastuzumab +/- pertuzumab APHINITY (OS interim analiz)

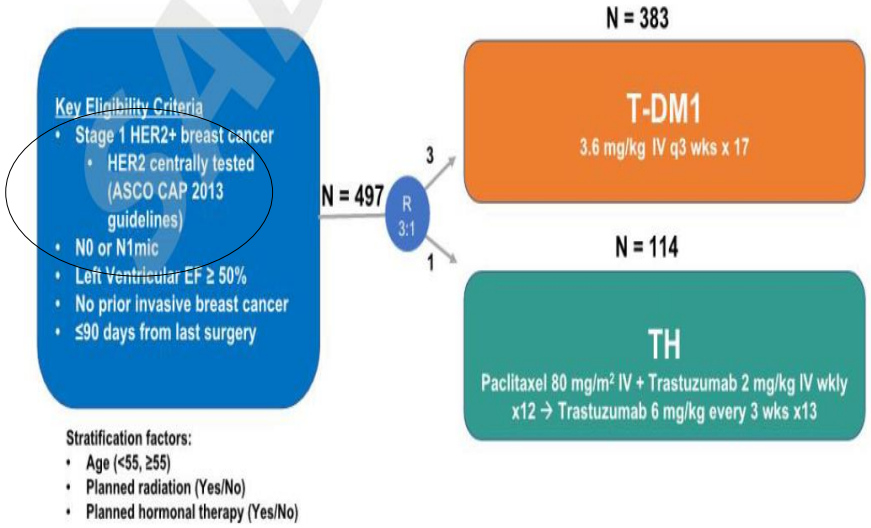
TBCRC 033: A Randomized Phase 2 Trial of Adjuvant Trastuzumab Emtansine (T-DM1) vs. Paclitaxel with Trastuzumab for Stage 1 HER2+ Breast Cancer (ATEMPT

Sara M. Tolaney[1,2], Jiani Hu[1,2], Chau Dang[3], Denise Yardley[4], Steven J. Isakoff[5], Vicente Valero[6], Meredith Faggen[1], Therese Mulvey[5], Ror Bose[7], Nabihah Tayob[1,2], William Barry[1,2], Douglas Weckstein[1], Antonio C. Wolff[8], Katherine Reeder-Hayes[9], Hope S. Rugo[10], Bhuvaneswa Ramaswamy[11], Dan Zuckerman[12], Lowell Hart[13], Vijayakrishna K. Gadi[14], Michael Constantine[1], Kit Cheng[15], Frederick Briccetti[1], Bryan Schneider[16], Nadine Tung[1,2], Merrill Garrett[17], Kelly Marcom[18], Kathy Albain[19], Patricia DeFusco[20], Blair Ardman[21], Rita Nanda[22], Rachel Jankowitz[23], Mothaffar Rimawi[24], Vandana Abramson[25], Paula Pohlmann[26], Catherine Van Poznak[27], Andres Forero-Torres[28], Minetta Liu[29] Michelle DeMeo[1], Ann Partridge[1,2], Harold Burstein[1,2], Eric P. Winer[1,2], Ian Krop[1,2]

- **Co-primary Endpoints:**
  - **Evaluate 3 year disease-free survival (DFS) in the T-DM1 arm**
  - **Compare the incidence of clinically relevant toxicities (CRT) between the 2 arms**
    - **grade ≥3 non-hematologic toxicity**
    - **grade ≥2 neurotoxicity**
    - **grade ≥4 hematologic toxicity**
    - **febrile neutropenia**
    - **any toxicity requiring dose delay or discontinuation of protocol therapy**

***The study is not powered to evaluate the efficacy of TH or to compare the efficacy of T-DM1 to TH**

Study Design: ATEMPT Trial



Stratification factors:
- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

*Radiation and endocrine therapy could be initiated after 12 weeks on study therapy

Study Population

	T-DM1 (n = 383)	TH (n = 114)	All Patients (n = 497)
Median Age (Range)	56 (32-85)	55 (23-82)	56 (23-85)
Tumor Size			
<0.5 cm	42 (11%)	14 (12%)	56 (11%)
≥0.5-1.0 cm	121 (32%)	38 (33%)	159 (32%) — 43%
≥1.0-1.5 cm	118 (31%)	29 (25%)	147 (30%)
≥1.5-2.0 cm	102 (27%)	33 (29%)	135 (27%) — 57%
Histologic Grade			
Well Differentiated	11 (3%)	4 (4%)	15 (3%)
Moderately Differentiated	148 (39%)	46 (40%)	194 (39%)
Poorly Differentiated	219 (57%)	62 (54%)	281 (57%)
Unknown	5 (1%)	2 (2%)	7 (2%)
HR status			
Positive	289 (75%)	84 (74%)	373 (75%)
Negative	94 (25%)	30 (26%)	124 (25%)
HER2 Status (Central)			
1+	5 (1%)	1 (1%)	6 (1%)
2+	92 (24%)	25 (22%)	117 (24%)
3+	277 (72%)	87 (76%)	364 (73%)
Not done*	9 (2%)	1 (1%)	10 (2%)

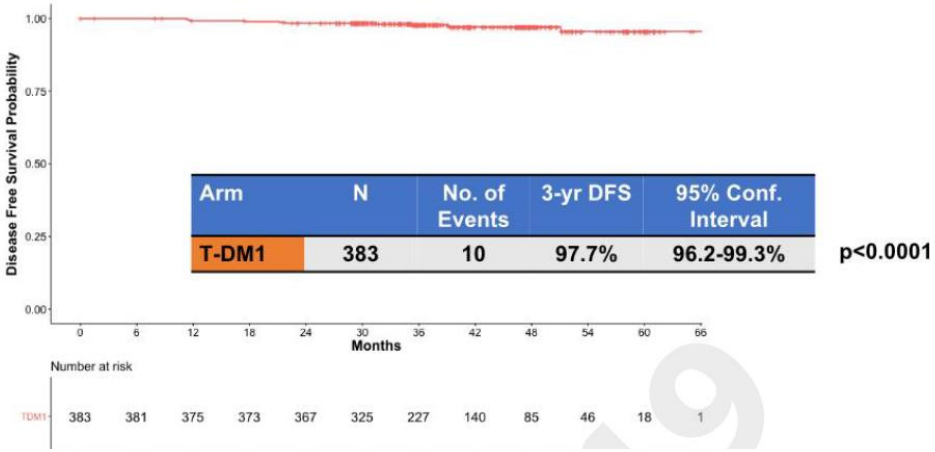
*FISH performed centrally without IHC

etkinlik karşılaştırma çalışması değil

3/1 randomize

ATEMPT: Evre I HER2(+) meme ca adjuvan TDM1 (vs TH)

Disease-Free Survival: T-DM1



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
T-DM1	383	10	97.7%	96.2-99.3%

p<0.0001

TDM-1 ile 3 yıllık DFS %97.7

HR- ve T< 1 cm de sonuçlar biraz daha iyi gibi

Daha uzun izlem gerekli

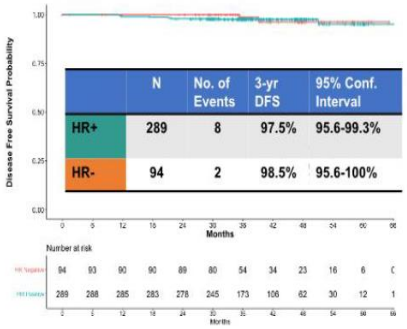
DFS olayları: 10 kişi

2 si uzak nüks

3 ölüm meme ca dışı sebep

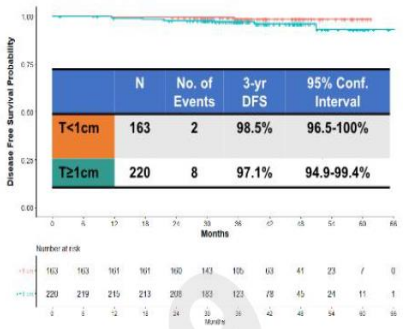
Disease-Free Survival: T-DM1

Hormone Receptor Status



	N	No. of Events	3-yr DFS	95% Conf. Interval
HR+	289	8	97.5%	95.6-99.3%
HR-	94	2	98.5%	95.6-100%

Tumor Size



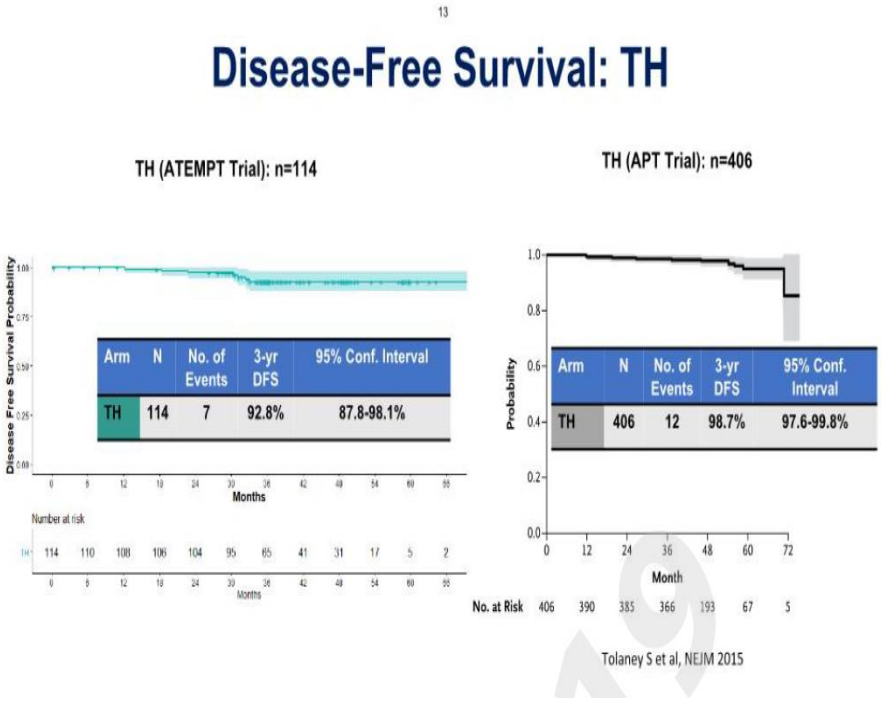
	N	No. of Events	3-yr DFS	95% Conf. Interval
T<1cm	163	2	98.5%	96.5-100%
T≥1cm	220	8	97.1%	94.9-99.4%

Disease-Free Survival Events: T-DM1

DFS Event: T-DM1	N (of 383)	Time to event (months)
Any recurrence or death	10	
Local/Regional Recurrence*		
Ipsilateral axilla (HER2+)	1	35
Ipsilateral breast (HER2-)	1	11
New Contralateral Primary Breast Cancer		
HER2+	0	
HER2-	3	12, 18, 21
Distant Recurrence	2	22, 51
Death		
Non-breast cancer related*	3	12, 32, 39

*Deaths due to: Diabetic coma, Stroke, Creutzfeldt Jakob disease

ATEMPT: Evre I HER2(+) meme ca adjuvan TDM1 (vs TH)



Kontrol kolu etkinliği biraz daha düşük

3 yıllık DFS

ATEMPT %92.8

APT %98.7

ATEMPT: Evre I HER2(+) meme ca adjuvan TDM1 (vs TH)

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Clinically Relevant Toxicity

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

p=0.91

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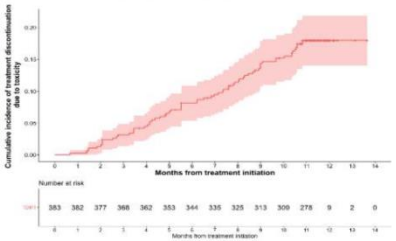
T-DM1 discontinuations

	n (%)
Discontinuations for any reason	90 (23.5%)
Discontinuations for toxicity[1]	67 (17.0%)
Discontinuations for toxicity that were protocol mandated	33 (9%)

[1]Most common toxicities leading to discontinuation include: liver enzyme elevation, bilirubin elevation, neuropathy, and thrombocytopenia

- 66% of patients who discontinued T-DM1 early for toxicity received further therapy with trastuzumab

Timing of Discontinuation



- Probability of discontinuing within 6 months: 8.2%
- Probability of discontinuing between months 6-12: 10.7%

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Treatment Related Adverse Events: Grade ≥2 by Arm

	T-DM1 (n = 383)	TH (n = 114)
Fatigue	84 (22%)	26 (23%)
Neuropathy	44 (11%)	27 (24%)
Neutropenia	13 (3%)	15 (13%)
Thrombocytopenia	43 (11%)	1 (1%)
Nausea	39 (10%)	8 (7%)
Hypertension	35 (9%)	7 (6%)
ALT increase	33 (9%)	5 (4%)
Headache	24 (6%)	4 (4%)
Bilirubin increase	21 (5%)	1 (1%)
Infusion related reaction	19 (5%)	12 (11%)
Arthralgia	18 (5%)	2 (2%)
Anemia	18 (5%)	2 (2%)

Beklenmeyen yan etki yok ancak

TDM1 daha az toksik değil (vs TH)

(klinik ilişkili toksisite açısından)

TDM1 toksisitesine bağlı bırakma %17 (vs TH ile %6)

Farklı toksisite profili (nöropati/anemi vs trombositopeni/ALT artışı/bill)

Hastanın doldurduğu anketler TDM1 lehine (daha az alopesi)

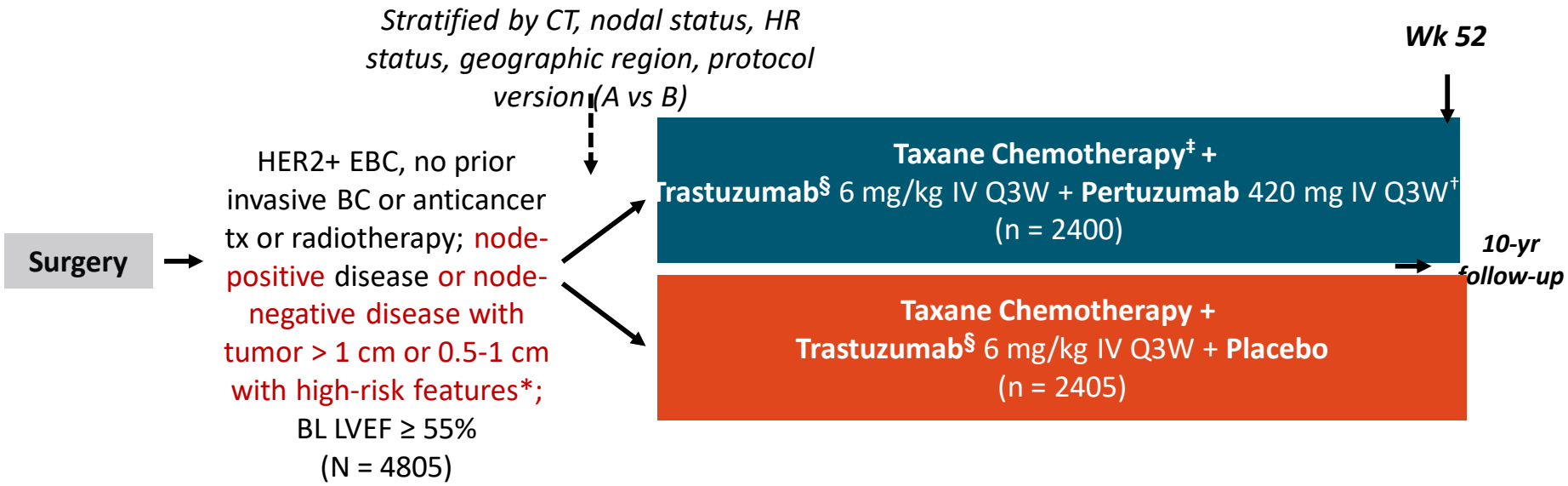
APHINITY: Interim OS Analysis of Adjuvant CT Plus Trastuzumab With vs Without Pertuzumab for Patients With HER2+ EBC

- Addition of trastuzumab, an anti-HER2 monoclonal antibody, to adjuvant chemotherapy reduced the risk of relapse and death in patients with HER2+, operable EBC[1-3]
- Pertuzumab is a humanized monoclonal antibody that binds to a different domain of HER2 than trastuzumab[4]
- Primary analysis of APHINITY trial showed improved IDFS for adjuvant chemotherapy with trastuzumab plus pertuzumab vs placebo[5]
  - 3-yr IDFS: 94.1% vs 93.2% (HR: 0.81; 95% CI: 0.66-1.00; *P* = .045) but no significant difference in first interim OS analysis: 96.7% with pertuzumab vs 96.3% with placebo (HR: 0.89; 95% CI: 0.66-1.21; *P* = .47)
  - FDA granted regular approval for pertuzumab in combination with chemotherapy and trastuzumab as adjuvant therapy for patients with HER2+ EBC at high risk of recurrence
- Current report is second interim OS analysis of the APHINITY trial[6]

1. Piccart-Gebhart. NEJM. 2005;353:1659. 2. Romond. NEJM. 2005;353:1673. 3. Slamon. NEJM. 2011;365;1273.
4. Scheuer. Cancer Res. 2009;69:9330. 5. von Minchwitz. NEJM. 2017;377:122 6. Piccart. SABCS 2019. Abstr GS1-04.

APHINITY: 1. Basamak Taksan + Trastuzumab +/- Pertuzumab

- International, randomized, double-blind, placebo-controlled phase III trial[1,2]



- Primary endpoint: IDFS per modified STEEP definition[3] (excludes second primary non-BC as event)
- Secondary interim analysis: preplanned, time-driven OS analysis after 2.5 yrs; descriptive analysis of IDFS and cardiac safety

1. Piccart. SABCS 2019. Abstr GS1-04. 2. von Minchwitz. NEJM. 2017;377:122. 3. Hudis. J Clin Oncol. 2007;25:2127.

*: grad 3, ER, PR neg veya <35 yaş

APHINITY: Baseline Characteristics in ITT Population

Characteristic, %		Pertuzumab (n = 2400)	Placebo (n = 2404)
Nodal status	▪ 0 positive nodes + T ≤ 1 cm	4	3
	▪ 0 positive nodes + T > 1 cm	34	34
	▪ 1-3 positive nodes	38	37
	▪ ≥ 4 positive nodes	25	25
Adjuvant CT regimen (randomized)	▪ Anthracycline containing	78	78
	▪ Nonanthracycline containing	22	22
HR status (central determination)	▪ Negative (ER- and PgR-)	36	36
	▪ Positive (ER+ and/or PgR+)	64	64
Protocol version	▪ A	76	76
	▪ Amendment B*	24	24
Geographic region	▪ Asia pacific	23	23
	▪ Eastern Europe	8	8
	▪ US	12	12
	▪ Latin America	3	3
	▪ Canada, W Europe, Australia/NZ, South Africa	54	54

*Capped node-negative enrollment in November 2012 (recruitment started November 2011); added 1000 node-positive patients and increased sample size to 4800 patients total.

Piccart. SABCS 2019. Abstr GS1-04.

APHINITY: Survival Outcomes in ITT Population

- Median follow-up of 74.1 mos

Outcome	Pertuzumab (n = 2400)	Placebo (n = 2404)
Overall survival events, n (%)	125 (5.2)	147 (6.1)
▪ Stratified HR (95% CI)	0.85 (0.67-1.07)	
▪ Stratified *P* value	.170*	
6-yr OS rate, %	94.8	93.9
▪ Difference in event-free rate, % (95% CI)	0.9 (-0.5-2.2)	
IDFS events, n (%)	221 (9.2)	287 (11.9)
▪ Stratified HR (95% CI)	0.76 (0.64-0.91)	
6-yr IDFS event-free rate, %	90.6	87.8
▪ Difference in event-free rate, % (95% CI)	2.8 (1.0-4.6)	

First IDFS Event Category, n (%)	Pertuzumab (n = 2400)	Placebo (n = 2404)
Distant recurrence	141 (5.9)	184 (7.7)
CNS metastases	49 (2.0)	49 (2.0)
Locoregional BC recurrence	28 (1.2)	49 (2.0)
Contralateral invasive BC recurrence	13 (0.5)	15 (0.6)
Death without prior event	39 (1.6)	39 (1.6)

**P* value of .0012 required to reach statistical significance. OS data are immature at current analysis.

Bu interim analizde anlamlı OS yararı gösterilemedi,
Pertuzumab eklenmesiyle daha az ölüm olayı (6-yr OS %94.8 vs %93.9) (sayısal olarak daha az uzak nüks ve lokorejyonel nüks)

Piccart. SABCS 2019. Abstr GS1-04.

APHINITY: Clinical Benefit in Primary vs Secondary Analysis

HR for IDFS (95% CI)	Primary Analysis (mFU: 45.4 Mos)	Updated Analysis (mFU: 74.1 Mos)
ITT population	0.81 (0.66-1.00)	**0.76 (0.64-0.91)**
Lymph node positive	0.77 (0.62-0.96)	**0.72 (0.59-0.87)**
Lymph node negative	1.13 (0.68-1.86)	1.02 (0.69-1.53)
Hormone receptor positive	0.86 (0.66-1.13)	0.73 (0.59-0.92)
Hormone receptor negative	0.76 (0.56-1.04)	0.83 (0.63-1.10)

IDFS at 6-Yr	Pertuzumab, %	Placebo, %	Absolute Benefit, % (95% CI)	45 aylık izlemde
ITT population	90.6	87.8	**2.8 (1.0-4.6)**	1.7
Lymph node positive	87.9	83.4	**4.5 (1.9-7.1)**	3.2
Lymph node negative	95.0	94.9	0.1 (-2.0-2.2)	0.5
Hormone receptor positive	91.2	88.2	3.0 (0.8-5.2)	1.4
Hormone receptor negative	89.5	87.0	2.5 (-0.7-5.6)	2.3

Klinik yarar devam etmekte:
6 yılda IDFS net yararı (ITT): % 2.8 (HR: 0.76; 95% CI: 0.64-0.91)
Klinik yarar nod+ hastalarda daha belirgin; net yarar % 4.5 (HR: 0.72; 95% CI: 0.59-0.87)
HR durumundan bağımsız yarar var

Piccart. SABCS 2019. Abstr GS1-04.

APHINITY: Cardiac Safety

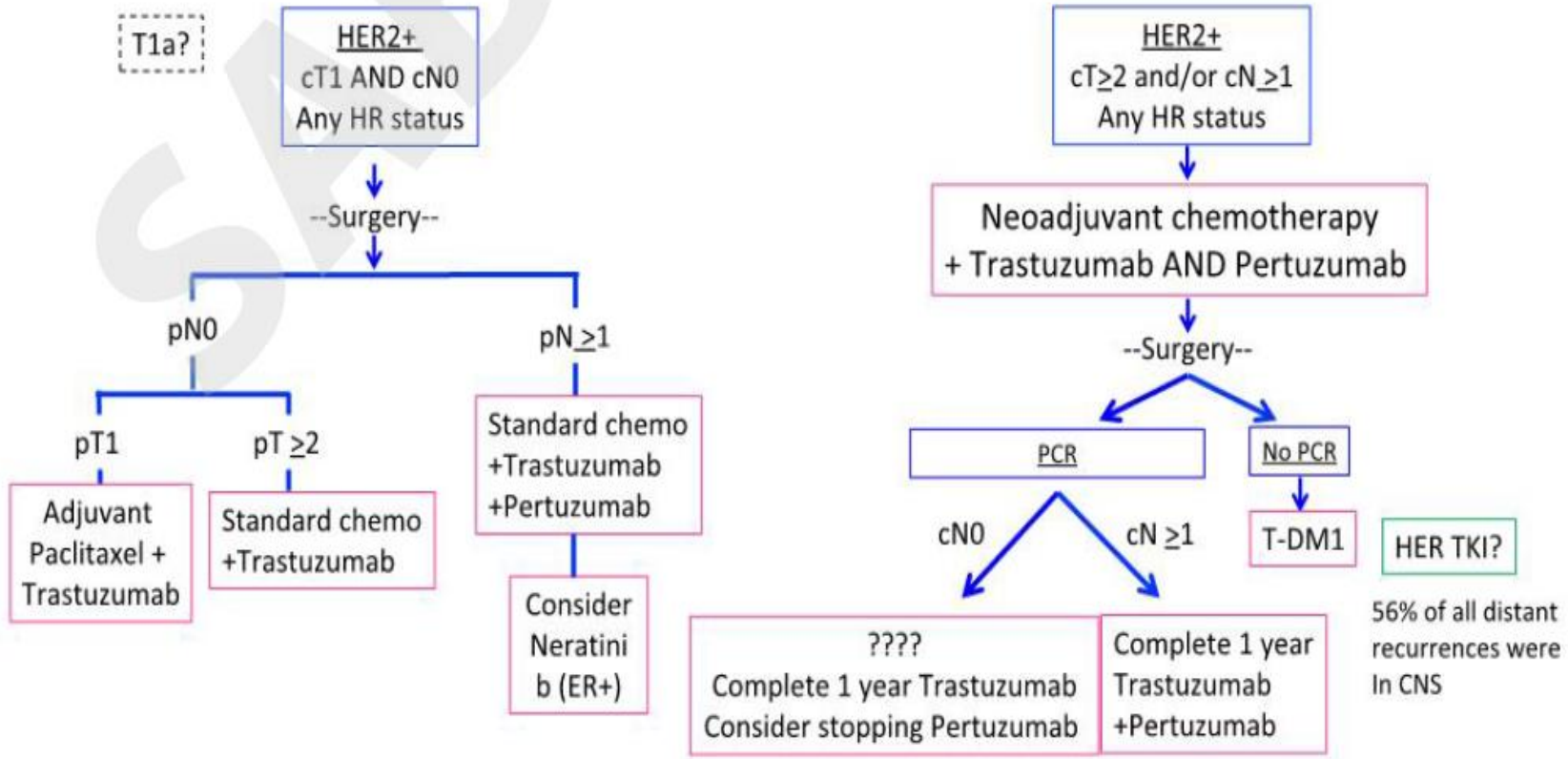
Characteristic, n (%)	Pertuzumab (n = 2364)	Placebo (n = 2405)
Primary cardiac event*	18 (0.8)	8 (0.3)
Cardiac death	2 (.08)	2 (0.08)
Secondary cardiac event†	65 (2.7)	68 (2.8)

*Heart failure New York Heart Association class III or IV plus ejection fraction drop ≥ 10% from baseline and to < 50% or cardiac death. †Asymptomatic or mildly symptomatic (New York Heart Association class II) ejection fraction drop ≥ 10% from baseline and to < 50%.

- At updated follow-up of 74.1 mos, 1 additional primary cardiac event in the pertuzumab arm and 1 additional patient in each arm had a secondary cardiac event
- No new cardiac safety issues were identified

Piccart. SABCS 2019. Abstr GS1-04.

Putting it all together: HER2+ EBC



Erken Evre ve Lokal İleri Evre: Özet

- Neoadjuvan Çalışmalar
- Neoadjuvan Kemoterapi
  - Germline BRCA mutasyonu olanlarda neoadjuvan sisplatin, AC den üstün değil (INFORM) (-) çalışma
  - GeparX: İdeal nab-paklitaxel şeması: haftalık nab-paklitaksel > 3 haftada 2 hf nab-pakl (pCR farkı %6)
- Triple negatif meme kanserinde Neoadjuvan İmmunoterapi
  - Neoadjuvan kemoterapiye pembrolizumab eklenmesi (KEYNOTE-522)ile pCR farkı % 14 (LN + lerde %20 veya evre IIIA/B de %25)
  - Neoadjuvan kemoterapiye (nabpakl-karbop) atezo eklenmesi (NeoTRIPaPDL1 Michelangelo) pCR farkı yaratmıyor (-) çalışma
- Neodjuvan Endokrin tedavi
  - Luminal B MK: Neoadjuvan ribociclib+letrozole vs. Kemoterapi (SOLTI-1402/CORALLEEN)- preop düşük ROR skorları benzer oranda
- Adjuvan Çalışmalar
  - De-eskalasyon stratejisi; Evre I HER2+ meme ca TDM1 (vs Trast + Pakl) ATEMPT 3 yıllık DFS %97.7, toksisite farklı (ama daha az değil), etkinlik karşılaştırma çalışması değil –APT standardını değiştiremeyecek-kısa izlem, tedavi bırakma oranları yüksek ve yüksek maliyet (? Kısa süreli TDM1)
  - Eskalasyon stratejisi- HER2+ meme ca adjuvan taksan + trastuzumab +/- pertuzumab APHINITY (OS interim analiz fark yok) IDFS net yararı (ITT) artarak devam ediyor % 2.8, aksiller LN + lerde daha belirgin %4.5

Teşekkürler