

CONVEGNO REGIONALE AIOM SICILIA
INNOVAZIONE, ACCESSIBILITA', SOSTENIBILITA', INFORMAZIONE
IN ONCOLOGIA

Il trattamento per il tumore triple negative

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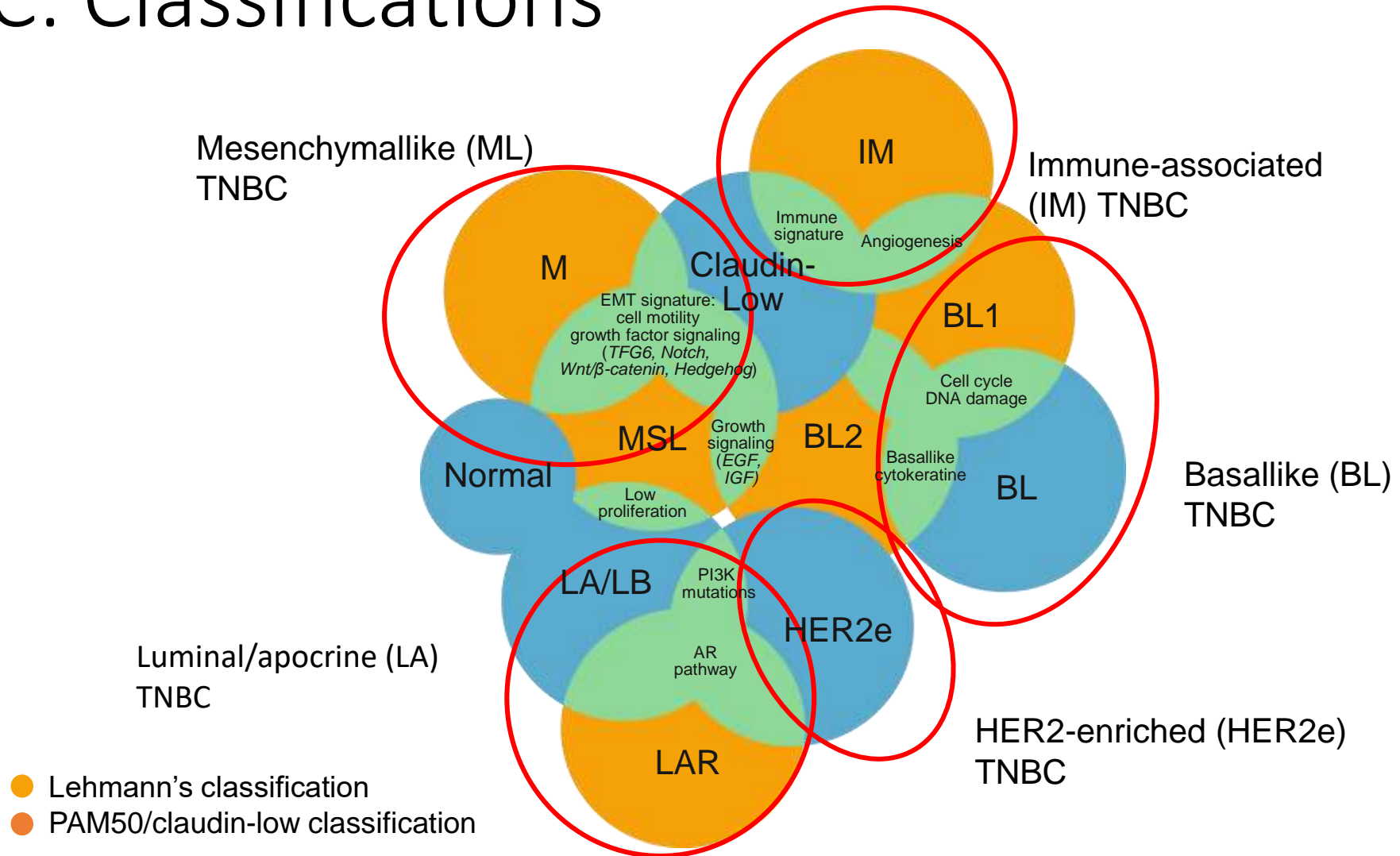
Asp SR

1-2 Marzo 2019

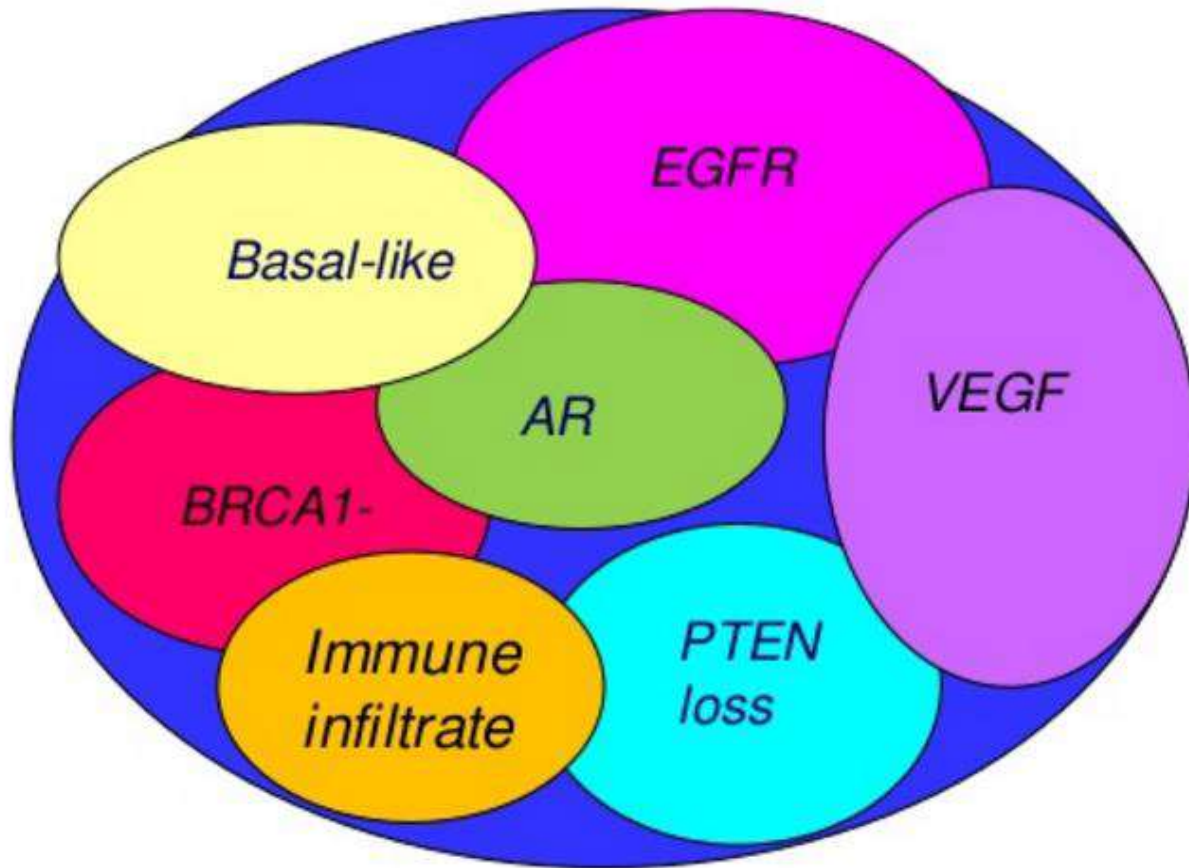
Triple-Negative Breast Cancer: Overview

- TNBC accounts for ~15% of all breast cancers
- A heterogeneous disease which is still not fully understood
- Associated with younger age, more aggressive disease, higher risk of distant recurrence and shorter survival compared with other breast cancer subtypes
- Visceral disease is more common in TNBC, with CNS involvement up to 46%

TNBC: Classifications



Heterogeneity of TNBC: It is not one disease



Many Approaches Under Evaluation for TNBC in Clinical Trials

Pathway/Drug type	Drugs in development
DNA repair	PARP inhibitors (olaparib, rucaparib, veliparib), platinum agents (cisplatin, carboplatin)
PI3K/Akt/mTOR	PI3K inhibitors (buparlisib, taselisib, GDC0941, AZD8186, many others); Akt inhibitors (GDC0068, others), mTOR inhibitors (everolimus, others)
Androgen (testosterone) signaling	Anti-androgens (bicalutamide, enzalutamide)
Immune	CTLA4 blockade (ipilimumab), PD1/PD-L1 blockade (nivolumab, pembrolizumab, atezolizumab),
Antibody-drug conjugates	IMMU-132, SGN-LIV1A, PF06647263, CDX-011
Cell cycle	Dinaciclib, seliciclib
Chk1	GDC0575
Bromodomain	TEN-101, GSK525762
Heat shock (stress)	Ganetespib, others
Angiogenesis	Ramucirumab, cedirininib

The evolution of breast cancer: 3500 BC to 2016

3500-3500 BC
(The Pyramid Age):
Egyptian texts described 8 cases of tumors that were treated by cauterization with a "hot drill"

Edwin Smith surgical Papyrus believed to be produced around the Pyramid Age

1800-1500 BC
Ebers Papyrus dated to a period that coincides with the reign of Amenhotep I in 1534 BC. It described the "swelling (tumor) of vessels"

3000 BC - 400 AD

460 B.C.: Hippocrates proposed the **Humoral Theory of Medicine** and attributed cancer to an excess of black bile. He believed the cancer should be left alone, because those who got treatment did not live as long as those who were untreated.

198 BC
Galen proposed that breast tumor was a coagulum of black bile in what is known as the **Galenic humoral theory**

100-200 BC

René Descartes (1596-1650) proposed the **lymphatic theory** for the origin of breast cancer

John Hunter (1728-1793) proposed that palpable breast tumors were caused by **coagulation of defective lymph**

1600-1799

In 1773, Bernardino Ramazzini observed that runs frequently had breast cancer; blamed **lack of sexual intercourse** as a cause of breast cancer

In 1757, Henri Le Dran postulated that cancer progressed in stages, and advocated surgery to prevent spreading of breast cancer

In 1828, Johannes Müller proposed that cancer cells developed from the blastema in the normal tissues

In 1846, William Morton demonstrated the use of ether anesthesia for surgery

1800-1899

In 1882, William Halsted introduced **radical mastectomy** for breast cancer treatment

In 1896, Thomas Swanson reported regression of metastatic breast cancer after oophorectomy (the **anti-humoral concept**)

The discovery of x-rays by Wilhelm Röntgen in 1895 laid the foundation of **mammography**

In 1926 Janet Elizabeth Lane-Claydon led an unprecedented study that identified **breast cancer risk factors**

1900-1999

From the 1930s, **radiotherapy** became an alternative to radical mastectomy

In 1976, Bernard Fisher showed that **less-invasive lumpectomy** was as effective as disfiguring radical mastectomies

Tamoxifen approved for treatment of metastatic breast cancer; FDA, 1977

Susan G. Komen Breast Cancer Foundation was founded in 1982

From the 1930s, **radiotherapy** introduced as alternative to radical mastectomy

In 1962, Robert Egan reported the first cases of breast cancer detected using **mammography**

Breast cancer awareness in the '70s promoted by First Lady Betty Ford and journalist Rose Kushner

Generation of the **MMTV-neu-MT transgenic mouse**, 1988

Herceptin, first targeted therapy; FDA, 1998

2000-2016

Breast cancer subtypes: HER+, ER+, basal etc. identified via gene expression profiling in 2000

The **human genome** sequenced in 2003

New genetic tests: -Oncotype DX for ER+ early diagnosis; MammaPrint for distant metastasis; FDA, 2007

The **Angelina Jolie effect** for prophylactic bilateral mastectomy started in 2013

Fulvestrant, second-line endocrine therapy; FDA, 2002

Aromatase Inhibitors: Letrozole, Anastrozole, Exemestane

HER2 and HER1 inhibitor Lapatinib FDA-approved in 2010

The **CLEOPATRA** study in 2010 in favor of combination therapy

Next-generation targeted drug called **trastuzumab emtansine** (Armed antibody drug); FDA 2013

What is new....??

....neoadjuvant setting

Sali di platino nei tumori triple negative

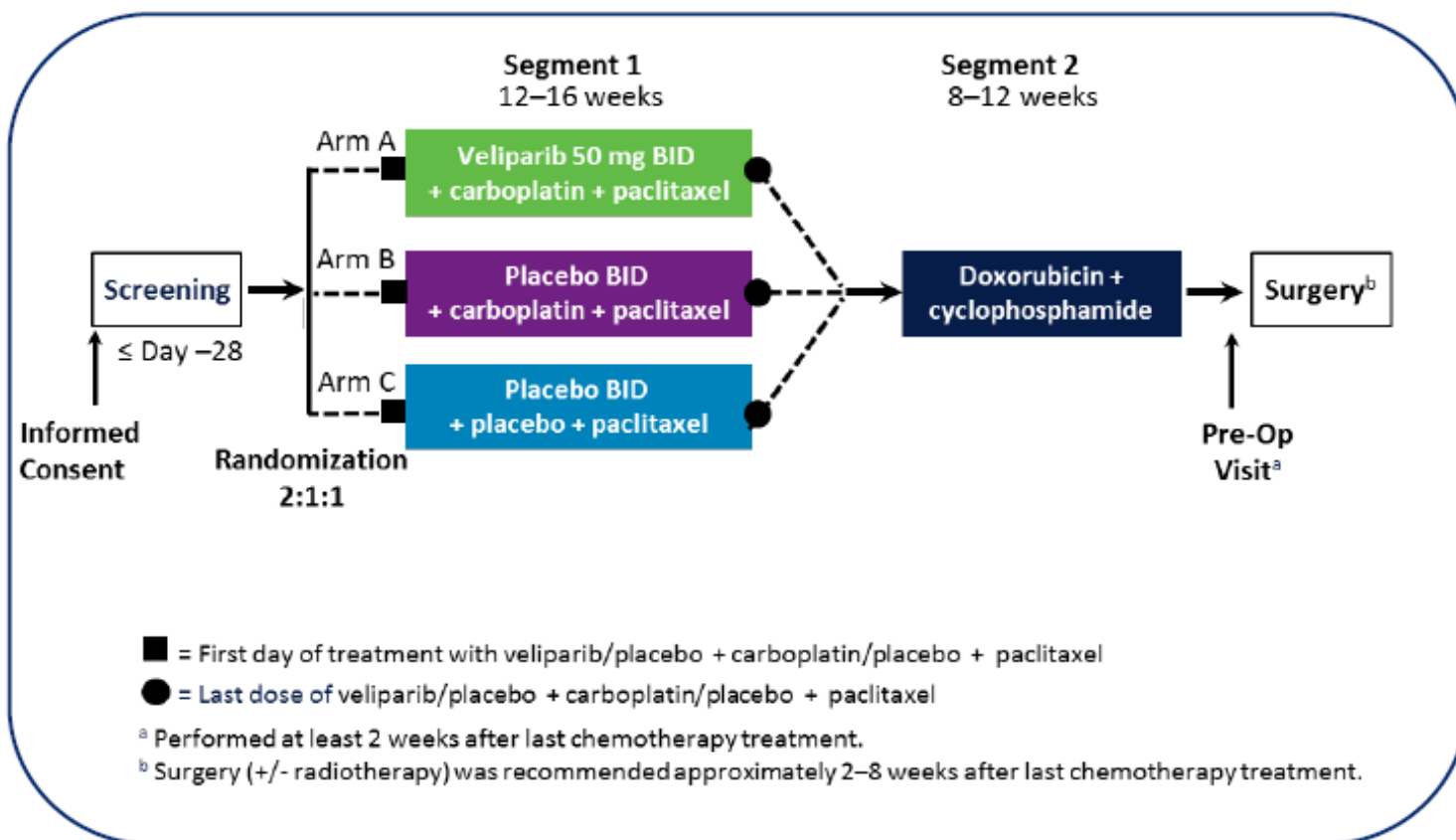
Trial	n	Drugs	Population	pCR
GEICAM	94	EC-D	Basal-like	30%
		EC-D+Cb		30%
GeparSixto	165	PM/bev	TNBC (subset)	38%
		PMCb/bev		59%
CALGB 40603	455	T-AC(bev)	TNBC	46%
		T/Cb-AC (bev)		60%
ADAPT-TN	336	Nab-P/weekly Gem	TNBC	29%
		Nab-P/weekly Cb		46%

Carboplatin augments pCR in TNBC

AC, doxorubicin and cyclophosphamide; Cb, carboplatin; EC-D, epirubicin and cyclophosphamide followed by docetaxel; PM, paclitaxel and methotrexate; PST, primary systemic therapy; T, trastuzumab; TNBC, triple-negative breast cancer

Alba E, et al. *Breast Cancer Res Treat.* 2012;136(2):487-493. von Minckwitz G, et al. *Lancet Oncol.* 2014;15(7):747-756. Sikov WM, et al. *J Clin Oncol.* 2015;33(1):13-21. Gluz O, et al. *J Natl Cancer Inst.* 2017 Dec 8. [Epub ahead of print].

Sali di platino nei tumori triple negative



Study Objectives

Primary objectives:

- Pathologic complete response (pCR) in breast and ipsilateral axillary lymph nodes

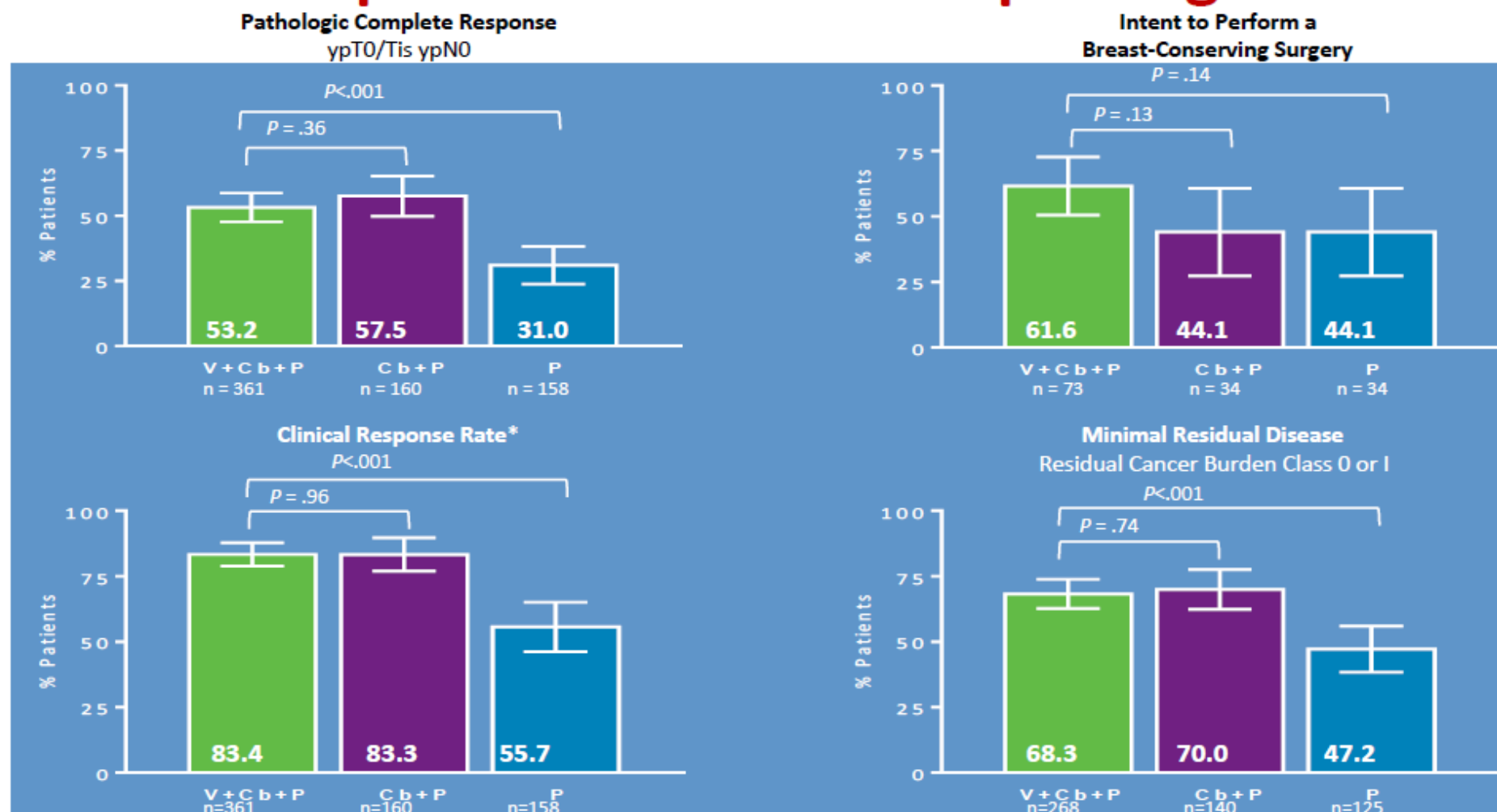
Secondary objectives:

- EFS, OS, and rate of eligibility for breast conservation after therapy

EFS, event free survival; P, paclitaxel; OS, overall survival; V, veliparib

Loibl S, et al. *Lancet Oncol.* 2018;19(4):497-509.

Sali di platino nei tumori triple negative



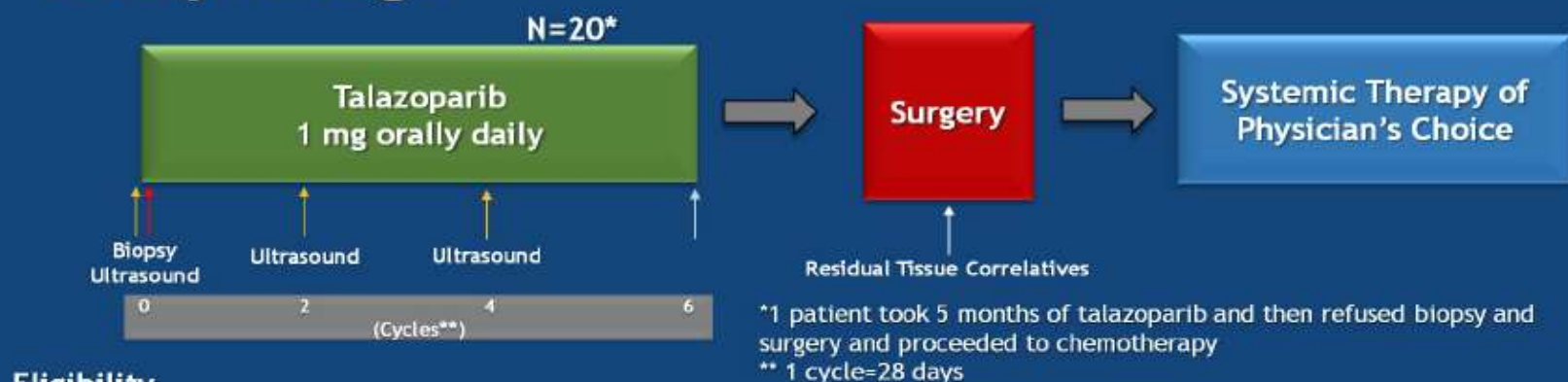
Error bars are 95% confidence intervals based on normal approximation. P values were calculated from Cochran-Mantel-Haenszel test versus Arm A (V+Cb+P).

*Clinical response rate after paclitaxel based treatment on serial MRI assessment

Loibl S, et al. *Lancet Oncol.* 2018;19(4):497-509.

Neoadjuvant talazoparib

Study Design



Eligibility

- Tumors > 1 cm
- Clinical Stage I-III
- Germline BRCA mutation
- No previous therapy for invasive breast cancer

Exclusion

- HER2 positive

Primary Objectives

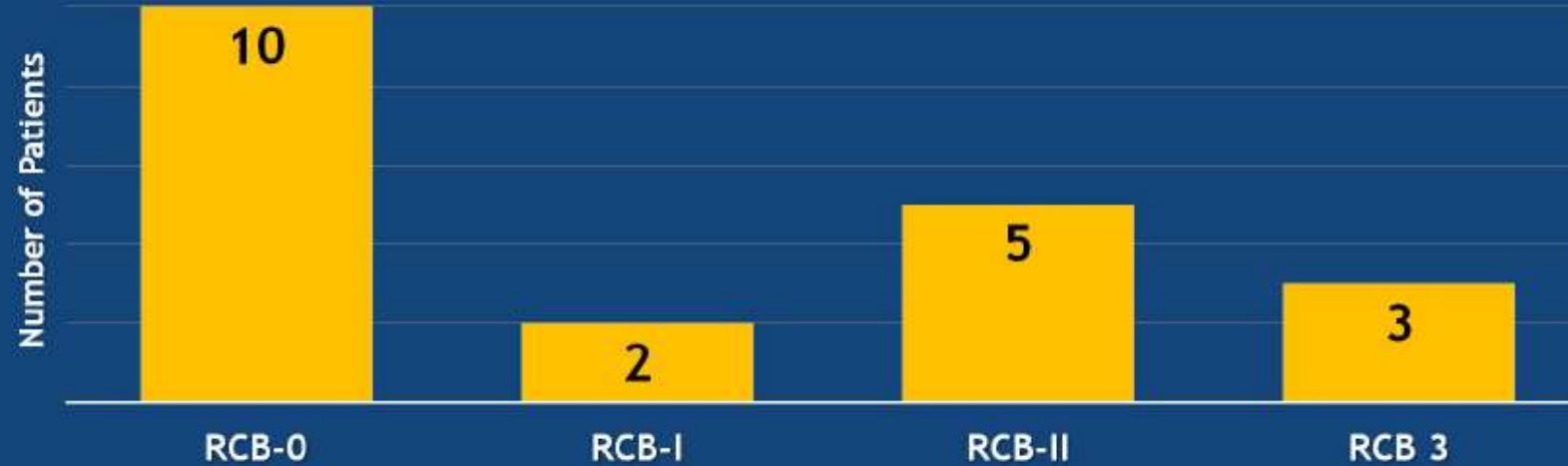
- pCR (ypT0/is ypN0)
- RCB-0 + RCB-I

Secondary Objective

- Evaluate toxicity

Neoadjuvant talazoparib

Pathologic Results



pCR (RCB-0): 10/19 = 53%, 95% CI = 32%, 73%

RCB-0+I: 12/19 = 63%, 95% CI = 41%, 81%

PARP inibitori o platino?

	Talazoparib	Cisplatin
Number of patients	20	107
BRCA 1	85%	100%
BRCA 2	15%	N/A
Neoadjuvant treatment duration	6 months	75 mg/m2 q21 days, 4 cycles = 3 months
Adjuvant chemotherapy	According to physician's choice	Doxorubicin + Cyclophosphamye
Toxicities	Hematological	Emesis, neuropathy, nephrotoxicity
pCR rates	53%	61%
Estimated costs of the neoadjuvant treatment	\$ 28.000*	\$ 240**

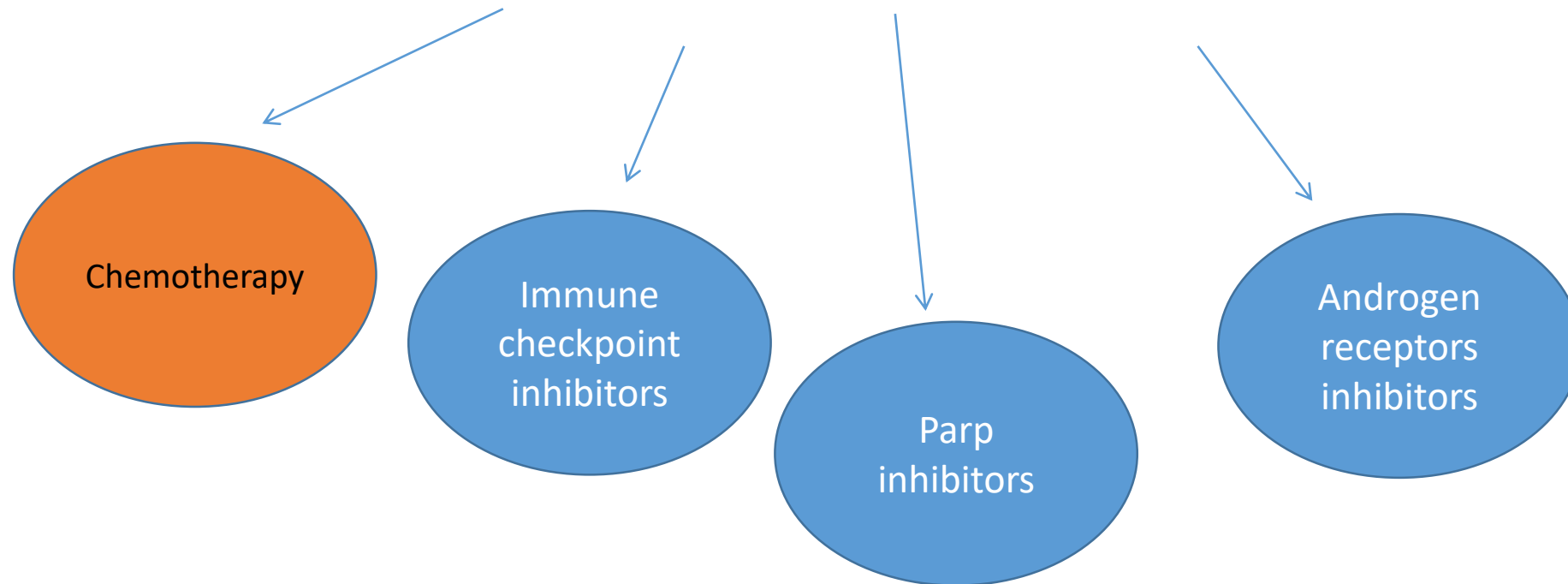
Take home messages

Preoperative treatment to be preferred in II/III stage

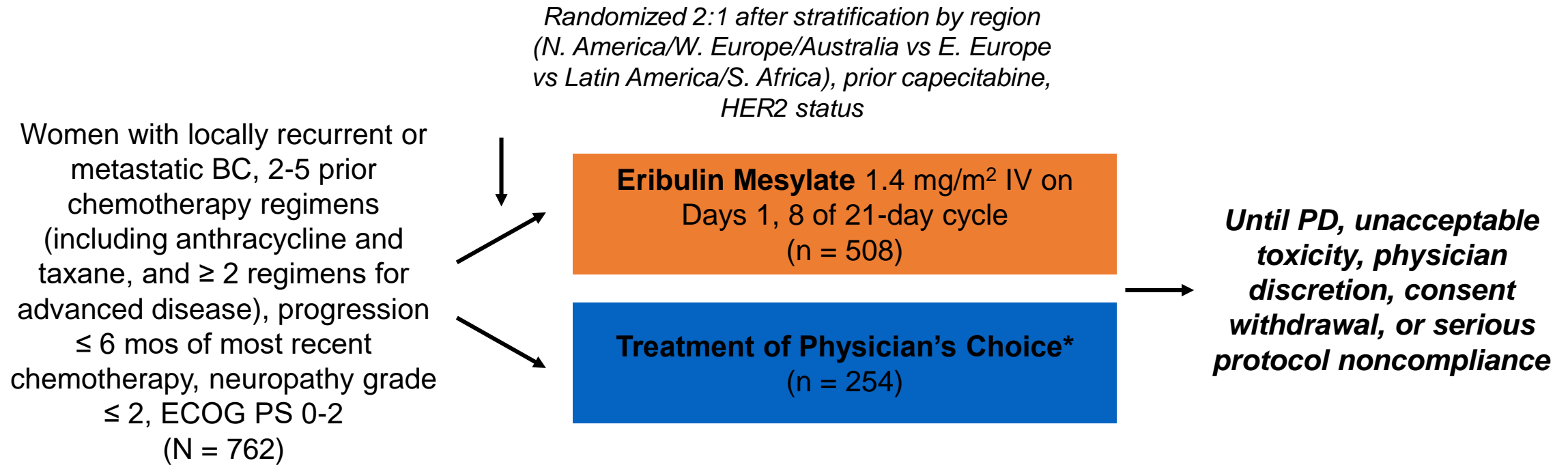
Cisplatin in the neoadjuvant setting only in the BRCA mutated or in all the TNBC?

What is new....??

...Advanced TNBC



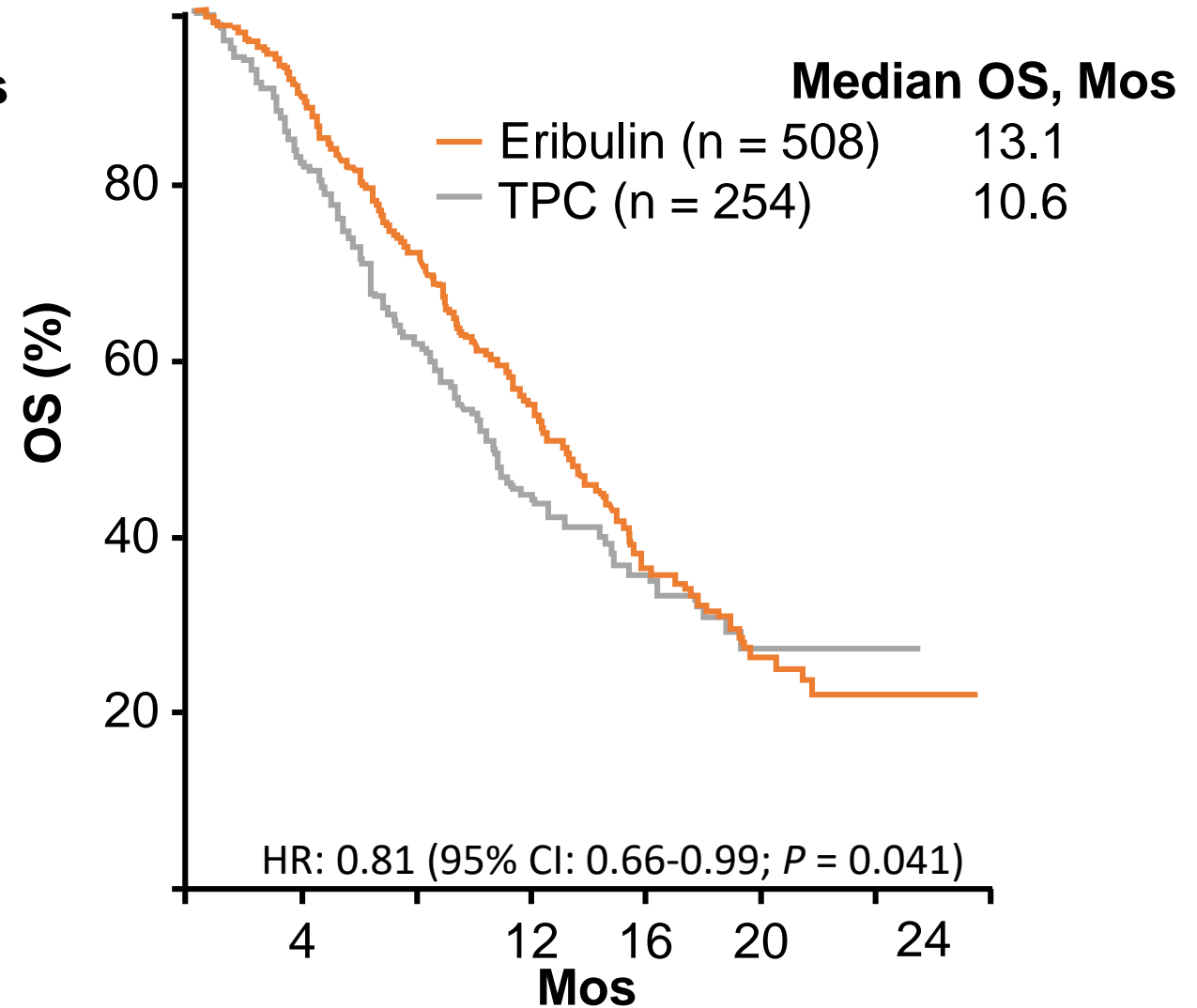
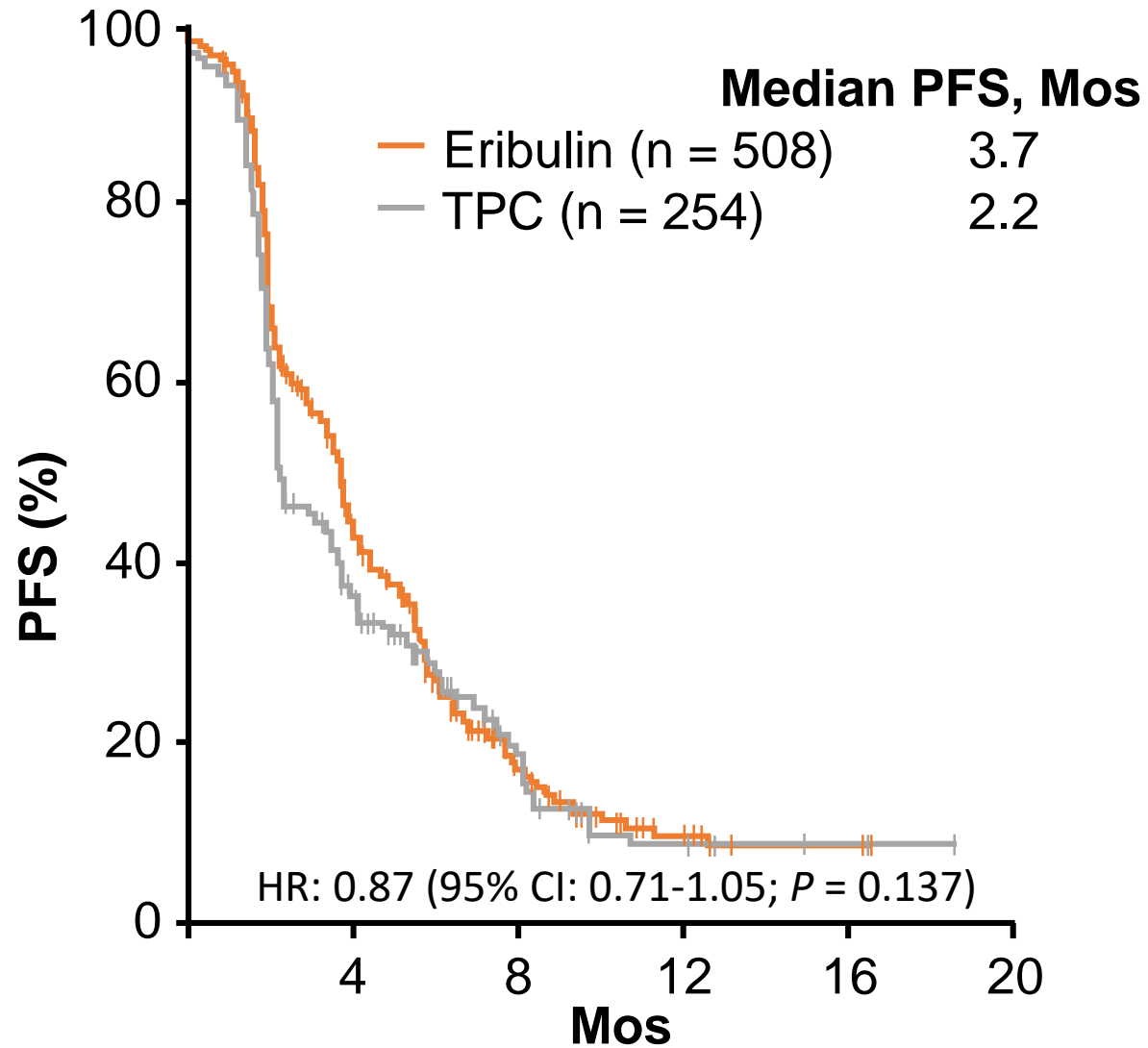
EMBRACE Trial of Eribulin vs TPC for Heavily Pretreated MBC



*TPC included any single-agent chemotherapy or hormonal/biological therapy approved for cancer treatment, administered per local practice; radiotherapy; or symptomatic therapy only.

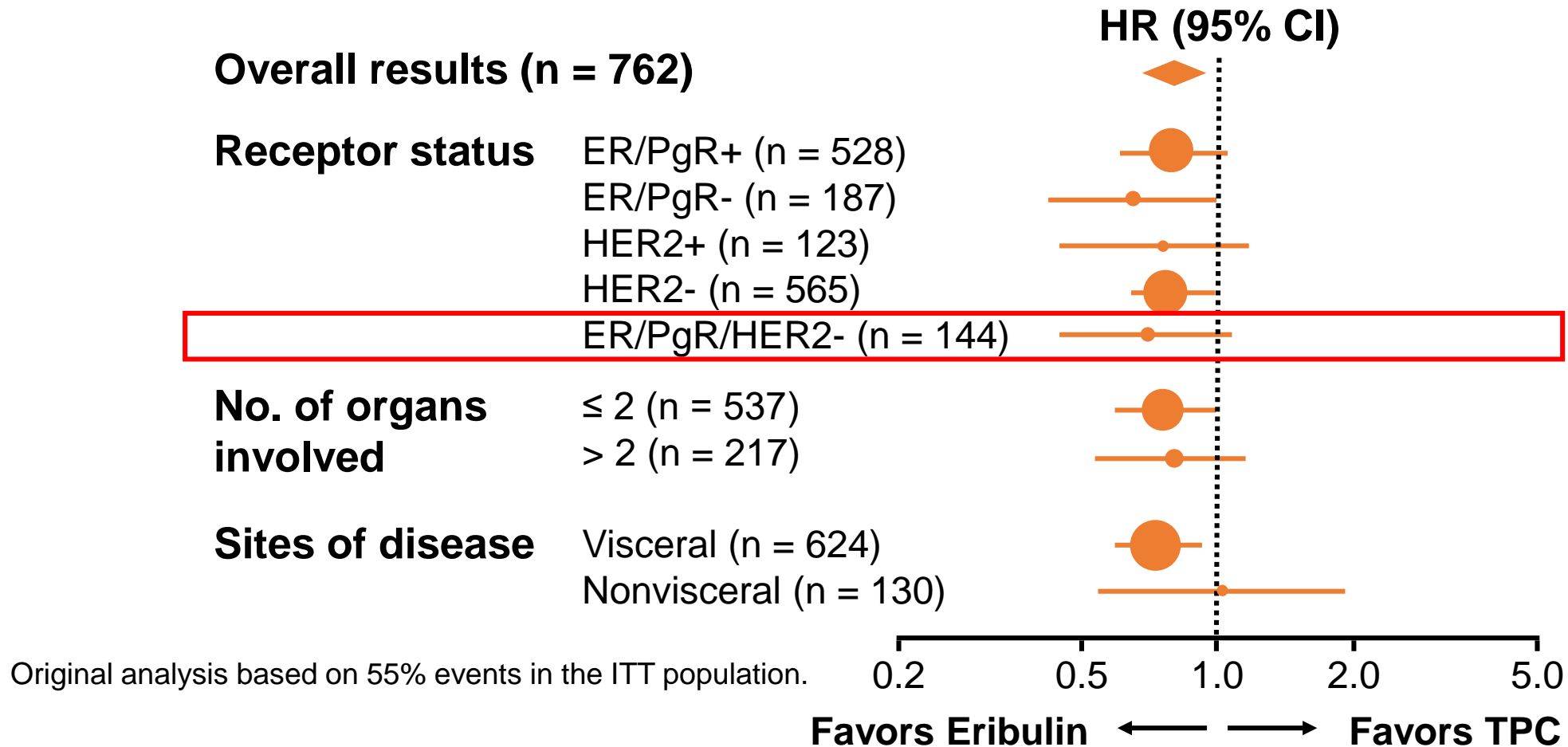
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety

EMBRACE: PFS and OS



Cortes J, et al. Lancet. 2011;377:914-923.

EMBRACE: Subset Analysis of OS by Disease Characteristics (ITT)*



EMBRACE: Grade 3/4 AEs

Grade 3/4 AEs in > 10% of Either Arm, %	Eribulin (n = 503)	TPC (n = 247)
Neutropenia	45	21
Leukopenia	14	6
Anemia	2	4
Asthenia/fatigue	9	10*
Peripheral neuropathy	8	2*
Nausea	1*	2*
Dyspnea	4*	3
Hand-foot syndrome	< 1*	4*

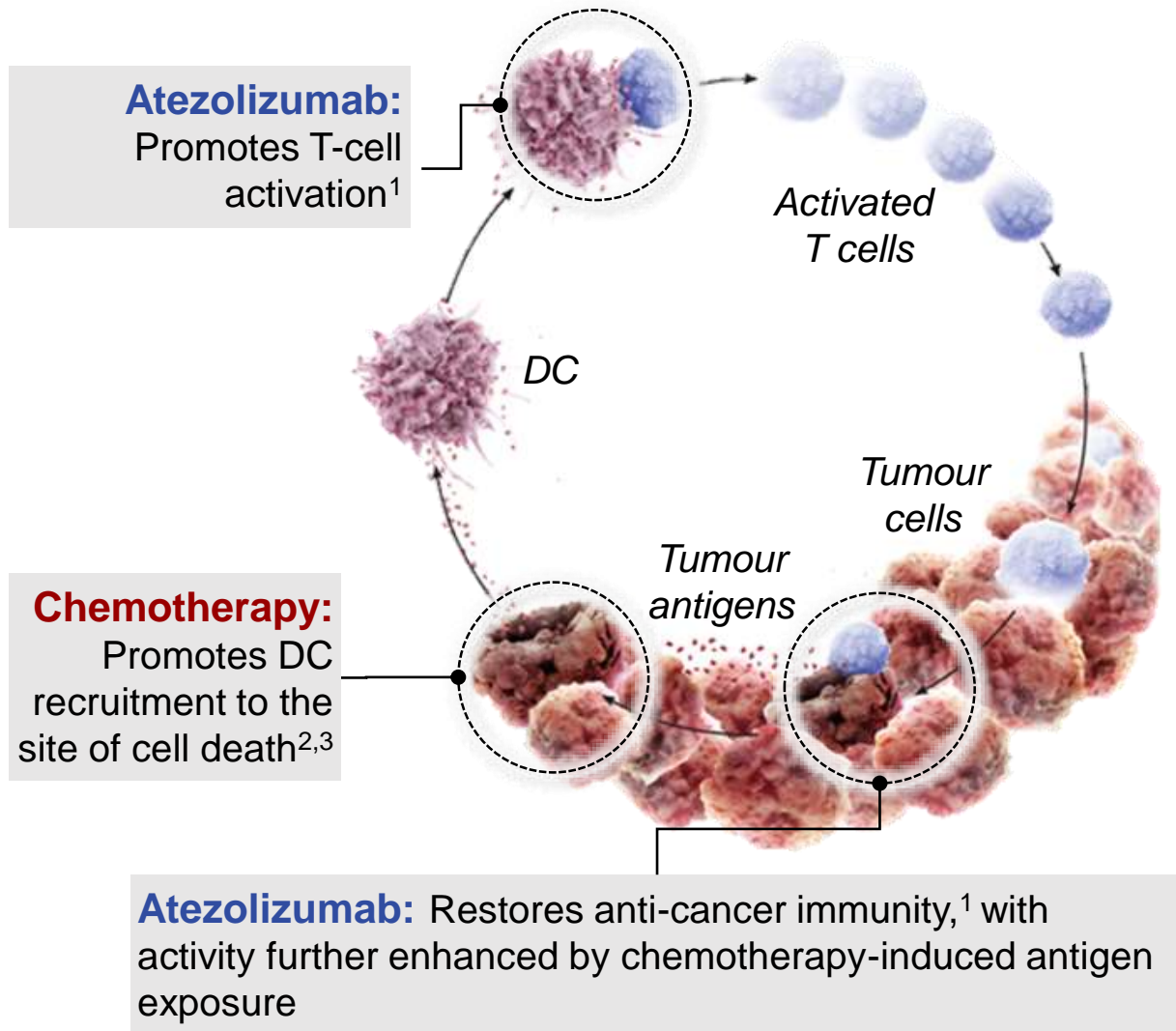
*Grade 3 only.

The incidence of fatal AEs related to treatment was 1% in both arms

Why is TNBC a good target for immunotherapy?

- High mutation rate, which can produce neoantigens that induce an immune response
- Increased number of tumor-infiltrating lymphocytes, which can facilitate an immune response
- Higher PD-L1 expression levels, which can inhibit T-cell antitumor responses, as compared with other breast cancer subtypes

Atezolizumab and chemotherapy



- Atezolizumab (anti-PD-L1) monotherapy is approved in the United States, Europe and elsewhere for certain types of metastatic urothelial carcinoma and lung cancer⁴
- In a Phase I study, atezolizumab monotherapy was active in multiple cancers, including TNBC,^{5,6} with greater activity in patients whose tumours had PD-L1 IC $\geq 1\%$ ⁶
- The addition of chemotherapy can enhance atezolizumab's anti-tumour activity^{7,8}
 - In a Phase Ib study in mTNBC, concurrent administration of *nab*-paclitaxel did not inhibit atezolizumab-mediated immunodynamic effects⁸

Phase III study IMpassion130^a

Previously untreated metastatic
or inoperable locally advanced TNBC^b
N = 902 patients randomized

Double blind; no crossover

R
1:1

Stratification factors:

1. *Prior taxane use*
2. *Liver metastases*
3. ***PD-L1 on IC^c***

Atezo + nab-P arm^d

ITT population: n = 451
PD-L1 IC+ patients: n = 185 (41%)

Plac + nab-P arm^d

ITT population: n = 451
PD-L1 IC+ patients: n = 184 (41%)

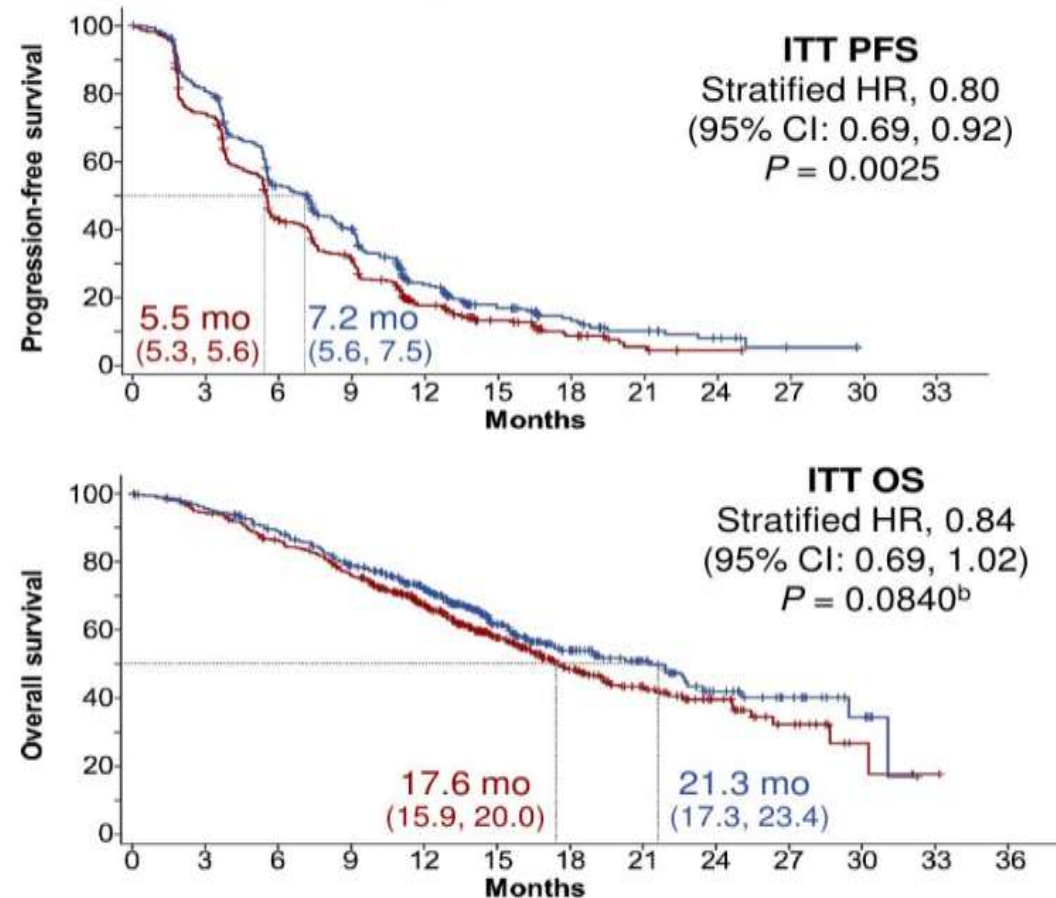
Key study endpoints

- Co-primary: PFS (ITT and PD-L1 IC+) OS (ITT and PD-L1 IC+)
- Secondary: ORR and DOR
- Safety and tolerability

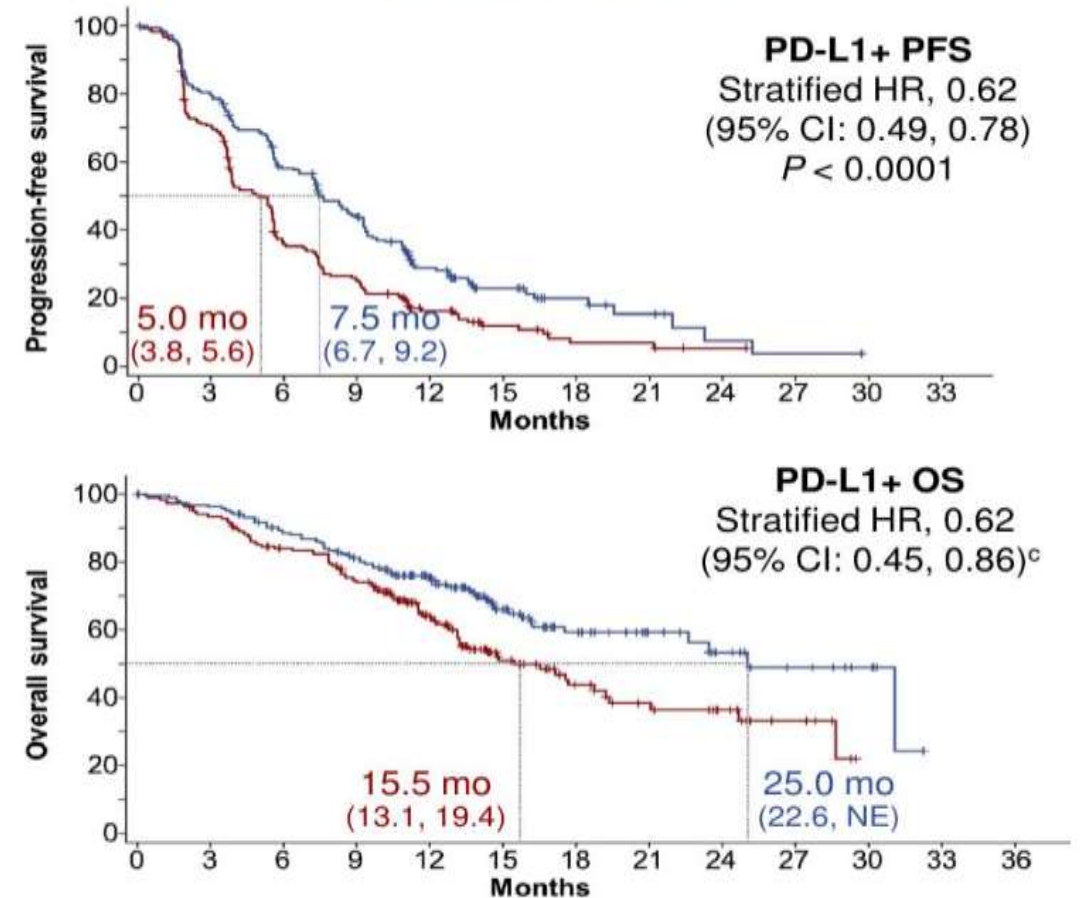
Primary PFS analysis

Interim OS analysis

ITT population



PD-L1+ population^a



NE, not estimable.

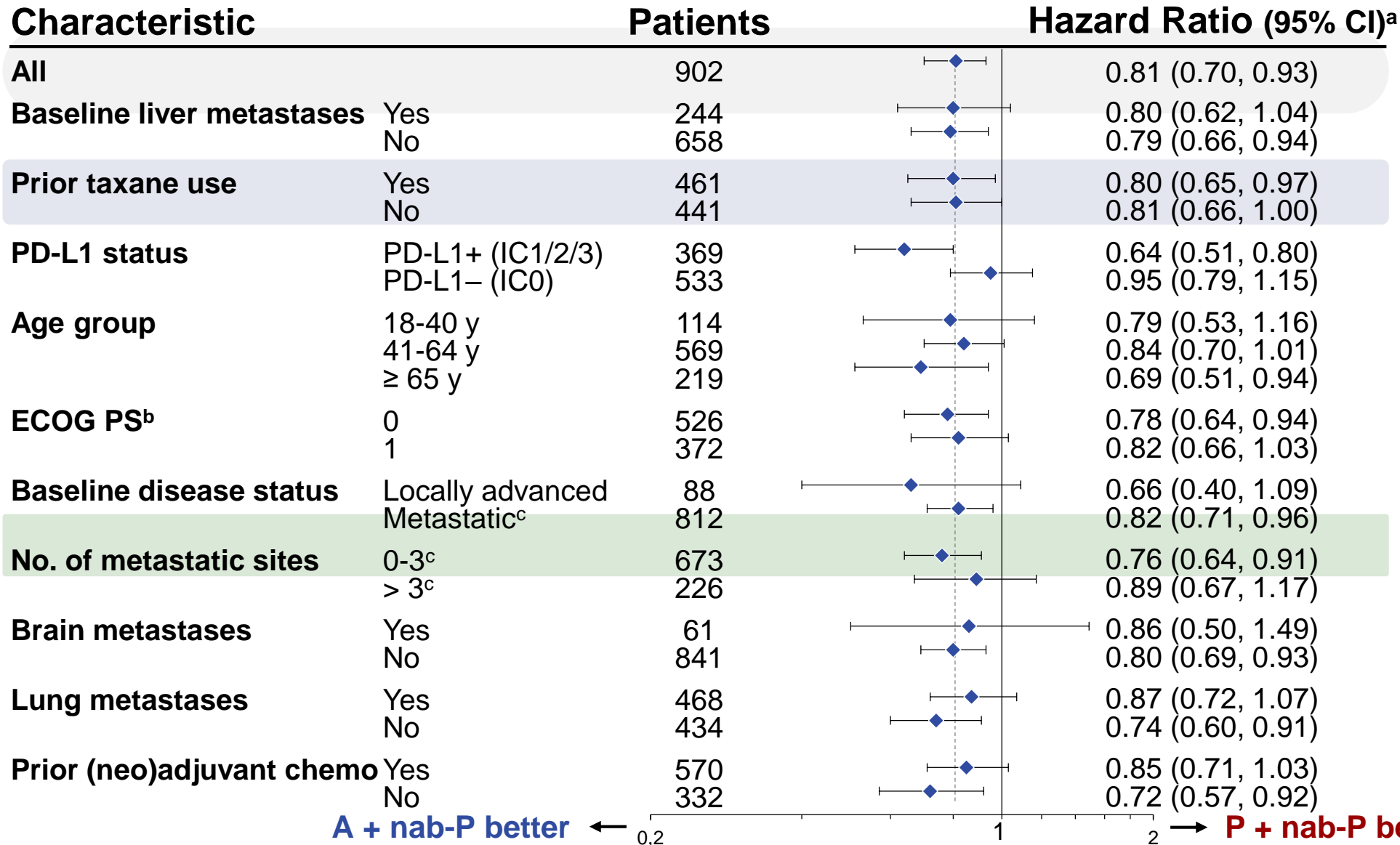
Median follow-up (ITT): 12.9 months.

^a PD-L1+: PD-L1 in $\geq 1\%$ of IC. ^b Not significant. ^c Not formally tested per hierarchical study design.

1. Schmid *N Engl J Med* 2018. 2. Schmid *ESMO* 2018 [LBA1_PR].

Emens LA, et al. IMpassion130 biomarkers.
SABCS 2018 (program #GS1-04)

PFS subgroup analysis: ITT population



Stratification factors

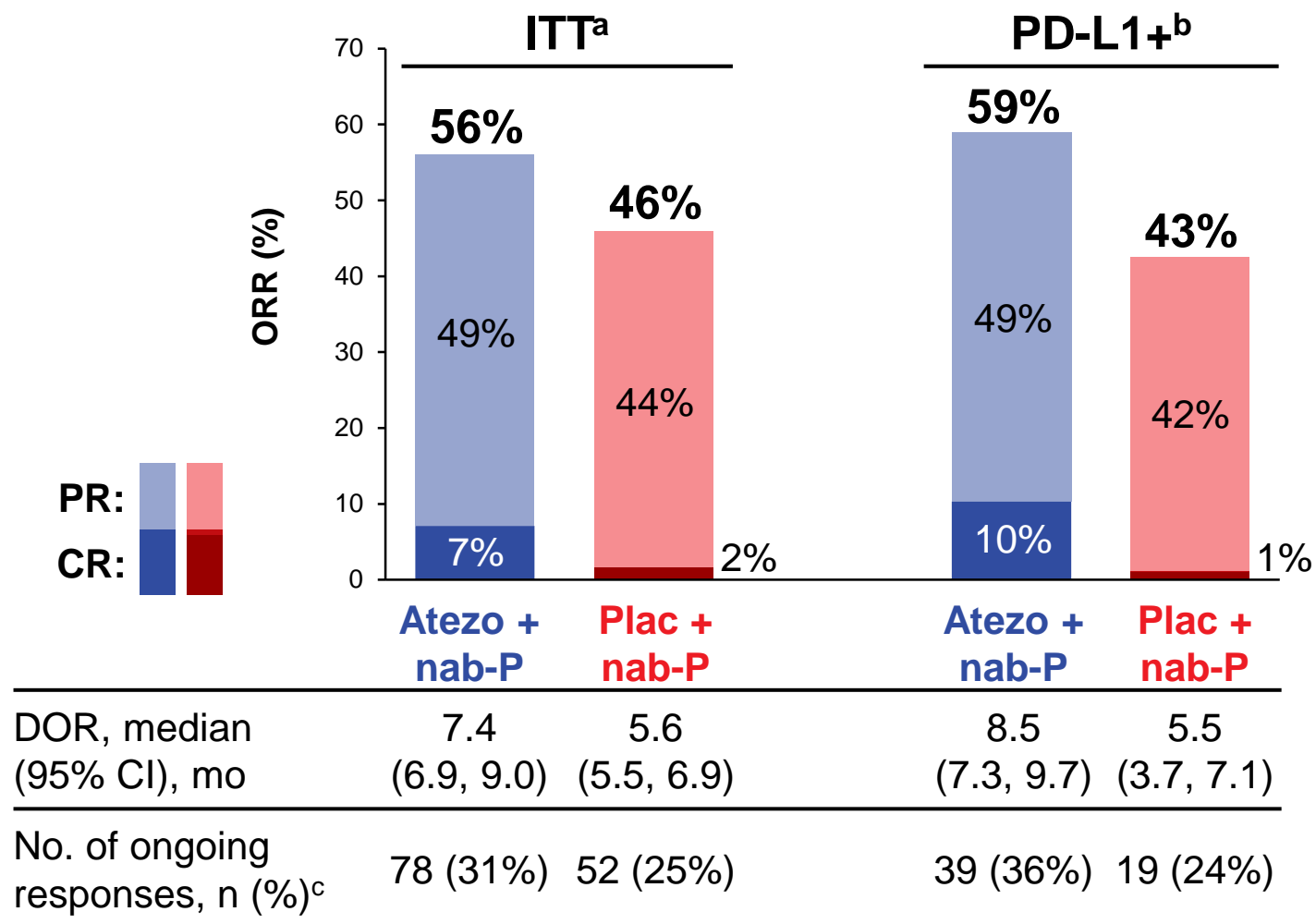
Data cutoff: 17 April 2018.

^a Unstratified HRs are shown; 95% CIs are plotted as error bars. Dashed vertical line represents value in ITT population.

^b Patients with ECOG PS 2 not plotted.

^c Excludes patients with unknown/other values.

Secondary efficacy endpoints



- Numerically higher and more durable responses were seen in the Atezo + nab-P arm
 - Differences were not significant based on α level = 0.1% (ITT: $P = 0.0021$; PD-L1+: $P = 0.0016$)
- The CR rate was higher in the Atezo + nab-P arm vs the Plac + nab-P arm
 - ITT population: 7% vs 2%
 - PD-L1+ patients: 10% vs 1%

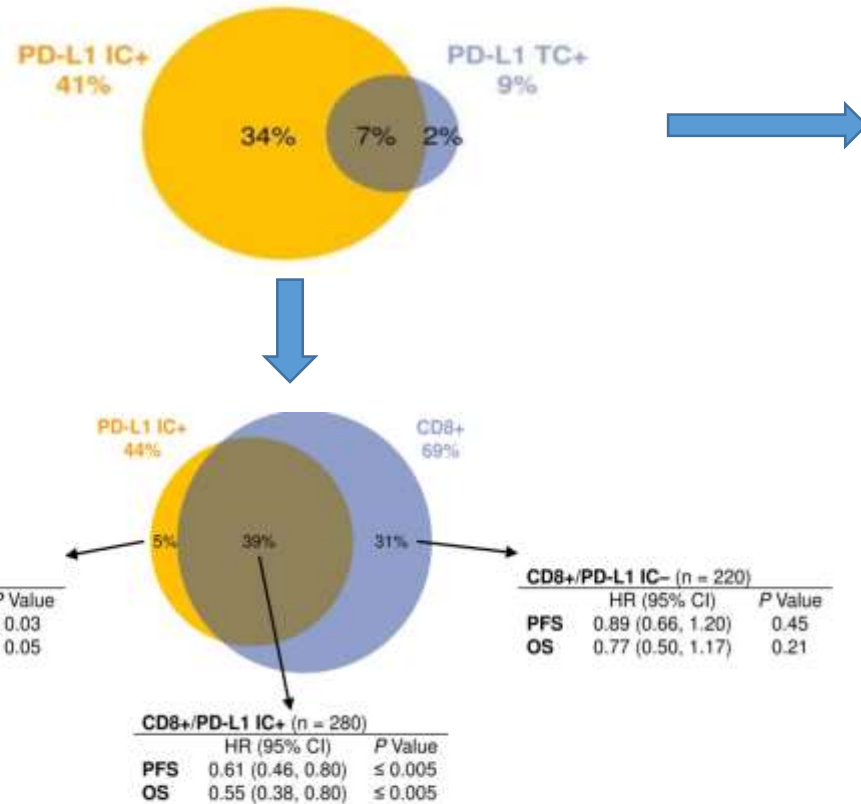
Most common AEs regardless of attribution

AEs in $\geq 20\%$ (all grade) or $\geq 3\%$ (grade 3-4) of patients in either arm, n (%)	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Alopecia	255 (56%)	3 (1%)	252 (58%)	1 (< 1%)
Fatigue	211 (47%)	18 (4%)	196 (45%)	15 (3%)
Nausea^a	208 (46%)	5 (1%)	167 (38%)	8 (2%)
Diarrhoea	147 (33%)	6 (1%)	150 (34%)	9 (2%)
Anaemia	125 (28%)	13 (3%)	115 (26%)	13 (3%)
Constipation	113 (25%)	3 (1%)	108 (25%)	1 (< 1%)
Cough^a	112 (25%)	0	83 (19%)	0
Headache	105 (23%)	2 (< 1%)	96 (22%)	4 (1%)
Neuropathy peripheral	98 (22%)	25 (6%)	97 (22%)	12 (3%)
Neutropaenia^a	94 (21%)	37 (8%)	67 (15%)	36 (8%)
Decreased appetite	91 (20%)	3 (1%)	79 (18%)	3 (1%)
Neutrophil count decreased	57 (13%)	21 (5%)	48 (11%)	15 (3%)
Hypertension	22 (5%)	4 (1%)	24 (5%)	11 (3%)

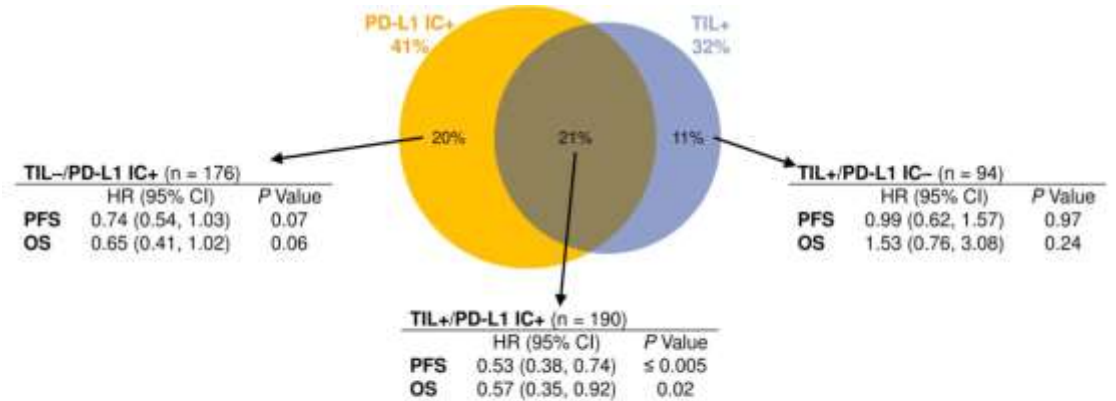
- The most common AEs were generally similar between arms
- Most common Grade 3-4 AEs: neutropaenia, decreased neutrophil count, peripheral neuropathy, fatigue, anaemia
 - Grade 3-4 AEs $\geq 2\%$ higher in the Atezo + nab-P arm included peripheral neuropathy (6% vs 3%)

Biomarkers

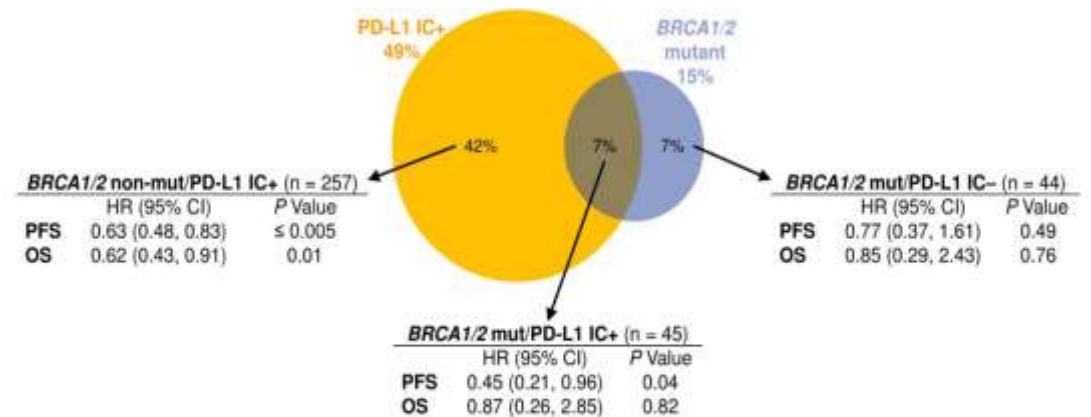
The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population



- PD-L1 IC+ are enriched in CD8+ ($P < 0.0001$) and CD8+ are enriched in PD-L1 IC+ ($P < 0.0001$)^a
- Patients with CD8+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+



- TIL+ were enriched for PD-L1 IC+ ($P < 0.0001$) but PD-L1 IC+ were not enriched for TIL+ ($P = ns$)^a
- Patients with TIL+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+



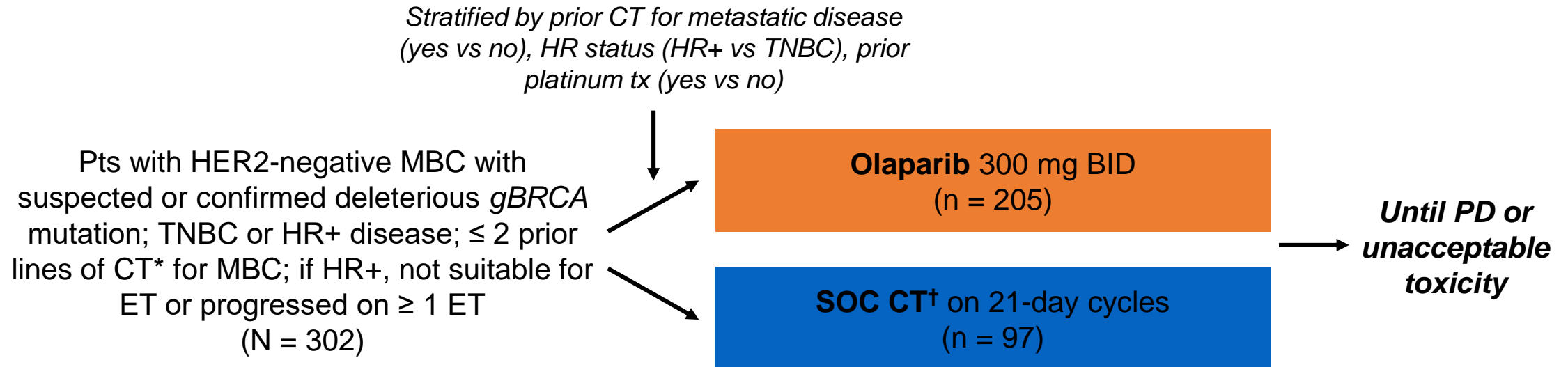
- BRCA1/2 mutants and PD-L1 IC+ are independent from each other ($P = ns$)^a
- Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+^b

IMpassion130 conclusions

- IMpassion130 is the first Phase III study to demonstrate a benefit with first-line immunotherapy in Mtnbc
- Atezolizumab + *nab*-paclitaxel resulted in statistically significant PFS benefit in the ITT and PD-L1+ populations (ITT HR = 0.80 [95% CI: 0.69, 0.92] and PD-L1+ HR = 0.62 [95% CI: 0.49, 0.78]), which was clinically meaningful in the PD-L1+ population
- At this first interim OS analysis, clinically meaningful improvement in OS with atezolizumab + *nab*-paclitaxel (vs placebo + *nab*-paclitaxel) was observed in the PD-L1+ population, with a HR of 0.62 and a median OS improvement from 15.5 months to 25.0 months (formal OS testing in PD-L1+ patients not performed per hierarchical study design)
- No detriment observed for the PD-L1– subgroup
- Atezolizumab + *nab*-paclitaxel was well tolerated, with a safety profile consistent with each agent
- For patients with PD-L1+ tumours, these data establish atezolizumab + *nab*-paclitaxel as a new standard of care

OlympiAD: Olaparib vs SOC for *gBRCA1/2+*, HER2-MBC

Randomized, open-label phase III study

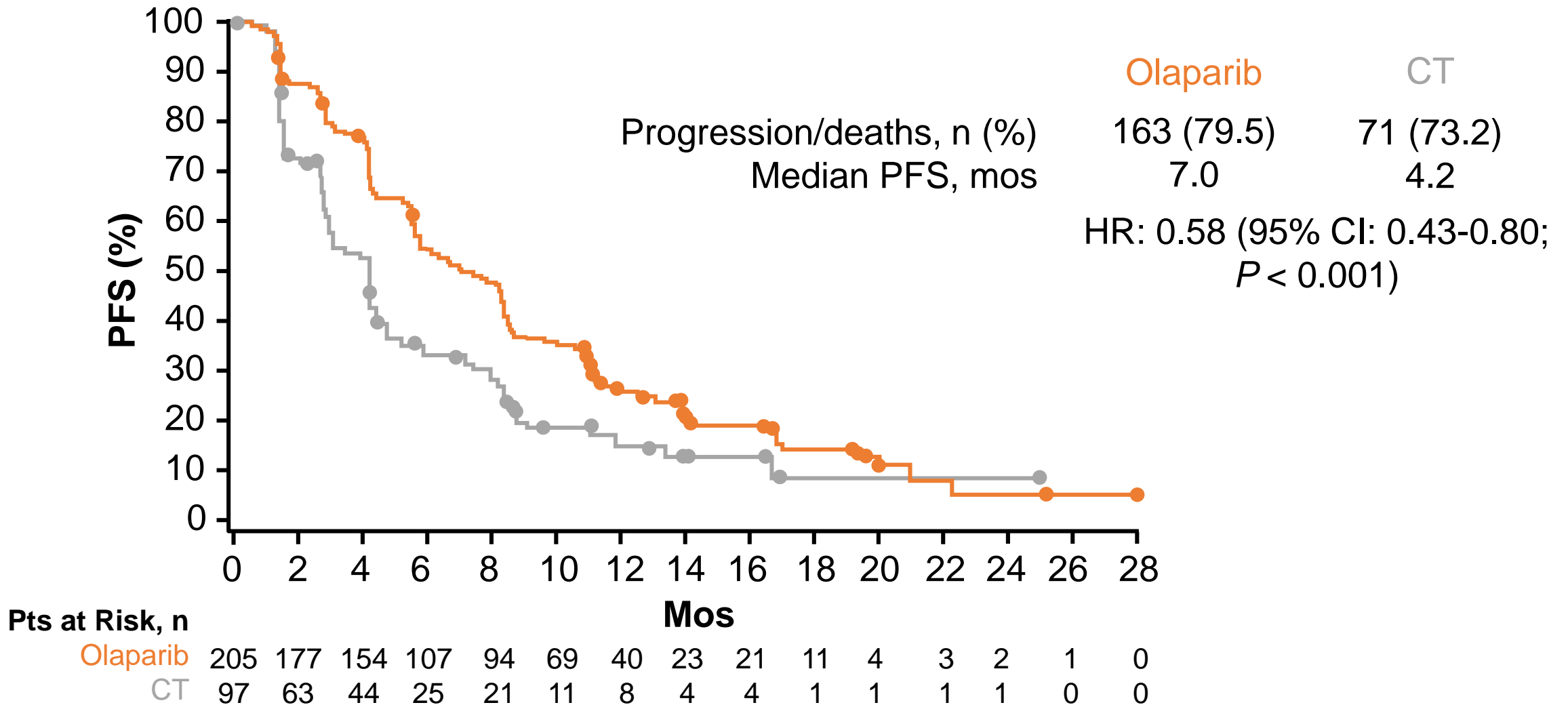


*Either (neo)adjuvant treatment or treatment for metastatic disease with an anthracycline (unless contraindicated) and taxane. If received platinum-based tx, pt either could not have progressed on tx in metastatic setting or must be ≥ 12 mos since (neo)adjuvant tx.

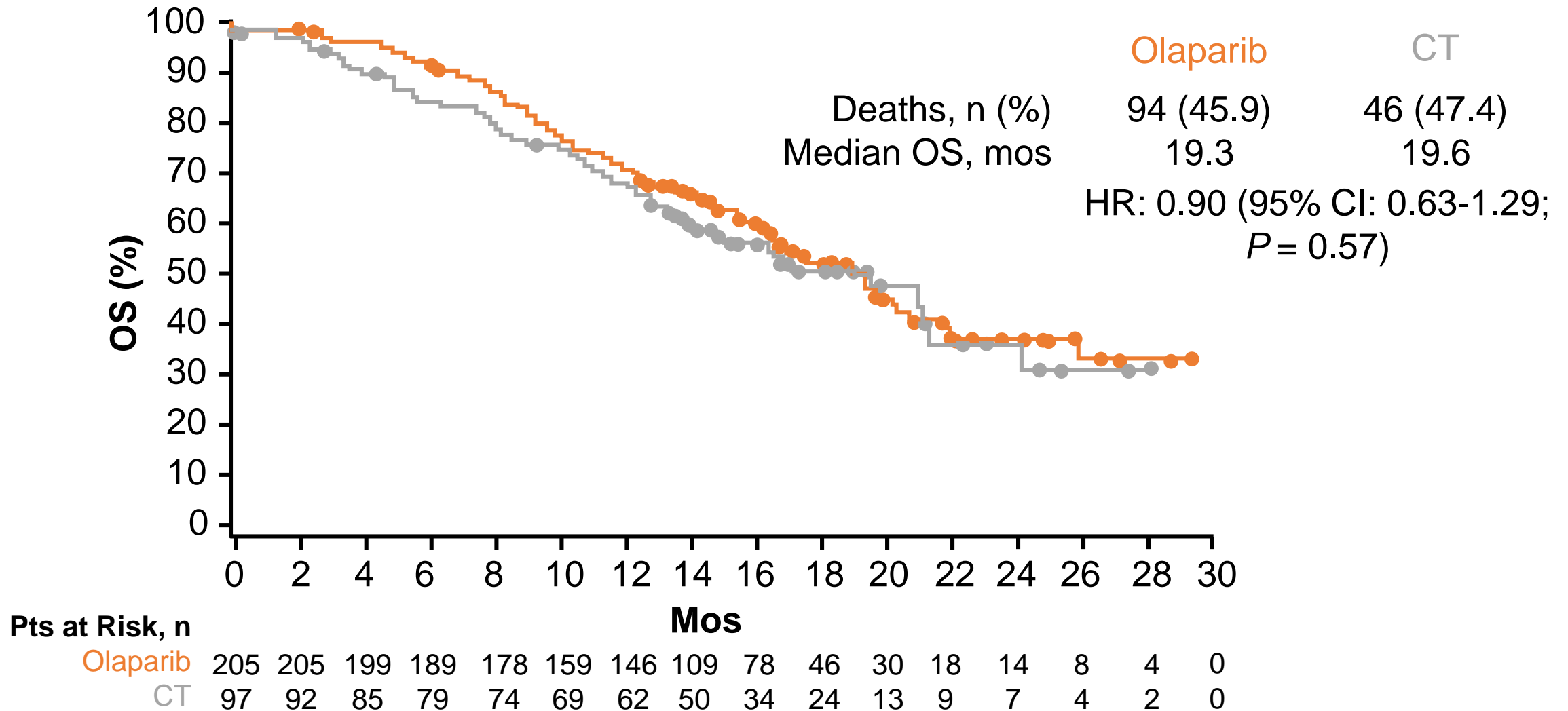
†Physician's choice of: capecitabine 2500 mg/m² PO Days 1-14; eribulin mesylate 1.4 mg/m² IV Days 1, 8; vinorelbine 30 mg IV Days 1, 8.

- Primary endpoint: PFS per mRECIST v1.1 (BICR)
- Secondary endpoints: time to second progression/death, OS, ORR, safety, HRQoL

OlympiAD: PFS by BICR (Primary Endpoint)

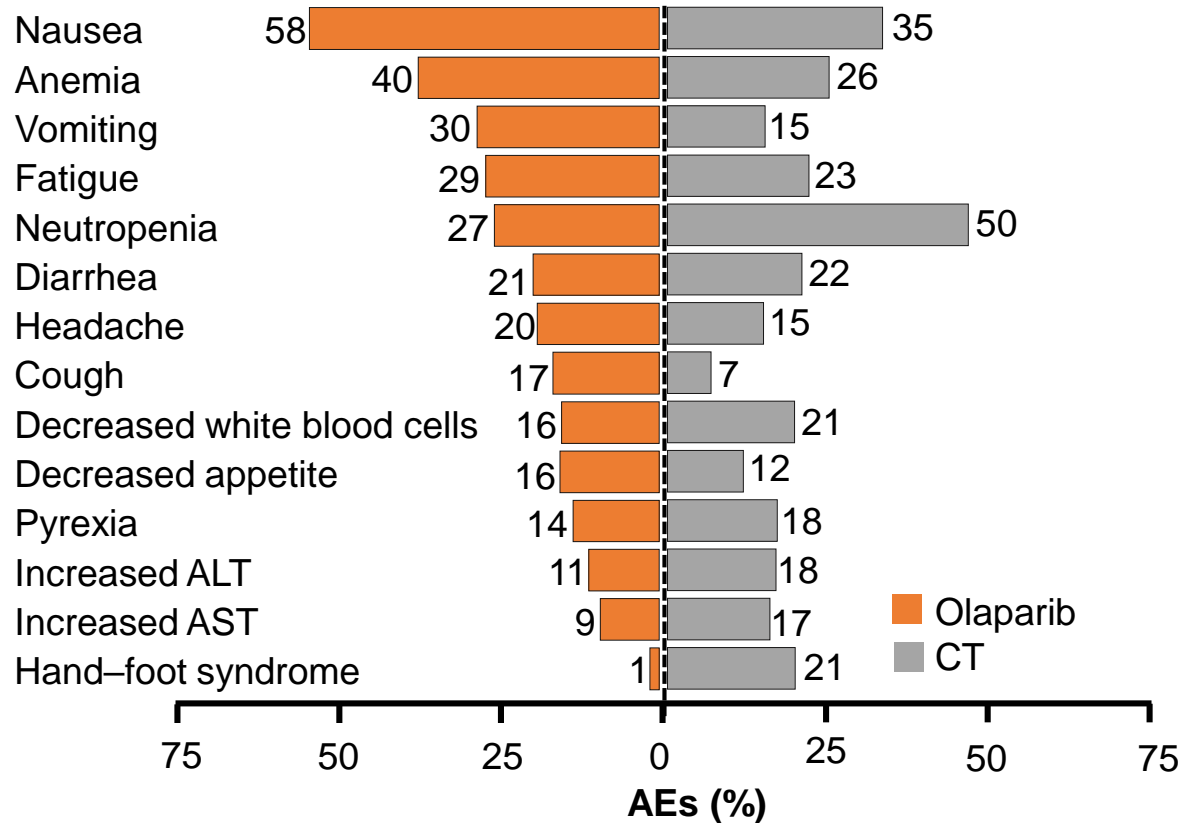


OlympiAD: OS by Investigator Assessment

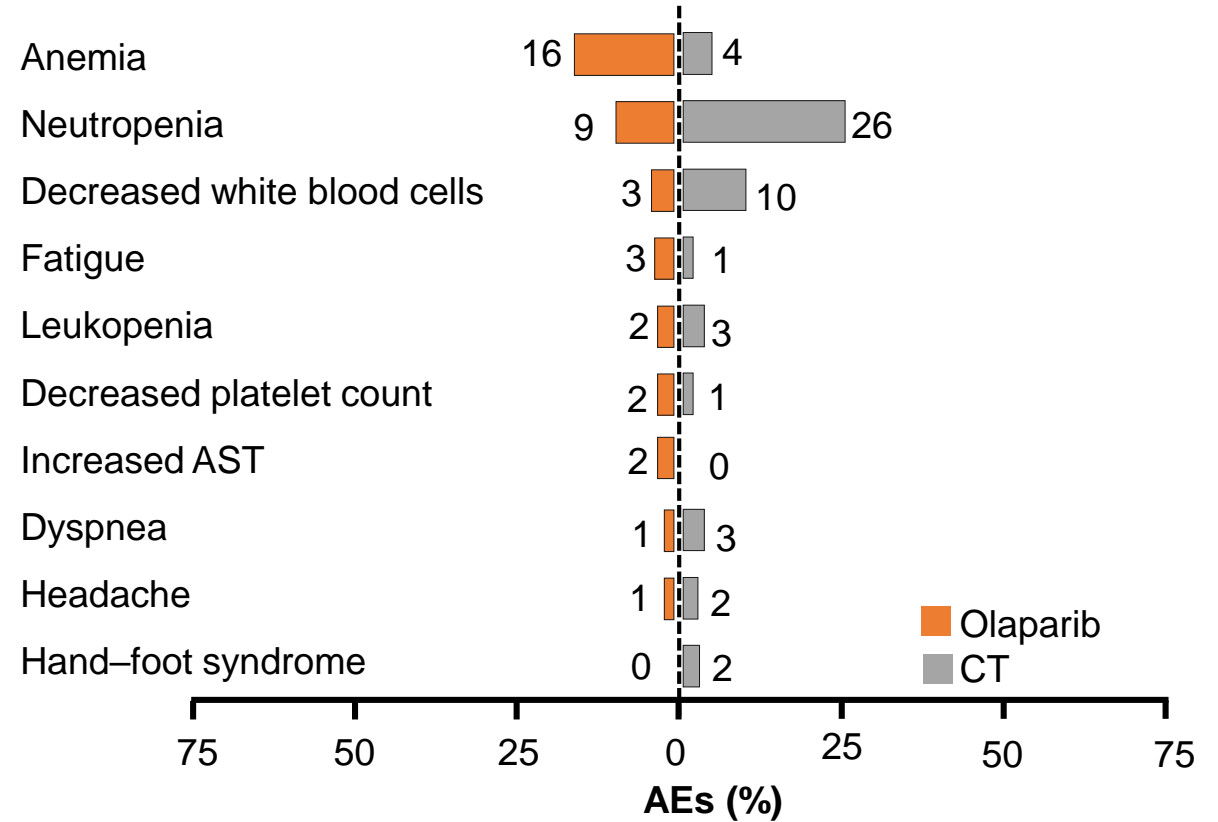


OlympiAD: Adverse Events

Any-Grade AEs in $\geq 15\%$ of Pts



Grade ≥ 3 AEs in $\geq 2\%$ of Pts



Talazoparib in BRCAmut tumors

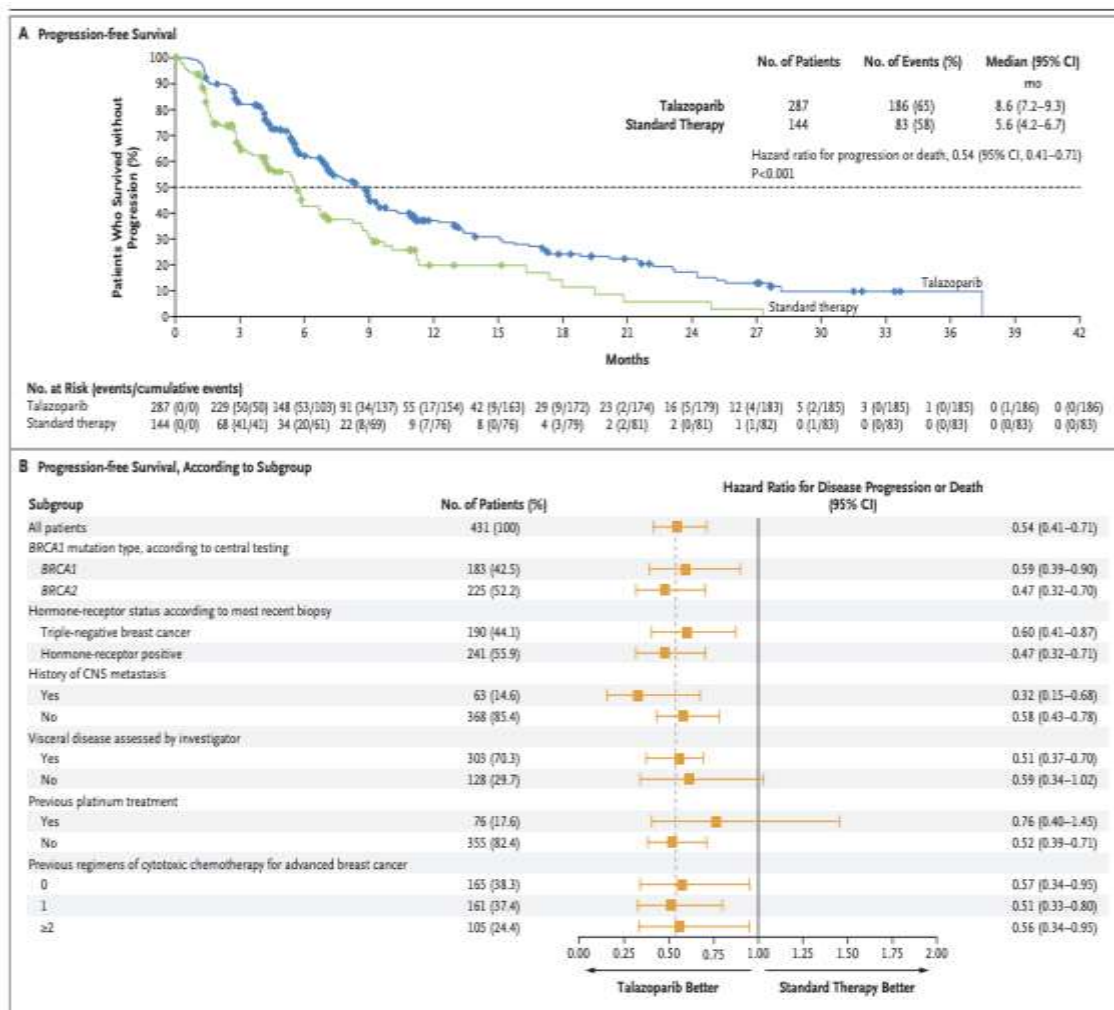


Table 2. Secondary and Exploratory Efficacy End Points.

Variable	Talazoparib Group (N = 219)	Standard-Therapy Group (N = 114)	Odds Ratio (95% CI)	P Value ^{a,b}
<i>number (percent)</i>				
Best overall response among patients with measurable disease — no. (%)†				
Complete response	12 (5.5)	0	—	—
Partial response	125 (57.1)	31 (27.2)	—	—
Stable disease	46 (21.0)	36 (31.6)	—	—
Could not be evaluated	4 (1.8)	19 (16.7)	—	—
Investigator-assessed overall objective response among patients with measurable disease — % of patients (95% CI)†	62.6 (55.8–69.0)	27.2 (19.3–36.3)	5.0 (2.9–8.8)	<0.001
Clinical benefit rate at 24 wk in intention-to-treat population				
Patients with clinical benefit — no./total no.	197/287	52/144	—	—
Percent of patients (95% CI)	68.6 (62.9–74.0)	36.1 (28.3–44.5)	4.3 (2.7–6.8)	<0.001
Investigator-assessed response in subgroup of patients with objective response				
No. with response	137	31	—	—
Median duration of response — mo	5.4	3.1	—	—
Interquartile range	2.8–11.2	2.4–6.7	—	—

Endocrine Therapy

Androgen Receptor in TNBC

- Present in 10-30% (1-10% cut off)
- Better survival
- Expressed in older patients, lower grade tumors (G1-G2), higher PD-L1 expression
- Rare co-expression in patients with BRCA-mutation

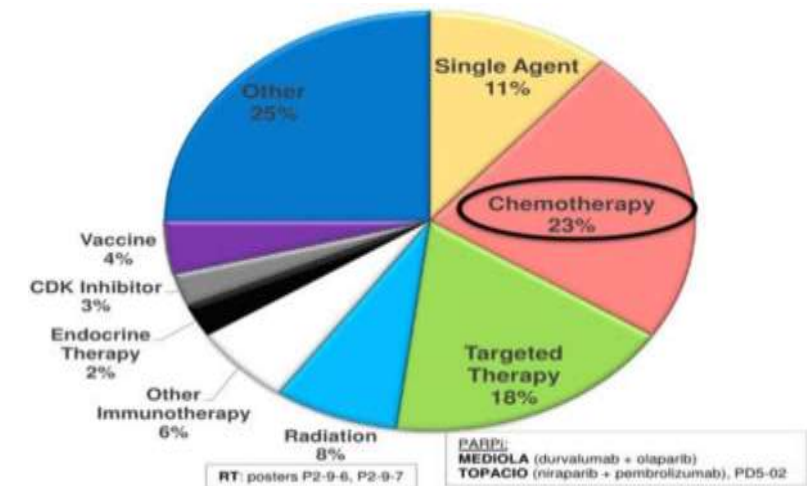
Endocrine Therapy

Ongoing studies in breast cancer

Agent	Phase	Population	Notes	References/clinicaltrials.gov
AR antagonist				
Bicalutamide	II	AR+ mTNBC	Gucalp <i>et al.</i> (2013)	NCT00468715 (closed)
Enzalutamide (MDV3100)	II	AR+ mTNBC		NCT01889238 (active, not recruiting)
Biosynthesis inhibitor				
Abiraterone acetate	I/II	ER+ or AR+ mBCa, post-menopausal	Prostate (Dreicer <i>et al.</i> (2014))	NCT00755885 (active, not recruiting)
Abiraterone acetate	II	AR+ TNBC, molecular apocrine		NCT01842321 (recruiting)
Orteronel (TAK-700)	Ib	HR+ mBCa		NCT01808040 (suspended)
Orteronel (TAK-700)	II	HR+ mBCa		NCT01990209 (recruiting)
Targeting the AR carrier molecule				
Ganetespib (STA-9090)	II	mBCa	Small-molecule HSP90 inhibitor	NCT01273896 (completed results pending)
Ganetespib (STA-9090)	II	mBCa (TNBC, ER+, HER2+)	Small-molecule HSP90 inhibitor	NCT01677455 (active, not recruiting)
Selective AR modulators (SARMs)				
Enobosarm (GTx-024)	II	mBCa		NCT01616758 (active, not recruiting)
Combination trials				
Trastuzumab + enzalutamide	II	mBCa, AR+, HER2+	O'Shaughnessy <i>et al.</i> (2014)	NCT02091960 (recruiting)
Fulvestrant + enzalutamide	I	ER+ AR+ mBCa		NCT01597193 (active, not recruiting)
Exemestane + abiraterone	II	mBCa, ER+		NCT01381874 (active, not recruiting)

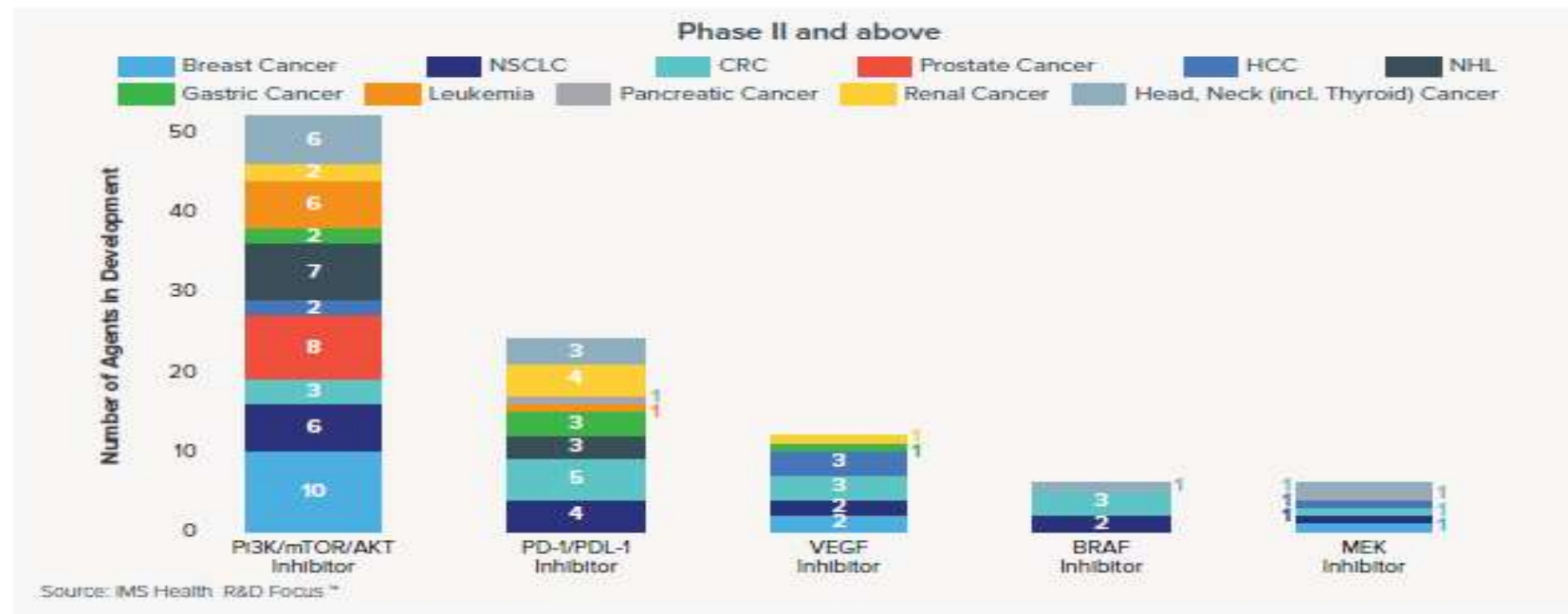
Take home messages

- After many years... new targeted therapies for treatment TNBC
- The real clinical significance of the results of PARP inhibitors on prognosis will elaborate strategies for testing BRCA mutations (selected groups, carpet screening, alternative tests?)
- The combination of chemotherapies and immunotherapy is effective in tumors PD-L1 +
- It is necessary to define best setting
- Define effective combinations

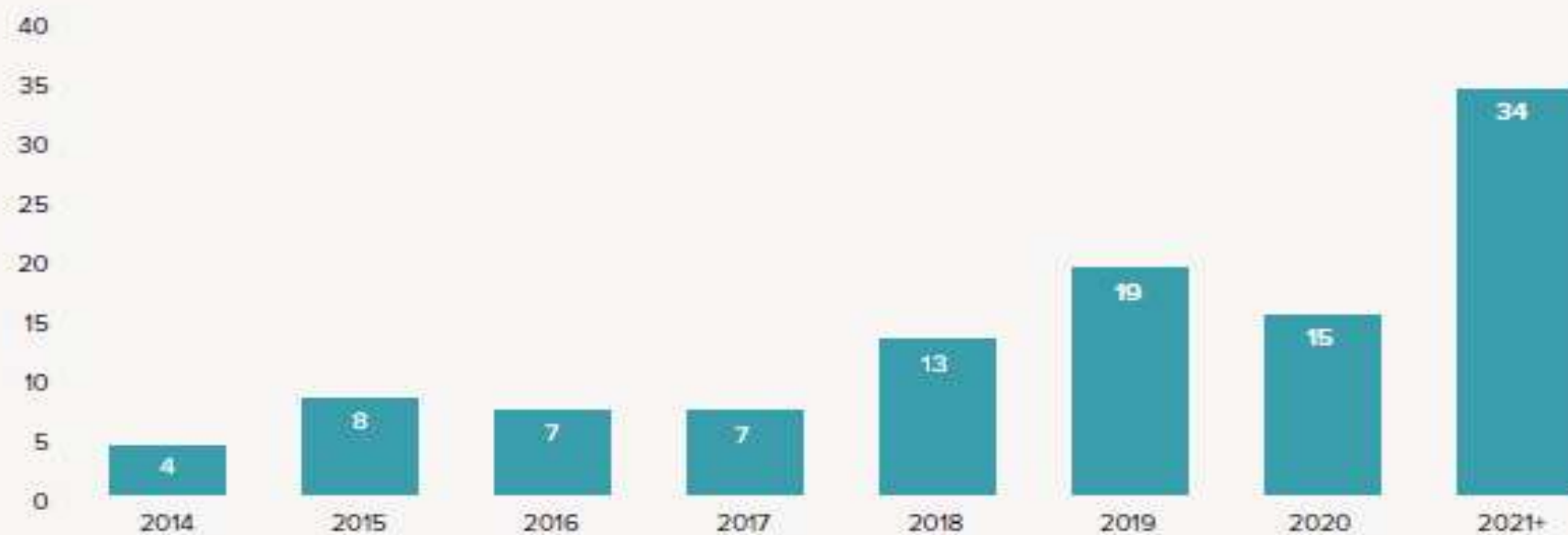


Innovation and sustainability

Pipeline by Number of Targeted Agents and Selected Pathways



Expected Combination Regimen Launches in Oncology



Sources: CenterWatch, FDA, clinicaltrials.gov, IMS R&D LifeCycle, IMSCG Analysis

Sustainability interventions

Unified strategy for the control of cancer from prevention, diagnosis, treatment and rehabilitation

Implementation of regional oncological networks

Appropriateness of performance (diagnostic and therapeutic)

National recommendations for patient selection care

Strategies based on biological and clinical criteria

Implementation and public/industrial cooperation in the search

Thanks...