THE UNIVERSITY OF CHICAGO MEDICINE

Triple-Negative Breast Cancer: Recent Updates and Ongoing Research

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Living Beyond Breast Cancer Webinar
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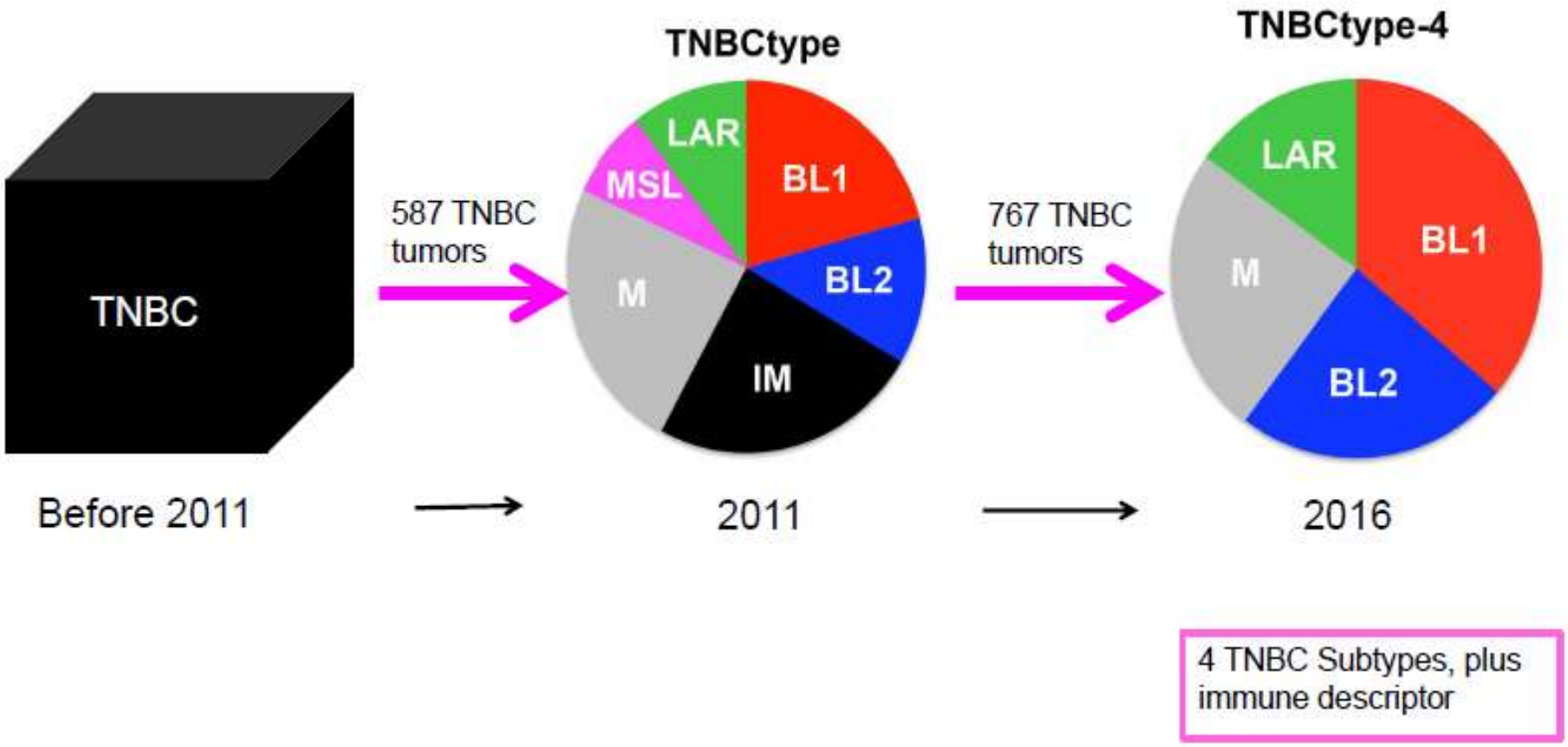
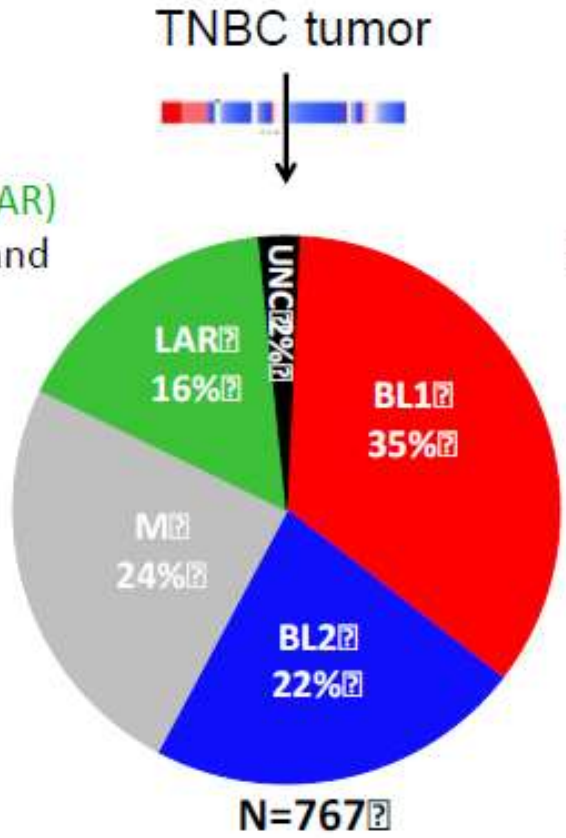
What we are learning about TNBC

- Research focused on TNBC is relatively recent
- TNBC is defined by characteristics it does not have
  - ER/PR negative
  - HER2 negative
- TNBCs are more common in young women and in those with a BRCA1 germline mutation
- There are different types of TNBC

TNBC Subtypes



TNBC Subtypes



Luminal/Androgen receptor (LAR)
Androgen-receptor signaling and PIK3CA mutations

Basal-like 1 (BL1)
Elevated expression of cell cycle and DNA damage response genes

Mesenchymal (M)
Trans-differentiation features and growth factor signaling (FGFR, PDGFR, NOTCH, TGFß)

Basal-like 2 (BL2)
Enriched in select growth factors (MET & EGFR) and myoepithelial cell features

Lehmann, Chen, Shyr, Pietenpol; PLoS One, June, 2016

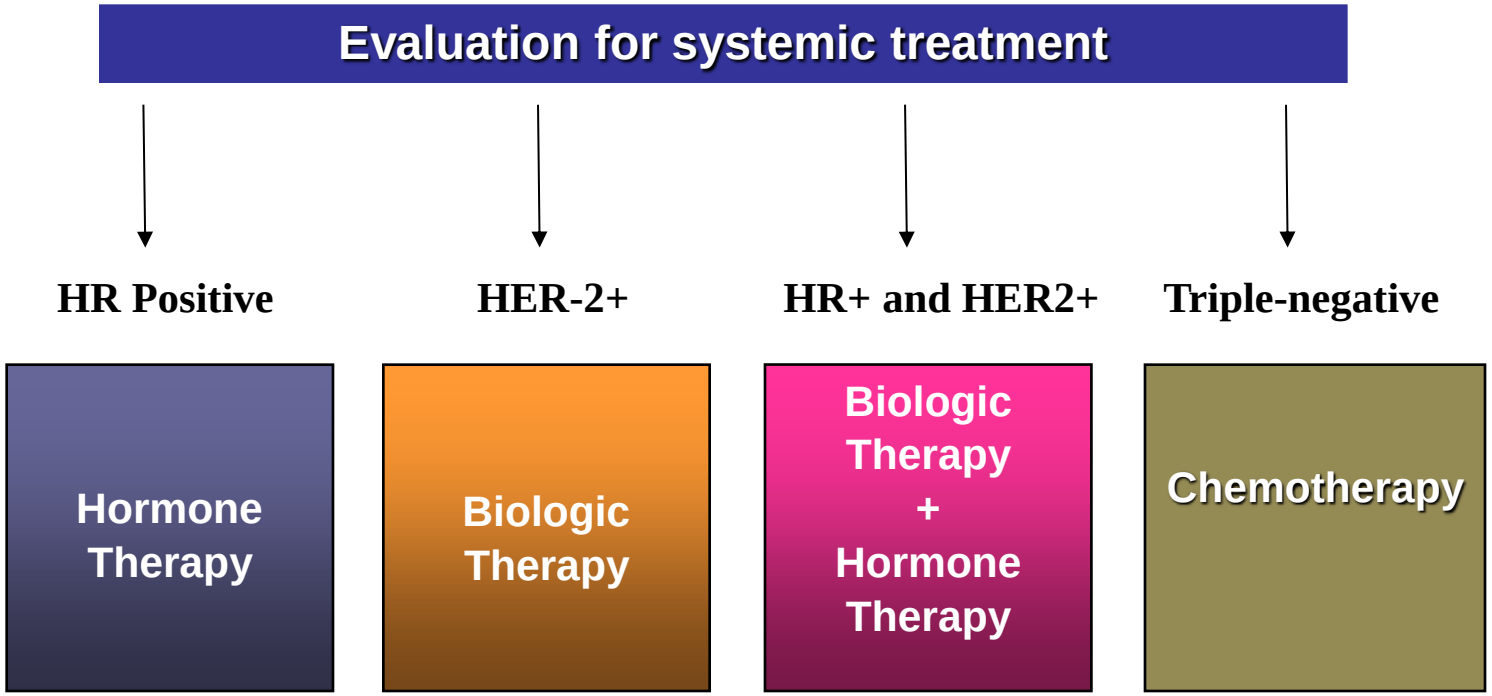
Other Methods of Classification

- Germline testing
  - To look for mutations in BRCA1/2
- Next generation sequencing (NGS)
  - To look for mutations in tumor DNA
- Expression of proteins
  - To look for expression of nuclear hormone receptors or cell surface receptors

What does this mean for those with TNBC?

- Being able to subdivide triple-negative breast cancers into subcategories will help us identify new targets for therapy
- Clinical research is ongoing to target pathways that are implicated in TNBC and newer trials are being developed based on this work

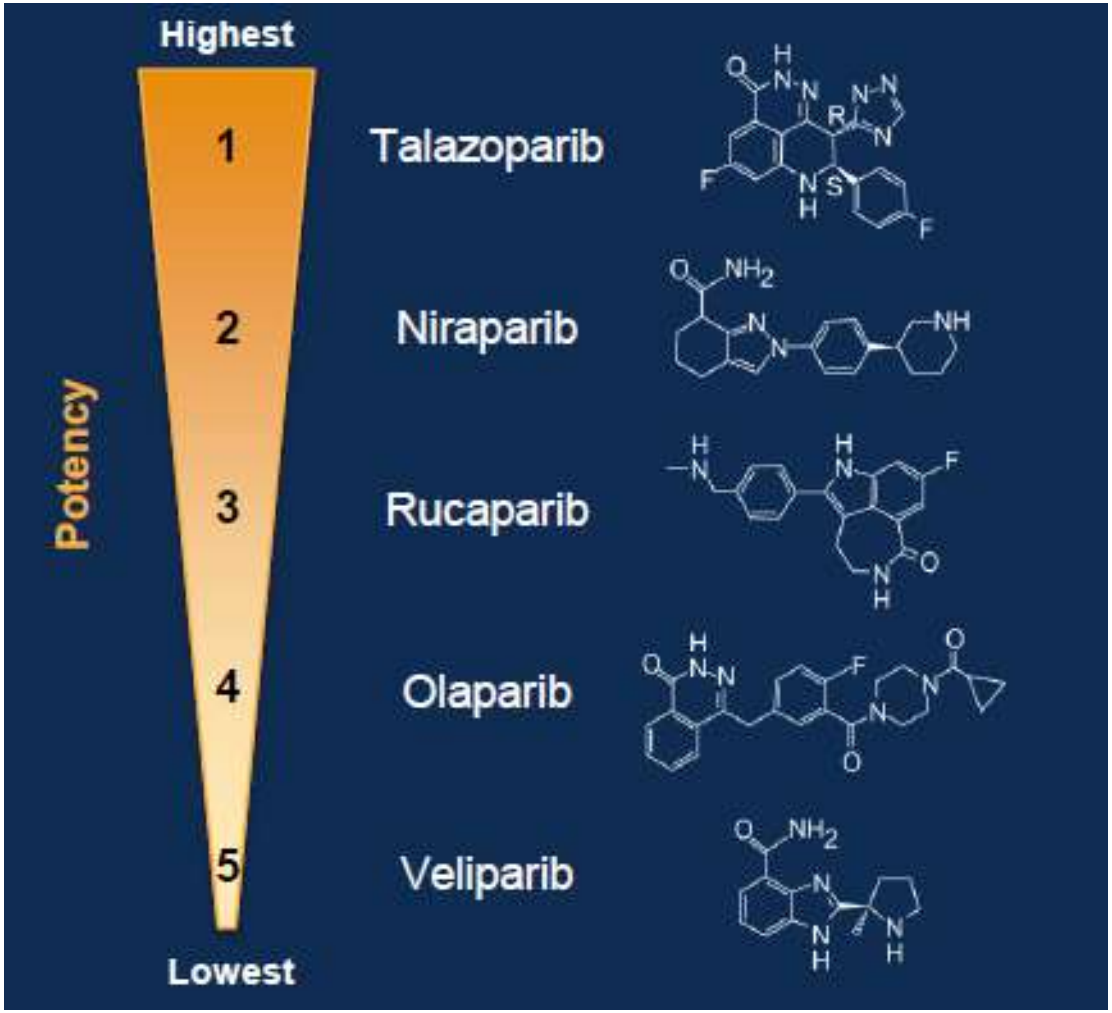
Systemic Treatment for Metastatic Breast Cancer



Targeted Therapies Showing Promise for Advanced TNBC

- Drugs that target DNA repair
  - PARP inhibitors (approved in BRCA1/2 mutation carriers)
- Drugs that target the immune system
  - Immune checkpoint inhibitors (PD-1/PD-L1 inhibitors)
- Drugs that target other receptors
  - Androgen receptor
  - Antibody drug conjugates (gpNMB, Trop2, LIV1A)
- Drugs that target pathways that lead to chemo resistance
  - AKT/PI3K/mTOR inhibitors

PARP Inhibitors



OlympiAD study design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

Olaparib
300 mg tablets bd

2:1 randomization

Chemotherapy treatment of physician's choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

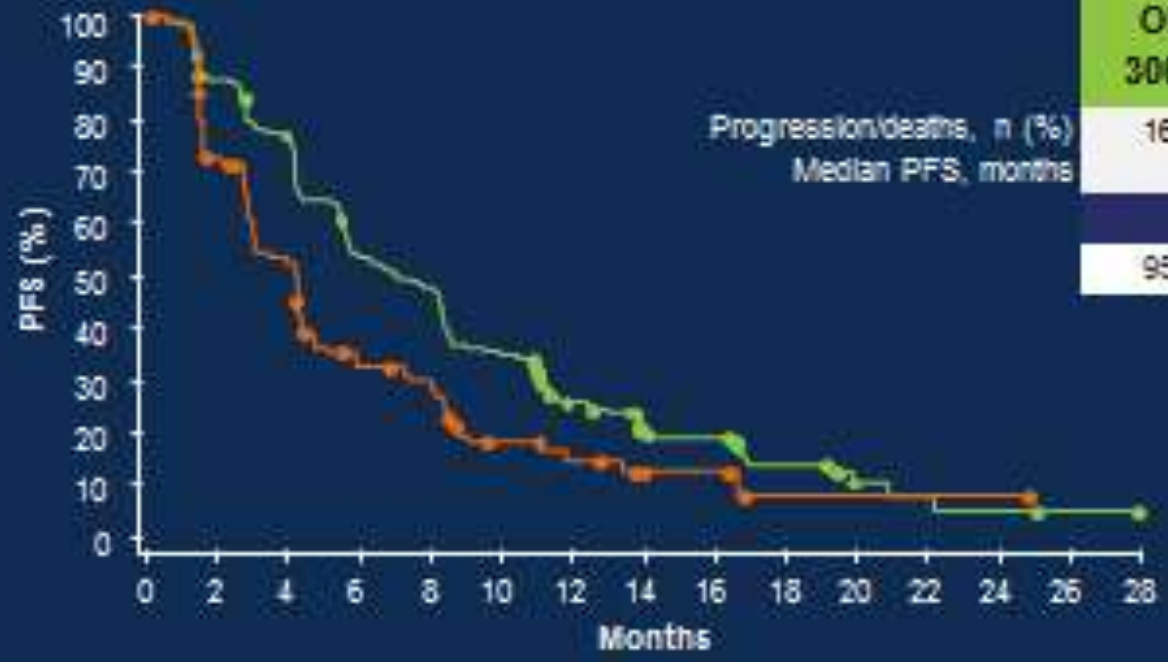
Treat until progression

Primary endpoint:
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints:
- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability
- Global HRQoL (EORTC-QLQ-C30)

BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

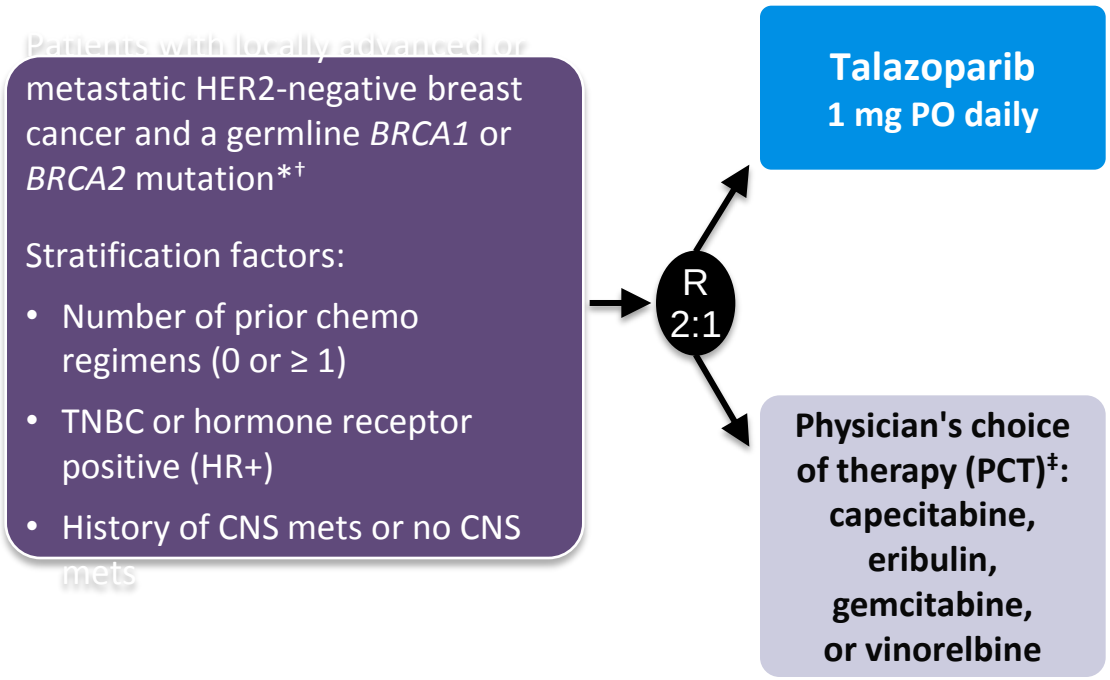
Primary endpoint: progression-free survival by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; P=0.0009		

At risk, n															
Olaparib 300 mg bd	205	177	154	107	94	69	40	23	21	11	4	3	2	1	0
Chemotherapy TPC	97	83	44	25	21	11	8	4	4	1	1	1	1	0	0

EMBRACA Study Design



Phase 3, international, open-label study randomized
431 patients in 16 countries and 145 sites

Primary endpoint

- Progression-free survival by RECIST by blinded central review

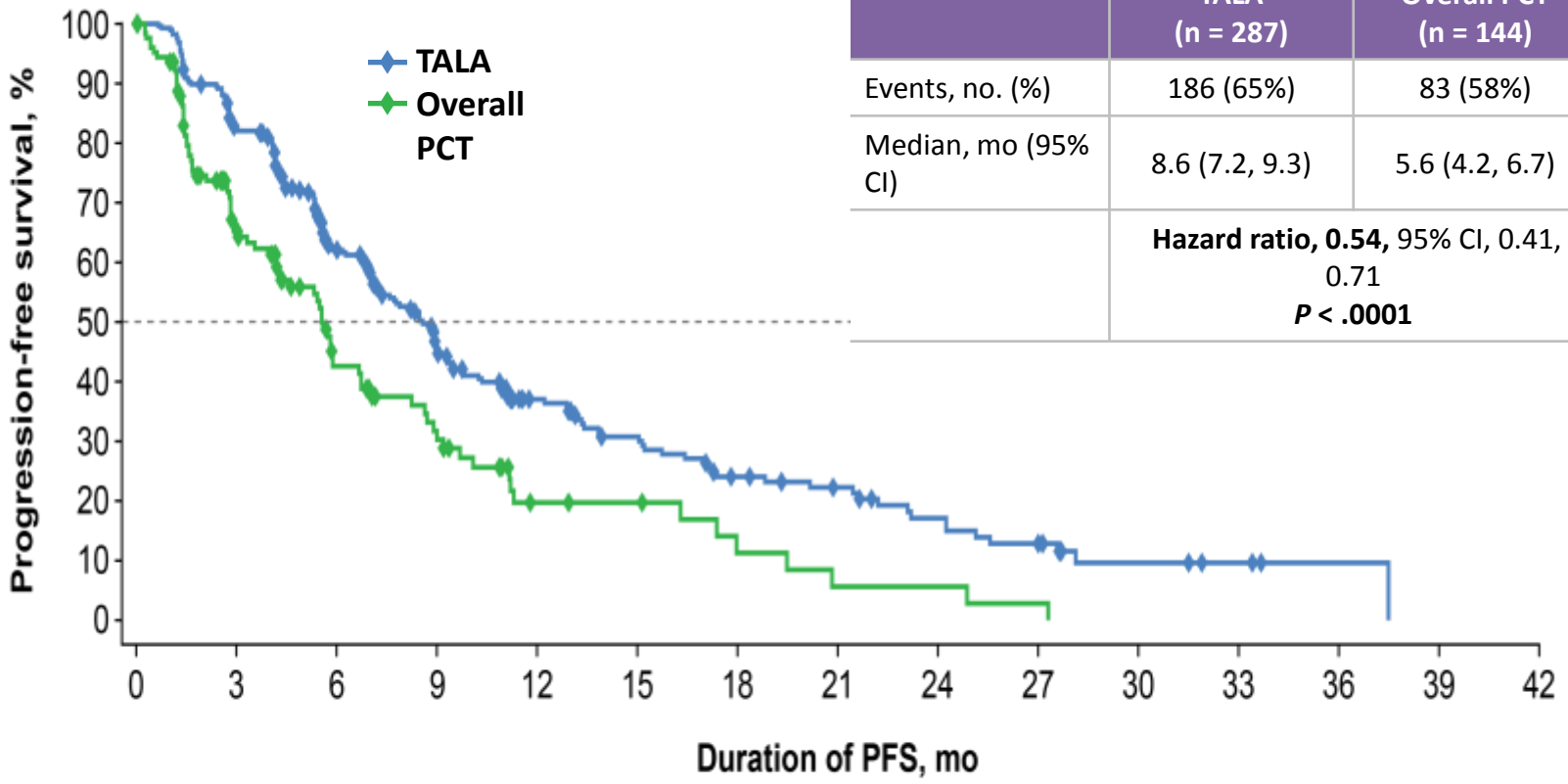
Key secondary efficacy endpoints

- Overall survival (OS)
- ORR by investigator
- Safety

Exploratory endpoints

- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

Primary Endpoint: PFS



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

No. at risk (events/cumulative events)

TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

KEYNOTE-086: Phase 2 Study of Pembrolizumab Monotherapy For mTNBC

Cohort A
- ≥1 prior systemic treatment for mTNBC with documented PD
- PD-L1 positive or negative

Cohort B
- No prior systemic treatment for mTNBC
- PD-L1 positive

All Patients
- Centrally confirmed TNBC[a]
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample
- No radiographic evidence of CNS metastases

Cohort A N = 170

Cohort B N = 84

Pembrolizumab 200 mg IV Q3W

for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

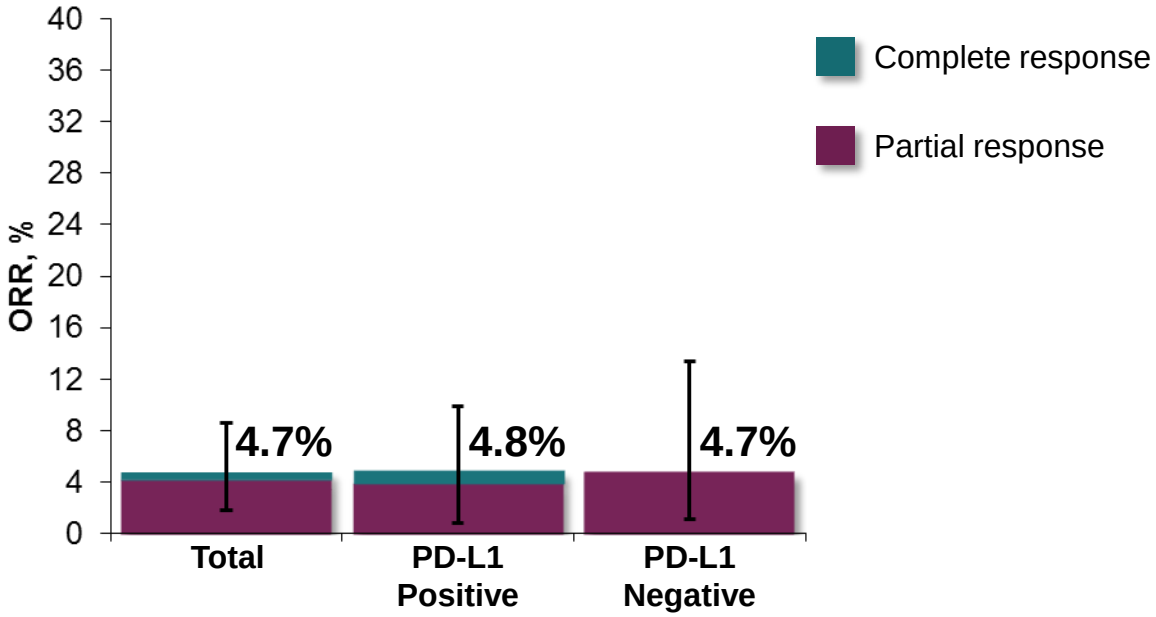
Protocol-specified follow-up

- Primary end points: ORR and safety
- Secondary end points: DOR, DCR,[b] PFS, OS

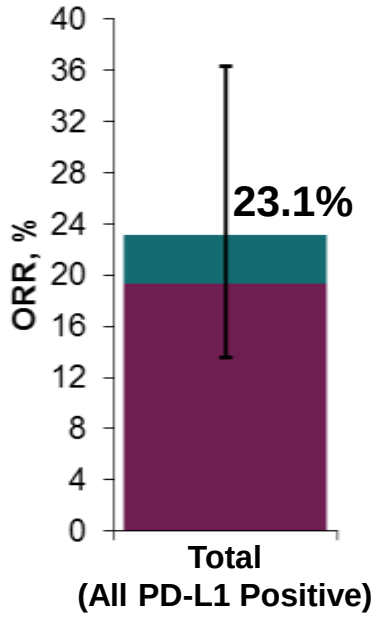
Adams et al. ASCO 2017; Loi et al. ESMO 2017

KEYNOTE-086: Antitumor Activity

Cohort A (N = 170)[1]:
Previously Treated mTNBC,
Regardless of PD-L1 Expression

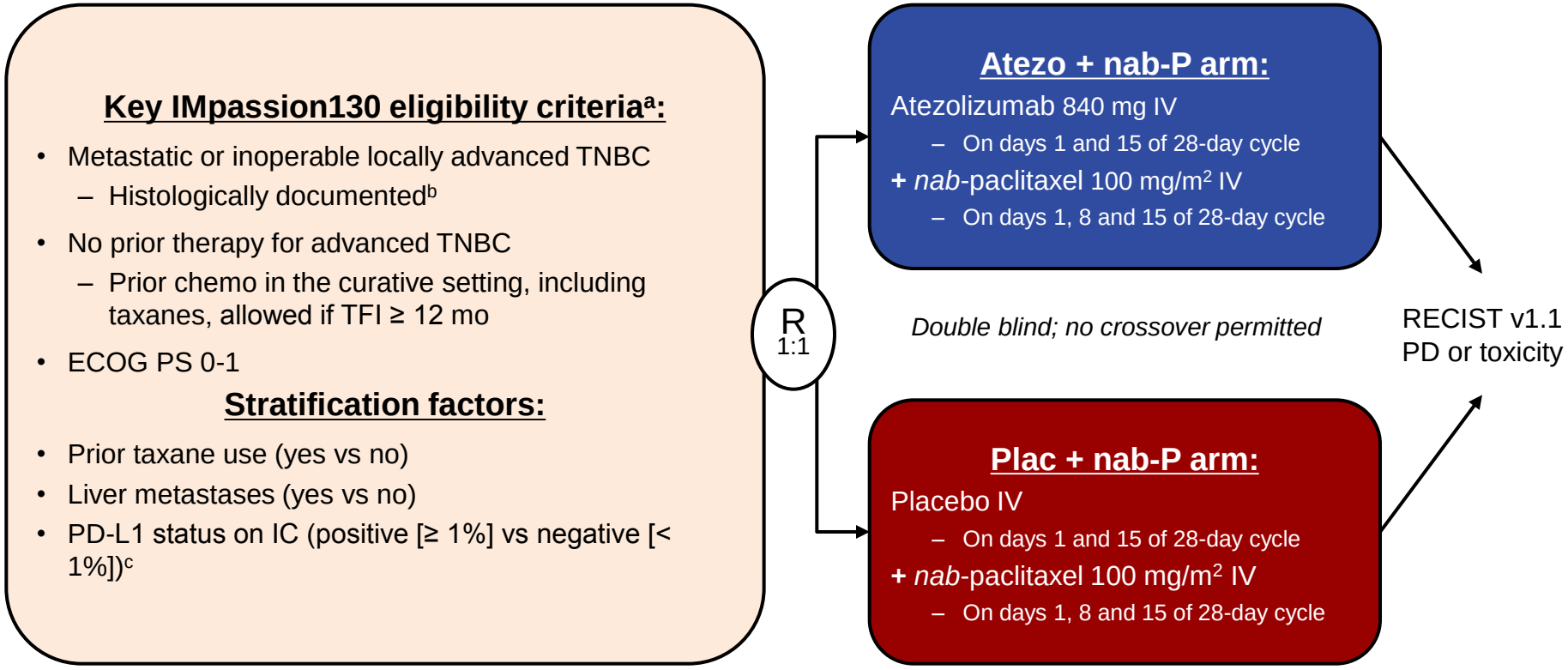


Cohort B (N = 52)[2]:
Previously Untreated mTNBC,
PD-L1 Positive



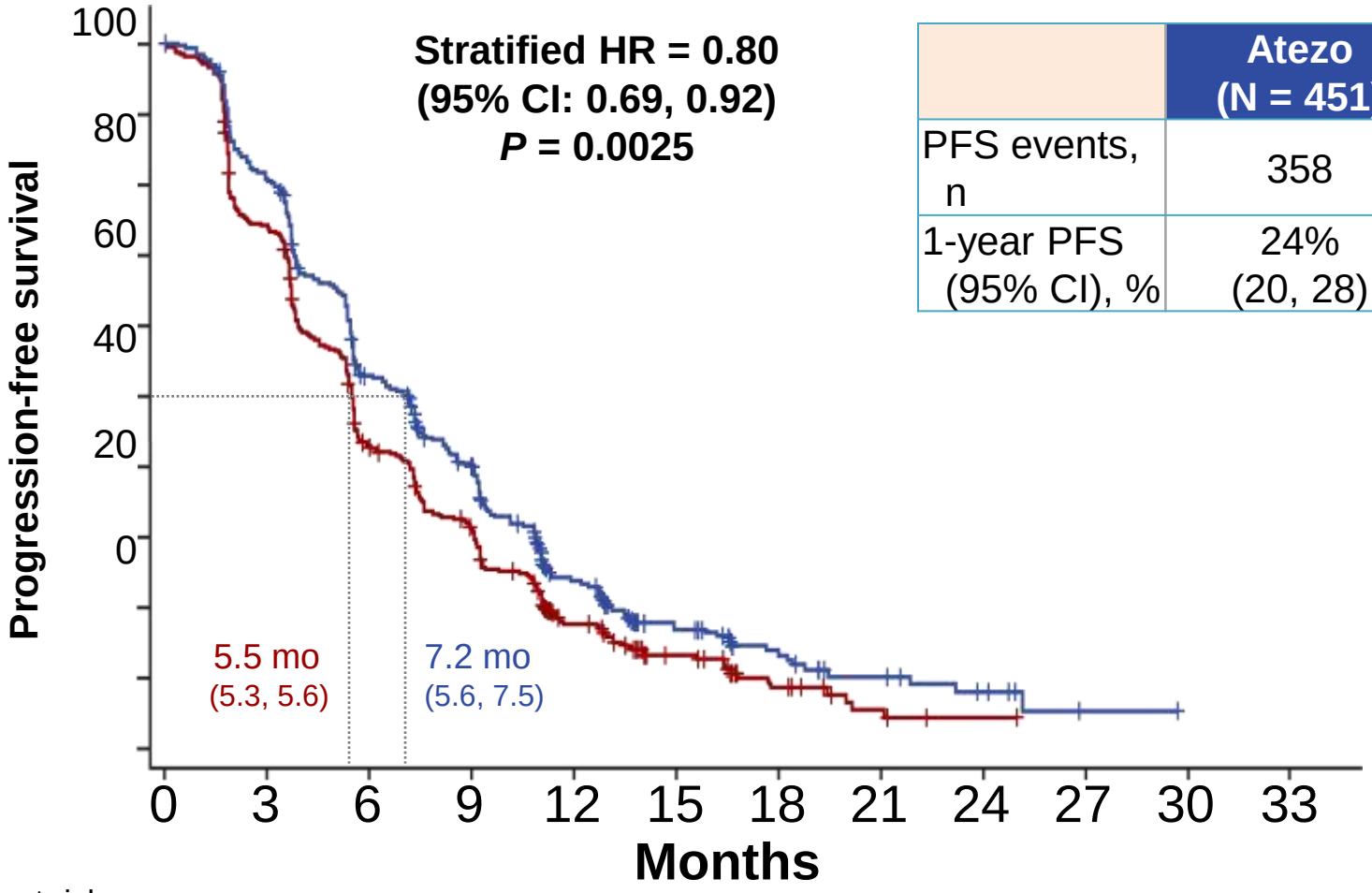
1. Adams S et al. Presented at ASCO 2017; Jun 2-6, 2017; Chicago, IL, USA; abstr 1008.
2. Adams S et al. Presented at ASCO 2017; Jun 2-6, 2017; Chicago, IL, USA; abstr 1088.

IMpassion130 study design



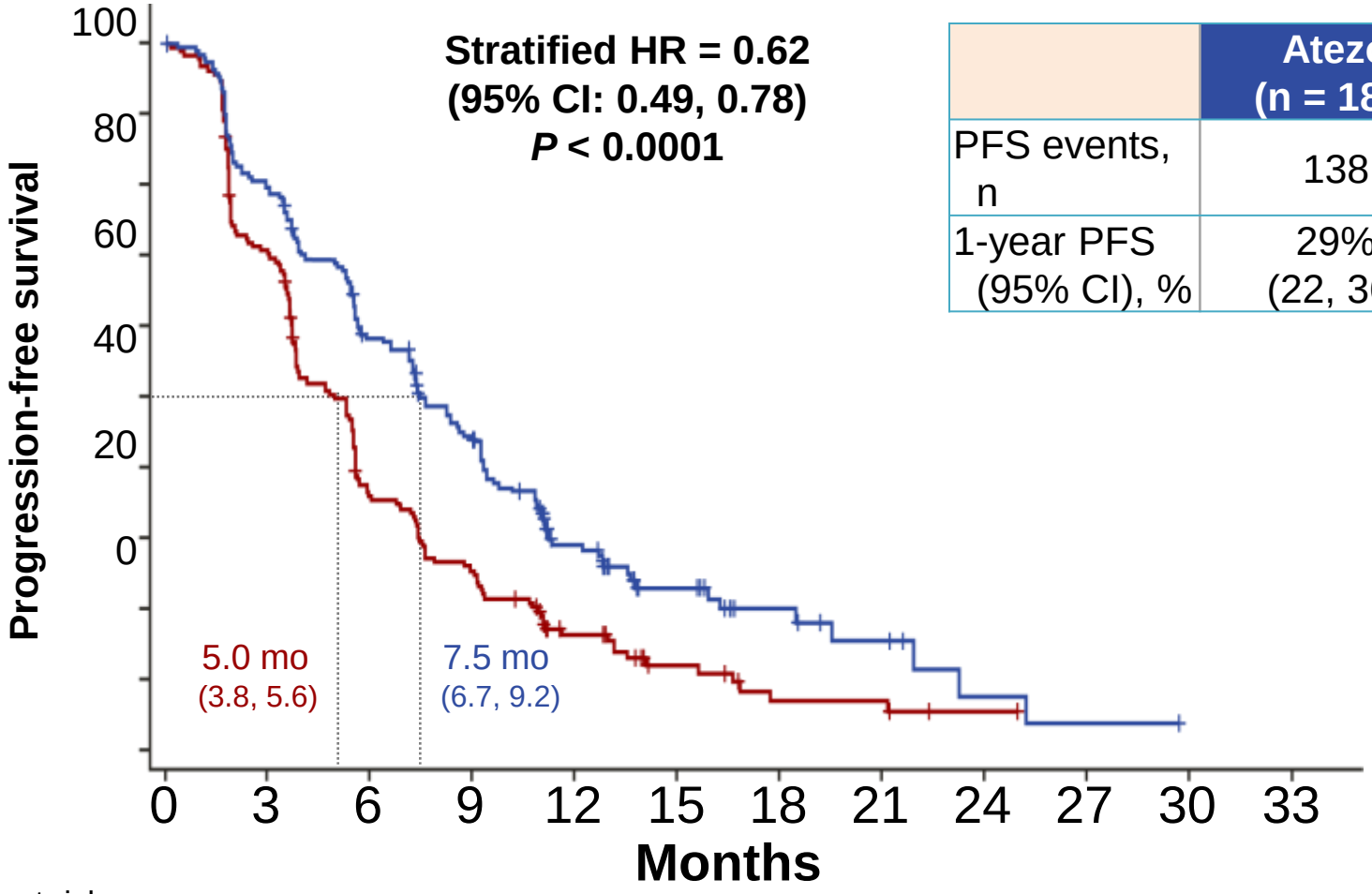
- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

Primary PFS analysis: ITT population



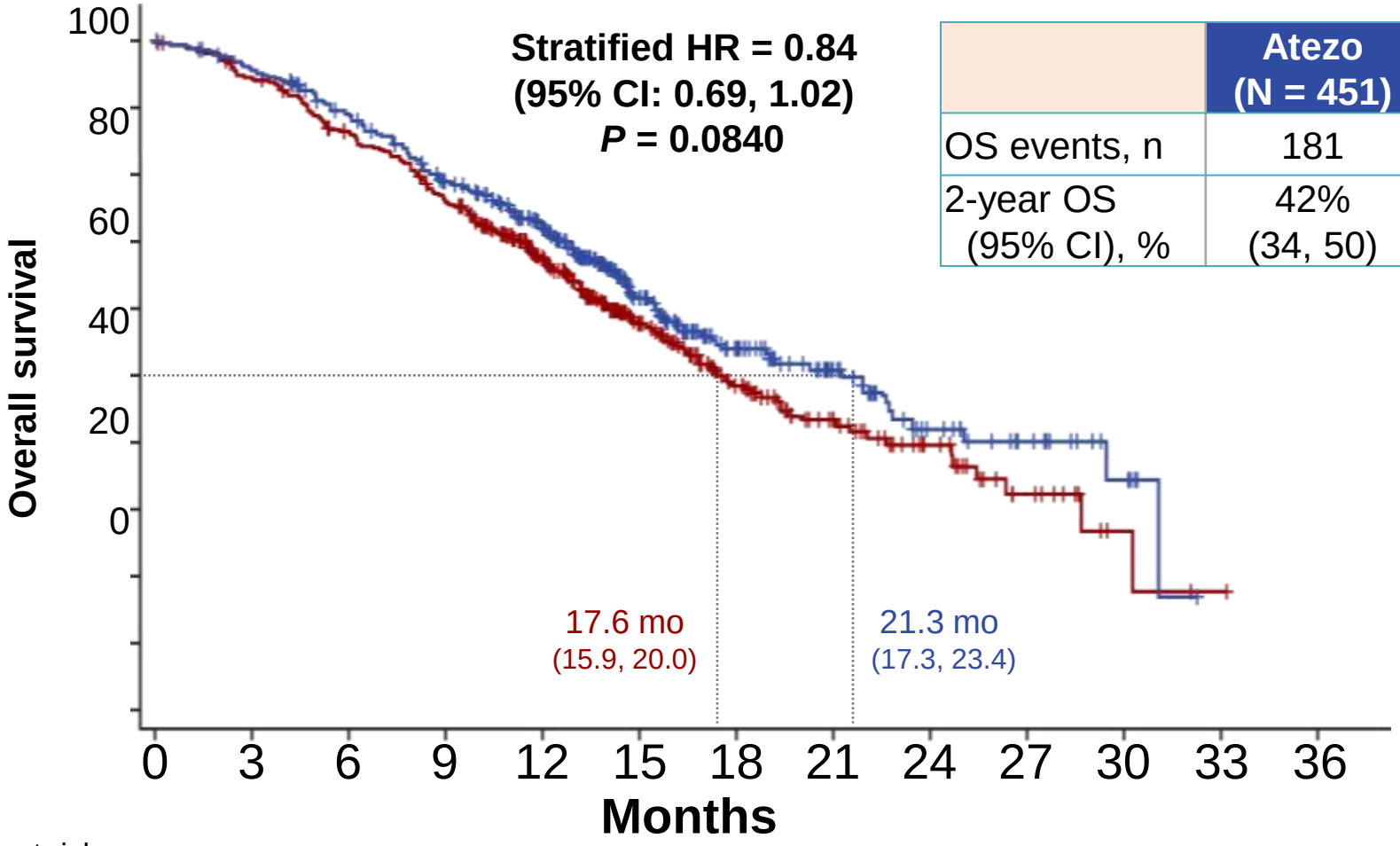
	Atezo (N = 451)	Plac (N = 451)
PFS events, n	358	378
1-year PFS (95% CI), %	24% (20, 28)	18% (14, 21)

Primary PFS analysis: PD-L1+ population



	Atezo (n = 185)	Plac (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

Interim OS analysis: ITT population



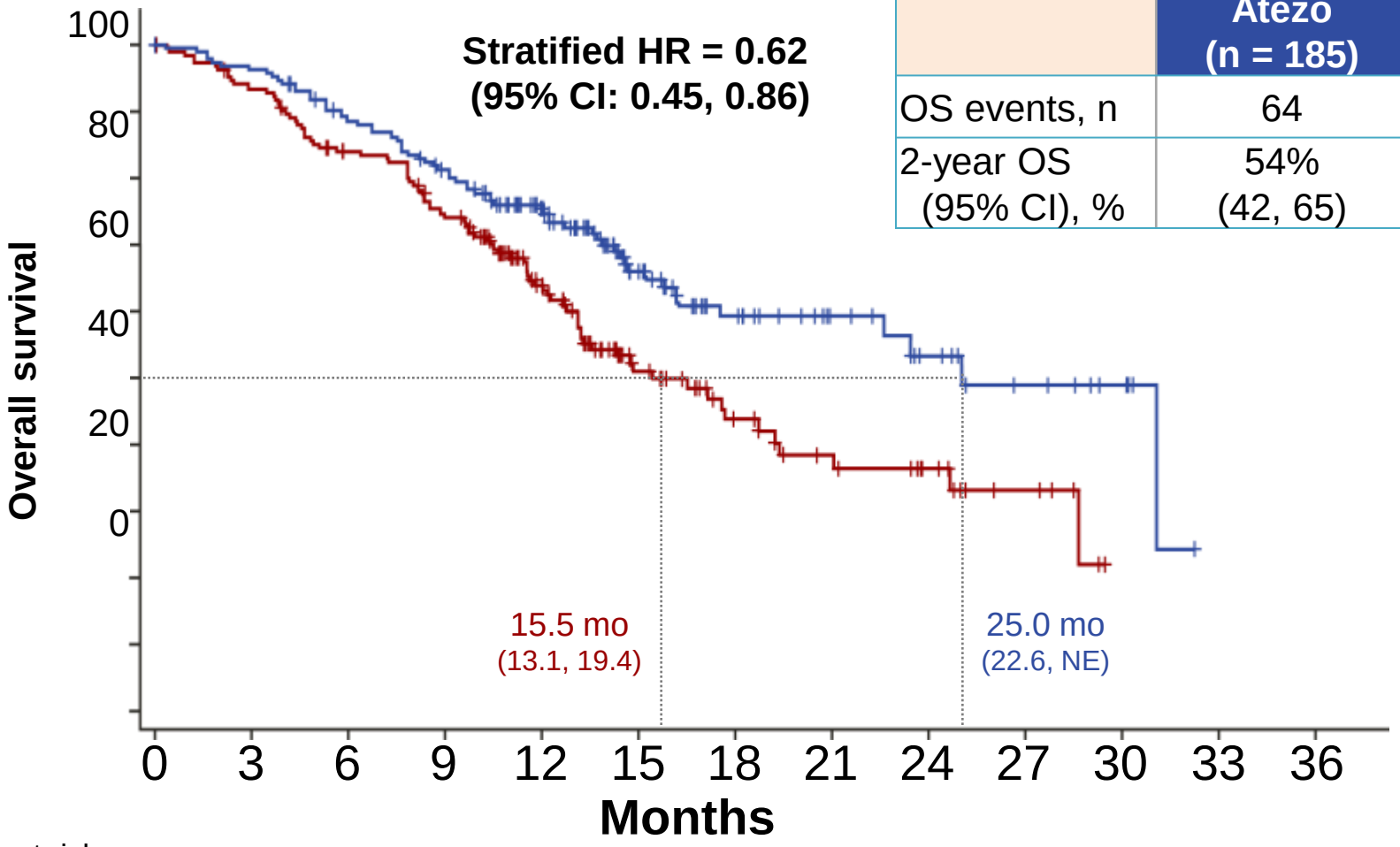
	Atezo (N = 451)	Plac (N = 451)
OS events, n	181	208
2-year OS (95% CI), %	42% (34, 50)	40% (33, 46)

No. at risk:

Atezo	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Plac	451	419	375	328	246	145	89	52	27	12	3	1	NE

Interim OS analysis: PD-L1+ population

	Atezo (n = 185)	Plac (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)



No. at risk:

Atezo + nab-P	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Plac + nab-P	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

Immunotherapy Drug Combinations

- Hormone Receptor Positive Breast Cancer
  - CDK4/6 inhibitors
- HER2 Positive Breast Cancer
  - HER2 directed therapy
- Triple-Negative Breast Cancer
  - PARP Inhibitors
  - Chemotherapy
  - Radiation therapy
  - Immunotherapy combinations

Targeting the Androgen Receptor in TNBC

- The AR appears to be a driving force for a subset of TNBCs
- About 10% of TNBCs are AR+
- Bicalutamide has previously been shown to be effective at keeping AR+ TNBCs stable
- Enzalutamide binds to the AR with higher affinity than bicalutamide
- Enzalutamide has being tested in women with AR+ TNBC

Traina et al, ASCO 2015

MDV3100-11: Study Schema

AR Testing

Optional consent for AR testing

IHC results reported as:

"Positive" (AR > 0%)

"Negative" (AR = 0%)

Screening

- AR "positive" TNBC*
- ECOG-PS ≤ 1
- Sufficient tissue to enable biomarker discovery
- No CNS metastases
- Any number of prior therapies permissible
- Evaluable bone-only disease allowed

Endpoints

Primary
- CBR16

Secondary
- CBR24
- Response rate
- PFS
- OS
- Safety

Exploratory
- AR biomarker discovery

Treatment

Enzalutamide 160 mg/day

Stage 1
"Go" to Stage 2
≥ 3 of 26 Evaluable have CBR16

Stage 2
Rejection of H_0
≥ 9 of 62 Evaluable have CBR16

Treat to progression

Definitions
- Evaluable = AR IHC ≥ 10% and ≥ 1 post-baseline tumor assessment
- ITT = any AR "positive" by central assessment and received ≥ 1 dose of drug

Statistical considerations
- 85% power to detect true CBR16 = 8% tested against 1-sided alternative (CBR16 ≥ 20%); alpha = 5%

Traina et al, ASCO 2015

Clinical Benefit in Evaluable and ITT Populations

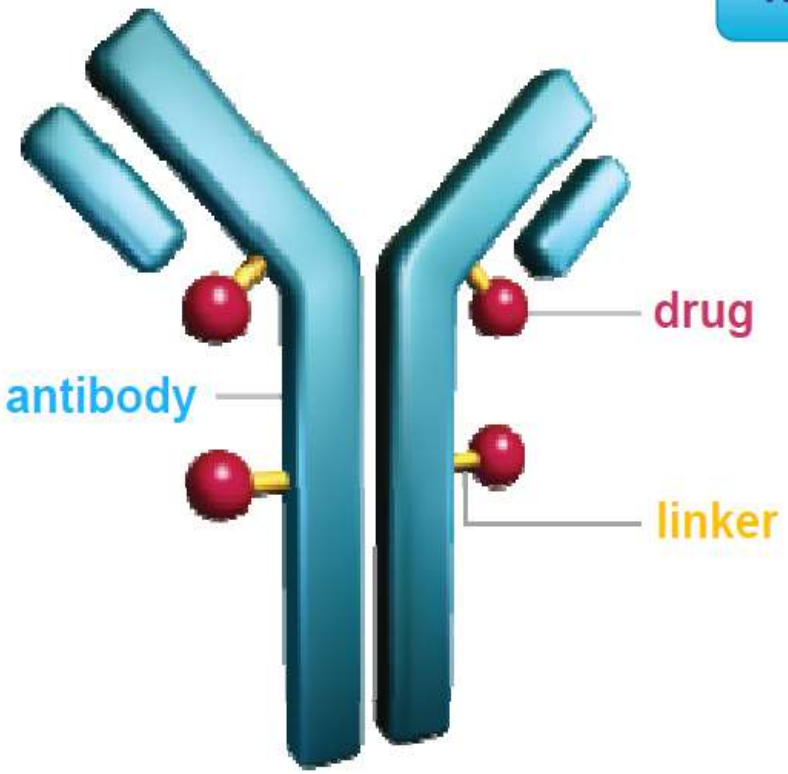
AR>10%

	Evaluable (n = 75)	ITT (n = 118)
CBR16, n (%) (95% CI)	26 (**35%**) (24, 46)	29 (**25%**) (17, 33)
CBR24, n (%) (95% CI)	22 (**29%**) (20, 41)	24 (**20%**) (14, 29)
CR or PR, n	6	7

Evaluable = AR IHC ≥ 10% and ≥ 1 post-baseline tumor assessment;
ITT = any AR "positive" by central assessment and received ≥ 1 dose of drug.

Traina et al, ASCO 2015

Antibody Drug Conjugates



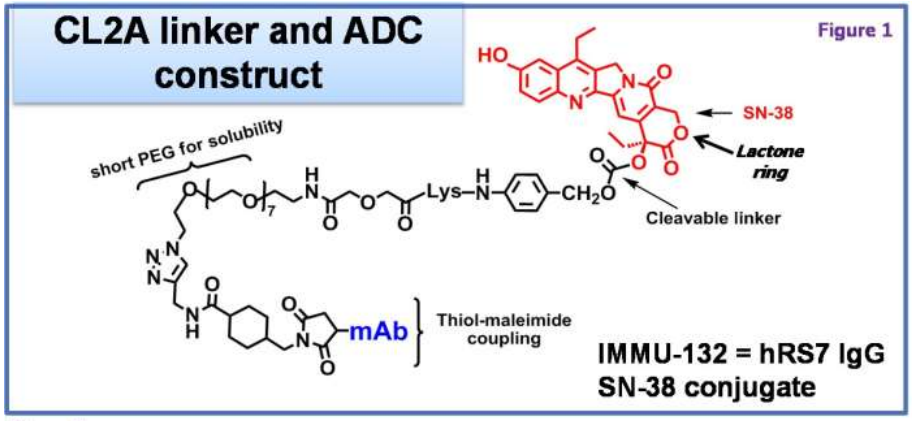
1. Monoclonal antibody specific for a tumor antigen with little/no expression on normal cells

2. Linker that is stable in circulation but releases the cytotoxic agent in target cells

3. Potent cytotoxic agent designed to induce target cell death when internalized and released

IMMU-132

- Target: Trop2 (EGP-1)
  - Pan-epithelial cancer antigen
  - Related to but distinct from EpCAM (EGP-2) – less expression on normal tissues.
  - Oncogene which signaling leading to increased tumorigenicity, aggressiveness, and metastasis.
  - Prognostic marker in several cancer types
- Linker: pH sensitive linker (CL2A)
- Cytotoxic: SN-38 (Irinotecan active metabolite)



Efficacy and Safety of Anti-Trop-2 Antibody Drug Conjugate Sacituzumab Govitecan (IMMU-132) in Heavily Pretreated Patients With Metastatic Triple-Negative Breast Cancer

Aditya Bardia, Ingrid A. Mayer, Jennifer R. Diamond, Rebecca L. Moroose, Steven J. Isakoff, Alexander N. Starodub, Nikita C. Shah, Joyce O'Shaughnessy, Kevin Kalinsky, Michael Guarino, Vandana Abramson, Dejan Juric, Sara M. Tolaney, Jordan Berlin, Wells A. Messersmith, Allyson J. Ocean, William A. Wegener, Pius Maliakal, Robert M. Sharkey, Serengulam V. Govindan, David M. Goldenberg, and Linda T. Vahdat

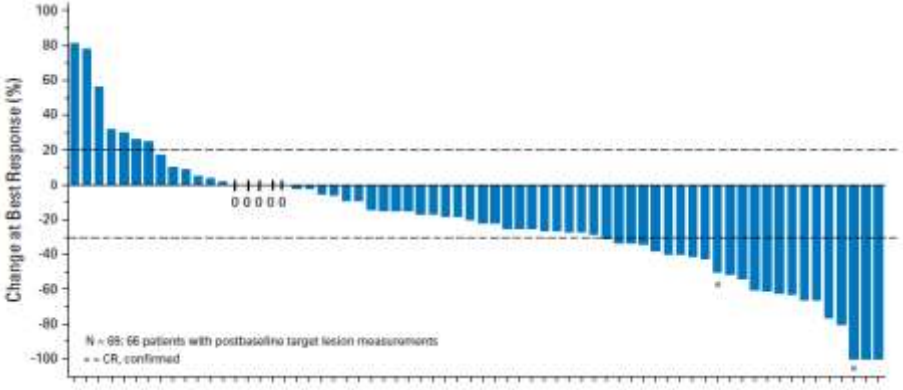


Table 3. Treatment Efficacy in Intention-to-Treat Data Set (N = 69)

Efficacy	Best Overall Response, No. (%)
CR	2 (3)
PR	19 (28)
SD	31 (45)
PD	17 (25)
Confirmed objective response (CR + PR)	21 (30)
95% CI	20 to 43
Clinical benefit (CR + PR + SD ≥ 6 months)	32 (46)
95% CI	34 to 59
Median duration of objective response, months (95% CI)	8.9 (6.1 to 11.3)
Median PFS, months (95% CI)	6.0 (5.0 to 7.3)
Median OS, months (95% CI)	16.6 (11.1 to 20.6)

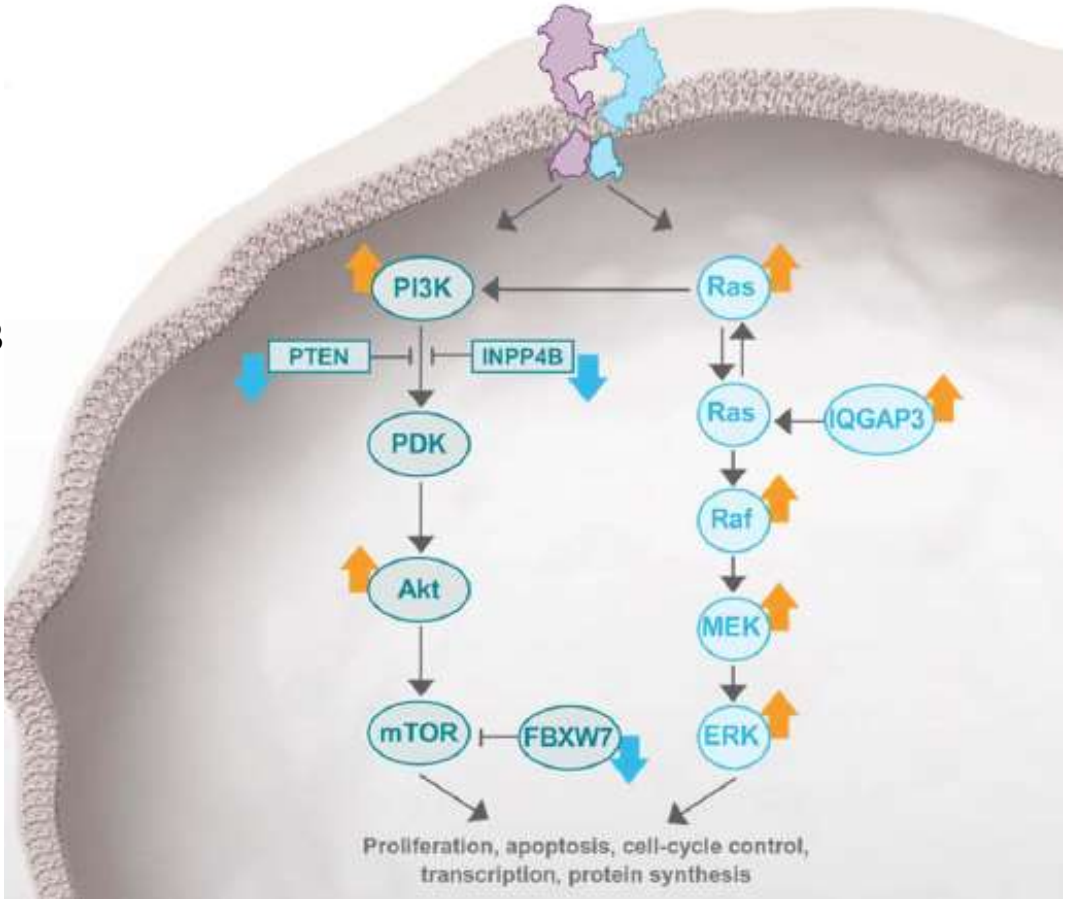
J Clin Oncol 35:2141-2148.

Select trials of Antibody-Drug Conjugates in Metastatic TNBC

Name	Phase	Arms	Clinicaltrials.gov
IMMU-132	III	Sacituzumab govitecan Capecitabine, eribulin, gemcitabine, vinorelbine	NCT02574455
CDX-011	II	Glembatumumab Capecitabine	NCT01997333
LIV1A	I/II	SGN-LIV1A	NCT01969643

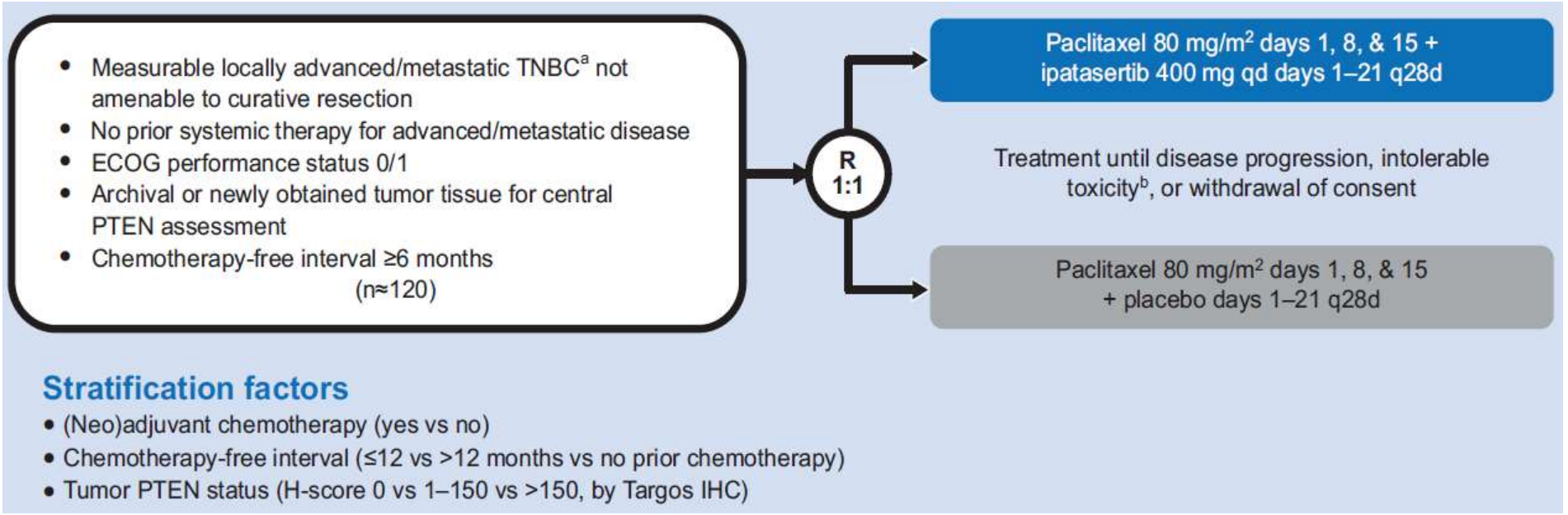
PI3K/AKT Pathway and Breast Cancer

- PI3K/AKT signaling pathway plays a crucial role in carcinogenesis, promoting cell survival and growth[1,2]
- Activated in 15-20% of TNBC[3]
- Ipatasertib is an oral, ATP-competitive inhibitor of all three isoforms of Akt
- LOTUS trial
  - evaluate efficacy and safety of paclitaxel +/-ipatasertib in advanced TNBC



1. Cantley LC. Science 2002;296:1655–7.
2. LoRusso PM. J Clin Oncol 2016;34:3803–15.
3. Basho RK, et al. JAMA Oncol 2017;3:509–15.

The LOTUS Trial

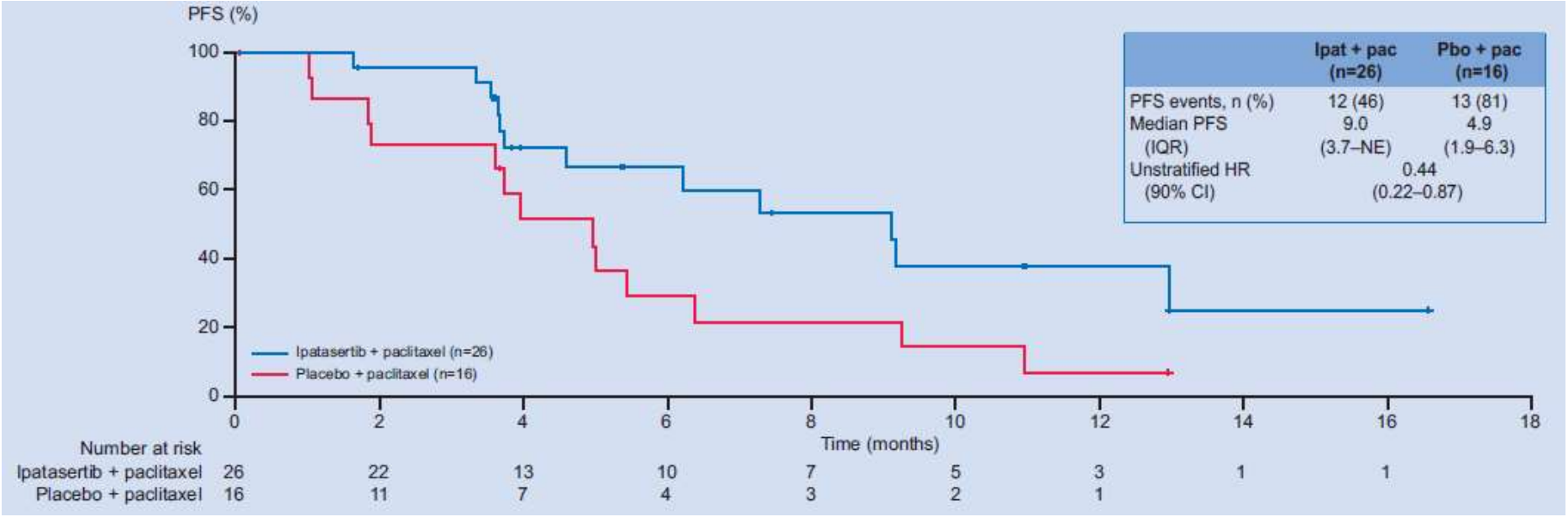


Co-primary endpoints:

- PFS in the ITT population
- PFS in the PTEN-low subgroup (IHC 0 in ≥50% tumour cells)

Dent et al. ASCO 2017

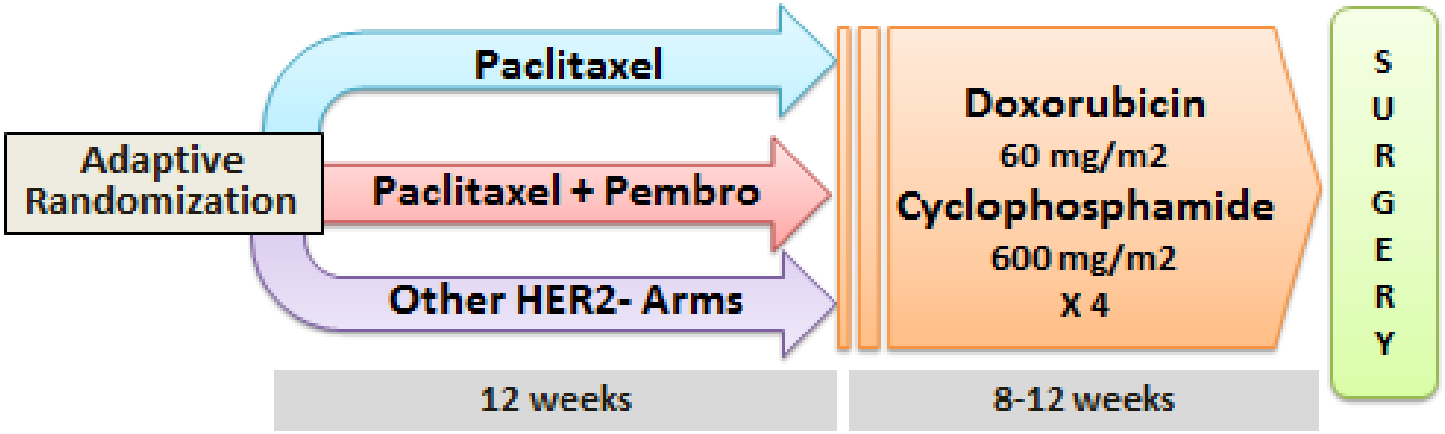
PFS in PIK3CA/AKT1/PTEN-altered Tumors



	Ipat + pac (n=26)	Pbo + pac (n=16)
PFS events, n (%)	12 (46)	13 (81)
Median PFS (IQR)	9.0 (3.7–NE)	4.9 (1.9–6.3)
Unstratified HR (90% CI)	0.44 (0.22–0.87)	

Dent et al. ASCO 2017

I-SPY 2 TRIAL Schema: HER2- Signatures



Control

Paclitaxel 80 mg/m2 every wk x 12

Experimental

Paclitaxel 80 mg/m2 every wk x 12

Pembro 200 mg every 3 wks x 4

12

Nanda et al, ASCO 2017

Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	**0.46** (0.34 – 0.58)	**0.16** (0.06 – 0.27)	**> 99%**	**99%**
TNBC	**0.60** (0.43 – 0.78)	**0.20** (0.06 – 0.33)	**>99%**	**>99%**
HR+/HER2-	**0.34** (0.19 – 0.48)	**0.13** (0.03 – 0.24)	**>99%**	**88%**

Nanda et al, ASCO 2017

Select ongoing phase II and III adjuvant/neoadjuvant trials in HER2 negative early stage breast cancer

Name	Phase	Arms	Clinicaltrials.gov
S1418	III	observation pembro x 1 year	NCT02954874
ISPY2	II	paclitaxel —> AC paclitaxel + pembro → pembro	NCT01042379
KEYNOTE 522	III	carboplatin/taxol→AC carboplatin/taxol + pembro →AC + pembro	NCT03036488
IMpassion031	III	nab-paclitaxel→AC nab-paclitaxel + atezo → AC + atezo	NCT02425891

Importance of Clinical Trials

The Role of Clinical Trials

- Phases of Clinical Trials
  - Phase I, II, III
- Clinical trials are designed to build on the current standard of care
- Without clinical trials we cannot develop better treatment for the future

Clinical Trial Phases

- Phases I
  - Safety, dose finding
  - New drugs
  - New combinations of old drugs
- Phase II
  - Efficacy, specific for tumor type
- Phase III
  - Testing again standard treatment
  - +/- placebo

Pros and Cons of Clinical Trials

- Pros
  - Access to newer promising therapies before they are approved
  - Help to move the field forward
  - Potentially help future patients who are diagnosed with cancer
- Cons
  - No guarantee trial treatment is better
  - No guarantee that you will be assigned to study treatment
  - Treatment has to be at sponsoring institution
  - Additional time/visits/biopsies

How can I find out about clinical trials in my area?

- Treating oncologist
- ClinicalTrials.gov
- Triple-negative breast cancer foundation www.tnbcfoundation.org

Future Promise

- Much research is ongoing for mets TNBC
  - Understand mechanisms of resistance to standard treatments
  - Develop more personalized therapy
- New therapies are being developed and tested in clinical trials specifically for patients with MBC
- Hope for the future
  - More effective therapies
  - Fewer side effects