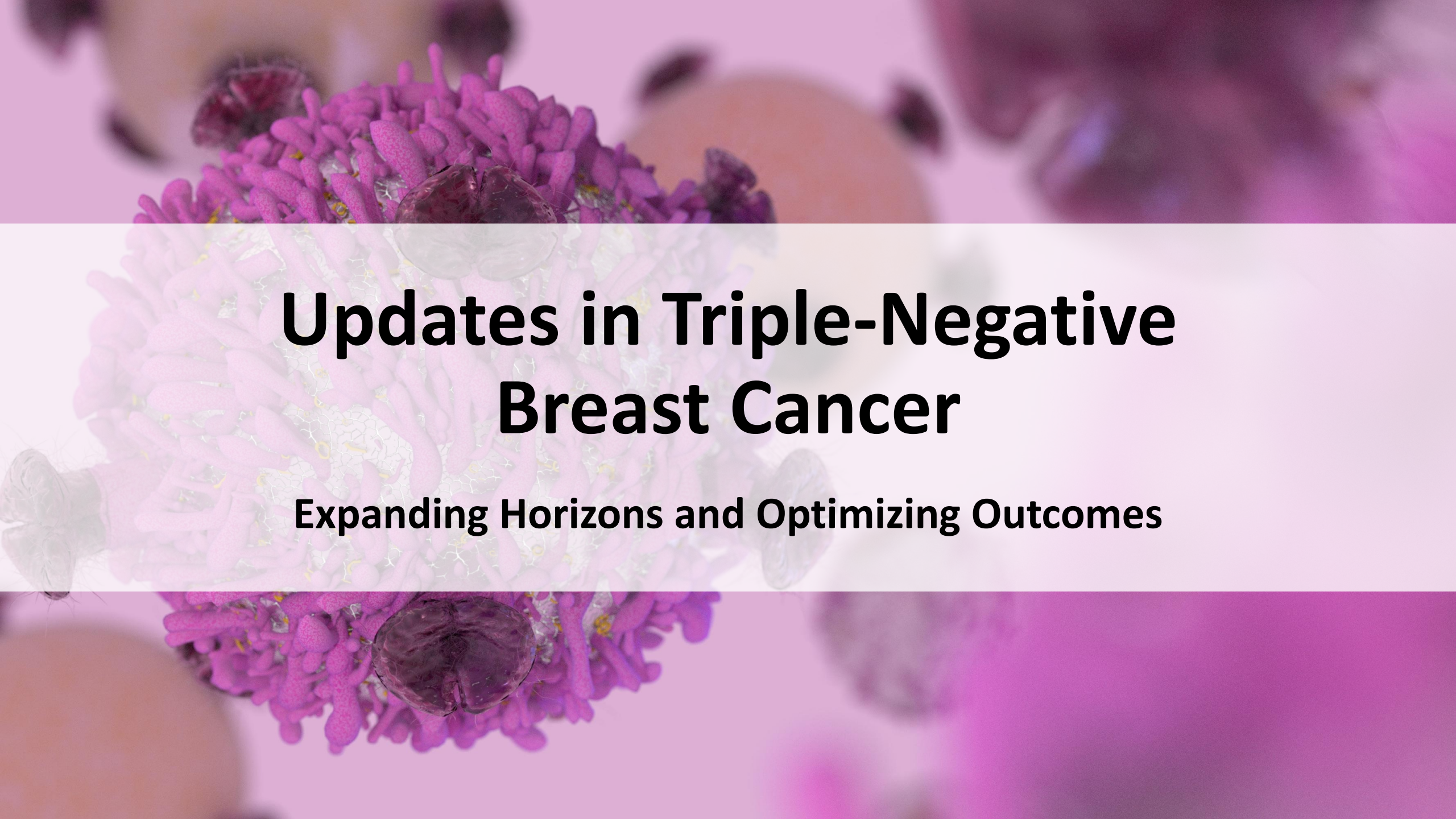

Updates in Triple-Negative Breast Cancer

Expanding Horizons and Optimizing Outcomes

This educational activity is sponsored by Postgraduate Healthcare Education, LLC and is supported by an educational grant from Bristol-Myers Squibb.

Faculty

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Disclosures

Dr. Armitage has disclosed that she has served as a consultant for Daiichi Sanyko.

The clinical reviewer, **Lisa Holle, PharmD, BCOP**, has disclosed that she has served as a consultant to McGraw Hill Education and has received honoraria from HOPA and PharmCon.

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Type of Activity: Application

Learning Objectives

- **Describe** the challenges of triple-negative breast cancer (TNBC) management
- **Discuss** currently available and emerging TNBC therapies
- **Explain** the role of biomarker testing in TNBC treatment selection
- **Formulate** strategies to provide effective patient-centered care to patients with TNBC

Background

- Breast cancer is the most common cancer diagnosed in women in the United States (U.S.)
- In the U.S. in 2020, there will be an estimated 279,100 new breast cancer cases and 42,690 deaths
- TNBC accounts for 10%–20% of all new breast cancer cases
- TNBC is more common in younger women than older
- TNBC is more common in Black or Hispanic women than White

American Cancer Society. https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html.;
Siegel RL, et al. *CA Cancer J Clin.* 2020;70(1):7-30.

TNBC Epidemiology

- TNBC has a poor prognosis
  - More aggressive
  - Higher rate of recurrence
  - Earlier risk of recurrence
  - Higher likelihood of brain and lung involvement and less frequent bone lesions than other breast cancer subtypes
  - Worse long-term outcomes than other breast cancer subtypes
  - Chemo-sensitive but with median overall survival (OS) of ONLY approximately 13–18 months with standard chemotherapy
  - Few non-chemotherapy treatment options

Badve S, et al. *Mod Pathol*. 2011;24(2):157-67.; Garrido-Castro AC, et al. *Cancer Discov*. 2019;9(2):176-98.

TNBC

- Heterogeneous disease with distinct phenotypes
- Molecular profiling has defined 4 major subtypes of TNBC
  - Basal-like 1 (BL1): 35%
  - Basal-like 2 (BL2): 22%
  - Mesenchymal subtype (M): 25%
  - Luminal androgen receptor (LAR): 16%
- More often associated with hereditary conditions
  - 35% of TNBC patients possess BRCA1 mutation and 8% have BRCA2 mutation
- TNBC is thought to be more immunogenic than other subtypes
- Higher levels of tumor-infiltrating lymphocytes (TILs) and PD-L1 expression and higher tumor mutational burden (TMB) are thought to make TNBC more amenable to immunotherapy

Mehanna J, et al. *Int J Womens Health*. 2019;11:431-7.

Prognostic Biomarkers in TNBC

Molecular biomarker	% TNBC with expression/mutation	Main function	Prognostic significance	Targeted therapies
BRCA1 and BRCA2 genes	14%–20% (germline mutations)	DNA double-strand break repair	Mutated status correlates with increased DFS	PARP inhibitors: olaparib & talazoparib
PD-L1 protein	15%–30%	Tumor immune evasion process	High expression correlates with higher survival rates in trials with checkpoint inhibitors	Immune checkpoint inhibitors (ICIs): atezolizumab, avelumab, pembrolizumab, nivolumab, cemiplimab, ipilimumab
Microsatellite instability	0–1.5% of all breast cancers	High immunogenic activity	Predictor of response to pembrolizumab; use as a prognostic or predictive biomarker is still under investigation	FDA approval allows using pembrolizumab for TNBC with MSI-H/dMMR
TMB	3.1%–5% of breast cancers are hypermutated, with higher prevalence in TNBC and metastatic tumors	Defined as the number of somatic mutations per megabase of interrogated genomic sequence	More sensitive to PD-1 inhibitors; no differences in terms of survival have been shown in patients with high TMB treated with immunotherapy	ICIs

DFS, disease-free survival; FDA, United States Food and Drug Administration; MSI-H/dMMR, microsatellite instability-high/deficient mismatch repair.

Cocco S, et al. *Int J Mol Sci*. 2020;21(13):4579.; Lopes da Silva J, et al. *Crit Rev Oncol Hematol.* 2020;145:102855.

Prognostic Biomarkers in TNBC

Molecular biomarker	% TNBC with expression/mutation	Main function	Prognostic significance	Targeted therapies
TILs	~20%	Involved in immune response against the tumor	High TILs correlates with more favorable survival and are predictive for increased response to neoadjuvant chemotherapy/ICIs	N/A
PI3-kinase pathway	~25%	Cell proliferation	Multiple genomic alterations lead to activated PI3-kinase pathway, including activation in PIK3CA, AKT, and mTOR or inactivation in tumor suppressor genes such as PTEN	PI3K inhibitor: alpelisib AKT inhibitors: ipatasertib, capivasertib
Androgen receptor	10%–55%	Cell proliferation and differentiation	Positive expression correlates with higher DFS; may be associated with chemo-resistance	Bicalutamide, enzalutamide, abiraterone

Cocco S, et al. *Int J Mol Sci*. 2020;21(13):4579.; Lopes da Silva J, et al. *Crit Rev Oncol Hematol.* 2020;145:102855.

Promising Biomarkers in TNBC

Molecular biomarker	% TNBC with expression/mutation	Main function	Prognostic significance	Targeted therapies
Trophoblast cell-surface antigen 2 (Trop-2)	~80%	Cell cycle progression, migration, proliferation, metastasis	Associated with more aggressive disease and poorer prognosis	Sacituzumab govitecan
Glycoprotein non-metastatic B (GPNMB)	Highly expressed	Cell migration, invasion, angiogenesis, epithelial-mesenchymal transition	Correlates with shorter recurrence times and reduced OS of breast cancer patients	Glembatumumab vedotin (CDX-011)
LIV-1	Highly expressed	Cell adhesion, epithelial-mesenchymal transition	Under investigation	Ladiratuzumab vedotin (SGN-LIV1A)
Mucin 1-attached sialoglycotope CA6	Overexpressed	Tumor cell survival and proliferation	Under investigation	SAR566658

Cocco S, et al. *Int J Mol Sci*. 2020;21(13):4579.

Emerging Biomarkers in TNBC

Molecular biomarker	% TNBC with expression/mutation	Main function	Prognostic significance	Targeted therapies
TP53 gene	75%–80%	Apoptosis	Low gene expression in TP53 missense mutations correlates with poor prognosis (worse DFS, but conflicting data)	N/A
Ki-67	45%–53% (high expression, >20%)	Cell proliferation	High index and high expression correlate with shorter DFS and OS	N/A
EGFR	13%–78%	Cellular growth	Increased expression associated with worst DFS	Erlotinib, gefitinib, afatinib
C-KIT	50%	Cell transformation and differentiation	Predictor of poor cancer-specific survival	Imatinib
VEGF	32%–62%	Angiogenesis	High levels associated with disease progression and metastasis rates	Bevacizumab
Notch pathway	~10%	Cell proliferation and differentiation	Potential target under development	AL101

Lopes da Silva J, et al. *Crit Rev Oncol Hematol.* 2020;145:102855.

Treatment

Multifactoral

- Surgery
  - Lumpectomy or mastectomy
- Radiation therapy
  - Whole breast, chest wall, and regional node irradiation
- Systemic therapy
  - Chemotherapy, immunotherapy, and PARP inhibitors

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 8, 2020.

Treatment Considerations

- Clinical & pathological characteristics
- Tumor histology
- Comorbidities
- ALN status
- Tumor hormone receptor status (ER/PR)
- Menopausal status
- Metastatic disease
- HER2 status
- Age

ALN, axillary lymph nodes; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 8, 2020.

Benefits of Neoadjuvant Therapy

- Facilitates breast conservation
- Can render inoperable tumors operable
- Provides important prognostic information at an individualized patient level based on response to therapy
- Allows the modification or addition of adjuvant regimens among patients with residual TNBC or HER2-positive disease
- Allows time for genetic testing to result
- Allows time to plan breast reconstruction in patients electing for a mastectomy

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 8, 2020.

Neoadjuvant Therapy Candidates

- Patients with inoperable breast cancer
  - Inflammatory breast cancer
  - Bulky or matted axillary lymph nodes
  - T4 tumors or N3 nodal disease
- If operable, preoperative therapy is preferred
  - HER2-positive disease or TNBC if T ≥2 or N ≥1
  - Large primary tumor relative to breast size in patient who desires breast conservation
  - Patient with node-positive disease likely to become node-negative with preoperative therapy
  - If time needed to decide surgical options

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 8, 2020.

NCCN Guidelines: Preoperative/Adjuvant Therapy

HER2-Negative Disease

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) → T (paclitaxel weekly or every 2 weeks)
- TC (docetaxel/cyclophosphamide)
- ***Capecitabine (if residual disease after preoperative therapy in TNBC*)**

Useful in certain circumstances:

- Dose-dense AC
- AC every 3 weeks (category 2B)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC every 3 weeks → paclitaxel weekly

Other recommended regimens:

- AC every 3 weeks → docetaxel every 3 weeks
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide)
- ***Select patients with TNBC in the preoperative setting ONLY***
  - ***Weekly carboplatin and paclitaxel***
  - ***Carboplatin and docetaxel***

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 8, 2020.

CALGB 40603: Neoadjuvant Paclitaxel with Carboplatin ± Bevacizumab in TNBC

Patients with stage II–III TNBC (N=443)

Paclitaxel 80 mg/m^2 weekly x 12	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 (dd AC) x 4
Paclitaxel 80 mg/m^2 weekly x 12 + bevacizumab 10 mg/kg q 2 w x 9	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 (dd AC) x 4
Paclitaxel 80 mg/m^2 weekly x 12 + carboplatin AUC 6 q 3 w x 4	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 (dd AC) x 4
Paclitaxel 80 mg/m^2 weekly x 12 + carboplatin AUC 6 q 3 w x 4 + bevacizumab 10 mg/kg q 2 w x 9	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 (dd AC) x 4

→ Surgery

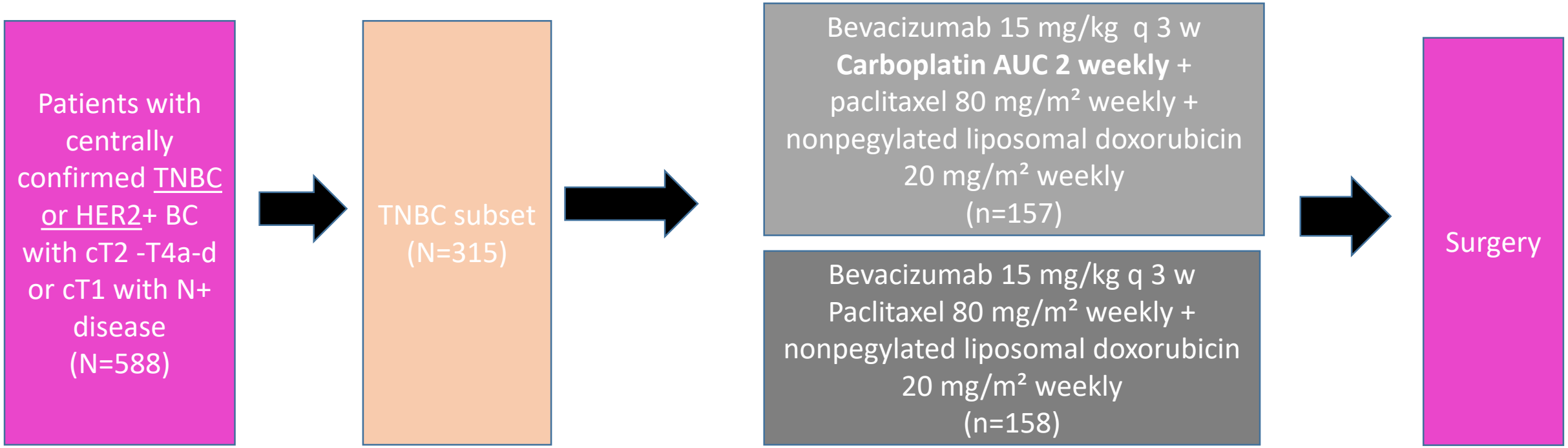
- **Randomized, open-label, phase II multicenter trial conducted in the U.S.**
- **Addition of carboplatin to chemo significantly increased pCR rates (54% vs. 41%, P=0.029)**
- **No improvement in DFS with addition of platinum to chemotherapy**

AUC, area under the curve; dd, dose-dense; pCR, pathologic complete response.

Sikov WM, et al. *J Clin Oncol*. 2015;33(1):13-21.; Sikov WM, et al. *J Clin Oncol.* 2019;37(15_suppl):591.

GeparSixto: Neoadjuvant Carboplatin + Chemotherapy

Randomized, phase IIb, multicenter study conducted in Germany



- **pCR rate in TNBC with carboplatin + chemo vs. chemo alone: 53.2% vs. 36.9% (P=0.005)**
- **A significantly better DFS (HR 0.56, 95% CI 0.34–0.93; P=0.022) was observed in patients with TNBC treated with carboplatin**

CI, confidence interval; HR, hazard ratio.

Hahnen E, et al. *JAMA Oncol*. 2017;3(10):1378-85.; Loibl S, et al. *Ann Oncol*. 2018;29(12):2341-7.; von Minckwitz G, et al. *Lancet Oncol.* 2014;15(7):747-56.

Adjuvant Therapy for TNBC

- The vast majority of TNBC patients benefit from adjuvant chemotherapy (except some low-risk histologic subtypes)
- Chemotherapy for TNBC may be given adjuvantly if tumor is >0.5 cm (and not given neoadjuvantly)
- Taxane and/or anthracycline combination
  - Dose-dense AC → T
  - TC
- Capecitabine (if residual disease after preoperative therapy)

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 8, 2020.

CREATE-X Trial: Adjuvant Capecitabine After Neoadjuvant Chemotherapy

Design	Phase III, multicenter, open-label, randomized trial
Patients	N=910 HER2(-), residual invasive breast cancer after neoadjuvant chemotherapy (containing anthracycline, taxane, or both) and surgery
Drug therapy	Capecitabine 1250 mg/m^2 PO BID days 1–14 every 21 days + standard therapy vs. placebo (standard therapy) • Duration: 6 or 8 cycles
Outcomes	5-year DFS was longer with capecitabine (74.1%) vs. placebo (67.6%), p=0.01 OS was longer with capecitabine (89.2%) vs. placebo (83.6%), p=0.01 Hand-foot syndrome was more common with capecitabine (73.4%)
Summary	The addition of adjuvant capecitabine therapy was safe and effective in prolonging DFS and OS in patients with HER2(-) breast cancer who had residual disease after surgery

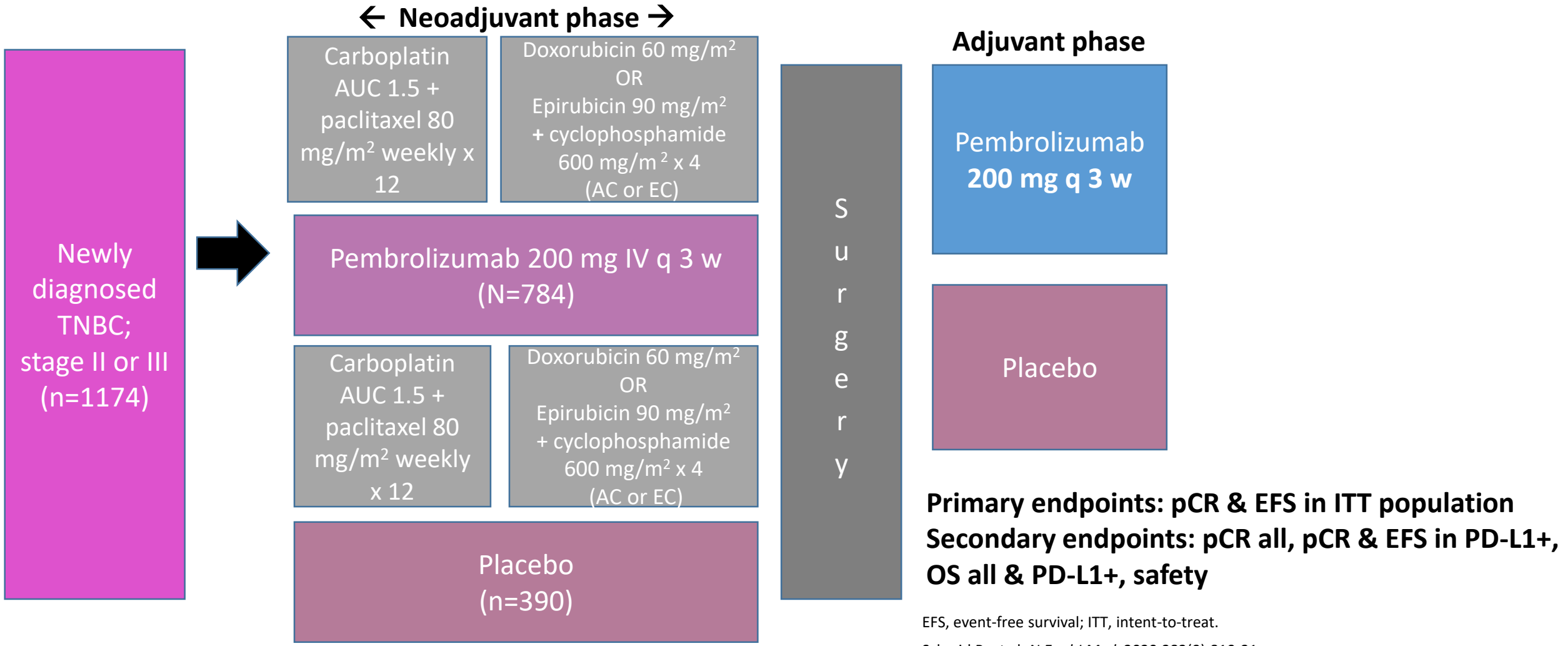
Masuda N, et al. *N Engl J Med*. 2017;376(22):2147-59.

I-SPY 2 Trial

- Ongoing, open-label, multicenter, adaptively randomized phase II platform trial for high-risk, stage II/III breast cancer patients evaluating multiple investigational arms in parallel
- Participants were randomized to receive taxane and anthracycline-based neoadjuvant chemotherapy ± pembrolizumab, followed by definitive surgery
- Primary endpoint = pCR
  - pCR in triple-negative cohort nearly tripled with addition of pembrolizumab (60% vs. 22%)
- Achieving a pCR appeared predictive of long-term outcome
  - Patients with pCR following pembrolizumab + chemotherapy had high event-free survival rates (93% at 2.8 years)
- Adverse events (AEs) included immune-related endocrinopathies
  - thyroid abnormalities (13.0%) and adrenal insufficiency (8.7%)

Nanda R, et al. *JAMA Oncol*. 2020;6(5):676-84.

Keynote-522: Benefit of Neoadjuvant Pembrolizumab

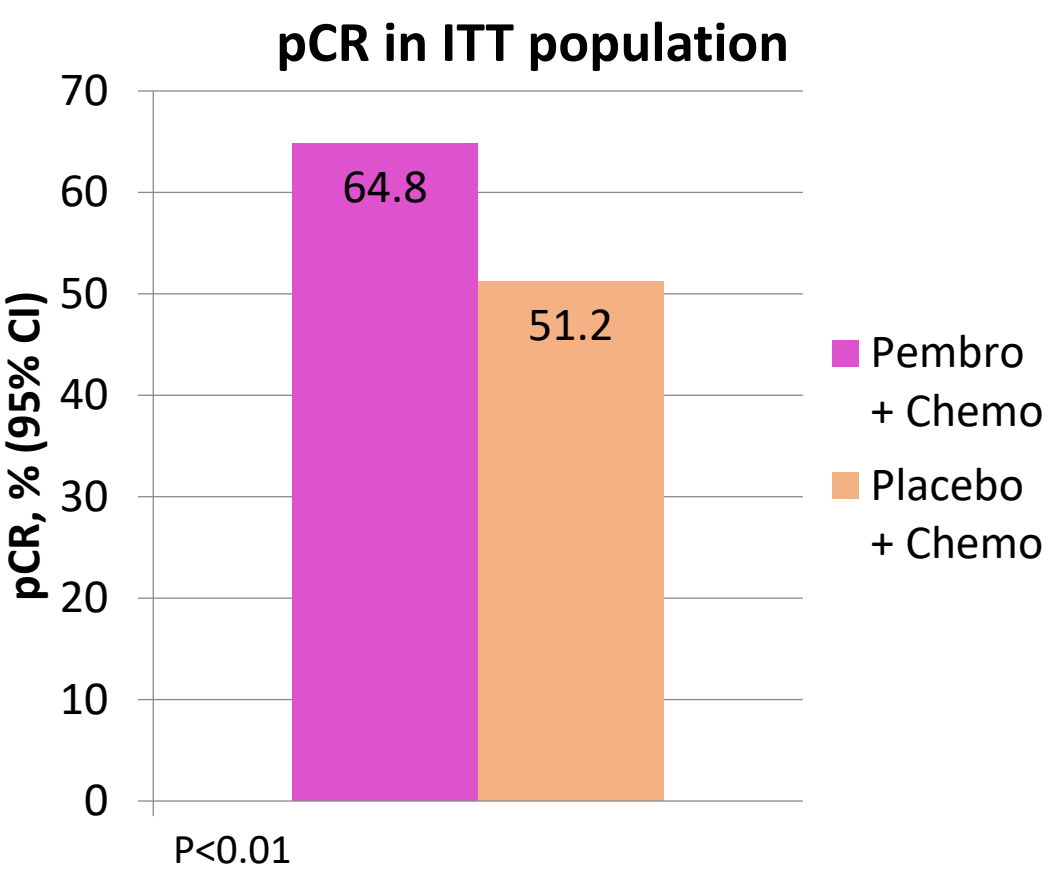


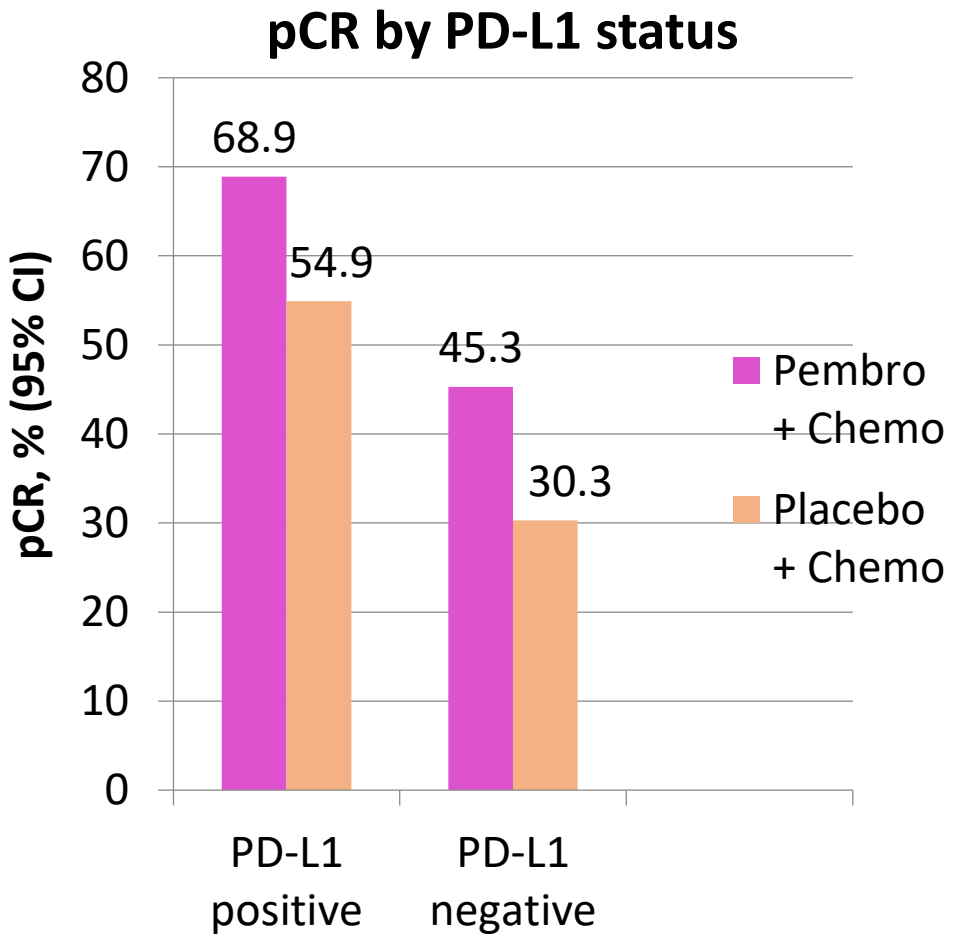
Primary endpoints: pCR & EFS in ITT population
Secondary endpoints: pCR all, pCR & EFS in PD-L1+, OS all & PD-L1+, safety

EFS, event-free survival; ITT, intent-to-treat.

Schmid P, et al. *N Engl J Med.* 2020;382(9):810-21.

Keynote-522: Results





Schmid P, et al. *N Engl J Med.* 2020;382(9):810-21.

Keynote-522 Trial

- EFS: 91.3% in pembrolizumab arm vs. 85.3% in placebo arm
- Grade ≥3 AEs: 76.8% in pembrolizumab arm vs. 72.2% in placebo arm
- FDA accepted a supplemental biologics license application (sBLA) on July 30, 2020 for pembrolizumab in early-stage TNBC supported by the results from Keynote-522
- A goal date for the FDA to make a decision about whether or not to approve new medication (PDUFA) set for March 29, 2021

BusinessWire. https://www.businesswire.com/news/home/20200730005275/en. July 30, 2020.;
Schmid P, et al. *N Engl J Med.* 2020;382(9):810-21.

IMpassion031 Trial

- Phase III trial of 333 patients with previously untreated, early stage II to III TNBC
- Randomized to received nab-paclitaxel weekly x 12, followed by dose dense AC every 2 weeks x 4 + atezolizumab vs placebo + nab-paclitaxel x 12, followed by dose dense AC every 2 weeks x 4
- After surgery, patients will continue to receive atezolizumab x 11 doses vs. placebo
- Coprimary endpoints: pCR in ITT and PD-L1+ subgroup
- Atezolizumab demonstrated a statistically significant and clinically meaningful improvement in pCR regardless of PD-L1 expression, meeting the primary endpoint of the trial
  - pCR in ITT atezolizumab 58% vs placebo 41%; p=0.0044
  - pCR in PD-L1+ atezolizumab 69% vs placebo 49%; p=0.021

Mittendorf EA, et al. www.lancet.com. Published online September 20, 2020 https://doi.org/10.1016/S0140-6736(20)31953-X.

Immunotherapy Trials in Early TNBC

Trial	Phase	Status	Intervention	Primary endpoint
SWOG S1418/BR006	III	Recruiting	Pembrolizumab x 1 year for residual invasive cancer >1 cm after NAC & surgery	iDFS
A-Brave	III	Recruiting	Avelumab as adjuvant or post-neoadjuvant treatment for high-risk TNBC	DFS & DFS in PD-L1+
NSABP B-59/GBC 96-GeparDouze	III	Recruiting	Neoadjuvant atezolizumab with NAC, followed by adjuvant atezolizumab	EFS, pCR in breast/nodes
Alexandra/IMpassion030	III	Recruiting	Adjuvant atezolizumab + chemo vs. chemo alone	iDFS, iDFS by PD-L1 status
NCT03742986 (inflammatory including TNBC)	II	Recruiting	Neoadjuvant nivolumab + paclitaxel, followed by dose-dense AC vs. placebo + NAC	pCR
NCT03546686	II	Recruiting	Nivolumab + ipilimumab + cryoablation, followed by post-op nivolumab vs. standard perioperative management for residual disease after NAC	3-year EFS

iDFS, invasive disease-free survival; NAC, neoadjuvant chemotherapy.

Current Treatment Options for mTNBC

- Sequential single-agent chemotherapy is preferred approach for most
- Combination chemotherapy can be used for patients requiring more rapid response but is associated with increased toxicity and no improvement in OS
- Patients should remain on a regimen until best response, disease progression, or significant toxicity
- Goal of therapy is palliation and prolongation of life
- NCCN recommends testing for potential biomarkers
  - BRCA 1/2 mutations (determines sensitivity to PARP inhibitors)
    - Up to 20% of patients with TNBC harbor a BRCA mutation (particularly in BRCA1) vs. only ~5% of patients in all breast cancers
  - PD-L1 expression (determines sensitivity to ICIs)
    - Expression on tumor-infiltrating immune cells, positive if >1%

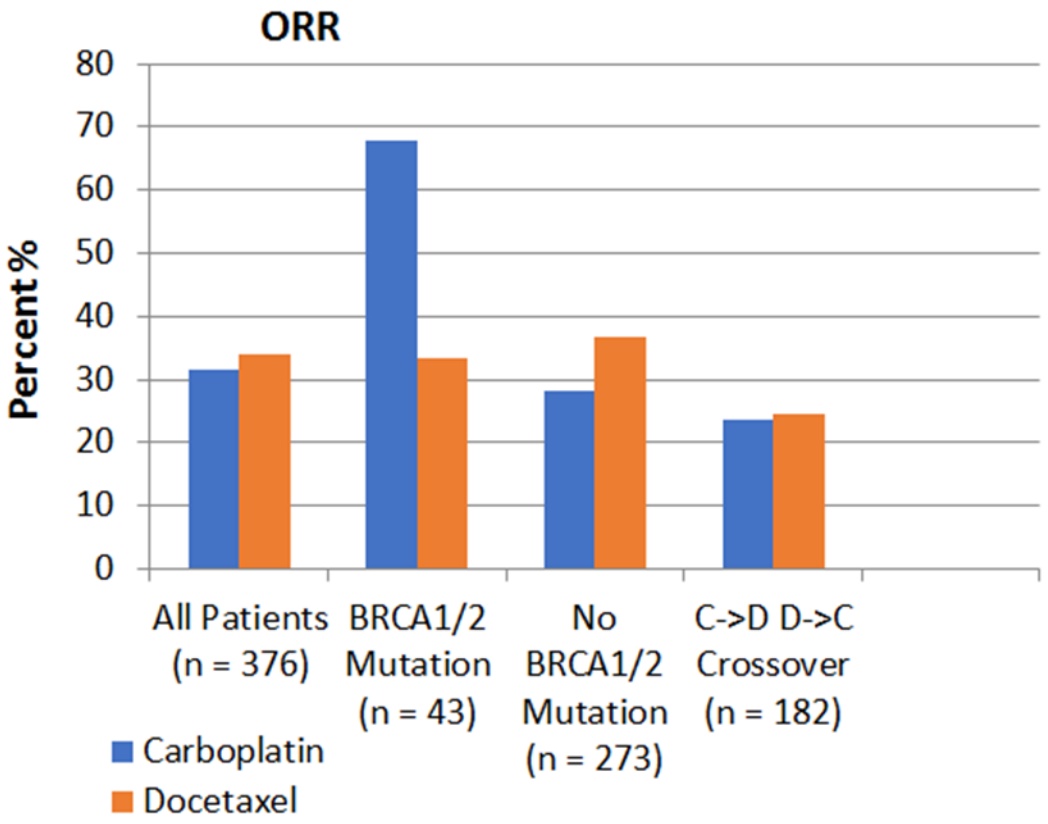
National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 8, 2020.

Treatment Options for mTNBC

Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Anthracycline: doxorubicin, liposomal doxorubicin • Taxanes: paclitaxel • Anti-metabolites: capecitabine, gemcitabine • Microtubule inhibitors: eribulin, vinorelbine	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone • Sacituzumab govitecan* *after progression on at least 2 prior lines of therapy	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/methotrexate, fluorouracil) • GT (gemcitabine/paclitaxel) • Docetaxel/capecitabine • Gemcitabine + carboplatin • Paclitaxel + bevacizumab • Carboplatin + paclitaxel or albumin-bound paclitaxel
If PD-L1 positive, atezolizumab + albumin-bound paclitaxel		
If BRCA 1/2 *mutated,* • PARP inhibitor: olaparib or talazoparib • Platinum: cisplatin or carboplatin		

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 8, 2020.

TNT Trial: Carboplatin vs. Docetaxel in Advanced TNBC or BRCA 1/2+ Breast Cancer



Significantly improved response to carboplatin in BRCA 1/2 patients (ORR 68% vs. 33%)

Median PFS	Carboplatin	Docetaxel	P-value
All patients	3.1 months	4.4 months	0.4
BRCA *1/2* patients	6.8 months	4.4 months	0.002

- PFS favored carboplatin in the BRCA 1/2 group
- No OS benefit found
  - carboplatin = 12.8 months and docetaxel = 12 months
- More grade 3/4 AEs in the docetaxel group

Conclusion: **Data from this trial confirm that carboplatin is active in BRCA 1/2-mutated advanced breast cancer**

Carboplatin is a viable option for treatment of patients with breast cancer with BRCA 1/2 mutation

ORR, overall response rate.

EMBRACE Trial: Eribulin vs. TPC for Heavily Pretreated MBC

Description: 762 patients who had received 2–5 prior chemo regimens with >2 for advanced disease randomized 2:1 to eribulin (n=508) vs. TPC (n=254)

Efficacy

Primary endpoint: OS

- OS was significantly improved in women assigned to eribulin (median, 13.1 months) compared with TPC (10.6 months); P=0.041
- 1-year survival rate was 53.9% with eribulin and 43.7% with TPC

Safety

- Most common AEs in both groups
  - Asthenia/fatigue: 54% eribulin vs. 40% TPC
  - Neutropenia: 52% eribulin vs. 30% TPC
- Febrile neutropenia occurred at low incidence
  - 5% eribulin and 2% TPC
- Grade 3/4 AEs more common with eribulin
  - Leukopenia (14%)
  - Peripheral neuropathy (8%): most common AE leading to discontinuation of eribulin (occurring in 5%)

This study established a potential new standard treatment for women with heavily pretreated MBC for whom there was previously no chemotherapy treatment with proven survival benefit

MBC, metastatic breast cancer; TPC, treatment of physician's choice.

Cortes J, et al. *Lancet*. 2011;377(9769):914-23.

Study 301: Eribulin vs. Capecitabine in MBC

Description	• Patients who received prior anthracycline and taxane were randomized to eribulin (n=544) or capecitabine (n=546) as 1st-, 2nd-, or 3rd-line therapy for locally advanced or MBC
Endpoints	• Co-primary: OS and PFS • Secondary: ORR; DOR; 1-, 2-, and 3-year survival; safety; QOL
Efficacy	• Median OS was 15.9 months for eribulin vs. 14.5 months for capecitabine; P=0.056 • Median PFS was 4.1 months for eribulin vs. 4.2 months for capecitabine; P=0.30

Safety	• Most common grade 3/4 AEs
	  • Eribulin: neutropenia (d/c in 1.7%), leukopenia, asthenia, and peripheral neuropathy
	  • Capecitabine: hand-foot syndrome (d/c in 2.2%), dyspnea (d/c in 1.1%), diarrhea, neutropenia, and asthenia
	• Febrile neutropenia occurred with eribulin (2%) and capecitabine (0.9%)
	• Serious AEs: 17.5% in eribulin vs. 21.1% in capecitabine
	• Fatal AEs (treatment related): 5 patients in eribulin and 4 in capecitabine

Conclusion	• Eribulin was NOT superior to capecitabine in either OS or PFS

DOR, duration of response; QOL, quality of life.

Kaufman PA, et al. *J Clin Oncol*. 2015;33(6):594-601.

Pooled Analysis of EMBRACE and Study 301 Trials

- Requested by European Medicines Agency (EMA) for analysis of trial data by HER2 status
- Evaluated a total of 1864 patients from phase III trials
  - 1062 received eribulin and 802 received control (capecitabine or TPC)
- Median OS was 15.2 months with eribulin vs. 12.8 months with control
  - HR 0.85 (95% CI, 0.77–0.95); P=0.003
- OS favored eribulin in all subgroups assessed, particularly in HER2-negative group
- In patients with TNBC, median OS was 4.7 months longer in the eribulin group
  - 12.9 months vs. 8.2 months; HR 0.74; P=0.006

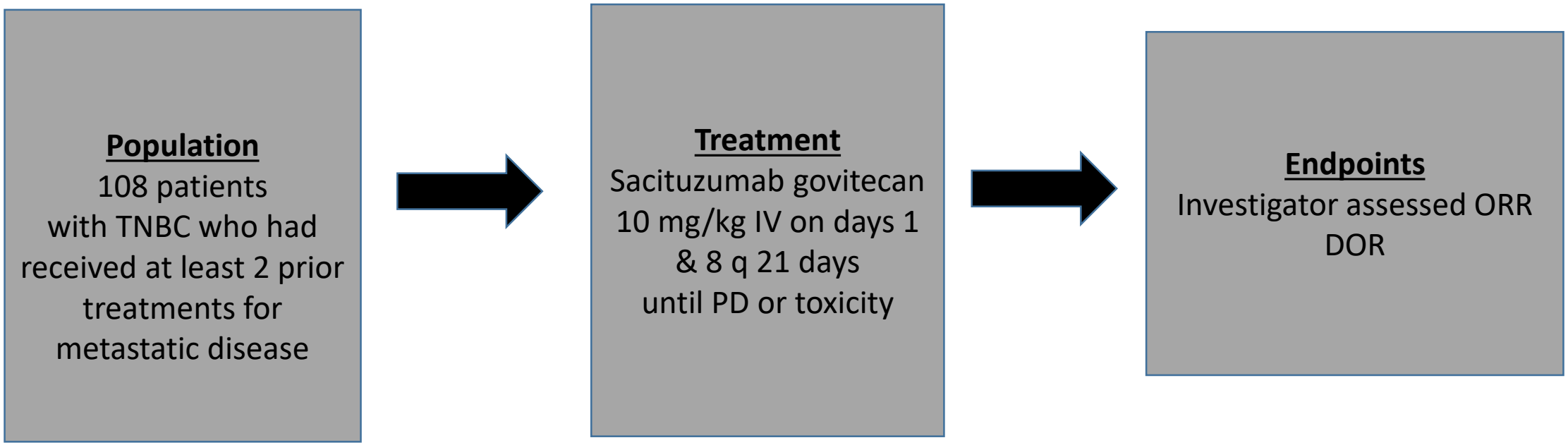
Twelves C, et al. *Breast Cancer Res Treat*. 2014;148(3):553-61.

Sacituzumab Govitecan-hziy

- Trop-2–directed antibody and topoisomerase inhibitor conjugate
- 3 components
  - Humanized monoclonal antibody hRS7 IgG1K (sacituzumab): binds to Trop-2
  - SN-38: topoisomerase I inhibitor
  - Hydrolysable linker (CL2A): links monoclonal antibody to SN-38
- Contains 7–8 molecules of drug SN-38 per antibody molecule
- Mechanism of action:
  - Sacituzumab binds to Trop-2–expressing cancer cells and is internalized with the release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single-stranded DNA breaks. DNA damage leads to apoptosis and cell death.

Trodelvy (sacituzumab govitecan-hziy) [prescribing information]. 2020.

IMMU-132-01 — Phase I/II Trial



IV, intravenous; PD, progressive disease.

Bardia A, et al. *N Engl J Med.* 2019;380(8):741-51.

IMMU-132-01 Demographics

Characteristics	Patients (n=108)
Median age, years (range)	55 (31–80)
White, %	75.9
ECOG performance status at study entry, % 0 1	 28.7 71.3
Visceral disease, %	76.9
Metastases, % Hepatic Lung/pleura Other	 41.7 56.5 6.5
Number of prior systemic therapies in metastatic setting, median (range) • Prior taxane (in neo(adjuvant) or metastatic setting) • Prior anthracycline (in neo(adjuvant) or metastatic setting)	3 (2–10) 98.1% 86.1%
Prior therapies in metastatic setting: platinum (68.5%), gemcitabine (54.6%), capecitabine (51.9%), eribulin (45.4%), vinorelbine (15.7%), cyclophosphamide (18.5%)	

Bardia A, et al. *N Engl J Med.* 2019;380(8):741-51.

IMMU-132-01 Efficacy

Endpoints	Sacituzumab govitecan (n=108)
Overall response rate	
ORR (95% CI)	33.3% (24.6–43.1)
Complete response	2.8%
Partial response	30.6%
Response duration	
Number of responders	36
Median, months (95% CI)	7.7 (4.9–10.8)

- **Received accelerated approval on April 22, 2020 for the treatment of metastatic TNBC in patients who have received more than 2 lines of therapy in the metastatic setting**
- The confirmatory phase III ASCENT study, which compared Sacituzumab govitecan to physician's choice chemotherapy in mTNBC, was stopped early by IDSMC for evidence of efficacy

IDSMC, independent data safety monitoring committee.

Bardia A, et al. *N Engl J Med.* 2019;380(8):741-51.

Adverse Reactions

- Serious adverse reactions reported in 32%
- Most common serious ADRs
  - Febrile neutropenia, vomiting, nausea, dyspnea, diarrhea
- Dose interruption: 44%
  - Neutropenia: 33%
- Dose reduction: 33%
  - One dose reduction: 24%
  - Two dose reductions: 9%
- Discontinuation: 3%
  - Anaphylaxis, anorexia/fatigue, headache

AE	Any grade, %	Grade 3/4, %
Nausea	67	6
Neutropenia	64	42
Diarrhea	62	8
Fatigue	55	8
Anemia	50	11
Vomiting	49	6
Alopecia	36	0
Constipation	34	1
Rash	28	2
Decreased appetite	30	0

ADR, adverse drug reaction.

Bardia A, et al. *N Engl J Med.* 2019;380(8):741-51.

Sacituzumab Dosing/Administration

- Dosed at 10 mg/kg IV on days 1 and 8 of 21-day cycle
- Premedicate with acetaminophen and H1 and H2 antagonists (such as diphenhydramine and famotidine) prior to infusion for prevention of infusion reactions
- Premedicate with 2–3-drug regimen of dexamethasone and 5-HT3 antagonist for emesis prevention (can add NK-1 antagonist as needed)
- Protect infusion bag from light
- Administer first infusion over 3 hours
- Administer subsequent infusions over 1–2 hours if prior infusion was tolerated
- Observe patients during the infusion and for at least 30 minutes after for signs or symptoms of infusion-related reactions

Trodelvy (sacituzumab govitecan-hziy) [prescribing information]. 2020.

Atezolizumab + Nab-Paclitaxel in mTNBC IMpassion130: Study Design

Metastatic or unresectable breast cancer
- Triple-negative
- No prior treatment in metastatic setting
- ≥12 months from curative chemotherapy/radiation

→

Atezolizumab 840 mg IV on days 1 & 15 + nab-paclitaxel 100 mg/m^2 IV on days 1, 8, & 15 q 28 days (n=451)

Placebo + nab-paclitaxel 100 mg/m^2 IV on days 1, 8, & 15 q 28 days (n=451)

→

Treatment until PD or unacceptable toxicity

Co-primary endpoints: PFS and OS
Secondary endpoints: response rates, safety

Schmid P. *N Engl J Med*. 2018;379(22):2108-21.; Schmid P, et al. *J Clin Oncol.* 2019;37(suppl_15):1003.

IMpassion130

Outcome	Atezolizumab	Placebo	HR (95% CI)	P-value
Median PFS, months				
All patients	7.2	5.5	0.8 (0.69–0.92)	0.002
PD-L1–positive patients	7.5	5	0.62 (0.49–0.78)	<0.001
Median OS, months				
All patients	21	18.7	0.86 (0.72–1.02)	0.077
PD-L1–positive patients	25	18	0.71 (0.54–0.93)	------
AEs leading to discontinuation, %	15.9	8.2	------	------

- Atezolizumab added to nab-paclitaxel improved PFS in ITT and PD-L1–positive subgroups, but not in the PD-L1–negative group
- OS in all patients not statistically significantly different
- 2nd interim analysis of PD-L1–positive patients produced 7-month benefit in OS

March 2019: atezolizumab + nab-paclitaxel approved for PD-L1–positive mTNBC patients

Schmid P. *N Engl J Med*. 2018;379(22):2108-21.; Schmid P, et al. *J Clin Oncol.* 2019;37(suppl_15):1003.

mTNBC, metastatic triple-negative breast cancer.

IMpassion130 Conclusions

- First phase III trial to show benefit of immunotherapy in TNBC
- Updated OS analysis demonstrated a 7-month improvement in the PD-L1–positive group
  - Median OS for PD-L1–positive subgroup: 25.0 vs. 18.0 months (HR, 0.71)
- Safety profile of atezolizumab + nab-paclitaxel was consistent with the known toxicities of each agent
- AEs that led to the discontinuation of any agent occurred in 15.9% of patients who received atezolizumab + nab-paclitaxel vs. 8.2% of those who received placebo + nab-paclitaxel
- Grade 3/4 ADRs of special interest were higher in atezolizumab arm (7.5% vs. 4.3% placebo)
  - Immune-related hypothyroidism: 17.3% in atezolizumab arm vs. 4.3% in placebo
  - Pneumonitis: 3.1% in atezolizumab arm vs. 0.2% in placebo

Schmid P. *N Engl J Med*. 2018;379(22):2108-21.; Schmid P, et al. *J Clin Oncol.* 2019;37(suppl_15):1003.

IMpassion131 Trial: Atezolizumab + Paclitaxel

- Phase III trial that evaluated atezolizumab + paclitaxel vs. placebo + paclitaxel for the initial (first-line) treatment of mTNBC
- Trial did not meet statistical significance on its primary endpoint of PFS in the PD-L1–positive population
- Interim OS results favored paclitaxel + placebo over paclitaxel + atezolizumab in both the PD-L1–positive population and total population (but the study was not powered for the secondary endpoint and data were immature at time of analysis)
- OS follow-up is planned to continue until final analysis

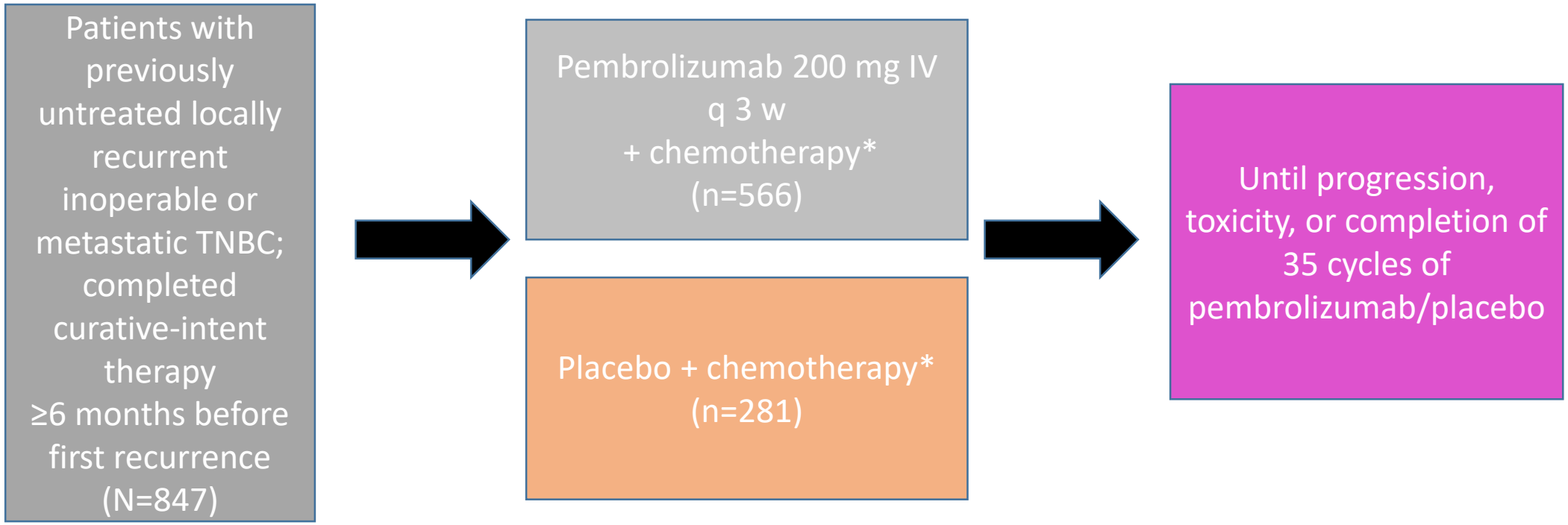
United States Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-issues-alert-about-efficacy-and-potential-safety-concerns-atezolizumab-combination-paclitaxel?utm_medium=email&utm_source=govdelivery.

IMpassion132 Trial: Atezolizumab + Capecitabine or Gemcitabine/Carboplatin

- Placebo-controlled, randomized phase III trial evaluating atezolizumab + first-line chemotherapy (capecitabine or gemcitabine/carboplatin) for inoperable, locally advanced/mTNBC
- Stratification factors: visceral metastases, tumor immune cell PD-L1 status, and selected chemotherapy
- Randomized to atezolizumab 1200 mg or placebo every 3 weeks with the chosen chemotherapy
  - Continued until progression, unacceptable toxicity, or withdrawal
- The primary endpoint is OS
- Trial is enrolling with expected completion January 2023

Cortes J, et al. *Future Oncol*. 2019;15(17):1951-61.

Keynote-355: Trial Design



Primary endpoints: PFS and OS in ITT, PD-L1 in CPS ≥10, PD-L1 in CPS ≥1

Secondary endpoints: ORR, DOR, DCR, safety

**Investigator's choice of chemotherapy was permitted:*
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, & 15 of 28-day cycle
Paclitaxel 90 mg/m^2 IV on days 1, 8, & 15 of 28-day cycle
Gemcitabine 1000 mg/m^2 + carboplatin AUC 2 on days 1 & 8 of 21-day cycle

Cortes J, et al. *J Clin Oncol*. 36(5_suppl):TPS18.; Cortes J, et al. *J Clin Oncol.* 38(15_suppl):1000.

Keynote-355 Summary

- Pembrolizumab + chemotherapy significantly improved PFS compared with chemotherapy alone as first-line therapy in patients with mTNBC (PD-L1 CPS ≥10)
  - PFS: 9.7 months vs. 5.6 months; HR 0.65 (95% CI, 0.49–0.86), p=0.0012
- PFS improvement reported across patient subsets
- Safety outcomes were consistent with previous data
- Grade 3–5 treatment-related AE rates
  - 68.1% with pembro + chemo (2 deaths) vs. 66.9% with chemo (0 deaths)
- Rates of grade 3/4 immune-mediated AEs and infusion reactions were 5.5% vs. 0%
- Investigators suggest that the addition of pembrolizumab to standard chemotherapy may have a role for the first-line treatment of mTNBC
- FDA accepted an sBLA for pembrolizumab for mTNBC on July 30, 2020
  - PDUFA date is set for November 28, 2020

BusinessWire. https://www.businesswire.com/news/home/20200730005275/en. July 30, 2020.; Cortes J, et al. *J Clin Oncol*. 36(5_suppl):TPS18.; Cortes J, et al. *J Clin Oncol.* 38(15_suppl):1000.

Enhance-1 Trial: Eribulin + Pembrolizumab for mTNBC

- Open-label, single-arm, multicenter, phase Ib/2 study of patients with mTNBC who had previously received 0–2 systemic therapies for metastatic disease (stratified by number of prior lines of therapy)
- Eribulin 1.4 mg/m^2 IV on days 1 and 8 + pembrolizumab 200 mg IV on day 1 of a 21-day cycle
- Primary endpoint: ORR
- Secondary endpoints: PFS, OS, DOR, and CBR overall and by PD-L1 status
- Presented at ASCO 2020
  - 167 patients enrolled
  - The combination of eribulin + pembrolizumab resulted in an **overall** ORR of 23.4% (95% CI, 17.2–30.5)
  - Overall median PFS was 4.1 months (95% CI, 3.5–4.2)
  - Overall median OS was 16.1 months (95% CI, 13.3–18.5)
  - The combination was well tolerated

ASCO, American Society of Clinical Oncology; CBR, clinical benefit rate.

Eisai. Eisai.mediaroom.com/2020-05-29-Eisai-Announces-Updated-Results-of-ENHANCE-1-a-Phase-1b-2-Trial-Investigating-HALAVEN-R-eribulin-mesylate-plus-KEYTRUDA-R-pembrolizumab-in-Patients-with-Metastatic-Triple-Negative-Breast-Cancer-at-ASCO-2020. May 29, 2020.; Enhance-1. American Society of Clinical Oncology's ASCO 2020 Virtual Scientific Program from May 29-31 (Abstract #1015 / Poster #100).

Enhance-1: Efficacy and Safety Results

Cohort A (0 lines of prior therapy)			Cohort B (1–2 prior lines of therapy)	
	PD-L1+	PD-L1–	PD-L1+	PD-L1–
ORR	34.5%	16.1%	24.4%	18.2%
PFS	6.1 months	3.5 months	4.1 months	3.9 months
OS	**21 months**	**15.2 months**	**14 months**	**15.5 months**
DOR	8.3 months	15.2 months	8.2 months	18.6 months

- Most common AEs: fatigue (66%), nausea (57%), neuropathy (41%), alopecia (40%), and constipation (37%)
- The most common possibly immune-related TEAEs for pembrolizumab were hypothyroidism (18%), pneumonitis (11%), hyperthyroidism (8%), and infusion-related reaction (3%)

TEAE, treatment-emergent adverse reactions.

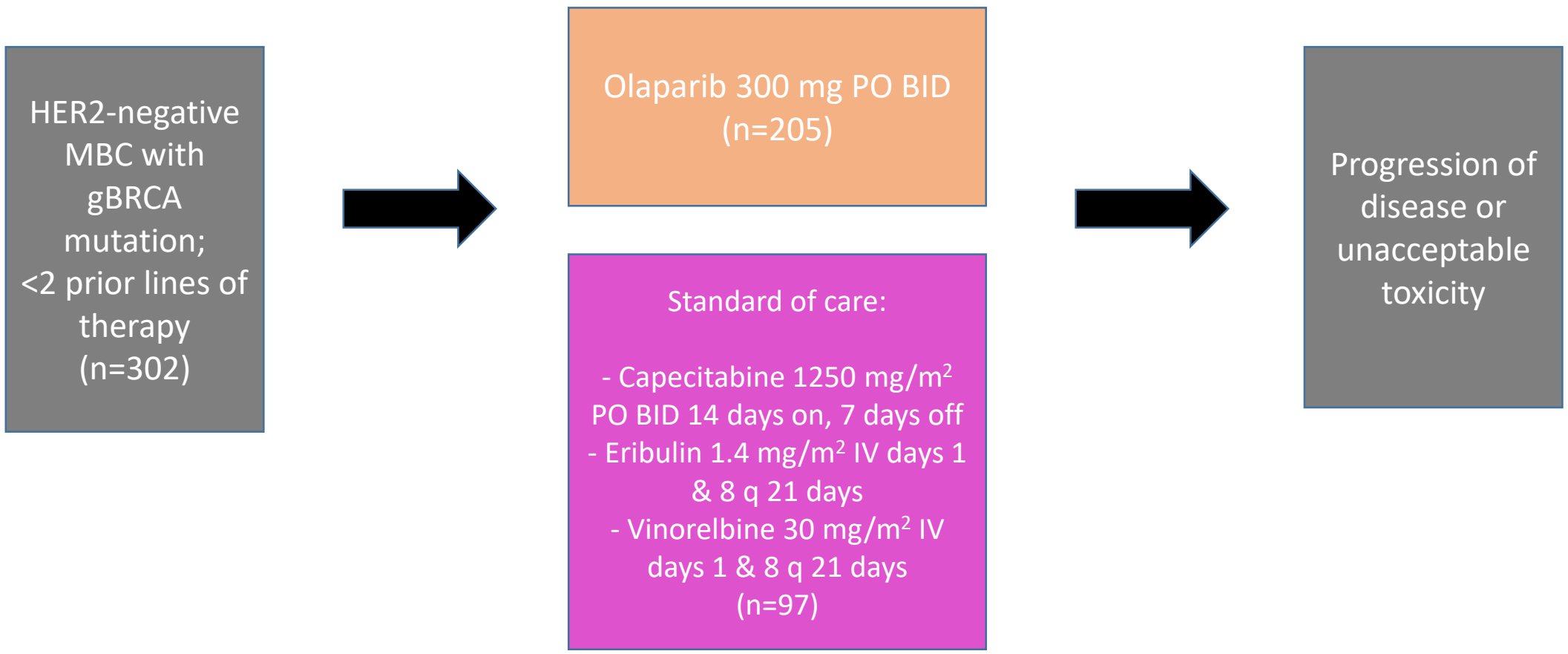
Eisai. Eisai.mediaroom.com/2020-05-29-Eisai-Announces-Updated-Results-of-ENHANCE-1-a-Phase-1b-2-Trial-Investigating-HALAVEN-R-eribulin-mesylate-plus-KEYTRUDA-R-pembrolizumab-in-Patients-with-Metastatic-Triple-Negative-Breast-Cancer-at-ASCO-2020. May 29, 2020.; Enhance-1. American Society of Clinical Oncology's ASCO 2020 Virtual Scientific Program from May 29-31 (Abstract #1015 / Poster #100).

Ongoing Clinical Trials of ICI + Chemotherapy

- NIMBUS trial: nivolumab + ipilimumab in metastatic hypermutated HER2-negative breast cancer
  - Open-label, single-arm, multicenter, phase II trial currently recruiting
  - Primary endpoint: ORR
  - Secondary endpoints: ORR (according to immune-related response criteria, CBR, PFS, OS)
- NCT03414684: randomized phase II trial of carboplatin with or without nivolumab in first- or second-line mTNBC
  - Open-label, multicenter trial enrolling 132 patients to receive carboplatin every 3 weeks with or without nivolumab
  - Primary endpoint: PFS
  - Secondary endpoints: ORR, OS, CBR, DOR, TTR, efficacy in BRCA carriers and incidence rate of each toxicity for overall and crossover patients

U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03414684.;
U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03789110.

OlympiAD: Olaparib vs. Chemotherapy in HER2-Negative MBC



Robson ME, et al. *N Engl J Med.* 2017;377(6):523-33; Robson ME, et al. *Ann Oncol.* 2019;30(4):558-66.

OlympiAD: Patient Characteristics

Characteristic	Olaparib (n=205)	Standard chemotherapy (n=97)
Median age (range)	44 (22–76)	45 (24–68)
Male sex	5 (2.4)	2 (2.1)
Race or ethnic group White Asian Other	 134 (65.4) 66 (32.2) 5 (2.4)	 63 (64.9) 28 (28.9) 6 (6.2)
Hormone receptor positive	103 (50.2)	49 (50.5)
Triple negative	102 (49.8)	48 (49.5)
New metastatic breast cancer	26 (12.7)	12 (12.4)
Previous chemo for metastatic disease	146 (71.2)	69 (71.1)
Previous platinum for breast cancer	60 (29.3)	26 (26.8)
Bone-only disease	16 (7.8)	6 (6.2)

Robson ME, et al. *N Engl J Med.* 2017;377(6):523-33; Robson ME, et al. *Ann Oncol.* 2019;30(4):558-66.

OlympiAD: Results

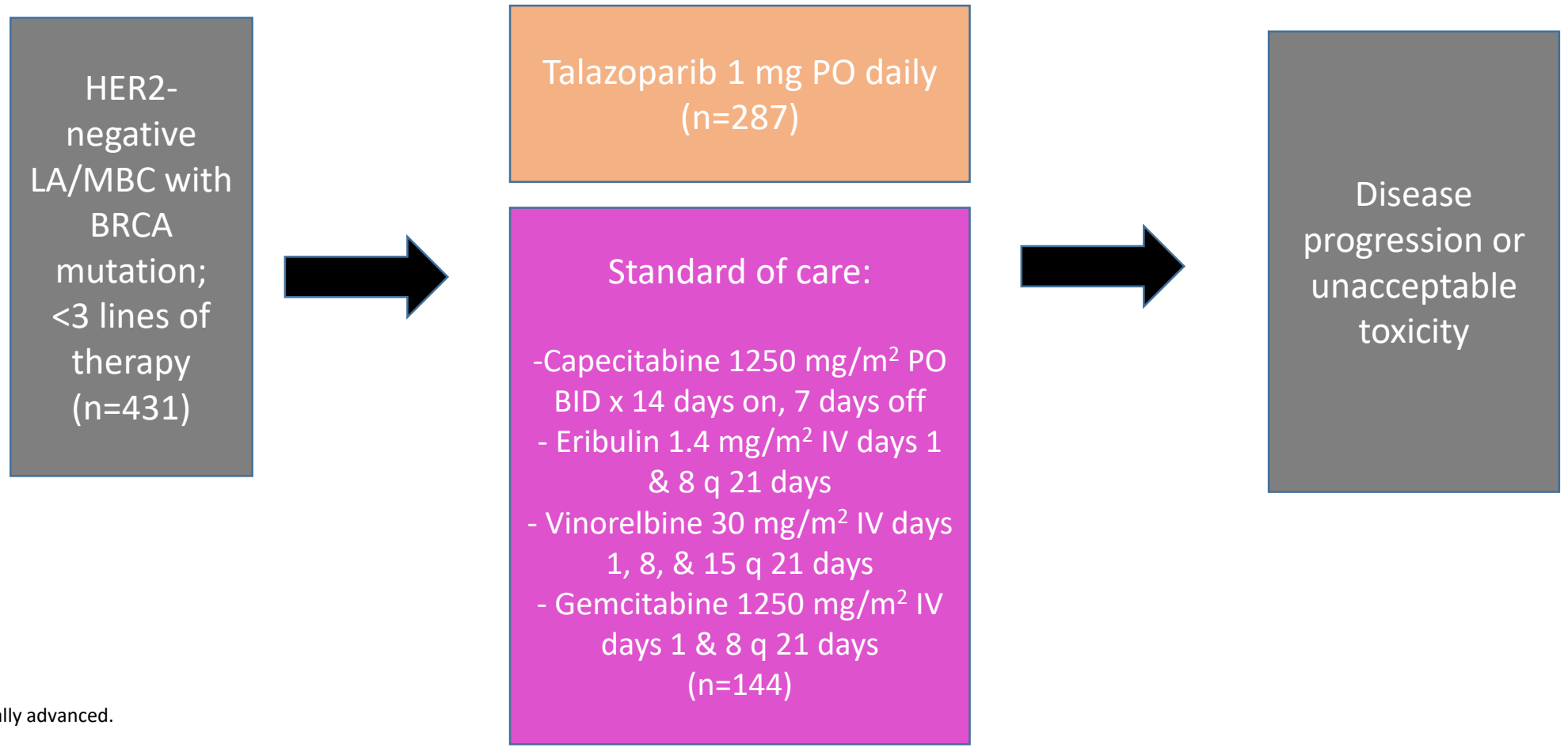
	Olaparib	TPC
Median PFS, months HR 0.58 (95% CI, 0.43–0.8); P<0.001	7 months	4.2 months
Median OS, months HR 0.9 (95% CI, 0.66–1.23); P=0.513 (NS)	19.3 months	17.1 months
Change in QOL (QLQ-C30 scale); P=0.0035	3.9 (SD, 1.2)	–3.6 (SD, 2.2)

- **PFS was significantly higher in the olaparib arm**
- Difference in OS with olaparib compared with TPC was NOT statistically significant
  - Subgroups: no difference in ER/PR+, TNBC, prior chemotherapy, or prior/no prior platinum
- No prior chemotherapy for MBC (1st line): OS 22.6 vs. 14.7 months; HR 0.51 (P=0.02)

NS, not significant; QOL, quality of life; SD, standard deviation.

Robson ME, et al. *N Engl J Med.* 2017;377(6):523-33; Robson ME, et al. *Ann Oncol.* 2019;30:558-66.

EMBRACA: Talazoparib vs. Chemotherapy in Advanced BRCA1/2-Positive, HER2-Negative Breast Cancer



LA, locally advanced.

Litton JK, et al. *N Engl J Med*. 2018;379(8):753-63.

EMBRACA: Patient Characteristics

Characteristic	Talazoparib (N=287)	Standard therapy (N=144)
Median age (range)	45 (27–84)	50 (24–88)
Male sex, %	1.4	2.1
Hormone receptor positive	157 (54.7)	84 (58.3)
Triple negative	130 (45.3)	60 (41.7)
Visceral disease	200 (69.7)	103 (71.5)
Previous adjuvant/neoadjuvant therapy	238 (82.9)	121 (84)
Previous platinum for breast cancer	46 (16)	30 (20.8)
Previous cytotoxic regimens for metastatic breast cancer 0 1 2 3	 111 (38.7) 107 (37.3) 57 (19.9) 12 (4.2)	 54 (37.5) 54 (37.5) 28 (19.4) 8 (5.6)

Litton JK, et al. *N Engl J Med*. 2018;379(8):753-63.

EMBRACA Trial: Results

	Talazoparib (n=287)	Standard chemotherapy (n=144)
Median PFS, months (95% CI) HR 0.54 (95% CI, 0.41–0.71); P<0.001	**8.6 months (7.2–9.3)**	**5.6 months (4.2–6.7)**
Median time to deterioration in QOL, months HR 0.38 (95% CI, 0.26–0.55); P significant	**26.3 months**	**6.7 months**
Median OS, months (95% CI) HR 0.85 (95% CI, 0.67-1.07); P=0.17	19.3 months (16.6–22.5)	19.5 months (17.4–22.4)

- **Among patients with advanced breast cancer and a germline BRCA1/2 mutation, single-agent talazoparib provided a significant PFS benefit over standard chemotherapy**
- **Improvements in patient-reported outcomes indicated that talazoparib had a good AE profile**

Litton JK, et al. *N Engl J Med*.2018;379(8):753-63; Litton JK, et al. Presented at: the 2020 AACR virtual annual meeting of the American Association for Cancer Research; April 27-28, 2020. Abstract CT071.

PARP Inhibitor Monitoring

- CBC monitoring
  - CBC prior and monthly thereafter (olaparib)
  - CBC monthly and as clinically indicated (talazoparib)
- Renal function
  - Olaparib
    - CrCl 31–50 mL/min: 200 mg twice daily
  - Talazoparib
    - CrCl 30–59 mL/min: 0.75 mg daily
    - CrCl 15–29 mL/min: 0.5 mg daily
- Drug interactions
  - Olaparib: 3A4 inhibitors
    - Moderate: 150 mg twice daily
    - Strong: 100 mg twice daily
  - Talazoparib: P-gp inhibitors (amiodarone, carvedilol, verapamil, itraconazole)
    - Start at 0.75 mg daily

CBC, complete blood count; P-gp, P-glycoprotein.

Lynparza [prescribing information]. 2018.

PARP Inhibitor Counseling

- Nausea/vomiting
  - Median time to onset of nausea 4 days for olaparib
  - Median duration of nausea ~34 days for olaparib
  - Taking with food decreases nausea
  - Anti-emetic prophylaxis
    - *Consider patient's prior history*
    - Olaparib: moderate emetogenicity; consider routine 5HT-3 antagonist
    - Talazoparib: low emetogenicity; PRN 5HT-3 antagonist
- Fatigue
  - Multifactorial
  - Monitor for s/sx of anemia, CBC
  - Hydration, routine exercise
- Myelosuppression
  - If hematological toxicities occur, hold PARP inhibitor and monitor CBC weekly until grade 1, restart at reduced dose
  - If hematological profile has not recovered to grade 1 or less after 4 weeks, refer to hematologist
  - Permanently d/c if MDS/AML confirmed
- Diarrhea: supportive care
  - Appropriate utilization of loperamide, hydration, BRAT diet

BRAT, bananas, rice, applesauce, toast; MDS/AML, myelodysplastic syndrome/acute myeloid leukemia; PRN, as needed.

Lynparza [prescribing information]. 2018.; Robson ME, et al. *Ann Oncol*. 2019;30:558-66.

MEDIOLA Trial: Durvalumab + Olaparib

- Multicenter, open-label, phase I/II, basket trial of durvalumab and olaparib in solid tumors (containing a germline BRCA-mutated breast cancer cohort of 34 patients)
- Breast cancer cohort was HER2-negative not receiving more than 2 lines of chemotherapy in metastatic setting
- Olaparib 300 mg PO BID x 4 weeks, followed by the combo of olaparib with durvalumab 1500 mg IV every 4 weeks until disease progression
- Primary endpoint: safety and tolerability, as well as 12-week DCR
- 11 (32%) patients experienced grade ≥3 AEs and 2 (9%) patients discontinued due to AEs
  - Most common: anemia (12%), neutropenia (9%), and pancreatitis (6%)
- Primary efficacy endpoint: 24/30 (80%; 90% CI, 64.3–90.9) had disease control at 12 weeks
- ORR at 12 weeks was 63.3% (90% CI, 48.9–80.1) and median OS (at follow-up of 19.8 months) was 21.5 months (95% CI, 16.2–25.7)
  - Similar to those reported in OlympiAD (60% & 19.3 months)
- At a median follow-up of 6.7 months, median PFS was 8.2 months (95% CI, 4.6–11.8)
- Median PFS in TNBC subgroup was 4.9 months

DCR, disease control rate.

Domchek SM, et al. Presented at San Antonio Breast Cancer Symposium; December 5-7, 2018; San Antonio, TX. Abstract PD5-04; Domchek SM, et al. *Lancet Oncol*. 2020; 21(9):1155-64.

Topacio/Keynote-162 Trial: Niraparib + Pembrolizumab

- Open-label, single-arm, phase II study enrolled 55 patients with advanced or mTNBC irrespective of BRCA mutation status or PD-L1 expression
- Niraparib 200 mg PO once daily + pembrolizumab 200 mg IV on day 1 of each 21-day cycle
- Primary endpoint was ORR and secondary endpoints were safety, DCR, DOR, PFS, and OS
- Combination niraparib + pembrolizumab achieved an ORR of 21% (90% CI, 12%–33%) and DCR of 49% (90% CI, 36%–62%)
  - Median DOR not yet reached
- Combination niraparib + pembrolizumab provides promising antitumor activity in mTNBC patients with numerically higher response rates in those with tumor BRCA mutations
- The combination therapy had a tolerable safety profile, warranting further investigation

Vinayak S, et al. *JAMA Oncol*. 2019;5(8):1132-40.

Immunotherapy with Targeted Agents: AKT Inhibitors — Ipatasertib

- **LOTUS trial**
  - Phase II, randomized, double-blind, placebo-controlled for first-line treatment of locally advanced or mTNBC
  - Patients received paclitaxel 80 mg/m^2 IV days 1, 8, and 15 ± ipatasertib 400 mg PO days 1–21 of 28-day cycle
  - Co-primary endpoints: PFS in ITT and PFS in PTEN-low group
  - Median PFS
    - ITT: 6.2 months (95% CI, 3.8–9) with ipatasertib vs. 4.9 months (95% CI, 3.6–5.4) with placebo
    - PTEN-low tumors: 6.2 months (95% CI, 3.6–9.1) with ipatasertib vs. 3.7 months (95% CI, 1.9–7.3) with placebo
- **ESMO 2020, final OS data**
  - Median OS
    - ITT population: 25.8 months in ipatasertib + paclitaxel arm vs. 16.9 months in placebo arm (HR 0.81; 95% CI, 0.53–1.23)
    - PTEN-low: 23.1 vs. 15.8 months in ipatasertib + paclitaxel vs. placebo
  - Overall survival
    - PIK3CA/AKT1/PTEN-altered: 25.8 vs. 22.1 months in ipatasertib arm vs. placebo
    - OS difference in patients younger than 50 years was 35.2 months with ipatasertib + paclitaxel vs. 15.1 months with placebo + paclitaxel (HR 0.41; 95% CI, 0.20–0.85)
- **IPATunity130 trial -** confirmatory trial for LOTUS; phase III randomized trial; cohort A = TNBC
  - Patients randomized to paclitaxel 80 mg/m^2 IV days 1, 8, and 15 ± ipatasertib 400 mg PO daily days 1–21 of 28-day cycle
  - The primary endpoint is investigator-assessed PFS and secondary endpoints include OS, ORR, DOR,QOL, and safety
  - Trial is active and recruiting

Dent R, et al. ESMO Breast Cancer Virtual 2020; May 23-24, 2020.; Dent R, et al. *J Clin Oncol.* 2018;36(15_suppl):1008.; Kim SB, et al. *Lancet Oncol.* 2017;18(10):1360-72.

Immunotherapy with Targeted Agents: AKT Inhibitors — Capivasertib

- **PAKT trial**
  - Double-blind, placebo-controlled, randomized phase II trial in first-line mTNBC
  - 140 patients assigned to paclitaxel 90 mg/m^2 IV days 1, 8, and 15 + capivasertib 400 mg PO BID or placebo (days 2–5, 9–12, 16–19) every 28 days until PD or unacceptable toxicity
  - Primary endpoint: PFS
  - Secondary endpoints: OS, PFS, OS in the PIK3CA/AKT1/PTEN-altered group, tumor response, and safety
  - Median PFS: 5.9 months with capivasertib + paclitaxel vs. 4.2 months with placebo group (HR 0.74; 95% CI, 0.50–1.08; 1-sided P=0.06) [predefined significance level, 1-sided P=0.10])
  - Median OS: 19.1 months with capivasertib + paclitaxel vs. 12.6 months with placebo (HR, 0.61; 95% CI, 0.37–0.99; 2-sided P=0.04)
  - PIK3CA/AKT1/PTEN-altered tumors, median PFS: 9.3 months with capivasertib + paclitaxel vs. 3.7 months with placebo (HR, 0.30; 95% CI, 0.11–0.79; 2-sided P=0.01)
- **BEGONIA trial**
  - Phase Ib/II, open-label, multicenter, platform trial consisting of 2 parts
    - Part 1 is a phase Ib study planned to be conducted in approximately 110 patients (20–30 per arm)
    - Assess the safety and tolerability of durvalumab 1500 mg IV every 3–4 weeks + various arms
      - Arm 1: paclitaxel 90 mg/m^2 IV days 1, 8, and 15 every 28 days
      - Arm 2: paclitaxel & capivasertib
      - Arm 5: paclitaxel & oleclumab
      - Arm 6: trastuzumab deruxtecan
    - Primary endpoint: AEs and lab findings
    - Secondary endpoints: ORR, PFS, DOR, OS, serum concentrations, presence of antidrug antibodies
    - Trial is active and recruiting

Schmid P, et al. *J Clin Oncol*. 2020;38(5):423-33.; U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03742102.

Immunotherapy with Targeted Agents: MEK Inhibitors — Cobimetinib

- COLET trial
  - Multi-stage, multi-cohort phase II study
  - Patients with mTNBC to receive first-line treatment with atezolizumab, cobimetinib, and paclitaxel or nab-paclitaxel until progression or toxicity
  - Primary endpoint: ORR
    - Additional endpoints: DOR, PFS, OS, safety, and exploratory efficacy by PD-L1 status
  - At 6.5 months of follow-up, ORRs were similar between the 2 groups
  - Numerically higher ORR and PFS were observed in patients with PD-L1–positive disease
  - The combination's safety profile was consistent with the known individual safety profiles
  - Trial is active and recruiting

Brufsky A, et al. *J Clin Oncol.* 2019;37(15_suppl):1013.

Immunotherapy with Targeted Agents: IL-2 Pathway Agonist — Bempegaldesleukin

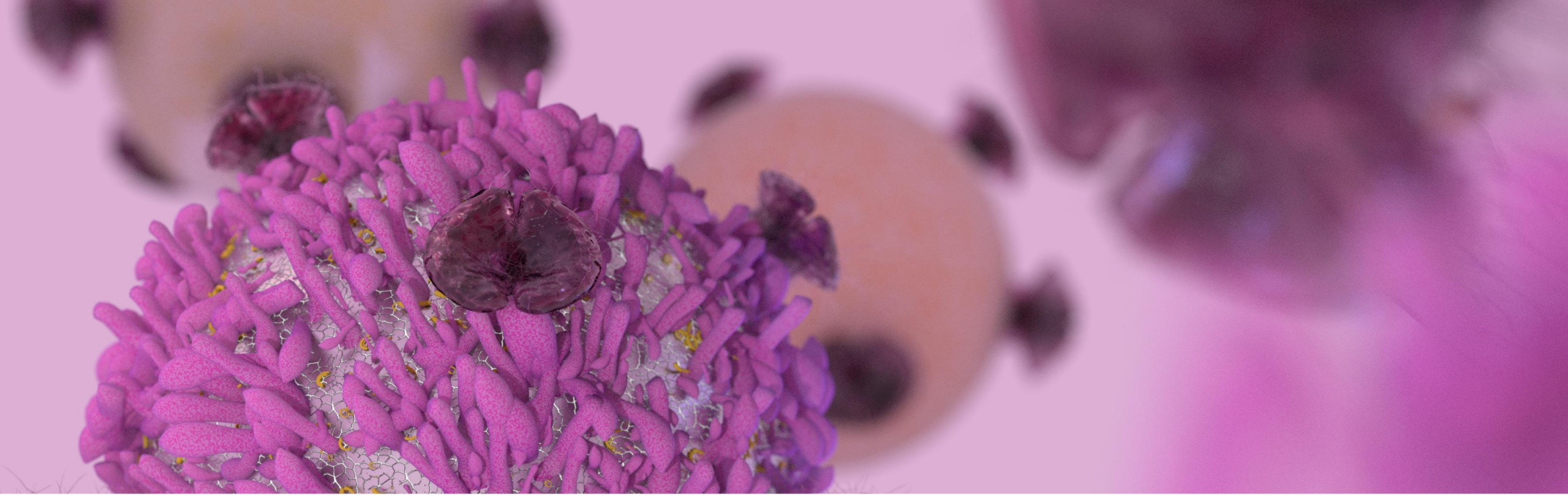
- Bempegaldesleukin (BEMPEG, NKTR-214): first-in-class agent that targets CD122, a protein found on the surface of immune T-cells and natural killer (NK) cells
  - Works by activating and stimulating the growth of these cancer-killing immune cells, without over-activating the entire immune system
- PIVOT-02 study
  - Includes TNBC cohort, 38 patients with mTNBC received Bempeg 0.006 mg/kg + nivolumab 360 mg IV every 3 weeks
  - Patients categorized by line of therapy and prognostic clinical factors: PD-L1 status, age, disease-free interval, LDH, number and type of metastatic sites, and prior taxane
  - ORR: 13% (5/38), regardless of PD-L1 status, with DCR of 45% (17/38)
  - ORR: 13.6% (3/22) in PD-L1–negative vs. 17% (2/12) in PD-L1–positive patients
- Treatment-related grade 3/4 AEs occurred in 23% with dehydration, hypotension, and myalgia as the most frequently reported (4.7% each), consistent with previous reports
- Clinical activity was observed in mTNBC patients treated with BEMPEG + NIVO, notably in patients with poor prognostic features or negative predictive clinical factors for benefit, including negative PD-L1 status
- Additional efficacy analyses, including ORR, DOR, and biomarker analyses, will be presented at a later date
- Data support future development of this doublet in mTNBC patients who are PD-L1–negative at baseline, have poor prognostic features, and/or are relapsed/refractory to prior chemotherapy regimens

LDH, lactate dehydrogenase.

Tolaney S, et al. In 2019 CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference September 23-26, 2019, Paris, France. https://www.nektar.com/application/files/9215/6949/4543/PIVOT-02_TNBC_CICON_2019_Poster.pdf.

Pharmacist's Role in Management of TNBC

- Optimize patient education and facilitate compliance
  - Patient counseling to aid in managing patient expectations, encourage adherence, and facilitate early detection of AEs
  - Provide patient calendars to help prevent missed clinic visits and infusion appointments
  - Monitor for treatment-emergent toxicities by way of chart checks, counseling in the infusion center, and/or telepharmacy programs and identify patients experiencing adverse effects
- Guide in selection of patients, planning of treatments, procurement of drugs, and management/prevention of AEs
  - Medication review to identify patients who may or may not be an ICI or PARP inhibitor candidate
    - Recommend appropriate doses due to presence of drug interactions or impaired renal function
  - Facilitate access to therapy by submitting documentation for pre-certification of therapy and accessing patient assistance programs/manufacturer discounts
  - Facilitate insurance appeals and peer-to-peer conversations
  - Assist with providing supportive care interventions and prevention/management of ADRs
    - Nausea and vomiting (PARP inhibitors): recommend appropriate antiemetics to decrease symptom severity
    - Immune-related adverse events: provide recommendations for treatment (e.g., steroids, additional immunosuppressants)



Questions and Answers

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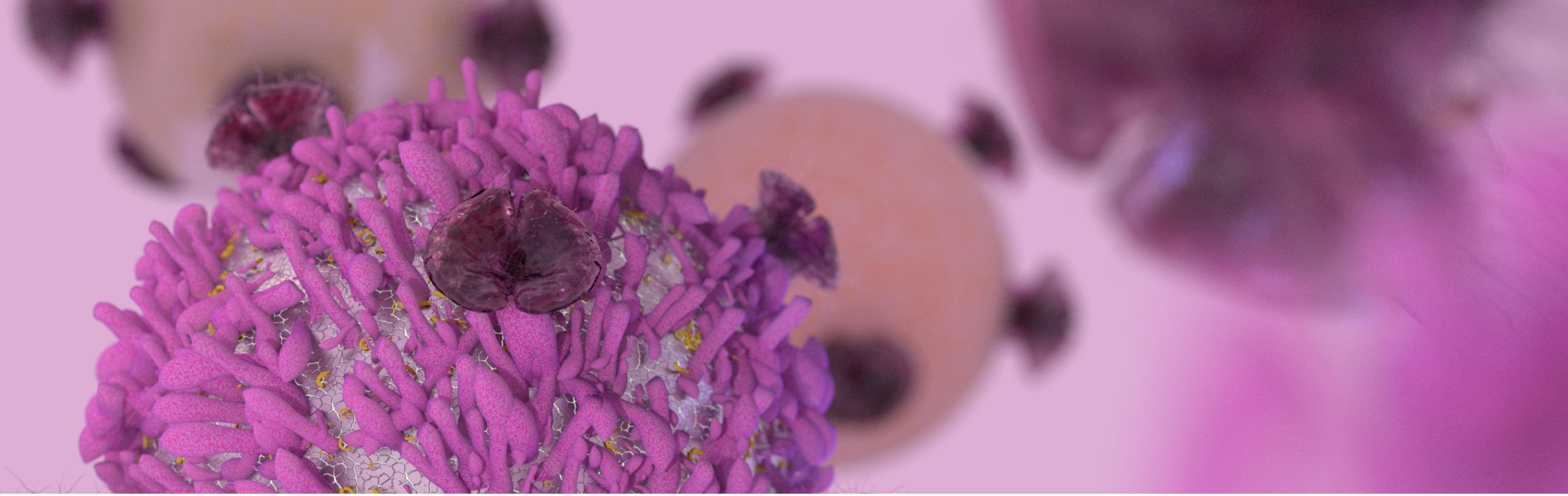

Thank You!