20th Congress of Iranian Society of Medical Oncology & Hematology

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IRANIAN SOCIETY OF MEDICAL ONCOLOGY AND HEMATOLOGY
ISMOH

# *Update on systemic treatment in early triple negative breast cancer*

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- Triple negative breast cancer (TNBC) is a heterogeneous disease representing about 15% of all breast cancers.

- TNBC are usually high-grade histological tumors, and are generally more aggressive and difficult to treat due to the lack of targeted therapies available, and chemotherapy remains the standard treatment.
- There is a close relationship between pathological complete response after chemotherapy treatment and higher rates of disease free survival and overall survival.

National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2022
# Invasive Breast Cancer

## WORKUP PRIOR TO PREOPERATIVE SYSTEMIC THERAPY

| CLINICAL STAGE | ADDITIONAL WORKUP[a] |
|---|---|
| c≥T2[rr] or cN+ and M0<br>or<br>cT1,N0 HER2-positive disease<br>or<br>cT1,N0 TNBC<br>(For preoperative systemic therapy criteria, see BINV-M, 1 of 2)[pp] | • Axillary assessment with exam<br>  ▸ Consider ultrasound<br>  ▸ Percutaneous biopsy of suspicious nodes[qq]<br>• CBC<br>• Comprehensive metabolic panel, including liver function tests and alkaline phosphatase<br>Additional tests to consider:[h]<br>• Chest diagnostic CT ± contrast<br>• Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast<br>• Bone scan or sodium fluoride PET/CT[ss] (category 2B)<br>• FDG PET/CT[tt] (optional)<br>• Breast MRI[b] (optional), with special consideration for mammographically occult tumors, if not previously done |

# Summary of Recommendations

## Clinical Question 3

- What neoadjuvant systemic therapy regimens are recommended for patients with TNBC?

## Recommendation 3.1

- Patients with TNBC who have clinically node positive and/or at least T1c disease should be offered an anthracycline- and taxane-containing regimen in the neoadjuvant setting.

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| High | Strong |

# Summary of Recommendations

## Recommendation 3.2

- Patients with cT1a or cT1bN0 TNBC should not routinely be offered neoadjuvant therapy outside of a clinical trial.

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| High | Strong |

## Recommendation 3.3

- Carboplatin may be offered as part of a neoadjuvant regimen in patients with TNBC to increase likelihood of pCR. The decision to offer carboplatin should take into account the balance of potential benefits and harms.

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Intermediate | Moderate |

# BACKGROUND

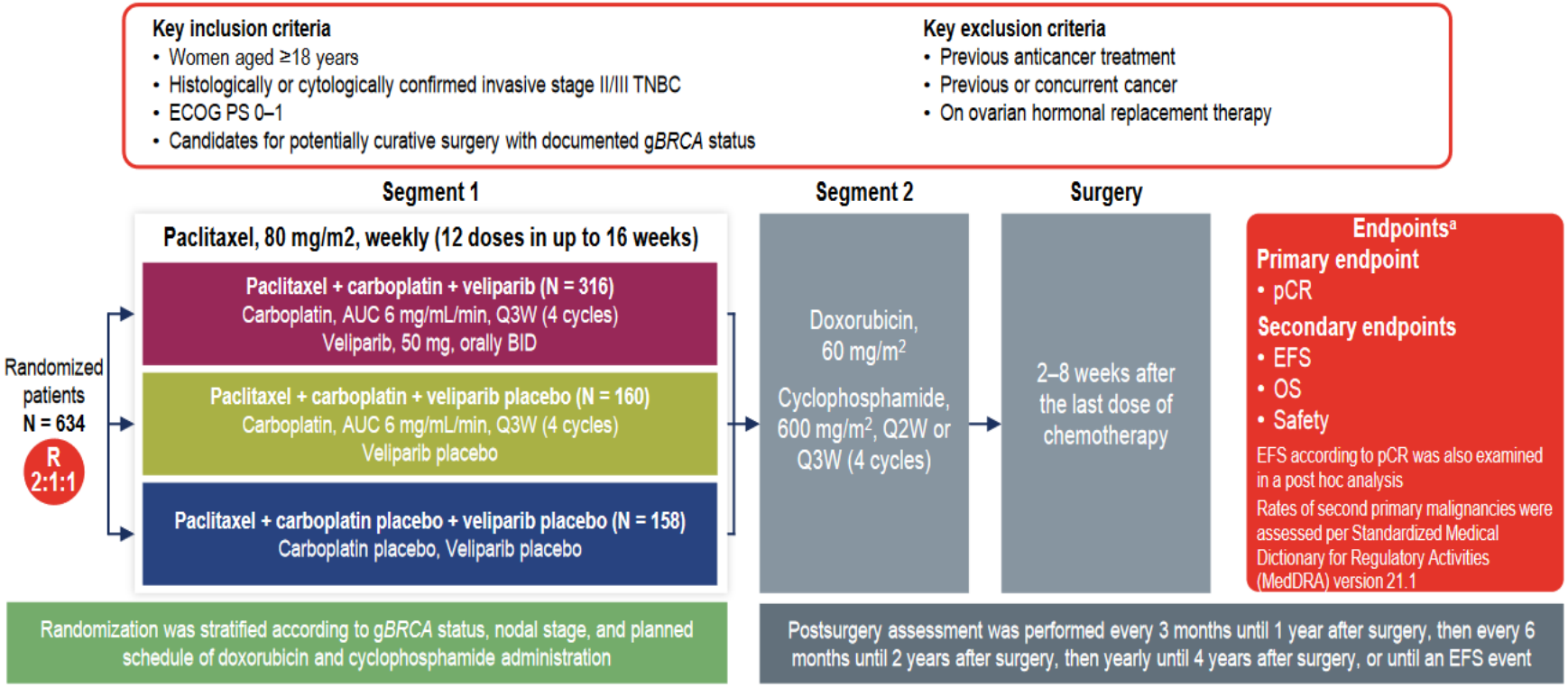
- Triple-negative breast cancer (TNBC) has higher risk of recurrence and worse overall prognosis and survival than other breast cancers[1,2]
- Due to a lack of targeted options, neoadjuvant chemotherapy (NACT) followed by surgery has become a standard treatment for patients with stage II-III TNBC[3-5]
- In the phase 3 **BrighTNess trial** (NCT02032277), carboplatin, with or without veliparib demonstrated[6]:
  - Significantly improved pathological complete response (pCR) in patients with operable TNBC compared with standard NACT alone (53% and 58%, respectively, versus 31%[a])
  - An acceptable safety profile in patients with operable TNBC
- Increased pCR rates with addition of carboplatin to NACT were also reported in other randomized breast cancer trials[7,8]
  - **CALGB 40603/Alliance:** 54% with carboplatin added to paclitaxel versus 41%[a] with conventional regimen +/- bevacizumab
  - **GeparSixto**: 53% with carboplatin added to paclitaxel and liposomal doxorubicin plus bevacizumab versus 43%[a] with chemotherapy plus bevacizumab
- Impact of neoadjuvant carboplatin on long-term outcomes remains uncertain



[a]Using a definition of pCR as ypT0/is ypN0.

1. Bianchini G et al. Nat Rev Clin Oncol 2016; 13(11): 674-90; 2. Otto H et al. BMC Genomics 2005; 6: 139; 3. Korde LA et al. J Clin Oncol 2021: Jco2003399; 4. Cardoso F et al. Ann Oncol 2019; 30(8): 1194-220;5. Thomssen C et al. Breast Care (Basel) 2021; 16(2): 135-43; 6. Loibl S et al. Lancet Oncol 2018; 19(4): 497-509; 7. von Minckwitz G et al. Lancet Oncol 2014; 15(7): 747-56; 8. Sikov WM et al. J Clin Oncol 2015; 33(1): 13-21.

# STUDY DESIGN




2021 ESMO congress

[a]Efficacy was assessed in all randomized patients and safety in all patients who received ≥1 dose

AUC, area under the curve; BID, twice a day; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; OS, overall survival; pCR, pathological complete response; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomization; TNBC, triple negative breast cancer.

# CONCLUSIONS

- Adding carboplatin to paclitaxel followed by doxorubicin and cyclophosphamide improved pCR significantly[1] and translated into an improved EFS after a median follow-up of 4.5 years
- Addition of veliparib did not impact pCR, EFS, or OS
- Patients with pCR had significantly better EFS; this was similar in patients with and without g*BRCA* mutations
- Higher rates of hematologic AEs with the addition of carboplatin with or without veliparib (previously reported) did not compromise treatment delivery or the impact of this treatment on the study's primary (pCR) or secondary (EFS/OS) endpoints
- The regimens had manageable safety profiles without increased risk of MDS, AML, or other secondary malignancies
- These findings support the inclusion of carboplatin in neoadjuvant chemotherapy for stage II-III TNBC, irrespective of g*BRCA* status

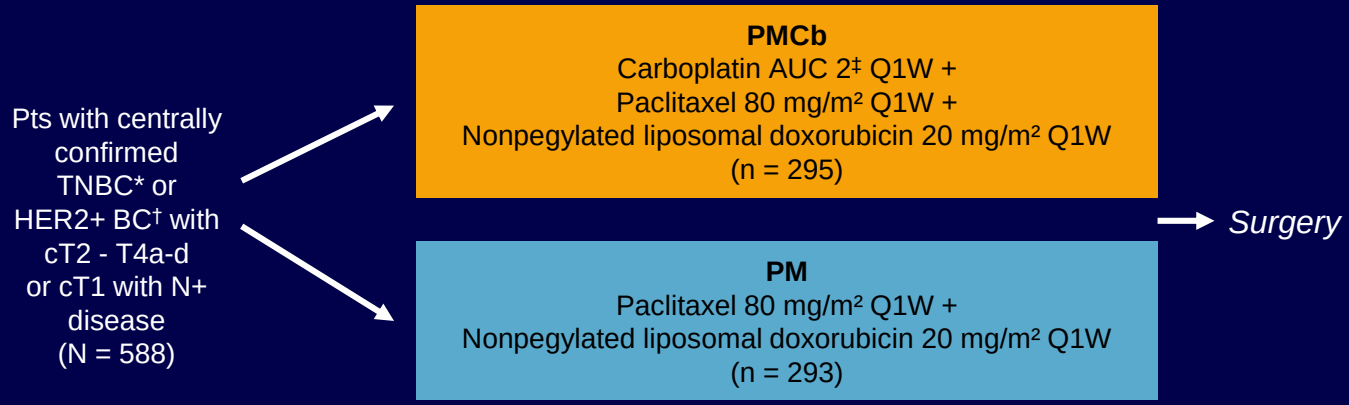


AE, adverse event; AML, acute myeloid leukemia; EFS, event-free survival; OS, overall survival; MDS, myelodysplastic syndrome; pCR, pathological complete response; TNBC, triple negative breast cancer.

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

# GeparSixto: Study Design

- Randomized phase IIb study in 51 German centers




*TNBC pts also received bevacizumab 15 mg/kg IV Q3W.
†HER2+ BC pts also received trastuzumab 8 mg/kg IV (initial dose), then 6 mg/kg IV Q3D (subsequent doses) and lapatinib 750 mg QD.
‡Dose reduced to AUC 1.5 after 330 pts enrolled.

- Primary endpoint: pCR
- Secondary endpoints: RFS, DFS, OS

von Minckwitz G, et al. SABCS 2015. Abstract S2-04.

Slide credit: clinicaloptions.com

# GeparSixto: pCR Outcomes

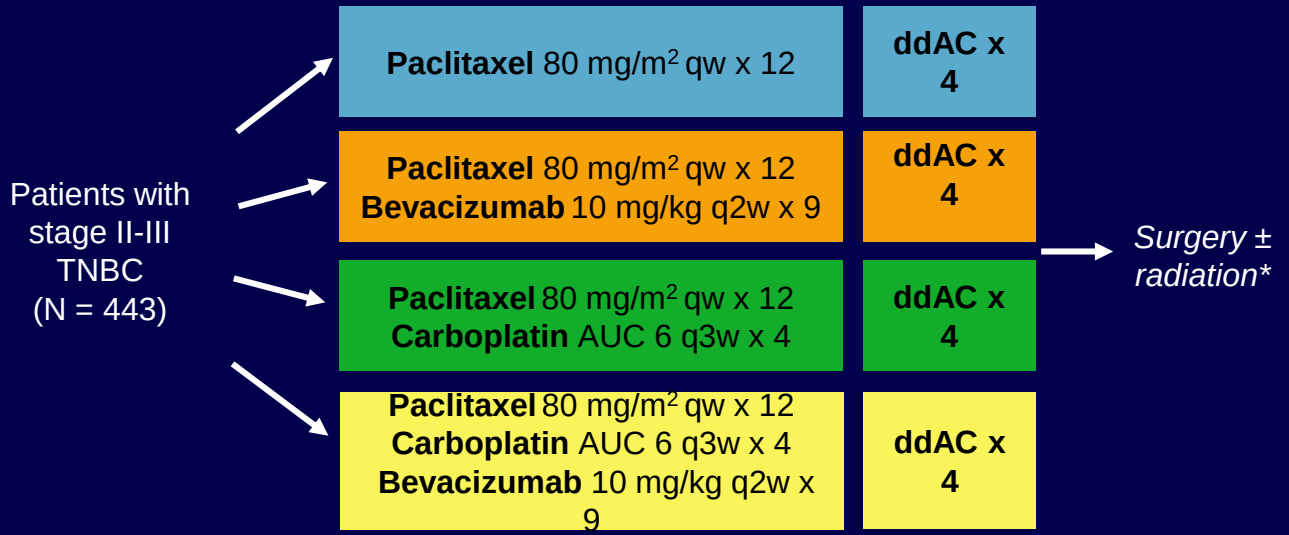
| pCR, % | PMCb | PM | Odds Ratio | *P* Value |
|---|---|---|---|---|
| All pts (n = 588) | 43.7 | 36.9 | | .107* |
| HER2+ BC (n = 273) | 32.8 | 36.8 | 0.84 | .6† |
| TNBC (n = 315) | 53.2 | 36.9 | 1.94 | .005† |
| ▪ g*BRCA* wild type (n = 241) | 50.8 | 33.1 | 2.09 | .005 |
| ▪ g*BRCA* mutant (n = 50) | 61.5 | 50.0 | 1.60 | .413 |

*Level for significance = 0.2
†Test for interaction, *P* = .015

von Minckwitz G, et al. SABCS 2015. Abstract S2-04.
von Minckwitz G, et al. Lancet Oncol. 2014;15:747-756.
von Minckwitz G, et al. ASCO 2014. Abstract 1005.

# CALGB 40603: Neoadjuvant Paclitaxel With Carboplatin ± Bevacizumab in TNBC

- Randomized, open-label phase II trial




*No systemic adjuvant treatment planned.

Sikov WM, et al. J Clin Oncol. 2015;33:13-21.

Slide credit: clinicaloptions.com

# CALGB 40603: pCR and Survival Outcomes

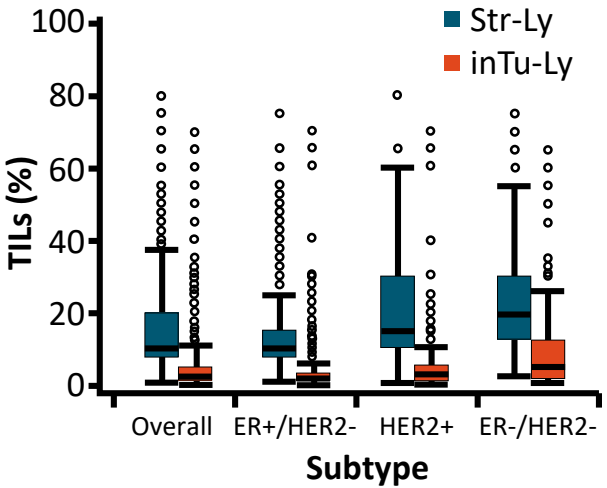
- pCR rate for breast/axilla significantly increased with addition of carboplatin (54% vs 41%, *P* = .0029)

| Outcome, % | pCR Breast/Axilla | | HR (95% CI) | *P* value |
|---|---|---|---|---|
| | Yes (n = 207) | No (n = 236) | | |
| 3-yr EFS | 86 | 62 | 0.30 (0.19-0.46) | <.0001 |
| 3-yr OS | 93 | 73 | 0.20 (0.11-0.36) | <.0001 |

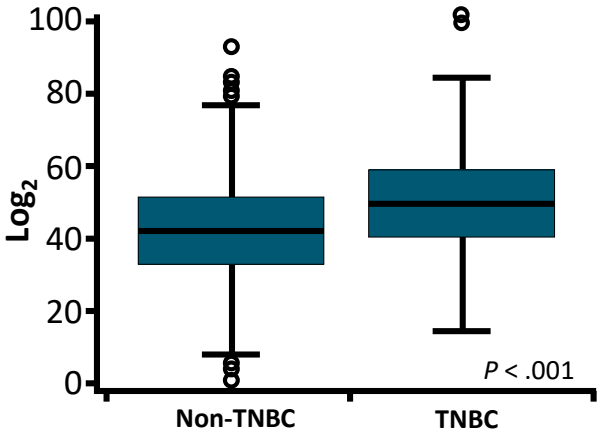
Sikov WM, et al. J Clin Oncol. 2015;33:13-21. Sikov WM, et al. SABCS 2015. S2-05.

# Immune Checkpoint Inhibition in TNBC: Rationale

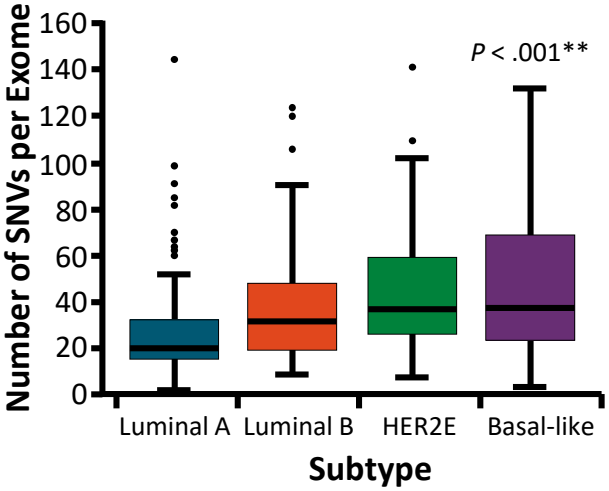
**Tumor-Infiltrating Lymphocytes[1]**




**PD-L1 Expression[2]**




**Nonsynonymous Mutations[3]**

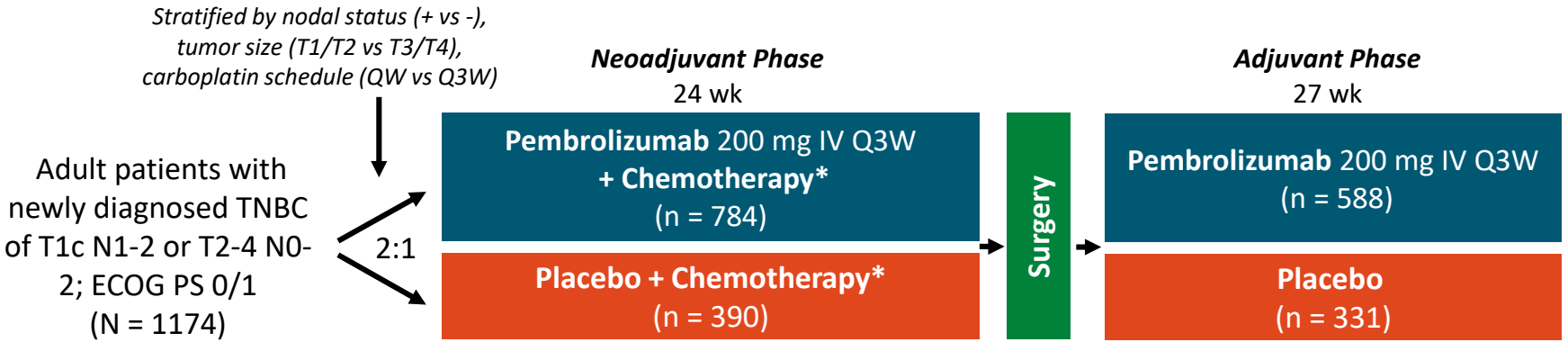



1. Loi. JCO. 2013;31:860. 2. Mittendorf. Cancer Immunol Res. 2014;2:361. 3. Luen. Breast. 2016;29:241.

Slide credit: clinicaloptions.com

# KEYNOTE-522: Neoadjuvant Pembrolizumab + CT Followed by Adjuvant Pembrolizumab in TNBC

- Randomized, double-blind, multicenter phase III trial




*Chemotherapy consisted of:
- Carboplatin AUC 5 Q3W or 1.5 QW + paclitaxel 80 mg/m$^2$ QW for cycles 1-4
- Doxorubicin 60 mg/m$^2$ Q3W + epirubicin 90 mg/m$^2$ Q3W + cyclophosphamide 600 mg/m$^2$ Q3W for cycles 5-8

- Primary endpoints: pCR (ITT), EFS (ITT)
  - Data previously reported
- Secondary endpoints: pCR (alternate definitions); OS; pCR, EFS, OS in PD-L1+; safety
- Exploratory analyses: EFS sensitivity analysis, EFS in patient subgroups
- Median follow-up: 39.1 mo for both arms

Schmid. SABCS 2021. Abstr GS1-01.

# KEYNOTE-522: EFS Subgroup Analyses

| EFS Events, n/N (%) | Pembro + CT/Pembro | Placebo + CT/Placebo | HR (95% CI) |
|---|---|---|---|
| Primary analysis | 123/784 (15.7) | 93/390 (23.8) | 0.63 (0.48-0.82)* |
| Nodal status | | | |
| ▪ Positive | 80/408 (19.6) | 57/196 (29.1) | 0.65 (0.46-0.91) |
| ▪ Negative | 43/376 (11.4) | 36/194 (18.6) | 0.58 (0.37-0.91) |
| Disease stage | | | |
| ▪ II | 65/590 (11.7) | 54/291 (18.6) | 0.60 (0.42-0.86) |
| ▪ III | 54/194 (27.8) | 39/98 (39.8) | 0.68 (0.45-1.03) |
| Menopausal status | | | |
| ▪ Premenopausal | 60/438 (13.7) | 47/221 (21.3) | 0.62 (0.42-0.91) |
| ▪ Postmenopausal | 63/345 (18.3) | 46/169 (27.2) | 0.64 (0.44-0.93) |
| HER2 status | | | |
| ▪ 2+ by IHC (but FISH negative) | 32/188 (17.0) | 24/104 (23.1) | 0.73 (0.43-1.24) |
| ▪ 0/1+ by IHC | 91/595 (15.3) | 69/286 (24.1) | 0.60 (0.44-0.82) |
| LDH | | | |
| ▪ >ULN | 29/149 (19.5) | 23/80 (28.8) | 0.65 (0.37-1.12) |
| ▪ ≤ULN | 93/631 (14.7) | 69/309 (22.3) | 0.63 (0.46-0.86) |

*$P < .00031$

Schmid. SABCS 2021. Abstr GS1-01.

Slide credit: clinicaloptions.com

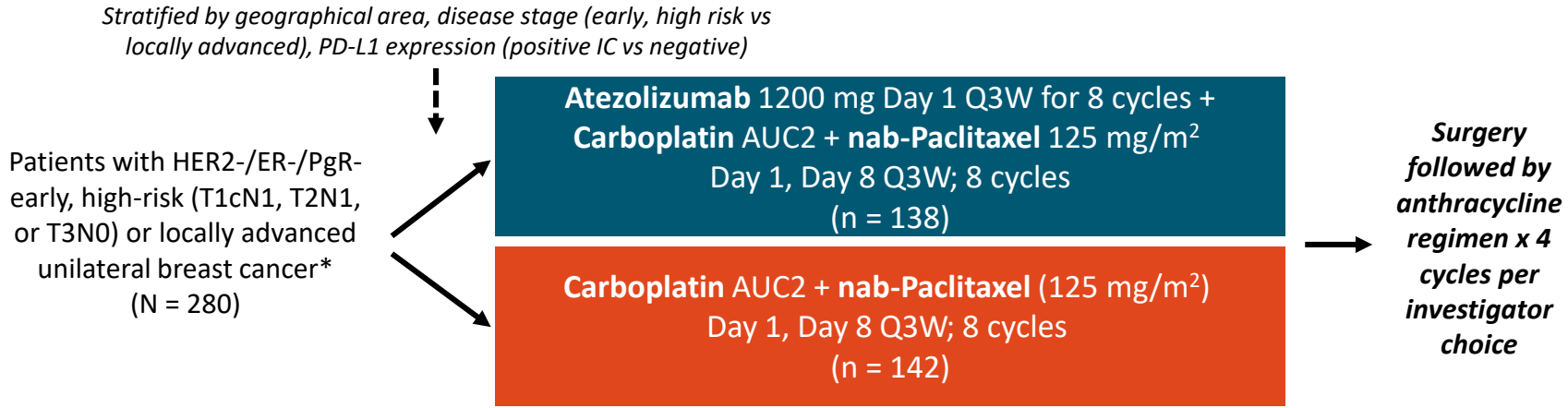
# KEYNOTE-522: Investigators' Conclusions

- Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab conferred statistically significant and clinically meaningful improvement in EFS in women with TNBC
  - 36-mo EFS: 84.5% with adjuvant pembrolizumab vs 76.8% with placebo (HR: 0.63)
  - Results consistent across prespecified sensitivity analyses
  - Improvements generally consistent across prespecified patient subgroups, including those defined by nodal status and disease stage
- Safety consistent with known profiles of pembrolizumab and chemotherapy, with no new safety concerns
- Results support neoadjuvant pembrolizumab + platinum-containing chemotherapy followed by adjuvant pembrolizumab as a new standard of care for patients with high-risk, early-stage TNBC

Schmid. SABCS 2021. Abstr GS1-01.

# NeoTRIPaPDL1: Study Design

- Open-label, randomized phase III trial

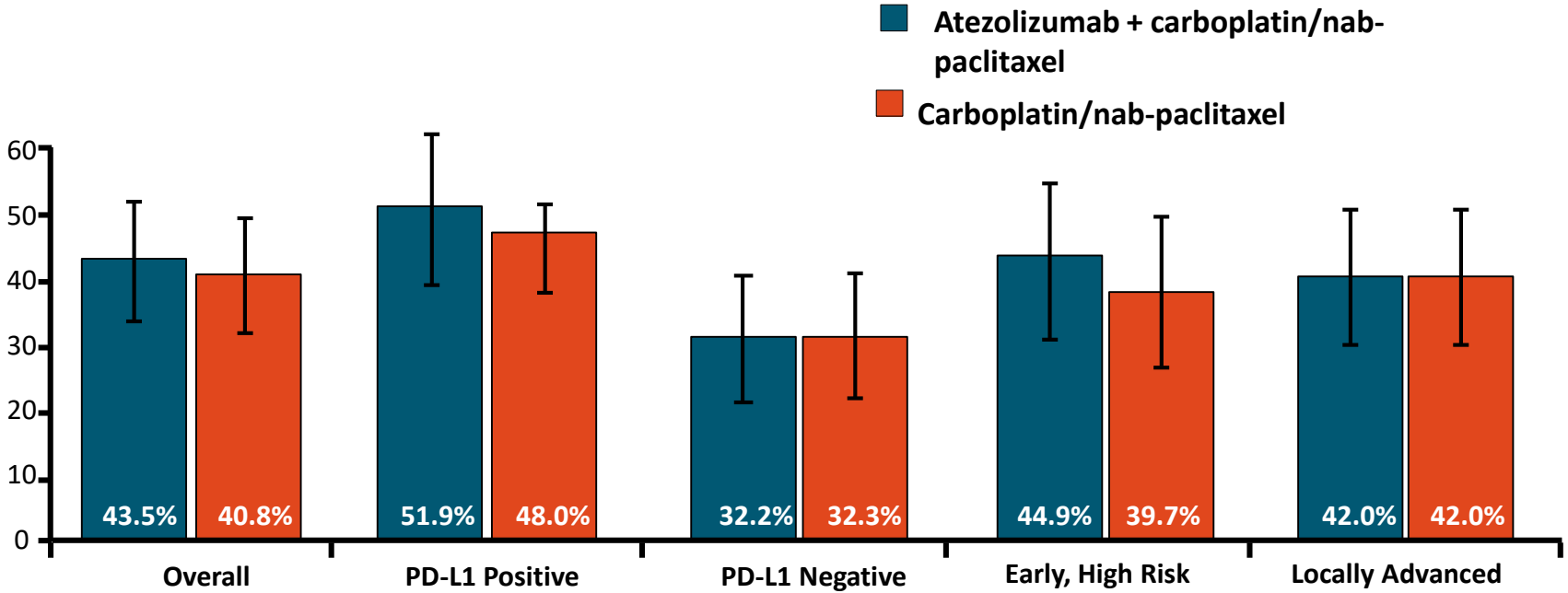



*ER, PgR, HER2, and PD-L1 centrally assessed before randomization. Tumor and blood banked for correlative studies.

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

Gianni. SABCS 2019. Abstr GS3-04.

# NeoTRIPaPDL1: pCR Rate (ITT)

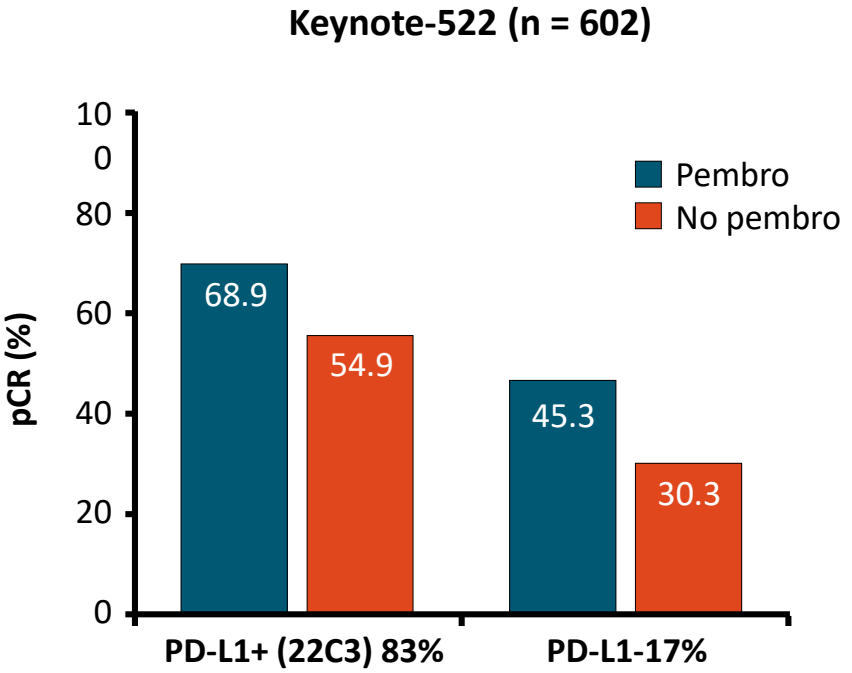


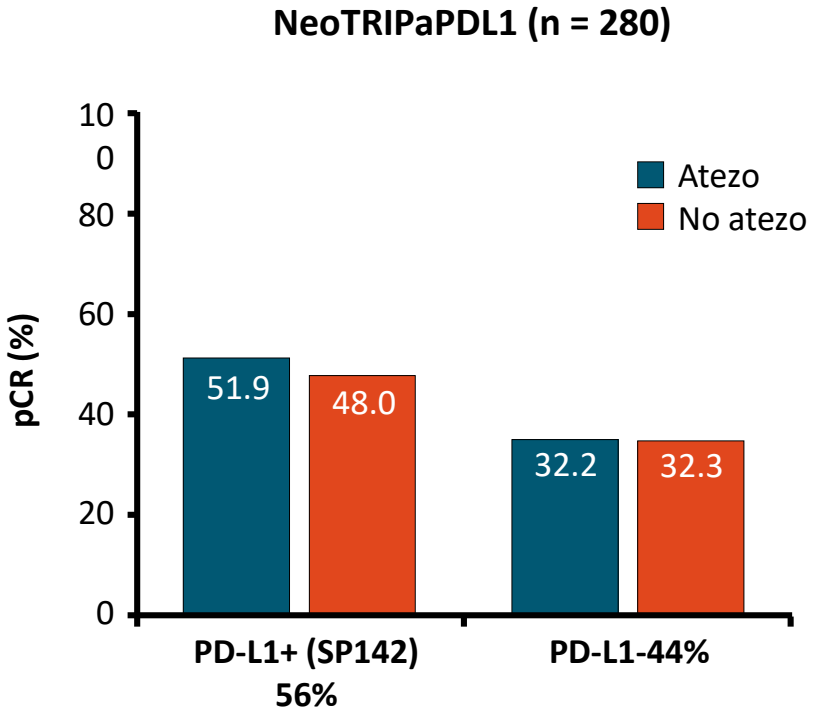

- Overall pCR rate difference: 2.63%; odds ratio: 1.11 (95% CI: 0.69-1.79); *P* = .66

Gianni. SABCS 2019. Abstr GS3-04.

Slide credit: clinicaloptions.com

# PD-L1+ Predicts Higher pCR Rate to Neoadjuvant CT but Not Who Benefits From Adding Checkpoint Inhibitor




Schmid. SABCS 2019. Abstr GS3-03. Gianni. SABCS 2019. Abstr GS3-04.

Slide credit: clinicaloptions.com

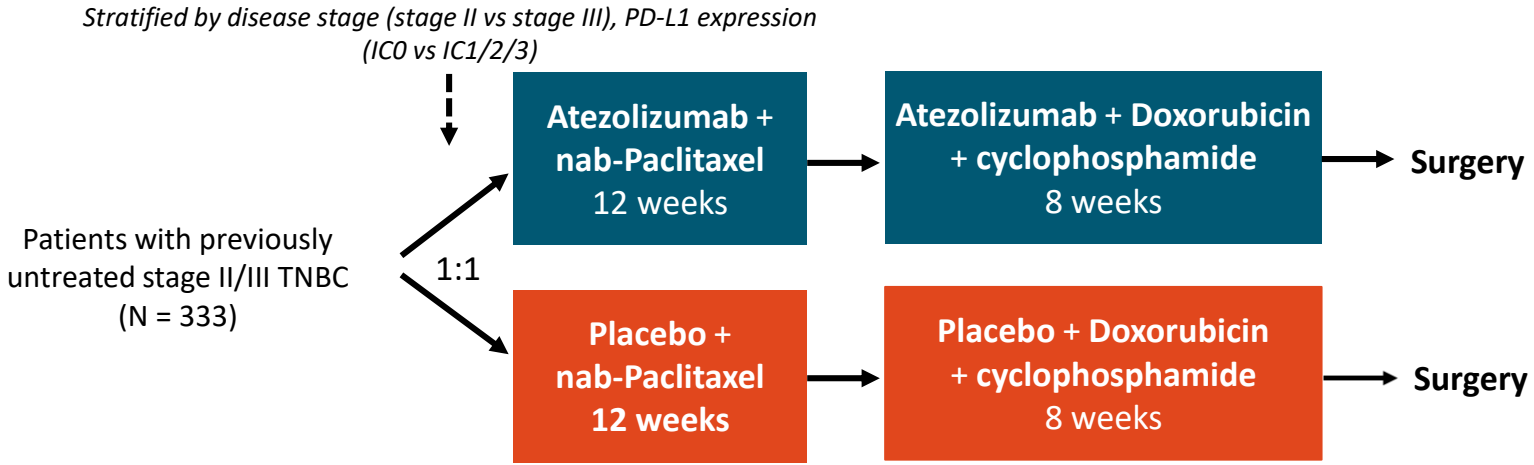
# Considerations: Keynote 522 vs. NeoTRIPaPDL1 trial differences

- Primary endpoint impact
- Different assays for PD-L1 status determination
- Differences in clinicopathologic features
- PD-1 vs. PD-L1 inhibitors
- Chemotherapy backbone
- Frequency and timing of administration

# IMpassion031: Study Design

**The trial met it primary endpoint of improving pCR regardless of PD-L1 status according to a press release on June 18, 2020**

- Double-blind, randomized phase III trial




- Primary endpoint: pCR using AJCC staging system in ITT population and PD-L1+ subpopulation
- Key secondary endpoints: EFS, DFS, OS in all patients and PD-L1+ subpopulation, safety

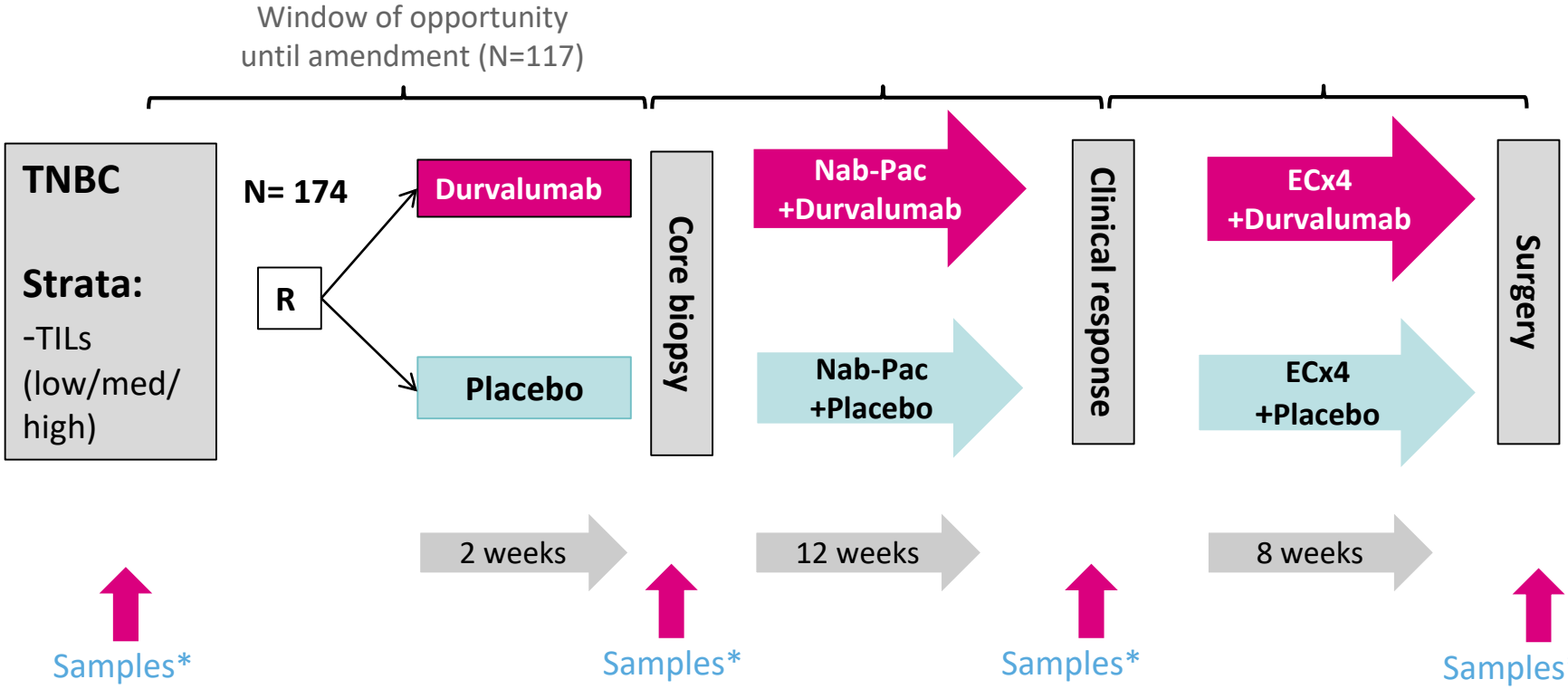
NCT03197935.

Slide credit: clinicaloptions.com

# IMpassion031: Conclusions

- Addition of atezolizumab to neoadjuvant CT significantly improved pCR rate vs placebo plus CT in overall patient population for stage II-III TNBC
  - This benefit observed regardless of PD-L1 status
- The most commonly reported AEs are those known to be associated with CT; no new AEs were observed
- Investigators suggest that this combination may offer an improvement in curative intent neoadjuvant therapy

# GeparNUEVO: Study Design




*Tissue: FFPE, fresh frozen;
Liquid biopsies: full blood; plasma, serum

Loibl. ASCO 2018. Abstr 104. Loibl. Ann Oncol. 2019;30:1279.

Slide credit: clinicaloptions.com

# GeparNUEVO Survival Analysis: Conclusions

- In this analysis of long-term survival outcomes from the phase II GeparNUEVO trial, the addition of durvalumab to neoadjuvant CT significantly prolonged iDFS, distant DFS, and OS vs placebo + neoadjuvant CT in patients with early TNBC
  - 3-yr rates: iDFS, 85.6% vs 77.2% (HR: 0.48; *P* = .0398); distant DFS, 91.7% vs 78.4% (HR: 0.31; *P* = .0078); OS, 95.2% vs 83.5% (HR: 0.24; *P* = .0108)
- In those achieving pCR, survival outcomes improved with addition of durvalumab vs placebo to neoadjuvant CT
- Subgroup analyses of iDFS suggested benefit potentially enriched in PD-L1–positive disease
- Investigators indicate that additional research into relationship between pCR improvement and long-term outcomes with neoadjuvant PD-1/PD-L1 therapy is warranted
- Investigators suggest that further assessment of PD-1/PD-L1 therapies in the adjuvant setting is warranted considering these findings

Loibl. ASCO 2021. Abstr 506.

Slide credit: clinicaloptions.com

**Table 2.** Comparison of characteristics between clinical trials with neoadjuvant immunotherapy in TNBC.

| Clinical trial | Phase | Immunotherapy drug | NACT scheme | Primary endpoint | pCR |
|---|---|---|---|---|---|
| GeparNew | II | Durvalumab | Nab-paclitaxel followed by anthracyclines and cyclophosphamide | pCR | 53.4% |
| KEYNOTE-522 | III | Pembrolizumab | Paclitaxel and carboplatin followed by anthracyclines and cyclophosphamide | pCR and DFS | 64.8% |
| NeoTRIP | III | Atezolizumab | Nab-paclitaxel and carboplatin | DFS | 43.5% |
| IMPassion 031 | III | Atezolizumab | Nab-paclitaxel followed by anthracyclines and cyclophosphamide | pCR | 57.6% |

DFS, disease-free survival; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple negative breast cancer

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# NCCN Guidelines Version 2.2022
# Invasive Breast Cancer

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Discussion

## PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

| HER2-Negative[b] | |
|---|---|
| **Preferred Regimens:**<br>• Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks[c]<br>• Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel[c]<br>• TC (docetaxel and cyclophosphamide)<br>• Olaparib, if germline *BRCA1/2* mutations[d,e]<br>• High-risk[f] triple-negative breast cancer (TNBC): Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab<br>• TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[e] Capecitabine | |
| **Useful in Certain Circumstances:**<br>• Dose-dense AC (doxorubicin/cyclophosphamide)<br>• AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)<br>• CMF (cyclophosphamide/methotrexate/fluorouracil)<br>• AC followed by weekly paclitaxel[c]<br>• Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy) | **Other Recommended Regimens:**<br>• AC followed by docetaxel every 3 weeks[c]<br>• EC (epirubicin/cyclophosphamide)<br>• TAC (docetaxel/doxorubicin/cyclophosphamide)<br>• Select patients with TNBC:[g]<br>▸ Paclitaxel + carboplatin[g] (various schedules)<br>▸ Docetaxel + carboplatin[g] (preoperative setting only) |

- NACT in all patients with TNBC tumors ⩾T1c

- A sequential regimen of anthracyclines and taxanes is recommended for the vast majority of patients .

- Weekly nab-paclitaxel could replace neoadjuvant paclitaxel .

- The addition of a platinum (usually carboplatin) compound in the NACT scheme may be considered .

- Immunotherapy drugs such as, pembrolizumab should be considered during NACT .

# پایان