# New Landscape in the Adjuvant Treatment of Breast Cancer: Keynote 522 and monarchE

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# Disclosures

- AstraZeneca/ Daiichi-Sankyo: Speakers' Bureau
- Gilead: Speakers' Bureau

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# Agenda

- ER+/ HER2- LN+ Case
- Discussion of monarchE

- TNBC Case
- Discussion of Keynote 522

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# Estrogen Receptor Positive Breast Cancer – Clinical Case

- 64yo AA woman self-palpated a L breast mass
- Mammogram was unrevealing but ultrasound showed a 4cm mass and L axillary adenopathy

- Biopsy: INVASIVE LOBULAR CARCINOMA (ILC), grade 1
  - ER 91-100%/ PR 1-10%/ HER2 1+
- Mastectomy w ALND: ILC, grade 2, 6.5cm; 28/47 Lymph nodes positive

- Adjuvant Chemotherapy: dose dense Adriamycin/ Cytoxan followed by weekly Taxol x 12 doses
- Completed adjuvant radiation
- Started Arimidex 1mg daily + Verzenio 150mg BID

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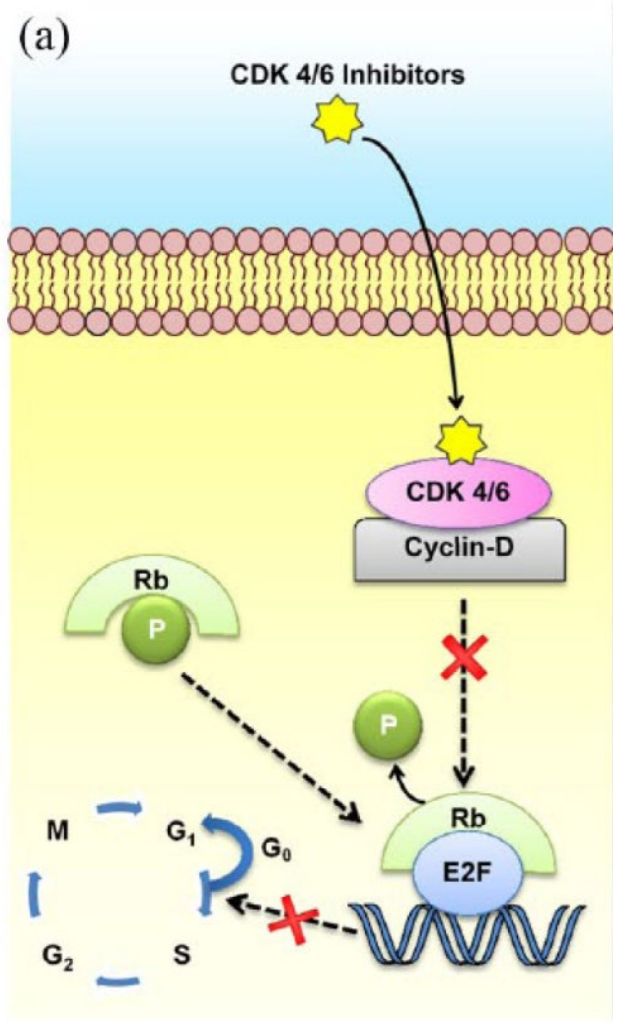
# CDK4/6 inhibitors – Abemaciclib

- Cell cycle progression is regulated by cyclins which pair/activate kinases (CDK)
- A unique target of cyclin-D/CDK is the retinoblastoma (Rb) protein
- Rb controls the progression from Phase G1 to S of the cell cycle
- Abemaciclib selectively inhibits CDK4 and CDK6, inhibiting Rb phosphorylation resulting in G1 arrest and inhibition of proliferation
  - Activity is specific for Rb-proficient cells
- Abemaciclib is more selective for CDK4 than CDK6 which allows for continuous suppression




Nur Husna SM et al. Therapeutic Advances in Medical Oncology. 2018;10

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# monarchE

- Phase III trial in patients with HR+/HER2−, node-positive, high-risk early stage breast cancer
  - High risk was defined as:
  - ≥4 positive lymph nodes
  - 1-3 positive axillary lymph nodes and
    - tumor size ≥ 5 cm
    - histologic grade 3
    - centrally assessed Ki-67 ≥ 20%
- 1:1 abemaciclib (CDK4/6 inhibitor) vs placebo x 2 years with standard adjuvant endocrine therapy (5-10 years) – 2808 pts vs 2829 pts
- Primary endpoint: IDFS in ITT population
- Secondary endpoints: IDFS in patients with high Ki-67, DRFS, OS, and safety

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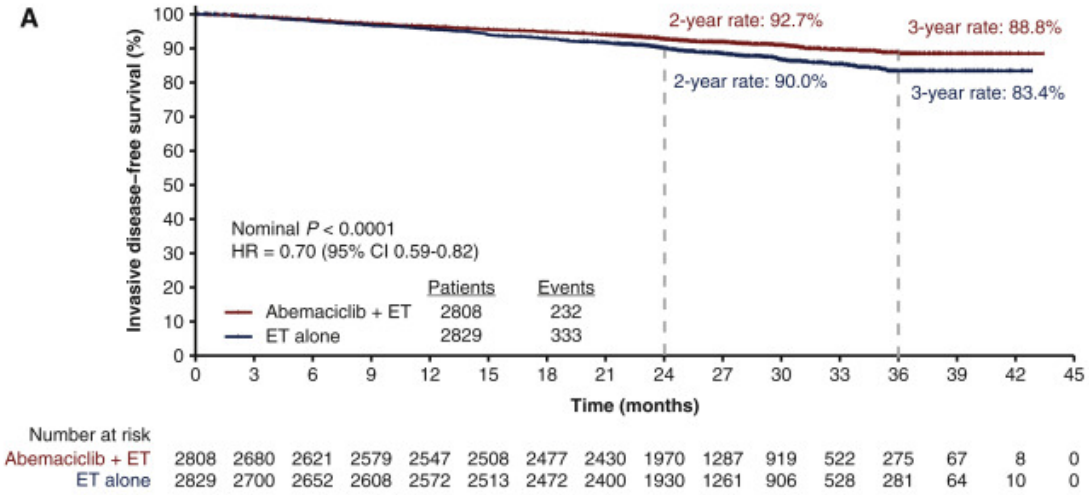
# monarchE – Results

- 2 year follow up:
  - IDFS: abemeciclib/ET vs ET alone: 92.2% vs 88.7%
  - Distant relapse free survival (DRFS): abemaciclib/ET vs ET alone 93.6% vs 90.3%

- ESMO 2021 – 3 year follow up:
  - IDFS improvement: 88.8% vs 83.4% (Δ 5.4%)
  - DRFS improvement: 90.3% vs 86.1% (Δ 4.2%)

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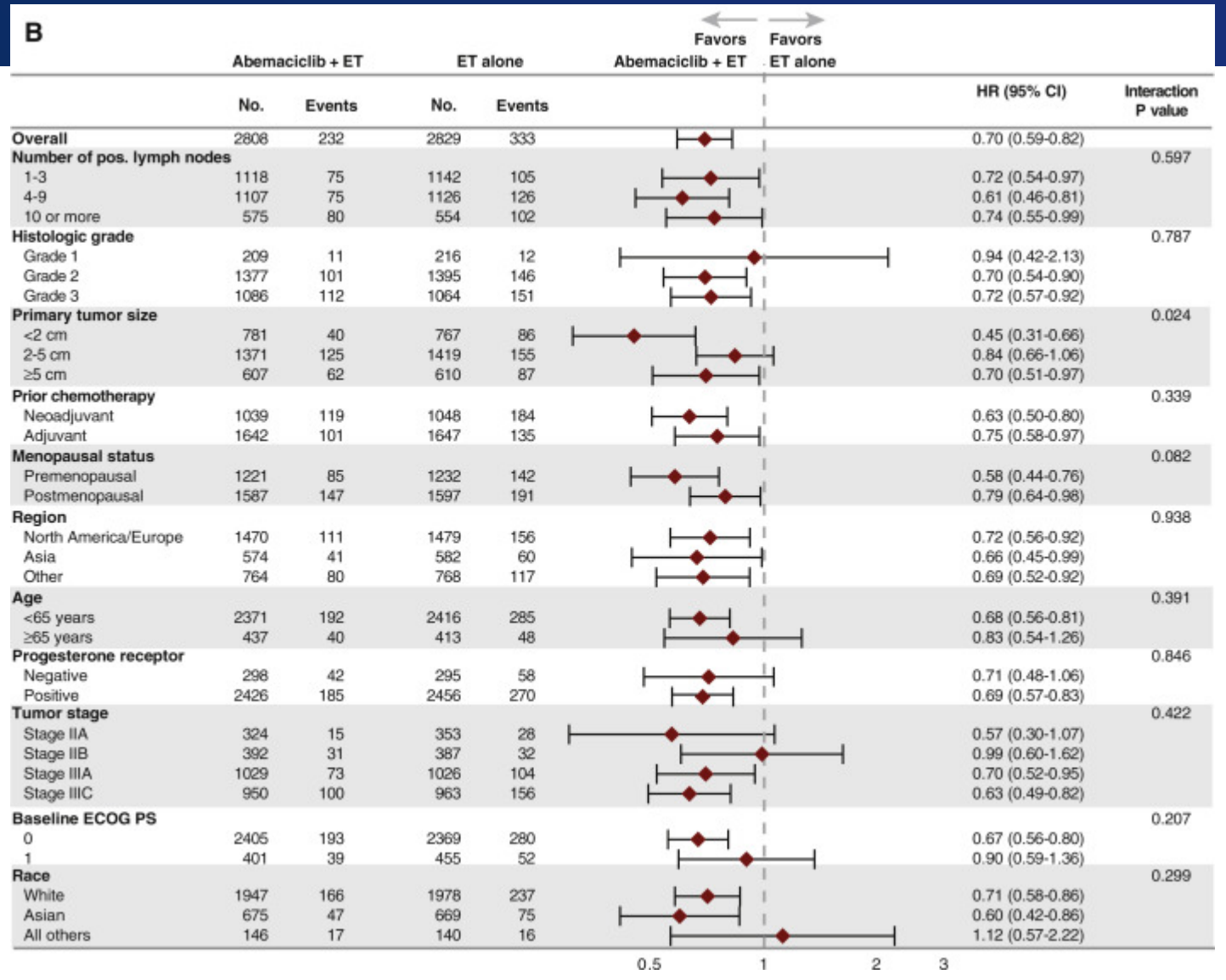
Harbeck N et al, *Annals of Oncology;* VOLUME 32, ISSUE 12, P1571-1581, DECEMBER 01, 2021

# monarchE Subset Outcomes




| | Abemaciclib + ET No. | Abemaciclib + ET Events | ET alone No. | ET alone Events | HR (95% CI) | Interaction P value |
|---|---|---|---|---|---|---|
| **Overall** | 2808 | 232 | 2829 | 333 | 0.70 (0.59-0.82) | |
| **Number of pos. lymph nodes** | | | | | | 0.597 |
| 1-3 | 1118 | 75 | 1142 | 105 | 0.72 (0.54-0.97) | |
| 4-9 | 1107 | 75 | 1126 | 126 | 0.61 (0.46-0.81) | |
| 10 or more | 575 | 80 | 554 | 102 | 0.74 (0.55-0.99) | |
| **Histologic grade** | | | | | | 0.787 |
| Grade 1 | 209 | 11 | 216 | 12 | 0.94 (0.42-2.13) | |
| Grade 2 | 1377 | 101 | 1395 | 146 | 0.70 (0.54-0.90) | |
| Grade 3 | 1086 | 112 | 1064 | 151 | 0.72 (0.57-0.92) | |
| **Primary tumor size** | | | | | | 0.024 |
| <2 cm | 781 | 40 | 767 | 86 | 0.45 (0.31-0.66) | |
| 2-5 cm | 1371 | 125 | 1419 | 155 | 0.84 (0.66-1.06) | |
| ≥5 cm | 607 | 62 | 610 | 87 | 0.70 (0.51-0.97) | |
| **Prior chemotherapy** | | | | | | 0.339 |
| Neoadjuvant | 1039 | 119 | 1048 | 184 | 0.63 (0.50-0.80) | |
| Adjuvant | 1642 | 101 | 1647 | 135 | 0.75 (0.58-0.97) | |
| **Menopausal status** | | | | | | 0.082 |
| Premenopausal | 1221 | 85 | 1232 | 142 | 0.58 (0.44-0.76) | |
| Postmenopausal | 1587 | 147 | 1597 | 191 | 0.79 (0.64-0.98) | |
| **Region** | | | | | | 0.938 |
| North America/Europe | 1470 | 111 | 1479 | 156 | 0.72 (0.56-0.92) | |
| Asia | 574 | 41 | 582 | 60 | 0.66 (0.45-0.99) | |
| Other | 764 | 80 | 768 | 117 | 0.69 (0.52-0.92) | |
| **Age** | | | | | | 0.391 |
| <65 years | 2371 | 192 | 2416 | 285 | 0.68 (0.56-0.81) | |
| ≥65 years | 437 | 40 | 413 | 48 | 0.83 (0.54-1.26) | |
| **Progesterone receptor** | | | | | | 0.846 |
| Negative | 298 | 42 | 295 | 58 | 0.71 (0.48-1.06) | |
| Positive | 2426 | 185 | 2456 | 270 | 0.69 (0.57-0.83) | |
| **Tumor stage** | | | | | | 0.422 |
| Stage IIA | 324 | 15 | 353 | 28 | 0.57 (0.30-1.07) | |
| Stage IIB | 392 | 31 | 387 | 32 | 0.99 (0.60-1.62) | |
| Stage IIIA | 1029 | 73 | 1026 | 104 | 0.70 (0.52-0.95) | |
| Stage IIIC | 950 | 100 | 963 | 156 | 0.63 (0.49-0.82) | |
| **Baseline ECOG PS** | | | | | | 0.207 |
| 0 | 2405 | 193 | 2369 | 280 | 0.67 (0.56-0.80) | |
| 1 | 401 | 39 | 455 | 52 | 0.90 (0.59-1.36) | |
| **Race** | | | | | | 0.299 |
| White | 1947 | 166 | 1978 | 237 | 0.71 (0.58-0.86) | |
| Asian | 675 | 47 | 669 | 75 | 0.60 (0.42-0.86) | |
| All others | 146 | 17 | 140 | 16 | 1.12 (0.57-2.22) | |

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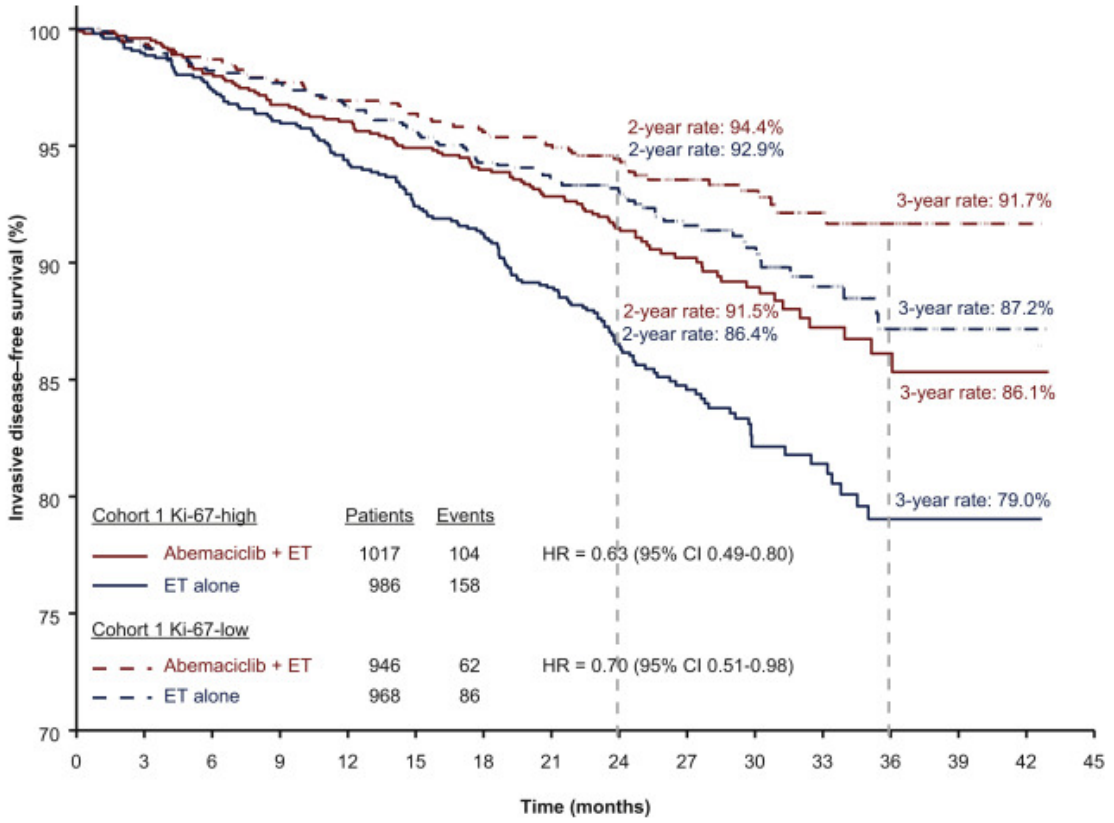
# Ki-67 Analysis in monarchE

- Ki-67 was prognostic, but not predictive of abemaciclib benefit
  - IDFS risk reduction Ki67 high vs low: 36% vs 31%
- ITT Population:
  - 30% risk reduction in IDFS
  - 31% risk reduction in DRFS

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# HR+ Early BC treatment (suggested) approach

## Post-menopausal patients

**Stage I-II (up to 3+ LNs)**

- **MP ultra-low risk** → AI x 5 years or no adjuvant therapy needed?????
- **MP low risk** → AI x 5 years
- **RS ≤ 25** → AI x 5 years
- **RS > 25** → (Neo)Adjuvant Chemotherapy → AI x 10 years → **Stage IIB with Ki67 ≥ 20%; Stage III N+** → Abemaciclib x 2 years
- **MP high risk** → (Neo)Adjuvant Chemotherapy → AI x 10 years → **Stage IIB with Ki67 ≥ 20%; Stage III N+** → Abemaciclib x 2 years

**Stage III**

- (Neo)Adjuvant Chemotherapy → AI x 10 years → **Stage IIB with Ki67 ≥ 20%; Stage III N+** → Abemaciclib x 2 years
- ***BRCA* mutation** → Olaparib x 1 year

**2021 Updated Recommendation:** Based on a secondary pre-defined analysis conducted by the FDA , two years of abemaciclib (150 mg twice daily) plus ET may be offered to patients with HR-positive, HER2-negative, node-positive early breast cancer with a high risk of recurrence and a Ki-67 score of ≥20% as determined by an FDA-approved test. (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

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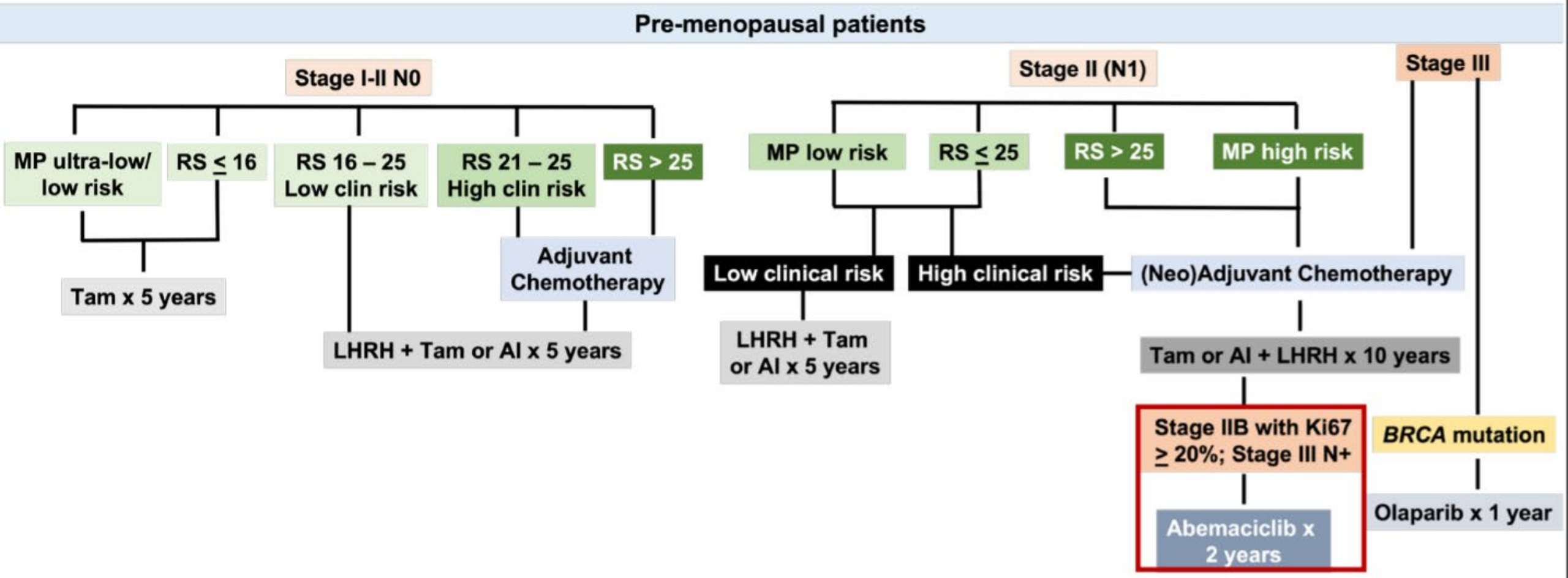
- The Panel also recommends, based on analyses reported by Harbeck et al, that abemaciclib for two years plus ET for ≥5 years may be offered to the broader intent-to-treat population of patients with resected, HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence, defined as having > 4 positive axillary lymph nodes, or as having 1-3 positive axillary lymph nodes and one or more of the following features: histologic grade 3 disease, tumor size > 5 cm, or Ki-67 index > 20%. (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

**Qualifying Statements**: Although exploratory analyses suggested similar HRs in favor of abemaciclib regardless of Ki-67 status, there were relatively few Ki-67 low tumors in monarchE. When discussing treatment options with patients, the potential benefits (improved IDFS) should be weighed against the potential harms (treatment toxicity, financial cost).

San Antonio Breast Cancer Symposium®, December 7-10, 2021

# HR+ Early BC treatment (suggested) approach




Mayer I. SABCS 2021

# Triple Negative Breast Cancer – Clinical Case

- 37yo White Woman palpated a R breast
- Mammogram/ ultrasound showed a 39 mm right breast mass
- MRI showed 4.7cm mass, no suspicious axillary adenopathy
- Ultrasound-guided biopsy: IDC, grade 3, ER-/PR-/HER2-

- Neoadjuvant Chemo: Carboplatin/ Taxol/ Keytruda followed by Adriamycin/ Cytoxan/ Keytruda
  - (Keynote 522)

- R breast mastectomy with Sentinel Lymph Nodes: pCR, 0/3 LN+

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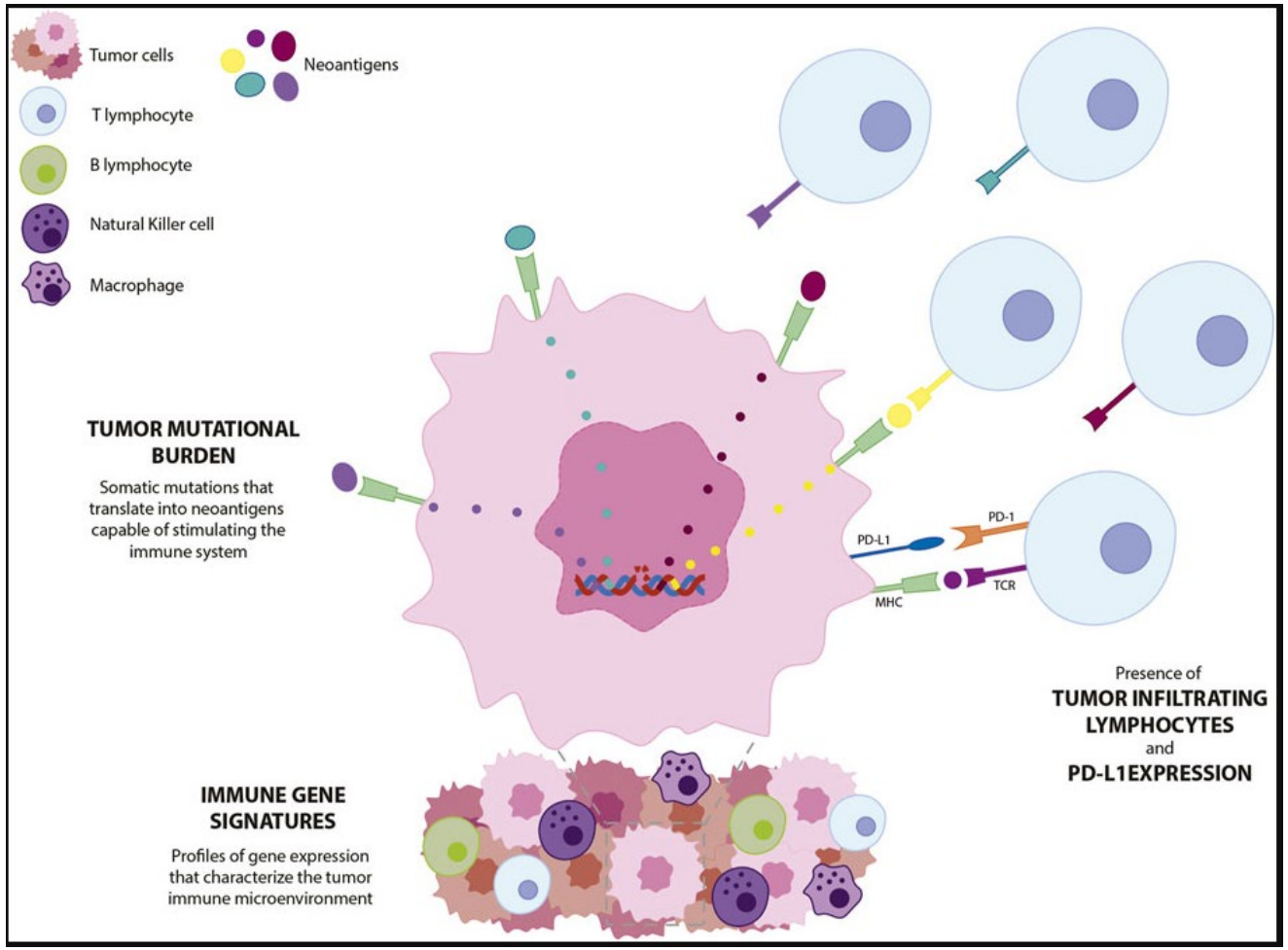
# Triple Negative Breast Cancer (TNBC) & Immunogenicity

- High tumor mutational burden
  - Compared with other BC subtypes
- High immune cell infiltrates (TILs)
- PD-L1 expression

- Chemotherapy may increase immune response of tumors

- Inverse relationship between mortality and pathologic complete response (pCR)

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# Neoadjuvant Triple Negative Therapy – Keynote 522

- Phase 3 Trial - previously untreated stage II or stage III triple-negative breast
  - 1174 patients

- 2:1 ratio of neoadjuvant therapy with four cycles of pembrolizumab (200 mg) or placebo every 3 weeks plus paclitaxel and carboplatin followed by four cycles of pembrolizumab (200mg) or placebo with anthracycline–cyclophosphamide
- After definitive surgery, adjuvant pembrolizumab or placebo every 3 weeks for up to nine cycles

- Primary end-points: pCR, EFS in ITT
  - pCR: pathological stage ypT0/Tis ypN0

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# Keynote 522 – Intent to Treat Population

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Pembrolizumab–Chemotherapy (N=784) | Placebo–Chemotherapy (N=390) |
|---|---|---|
| Age | | |
| Median (range) — yr | 49 (22–80) | 48 (24–79) |
| <65 yr — no. (%) | 701 (89.4) | 342 (87.7) |
| Menopausal status — no. (%) | | |
| Premenopausal | 438 (55.9) | 221 (56.7) |
| Postmenopausal | 345 (44.0) | 169 (43.3) |
| PD-L1 status — no. (%)† | | |
| Positive | 656 (83.7) | 317 (81.3) |
| Negative | 127 (16.2) | 69 (17.7) |
| ECOG performance-status score — no. (%)‡ | | |
| 0 | 678 (86.5) | 341 (87.4) |
| 1 | 106 (13.5) | 49 (12.6) |
| Lactase dehydrogenase level — no. (%) | | |
| ≤ULN | 631 (80.5) | 309 (79.2) |
| >ULN | 149 (19.0) | 80 (20.5) |
| Administration of carboplatin — no. (%) | | |
| Every 3 wk | 335 (42.7) | 167 (42.8) |
| Weekly | 449 (57.3) | 223 (57.2) |
| Primary tumor classification — no. (%) | | |
| T1 to T2 | 580 (74.0) | 290 (74.4) |
| T3 to T4 | 204 (26.0) | 100 (25.6) |
| Nodal involvement — no. (%) | | |
| Positive | 405 (51.7) | 200 (51.3) |
| Negative | 379 (48.3) | 190 (48.7) |
| Overall disease stage — no. (%) | | |
| Stage II | 590 (75.3) | 291 (74.6) |
| Stage III | 194 (24.7) | 98 (25.1) |
| HER2 status score — no. (%)§ | | |
| 0–1 | 595 (75.9) | 286 (73.3) |
| 2+ | 188 (24.0) | 104 (26.7) |

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# Keynote 522 – Primary Endpoint

- pCR 64.8% vs 51.2%
- PDL1+: 68.9% vs 54.9%
- PDL1-: 45.3% vs 30.3%

**Table 2. Pathological Complete Response, According to Pathological Stage.***

| Variable | Pembrolizumab–Chemotherapy (N=401) | Placebo–Chemotherapy (N=201) | Estimated Treatment Difference† | P Value |
|---|---|---|---|---|
| | | | *percentage points (95% CI)* | |
| Pathological stage ypT0/Tis ypN0 | | | | |
| No. of patients | 260 | 103 | | |
| Percentage of patients with response (95% CI) | 64.8 (59.9–69.5) | 51.2 (44.1–58.3) | 13.6 (5.4–21.8) | P<0.001 |
| Pathological stage ypT0 ypN0 | | | | |
| No. of patients | 240 | 91 | | |
| Percentage of patients with response (95% CI) | 59.9 (54.9–64.7) | 45.3 (38.3–52.4) | 14.5 (6.2–22.7) | |
| Pathological stage ypT0/Tis | | | | |
| No. of patients | 275 | 108 | | |
| Percentage of patients with response (95% CI) | 68.6 (63.8–73.1) | 53.7 (46.6–60.8) | 14.8 (6.8–23.0) | |

Schmid P et al, N Engl J Med 2020; 382:810-821

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# EFS in Keynote 522

- Initially presented with 18 mos, updated with 36 mos published February 2022
- EFS: randomization to disease progression, recurrence, second primary, or death
- Follow-up for disease status and survival was scheduled every 3 months for the first 2 years after randomization, then every 6 months for years 3 through 5, and annually thereafter.

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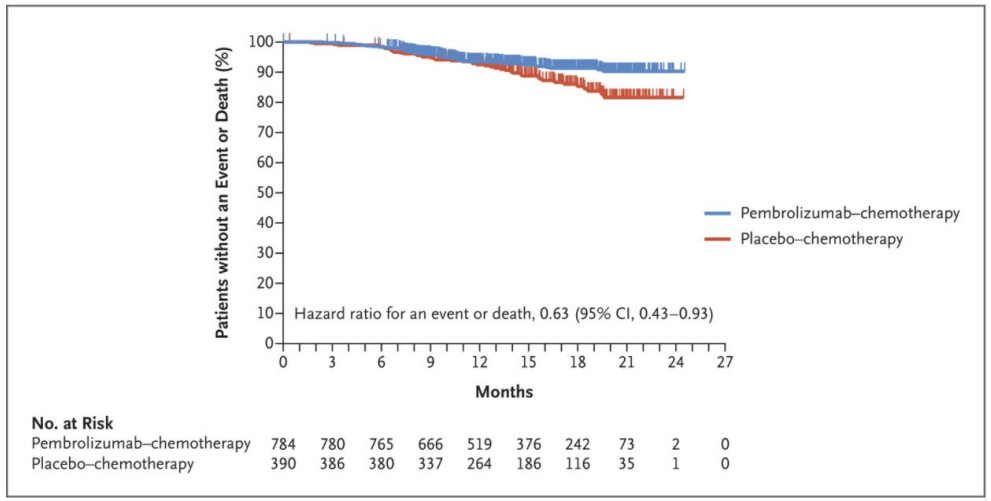
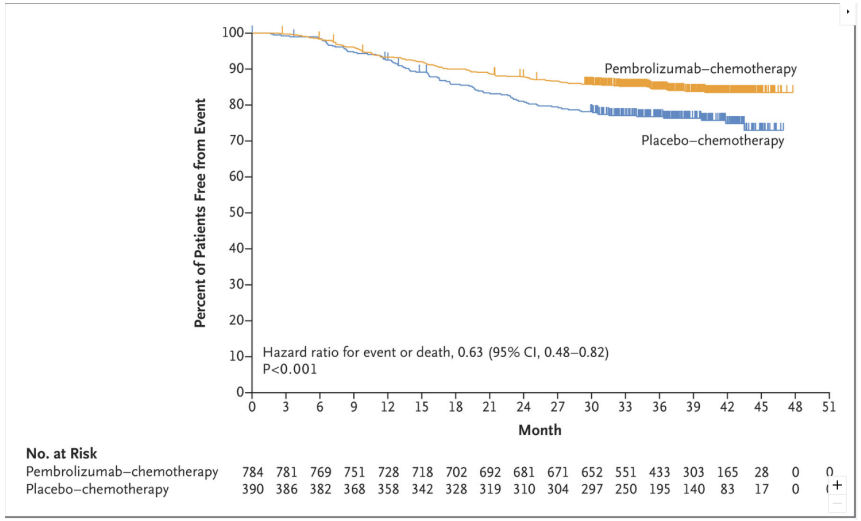
# Keynote 522 – Preliminary EFS

- 18 month EFS:
  - 91.3% Pembrolizumab arm
  - 85.3% placebo arm




Schmid P et al, N Engl J Med 2020; 382:810-821

- 36 month EFS:
  - 84.5% Pembrolizumab arm
  - 76.8% placebo arm




Schmid P et al, N Engl J Med 2022; 386:556-567

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# Exploratory analysis of RCB in Keynote 522

- Keynote-522: 35.2% of patients on pembrolizumab arm did NOT achieve pCR
- Exploratory analysis of RCB in Keynote 522 presented at ASCO 2022

| | RCB-0 Pembro | RCB-0 Pbo | RCB-1 Pembro | RCB-1 Pbo | RCB-2 Pembro | RCB-2 Pbo | RCB-3 Pembro | RCB-3 Pbo |
|---|---|---|---|---|---|---|---|---|
| **Frequency, n/N (%)** | 497/784 (63.4) | 219/390 (56.2) | 69/784 (8.8) | 45/390 (11.5) | 145/784 (18.5) | 79/390 (20.3) | 40/784 (5.1) | 26/390 (6.7) |
| **Any EFS event, n/N (%)** | 26/497 (5.2) | 16/219 (7.3) | 12/69 (17.4) | 9/45 (20.0) | 37/145 (25.5) | 35/79 (44.3) | 29/40 (72.5) | 18/26 (69.2) |
| **Distant recurrence, n (%)** | 16 (3.2) | 12 (5.5) | 6 (8.7) | 4 (8.9) | 22 (15.2) | 18 (22.8) | 14 (35.0) | 14 (53.8) |
| **36-mo EFS, % (95% CI)** | 94.7 (92.2 - 96.4) | 92.6 (88.2 - 95.4) | 83.8 (72.6 - 90.7) | 84.4 (70.1 - 92.3) | 75.7 (67.8 - 81.9) | 55.9 (44.1 - 66.2) | 26.2 (13.5 - 41.0) | 34.6 (17.5 - 52.5) |

Pusztai L, et al. JCO, 40, no. 16_suppl (June 01, 2022) 503-503

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# Safety of Pembrolizumab + Capecitabine

- Keynote 522 (neoadjuvant) recommends 9 doses of adjuvant Pembrolizumab
- CREATE-X / SYSUCC show benefit of adjuvant Capecitabine
- No concrete data on efficacy of combined therapy in residual disease
- Safety data is available

**Table 2** Treatment-related toxicities

| | Grade 1–2 | Grade >3 | All grades |
|---|---|---|---|
| Gastrointestinal | | | |
| Elevated akaline phosphatase | 57% | 10% | 67% |
| Elevated AST | 50% | 3% | 53% |
| Nausea | 53% | 0% | 53% |
| Diarrhea | 47% | 3% | 50% |
| Elevated ALT | 37% | 3% | 40% |
| Abdominal pain | 33% | 0% | 33% |
| Constipation | 33% | 0% | 33% |
| Vomiting | 30% | 0% | 30% |
| Hepatic failure | 0% | 3% | 3% |
| Dermatological and other | | | |
| Fatigue | 57% | 0% | 57% |
| Hand-foot syndrome | 30% | 13% | 43% |
| Headache | 40% | 0% | 40% |
| Pain in extremity | 37% | 0% | 37% |
| Back pain | 33% | 0% | 33% |
| Sinus tachycardia | 30% | 0% | 30% |
| Hypertension | 20% | 7% | 27% |
| Edema | 27% | 0% | 27% |
| Maculopapular rash | 13% | 3% | 17% |
| Peripheral neuropathy | 17% | 0% | 17% |
| Hematological | | | |
| Anemia | 50% | 10% | 60% |
| Lymphopenia | 33% | 20% | 53% |
| Leukopenia | 40% | 0% | 40% |
| Neutropenia | 17% | 7% | 23% |
| Thrombocytopenia | 23% | 0% | 23% |
| Other laboratory abnormalities | | | |
| Hyperglycemia | 83% | 3% | 87% |
| Hypoalbuminemia | 33% | 3% | 37% |
| Hypokalemia | 30% | 3% | 33% |
| Acute kidney injury | 0% | 3% | 3% |

ALT, alanine transaminase; AST, aspartate transaminase.

Shah, Ami N et al. *Journal for immunotherapy of cancer*; 2020 vol. 8,1

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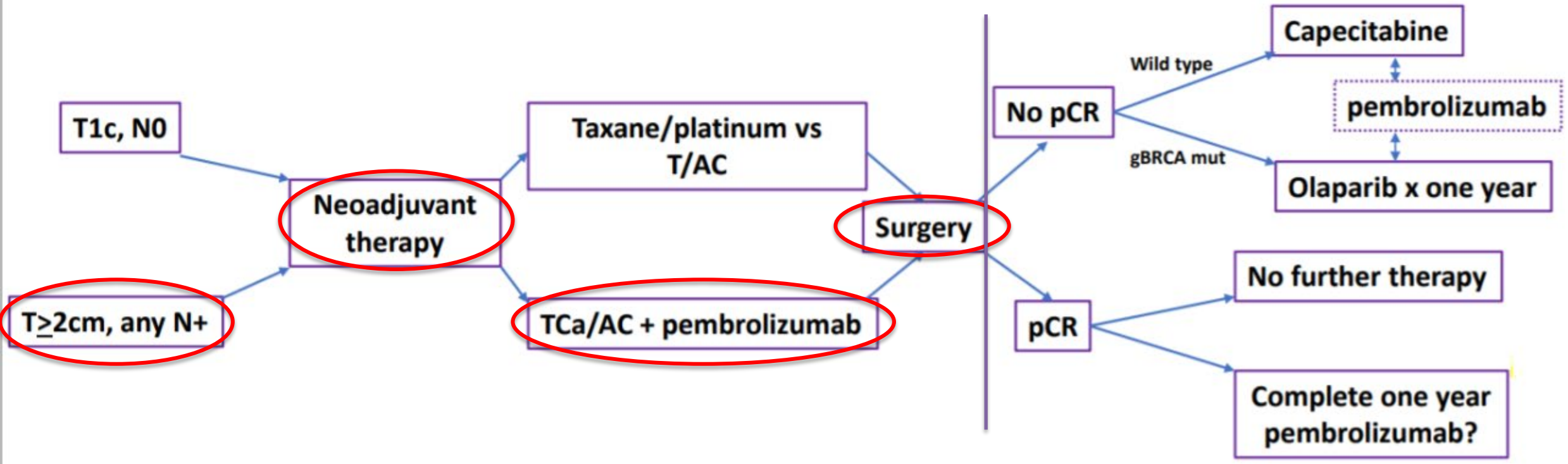
# Roadmap for Early TNBC




T1a/b, N0 → Surgery → +/- chemotherapy → taxane/carboplatin vs docetaxel/cyclophosphamide

Rugo H. SABCS 2021

# Thank you!

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