Adjuvant and Neoadjuvant Therapies for Breast Cancer, Including SABCS Updates

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Neoadjuvant Therapies for Breast Cancer, Including SABCS Updates

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Treatment decisions: personalized risk assessment

AJCC 2018

8th Edition Prognostic Stage Group

Tumor Size

Nodal Status

Metastasis

ER/PR HER2 Status

Recurrence Score (0-11)

Gene Expression Assays
Created to help de-escalate treatment in HR+ BC

<table>
<thead>
<tr>
<th>Assay</th>
<th>Nodal Involvement</th>
<th>Predictive</th>
<th>Prognostic</th>
<th>Category of Preference</th>
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<tbody>
<tr>
<td>Oncotype DX (21-gene)</td>
<td>pN0 or node negative</td>
<td>Yes</td>
<td>Yes</td>
<td>Preferred*</td>
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<td>MammaPrint (70-gene)</td>
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<td>EndoPredict (12-gene)</td>
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<tr>
<td>Breast Cancer Index</td>
<td>NS</td>
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<td>Other*</td>
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</table>

Adapted from the NCCN Guidelines for Breast Cancer

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Recurrence Score®: Continuous predictor of recurrence risk

RS = + 0.47 x HER2 Group Score
  - 0.34 x ER Group Score
  + 1.04 x Proliferation Group Score
  + 0.10 x Invasion Group Score
  + 0.05 x CD68
  - 0.08 x GSTM1
  - 0.07 x f

RS of 11 and 25 chosen as they represent the upper confidence interval for 10% and 20% risk of distant recurrence.

Paik et al. NEJM 2004
TAILORx: prospective validation of a 21-gene expression assay in breast cancer

Eligible 10,253 pts prospectively enrolled (2006-2010)

- Age < 50 years = 33-34%
- Age < 40 years = 5%
- ER and PR positive = 92%
- T size 2.1-3 cm = 19%
- T size > 3 cm = 5%
- Grade III = 13%
- Low clinical risk (per MINDACT criteria) = 74%

Sparano et al. NEJM 2015
TAILORx
iDFS and RFS

(IIT population)
9-Year Event Rates

Sparano et al. NEJM 2018
Are there subgroups that might derive some benefit from chemotherapy? Women ≤ 50 years of age

**Statistically significant chemo treatment interactions**

**Age (≤ 50, 51-65, > 65 years) and chemo benefit**
- IDFS (p = 0.003)
- DRFI (p = 0.02)

**Age, Menopause, RS (11-15, 16-20, 21-25), and chemo benefit**
- IDFS - Age-RS (p = 0.004)
- IDFS - Menopause-RS (p = 0.02)

- **RS 0-15**: 3% distant recurrence with ET alone, no evidence for chemo benefit
- **RS 16-20**: 9% fewer IDFS events with ET + Chemo, including 3.4% fewer local + distant recurrences
- **RS 21-25**: 6% fewer IDFS events with ET + Chemo, including 9.7% fewer local + distant recurrences

Sparano et al. NEJM 2018
**Key Entry Criteria**
- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

**Stratification Factors**
- Recurrence Score: 0-13 vs. 14-25
- Menopausal Status: pre vs. post
- Axillary Surgery: ALND vs. SLNB

**Primary Objective:** Determine the effect of chemotherapy on invasive disease-free survival (IDFS) in pts with 1-3 LN+ breast cancer and a RS < 25 and assess whether the effect depends on the RS

* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.
** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.

Kalinsky et al, SABCS 2020
RxPONDER Results: Accrual and ITT population

- 50% randomized to chemotherapy received TC (4 or 6 cycles)
- Ovarian function suppression use in premenopausal pts (6-month post randomization data)
  - 16% in the ET arm and 3% in Chemotherapy + ET arm
- 2 treatment-related deaths in ET arm (stroke) and 3 in chemotherapy + ET arm (sepsis, typhlitis, and liver necrosis)

Kalinsky et al, SABCS 2020
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Endocrine Therapy (n=2,506)</th>
<th>Chemotherapy (n=2,509)</th>
<th>Overall (n=5,015)</th>
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<td>19.4%</td>
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<td>Menopausal status</td>
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<tr>
<td>Postmenopausal</td>
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<td>Recurrence Score</td>
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<tr>
<td>RS 0-13</td>
<td>42.7%</td>
<td>42.9%</td>
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<tr>
<td>RS 14-25</td>
<td>57.3%</td>
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<tr>
<td>Nodal Dissection</td>
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<tr>
<td>Full ALND</td>
<td>62.7%</td>
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<td>Sentinel nodes only</td>
<td>37.4%</td>
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<td>Positive Nodes</td>
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<td>65.5%</td>
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<td>3 nodes</td>
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<tr>
<td>Low</td>
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<td>High</td>
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<td>Tumor size</td>
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<td>T1</td>
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<td>T2/T3</td>
<td>41.5%</td>
<td>42.3%</td>
<td>41.9%</td>
</tr>
</tbody>
</table>

Kalinsky et al, SABCS 2020
IDFS in Overall Population by Treatment Arm

447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

CET 5-year IDFS 92.4%
ET 5-year IDFS 91.0%

5 year IDFS Absolute Difference: 1.4%

Number at risk
CET 2509 2277 2104 1893 1648 1397 857 403 122 4
ET 2506 2327 2161 1910 1696 1404 846 397 135 11

CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

Kalinsky et al, SABCS 2020
IDFS Stratified by Menopausal Status

**Postmenopausal**

- **IDFS Event**
  - Distant: 39, 44, 83 (27%)
  - Local-Regional: 10, 14, 24 (8%)
  - Contralateral: 10, 9, 19 (8%)
  - Non-Breast Primary: 44, 47, 91 (30%)
  - Recurrence Not Classified: 9, 7, 16 (8%)
  - Death not due to Recurrence or Second Primary: 35, 37, 72 (24%)

- **Number at risk**
  - CET: 1675, 1514, 1400, 1268, 1113, 943, 555, 287, 86, 3
  - ET: 1675, 1587, 1462, 1308, 1167, 975, 601, 298, 104, 9

- CET 5-year IDFS: 91.6%
- ET 5-year IDFS: 91.2%

- Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

**Premenopausal**

- **IDFS Event**
  - Distant: 26, 50, 76 (54%)
  - Local-Regional: 8, 17, 25 (18%)
  - Contralateral: 4, 8, 12 (8%)
  - Non-Breast Primary: 10, 10, 20 (14%)
  - Recurrence Not Classified: 1, 1, 2 (1%)
  - Death not due to Recurrence or Second Primary: 2, 5, 7 (5%)

- **Number at risk**
  - CET: 834, 763, 704, 625, 535, 454, 272, 116, 34, 1
  - ET: 831, 760, 699, 602, 529, 429, 245, 99, 31, 2

- CET 5-year IDFS: 94.2%
- ET 5-year IDFS: 89.0%

- 5-year IDFS Absolute Difference: 5.2%

No Statistically Significant IDFS Difference

Kalinsky et al, SABCS 2020
IDFS Stratified by Recurrence Score and Menopausal Status

**Postmenopausal**

- **RS 0-13**
  - No Statistically Significant IDFS Difference
  - Number at risk
    - CET: 765, ET: 736

- **RS 14-25**
  - No Statistically Significant IDFS Difference
  - Number at risk
    - CET: 910, ET: 939

**Premenopausal**

- **RS 0-13**
  - 5-year IDFS Absolute Difference 3.9%
  - Number at risk
    - CET: 344, ET: 334

- **RS 14-25**
  - 5-year IDFS Absolute Difference 6.2%
  - Number at risk
    - CET: 523, ET: 407

Kalinsky et al, SABCS 2020
IDFS Stratified by Number of Nodes and Menopausal Status

Postmenopausal

1 Node

No Statistically Significant IDFS Difference

2-3 Nodes

No Statistically Significant IDFS Difference

Premenopausal

1 Node

5-year IDFS Absolute Difference 5.2%

2-3 Nodes

5-year IDFS Absolute Difference 5.1%

Kalinsky et al, SABCS 2020
Overall Survival by Menopausal Status

**Postmenopausal**
- CET 5-year OS 96.2%
- ET 5-year OS 96.1%
- No Statistically Significant OS Difference

**Premenopausal**
- CET 5-year OS 98.6%
- ET 5-year OS 97.3%
- 5-year OS Absolute Difference 1.3%

Kalinsky et al, SABCS 2020
So how do we incorporate this into practice?

Since postmenopausal women don’t seem to benefit from chemo, do they really need ALND if + SNLB?

How much benefit do premenopausal women really get from chemo vs. ovarian suppression??
**MINDACT Trial Design: 8.7 years median follow-up**

- **MINDACT population:**
  - HR+/HER2- 81%
  - HER2+ 9.5%
  - TNBC 9.6%
  - Enrolment 2007-2011

- **6693 patients**
- **112 hospitals, 9 countries**

- **Registration & Screening**
- **Surgery**

**Clinical-Pathological (C) risk**
- **Genomic (G) risk**
  - (70-gene signature)

**1st randomization to treatment**
- Use Clinical vs. Genomic risk

**Discordant cases**
- C-low/G-high or C-high/G-low

**2nd randomization**
- Anthracycline –based vs. Capecitabine-Docetaxel

**3rd randomization**
- Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

**MINDACT main hypothesis:**
- Can C-High / G-Low patients safely forego chemotherapy?

**C-Low** per modified Adjuvant! Online:
- 10-year BCS without AT
- Of >88% for ER+ and >92% for ER-
At 8.7y median FU, DMFS in 4 risk groups:

- Excellent prognosis and low rate of events in all groups except Clinical High/Genomic High.

**MINDACT results: all patients across 4 risk groups**

| Type of first event (n = 650) | distant recurrences: 68.8% | death of any cause: 31.2% |

**Concordant C-Low / G-Low** N=2744

**Discordant C-Low / G-High** N=593

**Discordant C-High / G-Low** N=1551

**Concordant C-High / G-High** N=1805

Vantveer et al., SABCS 2020
At 8.7 years medium F/U:

- **Primary endpoint continues to be met in CT untreated C-High/G-Low risk patients, confirming MINDACT as a positive de-escalation study**
- The estimated **DMFS gain for CT administration in C-High/G-Low is 2.6%** and must be balanced with CT harmful side effects
- Among clinical high-risk patients, **reduction of the use of CT in 46% patients**, when following genomic risk strategy

**SECONDARY ENDPOINT**

Clinical-High/Genomic-Low ACT vs no ACT

Distant Metastasis Free Survival (% at 5 years (95% CI) % at 8 years (95% CI))

- **ACT**
  - 95.7% (93.9-96.9%)
  - 92.0% (89.6-93.8%)
- **No ACT**
  - 94.8% (92.9-96.2%)
  - 89.4% (86.8-91.5%)
- **Abs Diff**
  - 0.9% ± 1.1% points
  - 2.6% ± 1.6% points

**Exploratory analysis by age (≤ 50 and > 50 years) omitting CT in C-High/G-Low in:**

- **postmenopausal women** continues to be safe (DMFS gain 0.2% ± 2.3%) at 8 years
- **premenopausal women** show a clinically relevant difference of DMFS gain 5% ± 2.8% at 8 years. *This later effect may possibly be related to chemotherapy-induced ovarian function suppression*

Vantveer et al., SABCS 2020
So how do we incorporate this into practice?

- **Mammaprint®**
  - « low risk » (64%)
  - « high risk » (36%)

**Postmenopausal**
- Low clin risk
- High clin risk

**Premenopausal**
- Low clin risk
- High clin risk

*Uncertain chemo benefit* Abst GS4-11 L. van’t Veer et al.

*Chemotherapy (discuss OFS + AI as an alternative)*
Risk of recurrence remains after 5 years adjuvant ET across all clinical stages

...especially in patients with high-risk features

Metzger-Filho et al. JCO 2013; Pan et al. NEJM 2017
EBCTG metanalysis: benefit of extended ET in +LNs

EBCTG - Lancet
Benefit of extended endocrine therapy in recurrence by nodal status – all trials

Node-negative
10620 women

RR 0.82 (0.71–0.95)
Logrank 2p = 0.009
5-y gain 1.1% (CI 0.1–2.0)

1-3 N+
6919 women

RR 0.74 (0.64–0.85)
Logrank 2p = 0.0003
5-y gain 3.8% (CI 2.2–5.4)

4+ N+
1621 women

RR 0.71 (0.56–0.89)
Logrank 2p = 0.003
5-y gain 7.7% (CI 3.9–11.6)

5-year gain:
1.1% (95% CI 0.1–2.0)

5-year gain:
3.8% (95% CI 2.2–5.4)

5-year gain:
7.7% (95% CI 3.9–11.6)

Control
6.2%
5.1%

AI
12.5%
6.7%

Control
19.9%
12.2%

AI
Can we refine who needs extended (~10 years) endocrine therapy?

It is reasonable to use BCI (H/I) to detect patients with +LNs that could be SPARED of (over)extended ET, but longer follow-up may be needed.

More data is needed to explore the PREDICTIVE role of BCI (H/I) for extended ET in clinical low risk patients.

BCI (H/I) High: detects clinically low risk patients at risk for late recurrence (prognosis) … But we don’t know if and how much benefit this specific group derives from extended ET (prediction???)

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Which ER+ breast cancers can safely forego, or need adjuvant chemotherapy in addition to endocrine therapy?

- **Anatomical risk**
  - Tumor size
  - Nodal status

- **Baseline gene expression profiles (GEP)**
  - Recurrence Score®
  - MammaPrint
  - EndoPredict
  - Breast Cancer Index
  - Prosigna ROR

- **Endocrine therapy response-guided**
  - Ki-67 response
  - PEPI score

| Defines risk of recurrence but not sensitivity to any treatment modality |
| Capture elements of endocrine and chemotherapy sensitivity AND are prognostic risk variables independent of anatomical risk |

Accurate absolute risk prediction requires both anatomic and GEP variables

1. Could early (week 2-4) Ki67 response identify patients who do, or do not, need chemo?
2. Is this strategy “superior” or “additive” to GEP-based treatment recommendations?
Do patients with an RS between 12 - 25 who had a Ki67 response to < 10% after 3-4 weeks of ET have the same excellent outcome as patients with RS < 12 when treated with ET alone?

**Neoadjuvant chemotherapy sub-trial criteria:**
- cN2-3 or
- Or RS 12-25 and Ki67$_{post}$$>$10% in cN0-1 tumors or
- RS$>$25 or
- G3 with Ki67$\geq$40% in tumors $>$1 cm

- Female patients $\geq$18 years old
- ER and/or PR positive (1%)/ HER2-negative unilateral EBC
- cT1-4c, cN0-3 stage
- **Candidates for adjuvant chemotherapy by conventional prognostic criteria:** cT2 or G3 or Ki67$>15%$ or $<$35 years old or cN$+$

**ADAPT HR+/HER2- trial**

Harbeck et al. SABCS2020
5-year iDFS is not significantly different by non-inferiority threshold between the two RS cohorts

Harbeck et al. SABCS2020
UNANSWERED QUESTIONS:

- RS 12-25 group with Ki67 > 10% after 3 weeks of ET: would they have done well with ET alone?

- Is the week-3 Ki67 information necessary, or is the RS score alone sufficient to recommend ET alone if RS <26?
  
  ➢ 75% patients had < 10% Ki67
Neoadjuvant chemotherapy response in postmenopausal women with clinical stage II or III ER+ BC resistant to endocrine therapy in the ALTERNATE trial (Alliance A011106)

Eligible Patients:
Postmenopausal cT2-T4c, anyN, M0
ER pos (Allred 6-8)
HER2 neg BC

N=1,382
(Feb 2014 to Nov 2018)

(36% AC-taxol, 33% qwTaxol, 20% TC, 11% other)

The Primary Endpoint: The Endocrine Sensitive Disease (ESD: pCR + mPEPI 0) rate in FULV or FULV + ANA arm was not significantly higher than that of the ANA arm (Ma, C et al ASCO 2020).

Ma et al, SABCS2020
Ki67 is not a very strong predictor of pCR

As the bulk of the Ki67 levels were between 10-30% in the ALTERNATE trial, the low pCR rate is not surprising.

Longer follow-up needed to know if the lack of pCR will indeed imply lack of IDFS benefit from chemotherapy in these patients.
Conclusions

“Less is more”:

• Tailoring chemotherapy recommendations for patients with HR+ BC:
  ➢ RS < 26 in post-menopausal women with 0-3+LN s – no chemo needed
  ➢ Jury still out in pre-menopausal women with RS < 26
    ❑ No point in ordering RS in LN+ disease for now
    ❑ (VERY limited) benefit of chemo in LN- disease in RS 16 – 25 may be due to ovarian suppression

• Extended AI therapy could be considered in high-risk post-menopausal patients with HR+
  ➢ BCI (H/I) low may spare women with LN+ from prolonged treatment

• Ki67 as a “triage” marker for chemo or endocrine therapy benefit may not be so useful in the era of gene expression signatures…
THANK YOU!
Adjuvant Therapies for Breast Cancer, Including SABCS Updates

Erica M. Stringer-Reasor, MD
O'Neal Comprehensive Cancer Center at UAB
ADJUVANT THERAPY UPDATES -- OUTLINE

• De-escalation
  • RxPonder (SABCS 2020)
  • RS-Clin -> validation of individualization tool (SABCS 2020)
  • ADAPT HR+/HER2-: Short pre-op ET to select patients for ET alone (SABCS 2020)

• Extended Adjuvant Endocrine Therapy
  • BCI (SABCS 2020)

• CDK4/6 inhibitors
  • MonarchE (SABCS 2020)
  • PENEOLOPE-B (SABCS 2020)
  • PALLAS (ESMO 2020)
PALLAS: Phase III open-label study of palbociclib and adjuvant endocrine therapy

**Eligibility:**
- Stage II-III HR+/HER2-breast cancer
- Completion of prior surgery, +/- chemo, RT
- Within 12 mo of diagnosis
- Within 6 mo of starting adjuvant endocrine treatment
- FFPE tumor block submitted

**N=5,600**

**Stratification:**
- Stage (IIA vs IIB/III)
- Chemotherapy (yes vs no)
- Age (≤50 vs >50)
- Geographic region (N. America vs Europe vs Other)

**Randomize 1:1**

**Arm A**
- Palbociclib x 2 years
  - (125 mg qd, 3 wks on/1 wk off)
  - + Endocrine Treatment*

**Arm B**
- Endocrine Treatment

**Primary Endpoint:** invasive Disease-Free Survival (iDFS)

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**PALLAS: Patient Characteristics**

- Between 9/2015 and 11/2018, 5,760 patients were randomized and included in the ITT set.
- The majority had higher stage disease and had received prior chemotherapy.
- 58.7% had high clinical risk disease, described as:
  - ≥4 nodes involved (≥N2), or
  - 1-3 nodes with either T3/T4 and/or G3 disease

<table>
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<tr>
<th>Variable</th>
<th>Palbociclib + ET (N=2,883)</th>
<th>ET (N=2,877)</th>
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<td>Age (y) – median (range)</td>
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<td>52 (22 – 85)</td>
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<td>Stage</td>
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<td>II A</td>
<td>504 (17.5%)</td>
<td>509 (17.7%)</td>
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<tr>
<td>II B</td>
<td>968 (33.6%)</td>
<td>951 (33.1%)</td>
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<tr>
<td>III</td>
<td>1402 (48.6%)</td>
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<td>T-Stage</td>
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<td>557 (19.3%)</td>
<td>500 (17.4%)</td>
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<tr>
<td>T2</td>
<td>1603 (55.6%)</td>
<td>1636 (56.9%)</td>
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<td>T3/T4</td>
<td>722 (25.0%)</td>
<td>741 (25.8%)</td>
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<tr>
<td>N1</td>
<td>1427 (49.5%)</td>
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<tr>
<td>N2</td>
<td>703 (24.4%)</td>
<td>709 (24.8%)</td>
</tr>
<tr>
<td>N3</td>
<td>385 (13.4%)</td>
<td>370 (12.9%)</td>
</tr>
<tr>
<td>Histologic Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>300 (10.4%)</td>
<td>313 (10.9%)</td>
</tr>
<tr>
<td>G2</td>
<td>1622 (56.3%)</td>
<td>1658 (57.6%)</td>
</tr>
<tr>
<td>G3</td>
<td>836 (29.0%)</td>
<td>767 (26.7%)</td>
</tr>
<tr>
<td>Prior Chemotherapy</td>
<td>2384 (82.7%)</td>
<td>2370 (82.4%)</td>
</tr>
<tr>
<td>Initial Adjuvant Endocrine Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>1954 (67.8%)</td>
<td>1918 (66.7%)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>923 (32.0%)</td>
<td>949 (33.0%)</td>
</tr>
<tr>
<td>Concurrent Adjuvant LHRH Agonist</td>
<td>532 (18.5%)</td>
<td>604 (21.1%)</td>
</tr>
</tbody>
</table>
At a median follow-up of 23.7 months, no significant difference in either 3-year iDFS or DRFS was observed.

Mayer E et al. ESMO 2020
PALLAS – IMPACT OF TREATMENT MODIFICATION

- Did treatment discontinuation or decreased treatment intensity affect outcome?
  - Looked at both dose of drug as well as question of whether time off drug more important
  - 42% discontinued drug early (27.2% due to AE)
  - 55% dose reduced to 100 mg, 34% to 75 mg at some point during treatment

- Evaluated the relationship between exposure and iDFS
  - Duration of palbociclib
  - Exposure intensity of palbociclib

![Graphs showing the relationship between exposure and iDFS](image)
Phase III study of palbociclib combined with endocrine therapy in patients with hormone-receptor-positive, HER2-negative primary breast cancer and high relapse risk after neoadjuvant chemotherapy: First results from PENELOPE-B


on behalf of the PENELOPE-B investigators
CPS-EG: includes pretreatment clinical stage, pathological stage, plus estrogen receptor and grade
### Main Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category</th>
<th>Palbociclib (N=631) N (%)*</th>
<th>Placebo (N=619) N (%)*</th>
<th>Overall (N=1250) N (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>median (range)</td>
<td>49 (22.76)</td>
<td>48 (19.79)</td>
<td>49 (19.79)</td>
</tr>
<tr>
<td>Age, years</td>
<td>≤50</td>
<td>353 (55.9)</td>
<td>348 (56.2)</td>
<td>701 (56.1)</td>
</tr>
<tr>
<td>Histological lymph node status at surgery</td>
<td>ypN 0-1</td>
<td>310 (49.1)</td>
<td>310 (50.1)</td>
<td>620 (49.6)</td>
</tr>
<tr>
<td></td>
<td>ypN 2-3</td>
<td>321 (50.9)</td>
<td>309 (49.9)</td>
<td>630 (50.4)</td>
</tr>
<tr>
<td>Ki-67%, central pathology</td>
<td>&gt;15%</td>
<td>161 (25.5)</td>
<td>158 (25.5)</td>
<td>319 (25.5)</td>
</tr>
<tr>
<td>CPS-EG score</td>
<td>2 and ypN+</td>
<td>253 (40.1)</td>
<td>255 (41.2)</td>
<td>508 (40.6)</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>378 (59.9)</td>
<td>364 (58.8)</td>
<td>742 (59.4)</td>
</tr>
<tr>
<td>Tumor stage at surgery</td>
<td>ypT0-1</td>
<td>238 (37.7)</td>
<td>208 (33.7)</td>
<td>446 (35.7)</td>
</tr>
<tr>
<td></td>
<td>ypT2-3</td>
<td>368 (58.3)</td>
<td>389 (62.9)</td>
<td>757 (60.6)</td>
</tr>
<tr>
<td></td>
<td>ypT4</td>
<td>25 (4.0)</td>
<td>21 (3.4)</td>
<td>46 (3.7)</td>
</tr>
<tr>
<td>Histological type</td>
<td>lobular</td>
<td>58 (9.2)</td>
<td>52 (8.5)</td>
<td>110 (8.8)</td>
</tr>
<tr>
<td>Grading</td>
<td>G3</td>
<td>294 (46.7)</td>
<td>297 (48.1)</td>
<td>591 (47.4)</td>
</tr>
<tr>
<td>Ovarian ablation</td>
<td></td>
<td>108 (17.1)</td>
<td>113 (18.3)</td>
<td>221 (17.7)</td>
</tr>
<tr>
<td>Endocrine therapy Tamoxifen</td>
<td>overall</td>
<td>314 (49.8)</td>
<td>308 (49.8)</td>
<td>622 (49.8)</td>
</tr>
</tbody>
</table>

*valid percent

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80% of patients completed all cycles of palbo
RDI palbo 82%; RDI placebo 89%

As expected from stats
Type of iDFS Events

- iDFS, overall: N=156
- Distant recurrences: N=116
  - Palbociclib: N=111
  - Placebo: N=27
  - Palbociclib: N=27
- Invasive locoregional recurrences: N=48
- Contralateral breast cancer: N=2
- Second primary invasive non-breast cancer: N=18
- Death without previous event: N=4

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Overall Survival (Interim Analysis)

San Antonio Breast Cancer Symposium, December 08-11, 2020

Overall Survival Rate (%)

Median Follow-Up 42.8 Months

Patients at risk:
- Placebo: 619
- Palbociclib: 631

Time (months)

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PENELlopeB CONCLUSIONS

• With median follow-up of 43 months, no improvement in outcome with addition of 1 year of palbociclib to endocrine therapy
• Compliance declined over time but remained good
  • 80.5% vs 84.5% completed therapy
  • Relative total dose intensity 82% vs 99%
MONARCHE STUDY – PRIMARY OUTCOME ANALYSIS

**HR+, HER2-, Node+ high risk early breast cancer**

**Cohort 1:** Inclusion based on clinicopathological risk factors:
- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Histologic Grade 3
  - Tumor size ≥5 cm

**Cohort 2:** Inclusion based on Ki-67:
- 1-3 ALN and
- Centrally tested Ki-67 ≥20%

- No Grade 3 and tumor size not ≥5 cm

**Other criteria:**
- Women or men
- Pre-/post menopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No distant metastasis
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

**Abemaciclib** (150mg twice daily for up to 2 years)
- + Standard of Care Endocrine Therapy
  - (5 to 10 years as clinically indicated)

**R 1:1**

**ITT includes both C1 and C2**

**Stratified for:**
- Prior chemotherapy
- Menopausal status
- Region

**Primary Objective:** Invasive disease-free survival (IDFS) (STEEP criteria)

**Key Secondary Objectives:** IDFS in Ki-67 high (≥20%) population, Distant relapse-free survival (DRFS), Overall survival, Safety, Patient reported outcomes, and Pharmacokinetics

**Median follow-up:** 19.1 months in both arms (15.5 months at IA2)

**Recruitment from July 2017 to August 2019; Treatment period = first 2 years on study treatment after randomization; Endocrine therapy of physician’s choice (e.g., aromatase inhibitors, tamoxifen, LHRH agonist); Ki-67 expression assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry Assay by Dako/Agilent**

6Johnston SD et al JCO 2020
Joyce O'Shaughnessy et al SABCS 2020
### High risk disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Abemaciclib + ET N = 2808, n (%)</th>
<th>ET Alone N = 2829, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of positive lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (0.2)</td>
<td>7 (0.2)</td>
</tr>
<tr>
<td>1-3</td>
<td>1119 (39.9)</td>
<td>1143 (40.4)</td>
</tr>
<tr>
<td>≥4 or more</td>
<td>1680 (59.8)</td>
<td>1679 (59.3)</td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>209 (7.4)</td>
<td>215 (7.6)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1373 (48.9)</td>
<td>1395 (49.3)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1090 (38.8)</td>
<td>1066 (37.7)</td>
</tr>
<tr>
<td>Primary tumor size by pathology following definitive surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>780 (27.8)</td>
<td>765 (27.0)</td>
</tr>
<tr>
<td>2-5 cm</td>
<td>1369 (48.8)</td>
<td>1419 (50.2)</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>610 (21.7)</td>
<td>612 (21.6)</td>
</tr>
<tr>
<td>Central Ki-67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20%</td>
<td>953 (33.9)</td>
<td>973 (34.4)</td>
</tr>
<tr>
<td>≥20%</td>
<td>1262 (44.9)</td>
<td>1233 (43.6)</td>
</tr>
<tr>
<td>Unavailable</td>
<td>593 (21.1)</td>
<td>623 (22.0)</td>
</tr>
<tr>
<td>Progesterone receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2421 (86.2)</td>
<td>2453 (86.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>298 (10.6)</td>
<td>294 (10.4)</td>
</tr>
</tbody>
</table>

**Additional high risk eligibility criteria for patients with 1-3 nodes**

- Tumor size ≥5 cm (pathology)\(^a\)
- Tumor size ≥5 cm (imaging)\(^a, b\)
- Histologic grade 3\(^a\)
- Central Ki-67 ≥20% only\(^c\)

**Note:** where values do not add up to 100%, remaining data are missing, unavailable or could not be assessed.

- Median Age: 51 (15% age 65 or older)
- 56% postmenopausal
- 95% prior (neo)adjuvant chemo

---

\(^a\) Patients could be counted in more than one of the subcategories under 1-3 positive lymph nodes; \(^b\) Patients who received neoadjuvant chemotherapy may have been eligible based on imaging tumor size prior to receiving systemic therapy; \(^c\) Patients not double counted; patients did not have tumor size ≥5 cm (either by pathology or imaging) or histologic grade 3.
INVASIVE DISEASE-FREE SURVIVAL (ITT) AT PO ANALYSIS

Statistically significant and clinically meaningful improvement in IDFS with greater treatment benefit at PO analysis.

Two-year IDFS rates were 92.3% in the abemaciclib + ET arm and 89.3% in the ET arm - 3.0% difference.

Two-year IDFS rates were 92.2% (abemaciclib + ET arm) and 88.7% (ET arm) – 3.5% absolute difference.

Number of IDFS events

<table>
<thead>
<tr>
<th></th>
<th>Abemaciclib + ET</th>
<th>ET Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>163</td>
<td>232</td>
</tr>
</tbody>
</table>

Nominal p = 0.0009 (2-sided)
HR (95% CI): 0.713 (0.583, 0.871)

Risk of developing an IDFS event reduced by 28.7%

IA2 HR (95% CI)^2 = 0.747 (0.598, 0.932)

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### IDFS in Prespecified Subgroups at PO Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Abemaciclib + ET</th>
<th>ET Alone</th>
<th>Abemaciclib + ET</th>
<th>ET Alone</th>
<th>Interaction (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2816</td>
<td>103</td>
<td>2596</td>
<td>330</td>
<td>0.713 (0.683, 0.741)</td>
</tr>
<tr>
<td>Number of Pos. Lymph Nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>1184</td>
<td>62</td>
<td>1142</td>
<td>74</td>
<td>0.713 (0.683, 0.741)</td>
</tr>
<tr>
<td>10-19</td>
<td>1015</td>
<td>54</td>
<td>1102</td>
<td>87</td>
<td>0.644 (0.603, 0.687)</td>
</tr>
<tr>
<td>20 or more</td>
<td>575</td>
<td>34</td>
<td>354</td>
<td>71</td>
<td>0.749 (0.680, 0.822)</td>
</tr>
<tr>
<td>Histologic Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>209</td>
<td>9</td>
<td>215</td>
<td>10</td>
<td>0.919 (0.783, 1.083)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1027</td>
<td>50</td>
<td>1051</td>
<td>101</td>
<td>0.989 (0.901, 1.082)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1056</td>
<td>61</td>
<td>1054</td>
<td>106</td>
<td>0.731 (0.562, 1.000)</td>
</tr>
<tr>
<td>Primary Tumor Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 cm</td>
<td>781</td>
<td>36</td>
<td>777</td>
<td>61</td>
<td>0.984 (0.886, 1.096)</td>
</tr>
<tr>
<td>&gt;7 cm</td>
<td>1079</td>
<td>60</td>
<td>1110</td>
<td>183</td>
<td>0.966 (0.844, 1.106)</td>
</tr>
<tr>
<td>Adjuvant Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>1039</td>
<td>57</td>
<td>1048</td>
<td>143</td>
<td>0.900 (0.808, 1.002)</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>1838</td>
<td>97</td>
<td>1651</td>
<td>80</td>
<td>0.986 (0.886, 1.101)</td>
</tr>
<tr>
<td>Neoadjuvant + Postoperative</td>
<td>1222</td>
<td>50</td>
<td>1222</td>
<td>54</td>
<td>0.984 (0.852, 1.124)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North Central/West</td>
<td>1510</td>
<td>74</td>
<td>1524</td>
<td>107</td>
<td>0.707 (0.610, 0.821)</td>
</tr>
<tr>
<td>Asia</td>
<td>674</td>
<td>33</td>
<td>690</td>
<td>42</td>
<td>0.779 (0.618, 1.000)</td>
</tr>
<tr>
<td>Europe</td>
<td>754</td>
<td>34</td>
<td>780</td>
<td>82</td>
<td>0.902 (0.767, 1.061)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65 years</td>
<td>2371</td>
<td>130</td>
<td>2410</td>
<td>264</td>
<td>0.994 (0.891, 1.103)</td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>327</td>
<td>20</td>
<td>347</td>
<td>26</td>
<td>1.041 (0.888, 1.218)</td>
</tr>
<tr>
<td>Hormone Receptor Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>2465</td>
<td>131</td>
<td>2506</td>
<td>165</td>
<td>0.706 (0.591, 0.850)</td>
</tr>
<tr>
<td>Positive</td>
<td>3436</td>
<td>157</td>
<td>3458</td>
<td>185</td>
<td>0.908 (0.802, 1.027)</td>
</tr>
<tr>
<td>Turner Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IA</td>
<td>504</td>
<td>17</td>
<td>521</td>
<td>18</td>
<td>0.725 (0.631, 1.202)</td>
</tr>
<tr>
<td>Stage IB</td>
<td>356</td>
<td>17</td>
<td>373</td>
<td>15</td>
<td>0.576 (0.455, 0.735)</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>506</td>
<td>21</td>
<td>527</td>
<td>18</td>
<td>0.725 (0.631, 1.202)</td>
</tr>
<tr>
<td>Stage III</td>
<td>590</td>
<td>21</td>
<td>611</td>
<td>19</td>
<td>0.544 (0.437, 0.675)</td>
</tr>
<tr>
<td>Breast Cancer DCIS</td>
<td>12</td>
<td>1</td>
<td>13</td>
<td>2</td>
<td>0.008 (0.021, 0.347)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>110</td>
<td>17</td>
<td>117</td>
<td>13</td>
<td>0.073 (0.412, 0.828)</td>
</tr>
<tr>
<td>IB</td>
<td>765</td>
<td>36</td>
<td>801</td>
<td>60</td>
<td>0.789 (0.625, 1.013)</td>
</tr>
<tr>
<td>IIA</td>
<td>706</td>
<td>32</td>
<td>738</td>
<td>13</td>
<td>0.077 (0.188, 0.366)</td>
</tr>
</tbody>
</table>

No statistically significant interactions observed supporting consistent benefit across all subgroups at PO analysis.
ABEMACICLIB DISCONTINUATIONS AT PO ANALYSIS

Over half of the early discontinuations due to AEs occurred within the first 5 months of treatment.

Some patients who discontinued abemaciclib and remained on ET may have been double counted for an early discontinuation due to a different reason once ET was discontinued.

Other includes lost to follow-up (0.3, 0.4), physician decision (0.5, 0.1), protocol deviation (0, 0.3), study terminated (0, 0.1) and other (0.3, 0) in the abemaciclib + ET alone and ET alone arm, respectively.

6.2% of patients discontinued both abemaciclib and ET due to AEs.

### Discontinuations of abemaciclib due to AEs

<table>
<thead>
<tr>
<th>Treatment Discontinuation</th>
<th>Abemaciclib + ET N=2791, n (%)</th>
<th>ET alone N=2800, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For any reason</td>
<td>773 (27.7)%</td>
<td>410 (14.6)%</td>
</tr>
<tr>
<td>Due to AEs, including deaths due to AEs</td>
<td>481 (17.2)%</td>
<td>23 (0.8)%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>141 (5.1)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>53 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal by subject</td>
<td>156 (5.6)</td>
<td>160 (5.7)</td>
</tr>
<tr>
<td>IDFS/DRFS events</td>
<td>136 (4.9)</td>
<td>204 (7.3)</td>
</tr>
<tr>
<td>Deaths due to study disease</td>
<td>2 (&lt;0.1)</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>8 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Otherb</td>
<td>32 (1.1)</td>
<td>21 (0.8)</td>
</tr>
</tbody>
</table>

a Some patients who discontinued abemaciclib and remained on ET may have been double counted for an early discontinuation due to a different reason once ET was discontinued.
b Other includes lost to follow-up (0.3, 0.4), physician decision (0.5, 0.1), protocol deviation (0, 0.3), study terminated (0, 0.1) and other (0.3, 0) in the abemaciclib + ET alone and ET alone arm, respectively.
c 0.2% of patients discontinued both abemaciclib and ET due to AEs.

c6% of patients discontinued both abemaciclib and ET due to AEs.
# ADJUVANT TRIALS WITH CDK4/6I

<table>
<thead>
<tr>
<th></th>
<th>MonarchE</th>
<th>PALLAS</th>
<th>Penelope®</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5637</td>
<td>5600</td>
<td>1250</td>
</tr>
<tr>
<td>CDKi</td>
<td>Abemaciclib</td>
<td>Palbociclib</td>
<td>Palbociclib</td>
</tr>
<tr>
<td>Eligibility</td>
<td>≥ N2 or</td>
<td>≥ N1 and G3 or T3 (1) (N1 and Ki67 ≥ 20% (2))</td>
<td>Anatomic stage 2 or 3 (59% N2 or N1 and G3 or T3)</td>
</tr>
<tr>
<td>CDKi duration</td>
<td>24 months</td>
<td>24 months</td>
<td>12 months</td>
</tr>
<tr>
<td>F/UP</td>
<td>19 months</td>
<td>24 months</td>
<td>43 months</td>
</tr>
<tr>
<td>IDFS 2 year (∆)</td>
<td>92% vs 89% (3%)</td>
<td>NR</td>
<td>88% vs 84% (4%)</td>
</tr>
<tr>
<td>IDFS 3 year (∆)</td>
<td>NR</td>
<td>88% vs 89% (-1%)</td>
<td>81% vs 78% (3%)</td>
</tr>
<tr>
<td>IDFS 4 year (∆)</td>
<td>NR</td>
<td>NR</td>
<td>73% vs 72% (0.6%)</td>
</tr>
<tr>
<td>DRFS (∆)</td>
<td>94% vs 91% (3%) @ 2 yr</td>
<td>89% vs 90% @ 3 yr</td>
<td>No difference</td>
</tr>
<tr>
<td>Discontinuation rate</td>
<td>28%</td>
<td>42%</td>
<td>20%</td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>17%</td>
<td>27%*</td>
<td>5%</td>
</tr>
<tr>
<td>Completed Rx</td>
<td>72%</td>
<td>32%</td>
<td>80%</td>
</tr>
</tbody>
</table>

* 64% of discontinuations

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ADJUVANT CDK4/6I
WHY WAS MONARCHE POSITIVE AND PALBO TRIALS NEGATIVE?

• Different patient populations?
  • N2/N3 59% monarchE vs 37% in PALLAS
  • But no benefit in PALLAS high risk subset or PENEOLOPEB

• Duration of follow-up?
  • Benefit with palbo early in PENEOLOPEB that disappeared over time
  • Effect diminishing (a bit) over time: ▲3.5% (mF/U 15.5 mos) and ▲3.0% (mF/U 19.1 mos)

• Different drugs in terms of CDK4/6 inhibition and dosing (intermittent vs continuous)
  • Highly selective use of abemaciclib in the adjuvant setting

• High discontinuation rate in PALLAS
  • Analysis does not support a difference in benefit based on dose modification

• NATALEE (3 yrs adjuvant ribociclib) results pending

• Awaiting biomarker studies
• **Who We Are**
  An alliance of leading cancer centers devoted to patient care, research, and education

• **Our Mission**
  To improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives

• **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally