The American Society of Clinical Oncology (ASCO) recently hosted the virtual annual meeting May 29th - 31st, 2020. This CARE™ Update from ASCO focuses on trials presented in breast cancer.

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In this chapter of the CARE™ Perspectives ASCO Conference Report:

Breast Cancer Plenary and Oral Session Highlights

- E2108
- KAITLIN
- KEYNOTE-355
- HER2CLIMB
- PARSIFAL

Abstract selection provided by CARE™ Oncology Faculty member:

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Medical Oncology
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CARE™ GU Faculty
**ASCO 2020 LBA2.** A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: A trial of the ECOG-ACRIN Research Group (E2108).

**Trial Background/Summary:**
- About 6% of newly diagnosed breast cancer patients present with Stage IV disease and an intact primary tumor (IPT). Locoregional treatment (LRT) for the IPT is hypothesized to improve survival based on retrospective analyses, but randomized trials have provided conflicting data.
- 390 patients were enrolled between 2/8/11 and 7/23/15, and received OST. Of these, 256 eligible patients were randomized to either continued OST alone (N = 131) or OST+LRT (N = 125).
- There were 121 deaths and 43 locoregional progression events after a median follow up of 59 months (range: 0-91).
- There was no significant difference in OS (3-year OS rate 68.4% in OST+LRT vs. 67.9% OST alone arm, stratified log-rank p = 0.63, HR = 1.09, 90% CI: 0.80, 1.49) or in progression-free survival (p = 0.40).
- The locoregional recurrence/progression was significantly higher in the OST alone arm (3-year rate 25.6% vs 10.2%, Gray test p = 0.003).
- Health-related quality of life (HRQOL) measured by FACT-B Trial Outcome Index was significantly worse in the OST+LRT arm than OST alone arm at 18 months post randomization (60% completion, Wilcoxon rank sum test p = 0.01), but no difference was observed at time points 6 months (74% completion) or 30 months (56% completion).

**Study Conclusion:**
Early local therapy does not improve survival in patients with de novo metastatic breast cancer and an IPT. Although there was a 2.5-fold higher risk of local disease progression without LRT, LRT of the IPT did not lead to improved HRQOL.

**ASCO 2020 Abstract 500.** Primary analysis of KAITLIN: A phase III study of trastuzumab emtansine (T-DM1) + pertuzumab versus trastuzumab + pertuzumab + taxane, after anthracyclines as adjuvant therapy for high-risk HER2-positive early breast cancer (EBC).

**Trial Background/Summary:**
- Recurrence in HER2-positive EBC—particularly in high-risk populations—remains a problem, as does systemic chemotherapy-associated toxicity.
- In KAITLIN, we aimed to improve efficacy and reduce toxicity by replacing taxanes and trastuzumab with T-DM1.
- The study did not meet its co-primary endpoints.
- In LN+ patients (n = 1658), there was no significant difference between arms in IDFS event risk (stratified hazard ratio = 0.97; 95%CI 0.71–1.32).
- Three-year IDFS was 94.1% with AC-THP and 92.7% with AC-KP.
- Results were similar in the ITT population (stratified hazard ratio = 0.98; 95%CI 0.72–1.32; 3-year IDFS: 94.2% vs 93.1%).
- OS data are immature with an event rate of ~4%–5% in each arm.
- There was a similar incidence of grade ≥3 AEs (55.4% vs 51.8%) and SAEs (23.3% vs 21.4%) with AC-THP and AC-KP, respectively.
- More patients receiving AC-KP than AC-THP discontinued T-DM1 or trastuzumab, respectively, because of AEs (26.8% vs 4.0%).

**Study Conclusion:**
Replacing adjuvant taxane and trastuzumab with T-DM1 did not result in significantly improved efficacy or overall safety. Nonetheless, in this high-risk population, a favorable IDFS outcome was achieved in both study arms. HP + chemotherapy remains the standard of care for patients with high-risk HER2-positive EBC.
ASCO 2020 Abstract 1000. KEYNOTE-355: Randomized, double-blind, phase III study of pembrolizumab + chemotherapy versus placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer

Javier Cortes et al.

Trial Background/Summary:

- Pembrolizumab (pembro) monotherapy showed promising antitumor activity and manageable safety in patients (pts) with metastatic TNBC in KEYNOTE-012, -086 and -119. KEYNOTE-355 (ClinicalTrials.gov, NCT02819518) compared pembro + chemotherapy (chemo) vs placebo (pbo) + chemo for previously untreated locally recurrent inoperable or metastatic TNBC.
- As of Dec 11 2019, median follow-up was 17.5 mo for pembro + chemo (n=566) and 15.5 mo for chemo (n=281).
- Pembro + chemo significantly improved PFS vs chemo alone in pts with CPS ≥10 tumors (Table).
- OS follow-up is ongoing. Grade 3-5 treatment-related AE rates were 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%.

Table. KEYNOTE-355 Study results

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Median PFS, mo</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>P-value boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPS ≥10</td>
<td>P + C (n=220) vs C (n=103)</td>
<td>9.7 vs 5.6</td>
<td>0.65 (0.49-0.86)</td>
<td>0.0012</td>
<td>0.00411</td>
</tr>
<tr>
<td>CPS ≥1</td>
<td>P + C (n=425) vs C (n=211)</td>
<td>7.6 vs 5.6</td>
<td>0.74 (0.61-0.90)</td>
<td>0.0014</td>
<td>0.00111</td>
</tr>
<tr>
<td>ITT</td>
<td>P + C (n=566) vs C (n=281)</td>
<td>7.5 vs 5.6</td>
<td>0.82 (0.69-0.97)</td>
<td>-</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Study Conclusion:

Pembro combined with several chemo partners showed a statistically significant and clinically meaningful improvement in PFS vs chemo alone in pts with previously untreated locally recurrent inoperable or metastatic TNBC whose tumors expressed PD-L1 (CPS ≥10). Pembro + chemo was generally well tolerated, with no new safety concerns.
**ASCO 2020 Abstract 1005.** Tucatinib versus placebo added to trastuzumab and capecitabine for patients with previously treated HER2+ metastatic breast cancer with brain metastases (HER2CLIMB).

*Nancy U. Lin et al.*

**Trial Background/Summary:**
- Tucatinib (TUC) is an investigational, highly selective HER2 kinase inhibitor. HER2CLIMB (NCT02614794) showed clinically meaningful and statistically significant improvements in overall survival (OS) and progression free survival (PFS) in all pts, prolongation of PFS in pts with brain metastases (BM), and objective response rate (ORR) when TUC was added to trastuzumab (T) and capecitabine (C).
- Overall, 291 pts (48%) had BM at baseline: 198 (48%) in the TUC arm and 93 (46%) in the control arm.
- There was a 68% reduction in risk of CNS-PFS in the TUC arm (HR: 0.32; 95% CI: 0.22, 0.48; P < 0.0001).
- Risk of death overall was reduced by 42% in the TUC arm (OS HR: 0.58; 95% CI: 0.40, 0.85; P = 0.005).
- Median CNS-PFS was 9.9 mo in the TUC arm vs 4.2 mo in the control arm.
- Median OS was 18.1 mo vs 12.0 mo. ORR-IC was higher in the TUC arm (47.3%; 95% CI: 33.7, 61.2) vs the control arm (20.0%; 95% CI: 5.7, 43.7). Median DOR-IC was 6.8 mo (95% CI: 5.5, 16.4) vs 3.0 mo (95% CI: 3.0, 10.3).
- In pts with isolated brain progression who continued study therapy after local treatment (n = 30), risk of second progression or death was reduced by 67% (HR: 0.33; 95% CI: 0.11, 1.02), and median PFS from randomization was 15.9 mo vs 9.7 mo, favoring the TUC arm.

**Study Conclusion:**
In pts with heavily previously treated HER2+ MBC with BM, TUC in combination with T and C doubled the ORR-IC, reduced risk of IC progression or death by two thirds and reduced risk of death by nearly half. If approved, TUC in combination with T and C has the potential to become a new standard of care in pts with HER2+ MBC with and without BM.

**ASCO 2020 Abstract 1007.** PARSIFAL: A randomized, multicenter, open-label, phase II trial to evaluate palbociclib in combination with fulvestrant or letrozole in endocrine-sensitive patients with estrogen receptor [ER][+]HER2[-] metastatic breast cancer.

*Antonio Llombart-Cussac et al.*

**Trial Background/Summary:**
- PARSIFAL aimed to identify the best endocrine agent to combine with P in this first-line scenario
- By March 9th, 2020, 256 PFS events occurred.
- At median follow-up of 32 mo, median PFS was 27.9 mo (95% confidence interval [CI], 24.2-33.1) with PF and 32.8 mo (95% CI, 25.8-35.9) with PL (HR: 1.1; 95% CI, 0.9-1.5; P = 0.321).
- No differences were observed for pts with or without visceral involvement (HR: 1.3 and HR: 0.97 respectively, interaction P = 0.275), and for “de novo” or recurrent metastatic disease (HR: 1.1 and HR: 1.1 respectively, P = 0.979).
- The 4-year OS rate was 67.6% in PF and 67.5% in PL arm (HR: 1; 95% CI, 0.7-1.5; P = 0.986).
- No differences were observed in ORR or CBR between arms.
- Grade ≥3 adverse events were similar in both arms, being neutropenia and leukopenia the most frequent. No treatment-related deaths were reported.

**Study Conclusion:**
This study was not able to identify an improvement in PFS for PF over PL in patients with endocrine-sensitive ER[+]HER2[-] MBC. As both arms demonstrated comparable 4 years-OS, PF is a reasonable alternative to PL in this setting.
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