ASCO 2020 Virtual Congress Breast Cancer Highlights

American Society of Clinical Oncology
29th – 31st May 2020

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ASCO 2020 Breast Cancer Highlights
Introduction

Roche ASCO 2020 Steering Committee

Data covered in the ASCO 2020 Breast Cancer Highlights were chosen by a Steering Committee of UK Breast Cancer Experts, who provided feedback on what they thought was most relevant to the UK clinical community:

- Dr Andreas Makris, Consultant Clinical Oncologist (Mount Vernon Cancer Centre, Middlesex) – Steering Committee Chair
- Professor Andrew Wardley, Consultant and MAHSC Professor in Medical Oncology (The Christie Hospital, Manchester)
- Dr David Miles, Consultant Medical Oncologist (Mount Vernon Cancer Centre, Middlesex)
- Dr Duncan Wheatley, Consultant Clinical Oncologist (Royal Cornwall Hospital, Truro)
- Dr Fharat Raja, Consultant Medical Oncologist (University College London Hospital, London)
- Professor Mark Beresford, Consultant Clinical Oncologist (Royal United Bath Hospital, Bath)
- Mr Mark Sibbering, Consultant Breast Surgeon (University Hospitals of Derby and Burton, Derby)
- Dr MB Mukesh, Consultant Clinical Oncologist (Colchester General Hospital, Colchester)
- Mr Stuart McIntosh, Clinical Senior Lecturer in Surgical Oncology (Queen's University, Belfast)

These individuals represent a range of specialities in breast oncology and are a group of key investigators in the field of breast cancer.

Abbreviations: ASCO, American Society of Clinical Oncology; MAHSC, Manchester Academic Health Science Centre.

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Neoadjuvant Treatment

FELINE trial: letrozole (LET) + ribociclib (RIB) vs LET + placebo (PBO) as neoadjuvant therapy for ER+ BC

Breast Cancer – Local/Regional/Adjuvant [Oral Presentation #505]: Dr Qamar J. Khan (University of Kansas Medical Centre, Westwood, KS, USA)

Trial: FELINE (NCT02712723)

Population: Postmenopausal women with breast tumour >2 cm or N+, ER+/HER2- BC.

Study Design: Biomarker-based multicentre randomised trial comparing changes in Ki-67 and preoperative endocrine prognostic index (PEPI). Patients were randomised 1:1:1 to neoadjuvant LET+PBO (n=38), LET+RIB intermittent dose (RIBi; n=41) or LET+RIB continuous dose (RIBc; n=41).

Primary Outcome: PEPI 0 at surgery, defined as tumour size ≤5 cm, N0, Ki-67 ≤2.7% and Allred ER score 3-8 (LET+PBO vs LET+RIBi/c).

Secondary Outcomes: Complete cell cycle arrest (CCCA) and response rates (RECIST) at Day 14 Cycle 1 (D14C1), comparing LET+PBO vs LET+RIBi/c; efficacy (PEPI, CCCA, response rates) and toxicity, comparing LET+RIBi vs LET+RIBc.

Author's Conclusion: Addition of RIB to LET as neoadjuvant therapy did not result in more women with PEPI 0. Early suppression of Ki-67 by LET+RIBi/c at D14C1 was not maintained at surgery, suggesting early on-therapy acquired resistance to RIB in some patients.

Results:

- PEPI 0 at surgery was equal in the LET+PBO (25.8%; n/N=8/31) and LET+RIBi/c (25.4%, n/N=18/71) arms (p=0.96).
- More patients achieved CCCA at D14C1 with LET+RIBi/c compared to LET+PBO (92% vs 52%; p<0.0001; Table 1).
- There was no difference in efficacy (CCCA, PEPI) between LET+RIBi and LET+RIBc.
- Grade >3 AEs were observed in 4 (10%), 23 (56%) and 19 (46%) patients in the LET+PBO, LET+RIBi and LET+RIBc arms, respectively.

Table 1: Ki-67 and CCCA results

	LET+PBO	LET+RIBi/c	p-value
Baseline to D14C1			
Mean change in Ki-67 from baseline to D14C1, %	-15.7	-23.3	0.047
CCCA at D14C1, % (n/N)	51.7 (15/29)	91.9 (68/74)	<0.0001
D14C1 to surgery			
Increase in Ki-67 from D14C1 to surgery, % (n/N)	33.3 (8/24)	65.7 (44/67)	0.006
CCCA at surgery, %	61.3	71.4	0.4225

> **Prof Mark Beresford** noted how there was a significant difference in CCCA at D14C1 between the LET+PBO and LET+RIBi/c arms (p<0.001), but this difference was not maintained at surgery. He commented how the use of PET scans to assess early response may show an early response in cell cycle arrest or cell proliferation, but the end results would ultimately be no different.

ALTERNATE: Neoadjuvant endocrine treatment (NET) approaches for clinical Stage II or III ER+/HER2- BC in postmenopausal women

Breast Cancer – Local/Regional/Adjuvant [Oral Presentation #504]: Prof Cynthia Ma (Washington University School of Medicine, St. Louis, MO, USA)

Trial: ALTERNATE (NCT01953588)

Population: Postmenopausal patients with clinical Stage II or III ER+/HER2- BC.

Study Design: Patients were randomised 1:1:1 to NET (anastrazole [A], fulvestrant [FUL] or A+FUL) for 24 weeks prior to surgery. Patients with Ki67 >10% at Week 4 or 12 were switched to CT. Patients with mPEPI 0 at surgery were recommended to continue assigned ET for 1.5 years, followed by A for a total of 5 years ET.

Neoadjuvant Primary Outcome: Endocrine-sensitive disease rate (ESDR) – percentage of patients who have pCR or modified preoperative endocrine prognostic index (mPEPI) 0 disease (defined as pT1/2, pN0, Ki67 ≤2.7%) after 6 months of NET.

Correlative Outcome: Ki67 at Week 4 compared to BL.

Author's Conclusion: Neither FUL nor A+FUL significantly improved ESDR compared to A alone in postmenopausal patients with locally advanced ER+/HER2- BC. Fewer than 2% of patients treated with 6 months NET progressed in ALTERNATE, possibly due to the Ki67 triaging strategy.

Results:

- Neither FUL or A+FUL significantly improved ESDR compared to A (Table 1).
- Almost all patients with Ki67 ≤10% at BL remained Ki67 ≤10% at Week 4. Approximately two-thirds of patients with Ki67 >10% at BL had Ki67 ≤10% at Week 4.
- Common toxicities in the treatment arms included arthralgia, myalgia, hot flushes and hypertension. Most AEs were Grade 2-3, with 1 patient in the FUL arm having Grade 4 hypertension.

Table 1: ESDR (mPEPI 0 + pCR rate) after 6 months of NET

	A (n=434)	FUL (n=431)	A+FUL (n=434)
mPEPI 0, n (%)	77 (17.7%)	94 (21.8%)	87 (20.0%)
pCR, n (%)	4 (0.9%)	4 (0.9%)	2 (0.5%)
ESDR, n (%) [97.5% CI]	**81 (18.6%) [14.6-23.2]**	**98 (22.7%) [18.4-27.6]**	**89 (20.5%) [16.3-25.2]**
p-value vs A*		0.15	0.55

*Fisher's Exact Test.

> Based on ALTERNATE results, **Mr Stuart McIntosh** remarked that patients could be administered NET and only a low proportion of patients would progress (<2%) when triaged based on Ki67. He found these results reassuring for practice, as NET is still an underused treatment modality.

Abbreviations: A, anastrazole; AE, adverse event; BC, breast cancer; BL, baseline; CCCA, complete cell cycle arrest; CI, confidence interval; CT, chemotherapy; D14C1, Day 14 Cycle 1; ER(+), oestrogen receptor (positive); ESDR, endocrine-sensitive disease rate; (N)ET, (neoadjuvant) endocrine therapy; FUL, fulvestrant; HER2-, human epidermal growth factor receptor-2 negative; LET, letrozole; N(+), node (positive); PBO, placebo; pCR, pathological complete response; (m)PEPI, (modified) preoperative endocrine prognostic index; pN, pathological nodal status; pT, pathological tumour size; RECIST, Response Evaluation Criteria in Solid Tumours; RIB(i/c), ribociclib (intermittent/continuous dose).

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Adjuvant Treatment

KATHERINE exploratory biomarker analysis: KADCYLA®* (trastuzumab emtansine; K) vs HERCEPTIN®* (trastuzumab; H) in HER2+ patients with RID after neoadjuvant therapy

Breast Cancer – Local/Regional/Adjuvant [Oral Presentation #502]: Prof Carsten Denkert (Philipps University Marburg, Marburg, Germany)

Trial: KATHERINE (NCT01772472) exploratory biomarker analysis.

Primary Objective: To evaluate the relationship between IDFS and biomarkers potentially related to response.

Population: Patients with residual invasive HER2+ BC after neoadjuvant chemotherapy plus HER2-targeted therapy.

Study Design: Patients received a minimum of 6 cycles of neoadjuvant H + taxane ± anthracycline neoadjuvant therapy. Patients (N=1,486) with RID after surgery were randomised 1:1 to receive adjuvant H (n=743) or K (n=743) for 14 cycles. Tissue samples were collected before neoadjuvant treatment and/or at surgery for biomarker analysis.

Trial Primary Outcome: IDFS.

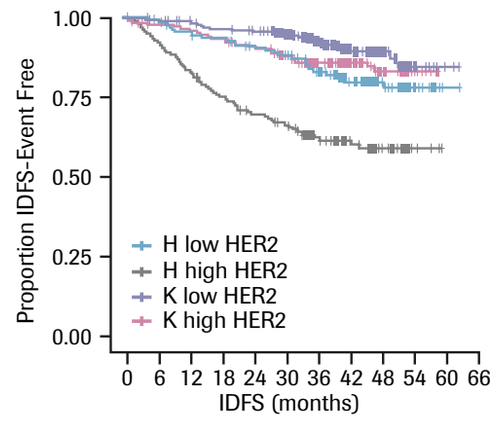
Author's Conclusion: A consistent IDFS benefit with K compared with H was observed across all biomarker subgroups. High HER2 gene expression was associated with worse outcomes in the H arm vs the K arm, suggesting resistance mechanisms could be present in patients with RID after HER2-targeted treatment in the neoadjuvant setting.

Results:

- Gene expression analyses were based on surgical samples from the H (n=398) and K (n=417) groups.
- Consistent treatment benefit with K vs H was observed across the single-gene and immune gene-signature subgroups as in the ITT population.
- High vs low PD-L1 expression was associated with better IDFS in the H arm (HR 0.66; 95% CI 0.44–1.00), but not within the K arm (HR 1.05; 95% CI 0.59–1.87).

Figure 1: HER2 gene expression association with IDFS

- High vs low HER2 expression was associated with worse IDFS within the H arm (HR 2.02; 95% CI 1.32–3.11), but not within the K arm (HR 1.01; 95% CI 0.56–1.83) (Figure 1).



*Manufactured by Roche

Prof Andrew Wardley and **Dr Andreas Makris** noted how the study did not identify any patient biomarker subgroups that did not benefit from K treatment. They felt that these results should be driving UK practice towards using neoadjuvant treatment in all appropriate patients, to open up the option of adjuvant KADCYLA for those patients with RID at surgery.

MINDACT: Long-term results using MammaPrint to guide de-escalation of adjuvant chemotherapy

Breast Cancer – Local/Regional/Adjuvant [Oral Presentation #506]: Dr Fatima Cardoso (Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal)

The 70-gene signature MammaPrint has been shown to identify BC patients for whom adjuvant CT could be omitted even in the presence of unfavourable standard clinical-pathological criteria. The **MINDACT** (NCT00433589) primary objective at 5 years median follow-up was met in 2016 with a distant metastasis free survival (DMFS) rate at 5 years of 94.7% (95% CI 92.5–96.2) in clinical high (C-High)/genomic low (G-Low) risk patients who received no CT. Longer follow-up is now available.

Study Design: 6,693 patients were classified using Adjuvant! Online (C-Risk) and MammaPrint (G-Risk), and patients with a discordant result (C-Low/G-High or C-High/G-Low) were randomised to receive adjuvant CT or no CT.

Primary Outcome: DMFS at 5 years for C-High/G-Low without CT.

Secondary Outcomes: Efficacy of CT vs no CT in populations of discordant risk (C-Low/G-High or C-High/G-Low) in the ITT, though the trial was not powered for comparisons of CT use.

Results:

- At the time of this analysis median follow-up was 8.7 years.
- The updated 5-year DMFS rate for the primary test population (C-High/G-Low, no CT; n=644) was 95.1% (95% CI 93.1–96.6). The lower bound of the 95% CI exceeded 92%, therefore the result was concluded significant, supporting the primary analysis.
- As shown in Table 1, DMFS in the C-High/G-Low group (ITT population) was marginally higher in the patients that received adjuvant CT vs no adjuvant CT. Patients ≤50 years old receiving adjuvant CT had a numerical benefit in 8-year DMFS vs no adjuvant CT (93.6% vs 88.6%).

Table 1: DMFS according to CT

	% at 5 years (95% CI)	% at 8 years (95% CI)
Adjuvant CT	95.7% (93.9–96.9)	92.0% (89.6–93.8)
No adjuvant CT	94.8% (92.9–96.2)	89.4% (86.8–91.5)
Absolute difference (±SE)	0.90 ± 1.1%	2.6 ± 1.6%

Author's Conclusion: The primary DMFS objective at 5 years continues to be met in CT untreated C-High/G-Low risk women, confirming MINDACT as a positive de-escalation study. With longer follow-up and in line with the natural history of luminal breast cancer, more distant relapses do occur but the estimated gain of 2.6% for CT administration in C-High/G-Low patients remains small in light of CT harmful effects.

Prof Andrew Wardley and **Dr Andreas Makris** highlighted that this was a positive de-escalation study showing that a group of women can be identified using MammaPrint who can reasonably avoid CT. Like the TAILORx study, they questioned whether the treatment effect seen in premenopausal women was a true CT effect, or due to ovarian suppression. The OPTIMA trial, where premenopausal women are required to have ovarian suppression, should answer the question of which patients can reasonably omit CT.

Abbreviations: AE, adverse event; (e)BC, (early) breast cancer; C, clinical; CI, confidence interval; CT, chemotherapy; DMFS, distant metastasis free survival; ET, endocrine therapy; FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; G, genomic, HER2+, human epidermal growth factor receptor-2 positive; IDFS, invasive disease-free survival; ITT, intention to treat, P, pertuzumab; pCR, pathological complete response; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria In Solid Tumours; SAE, serious adverse event; SE, standard error; SUV, standard uptake value; T, trastuzumab.

HERCEPTIN (trastuzumab) prescribing information can be found here; KADCYLA (trastuzumab emtansine) prescribing information can be found here.

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Adjuvant Treatment

GAIN-2: Phase 3 trial comparing intense vs tailored dose-dense chemotherapy (CT) in patients with high risk eBC – interim IDFS analysis

Breast Cancer – Local/Regional/Adjuvant [Poster #516]: Prof Volker Möbus (Universitätsklinikum Frankfurt, Germany)

Trial: GAIN-2 (NCT01690702)

Population: Patients with luminal A ≥N2; luminal B N+; HER2+ BC and TNBC.

Study Design: Multicentre, prospective, randomised, open-label Phase 3 trial, in which patients were randomised between intense dose-dense (idd) epirubicin, nab-paclitaxel and cyclophosphamide (iddEnPC) or dose-dense, dose-tailored (dt) epirubicin/cyclophosphamide followed by dose-dense, dose-tailored docetaxel (dtEC-dtD). Patients with HER2+ BC received PERJETA®* (pertuzumab) and trastuzumab in the neoadjuvant setting.

Primary Outcome: IDFS (time between randomisation and first event).

Secondary Outcomes: Tolerability and treatment adherence.

Results:

- Overall, 88.1% of patients completed all treatment in both arms.
- Grade 3-4 leukopenia, neutropenia, arthralgia and peripheral sensory neuropathy were significantly higher in the iddEnPC arm vs the dtEC-dtD arm (Table 1). Two deaths occurred during dtEC-dtD.
- Both arms had 4-year IDFS rates of 84.3% (95% CI 82.0%-86.4%). Among all predefined subgroups, only luminal B/HER2- predicted shorter IDFS in the iddEnPC arm vs dtEC-dtD (HR 1.44; 95% CI 1.02-2.02; p=0.036).

Table 1: Selected Grade 3-4 toxicities

Adverse Event	iddEnPC (n=1,430)	dtEC-dtD (n=1,427)	p-value
Leukopenia	1,332 (93.1%)	1,255 (87.9%)	<0.001
Neutropenia	1,275 (89.2%)	1,194 (83.7%)	<0.001
Arthralgia	83 (5.8%)	32 (2.2%)	<0.001
Peripheral sensory neuropathy	165 (11.5)	51 (3.6%)	<0.001

Author's Conclusion: Use of both iddEnPC and dtEC-dtD appears feasible in the (neo)adjuvant treatment of high risk eBC. No new safety concerns were observed in either treatment arm.

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> **Dr Andreas Makris** noted that the data presented in the GAIN-2 trial is unlikely to be relevant to the UK as the benefit of dose-dense chemotherapy is still being debated, let alone a comparison of different dose-dense schedules.

Statistical machine learning model to predict Oncotype DX® risk category in women >50 years old

Breast Cancer – Local/Regional/Adjuvant [Abstract #524]: Dr Kate Pawloski (Memorial Sloan Kettering Cancer Centre, New York, USA)

The 21-gene Oncotype DX Breast Recurrence Score multigene assay (RS) identifies women with ER+/HER2-, N- BC for whom chemotherapy provides no IDFS benefit compared to ET alone. A supervised statistical machine learning model that used standard clinicopathologic data to predict the RS risk category in women >50 years old was created.

Methods:

- Between 2012-18, 5,364 unique tumours in 5,189 women with ER+, HER2-, pathologically N- BC of all ages were retrospectively identified from a prospective institutional database; clinicopathologic data and RS were collected.
- Data were randomly split into training (n=3,755) and validation (n=1,609) sets. A random forest plot model was developed on the training set and then evaluated on the validation set.
- The model was used to predict RS category (low-risk: RS ≤25 or high-risk: RS >25) in women >50 years old. Model predictors included age, tumour size, histologic subtype, HR status, lymphovascular invasion and overall Grade.

Results:

- The model correctly classified 96.8% of patients as **low-risk** (95% CI 95.7-97.7). Negative predictive value for identifying low-risk women was also high (92.3%; 95% CI 90.7-93.6; Table 1).
- Sensitivity for identifying **high-risk** women was 44.7% (95% CI 37.4-52.1) and positive predictive value was 67.2% (95% CI 58.2-75.3). True RS >25 was not as well predicted; the model will be refined further to reduce false negatives (Table 1).

Table 1: Classification table of the validation set (n=1,467)

	True RS >25	True RS ≤25
Model predicted RS >25	84	41
Model predicted RS ≤25	104	1,238

Author's Conclusion: The model was highly specific (96.8%) for identifying women >50 with RS ≤25 who do not benefit from adjuvant chemotherapy. This model may be utilised in lieu of RS testing if cost and availability are prohibitive.

> **Prof Mark Beresford** was impressed at the ability of the statistical machine learning model to predict low Oncotype DX score accurately (96.8%). **Dr Andreas Makris** highlighted that although the model wasn't as good at identifying high-risk patients, it is more valuable to be able to identify the low-risk patients to identify patients that do not require further costly genomic testing.

Abbreviations: (e)BC, (early) breast cancer; CI, confidence interval; CT, chemotherapy; dt, dose-tailored; dtEC-dtD, dose-dense, dose-tailored epirubicin/cyclophosphamide followed by dose-dense, dose-tailored docetaxel; ER+, oestrogen receptor positive; ET, endocrine therapy; HER2(+/-), human epidermal growth factor receptor-2 (positive/negative); HR, hazard ratio; HR, hormone receptor; idd, intense dose-dense; iddEnPC, intense dose-dense epirubicin, nab-paclitaxel and cyclophosphamide; IDFS, invasive disease-free survival; N(+/-), node (positive/negative); RS, 21-gene Oncotype DX Breast Recurrence Score multigene assay; TNBC, triple negative breast cancer. PERJETA (pertuzumab) prescribing information can be found here.

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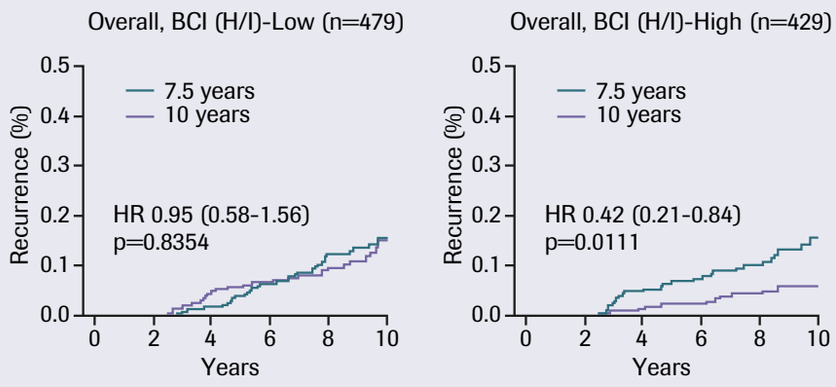
Adjuvant Treatment

Using Breast Cancer Index (BCI) HOXB13/IL17BR ratio (H/I) to predict the benefit of extended endocrine therapy (EET): the IDEAL and Trans-aTTom trials

Breast Cancer – Local/Regional/Adjuvant [Poster #512]: Dr Gerrit-Jan Liefers (Leiden University Medical Centre, Leiden, Netherlands)
Breast Cancer – Local/Regional/Adjuvant [Poster #522]: Dr John Bartlett (Ontario Institute for Cancer Research, Toronto, ON, Canada)

- The **IDEAL** trial examined the ability of BCI (H/I) to predict endocrine benefit from 2.5 vs 5 years of extended LET after 5 years of primary adjuvant therapy in women with HR+ BC.
- BCI by H/I status (high vs low) was significantly predictive of response to extended LET in the overall cohort (n=908; Figure 1) and in the subset of patients that received any primary adjuvant therapy with an AI (n=974).

Figure 1: Prediction of EET benefit by BCI (H/I) in the overall cohort



Author's Conclusion: BCI (H/I) predicted preferential benefit from 5 vs 2.5 years of EET and identified a population with improved outcomes from completing 10 years of adjuvant endocrine therapy.

- BCI (H/I) previously predicted benefit from extending Tam therapy from 5 to 10 years in patients with N+ BC in the **Trans-aTTom** study. In this updated analysis of the N+ cohort (n=789), the predictive performance of BCI (H/I) was evaluated in the context of HER2 status.
- 90% (n=711) of patients were HR+/HER2-; 9% (n=72) were HR+/HER2+ and 1% (n=6) were HR+/HER2 unknown.
- In the N+ HER2- subset, BCI (H/I)-High (48%) patients showed significant recurrence-free interval benefit from 10 vs 5 years of tamoxifen (Δ9.4%; HR 0.35; 95% CI 0.15-0.81; p=0.047) while BCI (H/I)-Low patients did not (Δ-2.2%; HR 1.15; 95% CI 0.78-1.69; p=0.491).
- Significant interaction between BCI (H/I) and treatment was shown in the HER2- subset (RFI p=0.045; DFI p=0.044).

Author's Conclusion: In this updated analysis with HER2 data, BCI (H/I) showed similar predictive performance for EET response in the HER2- subset when compared to the overall N+ cohort. These data further support the utility of BCI (H/I) as a predictive biomarker for informing EET benefit regardless of HER2 status.

" **Dr Andreas Makris** highlighted that the IDEAL trial used BCI to identify patients who are benefiting from extended endocrine therapy. While the presented results are consistent with Trans-aTTom and MA.17, he noted that a comparison with the free online CTS5 tool would have been useful.

Locoregional Treatment

Analysis of the US National Cancer Database (NCDB): trends in utilisation of hypofractionated radiation (HfR) in breast conservation therapy (BCT)

Breast Cancer – Local/Regional/Adjuvant [Posters #536 and #539]: Dr Steven Woodward (Thomas Jefferson University Hospital, Philadelphia, USA)

[Poster 536] Utilisation of HfR in BCT.

Objective: To evaluate contemporary use of HfR in the US, and identify populations at risk of not receiving the benefit of this therapy.

Study Design: Retrospective review of the US NCDB from 2012 to 2016. Patients undergoing BCT were divided into HfR and traditional radiation (TR) cohorts. Logistic regression modelling was used to identify the relationship between patient, hospital and tumour factors and the use of HfR or TR.

Results:

- A total of 360,834 cases of BCT were identified: 65% (n=235,783) undergoing TR vs 35% (n=125,051) undergoing HfR.
- The odds of HfR utilisation in BCT increased with year of diagnosis, patient age, higher median income, private insurance, lower risk tumours, treatment at academic centres and increased distance to treatment centre (all p<0.0001).

Author's Conclusion: Despite studies demonstrating the efficacy of HfR, its utilisation in the US is still lacking.

[Poster 539] Association of HfR with timely completion of adjuvant radiation in BCT.

Objective: To evaluate timely completion rates of HfR and TR as part of BCT and to identify associated patient, tumour and facility factors.

Study Design: Retrospective review of the US NCDB from 2012 to 2016. Patients undergoing BCT were divided into HfR and TR cohorts. Multivariable logistic regression was used to compare timely completion of HfR (within 5 weeks of initiation) and TR (within 7 weeks of initiation).

Results:

- Timely completion was achieved in 93.5% of HfR patients and 74.2% of TR patients (p<0.0001).
- Patient age, year of diagnosis, ethnicity, facility type, chemotherapy use and lymph node status had the strongest impact on timely completion (all p<0.0001).

Author's Conclusion: Mortality and DFS may be improved by identifying patients who are more likely to finish HfR or TR on time based on patient, facility and tumour factors.

" The group questioned why HfR was not more commonly used in practice in the US, and were interested to see that treatment at academic centres and patients with higher income were associated with increased odds of HfR utilisation. **Prof Mark Beresford** commented how breast cancer radiation therapy does not often need to be interrupted in the UK where HfR is standard, and questioned what might have happened to the patients who did not have timely completion of radiotherapy. **Dr Andreas Makris** considered these results important for health policy in the US.

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; BCI, Breast Cancer Index; BCT, breast conservation therapy; CI, confidence interval; DFI, disease-free interval; DFS, disease-free survival; EET, extended endocrine therapy; HER2, human epidermal growth factor receptor-2; HfR, hypofractionated radiation; H/I, HOXB13/IL17BR ratio; HR, hazard ratio; HR+, hormone receptor-positive; LET, letrozole; N+, node-positive; NCDB, National Cancer Database; RFI, recurrence-free interval; Tam, tamoxifen. TC, timely completion; TR, traditional radiation; US, United States.

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Locoregional Treatment

Ipsilateral invasive cancer (iIBC) risk after diagnosis with DCIS: Comparison of patients with and without index surgery

Breast Cancer – Local/Regional/Adjuvant [Abstract #519]: Dr Marc Ryser (Duke University, Durham, North Carolina, USA)

Background: Most women with DCIS undergo surgery. This leads to potential overtreatment in patients who would not otherwise develop clinically significant BC. This study compared iIBC risk and disease-specific survival (DSS) between patients undergoing BCS vs patients undergoing surveillance (SV).

Methods: A treatment-stratified random sample of patients diagnosed with screen-detected and biopsy-confirmed DCIS in 2008-14 was selected from 1,330 centres (n=14,245; 88.2% BCS and n=1,914; 11.8% SV patients). Subsequent breast events were abstracted up to 10 years after diagnosis.

Primary outcome: 8-year absolute difference in iIBC risk between BCS and SV patients; a subgroup analysis was performed for Grade I/II patients.

Results:

- Median follow-up was 5.8 years (95% CI 5.7-6.1)
- The 8-year iIBC risk for all patients and those with Grade I/II tumours are presented in Table 1.

Table 1: 8-year iIBC risk

	BCS	SV	Absolute Risk Difference*	p-value
All patients, % (95% CI)	3.0 (2.4-3.6)	7.7 (4.9-10.5)	4.7 (4.5-4.9)	<0.001
Patients with Grade I/II tumours, % (95% CI)	3.1 (2.3-4.0)	6.1 (2.5-9.8)	3.0 (2.7-3.2)	0.005

*Absolute risk differences were estimated using propensity score and sampling design weighted Kaplan Meier estimators.

Author's Conclusions: Despite an increased iIBC in SV patients compared to BCS patients, 8-year iIBC risk did not exceed 10% in either group. These data suggest a considerable degree of overtreatment, especially among patients with non-high grade DCIS.

" **Dr Andreas Makris** highlighted how the results of this study show that some patients with DCIS are being overtreated, making the case for trials comparing surgery with active monitoring. **Mr Mark Sibbering** commented that de-escalation trials like these are difficult to recruit into since they involve not operating on "cancer", and that the terminology around low/intermediate-grade DCIS could be changed or conveyed differently to encourage patients into them. **Mr Stuart McIntosh** concluded that results from studies such as LORIS need to be awaited to fully answer the question regarding overtreatment in patients with DCIS.

ECOG-ACRIN 2108: Early locoregional treatment (LRT) for the intact primary tumour in women with *de novo* mBC

Plenary [LBA2]: Prof Seema Ahsan Khan (Northwestern Memorial Hospital, Chicago, IL, USA)

LRT for the intact primary tumour is hypothesised to improve survival for patients with *de novo* mBC based on retrospective analyses; however, randomised trials have provided conflicting data.

Trial: A randomised, Phase 3 study by the ECOG-ACRIN Research Group (E2108; NCT01242800)

Population: Women with a diagnosis of *de novo* mBC and an intact primary tumour.

Study Design: 390 patients were treated with optimal systemic therapy based on patient and tumour characteristics; those with no progression of distant disease following 4-8 months of optimal systemic therapy (n=256; 65.6%) were randomised to receive either:

- Early LRT: complete tumour resection with free surgical margins and post-operative RT per SoC (n=125), or
- Continued systemic therapy alone (n=131).

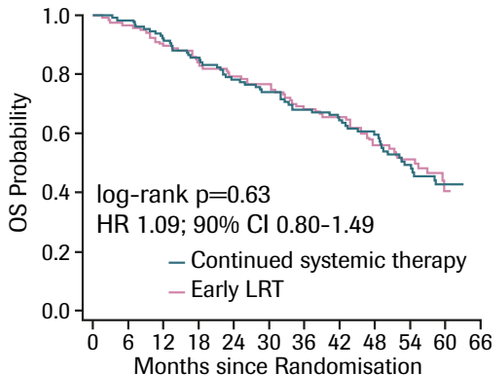
Primary Outcome: OS.

Secondary Outcomes: Time to locoregional progression, HRQoL measured by FACT-B Trial Outcome Index, absolute value of circulating tumour burden, biological samples.

Results:

- At a median follow-up 53 months (range: 0-91) there had been 121 deaths. Median OS was 54 months, with no difference in OS between the study arms (Figure 1). No OS benefit was seen with early LRT in any tumour subtype.
- Locoregional recurrence/progression was significantly higher in the optimal systemic therapy alone vs early LRT arm (3-year rate 25.6% vs 10.2%; HR 0.37; 95% CI 0.19-0.73).
- HRQoL was significantly worse in the early LRT arm at 18 months post-randomisation, but there was no significant difference at any other assessment timepoint.

Figure 1: OS result



Author's Conclusion: Early LRT does not improve OS in patients with *de novo* mBC and an intact primary tumour. Although there was a 2.5-fold higher risk of local disease progression without LRT, the use of LRT did not lead to improved HRQoL.

" The group discussed the ongoing debate regarding the role of surgery to the primary tumour for patients with *de novo* mBC, and how the ECOG-ACRIN 2108 study is an important study that will influence how clinicians manage these patients. **Mr Stuart McIntosh** and **Dr Fharat Raja** were both impressed by the OS result in patients with mBC in both arms. **Dr Andreas Makris** concluded that this study more closely represents treatment practices in the UK compared to previous studies and is the definitive study regarding treatment for *de novo* mBC.

Abbreviations: BCS, breast conserving surgery; CI, confidence interval; DCIS, ductal carcinoma in situ; DSS, disease-specific survival; ER-, oestrogen receptor negative; FACT-B, functional assessment of cancer therapy-breast; HR, hazard ratio; HRQoL, health-related quality of life; iIBC, ipsilateral invasive cancer; LRT, locoregional treatment; mBC, metastatic breast cancer; mo, months; OS, overall survival; RT, radiotherapy; SoC, standard of care; SV, surveillance.

ASCO 2020 Breast Cancer Highlights

29th – 31st May 2020

Metastatic Breast Cancer

KEYNOTE-355: KEYTRUDA® (pembrolizumab; pembro) + chemotherapy (CT) vs placebo + CT for previously untreated locally recurrent inoperable or mTNBC

Breast Cancer – Metastatic [Oral Presentation #1000]: Dr Javier Cortes (IOB Institute of Oncology, Madrid & Barcelona, Spain)

Trial: KEYNOTE-355 (NCT02819518)

Population: Patients with previously untreated, locally recurrent, inoperable or mTNBC, with ≥6 month disease-free interval since any treatment for curative intent.

Study Design: Patients were randomised 2:1 to pembro + CT (either paclitaxel, nab-paclitaxel or gemcitabine/carboplatin; n=566) or placebo (PBO) + CT (n=281).

Primary Outcomes: PFS and OS in patients with PD-L1-positive tumours (CPS ≥10 and CPS ≥1 measured using the PD-L1 IHC 22C3 assay) and in the ITT population.

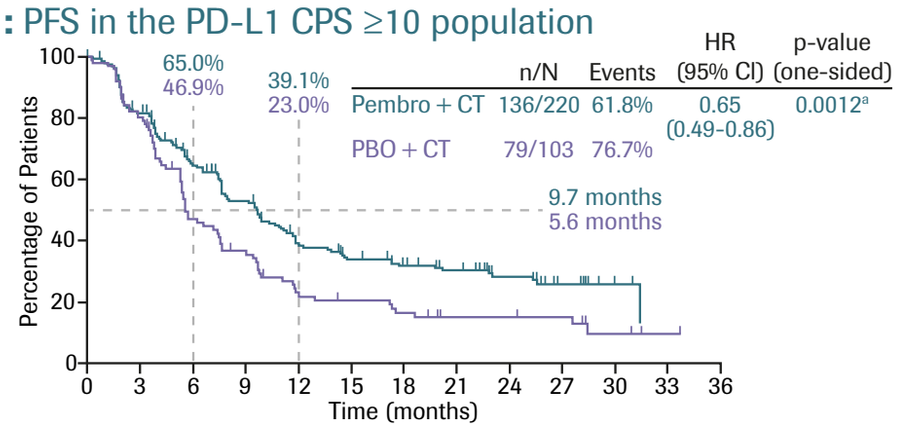
Secondary Outcomes: ORR, DOR, DCR, and safety in all treated patients.

Author's Conclusion: Pembro combined with several CT partners showed a statistically significant and clinically meaningful improvement in PFS vs CT alone in patients with previously untreated, locally recurrent, inoperable or mTNBC whose tumours expressed PD-L1 (CPS ≥10). Pembro + CT was generally well tolerated with no new safety concerns.

Results:

- Pembro + CT improved median PFS in the PD-L1 CPS ≥10 population compared to PBO + CT (Figure 1), meeting the pre-specified p-value boundary. The pre-specified p-value for PFS was not met in patients with PD-L1 CPS ≥1 (HR 0.74; p=0.0014 exceeded the boundary of 0.0011), hence statistical significance of PFS in the ITT population (HR 0.82) was not tested.
- Grade 3-5 TRAE rates were 68.1% with pembro + CT (2 deaths) vs 66.9% with PBO + CT (0 deaths); rates of Grade 3-5 immune-mediated AEs and infusion reactions were 5.2% vs 0.0%.

Figure 1: PFS in the PD-L1 CPS ≥10 population



[a]Pre-specified p-value boundary of 0.00411 met. HR (CI) analysed based on a Cox regression model with treatment as a covariate stratified by the randomisation stratification factors. Data cut-off December 11, 2019.

> **Dr David Miles** and **Dr Duncan Wheatley** liked the design of KEYNOTE-355 in that the choice of CT was down to the treating clinician, and were reassured that the efficacy of pembro was reasonably consistent regardless of the choice of CT. **Dr Fharat Raja** and **Dr David Miles** both commented on the statistical design of the trial, and felt there is still a question around whether patients with PD-L1 CPS ≥1 may benefit from the addition of pembro, but due to the design of the trial no significant benefit could be concluded in this study.

KEYTRUDA® (pembrolizumab; pembro) in KEYNOTE-119 exploratory analysis and ENHANCE 1

Breast Cancer – Metastatic [Poster #1013]: Dr Eric Winer (Dana-Farber Cancer Institute, Boston, MA, USA); [Poster #1015]: Dr Sara Tolaney (Dana-Farber Cancer Institute, Boston, MA, USA)

Trial: KEYNOTE-119 (NCT02555657), an exploratory analysis

Objective: To evaluate the association between tumour mutational burden (TMB; measured using FoundationOne CDx™) and clinical outcomes.

Population: Patients with previously treated mTNBC (N=622).

Study Design: Randomised, open-label, Phase 3 study of pembro vs chemotherapy (CT; investigator's choice of capecitabine, eribulin [Eri], gemcitabine or vinorelbine).

Results:

- TMB data were available in 42.1% of treated patients (n/N=253/601).
- The area under the Receiver Operating Characteristics curve for the association between TMB and ORR was 0.58 (95% CI 0.43-0.73) for pembro and 0.43 (95% CI 0.27-0.59) for CT.

Author's Conclusion: Trends from this exploratory analysis suggest a positive association between TMB and clinical benefit with pembro but not with CT in patients with mTNBC.

Trial: ENHANCE 1 (NCT02513472)

Objective: To evaluate safety and efficacy (ORR) of Eri + pembro.

Population: 167 patients with mTNBC, stratified by prior lines of systemic anticancer therapy (0 vs 1/2)

Study Design: Phase 1b/2, open-label, single-arm, multicentre study, in which patients received IV Eri + IV pembro.

Results:

- No dose-limiting toxicities were observed in Phase 1. The most common TEAEs were fatigue (66%), nausea (57%), peripheral sensory neuropathy (41%), alopecia (40%) and constipation (37%).
- The overall ORR was 23.4% (95% CI 17.2-30.5), 25.8% (95% CI 15.8-38.0) in the first line setting and 21.8% (95% CI 14.2-31.1) in the second/third line setting. The overall median PFS was 4.1 months (95% CI 3.5-4.2) and median OS was 16.1 months (95% CI 13.3-18.5).

Author's Conclusion: Eri + pembro had encouraging anticancer activity in patients with mTNBC in first to third-line settings.

> **Dr David Miles** felt that tumour mutational burden could potentially be used as a marker for the benefit of pembro, with KEYNOTE-119 results hinting at a better response as mutational load increased. **Dr Duncan Wheatley** remarked that it will be increasingly challenging to recruit patients into immune-oncology (IO) trials for metastatic cancer because patients will have received IO therapy in the neoadjuvant setting. The group felt that the ENHANCE 1 study is a start in determining optimal treatments for patients with metastatic disease who have received prior treatments.

Abbreviations: AE, adverse event; CI, confidence interval; CPS, Combined Positive Score; CT, chemotherapy; DCR, disease-control rate; DOR, duration of response; Eri, eribulin; HR, hazard ratio; IHC, immunohistochemistry; ITT, intention-to-treat; IV, intravenous; (m)TNBC, (metastatic) triple negative breast cancer; PBO, placebo; pembro, pembrolizumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; pembro, pembrolizumab; TEAE, treatment emergent adverse event; TMB, tumour mutational burden; TRAE, treatment-related adverse event.

ASCO 2020 Breast Cancer Highlights

29th – 31st May 2020

Metastatic Breast Cancer

SWOG S1416: Phase 2 randomised trial of cisplatin (cis) + the PARPi veliparib (vel) or placebo (PBO) in mTNBC and/or germline (g)*BRCA*-associated mBC

Breast Cancer – Metastatic [Abstract #1001]: Dr Priyanka Sharma (University of Kansas Medical Centre, Westwood, KS, USA)

Trial: SWOG S1416 (NCT02595905)

Population: Patients with mTNBC or g*BRCA1/2*-associated mBC.

Study Design:

- Patients received <1 line of prior cis (75 mg/m^2) + vel (300 mg BID on Days 1-14) or PBO every 3 weeks.
- 323 patients underwent central g*BRCA* testing. 248 patients were classified into 3 groups: g*BRCA*+ (n=37), *BRCA*-like (n=101), and non-*BRCA*-like (n=110); 75 patients could not be classified due to missing biomarker information.

Primary Outcome: PFS.

Secondary Outcomes: ORR, OS and toxicity.

Author's Conclusion: In patients with *BRCA*-like mTNBC, cis+vel significantly improved PFS and showed a trend towards improved OS compared to cis+PBO. Integral biomarkers identified a subgroup of *BRCA*-wildtype patients with TNBC who benefited from the addition of a PARPi to cis, which should be explored further in this population.

Results:

- PFS, OS and ORR results for the g*BRCA*+, *BRCA*-like, non-*BRCA*-like and unclassified groups are shown in Table 1.
- Grade 3/4 neutropenia (46% vs 19%) and anaemia (23% vs 7%) occurred more frequently with cis+vel treatment compared to cis+PBO.

Table 1: PFS, OS and ORR based on g*BRCA* classification

	cis+vel	cis+PBO	HR	p-value
g*BRCA*+				
PFS	NR	NR	0.64	0.26
BRCA-like				
Median PFS, months	5.7	4.3	0.58	0.023
1-year PFS, %	20%	7%	NR	NR
Median OS, months	13.7	12.1	0.66	0.14
ORR, %	45%	35%	NR	0.38
Non-*BRCA*-like				
PFS	NR	NR	0.85	0.43
Unclassified				
PFS	NR	NR	0.97	NR

> **Dr MB Mukesh** highlighted that this is a negative study and that adding a PARPi to platinum therapy did not have an added benefit overall. He noted that the data presented is unlikely to impact UK clinical practice.

Olaparib Expanded: Olaparib monotherapy in mBC patients with germline or somatic mutations in DNA damage response (DDR) pathway genes

Breast Cancer – Metastatic [Oral Presentation #1002]: Dr Nadine Tung (Beth Israel Deaconess Medical Centre and Dana-Farber Cancer Institute, Boston, USA)

Trial: Olaparib Expanded (TBCRC 048; NCT03344965)

Population: Patients (pts) with mBC who had progressed on <2 CT regimens in the metastatic setting, with no prior exposure to a PARPi, and who did not have platinum-refractory disease. Pts had to have a germline or somatic (likely) pathogenic variant (mutation) in a DDR pathway gene such as *ATM*, *CHEK2* or *PTEN* or a somatic *BRCA1/2* mutation in the absence of a g*BRCA* mutation.

Study Design:

- Cohort 1: Pts with germline mutations in non-*BRCA1/2* DDR-pathway genes.
- Cohort 2: Pts with somatic mutations in DDR-pathway genes including *BRCA1/2*.

Pts received olaparib 300 mg bid until progression or unacceptable toxicity. In each cohort, a single-arm Simon 2-stage design was used with 13 (stage 1) then 14 (stage 2) pts.

Primary Outcome: ORR (CR+PR by RECIST 1.1).

Secondary Outcomes: CBR (CR+PR+SD ≥18 weeks), duration of response, PFS, toxicity.

Results:

- In total, 53 pts were included: 75% ER+/HER2-, 19% TNBC and 5% HER2+. 5% of pts had received prior platinum therapy and 93% of ER+/HER2- pts had received a prior CDK4/6i. 87% of pts had a mutation in *ATM*, *CHEK2*, *PALB2* or *sBRCA1/2*.
- Results in each cohort are presented in Table 1. In Cohort 1, all responses were in pts with *PALB2* mutations. In Cohort 2, all confirmed PRs were in pts with s*BRCA1/2* mutations.

Table 1: ORR and CBR results

	Cohort 1 (Germline; n=27)	Cohort 2 (Somatic; n=26)
ORR, %, n/N [90% CI]	33% (9/27) [19-51%]	31% (8/26) [16-49%]
CBR (18 weeks)	44% (11/25) [27-62%]	44% (11/25) [27-62%]

- The most common Grade 3/4 AEs potentially related to olaparib were anaemia (10%), lymphopenia (4%) and abnormal AST/ALT (4%).

Author's Conclusion: In this proof-of-principle study, the primary objective was met in both cohorts but responses to olaparib were gene-specific. Responses were observed in all breast cancer subtypes and after CDK4/6is.

> **Dr MB Mukesh** felt that these were exciting results, with a strong indication of activity in patients with a *PALB2* mutation in particular. However, he noted that this is a very small trial, so a confirmatory study will be needed. The group highlighted the challenges faced in the UK in relation to genetic testing – the majority of patients in this trial were ER+ and these patients would not be considered for *BRCA* testing in the NHS.

Abbreviations: AE, adverse event; bid, twice daily; CBR, clinical benefit rate; CI, confidence interval; cis, cisplatin; CR, complete response; CT, chemotherapy; DDR, DNA damage response; DNA, deoxyribonucleic acid; ER, oestrogen receptor; g*BRCA*, germline BReast CAncer gene; HER2(+/-), human epidermal growth factor receptor-2 (positive/negative); HR: hazard ratio; mBC, metastatic breast cancer; NR, not reported; ORR, objective response rate; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PBO, placebo; PFS, progression-free survival; PR, partial response; pts, patients; RECIST, Response Evaluation Criteria in Solid Tumours; s*BRCA*, somatic BReast CAncer gene; SD, stable disease; (m)TNBC, (metastatic) triple negative breast cancer; vel, veliparib.

ASCO 2020 Breast Cancer Highlights

29th – 31st May 2020

Metastatic Breast Cancer

Treatment options post-CDK4/6i in mBC: studies of alpelisib (BYLieve) and lenvantinib

Breast Cancer – Metastatic [Oral Presentation #1006]: Prof Hope S. Rugo (University of California, San Francisco, CA, USA); [Poster #1019]: Dr Joline SJ Lim (National University Cancer Institute, Singapore)

Trial: BYLieve (NCT03056755)

Population: Men or pre-/postmenopausal women with HR+/HER2- mBC with a *PIK3CA* mutation.

Study Design: Non-comparative Phase 2, open-label study which enrolled patients who had received immediate prior treatment with CDK4/6i+AI, CDK4/6i+fulvestrant (FUL), systemic chemotherapy or ET. Patients were randomised to alpelisib (Alp; -selective PI3K inhibitor) + FUL or Alp + letrozole (LET), with 112 patients in each cohort. Here, results were presented for patients on Alp+FUL who received CDK4/6i+AI as immediate prior treatment only.

Primary Outcome: Proportion of patients alive without disease progression at 6 months (RECIST v1.1).

Secondary Outcomes: PFS, PFS on next-line treatment, ORR, clinical benefit rate, DOR, OS and safety.

Author's Conclusion: At this analysis, BYLieve demonstrates clinically meaningful efficacy of Alp+FUL in *PIK3CA*-mutated HR+/HER2- mBC post progression on CDKi + AI, with manageable side effects.

Results:

- Median follow-up in the Alp+FUL arm was 11.7 months.
- The primary objective for the Alp+FUL arm was met, as the proportion of patients without disease progression at 6 months was 50.4% (95% CI 41.2-59.6).
- Median PFS in the Alp+FUL arm was 7.3 months (95% CI 5.6-8.3).
- Incidence of all-Grade AEs and Grade ≥3 AEs leading to discontinuation were 20.5% and 11.8% in the Alp+FUL arm, respectively. Most frequent AEs leading to discontinuation were rash (3.9%), colitis, hyperglycaemia, urticaria and vomiting (1.6% each).

In **Poster 1019**, lenvatinib (Len; *RET* inhibitor) + LET was investigated in a cohort of patients with heavily pre-treated ER+ mBC (median 4 lines of prior treatment, 30/43 had received prior CDK4/6i + ET). Len+LET showed significant anti-tumour activity with meaningful duration of response, even in patients who failed prior CT or CDK4/6i + ET.

" **Dr MB Mukesh** noted that treatment post-CDK4/6i is a hot topic, with this area being a relatively open field in terms of standard of care. **Dr MB Mukesh** and **Dr Duncan Wheatley** specifically noted the safety profiles of alpelisib and lenvantinib, and whether their benefits in terms of efficacy outweigh their AE profiles.

Guidelines

Management of hereditary breast cancer: ASCO, American Society for Radiation Oncology and Society of Surgical Oncology guideline

Tung NM, Boughey JC, Pierce LJ, et al. Journal of Clinical Oncology [Published online ahead of print on April 3, 2020]

To develop recommendations for the management of patients with BC with germline mutations in BC susceptibility genes, ASCO, the American Society for Radiation Oncology and the Society of Surgical Oncology convened an Expert Panel to develop recommendations based on a systematic review of the literature and a formal consensus process.

Fifty-eight articles met the eligibility criteria and formed the evidentiary basis for the local therapy recommendations; 6 RCTs of systemic therapy met the eligibility criteria.

Key Recommendations:

- Patients with newly diagnosed BC and *BRCA1/2* mutations may be considered for breast conserving therapy (BCT), with local control of the index cancer similar to that of noncarriers.
- The significant risk of a contralateral BC (CBC), especially in young women, and the higher risk of new cancers in the ipsilateral breast warrant discussion of bilateral mastectomy.
- Patients with mutations in moderate-risk genes should be offered BCT and mutation status alone should not determine local therapy decisions.
- For women with mutations in *BRCA1/2* or moderate-penetrance genes who are eligible for mastectomy, nipple-sparing mastectomy is a reasonable approach.
- There is no evidence of increased toxicity or CBC events from radiation exposure in *BRCA1/2* carriers. Radiation therapy should not be withheld in *ATM* carriers.
- For patients with germline *TP53* mutations, mastectomy is advised; radiation therapy is contraindicated except in those with significant risk of locoregional recurrence.
- Platinum agents are recommended vs taxanes to treat mBC in *BRCA* carriers who had not previously received platinum. In the adjuvant/neoadjuvant setting, data do not support the routine addition of platinum to anthracycline- and taxane-based chemotherapy.
- PARPis (olaparib and talazoparib) are preferable to nonplatinum single-agent chemotherapy for treatment of HER2-negative mBC in *BRCA1/2* carriers; data are insufficient to recommend PARPi use in the early setting or in moderate-penetrance carriers.

" **Mr Mark Sibbering** flagged these guidelines, published earlier in the year but publicised during the ASCO virtual meeting, as a helpful resource for UK clinicians.

Abbreviations: AE, adverse event; AI, aromatase inhibitor; Alp, alpelisib; ASCO, American Society of Clinical Oncology; ATM, Ataxia-Telangiesctasia Mutated gene; BC, breast cancer; BCT, breast conserving therapy; BRCA, BReast CAncer gene; CBC, contralateral breast cancer; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; FUL, fulvestrant; HER2-, human epidermal growth factor receptor-2 negative; HR+, hormone receptor positive; Len, lenvatinib; LET, letrozole; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PARPi, Poly ADP-ribose polymerase inhibitors; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; RCT, randomised controlled trial; RECIST, Response Evaluation Criteria in Solid Tumours.