Introduction:

For many years there has been healthy debate on differing approaches for patients with early-stage estrogen receptor-positive breast cancer which weigh the modest efficacy of extended endocrine treatment against the well documented adverse events.

In an effort to clarify the state of the art on the issue of extended adjuvant endocrine therapy in early-stage, estrogen receptor-positive breast cancer patients, an expert discussion to provide clinical insights was held on Saturday, March 11th 2017 at the Fontainebleau hotel in Miami Beach, Florida. After a review of the data, including trials reported in 2016, a series of questions were asked of the panelists.

Moderator Dr Michael Naughton began the discussion by reviewing data from the EBCTCG examining long term outcomes in patients with ER+ early-stage breast cancer, which showed quite clearly that despite a beneficial effect of tamoxifen treatment in reducing recurrences, recurrences do not stop after 5 years of tamoxifen therapy. Dr Naughton also reviewed more detailed data from an Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis, showing that clinicopathologic risk factors, including tumor size (T) and nodal status, are prognostic for recurrence risk beyond 5 years.2 “In the T1N0 patients, for the 15 years between years 5 and 20, there is approximately 1% per year risk of recurrence for these clinically low risk patients, and as you go up in T size or add node positivity, the risk goes up,” Dr Naughton said. “Grade also continues to be prognostic, with low grade patients having less risk,” but he added that even lower risk (T1N0G1) patients had about 0.75% per year risk in the EBCTCG study.
Eleftherios (Terry) P. Mamounas, MD, MPH

Dr Terry Mamounas outlined results from the major extended adjuvant endocrine therapy trials, including: MA.17 (letrozole), NSABP B-33 (exemestane), and ABCSG6A (anastrozole), which examined use of an aromatase inhibitor (AI) or placebo following 5 years of tamoxifen therapy; ATLAS and aTTom, which examined the use of an additional 5 years of tamoxifen (or no further therapy) following an initial 5 years of tamoxifen; and MA.17R, which examined the use of endocrine therapy out to 10 or 15 years (Table 1).\(^3,4,5,6,7,8,9\)

Dr Mamounas explained that all of these trials showed similar absolute benefits in terms of disease-free survival (DFS) and number needed to treat (NNT) to prevent recurrences and distant recurrences.

Dr Mamounas then focused on the results from the two trials that investigated extended AI therapy (MA.17R and NSABP B-42).

MA.17R enrolled over 1900 patients who had received 4.5 to 6 years of an AI (in most cases preceded by tamoxifen) and were randomized within 2 years after the AI to an additional five years of AI (letrozole) or placebo. The results for the primary endpoint (DFS, defined as disease recurrence or contralateral breast cancer, but not including death or second non-breast cancers) at a median follow up of 6.3 years demonstrated that extended AI led to a 4% increase in DFS (95% vs 91%; \(p=0.01\)); however, there was no improvement in overall survival (93% vs 94%; \(p=0.83\)). Notably, much of the benefit was due to prevention of contralateral breast cancers (CBC; Table 2).\(^8\)

Dr Mamounas noted that MA.17R used a distinct definition for the DFS primary endpoint, which differed from the traditional definition used in randomized controlled trials (RCTs) in which breast cancer recurrence, CBC, second non-breast primary cancer, and deaths are recorded as a first event.

Table 1: Extended Endocrine Therapy Randomized Trials\(^3,4,5,6,7,8\)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration of Therapy (y)</th>
<th>N</th>
<th>Median Follow-up (y)</th>
<th>Disease-free Survival(^1)</th>
<th>Absolute Benefit</th>
<th>Hazard Ratio (95%CI)</th>
<th>NNT (All)(^2)</th>
<th>NNT (DR)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA.17</td>
<td>TAM x 5y → Placebo x 5y → AI x 5y</td>
<td>2587</td>
<td>2.5</td>
<td>89.8%</td>
<td>4.6%</td>
<td>0.58 (0.45–0.76)</td>
<td>P&lt;0.001</td>
<td>41</td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>TAM x 5y → Placebo x 5y → AI x 5y</td>
<td>779</td>
<td>2.5</td>
<td>89%</td>
<td>2%</td>
<td>RR: 0.68</td>
<td>P=0.07</td>
<td>39</td>
</tr>
<tr>
<td>ABCSG 6A</td>
<td>TAM x 5y → Placebo x 3y → AI x 3y</td>
<td>469</td>
<td>5.2</td>
<td>88.2%</td>
<td>4.7%</td>
<td>0.62 (0.40–0.96)</td>
<td>P=0.031</td>
<td>23</td>
</tr>
<tr>
<td>ATLAS</td>
<td>TAM x 5y → No Further Rx → TAM x 5y</td>
<td>3418</td>
<td>7.6</td>
<td>74.9%</td>
<td>3.7%</td>
<td>RR 0.84 (0.76–0.94)</td>
<td>P=0.002</td>
<td>36</td>
</tr>
<tr>
<td>aTTom</td>
<td>TAM x 5y → No Further Rx → TAM x 5y</td>
<td>3485</td>
<td>10</td>
<td>68%</td>
<td>4%</td>
<td>RR 0.85 (0.76–0.95)</td>
<td>P=0.003</td>
<td>38</td>
</tr>
<tr>
<td>MA.17R</td>
<td>TAM x 0-5y → Placebo x 5y → AI x 5y</td>
<td>959</td>
<td>6.3</td>
<td>91%</td>
<td>4%</td>
<td>0.66 (0.48–0.91)</td>
<td>P=0.01</td>
<td>31</td>
</tr>
</tbody>
</table>

1. Based on disease-free survival or cumulative risk of recurrence rates as reported in the primary publications (note that the definitions of disease-free were not identical across trials).
2. Number needed to treat (NNT) based on all recurrences (local, regional, and distant) and contralateral events.
3. Number needed to treat (NNT) based on distant recurrences (DR) only.

all of these trials showed similar absolute benefits in terms of disease-free survival (DFS) and number needed to treat (NNT) to prevent recurrences and distant recurrences*
The primary endpoint was DFS, defined according to the standard RCT criteria; secondary endpoints included overall survival (OS), breast cancer free interval (BCFI), defined as recurrence or CBC as a first event, distant recurrence (DR), osteoporotic fractures (OF), or arterial thrombotic events (AT). Dr Mamounas explained that for the 3,923 patients included in the efficacy analysis, the median follow up was 6.9 years. Characteristics of the cohort are shown in Table 3.

### Table 2: Results from MA.17R for Letrozole versus Placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Letrozole</th>
<th>Placebo</th>
<th>Hazard Ratio (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Year DFS</td>
<td>95%</td>
<td>91%</td>
<td>0.66; $P = 0.01$</td>
</tr>
<tr>
<td>5-Year OS</td>
<td>93%</td>
<td>94%</td>
<td>0.97; $P = 0.83$</td>
</tr>
<tr>
<td>CBC, Annual Incidence</td>
<td>0.21%</td>
<td>0.49%</td>
<td>0.42; $P = 0.007$</td>
</tr>
</tbody>
</table>

Post hoc sensitivity analysis of DFS that included all deaths as events (but not second non-Breast primary cancers): 5-year DFS L: 90% vs. P: 88% (HR:0.89; $P = 0.005$)

Dr Mamounas then detailed the schema for the NSABP B-42 trial, results of which were presented at the San Antonio Breast Cancer Symposium (SABCS) in December 2016. Patients in the trial had received an AI for 5 years (or tamoxifen for up to 3 years, followed by an AI to complete 5 years). (Figure 1)

### Figure 1: Schema for the NSABP B-42 Trial

- Postmenopausal Pts with ER+ or PR+ Breast Cancer
- Stage I, II, or IIIa invasive BC at diagnosis
- Disease-free After 5 Years of Endocrine Therapy

\[ \text{AI X 5 Yrs} \quad \text{OR} \quad \text{TAM X } 3 \text{ yrs } \rightarrow \text{AI to Complete 5 yrs} \]

Stratification:
- Pathological nodal status (Negative, Positive)
- Prior adjuvant TAM (Yes, No)
- Lowest BMD T score: spine, hip, femur (>2.0, ≤2.0 SD)

There were no significant differences in the distribution of patient, tumor and prior treatment characteristics. The percentage of patients completing 5 years of therapy was 62.5% in the placebo and 60.3% in the letrozole patients and median duration of treatment was 59.8 months. Dr Mamounas noted the similarity of the B-42 results with other trials in Europe presented at SABCS, which also showed that about 60% of patients were able to complete 5 years of extended endocrine therapy. Reasons for discontinuation are shown in Table 4.

### Table 3: Characteristics of Patients in NSABP B-42

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 60 years of age</td>
<td>34 – 35%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>- White</td>
<td>93%</td>
</tr>
<tr>
<td>- Black</td>
<td>4%</td>
</tr>
<tr>
<td>Node-negative</td>
<td>57 – 58%</td>
</tr>
<tr>
<td>Had lowest BMD score &lt; -2.0</td>
<td>25%</td>
</tr>
<tr>
<td>Received prior tamoxifen</td>
<td>39%</td>
</tr>
<tr>
<td>Breast-conserving surgery</td>
<td>61%</td>
</tr>
<tr>
<td>HER-2 negative</td>
<td>78% (8% unknown)</td>
</tr>
</tbody>
</table>

The primary endpoint was DFS, defined according to the standard RCT criteria; secondary endpoints included overall survival (OS), breast cancer free interval (BCFI), defined as recurrence or CBC as a first event, distant recurrence (DR), osteoporotic fractures (OF), or arterial thrombotic events (AT). Dr Mamounas explained that for the 3,923 patients included in the efficacy analysis, the median follow up was 6.9 years. Characteristics of the cohort are shown in Table 3.

### Table 4: Reasons for Treatment Discontinuation in NSABP B-42

<table>
<thead>
<tr>
<th>Reason for Discontinuing Letrozole</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient withdrawal/refusal</td>
<td>13.8%</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>9.6%</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>4.1%</td>
</tr>
<tr>
<td>Other complicating disease/death</td>
<td>2.7%</td>
</tr>
<tr>
<td>Declining Bone Density/Osteoporotic fracture</td>
<td>1.4%</td>
</tr>
</tbody>
</table>
In terms of BCFI, which, Dr. Mamounas noted, could be considered comparable to the distinct DFS endpoint in MA.17R, there was a 29% relative reduction and a 3.3% absolute difference in event rate (P=0.003) (Figure 3A). Similar results were also seen for the endpoint of DR (Figure 3B), with a 1.9% reduction with extended letrozole (P=0.03).

Speaking on the DR endpoint, Dr. Mamounas emphasized, “What we also see here is that, in the first 4 years, there was absolutely no difference in distant recurrence, and the difference emerged later.” He also noted that “maybe by following these patients longer, we may see a little more deviation in these curves — but — it remains to be seen obviously, because then the patients stop treatment.” Dr. Mamounas also reviewed the OS results (Figure 3C) which showed no difference between the treatment arms (P=0.22).
A comparison between the MA.17R and NSABP B-42 trials\textsuperscript{8,10} shows that the MA.17R primary endpoint is most comparable to the BCFI endpoint of B-42, with both endpoints showing a significant benefit with extended letrozole treatment (Table 5). Dr Mamounas also noted the similarity in results between the two trials when deaths from other causes were included in the primary endpoint for MA.17R (Table 5).

In comparing the results of the extended adjuvant endocrine trials (ATLAS, MA.17, MA.17R, NSABP B-42) on the basis of clinicopathologic factors, Dr Mamounas said “You can’t really find groups that benefit a lot more or a lot less, by looking at different clinicopathologic characteristics.”

He also compared the key toxicities observed across the trials, with AIs associated with bone fractures and new onset osteoporosis, and tamoxifen associated with endometrial cancers and pulmonary embolism. Dr Mamounas stressed that OS was not significantly different in most of the extended endocrine therapy trials, with the exception of the ATLAS trial, which showed significant reductions in breast cancer mortality, as well as overall mortality with tamoxifen. Dr Mamounas believed the latter result may be due, at least in part, to a differential effect on non-breast cancer deaths with continued tamoxifen, perhaps by improving cholesterol and reducing cardiovascular deaths.

In concluding his presentation, Mamounas said that the results of these multiple trials indicate that an extended duration of endocrine therapy reduces risk of recurrence and CBC in unselected populations, although it does not significantly prolong overall survival. Importantly, he noted the number needed to treat (NNT) is approximately 30-40 patients to prevent 1 event, and closer to 100 to prevent 1 metastatic event and that extended duration is associated with increases in tamoxifen- and AI-specific toxicities. As such, Dr Mamounas believes that assessment of potential risks and benefits is important before recommending extended AI therapy in patients with early-stage breast cancer.

Table 5: A Comparison of NSABP B-42 and MA.17R Outcomes\textsuperscript{8,10}

<table>
<thead>
<tr>
<th>Trial</th>
<th>Effect</th>
<th>Endpoint</th>
<th>DFS</th>
<th>BCFI</th>
<th>DR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-42 (n=3,923 631 events)</td>
<td>HR</td>
<td></td>
<td>0.85*</td>
<td>0.71</td>
<td>0.72</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td></td>
<td>0.048</td>
<td>0.003</td>
<td>0.03</td>
<td>0.22</td>
</tr>
<tr>
<td>MA.17R (N=1,918 165 events)</td>
<td>HR</td>
<td></td>
<td>0.80***</td>
<td>0.66**</td>
<td>NR</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td></td>
<td>0.06</td>
<td>0.01</td>
<td>NR</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*DFS (Recurrence + CBC + second non-breast primary cancer + deaths as first events) **Selected as DFS in MA.17R (Recurrence + CBC) ***DFS (Recurrence + CBC + Deaths from any cause)
Hope Rugo, MD

“It’s an interesting time, because we’re changing [clinical practice] faster than we can see any outcome in trials — these are events that occur over a long period of time,” Dr Rugo noted, highlighting the fact that patients have a long period of recurrence risk. “With trials, we start the trial, and we’re already starting to change what we’re doing with patients, change what we’re assessing, etc.,” she said, noting that in trials like MA.17R the results have been around for a long period, and clinical practice has already changed over the interim. “In addition, we’re looking at slightly different patient sets when we interpret current results in the light of prior trials — ATLAS and aTTom are complicated trials, a lot of patients, but some people didn’t follow the study therapy, some people didn’t have ER+ disease — they took a subset of patients that actually fit the intended criteria” she said. “One thing that all the trials show that is very similar, is that if you extend hormone therapy you reduce the number of events,” Dr Rugo said, with the caveat that, “when you’re extending after 10 years, we just don’t know enough, and we probably never will — it just takes too long.” She also noted in the case of trials like NSABP B-42, “This is a very early look at the data relative to the risk [of recurrence] for patients. When you really go through the data, and hear it analyzed … you realize that this is an early look, and we’re already seeing a benefit,

Adam Brufsky, MD, PhD

For NSABP B-42 as well as MA.17R, Dr Brufsky noted that the majority of recurrences being prevented are either locoregional or CBC events, and that while these are serious recurrence events, they do not kill patients. “What kills patients with breast cancer is distant recurrence,” he said, noting the previously presented results on distant recurrence after 4 or 5 years. He also noted, in agreement with Dr Rugo’s comments, “We’re not going to see the results of the things were are doing now, until maybe year 10 to 15 — this is an early look at the data.” Another important aspect of the data from MA.17R which Dr Brufsky noted was the risk of osteoporosis.

“We’re trading one set of issues for another …” he said, noting the current dilemma of balancing the reduced recurrence risk with osteoporosis and fracture risk.”

He also noted the recommendations of a recent ASCO consensus panel, in which adjuvant bisphosphonates may now be used to reduce breast cancer mortality in all women on AIs (not just those with osteoporosis). More frequent use of bisphosphonates, Dr Brufsky believed, may be another potential confounder in the interpretation of long-term adjuvant trial results.
Challenges in the application of extended adjuvant endocrine therapy trial results into clinical practice

**Michael J. Naughton, MD**

As an introduction to the next segment of discussion, Dr Naughton then summarized some of the challenges in the application of extended adjuvant endocrine therapy trial results into clinical practice. He outlined the goals of extended adjuvant endocrine therapy, specifically reducing the risk of distant recurrence and new cancers, and balancing this benefit against continued toxicity and the impact on patient safety and quality of life. The challenge, he suggested, is to determine this risk versus benefit at the individual level.

Dr Naughton also outlined the major clinicopathological characteristics that help to inform risk, such as tumor size and grade, and nodal status. In addition, he explained that there are patient factors such as age, menopausal status, and patient preference which must be considered, and finally, genomic testing, which can be used to further inform treatment decisions.

Dr Naughton explained that such genomic tests can be either prognostic (helping to select patients more or less likely to have a recurrence) or predictive (helping to determine which patients are likely to benefit from a given intervention).

“Low risk patients, we can’t necessarily help, since they don’t have much risk to reduce,” he explained. “However,” he continued, “even low risk clinical patients do not necessarily have insignificant risk, when we consider 5 and 10 years out … and with more clinical burden, the risk goes up.” He noted that in the major extended adjuvant trials, all subgroups appeared to benefit, and that while the absolute risk is different, the relative benefit in terms of risk reduction was similar. In view of these results, Dr Naughton suggested the major question that arises with using extended adjuvant endocrine therapy is “Are they at risk, and can we alter that risk with therapy?”

**Part 1: Discussion about applying the data in clinical practice**

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**Part 1: Question series 2 to the panel**

How do you use and prioritize clinical and pathologic risk factors in formulating your recommendation for extended AI therapy, and secondly, what are the potential limitations of using clinicopathologic factors for extended adjuvant endocrine therapy decision-making?

**Adam Brufsky, MD, PhD**

Dr Brufsky explained that there was a “real benefit” of AI therapy in the extended adjuvant endocrine setting shown 8 or 9 years ago, particularly in the N+ subset in MA.17, who are the main candidates to whom he offers extended adjuvant endocrine therapy. He explained that he occasionally also offers treatment to patients with node negative disease and larger tumors. Another important determinant Dr Brufsky noted was “how is the patient doing with the therapy?” — in view of the approximately 40% of patients that discontinued in the placebo arm of the B-42 trial. He also noted the limitations of clinicopathologic characteristics as a prognostic tool, in that

> … We know there are node negative tumors that do really badly, and there are node positive tumors that do really well.”
Dr Rugo explained that she takes a similar overall approach, and that the recent extended adjuvant endocrine results have not changed that, “except to be, potentially, a little more sparing” with its use.

The frustration for us is, node negative disease with 12, or 8 year recurrences, we’ve all seen them, and we really don’t know how to pick out those patients.”

She noted her use of extended adjuvant endocrine therapy for larger node negative tumors, those who are tolerating AI therapy well, and in those who don’t have a desire to discontinue. For node positive disease, she explained, “We try to push to 10 years.”

As a final word, Dr Rugo raised the cautionary issue of “by extending out the same therapy — are we increasing [endocrine] resistance pathways in some groups?,” citing the benefit of potentially identifying such patients in the future, and then using some type of alternating treatment. “But … ” she said, “That’s a whole other set of trials.”

Dr Mamounas agreed with the overall selection approach for extended adjuvant endocrine therapy. “Look at patients, look at the tumor … for node positive patients, if they tolerate [AI therapy] well, it’s an easy decision” he said, adding that for node negative, smaller (< 1 cm) tumors, additional factors need to be considered.

Dr Naughton went on to summarize the data from most of the extended adjuvant endocrine trials which show overall poor adherence and persistence and discontinuation rates of between 31% and 73% during the first 5 years of therapy.8,11,12,13 In the extended adjuvant setting, he noted, discontinuation rates were approximately 40%, and side effects were the primary reason for discontinuation.8,10 Dr Brufsky added the issue of costs entering into the equation — “Even though [AIs] are supposed to be generic, some of these medicines are really expensive depending on where you come from,” he said, noting the cost in western Pennsylvania of $300 monthly for generic exemestane, and the fact that some patients have to pay out of pocket.

Dr Rugo agreed with the cost, again citing an out of pocket expense of approximately $300 for patients with no medication coverage.

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**Part 2: Genomic Tests**

Hope S. Rugo, MD

Dr Rugo provided an overview of genomic testing, and explained that toxicity, clinicopathologic factors, and patient preference are the key issues that weigh into her process of making decisions on the use of extended adjuvant endocrine therapy. “Now we are really telling patients that there isn’t a 5-year mark where now you are cured,” she said, “So, we are educating patients a little bit differently. “Some of these clinical and tumor-related factors play more of a role than others,” she added, noting that she used the intrinsic subtype infrequently; “I don’t think we really have a clue yet how the intrinsic subtype plays a role — we tend to think of the more proliferative tumors recurring early, and the slower proliferating tumors recurring late, so you might think high-risk, slow proliferating tumor might be better treated with extended endocrine therapy, but we don’t really know, and we’re not that good at guessing intrinsic subtype,” she said. For the parameter of age, she explained, “For younger patients it’s a much bigger issue to continue hormone therapy, particularly our premenopausal patients, where we are adding ovarian suppression. We really don’t have any data on extending hormone therapy in that setting.” Conversely, she explained that for elderly patients (for example, those older than 80), “Extending hormone therapy may have more toxicity than benefit — depending on their comorbidities, etc.”
She also noted that “Of course, patient preference is really important,” and that “Once we take all of that into account,

“We’re still left with a big grey area of not really understanding who we should offer therapy to or not, and genomic tests offer us the potential for really being able to make better decisions.”

Dr Rugo explained that all of the genomic tests available such as Oncotype DX®, MammaPrint®, Breast Cancer Index™ (BCI), Prosigna®, and EndoPredict® (Table 6) provide prognostic information, and some have the ability to predict benefit from classes of therapies (eg; chemo- or endocrine therapy). She noted, however, that at present, none of the tests can predict benefit from specific adjuvant therapies. “Actually there’s not a single test that tells us whether to add a taxane to an anthracycline, or whether you could get rid of an anthracycline, or whether you should use an AI, for example versus tamoxifen,” she said. Dr Rugo explained that such tests can now be integrated into practice for the purposes of decision-making, and she highlighted forthcoming data that is expected from larger trials such as TAILORx, RxPONDER, and MINDACT.

In considering whether to offer extended adjuvant endocrine therapy from year 5 on, Dr Rugo cited three of these tests, BCI, Prosigna, and EndoPredict, which may help with decision-making in the extended setting. “As we all know from looking at circulating tumor cells, it doesn’t help to know that you’re not going to do well —

“What we want to know is who’s not going to do well — that’s what we have right now — but we also want to know whose tumor is most likely to benefit from continuing hormone therapy.”

Table 6: Genomic Biomarker Tests

<table>
<thead>
<tr>
<th></th>
<th>Oncotype DX® (Genomic Health)</th>
<th>MammaPrint® (Agendia)</th>
<th>Breast Cancer Index™ (BCI) (Biotheranostics)</th>
<th>Prosigna® (Nanostring)</th>
<th>EndoPredict® (Myriad)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of genes</td>
<td>21</td>
<td>70</td>
<td>11 (+ tumor size &amp; grade for N1 patients)</td>
<td>46 (+ tumor size)</td>
<td>12 (+ tumor size + nodal status)</td>
</tr>
<tr>
<td>Prognostic 0-10 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Predictive of adjuvant chemotherapy benefit</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prognostic 5-10 yr</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Predictive of extended endocrine therapy benefit</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Information gathered from respective corporate websites
Dr Rugo then reviewed data for each biomarker with prognostic data in the late setting. She highlighted data which showed that, for patients with high or intermediate scores on the BCI from year 5 to year 10 (Figure 4A), “your risk is substantially higher — an absolute risk of 10%, compared to patients with a low risk.” She also presented similar data on assessment of late recurrence for Prosigna and EndoPredict.15,16

She then reviewed data from TransATAC evaluating the performance of 6 genomic signatures for distant recurrence in a cohort of 818 postmenopausal women with ER+/HER2 negative disease.17 The study assessed the strength of the biomarkers alone or when combined with an algorithm of clinical variables Clinical Treatment Score, CTS. The genomic signatures tested included Oncotype DX Recurrence Score, Breast Cancer Index, Prosigna Risk of Recurrence (ROR; statistical model included genomic biomarker plus tumor size) and EndoPredict (EPclin; statistical model included genomic biomarker plus tumor size and number of positive nodes).

**Table 7. Pan-Genomic assessment of prognostic ability for late distant recurrence in node negative patients: a TransATAC study**17

<table>
<thead>
<tr>
<th>Test</th>
<th>Assay Includes</th>
<th>Results</th>
<th>Statistical significance beyond Clinical Treatment Score (CTS) (CTS: Nodal status, grade, tumor size, age, treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX Recurrence Score (RS)</td>
<td>✅ no no no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer Index (BCI)</td>
<td>✅ no</td>
<td>✅ yes</td>
<td></td>
</tr>
<tr>
<td>Prosigna Risk of Recurrence (ROR)</td>
<td>✅ Tumor size</td>
<td>✅ yes</td>
<td></td>
</tr>
<tr>
<td>EPclin</td>
<td>✅ Tumor size, nodal status</td>
<td>✅ yes</td>
<td></td>
</tr>
</tbody>
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The results showed that BCI, Prosigna ROR, and EPclin provided the most prognostic value for late distant recurrence in node-negative patients, whereas adding clinical factors to genomic profilers was important in lymph node-positive patients.

**Figure 4: Risk of Late Distant Recurrence Based on (A) BCI, (B) Prosigna and (C) EndoPredict Genomic Tests**14,15,16

A. Breast Cancer Index

B. Prosigna

C. EndoPredict
As balance, Dr Rugo highlighted that similar results have been shown with BCI in node positive patients when the BCI genomic data is combined with clinical factors. In a study of 349 patients with 1-3 positive nodes, the BCIIN+ algorithm (BCI + tumor size + tumor grade) demonstrated significant prognostic ability in identifying groups at low vs high risk of late distant recurrence (Figure 5).18

**Figure 5:** BCI prognostic assessment in N1 patients (BCI+size+grade)18

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Dr Rugo then reviewed the current status of predictive biomarker tests. She explained that the BCI has used the HoxB13/IL-17BR (H/I) component to examine predictive ability across several cohorts, including MA.17.

> This was really the best data set to look at to try and understand whether or not you could predict the benefit using 5 years of an AI after 5 years of tamoxifen,” she said.

In patients with High H/I, there was a 16.5% absolute benefit with continued endocrine therapy, a 67% relative risk reduction, while in patients with Low H/I, there was no significant benefit of extended endocrine therapy (Figure 6).20 She explained that in the overall population, “It was difficult to find anything that really told us about predicting benefit, but if you looked at the score, that helped to really differentiate the patients who were going to benefit from extended therapy with letrozole … basically, patients who had a high score benefitted from continuing letrozole, whereas patients with a low score didn’t seem to have a different outcome — that was actually very encouraging information,” she said.

Summarizing the current data, Dr Rugo explained, “Genomic tests have really shown that they can predict a risk of late distant recurrence, which is really important to us.” She also noted the predictive value of genomic testing, emphasizing the need to determine who will benefit from extended adjuvant hormone therapy.

“We have this really intriguing data from MA.17, and depending on how quickly NSABP [B-42] moves, we’ll have some very critical data looking at these tests as well, moving forward.”
Part 2: Questions to the panel

In clinical practice, how do you value endocrine predictive data compared to late recurrence prognostic data?

Eleftherios (Terry) P. Mamounas, MD, MPH

Dr. Mamounas saw the value of predictive data.

“... If you have a test that actually predicts significant benefit, then in another group, no benefit at all, or very, very little benefit, I think that’s even more important than the prognosis.”

“But it has to be also a significant differentiating factor,” he added, “meaning, if you have 30% reduction in one group, then a 20% in another group, that doesn’t help you much — but if you find a group that doesn’t benefit ... I think that would be very important.” He added that such data have also been helpful in terms of determining the need for upfront chemotherapy. “That is what actually pushed the use of the Recurrence Score — not so much the prognosis, but the predictive ability,” he said.

Dr. Mamounas asserted that in such a case, the overall decision would be to treat anyway. “Say, maybe there’s a little bit of benefit, but there’s a lot of risk, that gets magnified,” he said, noting that such scenarios occur in the upfront setting as well. “Let’s say you got a low recurrence score, but you have 5 positive nodes — you may choose to treat, even though in your heart of hearts, you believe there is not benefit.” Dr. Rugo agreed, adding that “if you have a high risk of recurrence, you’re going to use it anyway, but when you have that ‘muddy zone’, the predictive ability may be much more important to you.”

What new studies/data are you anticipating for genomic biomarkers in the extended endocrine context?

Dr. Rugo and Dr. Brufsky agreed that the forthcoming data expected from the NSABP B-42 trial would be especially valuable, and a powerful data set. Dr. Mamounas added “We’ve talked to a lot of companies, we have these markers, and so hopefully we will put the studies together to test all this in the extended adjuvant setting. We have over 3,000 blocks in [NSABP] B-42.”
Adam M. Brufsky, MD, PhD

Dr. Brufsky began by reiterating the question of how to integrate genomic with clinicopathologic characteristics, and recalled the data presented earlier, showing that some patients with higher risk disease according to clinical parameters (e.g., LN+) may in fact be classified as low risk with genomic tests and have very good outcomes. Referring to Dr. Rugo’s earlier presentation of the BCI assessment within the pan-genomic analysis, “I think it’s unfortunate that the lymph node positive data was not included in the TransATAC data that was presented at San Antonio,” he said, “But I think clearly what has come out is that clinicopathologic characteristics are probably going to have to be incorporated into some of these assays.” Dr. Brufsky then raised the opposing issue of:

“What about patients at really low risk, that look clinically low risk, but potentially have a higher risk of late recurrence based on the tumor biology — can we even identify patients like that?”

He then reviewed some collaborative data from his group at UPMC and a group at Massachusetts General Hospital as well as data from the Stockholm randomized controlled trial (RCT) cohort on patients with clinically low risk disease (Figure 7).21 He explained that these were patients with T1, N0, and HER2 negative disease and mostly Grade 1 or 2. The BCI identified a subgroup of these patients, 32-36%, with a higher risk of late distant recurrence. He further described that roughly 2/3 of patients who were BCI high-risk also had high H/I score, “meaning they would benefit from endocrine therapy.” As such, Dr. Brufsky noted that even patients who would otherwise be considered relatively low risk (i.e., small tumor, low grade) who may not be tolerating therapy well and may want to discontinue, may still be at significant recurrence risk and can benefit from therapy.

“I think it tells us that there may be a little bit more to this … especially in these low risk patients, other than clinicopathologic factors” he said.

Figure 7: BCI stratification of patients with clinically low risk disease (T1N0) in two cohorts21
How do you actually apply this data in the clinic, and are you thinking about extended adjuvant endocrine therapy in early-stage patients?

Adam M. Brufsky, MD, PhD

Dr. Brufsky noted he had not been generally considering extended adjuvant endocrine therapy in early-stage patients, but that the data had caused him to rethink his position. Dr. Mamounas agreed; “Obviously T1, it’s a broad category, T1b, T1c. There potentially could be significant risk, so that may be the population you want to try and predict who among those are the high risk patients,” he said. “So it’s very provocative, I think it’s clearly something we have to look into.” Dr. Rugo was also in agreement with the other panel members. “I think we knew this, and, you know, my mother had a T1 tumor she died of, so those recurrences are late, and we know there is a risk. So I think that you really have to understand more about the tumor itself, and which tumors have a higher risk of late recurrence. And right now, I think in terms of clinicopathologic features, it’s somebody who will be at risk who is not falling apart on aromatase inhibitors,” she said, adding that she would most likely consider extended adjuvant endocrine therapy for T1c disease; “I don’t think that I would treat a T1a or b right now.”

In the final portion of the discussion, Dr. Brufsky reviewed data on incorporating genomic tools into clinical practice. He noted that genomic tools have been available for a number of years, and that it is important to consider their impact on clinical decision-making, their impact on outcomes, and their impact on costs. “When we consider what is the value of these novel technologies — these are all things we need to think about,” he said.

Dr. Brufsky described a decision-impact study his group at UPMC completed in collaboration with Yale University, which had the doctor and the patient fill out questionnaires before and after they ordered BCI testing. The data set included 141 patients, most of whom were postmenopausal and lymph node negative. He then reviewed the results of the study, which showed a change in treatment recommendations from ‘yes’ to ‘no’ in 21%, and from ‘no’ to ‘yes’ in 9% of physicians (Figure 8).

**Figure 8:** Impact of Breast Cancer Index On Treatment Decisions

<table>
<thead>
<tr>
<th>Pre-test</th>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
<td>N=30 (21%)</td>
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<tr>
<td>N=12 (9%)</td>
<td>No</td>
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<tr>
<td>N=37 (26%)</td>
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**Interestingly enough, the physician treatment recommendations changed about 30% of the time (after the BCI result).**

“This is consistent,” he continued, “When you look at the old Oncotype DX data, which is about probably 8 to 10 years old, you see kind of the same thing — it does change minds — so it’s not just something that’s out there that’s theoretical, but actually people are changing their recommendations based on the assay” he said.

He also noted that the patients were less anxious, with less “decisional conflict” — likely related to the reduction in anxiety. “They actually felt better is the bottom line” he said, and

**82% of the patients in this decisional outcome study reported knowing the results would make them more likely to be compliant with extended adjuvant therapy.”**

Dr. Brufsky found the latter result to be especially noteworthy; “When we can see that even there’s a 40% discontinuation rate in the placebo arm of a clinical trial — more information might actually be better.”
Lastly, Dr Brufsky reviewed the health economic analysis from the study, which projected that there would be a cost savings with BCI of approximately $5,000 ($5,190 USD). While he conceded that payers might challenge the data in terms of being able to treat their breast cancer patients at a lower cost, he believes that testing of this kind “has the potential to be cost effective,” particularly in view of the considerable cost of even generic AIs: “If some generic drugs are now $300 per month, the cost savings can be significant” he said, “So I think this is something we really need to consider as we look at global populations of patients.”

**In what clinical scenarios would a genomic biomarker be most helpful for whether to recommend extended endocrine therapy?**

Dr Brufsky said, “I think someone who is really having trouble with an endocrine therapy, who you really would want to give it to anyway … those are the women I’m really in a dilemma about — I think they would probably benefit from [extended adjuvant endocrine therapy] but — they’re just miserable.” Dr Rugo said, “I think it’s really those people who don’t have the highest risk, but they’re not at the lowest risk — and it’s going to be the individual patient — T1c tumors; (patients with) 1-3 positive nodes, probably more on the 1-2 positive nodes” she said. “People who have high risk criteria, but they just don’t fit into the high risk group – you want to really understand better their risks – we have a fair number who are young, have had neoadjuvant therapy, had residual disease … you already have those risks, but they really want to have some other determining factors about continuing hormone therapy” she said. Dr Mamounas was also in agreement, “The bulk of these patients would be the patients that, if they tolerate [endocrine therapy] well, I think that [genomic biomarkers] would be pretty valuable.”
References


