Table 1. Breast Cancer Mortality and Overall Survival in the ATLAS and aTTOm Studies

	HR (95% CI)	
Years	Breast Cancer Mortality	Overall Survival
5-9	0.97 (0.84 to 1.15)	0.99 (0.89 to 1.10)
10+	0.75 (0.65 to 0.86)[a]	0.84 (0.77 to 0.93)[a]
All	0.85 (0.77 to 0.94)[a]	0.91 (0.84 to 0.97)[a]

ATLAS, Adjuvant Tamoxifen, Longer Against Shorter trial; aTTOm, Adjuvant Tamoxifen: To Offer More trial.

[a]$P < .05$ favoring 10 years.

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Source: Gray et al. ASCO. 2013.

Table 2. Outcomes in the Joint Analysis of the TEXT and SOFT Trials

	Exemestane + OFS vs Tamoxifen + OFS	
Outcome	HR (95% CI)	*P*
Disease-free survival	0.72 (0.60 to 0.85)	.0002
Breast cancer–free interval	0.66 (0.55 to 0.80)	< .0001
Distant disease–free interval	0.78 (0.62 to 0.97)	.02
Overall survival	1.14 (0.86 to 1.51)	.37

Median follow-up of 5.7 years.

OFS, ovarian function suppression.

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Source: Pagani O et al. *N Engl J Med*. 2014.

$P = .62$) [Tevaarwerk AJ et al. *J Clin Oncol*. 2014]. OS was also similar at 97.6% and 95.2%, respectively (log-rank $P = .67$). Dr Davidson noted that this trial was terminated early and that it was not sufficiently powered for these outcomes. However, the quality-of-life measures were worse in the women taking OFS vs those who did not, although this difference seemed to be mitigated over time, and she questioned whether this may be due to the women naturally moving toward menopause or adjusting to the changes.

Regarding the role of AIs in women treated with OFS, the joint analysis of the TEXT and SOFT trials showed that EXE + OFS vs OFS + TAM improved DFS, the BC-free interval, and the disease-free interval, although OS was similar with both treatments (Table 2) [Pagani O et al. *N Engl J Med*. 2014]. In ER-positive BC, the ABCSG12 trial showed that there was no difference in DFS at 94 months with anastrozole vs TAM (HR, 1.13; 95% CI, 0.88 to 1.45; $P = .33$), but OS was worse with anastrozole vs TAM (HR, 1.63; 95% CI, 1.05 to 1.45; $P = .03$) [Gnant M et al. *Ann Oncol*. 2014].

Based on these data, Dr Davidson states that there are now several evidence-based options available for AET in premenopausal women. These include TAM for 5 to 10 years, TAM for 5 years with a switch to an AI for 5 years, OFS + TAM, or OFS + AI. In her view, for patients at low risk, TAM alone for 5 to 10 years is sufficient. For women at higher risk—including those who have had chemotherapy, are aged < 35 years, or have multiple positive nodes—OFS + TAM or OFS + AI can be considered. The optimal duration of OFS-based therapy is uncertain, and long-term follow-up to determine the toxicity and benefit is needed.

Identification of Drivers of Metastasis in BC

Written by Lynne Lederman

Upon receiving the AACR Outstanding Investigator Award for Breast Cancer Research, Yibin Kang, PhD, Princeton University, Princeton, New Jersey, USA, discussed his research into the origin of metastatic traits in breast cancer (BC). Because the majority of patients with BC will develop metastatic disease, identification of the mechanisms of metastasis will provide new therapeutic targets.

Key questions include, what genes give metastatic tumor cells the ability to escape from the intrinsic constraints of the epithelium and initiate new tumors in a distinct microenvironment, and when does this occur? One level of research involves examining the natural heterogeneity of cells in tumors (intratumoral heterogeneity) to identify metastasis genes.

Another level involves looking at intertumoral heterogeneity, important because tumors of the same type from different patients behave differently. One hypothesis for this is the cell-of-origin model, in which tumors develop from different normal cells: aggressive tumors develop from stemlike cells, which become more metastatic after oncogenic events. Other tumors, derived from fully differentiated cells, are less likely to metastasize.

Another hypothesis, the oncogenic driver mutation model, suggests that poor-prognosis tumors result from oncogenic driver events during tumor initiation. Tumors may come from the same cell of origin but, through different oncogenic driver events, give rise to tumor cells that have little chance of metastasizing; another oncogenic driver event may lead to formation of highly aggressive metastatic tumors.

One amplicon associated with poor prognosis in breast cancer was identified by a computational biology in 8q22 [Hu G et al. *Cancer Cell*. 2009]. This small region contains about a dozen genes, half of which are highly differentially

Table 1. Tumor Incidence in In Vivo Tumor Initiation Assay

Injected Cells From PyMT Mice	Tumor Incidence in Mice	
	Wild Type (n = 10)	MTDH Knockout (n = 10)
Unsorted pMECs, No.		
100	1	0
500	3	0
2000	10	4
P value	< .001	
	Wild Type (n = 12)	MTDH Knockout (n = 12)
Sorted luminal cells, No.		
100	1	0
1000	5	0
10000	7	1
P value	< .0001	

MTDH, metadherin; pMEC, primary mammary epithelial cells; PyMT, mouse mammary tumor model with high rate of lung metastases (mouse polyomavirus middle-T antigen under the control of mouse mammary tumor virus).

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Adapted from *Cancer Cell*, Copyright 2014;26:92-105, Wan L et al. MTDH-SND1 Interaction Is Crucial for Expansion and Activity of Tumor-Initiating Cells in Diverse Oncogene- and Carcinogen-Induced Mammary Tumors. With permission from Elsevier.

expressed. These were cloned and overexpressed in tumor cells to determine which could drive lung metastases in a mouse model, leading to the identification of one gene, metadherin (MTDH), a poor prognosis marker and functional driver of breast cancer metastasis.

Knockout of MTDH does not affect embryonic or postnatal development in mice; in a model of a highly aggressive tumor, it slows tumor progression, reduces total tumor burden, and eliminates metastases. Tumor formation in MTDH knockouts in an in vivo model of tumor initiation is shown in Table 1.

Staphylococcal nuclease domain containing 1 (SND1) is associated with poor prognosis and interacts with MTDH. Knockdown of SND1 reduces lung metastases and sensitizes cells to chemotherapy-induced apoptosis [Blanco MA et al. *J Biol Chem*. 2011; Wan L et al. *Cancer Cell*. 2014]. Dr Kang's group has used crystal structural analysis to determine the sites of interaction between MTDH and SND1 [Guo F et al. *Cell Reports*. 2014]. Mutation at either 1 of 2 tryptophans eliminates the binding of MTDH to SND1 and the ability of MTDH to rescue tumor-initiating functions. The group is now screening small molecular compounds to interfere with the cooperative activity of MTDH and SND1 in tumor initiation.

Genes that confer survival advantage to primary tumor cells during tumor initiation may play crucial roles in metastasis via several mechanisms, including promotion of the development of tumor-initiating cells or by mediation of crosstalk between tumor cells and their environment. Therapeutic targeting of metastasis genes may have a far-reaching impact on the prevention and treatment of metastatic diseases.

Overcoming Tumor Diversity and Adaptability Key to Effective Therapies in BC

Written by Muriel Cunningham

While the current outlook for most patients with breast cancer (BC) is positive, challenges remain in finding the optimal therapies for the patients diagnosed with metastatic disease, according to Joan S. Brugge, PhD, Harvard Medical School, Boston, Massachusetts, USA, who shared her thoughts on the future treatment of these patients.

Advances in the genetic analysis of tumors have revealed astounding genetic diversity in BC. Multiple alterations are possible, with each patient having individual patterns of alterations. Questions that have emerged include how current therapies are affected by these variable alterations and whether therapies will need to be based on the genetic patterns of each patient. For example, research has shown that human epidermal growth factor receptor 2 (HER2)–targeted therapies are less effective in patients with amplified HER2 and PIK3CA alterations; adding a PIK3CA inhibitor may increase the effectiveness of HER2 therapies in patients with these combined alterations. Dr Brugge said that not all of the alterations influence sensitivity to therapy, and clinicians may be able to stratify patients into a still large but manageable number of subsets, which can be treated with different combinations.

Within each tumor, there may also be significant heterogeneity. Within a tumor, cells that are sensitive to a particular agent will be killed, leaving the surviving resistant cells. This can lead to variable success in the treatment of each tumor within a patient. Recent evidence suggests that a single residual cell can develop into a recurrent tumor. A patient with metastatic BC did not respond to standard chemotherapy and was found to have an activating PIK3CA mutation [Juric D et al. *Nature*. 2014]. The patient was treated with the PIK3CA-specific inhibitor BYL719 in a clinical trial. After an initial response, the patient developed resistance to the drug and died. Genetic sequencing of metastatic sites showed additional and different PTEN genetic alterations in nonresponding tumors. The fact that