Novel Agents Show Promise Against Acquired Endocrine Resistance in ER+ Advanced Breast Cancer

For patients with advanced estrogen receptor (ER)-positive breast cancer, acquired resistance to endocrine therapy is a common clinical challenge. Several agents with novel mechanisms of action are demonstrating promising antitumor activity in this setting, suggesting a new wave of therapeutic strategies for patients with heavily pretreated, ER-positive, advanced and metastatic breast cancer.

Giredestrant: Selective Estrogen Receptor Antagonist

Giredestrant is an oral, non-steroidal, selective ER antagonist with promising single-agent activity. Komal L. Jhaveri, M.D., of Memorial Sloan Kettering Cancer Center, presented findings from a phase I trial of giredestrant in 111 patients with ER-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer [1].

All patients had breast cancer that progressed while receiving endocrine therapy in the adjuvant setting for at least 24 months and/or in the advanced setting for at least 6 months. Prior therapies included a CDK4/6 inhibitor (64%), fulvestrant (21%), and/or chemotherapy for metastatic disease (16%).

The median patient age was 58 years and 65% of patients had visceral disease at baseline. Nearly half of patients (47%) had an *ESR1* mutation. Patients were assigned to treatment with giredestrant across 4 dose cohorts: 10 mg ($n = 6$), 30 mg ($n = 41$), 90/100 mg ($n = 55$), and 250 mg ($n = 9$).

Giredestrant exhibited antitumor activity across all dose cohorts and patient subgroups, regardless of *ESR1* mutation status or prior treatment with CDK4/6 inhibitors, fulvestrant, or chemotherapy. The overall response rate (ORR) among patients treated with giredestrant 30 mg was 55%.

Treatment with giredestrant was well tolerated; the maximum tolerated dose was not reached. The most common adverse events (AEs) of any grade were fatigue, arthralgia, back pain, nausea, and diarrhea. Grade 1–2 sinus bradycardia was observed in 9 patients.

Based on promising phase I findings, giredestrant 30 mg is currently undergoing additional evaluation in randomized phase II and III trials as a single agent and in combination with CDK4/6 inhibitors in patients with ER-positive breast cancer.

H3B-6545: Selective Estrogen Receptor Covalent Antagonist

H3B-6545 is a first-in-class selective estrogen receptor covalent antagonist that targets both wild-type and mutant ER proteins. Erika P. Hamilton, M.D., of the Sarah Cannon Research Institute, presented findings from a phase I/II trial of H3B-6545 in 94 patients with metastatic ER-positive, HER2-negative breast cancer refractory to endocrine therapy [2].

In this heavily pretreated cohort, patients received a median of three prior lines of therapy, most commonly including prior CDK 4/6 inhibitor therapy (85%), fulvestrant (72%), and chemotherapy (50%). At study entry, 81% of patients had visceral metastases and 31% had high-risk molecular features, including clonal Y537S or clonal D538G mutations. All patients were treated with H3B-6545 450 mg daily.

The ORR was 17%. The clinical benefit rate at 6 months—defined as complete response, partial response, or stable disease for at least 23 weeks—was 40%. Median progression-free survival (PFS) for all patients was 5.1 months.

Responses were observed across patient groups, including those with visceral metastases, *ESR1* mutations, and after prior therapy with CDK 4/6 inhibitors, fulvestrant, and chemotherapy. Results suggested greater antitumor activity with H3B-6545 among patients with *ESR1* Y537S clonal mutations ($n = 10$). In this group, the ORR was 40% and the median PFS was 7.3 months.

Treatment with twice-daily oral H3B-6545 was well tolerated. The most common grade ≥ 2 AEs were anemia, nausea, and diarrhea. Cardiovascular toxicities included grade 1–2 sinus bradycardia in 40% of patients and grade 2–3 QTcF prolongation in 5% of patients, suggesting the need for close cardiovascular monitoring in future trials.

Proxalutamide: Androgen Receptor Antagonist

Proxalutamide (GT0918) is an investigational, potent AR antagonist. Huiping Li, M.D., of the Beijing Cancer Hospital, presented results from a phase Ib trial of 45 patients with metastatic AR-positive breast cancer that progressed on first-line therapy [3]. The study cohort included 14 patients (31%) with triple-negative breast cancer (TNBC).

Patients received proxalutamide 200 mg ($n = 30$) or 300 mg ($n = 15$) once daily. The disease control rate was 22.2% for all patients at both 8 and 16 weeks. By comparison, the disease control rate at 8 weeks was 35.7% for patients with TNBC, suggesting an increased treatment benefit in this subgroup.

Median PFS was 1.9 months for all patients, 7.8 months for those who completed at least 2 cycles of proxalutamide 200 mg ($n = 10$), and 3.6 months for those who completed at least 2 cycles of proxalutamide 300 mg ($n = 5$).

The most common grade 3-4 AEs included elevated aspartate aminotransferase, elevated alanine aminotransferase,

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elevated blood alkaline phosphatase, elevated gamma-glutamyl transferase, decreased platelet count, fatigue, decreased appetite, anemia, and depression.

Enobosarm: Selective Androgen Receptor Modulator

Selective androgen receptor modulators (SARMs) are a new class of endocrine therapies that exhibit both agonist and antagonist activity, depending on the tissue type. Enobosarm is an investigational, oral, first-in-class SARM that targets the AR receptor and inhibits the growth of AR-positive, ER-positive breast cancer cells.

Carlo Palmieri, Ph.D., M.B.B.S., of the Clatterbridge Cancer Centre NHS Foundation Trust, presented results from a phase II trial of enobosarm in 136 postmenopausal women with AR-positive, ER-positive metastatic or locally recurrent breast cancer [4].

Eligible patients had responded to adjuvant therapy for at least 3 years or responded to their most recent line of endocrine therapy for metastatic disease for at least 6 months. Tumor samples were assessed for AR expression by immunohistochemistry; AR-positive tumors were defined as those with >10% nucleic AR expression. Patients were randomly assigned to treatment with enobosarm 9 mg ($n = 72$) or 18 mg ($n = 64$).

The clinical benefit rate at 24 weeks was 32% in the 9-mg cohort and 29% in the 18-mg cohort. All responses occurred in patients with AR-positive tumors.

Table 1. Extent of tumor AR staining and response to enobosarm in AR-positive advanced breast cancer

Parameter	AR staining <40% ($n = 22$)	AR staining ≥40% ($n = 24$)
Mean PFS	2.92 months	7.89 months
Median PFS	2.75 months	5.5 months
ORR	0%	50%*
CBR	18%	79%*
PD	82%	21%*

[a]p value <.0001 vs. AR staining <40%.
Abbreviations: AR, androgen receptor; CBR, clinical benefit rate; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival.

In an evaluation of treatment response by extent of AR staining, researchers considered the threshold of ≥40% AR expression to be optimal for identifying which patients were most likely to benefit from treatment with enobosarm (Table 1). Compared with patients with <40% positive staining, patients with ≥40% positive AR staining had a significantly greater ORR (0% vs. 50%; $p < .0001$).

The phase III ARTEST trial will compare enobosarm monotherapy versus active control (exemestane or SERM) in patients with AR-positive (≥40% nuclei staining), ER-positive, HER2-negative MBC that progressed on prior therapy with a nonsteroidal aromatase inhibitor, fulvestrant, and a CDK4/6 inhibitor.

References

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