

# Major Advances in Clinical Cancer Research in 2012

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A list of 17 major advances in clinical cancer research, considered to be practice-changing, has been issued by the American Society of Clinical Oncology (ASCO) in its annual report, entitled [Clinical Cancer Advances 2012](#).

The report, which covers the period from October 2011 to September 2012, also highlights 70 "notable advances" that are promising but not immediately applicable to practice.

"Consistent, significant achievements are being made in oncology care with novel therapeutics, even in malignancies that have previously had few treatment options, as well as in defining factors that will predict response to treatment. ASCO's report distills the most significant of these advances that [will affect] the lives of cancer patients today," said Bruce Roth, MD, coexecutive editor of the report.

The 17 major advances considered to be practice-changing are listed below; the top 5 were identified as such by ACSO; the others follow in no particular order.

- **Everolimus ( *Afinitor*) in hormone-receptor positive breast cancer.** Everolimus, an mTOR inhibitor used in the treatment of renal cell cancer, [was approved](#) for use in combination with exemestane ( *Aromasin*) for women with hormone-positive breast cancer that has spread despite initial treatment with an aromatase inhibitor. This indication was based on results from the 724-patient BOLERO-2 trial, which was [halted early](#) because of the benefit observed. The combination of everolimus plus exemestane increased the median time to disease progression to 10.6 months, compared with 4.1 months with exemestane alone ( *N Engl J Med.* 2012;366:520-529).
- **T-DM1 in *HER2*-positive metastatic breast cancer.** T-DM1, which is currently [awaiting approval](#) by the US Food and Drug Administration (FDA), consists of the anti- *HER2* antibody trastuzumab ( *Herceptin*) linked to the cytotoxic emansine. "We've taught an old friend a new trick — we're using [trastuzumab] as a delivery vehicle," said [one expert](#). In the pivotal EMILIA trial of 991 women with *HER2*-positive metastatic breast cancer who had stopped responding to trastuzumab, T-DM1 improved survival, compared with the current standard treatment of capecitabine ( *Xeloda*) and lapatinib ( *Tykerb*) ( *N Engl J Med.* 2012;367:1783-1791). After 2 years, the median survival rates were 65.4% with T-DM1 and 47.5% with the standard combination.
- **Preoperative chemo and radiation for esophageal cancers.** A [phase 3 trial](#) of 366 patients with cancer of the esophagus or gastroesophageal junction showed that preoperative treatment with chemotherapy (carboplatin and paclitaxel) plus radiation, followed by surgery, yielded substantial benefits, compared with surgery alone ( *N Engl J Med.* 2012;366:2074-2084). Patients who had preoperative treatment survived for twice as long (median overall survival, 49 vs 24 months), and 29% had a complete remission.

- **Screening with flexible sigmoidoscopy reduces colorectal cancer deaths.** A large American study, involving 154,000 patients with a median follow-up of 11.9 years, showed a significant decrease in the incidence of colorectal cancer (reduced by 21%) and death (26%) ( *N Engl J Med.* 2012;366:2345-2357). This study, hailed as a **landmark trial**, confirmed benefits seen in previous British and Italian studies, and has prompted much discussion about how flexible sigmoidoscopy compares with colonoscopy, the preferred screening method in the United States.
- **Enzalutamide ( *Xtandi* ) for late-stage prostate cancer.** Enzalutamide **was approved** by the FDA in August for use in men with metastatic castration-resistant prostate cancer previously treated with docetaxel after the ARRIRM trial of 1199 men was stopped early because it showed a survival benefit. Median overall survival was 18.4 months with enzalutamide and 13.6 months with placebo ( *N Engl J Med.* 2012;367:1187-1197). It is predicted that this first-in-its-class drug will be a "**game-changer**" in prostate cancer.
- **Lenalidomide ( *Revlimid* ) maintenance in multiple myeloma.** The finding that lenalidomide **delays relapse** after stem cell transplantation comes from 2 placebo-controlled phase 3 trials. In the first study ( *N Engl J Med.* 2012;366:1782-1791), conducted in 615 patients younger than 65 years, the disease returned after 41 months with lenalidomide and after 23 months with placebo; after 4 years of follow-up, more than 70% of patients were alive in both groups. In the second study ( *N Engl J Med.* 2012;366:1759-1769), conducted in 460 patients younger than 71 years, median time to progression was 46 months with lenalidomide and 27 months with placebo. Lenalidomide also increased overall survival (35 deaths in the lenalidomide group and 53 in the placebo group). However, lenalidomide was associated with more adverse events and a higher incidence of second cancers than placebo (7%–8% vs 3%–4%), the report notes.
- **Pertuzumab ( *Perjeta* ) in HER2-positive metastatic breast cancer.** Pertuzumab is an anti-*HER2* antibody that **was approved** in June in the United States and just **cleared for approval** in Europe. The **CLEOPATRA trial** showed that adding pertuzumab to the combination of trastuzumab plus docetaxel in the initial treatment of *HER2*-positive breast cancer can overcome or delay the resistance that develops to trastuzumab when it is used alone. In the 808 women, the median time to progression was 18.5 months when pertuzumab was added to the initial treatment, and 12.4 months when it was not ( *N Engl J Med.* 2012;366:109-119).
- **Regorafenib ( *Stivarga* ) in metastatic colorectal cancer.** This multitargeted drug **was approved** by the FDA in September, after the CORRECT trial showed that regorafenib extended overall survival in patients with metastatic colorectal cancer whose disease had progressed after all approved standard therapies. Median overall survival was 6.4 months with regorafenib and 5.0 months with best supportive care. These results **were presented** at the Gastrointestinal Cancers Symposium in January, and so far the data are available only in abstract form ( *J Clin Oncol.* 2012;30(4 Suppl): **abstract LBA385**).
- **Bevacizumab ( *Avastin* ) in recurrent ovarian cancer.** Women with ovarian cancer who progress after platinum-based chemotherapy are then treated nonplatinum-containing chemotherapy, such as pegylated liposomal doxorubicin, topotecan, and weekly paclitaxel. The AURELIA trial of 361 women who had received up to 2 previous treatment regimens showed that median time to disease progression was better with bevacizumab plus this

chemotherapy than with chemotherapy alone (6.7 vs 3.4 months). These results [were presented](#) at the 2012 ASCO annual meeting, and so far are available only in abstract form ( *J Clin Oncol*. 2012;30:30(15 Suppl): [abstract LBA5002](#)).

- **Cabozantinib ( *Cometriq*) in medullary thyroid cancer.** This drug [was approved](#) by the FDA in November on the basis of the pivotal EXAM trial of 330 patients with progressive, inoperable, metastatic, or locally advanced disease, and tumors that were actively growing. The results showed that cabozantinib improved time to disease progression over placebo (11.2 vs 4.0 months). In addition, tumor shrinkage was seen in 26% of patients in the cabozantinib group, compared with 0% in the placebo group, and these responses lasted a median of 14.6 months. These results have [been presented](#) at meetings and are available only in abstract form ( *J Clin Oncol* 2012;30:(15 Suppl): [abstract 5508](#)). Cabozantinib is also being studied in other cancer types, and "unprecedented" results were [recently reported](#) in advanced prostate cancer.
- **Carboplatin and pemetrexed combination in nonsmall-cell lung cancer (NSCLC).** Patients with NSCLC who have a performance score of 2 (capable of caring for themselves, but not carrying out work activities) are currently treated with a single chemotherapy, but a new study suggests they might live longer if they are treated with a 2-drug combination. This represents a "paradigm shift in the standard care for advanced NSCLC," and underscores the importance of not undertreating this patient population, according to the ASCO report. The 205-patient study showed that the combination of carboplatin plus pemetrexed increased median overall survival to 9.1 months, compared with 5.6 months for pemetrexed alone. In addition, tumor shrinkage was seen in 24% of patients in the combination group and in 10% of the monotherapy group ( *J Clin Oncol* 2012;30(15 Suppl): [abstract 7506](#)).
- **Vismodegib ( *Erivedge*) for basal cell carcinoma.** Basal cell carcinoma is the most common form of skin cancer, and vismodegib is the [first drug approved](#) by the FDA for the treatment of advanced disease that has metastasized or relapsed after treatment with surgery, or for patients who are not candidates for surgery or radiation. Two studies showing efficacy ( *N Engl J Med*. 2012;366: 2171-2179, 2180-2188) were accompanied by an editorial ( *N Engl J Med*. 2012;366:2225-2226) declaring that vismodegib is "the [greatest advance](#) in therapy yet." One of the studies ( *N Engl J Med*. 2012;366:2180-2188) involved 41 patients with basal cell nevus syndrome, which can lead to hundreds or thousands of lesions. During treatment with vismodegib, no tumors progressed and in some patients, all tumors regressed. However, more than half of the patients receiving vismodegib had to stop treatment because of adverse events (including loss of taste, muscle cramps, weight loss, and hair loss), according to the ASCO report. It highlights the fact that vismodegib has a novel mechanism of action — blocking the Hedgehog signaling pathway — and that the drug is being investigated in other cancer types, including colorectal, stomach, and pancreatic cancers.
- **Pazopanib ( *Votrient*) for soft tissue sarcoma.** Pazopanib is already marketed for the treatment of renal cell carcinoma, but this year it was approved [in the United States and in Europe](#) for use in the treatment of patients with advanced soft tissue sarcomas (excluding adipocytic sarcomas and gastrointestinal stromal tumors) who have received previous chemotherapy. The PALETTE trial of 369 such patients showed an increase in the median time to disease progression with pazopanib, compared with placebo (4.6 vs 1.6 months), although median overall survival times were similar (12.5 vs 10.7 months) ( *Lancet*.

2012;379:1879-1886). Although this led to [questions about benefit](#), experts treating sarcoma feel it offers an [important new option](#) for their patients. This is the first positive trial and the first new drug in sarcoma for decades, according to the ASCO report.

- **Olanzapine ( Zyprexa) for chemo-induced nausea and vomiting.** Olanzapine, marketed as an antipsychotic drug, was shown to be an [effective rescue medication](#) for patients who were suffering from breakthrough chemotherapy-induced nausea and vomiting (CINV), despite having received standard prophylactic treatment. In 80 of 205 patients who developed breakthrough CINV, olanzapine significantly outperformed the conventional anti-nausea drug metoclopramide. More patients in the olanzapine group than in the metoclopramide group reported no vomiting (71% vs 32%) and no nausea (67% vs 24%). The study was presented at the 2012 ASCO annual meeting, and so far is available only in abstract form ( *J Clin Oncol.* 2012;30(15 Suppl): [abstract 9064](#)).
- **Duloxetine ( Cymbalta) for chemo-induced peripheral neuropathy.** Duloxetine is marketed as an antidepressant but is also approved for use in painful diabetic peripheral neuropathy. In a [phase 3 trial](#), it was shown to be useful in alleviating pain from chemotherapy-induced peripheral neuropathy (CIPN). The trial involved 231 cancer patients who had been treated with oxaliplatin or paclitaxel and had developed CIPN, and duloxetine was associated with a greater average decrease in the pain score than placebo. These results are also available only in abstract form ( *J Clin Oncol* 2012;30(15 Suppl): [abstract CRA9013](#)).
- **Factors in elderly patients that increase chemotherapy risks.** Few clinical trials are conducted specifically in the elderly, so deciding on cancer treatment in an elderly patient is difficult, the ASCO report notes. A trial published this year identified factors that are important to consider when deciding whether an elderly patient should undergo chemotherapy, and explained how they affect the risk for fatality after initiating chemotherapy ( *J Clin Oncol.* 2012;30:1829-1834). A baseline abbreviated comprehensive geriatric assessment was carried out on 348 patients older than 70 years who were scheduled for initial chemotherapy for various cancers; advanced disease, low nutritional assessment score, and poor mobility predicted early death (in less than 6 months) after beginning chemotherapy.
- **Predicting risk for chemo adverse effects in elderly patients.** Another trial in elderly patients proposed a predictive model to identify those at elevated risk for adverse effects from chemotherapy ( *J Clin Oncol.* 2011;29:3457-3465). The trial involved 500 patients 59 to 91 years of age with a variety of cancers who underwent detailed assessment of tumor characteristics, laboratory tests, and geriatric status (including function, comorbidity, cognition, physiological state, social activity/support, and nutrition), and were then observed going through 1 round of chemotherapy. On the basis of responses, the researchers developed a scoring system and risk-stratification model that identify older adults at low, intermediate, and high risk for adverse events from chemotherapy.

### Progress in Clinical Cancer Research

"I hope you will share my unabashed enthusiasm — and pride — in how far we have come," writes ASCO president Sandra Swain MD, FACP, in the introduction to the report.

To appreciate what this progress in clinical cancer research has achieved, she notes that:

- 2 of 3 people in the United States live for at least 5 years after receiving a cancer diagnosis (up from around 1 in 2 in the 1970s)
- the cancer death rate in the United States has fallen by 18% since the early 1990s, reversing decades of increases
- people with cancer are increasingly able to live active, fulfilling lives because of better management of symptoms and treatments with fewer adverse effects.

However, this progress is only part of the story, Dr. Swain notes.

Cancer remains a challenge, and tragically kills more than 500,000 people in the United States every year, she writes; the global burden is growing rapidly. Dr. Swain calls for a renewal of the commitment to cancer research and its funding, because "millions of lives depend on it."

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