Breast Cancer

Major finding: The CDK4/6 inhibitor palbociclib is active and safe in advanced ER$^+$, HER2$^-$ breast cancer.

Clinical relevance: Addition of palbociclib to the aromatase inhibitor letrozole prolongs progression-free survival.

Impact: These data support further clinical trials of palbociclib in combination with antihormonal therapy.

CDK4/6 INHIBITION IMPROVES SURVIVAL IN ER$^+$, HER2$^-$ BREAST CANCER

Aberrant activation of cyclin-dependent kinases (CDK) leads to dysregulated cell-cycle progression from G1 to S phase and is a common feature of many tumors, including breast cancer. Preclinical studies indicated that palbociclib, a reversible, oral, small-molecule inhibitor of CDK4 and CDK6, synergized with anti-estrogen therapy to inhibit the growth of estrogen receptor–positive (ER$^+$) breast cancer cell lines *in vitro*, prompting Finn and colleagues to assess the efficacy and safety of palbociclib in combination with the aromatase inhibitor letrozole in an open-label phase II clinical trial. One hundred sixty-five women with locally recurrent or metastatic ER$^+$, HER2$^-$ breast cancer were randomly assigned to receive palbociclib plus letrozole or letrozole alone as first-line treatment. Strikingly, dual treatment with palbociclib and letrozole resulted in a significant improvement in median progression-free survival (PFS) over treatment with letrozole alone (20.2 months versus 10.2 months). Of note, additional stratification of patients based on amplification of *CCND1* (encoding cyclin D1) and/or loss of *CDKN2A* (encoding p16) did not further improve PFS. In addition, a greater percentage of patients experienced an objective response and achieved clinical benefit from combined treatment with palbociclib plus letrozole, and the median duration of response was 20.3 months for the combination group as compared with 11.1 months for the letrozole-only group. Although adverse events, the most common of which included neutropenia, leukopenia, and fatigue, occurred more frequently in patients who received palbociclib plus letrozole, dual treatment was generally well tolerated, and no cases of neutropenic fever or treatment-related deaths were reported. These findings demonstrate the clinical antitumor activity of CDK4/6 inhibition in patients with advanced ER$^+$, HER2$^-$ breast cancer and support ongoing phase III clinical trials of palbociclib in combination with antihormonal therapies. ■

Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25–35.

Immunotherapy

Major finding: Human IgG2 confers immunostimulatory activity to costimulatory receptor monoclonal antibodies.

Concept: The unique disulfide bond conformation of IgG2 imparts FcγR-independent agonistic activity.

Impact: Rational optimization of immunomodulatory monoclonal antibodies may increase their clinical activity.

HUMAN IMMUNOGLOBULIN G2 HAS AGONISTIC PROPERTIES

Monoclonal antibodies (mAb) that bind agonistically to immunostimulatory coreceptors such as CD40, 4-1BB, and CD28 have shown promising clinical activity alone or in combination with other mAbs that directly target proteins expressed by cancer cells, but because only a small subset of patients experience durable responses, further optimization of these agents is needed. An emerging concept is that the therapeutic efficacy of immunostimulatory mAbs can be affected by variations in their heavy and light chain constant regions, collectively known as the immunoglobulin isotype, which can modulate interactions with Fcγ receptors (FcγR) expressed on the surface of immune cells. White and colleagues observed that chimeric antibodies had greater immunostimulatory activity *in vitro* and stimulated greater T cell and antibody responses *in vivo* when they included the IgG2 constant region compared with other human immunoglobulin isotypes. Notably, the response to IgG2 was FcγR independent, as FcγR inhibition or deletion did not prevent induction of immune cell activation and proliferation by an anti-CD40 antibody engineered to have an IgG2 isotype. The agonistic activity of IgG2 required both its CH1 and hinge domains, which are unique among human IgGs because they can adopt a range of disulfide bond configurations. Unlike the flexible IgG2A conformation, the more rigid, compact IgG2B conformation conferred FcγR-independent agonistic activity and induced greater immune responses, suggesting that the precise disulfide bond conformation of IgG2 dictates its immunostimulatory activity. Indeed, mutation of the IgG2 residues involved in disulfide bonds resulted in a range of agonistic activity, with a mutation locking IgG2 in the IgG2B conformation leading to greater activity than native IgG2. In addition to providing insight into the biologic activity of IgG2, these findings provide a framework for optimizing immunostimulatory mAbs to maximize their clinical efficacy. ■

White AL, Chan HT, French RR, Willoughby J, Mockridge CI, Roghanian A, et al. Conformation of the human immunoglobulin G2 hinge imparts superagonistic properties to immunostimulatory cancer antibodies. Cancer Cell 2015;27:138–48.