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Pertuzumab

Rec INN; USAN

Humanized Anti-HER2 Monoclonal Antibody
HER Dimerization Inhibitor
Oncolytic

2C4
R-1273

Immunoglobulin G_1, anti-(human neu (receptor)) (human-mouse monoclonal 2C4 heavy chain), disulfide with human-mouse monoclonal 2C4 κ-chain, dimer

CAS: 380610-27-5

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Abstract

Human epidermal growth factor receptor 2 (HER2) is an important driver of malignant growth and progression in many cancer types and is activated through dimerization with itself or other HER family members. Targeting of HER2 therefore represents a potentially effective strategy for the treatment of certain cancers. Pertuzumab is a humanized antibody designed as an inhibitor of HER2 heterodimerization and is the first example of a new class of targeted therapeutics referred to as HER dimerization inhibitors. Pertuzumab has shown broad-spectrum antitumor activity both in preclinical models and in several phase II clinical studies. The antibody is currently undergoing further clinical evaluation in combination with trastuzumab in breast cancer, and with selected cytotoxic agents in ovarian and lung cancer.

Background

The human epidermal growth factor receptor (HER), or erbB, family of receptor tyrosine kinases are major regulators of cell growth, survival and differentiation in many normal and malignant cell types. The family consists of four members: HER1/erbB-1, HER2 (erbB-2), HER3 (erbB-3) and HER4 (erbB-4) (1-3). These receptors are activated when bound by one of a family of ligands which induce conformational changes, resulting in dimerization of receptors. At least 12 ligands (4) have been shown to activate HER1, HER3 or HER4, but no ligand has been identified that binds directly to HER2 (1, 3). While both homodimerization between two similar family members and heterodimerization between different family members can occur, the preferred activation option is through heterodimerization with HER2 (5, 6). This is a result of HER2 being constitutively in the active conformation because the dimerization domain of HER2 is permanently exposed (7). Comparison of the potential receptor combinations has shown that heregulin (or neuregulin)-activated HER2-HER3 dimerization produces the most potent signaling responses (8, 9). Since both HER2 and HER1 are major growth regulators in many cancer types, this has led to the development of drugs that specifically target these receptors (2, 3). The two predominant classes of agents in current use are humanized antibodies and small-molecule tyrosine kinase inhibitors. A list of HER2-targeted drugs is shown in Table I (2, 3, 10).

Pertuzumab (2C4, formerly Omnitarg™) is a humanized monoclonal antibody designed as an inhibitor of HER2 dimerization (Fig. 1). While trastuzumab (Herceptin™), another humanized antibody targeted against HER2, has become standard treatment for carefully selected breast cancers, it is nevertheless only effective in tumors with high levels of HER2 expression (2, 3), such overexpression normally being the result of amplification of the *HER2* gene. Since pertuzumab binds to an epitope of HER2 different from the trastuzumab binding site, which enables inhibition of ligand-activated heterodimerization, it can potentially act in either low, moderate or high HER2-expressing cancers (11, 12). This clearly increases the number of patients for whom such therapy may be advantageous.

Pertuzumab was modified from the murine 2C4 antibody (13, 14), which was itself generated using a stably transfected NIH/3T3 cell line expressing human HER2 and was 1 of 10 $IgG_{1κ}$ antibodies generated that bound to the extracellular domain of HER2 but did not bind the epidermal growth factor receptor (EGFR, HER1). 2C4 was subsequently shown to bind to the dimerization

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Table I: HER2 inhibitors in clinical use.

Drug	Type	Target	Source	Current clinical status
Monoclonal antibodies				
Pertuzumab	Humanized	HER2	Genentech/Roche	Phase II trials in breast and ovarian cancer with other agents
Trastuzumab	Humanized	HER2	Genentech/Roche	Launched for breast cancer in combination with chemotherapy. Studies under way in gastric cancer
Tyrosine kinase inhibitors				
Lapatinib	Thioquinazoline	HER1/HER2	GlaxoSmithKline	Launched for second-line breast cancer treatment in combination with capecitabine Phase III trials in breast and head and neck cancers
EKB-569	Cyanoquinoline	HER1/HER2	Wyeth	Phase II trials in colorectal and non-small cell lung cancers
BIBW-2992	Quinazoline	HER1/HER2	Boehringer Ingelheim	Phase II trials in breast, non-small cell lung and head and neck cancers
Neratinib	Cyanoquinoline	Pan-HER	Wyeth	Phase II trials in breast and non-small cell lung cancers
AEE-788	Pyrrolopyrimidine	HER1/HER2	Novartis	Phase I/II
ARRY-543	Quinazoline	HER1/HER2	Array Biopharma	Phase I
BMS-599626	Pyrrolotriazine	Pan-HER	Bristol-Myers Squibb	Phase I

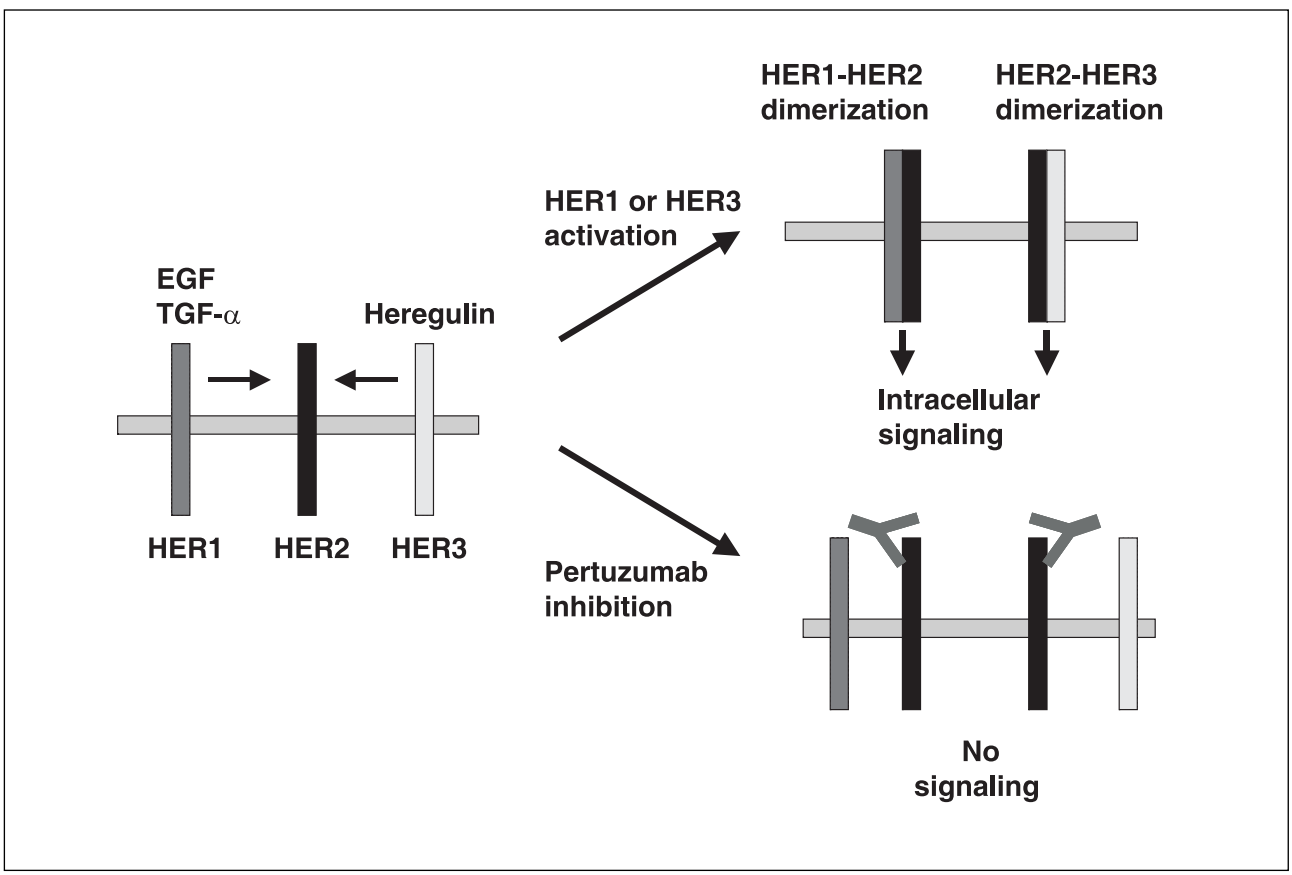

Fig. 1. Mechanism of action of pertuzumab. Pertuzumab acts as a heterodimerization inhibitor by binding to HER2 and modifying the interaction between HER2 and ligand-activated HER1 or HER3.

domain (domain II) of HER2, thereby providing a means to block HER2 activation (4). The murine antibody was demonstrated to have interesting *in vitro* growth-inhibitory activity against breast and ovarian cancer cell lines (15). However, since murine antibodies have limited clinical activity due to the production of a human anti-mouse antibody (HAMA) response (16), 2C4 was humanized. This was achieved by using consensus framework sequences for L and H chains, VLkI and VHIII (13). The antibody is therefore based on the human $IgG_{1\kappa}$ framework and consists of two heavy chains (440 residues) and two light chains (214 residues). It differs from trastuzumab in the epitope-binding region of the light chain (12 amino acid differences) and heavy chain (29 amino acid differences). Pertuzumab is commercially produced in Chinese hamster ovary (CHO) cells and is purified by chromatography.

The structure of the extracellular domain of HER2 complexed with pertuzumab (determined by X-ray crystallography) confirms that pertuzumab binds to HER2 near the center of domain II within HER2 and that it is sterically blocking a binding region which is necessary for receptor dimerization and cellular signaling (4). Since trastuzumab is unable to block the formation of HER2-HER3 dimers, it is likely that its HER2-binding region (domain IV) is not involved in dimerization (4).

Preclinical Pharmacology

Pertuzumab has been shown to be highly effective at inhibiting heregulin-driven HER3-HER2 signaling. This can result in growth inhibition in breast and prostate cancer cell lines both *in vitro* and *in vivo* (11, 12). Growth inhibition is associated with a reduction in both Akt and ERK (extracellular signal-regulated kinase) signaling (11). Further studies have demonstrated growth inhibition by pertuzumab in ovarian (17, 18), lung (19) and colon (20) cancer models. Comparison of pertuzumab with trastuzumab indicated that pertuzumab is far more effective at inhibiting heregulin-stimulated HER3-HER2 activation in low HER2-expressing cell lines (11, 12). In breast cancer cell lines, pertuzumab almost completely blocks heregulin-induced HER3-p85 association with phosphatidylinositol 3-kinase (PI3K), Akt activation and ERK1/2 activation, whereas trastuzumab only partially reduces heregulin-induced HER3-p85 association and activation of Akt or ERK1/2 (21). EGF- and TGF-α (transforming growth factor α)-activated signaling of HER1-HER2 is also inhibited by pertuzumab (11). Studies using breast and ovarian cancer cell lines have shown that while pertuzumab can reverse growth factor-stimulated proliferation (using heregulin or TGF-α) in many cases, there are also cell lines which clearly do not respond. Further investigation designed to characterize which cell lines respond or not respond, as the case may be, to pertuzumab have indicated associations with HER2 dimerization (18), phosphorylated HER2 (pHER2) (17) and downstream changes in pAkt and pERK (11, 17). Consistent with the proposed mechanism, pertuzumab was most effective in cell lines where ligand-induced HER2 heterodimers stimulated cell proliferation (18).

Pertuzumab has also shown activity against a large number of tumor xenografts, including lung, breast and both androgen-dependent and -independent prostate cancer. In a study of breast and non-small cell lung cancer (NSCLC) xenografts, HER2-HER3 dimers were found in all models in which pertuzumab demonstrated significant growth inhibition (22). Study of 6 xenografts that were sensitive to pertuzumab revealed that all 6 contained HER2-HER3 heterodimers, while only 2 of 12 that were insensitive to pertuzumab possessed these dimers (as measured by immunoprecipitation and Western blotting). These data suggest the possible value of a HER2 heterodimer assay for predicting response.

It has been speculated that combining pertuzumab with other HER inhibitors may provide a more complete blockade of HER signaling, resulting in more effective growth inhibition due to their complementary mechanisms of action. *In vitro* evaluation in the HER2-overexpressing BT-474 breast cancer cell line indicated synergy between pertuzumab and trastuzumab, which was at least in part due to enhanced apoptosis (23). Combination drug treatment resulted in both increased disruption of HER2 dimerization with HER1 and HER3, as well as reduced levels of both total and phosphorylated HER2 protein. The use of pertuzumab in combination with trastuzumab as second-line treatment was studied in a xenograft model progressing on trastuzumab treatment (24). Pertuzumab was more effective than either the HER1 inhibitor erlotinib or the HER1/HER2 inhibitor lapatinib when combined with trastuzumab in the Calu-3 NSCLC xenograft model (24). A synergistic interaction between these two drugs was also demonstrated in breast cancer xenograft models (25). The synergy of the trastuzumab plus pertuzumab combination is explained by the complementary modes of action of the two antibodies: while trastuzumab prevents HER2 ectodomain shedding, an important HER2 activation mechanism in some HER2-positive tumors, leaving the constitutively active p95HER2 in the cell membrane, pertuzumab prevents the formation of HER2 heterodimers. Combined treatment with pertuzumab, trastuzumab and gefitinib (Iressa®) to block all hetero- and homodimerization has been shown to be more effective than either single agents or dual combinations in an HER2-overexpressing breast cancer model (26). Whereas gefitinib is an HER1 tyrosine kinase inhibitor that can block HER1 tyrosine kinase in homo- and heterodimers, trastuzumab blocks several routes of HER2-activated signaling, but not HER3-HER2 heterodimer signaling (which pertuzumab does). Combined use of gefitinib and pertuzumab was furthermore able to effect more complete blockade of HER2 (and HER1) signaling. The combination of erlotinib (Tarceva®), another HER1 tyrosine kinase inhibitor, and pertuzumab has also shown additive and synergistic activity against both breast and lung cancer xenografts (19).

Pertuzumab has also shown preclinical promise when combined with either cytotoxic agents or bevacizumab

(Avastin®). The combination of pertuzumab with several different cytotoxic agents (cisplatin, paclitaxel, gemcitabine and irinotecan) has produced enhanced antitumor activity without an increase in toxicity in both high and low HER2-expressing NSCLC xenograft models (27). The combination of pertuzumab and bevacizumab has also been shown to synergistically inhibit the growth of HER2-overexpressing KPL-4 breast cancer xenografts (28).

Pharmacokinetics and Metabolism

Pharmacokinetic studies have been undertaken in rodents and monkeys, where both single- and multiple-dose studies demonstrated a biphasic distribution of the antibody that could be fitted to a two-compartment model. The distribution half-life was < 1 day, while the terminal half-life was approximately 10 days; the volume of distribution was 27-58 ml/kg. The pharmacokinetic profile of pertuzumab was predicted to be similar to that of other humanized antibodies such as trastuzumab and bevacizumab since they were designed with the same IgG_1 frame, and this was indeed the case (13).

Pharmacokinetic analyses were undertaken in both the initial phase I study and in two subsequent phase II trials. In the phase I trial, pertuzumab was given i.v. every 3 weeks at doses ranging from 0.5 to 15 mg/kg, administered as a 90-min infusion in the first cycle followed by 30-min infusions for subsequent cycles. Over the dose range 2.0-15 mg/kg, pharmacokinetic parameters were essentially unchanged. The mean systemic clearance was 3.4 ml/day/kg, the volume of distribution of the central compartment approximated the serum volume, with a mean of 40.6 ml/kg, and the mean volume of distribution at steady state was 80 ml/kg. The mean terminal half-life ranged from 14.9 to 22.3 days (29).

In subsequent phase II studies, fixed doses of pertuzumab were used (30, 31). The first dose level was 840 mg (90-min infusion) as a loading dose and then 420 mg (30-min infusion) every 3 weeks in subsequent cycles. The second dose level was 1050 mg every 3 weeks, again delivered i.v. as a 90-min infusion for the first cycle and over 30 min in subsequent cycles. A comparative analysis of the different data sets demonstrated that the pharmacokinetic profiles were similar after either fixed dosing, body weight-based dosing or body surface area-based dosing (32). These findings emphasized the feasibility of using a fixed dose of pertuzumab in ongoing and future studies. Preclinical studies using tumor xenograft models showed that > 80% suppression of growth can be achieved at steady-state trough concentrations of 5-25 μg/ml (33). The pharmacokinetic analysis demonstrated that pertuzumab infusion at > 5 mg/kg ensured that serum concentrations remained at > 20 μg/ml.

Safety

Safety evaluation of pertuzumab was performed in monkeys administered weekly doses of 15-150 mg/kg i.v. for 7 weeks. At these doses, diarrhea was the only observed side effect and was reversible upon cessation of treatment. Prolonged dosing over 26 weeks resulted in diarrhea-induced dehydration (13). Since the HER1 tyrosine kinase inhibitors gefitinib and erlotinib share this same toxicity, it has been suggested that for pertuzumab this may be a result of HER1-HER2 heterodimerization inhibition (11). Importantly, detailed study of possible cardiotoxic events, which have been observed for trastuzumab particularly in combination with anthracyline chemotherapeutics, did not show any signs of cardiotoxicity. No effects on blood pressure, heart rate, creatine kinase isozymes, troponin T or electrocardiogram were noted in these animals.

The initial phase I clinical trial included 21 patients with incurable, locally advanced recurrent or metastatic solid tumors that had progressed on standard therapy (29). As mentioned above, pertuzumab was given i.v. every 3 weeks at doses ranging from 0.5 to 15 mg/kg. Nineteen patients completed at least 2 cycles of therapy and the antibody was well tolerated. Of the 365 adverse events reported, 122 were judged to be drug-related and of these, 116 were grade 1 or 2 in intensity. The toxicities experienced included diarrhea, asthenia, vomiting, nausea, abdominal pain, rash and anemia, and while 12 of 21 patients experienced at least 1 grade 3 or 4 event, only 6 were thought to be drug-related. Of these 6 drug-related events, 4 occurred in 1 patient and were associated with a myocardial infarction which may have been related to treatment. Three patients had a fall in LVEF (left ventricular ejection fraction) of at least 5%. Rash and diarrhea were mainly grade 1 and occasionally grade 2, but no relationship between dose and incidence or severity was observed. In general, there was no association between any specific toxicity and dose level, nor any association with first *versus* subsequent cycles. The maximum tolerated dose (MTD) was not reached, nor were antibodies to pertuzumab detected.

Clinical Studies

Phase II clinical trials in ovarian, breast, prostate and lung cancer have now been completed and the antibody is currently being evaluated in selected combination studies (see Table II).

Of the 2 responses reported in the phase I trial, 1 occurred in an ovarian cancer patient (29) and a phase II trial was subsequently undertaken in refractory advanced ovarian cancer (30). Two doses were studied; the first group of 61 patients received a loading dose of 840 mg pertuzumab (equivalent to 12 mg/kg in a 70-kg patient) i.v. followed by 420 mg every 3 weeks; the second group of 62 patients received 1050 mg every 3 weeks. Within the first group, 55 of 65 patients were assessable for response, as were all 62 in the second group. Of the 117 assessable patients, 5 patients demonstrated a partial response (response rate = 4.3%), 8 patients (6.8%) had disease stabilization for at least 6 months and 10 patients had a CA125 reduction of > 50%. Overall clinical activity was therefore observed in a total of 14.5% of patients.

Table II: Summary of pertuzumab clinical trials.

Drug	Phase	Tumor type/patient group	Patient number	Key findings
Single-agent studies				
Pertuzumab	I	Multiple	21	2 PRs (1 ovarian, 1 pancreatic cancer), stable disease in 6 patients. Common adverse effects were asthenia, vomiting, nausea, abdominal pain, rash, diarrhea, pain and anemia
Pertuzumab	II	Breast	78	2 PRs, 32 disease stabilizations. Diarrhea in 59% of patients
Pertuzumab	II	Ovarian	123	5 PRs, 8 disease stabilizations for at least 6 months, 10 CA125 reduction of > 50%. Overall, clinical activity in 14.5% of patients. Diarrhea in 69% of patients
Pertuzumab	II	Prostate (chemotherapy-naïve, hormone-resistant)	68	No PSA decreases of > 50%. 37-48% had diarrhea
Pertuzumab	II	Prostate (taxane-resistant)	42	No PSA decreases of > 50% but 5 had stable disease. Survival improved *vs.* historical controls. Diarrhea in 61% of patients
Pertuzumab	II	Non-small cell lung	33	No activity
Combination studies				
Pertuzumab + Trastuzumab	II	Breast (trastuzumab-resistant)		18% response rate, 51% disease stabilization rate. Diarrhea in 57% of patients
Pertuzumab + Gemcitabine	II	Ovarian (platinum-resistant)	130	Progression-free survival at 4 months 49% (combination group) *vs.* 34% for gemcitabine alone. Adverse effects included fatigue, nausea and diarrhea

Diarrhea was observed in 69% of patients, with 11.4% of these showing grade 3 toxicity. One patient in group 1 and 4 patients in group 2 had asymptomatic LVEF decreases to < 50%.

In the phase II ovarian cancer trial, patients were not preselected by HER2 expression levels of their tumors. A series of ovarian cancer biopsies were analyzed for their pHER2 status by ELISA, and a trend towards improved 'time to progression' (TTP) was shown for patients with tumors that demonstrated HER2 phosphorylation (8 of 28 [28.6%] biopsies were pHER2-positive) when compared to those that did not show evidence of phosphorylation. Median progression-free survival (PFS) for pHER2-positive patients (n=8) was 20.9 weeks *versus* 5.8 weeks for pHER2-negative patients (n=20), suggesting that activated HER2 is indeed required for successful responsiveness (30). In a further study that evaluated material from this trial, data from microarray expression profiling was evaluated along with HER2 phosphorylation status (*i.e.*, activation of HER2) in individual fresh tumor biopsies from the same patients, to reveal that the expression levels of HER2 (along with HER1 and HER3), together with the expression of certain HER ligands, may be predictive of the phosphorylation state and thus the activation of HER2 (34).

In another randomized phase II trial in metastatic breast cancer (with low HER2 expression), patients received either 420 mg (loading dose of 840 mg) i.v. every 3 weeks (group A) or 1050 mg (group B) (31). Of 41 patients treated in group A, 2 patients had a partial response and 18 had stable disease. In arm B, 14 of 37 evaluable patients had stable disease. Overall, 6 of 78 patients responded or had stable disease for > 6 months. The most prevalent toxicity was diarrhea (59%) and decreases in LVEF were observed in 3 patients in each arm. The pharmacokinetic data supported a fixed dose of pertuzumab every 3 weeks. While the authors concluded that the antibody was safe and well tolerated but that its activity in HER2-negative breast cancer was limited when used as monotherapy, they did, however, propose that combination strategies might well be useful (see below).

The same doses of pertuzumab were also evaluated in a multicenter phase II trial in castrate chemotherapy-naïve patients with hormone-refractory prostate cancer (35). A total of 35 patients were treated with 420 mg (loading dose of 840 mg) and no PSA (prostate-specific antigen) declines of > 50% were observed and recruitment was therefore stopped. Similarly, a total of 33 patients were treated with 1050 mg and again no PSA declines were observed. The most prevalent adverse effect was grade 1-2 diarrhea (37% of patients in cohort A and 48% in cohort B). Six patients had LVEF decreases of between > 10% and < 50%.

In another phase II trial in prostate cancer, the dose of 420 mg (loading dose of 840 mg) was given every 3 weeks (36). This patient population was castration-resistant after progression from taxane therapy. Forty-two patients were treated, 41 of whom had assessable disease. While no complete or partial responses were observed, nor PSA decreases of > 50%, 5 patients did

nevertheless have stable disease for at least 23 weeks. Retrospective analysis using a validated nomogram suggested that survival was prolonged with pertuzumab treatment when compared with historic controls with comparable features. Diarrhea was again the most common adverse event and occurred in 61% of patients. Although LVEF was reduced by at least 10% in 11 of 38 (27%) patients, the investigators concluded that these effects were minor and asymptomatic, and that the drug was not associated with cardiac toxicity.

In a phase II trial in NSCLC, 33 patients were treated but no responses were obtained (36). Three of the 12 patients who underwent serial positron emission tomography (PET) scans had a decrease in the maximum standardized uptake value (SUV_{max}) of > 25% after pertuzumab treatment (37).

Although the biology of pertuzumab and preclinical studies suggest that it is effective in tumors with low HER2 expression, it is nevertheless important that any subgroup benefit not be missed, and patients should be selected on the basis of suitable tissue biomarkers. It has been shown that all HER family members may influence response to therapy and clinical outcome (38, 39), and this may be especially true of pertuzumab, where prevention of heterodimerization events is the major mechanism of action. Even if patients are not selected prospectively on the basis of HER2 protein expression or amplification status, tissue biomarkers should be analyzed in clinical trial specimens retrospectively in order to assess patient subgroup responses, which can further guide future clinical trials. In the case of pertuzumab, patient selection will need to be refined and standardized, in the same way that issues surrounding the detection and criteria for trastuzumab treatment in HER2-overexpressing tumours have evolved since early trials (40).

Since the phase II trials suggested a modest degree of activity, further trials were then undertaken to evaluate the antibody in specific combination contexts. Preclinical xenograft studies indicated synergistic interactions for pertuzumab in several contexts and these have therefore been taken forward into clinical trials. Two promising combinations recently reported are pertuzumab + gemcitabine in platinum-resistant ovarian cancer, and pertuzumab + trastuzumab in breast cancer patients with progressive disease during trastuzumab treatment (41, 42).

The combination of pertuzumab + gemcitabine was assessed in a randomized, placebo-controlled, double-blind phase II trial in patients with platinum-resistant ovarian, fallopian tube or primary peritoneal cancer (41). Patients received gemcitabine (800 mg/m^2 on days 1 or 8 of a 21-day cycle) with either pertuzumab or placebo. Pertuzumab was given as a 420-mg dose (loading dose of 840 mg) i.v. every 3 weeks. One hundred and thirty patients (n=65 for each treatment arm) were treated and the adjusted hazard ratio for PFS was 0.67 in favor of pertuzumab + gemcitabine (p = 0.06). The PFS rate at 4 months was 49% in the pertuzumab + gemcitabine arm *versus* 34% in the gemcitabine + placebo arm. The most common adverse events in the drug combination arm were fatigue, nausea and diarrhea. There were no significant differences in LVEF in the different treatment arms. The data suggest that pertuzumab may enhance the activity of gemcitabine. Of particular interest, exploratory biomarker analysis indicated that patients with tumors with a high HER2:HER3 ratio were most likely to benefit from the pertuzumab + gemcitabine combination.

The combination of pertuzumab + trastuzumab is currently under investigation and initial reports have indicated promising activity in patients with HER2-positive metastatic breast cancer who had progressed during treatment with trastuzumab (42, 43). An 18% response rate (including 1 complete response) and a 51% stabilization rate have been reported, with responses being obtained in lymph node and liver metastases. Toxicities included diarrhea (57%), fatigue (31%), nausea/vomiting (33%) and rash (28%), most being mild to moderate and none being treatment-limiting. There were no clinical cardiac events and no cases of reduction in LVEF of > 10% - < 50%, confirmed by central reading, among the 33 patients included at the time of interim analysis (42). A second report of 11 patients treated identified a similar tumor response rate (18%) and a 27% disease stabilization rate, confirming the efficacy of this combination. However, this study also identified 5 of 11 patients with left ventricular systolic dysfunction (43). This resolved rapidly in 3 of these patients when the drug was discontinued. Possible reasons for the differences in cardiotoxity between these two studies include the following: different patient selection criteria, different criteria for evaluating LVEF and different cutoff points for toxicity. In the former study, patients who had experienced falling LVEF while on previous trastuzumab therapy were excluded, while they were included in the latter study; furthermore, the cutoff points for dysfunction were more severe in the latter study. The combined data from these two studies clearly indicate that combination treatment with trastuzumab and pertuzumab is effective and can induce tumor remissions in progressive disease even in the absence of a cytotoxic agent, although more information is required on its toxicity.

Several other combination studies are under way or planned, including phase II and phase III studies in patients with HER2-positive breast cancer evaluating pertuzumab + trastuzumab + docetaxel *versus* pertuzumab + docetaxel *versus* trastuzumab + docetaxel *versus* pertuzumab + trastuzumab (44), or pertuzumab + trastuzumab + docetaxel *versus* trastuzumab + docetaxel (45), and a phase I/II trial of pertuzumab + cetuximab + irinotecan in patients with locally advanced or metastatic colorectal cancer (46).

Overall, pertuzumab when used as monotherapy appears to have valuable clinical activity, particularly in previously treated and resistant disease. However, pertuzumab would appear to have most promise when combined with other selected agents such as trastuzumab or gemcitabine. Furthermore, the molecular characterization studies undertaken in the phase II ovarian cancer trial offer hope that pertuzumab-sensitive tumors might even-

tually be identifiable just as trastuzumab-sensitive cancers are selected at present.

Sources

Genentech, Inc. (US); developed in collaboration with Roche (CH).

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