Anti-CD137 and PD-1/PD-L1 Antibodies En Route toward Clinical Synergy

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T-cell costimulation and coinhibition can be respectively exploited by blocking and agonist mAbs. Both strategies can be synergistically combined in mouse models. Early clinical results from combinations of anti-PD-1 mAbs in conjunction with agonist anti-CD137 (4-1BB) mAbs show excellent safety and promising efficacy. Clin Cancer Res; 23(18) September 15, 2017; 5326–8. ©2017 AACR.

See related article by Tolcher et al., p. 5349

In this issue of Clinical Cancer Research (CCR), Tolcher and colleagues report on the dose-escalation combination of the anti-CD137 agonist mAb utomilumab with standard 2 mg/kg every-3-week doses of the anti–PD-1–blocking mAb pembrolizumab, as tested in a phase Ib study for patients with a variety of solid tumors (1).

CD137 (4-1BB)-based cancer immunotherapy started with experiments in transplanted mouse tumors that showed CD8 T-cell mediated complete rejections of established tumors upon administration of agonist anti-CD137 mAbs, irrespective of the ability of such antibodies to inhibit binding of CD137 to its natural ligand (CD137L or 4-1BBL; ref. 2). CD137 (4-1BB, TNFRSF9) is a surface glycoprotein that belongs to the TNFR family and was discovered by Kwon and colleagues (3) as a T-cell costimulatory molecule that, importantly, was expressed on antigen-primed T lymphocytes, but not on their resting counterparts. It is also functionally expressed on activated natural killer (NK) cells, where its stimulation enhances antibody-dependent cellular cytotoxicity, and on dendritic cells and other leucocytes, where its function is less well studied.

Costimulation via CD137 upon binding to agonist mAb protects T lymphocytes from cell death, promotes memory differentiation, enhances effector functions, and favors clonal expansion (4). Clinical exploitation of such functions was started by scientists at Bristol-Myers Squibb with the development of urelumab, a non–ligand-blocking, antihuman CD137 mAb of the IgG4 subclass (5). Consistently with an excellent preclinical safety record, dose-escalation clinical trials revealed no unacceptable toxicity of repeated doses of up to 5 mg/kg, and some clinical objective responses both in melanoma and non-melanoma patients were observed (5). However, in the following phase Ib/II trials, serious liver inflammation was found in an important fraction of treated patients, thus precluding further clinical development at such dose levels (5).

Liver inflammation with potent CD137 agonist mAbs can be modeled in mice showing polyclonal periportal infiltration of T cells dominated by a CD8+ component, even if such side effects are mild in mice (6). Failure of cynomolgus macaques experiments to preclinically identify such a problem is probably related to the lower affinity of urelumab for the nonhuman primate target molecule. As a result of these safety problems, urelumab was dose rescalled to be declared safe at a much lower dose level, comprising a flat dose regimen of 8 mg/kg given with 3-week intervals that questionably would provide enough receptor triggering (7). In a parallel effort, Pfizer developed utomilumab, an anti-CD137 mAb of the IgG2 class, which prevents CD137–CD137L binding and reportedly acts as a CD137 agonist in several functional in vitro and in vivo assays. It also shows an excellent preclinical safety profile based on experiments including cynomolgus macaques (8).

In contrast to urelumab, utomilumab showed no dose-limiting toxicities in regimens with doses up to 10 mg/kg and showed early evidence of clinical activity in dose-escalation studies, including patients with refractory non-Hodgkin lymphoma who were cotreated with rituximab (9, 10). In our side-by-side comparison experiments, both utomilumab and urelumab exert agonist activity in terms of CD137 toward NF-kB activation signaling and ensuing T-cell costimulation, even though the agonist activity of utomilumab on the receptor is much more marked.

Cancer immunotherapy is at the crest of a revolution spawned by the efficacy of results from PD-1 and PD-L1 blockade across a broad spectrum of malignant diseases when given as a single-agent therapy or in combination. In mouse models that resist both treatment with anti–PD-1–blocking agents and CD137 agonists, the combination of these two immunotherapy agents exerts powerful synergistic effects (7, 11, 12) that correlate with stronger T-cell responses against tumor antigens. In part, the synergy comes from the fact that a fraction of tumor-infiltrating T lymphocytes coexpress on their surface both PD-1 and CD137, giving rise to a combined effect on individual T cells, which is very prominent even for very poorly immunogenic mouse cancer models (13). Interestingly, CD137 and PD-1 seem to be expressed mainly by CD8+ T lymphocytes recognizing tumor neoantigens (14).
Prompted by their preclinical efficacy, both urelumab and utomilumab are currently being tested for safety and efficacy in combination with the anti–PD-1 mAb nivolumab or utomilumab. To date, no publications reporting results from clinical trials combining urelumab and nivolumab are available. At the 2016 SICT meeting (15), information was presented indicating the excellent tolerability of utomilumab given at an 8-mg flat dose every 3 weeks, along with the standard doses of nivolumab. The most striking efficacy result was a high overall response rate of up to 47% in metastatic melanoma cases, with less than 1% of tumor cells expressing PD-L1. Even if some of these early results could be explained by nivolumab efficacy alone, the results in cases without PD-L1 expression warrant further development of the combination. However, it must be kept in mind that the doses of urelumab in the trials are extremely low. Thus, much of the efficacy in this combination scheme might be jeopardized by low dosing of the CD137 agonist component.

In this issue of CCR, the first phase I results of the utomilumab plus pembrolizumab combination are released. Again, safety results upon utomilumab dose escalation in combination with pembrolizumab are excellent and consistent with the side effects expected for pembrolizumab alone. It is too early to say whether additional clinical benefit exists, but complete responses in a case of a small-cell lung cancer and in a patient with renal cell carcinoma hold much hope. More intriguingly, a patient with anaplastic thyroid cancer experienced a durable, deep partial response. Unfortunately, insufficient immunobiology correlative studies were performed in connection with the trial, and it is not possible to conclude whether utomilumab plus pembrolizumab is modifying cancer immunity differently than pembrolizumab as a single agent.

Pharmaceutical and biotechnology industries are very actively pursuing ever smarter strategies to confine CD137 costimulation to the tumor microenvironment and draining lymph nodes. These approaches should bypass liver toxicity. Strategies to exploit this costimulatory pathway are to be deployed together with the PD-1 blockade backbone given the clinical efficacy of PD-1 monotherapy and preclinical evidence for therapeutic synergy in the anti–PD-1 plus anti–CD137 mAb combinations. Patients predicted to benefit from this combined approach are (i) those suffering from a disease not amenable to PD-1/PD-L1 blockade, (ii) those with tumors failing to show PD-L1 staining in the biopsy, and (iii) those who have already progressed to PD-1/PD-L1–blocking agents. Such cases in our opinion constitute the precise target population to demonstrate efficacy of the combination.

Biomarker discovery must progress in parallel. To begin, coexpression of CD137 and PD-1 in the pretreatment biopsy needs to be explored. Other parameters may narrow down who will ultimately benefit the most from this treatment. Of note, in patients treated with the combination, pharmacodynamic interactions are postulated to take place, including increases in CD137 expression upon PD-1 blockade (13) and increases in PD-L1 expression due to CD137–costimulated INFγ production (Fig. 1).

Disclosure of Potential Conflicts of Interest

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Pérez-Ruiz
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References
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