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Case report

Sequential therapy with INCAGN01949 followed by ipilimumab and nivolumab in two patients with advanced ovarian carcinoma

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ABSTRACT

Agonists of the co-stimulatory molecule OX40 (CD134) are in clinical assessment alone and in combination with other immunotherapies. Recent pre-clinical studies have suggested that concurrent administration of OX40 agonists with anti-PD1 therapy is detrimental to the efficacy of such combinations and maximal efficacy may require sequential administration of the OX40 agonist followed by anti-PD1 therapy. In this report, we detail two patients with advanced ovarian carcinoma were treated with INCAGN01949, an agonistic OX40 Ab, as part of a clinical trial until disease progression. Both patients then received the combination of ipilimumab and nivolumab and experienced unusually deep and durable responses. These cases support the hypothesis raised in pre-clinical studies and highlight the potential relevance of sequence in combinational immunotherapy.

1. Background

The antitumor efficacy of antibodies against programmed cell death protein 1 (PD-1) or one of its ligands (PD-L1) in advanced cancers has encouraged efforts to identify other potential immune targets. One that has attracted much attention is the costimulatory molecule OX40 (CD134), a member of the tumor necrosis factor receptor superfamily. Activation of OX40 signaling promotes expansion of effector T-cells and enhances survival and effector functions while also impairing the immunosuppressive effects of regulatory T-cells (Tregs) (So, 2006; Croft et al., 2009). Numerous agonistic antibodies against OX40 have been developed and entered clinical assessment in early phase clinical trials (Aspeslagh et al., 2016).

The enhanced clinical activity seen with the combination of PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibodies has stimulated efforts to develop other combinational regimens (Wolchok et al., 2013) Accordingly, the combination of OX40 and PD-1/PD-L1 Ab is also under assessment. Pre-clinical studies have suggested that the sequence in which such a combination is given may be critical. Shrimali *et al* recently showed in the TC-1 mouse model that concurrent administration of a PD-1 antibody (Ab) to an OX40 agonist abrogated the antitumor effects of either agent administered alone (Shrimali et al., 2017). This result was associated with reduced intratumoral T-cell infiltration and apoptosis of CD8 + T cells. Using a PD-1 Ab MMTV-polyoma induced mammary cancer xenograft model, Messenhemier *et al* likewise found that concurrent administration of PD-1 Ab with OX40 Ab significantly attenuated the therapeutic efficacy of OX40 Ab associated with increased frequency of T-cell exhaustion markers LAG-3 and TIM-3 and higher levels of intratumoral Tregs (Messenheimer et al., 2017). Sequential combination of OX40 Ab followed by PD-1 Ab resulted in significantly increased antitumor efficacy compared with PD-1 Ab alone while reducing markers of T cell exhaustion. These results highlight the complexity of the balance between costimulatory and coinhibitory signaling in T cells and suggest that in some cases, sequential rather than concurrent administration of immune agents may be most appropriate.

In this report, we describe two patients with metastatic ovarian cancer treated with an OX40 agonist Ab (INCAGN01949) as part of a clinical trial. Neither patient experienced an objective response and both were taken off study for progressive disease. Each patient was then treated off-label with the combination of ipilimumab and dnivolumab and experienced dramatic responses.

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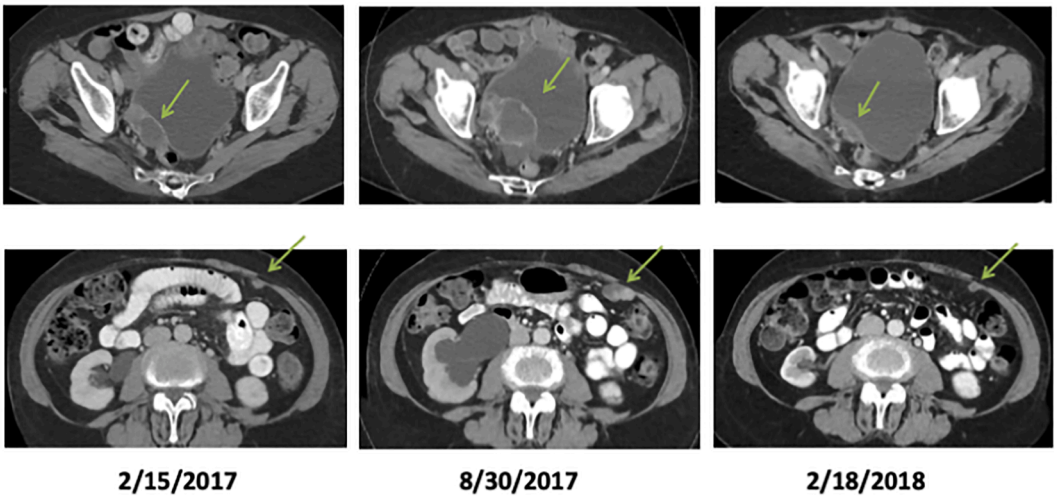

Fig. 1. Representative images of tumor lesions of Patient 1 immediately prior to the start of OX40 Ab therapy (2/15/2017), at time of progression on OX40 Ab (8/30/2017), and first scan following starting ipilimumab and nivolumab (2/18/2018).

2. Case presentation

2.1. Case 1

Patient 1 is a 79 year-old female originally diagnosed with stage IIIC high grade serous fallopian tube carcinoma in 2013. She underwent debulking surgery on 3/28/2013 followed by 6 cycles of carboplatin and paclitaxel. Disease recurrence was discovered in 7/2015 and she was treated with carboplatin and liposomal doxorubicin (Doxil) from 8/2015 until 7/2016, after which she was followed until experiencing disease progression in 1/2017. During this time, molecular profiling showed wild-type BRCA1/2, negative PD-L1 expression, and no other actionable mutations. She was enrolled on a clinical trial of INCAGN01949 and started treatment on 3/13/2017. She tolerated therapy very well and was treated for thirteen 14-day cycles. After an initial period of stable disease, she experienced disease progression on a scan performed on 8/30/2017 (Fig. 1), receiving her last treatment on 8/25/2017. She was subsequently started on off-label therapy with ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) every three weeks on 10/12/2017 and received 4 doses of combination therapy before moving to maintenance nivolumab at 480 mg every 4 weeks on 3/23/2018. A CT scan performed on 2/3/2018 showed a significant reduction in all tumors (32% reduction per RECIST) (Fig. 1). She continued on maintenance nivolumab with subsequent scans on 5/30/2018, 9/17/2018, and 12/20/2018 showing continued regression of disease with tumor reductions of 61%, 67%, and 73%, respectively, per RECIST. Per patient's decision her last dose of nivolumab was given on 1/7/2019 and she remains in clinical observation. Her most recent scans on 07/30/2020 showed a complete response with no evidence of disease.

2.2. Case 2

Patient 2 is a 58 year-old female who was originally diagnosed with moderately differentiated serous papillary cystadenocarcinoma in 2007. She underwent optimal debulking surgery in 7/2008 followed by intraperitoneal cisplatin and intravenous paclitaxel. Genetic evaluation showed a BRCA1 187DelAG mutation. She experienced disease recurrence in 6/2011 and she was treated with carboplatin and Doxil completing therapy in 1/2012. She experienced disease recurrence in 1/2013 after which she was treated with olaparib on a clinical trial for 11 months. From 4/2014 until 12/2015 she was treated sequentially with Doxil, carboplatin, and bevacizumab. She enrolled on a clinical trial

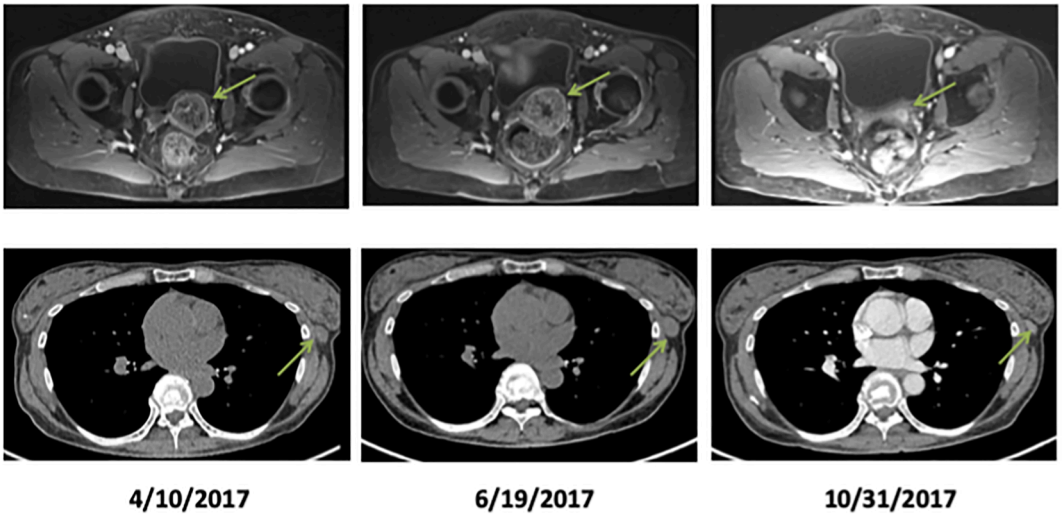

Fig. 2. Representative images of tumor lesions of Patient 2 immediately prior to the start of OX40 Ab therapy (4/10/2017), at time of progression on OX40 Ab (6/19/2017), and first scan following starting ipilimumab and nivolumab (10/31/2017).

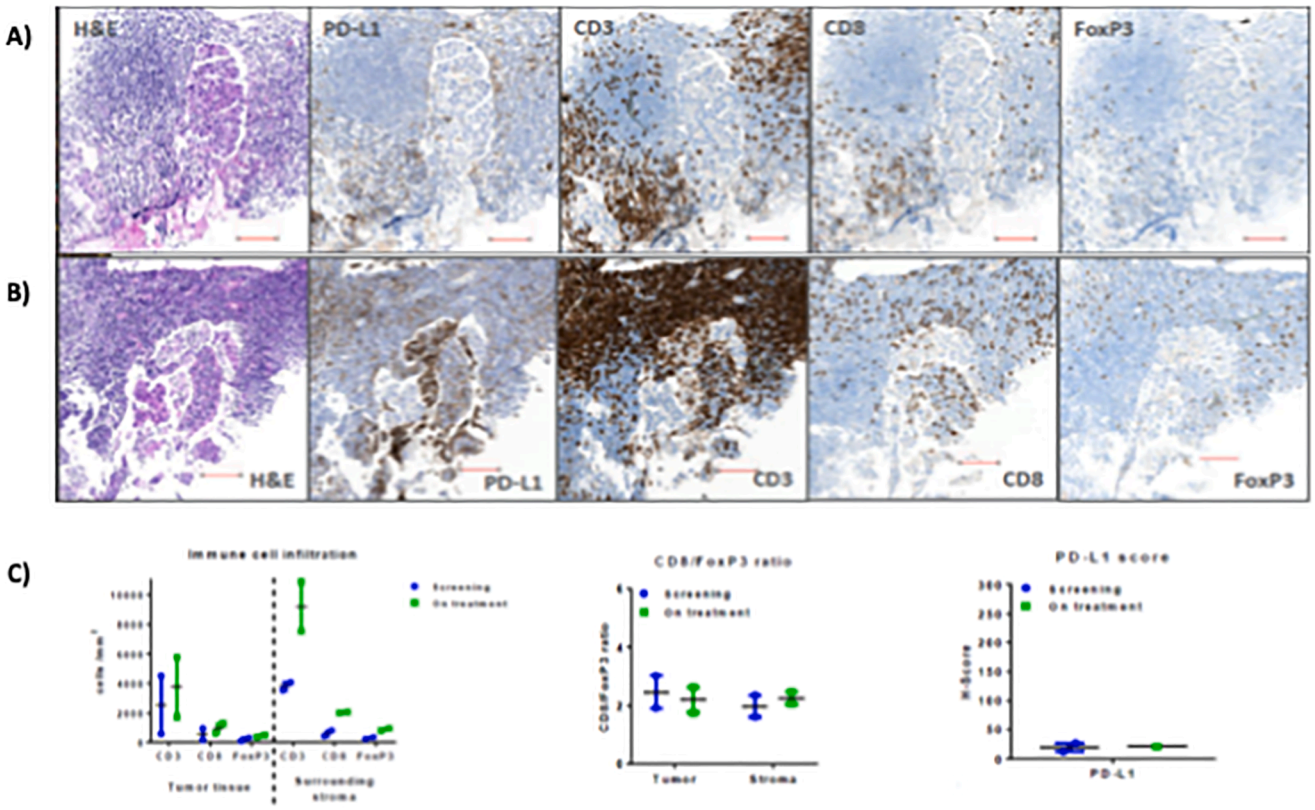

Fig. 3. Changes in PD-L1, CD3, CD8, and FOXP3 expression in pre-treatment biopsy specimen from patient 1 (Panel A), compared with post-treatment biopsy (Panel B). Quantification of expression showed an increase in total T cells, CD8 T cells, and Tregs in the surround stroma with a slight trend towards increase in all three populations in tumor tissue Panel C). No changes observed in CD8/FOXP3 ratio or PD-L1 expression on tumor cells.

with a PD-1 Ab plus cyclophosphamide, GM-CSF, and stereotactic radiation, starting treatment on 4/20/2016. She initially experienced a partial response by RECIST but eventually had disease progression on 3/1/2017.

The patient enrolled on a Phase 1 trial of INCAGN01949 on 4/25/2017. Her course was uncomplicated and she experienced no treatment-related adverse events. Progression of disease was noted on a CT scan on 6/19/2017 (Fig. 2) with last study treatment on 6/06/2017. She started on off-label ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) on 8/16/2018. Her course was complicated by elevated liver enzymes and she completed only three doses of the combination before moving to single-agent nivolumab at 240 mg every 2 weeks on 11/7/2017. Imaging performed on 10/31/2017 showed a significant reduction in all disease sites (61% reduction by RECIST) (Fig. 2). Subsequent imaging on 2/2/2018 showed a maintained response with a 60% reduction by RECIST but a subcutaneous nodule showed small growth and she was re-started on combination therapy with ipilimumab and nivolumab every three weeks for three doses and then continued on maintenance nivolumab at 240 mg every 2 weeks. Subsequent imaging studies on 5/22/2018 and 12/7/2018 showed continued response with tumor reduction of 71% by RECIST on both studies. Her course was complicated by the development of pneumonitis requiring oral corticosteroids. Disease progression was shown on imaging studies on 4/4/2019 and the patient discontinued immunotherapy.

This patient had pre- and on-treatment biopsies during the INCAGN01949 treatment. There was an increase in stromal T cell infiltrates following treatment. There was a marked CD3 increase but this was accompanied by a modest increase in T regulatory cells. The overall quantitation of the biopsies is shown in Fig. 3. These changes in T cells was not accompanied by a commensurate increase in PD-L1 expression. Subsequent molecular profiling showed 0% staining for PD-L1.

3. Discussion and conclusions

The cases described are notable in that they illustrate the potential efficacy of anti-PD1 therapy given in sequence following OX40 Ab in patients. The two cases differ in that Patient 1 was anti-PD1 therapy-naive while Patient 2 was anti-PD1 therapy-refractory following an initial response. Both cases also differ slightly from the pre-clinical studies by Shrimali *et al* and Messenhemier *et al* in that the PD-1 antibody was given in combination with ipilimumab. The activity of the combination of ipilimumab and nivolumab in ovarian cancer was recently reported in a randomized Phase II trial versus nivolumab alone (Zamarin et al., 2020). In this trial, patients treated with the combination experienced a superior objective response rate (31.4% versus 12.2% [Odds ratio, 3.28; 85% CI 1.53 to infinity; $p = 0.034$]) and progression free survival (3.9 months versus 2 months [HR 0.53, 95% CI 0.34 to 0.82]) compared with nivolumab alone. It remains possible that the OX40 Ab did not contribute to the observed clinical efficacy which can instead be attributed to the activity of nivolumab and ipilimumab. However, it must be noted the depth and duration of responses experienced by both patients described is unusual, particularly in patients whose tumors are negative for PD-L1 expression. Patient 1 ultimately experienced a complete response with a duration of response of at least 33 months. Patient 2 experienced a maximal tumor burden reduction of 70% with a duration of response of 23 months. Moreover, Patient 2 had already experienced disease progression on a PD-1 antibody. While there is currently no published data in ovarian cancer, in patients with melanoma the combination appears to have only modest activity in patients failing single-agent anti-PD1 therapy (Zimmer et al., 2017).

The clinical development of OX40 agents has been challenging. In animal models it appears that changes in CD8 T cell responses are critical to diminished activity with upregulation of inhibitory checkpoints and accompanying apoptosis. In patients it is interesting to speculate

that the OX40 agonist is driving the expansion of both T effector cells and Tregs with limited clinical activity. Animal models of experimental allergic encephalitis have shown that the effect of OX40 ligation is dependent upon the cytokine milieu present at the time of OX40 antibody administration and can drive Treg expansion (Ruby et al., 2009). Sequencing of therapeutic agents combined with and a better understanding of the tumor microenvironment may improve the clinical development of these agents.

As the field continues to focus on developing immunotherapies, the appropriate placement of co-stimulatory agonists remains a challenge. The single-agent activity of OX40 antibodies may be limited as the recently reported results from a Phase I trial of BMS-986178 noted no single-agent responses (Olszanski et al., 2017). Preliminary results from clinical assessment of other co-stimulatory agonists such as inducers of ICOS, CD27, or 4-1BB have also not shown robust single agent activity. As many of these agents are in active clinical assessment in combination with anti-PD1 therapy, the cases illustrated here add to the growing literature that the sequence in which immunotherapies are given may be critical to maximally exploit their therapeutic efficacy.

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