Purpose: The programmed death-1 ligand/programmed death-1 (PD-L/PD-1) pathway has been recently suggested to play a pivotal role in the immune evasion of tumors from the host immune system. In this study, we tried to reveal the clinical importance and therapeutic potential of the PD-L1/PD-1 pathway in pancreatic cancer, which is one of the most aggressive and intractable malignant tumors.

Experimental Design: We used immunohistochemistry to investigate PD-L1 expression in 51 patients with pancreatic cancer who underwent surgery and explored the therapeutic efficacy of blocking the PD-L1/PD-1 pathway in murine pancreatic cancer in vivo.

Results: PD-L1+ positive patients had a significantly poorer prognosis than the PD-L1− negative patients, whereas there was no significant correlation of tumor PD-L2 expression with patient survival. PD-L1 expression was inversely correlated with tumor-infiltrating T lymphocytes, particularly CD8+ T cells. These clinical data have suggested that the PD-L1/PD-1 pathway may be a critical regulator in human pancreatic cancer. Monoclonal antibodies against PD-L1 or PD-1 induced a substantial antitumor effect on murine pancreatic cancer in vivo. PD-L1 blockade promoted CD8+ T-cell infiltration into the tumor and induced local immune activation. Furthermore, the combination of anti-PD-L1 monoclonal antibody and gemcitabine exhibited a significant synergistic effect on murine pancreatic cancer and resulted in complete response without overt toxicity.

Conclusion: Our data suggest for the first time that PD-L1 status may be a new predictor of prognosis for patients with pancreatic cancer and provide the rationale for developing a novel therapy of targeting the PD-L1/PD-1 pathway against this fatal disease.

Pancreatic cancer is still one of the most aggressive and intractable human malignant tumors and a leading cause of cancer-related deaths worldwide (1, 2). Due to its extremely high malignant potential, it is usually diagnosed at an advanced stage and often recurs even after curative surgical excision (3). Despite significant advances in cancer therapy, including surgery, radiation, chemotherapy, or combinations of these, the overall pancreatic cancer mortality rate has not been dramatically changed (1, 2). Therefore, novel approaches against pancreatic cancer need to be developed and established to improve patient prognosis.

Programmed death-1 (PD-1) is an immunoglobulin superfamily member related to CD28 and CTLA-4 (4–6). PD-1 is induced on T cells, B cells, and monocytes on activation. Accumulating evidence indicates that PD-1 plays a crucial role in regulating peripheral tolerance and autoimmunity (4, 7). PD-1 has two ligands: PD-1 ligand 1 (PD-L1; B7-H1) and PD-1 ligand 2 (PD-L2; B7-dendritic cells; refs. 8–12). PD-L1 and PD-L2 are involved in the negative regulation of cellular and humoral immune responses by engaging PD-1 receptor (4). PD-L1 is expressed on resting T cells, B cells, dendritic cells, and macrophages. PD-L1 is also expressed on parenchymal cells, including vascular endothelial cells and pancreatic islet cells (7). In contrast, PD-L2 is inducibly expressed only on dendritic cells and macrophages (4, 8). The distinct expression patterns of PD-L1 and PD-L2 suggest that their relative functions may depend on the tissue microenvironment (4, 7, 10). Recent studies have also shown that the PD-L1/PD-1 pathway might play critical roles in tumor immunity (4, 13, 14). PD-L1 on tumors or antigen-presenting cells in tumor environment has been proposed to promote tumor growth and induce apoptosis...
of tumor-reactive T cells expressing PD-1 (13, 14). More
recently, we and others have also shown the potential negative
regulatory role for PD-L1 in clinical cancers (15–18). Thus, PD-
L1 may play an important role in the immune evasion from
host immune system in cancer patients. On the other hand,
some studies have suggested that, in contrast to PD-L1, PD-L2
might serve as a costimulator in tumors (19, 20). They have
shown that PD-L2 expression led to rapid tumor rejection by
enhancing tumor-reactive T-cell priming and effector function
(19). PD-L2 also augmented T helper 1 and CTL response
in vivo (21). However, analysis of the clinical data on tumor
PD-L2 expression has been limited at present (17).

In this study, we investigated the clinical significance of PD-
L1 and PD-L2 expression in human pancreatic cancer and the
therapeutic efficacy of targeting the PD-L/PD-1 pathway toward
future clinical application for the treatment of pancreatic
cancer.

Materials and Methods

Patients. We examined 51 patients with pancreatic cancer who
underwent surgery at Department of Surgery, Nara Medical University,
between 1996 and 2004. The median age of the patients was 63 years,
with a range of 46 to 73 years. Tissues were obtained from the resected
specimens and then were rapidly frozen at −80°C for storage until use.

For immunohistochemistry, a part of fresh tumor tissue specimen was
immediately embedded in optimum cutting temperature compound
(Miles, Kankakee, IL), and frozen sections were then cut on the cryostat
to thickness of 5 mm. A serial section from each specimen was stained with
H&E for histologic evaluation. The median follow-up for all patients was
22 months, with a range of 3 to 91 months. Most of the patients received
systemic chemotherapy after surgery. Positive surgical margin was
identified in 24 (47.1%) patients and negative in 27 (52.9%).

Animal and cell line. Female C57BL/6 mice (8-12 weeks old) were
obtained from CLEA Japan (Tokyo, Japan). All mice were maintained
under specific pathogen-free conditions in the animal facility at Nara
Medical University. All experiments were conducted under a protocol
approved by our institutional review board. A murine pancreatic
adenocarcinoma, PAN 02, was obtained from the DCTD Tumor
Repository, National Cancer Institute (Frederick, MD). Cells were
grown in RPMI 1640 supplemented with 10% heat-inactivated fetal
bovine serum. To evaluate the inducible expression of PD-L1 on PAN
02, cells were treated for 72 h with recombinant murine IFN-γ
(10 ng/mL; PharMingen, San Diego, CA). Then, PD-L1 expression was
measured by fluorescence-activated cell sorting analysis.

Antibodies. Monoclonal antibodies (mAb) against human PD-L1
(MIH1, mouse immunoglobulin G1) and PD-L2 (MIH18, mouse
immunoglobin G1) were previously described (17). RMP1-14 and MH6 against mouse PD-1 and PD-L1 (rat immunoglobin G) were generated as previously described (10). Antihuman CD4 and CD8 T-cell mAbs were purchased from Dako Japan (Kyoto, Japan). Anti mouse CD4 and CD8 T-cell mAbs and isotype immunoglobin were purchased from Pharmingen. Gemcitabine was a generous gift of Eli Lilly Japan (Kobe, Japan).

Immunohistochemistry. Immunohistochemical staining was done using Dako Envision system (Dako Japan) as previously described (17). After neutralization of endogenous peroxidase, cryostat sections on glass slides were preincubated with blocking serum and then were incubated overnight with each mAb. After three washes in PBS, the sections were incubated for 1 h with biotinylated antimouse immunoglobin G, washed thrice with PBS, incubated with avidin-biotinylated peroxidase complex for 1 h, and again washed for 10 min with PBS. Reaction products were visualized with 3,3’-diaminobenzidine tetrahydrochloride and the slides were counterstained with hematoxylin.

Evaluation of immunostaining. Immunohistochemistry for PD-L was evaluated as previously described (17). All of the immunostained sections were examined under low power (4× objective) to identify regions containing low-staining tumor cells. In case of multiple areas with low intensity, five randomly selected areas were scored, and in sections where all of the staining appeared intense, one field was selected at random. The proportion of tumor cells showing high and low staining in each selected field was determined by counting individual tumor cells at high magnification. At least 200 tumor cells were scored per ×400 field. Because most prognostic factors are usually considered as dichotomized, discontinuous variables, a cutoff point was selected to give the optimal separation between low risk and high risk of the overall survival as previously described by others and us (17, 22, 23). Then, we selected 10% as cutoff point based on preliminary analysis and recent report on PD-L1 expression in human cancer (16). Specimens with a ≥10% PD-L–positive tumor cells were classified as positive. Immunohistochemistry for CD4+ and CD8+ T cells was evaluated. An average number of >50 accumulating CD4+ and CD8+ tumor-infiltrating lymphocytes (TIL) per field at ×200 magnification were scored. We used the mean number of infiltrating cells as a cutoff point to divide all tumors into groups as having either positive or negative infiltration by TILs in tumor tissue. Fifty-one cases were classified as having positive (>150) levels of T-cell infiltration in tumor tissue and the remainder as having negative (<150) infiltration. Tumor samples were examined and classified by two observers who had no knowledge of the patients’ clinical status and outcome.

Extraction of total RNAs and real-time reverse-transcriptase PCR analysis. Total RNA was isolated using the guanidine isothiocyanate method (RNeasy Protect Mini Kit, Qiagen, Piscataway, NJ) according to the manufacturer’s protocol. A human tonsil tissue was used as the positive control for PD-L. Real-time quantitative PCR analysis was done by using ABI Prism 7700 sequence detector system (PE Applied Biosystems, Foster City, CA). All primer/probe sets were purchased from PE Applied Biosystems. PCR was carried out with the TaqMan Universal PCR Master Mix (PE Applied Biosystems) using 1 μL of cDNA in a 20-μL final reaction volume. The PCR thermal cycle conditions were as follows: initial step at 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 60°C for 1 min. The expression level of the housekeeping gene β2-microglobulin was measured as an internal reference with a standard curve to determine the integrity of template RNA for all of the specimens. The ratio of mRNA level of each gene was calculated as follows: (absolute copy number of each gene) / (absolute copy number of β2-microglobulin).

Animal experimental protocol. Cells (1 × 106 PAN 02) were s.c. inoculated on one side of the ventral surface in the lower flank region of syngeneic C57BL/6 mice. Treatment was started ~10 days later when a small palpable lump was evident, ranging from 3 to 4 mm in diameter. Some mice were injected i.p. with 0.3 mg of each mAb thrice per week. Control mice received control immunoglobin G. Gemcitabine was given i.p. at a dose of 60 μg/g every third day. The dose was elected based on our preliminary experiments as well as previous reports in murine tumor models. Tumor size was determined by caliper measurements. At 4 weeks after tumor establishment, mice were sacrificed and tumors were taken for further analysis.

Statistical analysis. The overall cancer-specific survival time was calculated from the date of surgery to the date of death from pancreatic cancer. The significance of the difference between PD-L expression and several clinical and pathologic variables was assessed by the χ2 test or Mann-Whitney U test. The Kaplan-Meier method was used to estimate the probability of survival, and significance was assessed by the log-rank test. Multivariate analysis was done using the Cox regression model to study four factors (PD-L1 status, tumor status, nodal status, and metastatic status). We use the term of tumor status as T factor, nodal status as N factor, and metastatic status as M factor in tumor-node-metastasis classification, respectively. Some data in murine model were analyzed using Student’s t test to determine significant differences between two different groups. P < 0.05 was considered as statistically significant.
Results

PD-L expression in human pancreatic cancer. Of the 51 tumors evaluated in this study, 20 (39.2%) were positive for PD-L1 expression at protein level and 31 (60.8%) were negative, whereas PD-L2 was positive in 14 (27.5%) and negative in 37 (72.5%). PD-L1 and PD-L2 were expressed mainly in the plasma membrane and cytoplasm of cancer cells (Fig. 1). In addition, PD-L1 and PD-L2 expression was also found in some infiltrating lymphocytes as well as stromal cells in pancreatic cancer tissue.

Correlation between PD-L expression and postoperative prognosis. Among the 51 patients, PD-L1–positive patients had significantly poorer survival than the PD-L1–negative patients (P = 0.016; Fig. 2A). One-year postoperative survival rate of PD-L1–positive and PD-L1–negative patients was 33.5% and 60.3%, respectively. On the other hand, there were no significant differences in postoperative prognosis between PD-L2–positive and PD-L2–negative patients (Fig. 2B). There was no significant correlation between tumor PD-L1 status and clinical indicators including tumor status, nodal status, metastatic status, and pathologic stage. However, subgroup analysis has indicated that significant differences were noted in 1-year survival rate after surgery between PD-L1–positive and PD-L1–negative patients when categorized by the following variables: T3 status, N0 status, M0 status, and pathologic stage IIa (40.8% versus 62.9%, P = 0.019; 20.0% versus 87.5%, P = 0.019; 33.3% versus 63.2%, P = 0.035; and 20.0% versus 100%, P = 0.006, respectively; Table 1). Surgical margin status had no significant effect on the prognosis of either PD-L1–positive or PD-L1–negative patients. Furthermore, the multivariate analysis using Cox regression model has shown that tumor PD-L1 status was defined to be a significant independent prognostic factor (χ² = 5.26, RR = 2.3, P = 0.022). Although there was a trend showing that advanced-stage tumors such as T4, N1, and M1 had poorer survival, T, N, M status did not reach statistical significance.

Inverse correlation between tumor PD-L1 and TILs. We then analyzed the correlation between tumor PD-L1 expression and TILs. There was a significant inverse correlation between PD-L1
expression and TILs, particularly CD8+ T cells (CD4+ T cells, \( P = 0.019 \); CD8+ T cells, \( P < 0.0001 \); Table 2).

**Therapeutic efficacy of PD-L1/PD-1 blockade in pancreatic cancer in vivo.** For clinical application, we explored the therapeutic efficacy of blocking the PD-L1/PD-1 pathway in pancreatic cancer in vivo. To this end, we used a murine pancreatic adenocarcinoma, PAN 02. Although constitutive expression of PD-L1 was minimal in PAN 02, IFN-γ stimulation induced its high expression (>95%) as estimated by flow cytometric analysis (Fig. 3A). In vivo treatment with either anti–PD-L1 or anti–PD-1 blockade on PAN 02 induced a substantial antitumor effect in vivo and significantly inhibited tumor growth (Fig. 3B). There was no significant difference in tumor growth between PD-L1 and PD-1 blockade. To define the underlying mechanisms in tumor growth inhibition by PD-L1 blockade, we first assessed the intratumoral T cells in this model. Marked CD8+, but minimal CD4+, T-cell infiltration in implanted tumor tissues was identified by immunohistochemistry (Fig. 3C). Quantification by real-time PCR further confirmed the effect of PD-L1 blockade on T cells [CD8+ T cells, \( P = 0.0004 \); CD4+ T cells, not significant \((P > 0.05)\), compared with controls]. Then, we analyzed local immune status in tumors. The expressions of IFN-γ, granzyme B, and perforin were significantly higher in tumors treated with anti–PD-L1 mAb than in controls \((P = 0.030, P = 0.012, and P = 0.015, respectively; Fig. 3D)\).

**Synergy between PD-L1 blockade and chemotherapy.** Finally, we evaluated the combination of chemotherapy with PD-L1 blockade in pancreatic cancer. We used gemcitabine that is currently the standard chemotherapeutic agent for pancreatic cancer. The delayed 2-week treatment of anti–PD-L1 mAb starting on day 15 after tumor establishment had minimal inhibitory effect on tumor progression (Fig. 4A). The treatment of gemcitabine alone resulted in significant inhibition of tumor growth (Fig. 4A). This antitumor effect of gemcitabine was further enhanced by the combination with the delayed PD-L1 blockade (Fig. 4A). Furthermore, the combined treatment of gemcitabine and 4-week treatment of PD-L1 blockade displayed a substantial synergistic antitumor effect on pancreatic cancer, thereby resulting in complete response in treated mice (Fig. 4B). There were no overt toxicity and death in mice during and after treatment.

**Discussion**

Pancreatic cancer is among the most lethal cancers due, in part, to a lack of effective therapies (1, 2). To improve the patient survival, a variety of both basic and clinical researches have been conducted. However, despite substantial efforts to develop novel therapy, there has been little change in the overall pancreatic cancer mortality rate (1). Among the proposed novel therapies, immunotherapy may be a potentially potent strategy (2). Several strategies such as vaccine to stimulate patient’s own immune system and achieve an antitumor response have been clinically attempted. Unfortunately, the therapeutic efficacy was only limited thus far, partly because tumor may evade host immune response through various mechanisms. Recent studies have suggested a novel mechanism of tumor escape through negative regulation of PD-L and PD-1 interaction (13, 14). The expression of PD-L on the cell surface of tumor itself or antigen-presenting cells in tumor environments might induce apoptosis on tumor-reactive T cells through engagement of PD-1 and promote tumor growth (13, 14). Several clinical studies conducted by us and others further showed that tumor PD-L1 expression has significant clinical implications (15–18).

In this study, we first investigated the tumor PD-L expression in human pancreatic cancer. Then we confirmed both PD-L1 and PD-L2 expression in several pancreatic cancer tissues and found that tumor PD-L1 but not PD-L2 expression significantly correlated with postoperative prognosis. We also found that PD-L1 expression was inversely correlated with TILs, particularly CD8+ T cells. Furthermore, the subgroup analysis has indicated the significance of PD-L1 in early stage including

### Table 1. One-year survival rate of 51 patients with pancreatic cancer according to clinicopathologic characteristics and tumor PD-L1 status

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>PD-L1 positive, n (%)</th>
<th>PD-L1 negative, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1 (100)</td>
<td>1 (ND)</td>
<td>0 (——)</td>
<td>ND</td>
</tr>
<tr>
<td>T2</td>
<td>7 (42.9)</td>
<td>3 (0)</td>
<td>4 (75.0)</td>
<td>0.093</td>
</tr>
<tr>
<td>T3</td>
<td>40 (54.7)</td>
<td>15 (40.8)</td>
<td>25 (62.9)</td>
<td>0.019</td>
</tr>
<tr>
<td>T4</td>
<td>3 (54.7)</td>
<td>1 (ND)</td>
<td>2 (ND)</td>
<td>ND</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>15 (61.9)</td>
<td>6 (20.0)</td>
<td>9 (87.5)</td>
<td>0.019</td>
</tr>
<tr>
<td>N1</td>
<td>36 (46.2)</td>
<td>14 (40.8)</td>
<td>22 (50.0)</td>
<td>0.252</td>
</tr>
<tr>
<td>Metastatic status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>45 (52.8)</td>
<td>17 (33.0)</td>
<td>28 (63.2)</td>
<td>0.035</td>
</tr>
<tr>
<td>M1</td>
<td>6 (33.3)</td>
<td>3 (33.3)</td>
<td>3 (33.3)</td>
<td>0.486</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia, Ib</td>
<td>2</td>
<td>50.0 (0)</td>
<td>— (2)</td>
<td>ND (ND)</td>
</tr>
<tr>
<td>IIa</td>
<td>13 (64.2)</td>
<td>6 (20.0)</td>
<td>7 (100)</td>
<td>0.006</td>
</tr>
<tr>
<td>IIb</td>
<td>29 (50.6)</td>
<td>11 (42.4)</td>
<td>18 (55.6)</td>
<td>0.426</td>
</tr>
<tr>
<td>III</td>
<td>1 (0)</td>
<td>0 (——)</td>
<td>1 (ND)</td>
<td>ND</td>
</tr>
<tr>
<td>IV</td>
<td>6 (33.3)</td>
<td>3 (33.3)</td>
<td>3 (33.3)</td>
<td>0.486</td>
</tr>
<tr>
<td>Total</td>
<td>51 (50.4)</td>
<td>20 (39.2)</td>
<td>31 (60.3)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not determined.
the up-regulation of several potent effectors including IFN-
thereby resulting in local immune activation as evidenced by
favorable effect on patient survival (1, 30). However, the effect of
cancer because several clinical trials have proved the some
currently the standard chemotherapeutic agent for pancreatic
cancer. Gemcitabine is exhibited significant synergistic effect on pancreatic cancer and induced
combination of gemcitabine with simultaneous blockade of PD-L1 has exerted a
delayed PD-L1 blockade significantly inhibited tumor growth of pancreatic cancer.
Our data corroborate several previous studies and
cancer model may depend on tumor biology and malignancy of each
cancer. Taken together with other recent studies, this study
might further corroborate that tumor-associated PD-L expression plays a critical role in human cancers (15–18).
Next, using a murine pancreatic cancer model, we investi-
gated the therapeutic efficacy of blocking the PD-L1/PD-1 pathway in pancreatic cancer toward future clinical application.
Then, we found several important data in this model. First,
both anti–PD-1 and anti–PD-L1 mAbs had a significant antitumor effect on the inhibition of tumor growth, suggesting that the PD-L1/PD-1 pathway is critical for growth of pancreatic cancer. Our data corroborate several previous studies and
strengthens the therapeutic potential of targeting the PD-L1/PD-
1 pathway for the treatment of cancer patients (13, 24–27).
Second, we confirmed that PD-L1 blockade promoted tumor-
reactive CD8+ T-cell infiltration into the established tumor,
thereby resulting in local immune activation as evidenced by
the up-regulation of several potent effectors including IFN-γ,
perforin. However, further studies may be required to clarify the therapeutic effect of PD-L1/PD-1 blockade on the metastasis of pancreatic cancer using other cancer metastasis models because metastasis and metastatic relapse are the most frequent causes of cancer-related death in pancreatic cancer (1, 3, 28). Third, more importantly, data
indicated that the combination of gemcitabine with PD-L1 blockade exerted a synergistic antitumor effect on pancreatic cancer. Chemotherapy and immunotherapy have usually been
regarded as unrelated or potentially antagonistic forms of
therapy (29). This is because most chemotherapies kill target
cells by apoptosis and similarly induce cell death of activated T
cells by recognizing tumor antigen. In addition, lymphopenia
is a common side effect of many anticancer drugs, and this has
been assumed to be detrimental to sufficient antitumor immune
response. Our data showed that the delayed PD-L1 blockade
following preceding gemcitabine treatment significantly aug-
mented antitumor efficacy. Furthermore, the combination of
gemcitabine with simultaneous blockade of PD-L1 has exerted a
significant synergistic effect on pancreatic cancer and induced
complete response without overt toxicity. Gemcitabine is
currently the standard chemotherapeutic agent for pancreatic
cancer because several clinical trials have proved the some
favorable effect on patient survival (1, 30). However, the effect of
gemcitabine alone is limited and most patients develop
resistance to the therapy. Therefore, gemcitabine in combination
with other approaches is currently under investigation (26, 30).
Thus, our data may be clinically important and support future
application of PD-L1/PD-1 blockade for the treatment of pancreatic cancer.
In conclusion, we have shown for the first time that PD-L1 is a
novel prognostic marker for human pancreatic cancer. Furthermore, our data have indicated that targeting PD-L1/
PD-1, especially in combination with standard chemotherapy,
exhibited significant therapeutic efficacy. Little change in
pancreatic cancer mortality for decades has created an urgent
demand for the development of new strategies directed toward
novel targets. Our data may provide the rationale of developing
a novel immunotherapy targeting the PD-L1/PD-1 pathway for
this fatal malignant disease.

<table>
<thead>
<tr>
<th>PD-L1</th>
<th>CD4 Positive</th>
<th>CD4 Negative</th>
<th>CD8 Positive</th>
<th>CD8 Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>9</td>
<td>11</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Negative</td>
<td>24</td>
<td>7</td>
<td>25</td>
<td>6</td>
</tr>
</tbody>
</table>

N0 and M0 status, suggesting that PD-L1 might play more
important role in tumor progression rather than in tumor
metastasis of pancreatic cancer. Our in vivo study in murine
pancreatic cancer model may further support that PD-L1 is a
critical regulator in tumor growth of pancreatic cancer. In
our previous study, in contrast to pancreatic cancer, both PD-L1
and PD-L2 status had a significant effect in advanced stage of
esophageal cancer with positive lymph node and distant meta-
stasis (17). Such differences between pancreatic and esophageal
cancer may depend on tumor biology and malignancy of each
cancer. Thus, our data may be clinically important and support future
application of PD-L1/PD-1 blockade for the treatment of pancreatic cancer.

Fig. 4. Combination of PD-L1 blockade and gemcitabine. A, gemcitabine and
delayed PD-L1 blockade significantly inhibited tumor growth of pancreatic cancer.
Gemcitabine was given i.p. on days 1, 4, 7, 10, and 13 at a dose of 60 μg/g.
Anti–PD-L1 mAb was given at a dose of 0.3 mg on days 15, 17, 19, 22, 24, and 26.
Tumor size at 4 wk after tumor establishment: gemcitabine + anti–PD-L1 mAb,
5.8 ± 0.2 mm; P = 0.0077, versus gemcitabine alone, 6.8 ± 0.2 mm; P < 0.0001,
versus anti–PD-L1 mAb alone, 9.0 ± 0.3 mm. B, gemcitabine and simultaneous
PD-L1 blockade had a synergistic antitumor effect and resulted in complete
response in treated mice. Anti–PD-L1 mAb was given at a dose of 0.3 mg for three
weeks for 4 wk. Tumor size at 4 wk after tumor establishment: gemcitabine +
anti–PD-L1 mAb, 1.2 ± 0.2 mm; P < 0.0001, versus gemcitabine alone, 6.8 ±
0.2 mm; P = 0.001, versus anti–PD-L1 mAb alone, 6.2 ± 1.0 mm. Points, mean
tumor size of five mice; bars, SE.
References

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