ESMO advanced Course on

*Unsolved questions in Immuno-Oncology*

Patients with previous organ transplant

16-17th February 2018
Amsterdam, Netherlands

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*Drug Development Department (DITEP)*
Gustave Roussy
Patients with previous organ transplant

Conflicts of interest
AstraZeneca, BMS, Janssen, MSD, Novartis, Roche

Stéphane Champiat, MD, PhDc
Drug Development Department (DITEP)
Gustave Roussy
Anti-checkpoint *in transplanted patients*

2 major difficulties

- Transplanted patients receive *immunosuppressive therapy*:
  
  Antitumor efficacy may be affected

- Checkpoint blockade may *activate anti-graft immune response*
  
  and lead to allograft rejection
Solid organ transplants have a higher incidence of cancer
Patients with previous organ transplant

A typical *Unsolved problem*

- Solid organ transplants have a higher incidence of cancer
- Clinical trials with immune checkpoint inhibitors excluded transplanted patients
Anti-checkpoint *in transplanted patients*

Reported cases with anti-CTLA4
Successful administration of ipilimumab to a kidney transplanted patient with metastatic melanoma.

Lipson et al. (2014) *Journal of Clinical Oncology*


2008: *8 mm ulcerated melanoma* on his left chest
⇒ local excision

January 2011: unresectable left chest wall metastases and a new liver lesion
⇒ temozolomide and a platinum-based regimen: progression disease
⇒ Tacrolimus was stopped: Pt remained on prednisone monotherapy at 5 mg/day

Six weeks later, in *August 2011*, ipilimumab was initiated:

Repeat PET/CT scans in *November 2011, April and October 2012, and January 2013*, demonstrated a **continued partial response to therapy**

*Serum creatinine remained stable during and after Ipilimumab*
CASE REPORT

Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation

67-year-old man, liver transplantation in 2006 (history of HCV and hepatocellular carcinoma) immunosuppressive regimen: tacrolimus and mycophenolate mofetil

2009: in situ melanoma => surgery

2010: metastatic HCC (adrenal)
=> tacrolimus switched to rapamycin 3 mg daily, mycophenolate mofetil 500 mg twice daily

2013: metastatic melanoma (lung, parotid, hepatic)
=> Paclitaxel then radiotherapy
  rapamycin was reduced from 3 mg to 1 mg daily and mycophenolate was discontinued

2014: melanoma progression => anti-CTLA4 ipilimumab, 4 doses 3 mg/kg
  rapamycin at 1 mg daily
Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation

67-year-old man, liver transplantation in 2006 (history of HCV and hepatocellular carcinoma)
immunosuppressive regimen: tacrolimus and mycophenolate mofetil

2014 : melanoma progression => anti-CTLA4 ipilimumab, 4 doses 3 mg/kg
rapamycin at 1 mg daily

a) dramatic tumor regression in the lungs and the liver

b) patient remains stable 10 months following induction of treatment

Morales et al. 2015
Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation

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2014: melanoma progression => anti-CTLA4 ipilimumab, 4 doses 3 mg/kg rapamycin at 1 mg daily

patient remained asymptomatic
No steroid therapy was started

Morales et al. 2015
Anti-checkpoint in transplanted patients

Reported cases with anti-PD1
Metastatic cutaneous SCC treated by pembrolizumab in a kidney transplanted patient
Lipson et al., NEJM, 2016.

57-year-old woman kidney transplantation in 1989
immunosuppression: cyclosporine and prednisone

metastatic cutaneous squamous-cell carcinoma in March 2014.
⇒ reduction of immunosuppression to 5 mg of prednisone daily.

Cutaneous SCC progression despite Cetuximab then Trametinib therapy

Pembrolizumab in September 2014

⇒ 2 months after initiation: acute allograft rejection

Transplanted kidney did not recover despite high-dose glucocorticoid
Histologic and immunohistochemical evaluation of the explanted kidney revealed severe acute and chronic cell-mediated rejection.

- **Intimal arteritis** (chronic vasculopathy)
- **Strong C4d** staining in the artery endothelium
- **Glomerulitis, severe tubular loss, tubulitis, and interstitial inflammation**
- Peritubular capillaries show capillaritis but negative C4d staining

![Images of histological sections](Image)

- **PD-L1**: on endothelial cells and infiltrating immune cells associated with glomeruli
- **PD-L2**: infiltrating T cells expressing PD-1 are associated with cells expressing PD-L1 and PD-L2

Metastatic cutaneous SCC treated by pembrolizumab in a kidney transplanted patient
Lipson et al., NEJM, 2016.
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Pembrolizumab in September 2014

⇒ 2 months after initiation : acute allograft rejection

Transplanted kidney did not recover despite high-dose glucocorticoid

 8 months after the initiation of pembrolizumab : partial response \((-85%)\)

Patient undergoing hemodialysis without unacceptable adverse events, and her performance status has returned to 0.
Preserved Renal-Allograft Function During Nivolumab for MSI duodenum carcinoma
Barnett et al. NEJM  2017

70-year-old man with kidney transplantation in 2010 (bilateral nephrectomies for renal-cell cancer)
initial immunosuppression : glucocorticoid, tacrolimus, and mycophenolate mofetil

early 2015 : microsatellite-stable metastatic adenocarcinoma of the duodenum, liver metastases

  => discontinuation of mycophenolate mofetil, decreased doses of tacrolimus
  No response to standard chemotherapy

  => March 2016 : nivolumab
Prednisone 40 mg /d preemptively, tacrolimus replaced by sirolimus
Preserved Renal-Allograft Function During Nivolumab for MSI duodenum carcinoma
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| Table 1. Immunosuppressive Regimen in a Patient Who Had Undergone Kidney Transplantation. |
|---|---|
| Timing | Drug and Dosage |
| 1 Wk before | Prednisone — 40 mg daily |
| Concurrent | Prednisone — 20 mg daily; sirolimus — target goal, 4–6 ng per milliliter |
| 1 Wk after | Prednisone — 20 mg |
| >2 Wk and ≤6 mo after | Prednisone — 10 mg/day; sirolimus — target goal, 10–12 ng per milliliter |
| >6 Mo after | Glucocorticoid — gradually decreased to 5 mg/day; sirolimus — continued to maintain goal of 10–12 ng per milliliter |

* Timing represents the initiation of the immunosuppressive regimen in relation to the administration of nivolumab.
Preserved Renal-Allograft Function During Nivolumab for MSI duodenum carcinoma
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Prednisone 40 mg/d preemptively, tacrolimus replaced by sirolimus

Patient’s donor-specific antibodies remained absent.

<table>
<thead>
<tr>
<th>Table 1. Immunosuppressive Regimen in a Patient Who Had Undergone Kidney Transplantation.</th>
</tr>
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<tbody>
<tr>
<td><strong>Timing</strong></td>
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<tr>
<td>1 Wk before</td>
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<tr>
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<tr>
<td>&gt;2 Wk and ≤6 mo after</td>
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<tr>
<td>&gt;6 Mo after</td>
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* Timing represents the initiation of the immunosuppressive regimen in relation to the administration of nivolumab.

Serum creatinine level remained normal and stable

<table>
<thead>
<tr>
<th>Serum Creatinine(mg/dl)</th>
<th>Apr-16</th>
<th>May-16</th>
<th>Jul-16</th>
<th>Sep-16</th>
<th>Oct-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone trough levels(ng/ml)</td>
<td>3.6</td>
<td>6.6</td>
<td>12.7</td>
<td>12.2</td>
<td></td>
</tr>
</tbody>
</table>
35yo Pt, liver transplant at age 15 (biliary atresia)
  Immunosuppression: tacrolimus
  Patient subsequently diagnosed with quiescent HCV infection (blood transfusion)

2012: stage IIC melanoma (right upper lip)
  => local excision and adjuvant radiation

2015: right lung melanoma metastasis: BRAF wild type
  => 4 cycles of carboplatin and paclitaxel: PD

=> pembrolizumab: 2 doses

  10 days after 2\textsuperscript{nd} dose of pembro: hepatitis
Pembrolizumab in a Liver Transplant Recipient With Melanoma
Schvartsman et al., (2017) *Annals of Internal Medicine*

**Figure.** Serum levels of ALT and AST during and after pembrolizumab administration.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; HCV = hepatitis C virus; PCR = polymerase chain reaction; QID = 4 times daily; TID = 3 times daily.
Pembrolizumab in a Liver Transplant Recipient With Melanoma
Schvartsman et al., (2017) Annals of Internal Medicine

Figure. Serum levels of ALT and AST during and after pembrolizumab administration.

initial course of steroids and mycophenolate because concerns about immune-mediated hepatitis and acute rejection

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; HCV = hepatitis C virus; PCR = polymerase chain reaction; QID = 4 times daily; TID = 3 times daily.
Pembrolizumab in a Liver Transplant Recipient With Melanoma
Schvartsman et al., (2017) *Annals of Internal Medicine*

*Figure.* Serum levels of ALT and AST during and after pembrolizumab administration.

**Figure Note:**
- Liver biopsy considered negative for acute rejection
- ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; HCV = hepatitis C virus; PCR = polymerase chain reaction; QID = 4 times daily; TID = 3 times daily.
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Complete response of Lung Metastasis
no evidence of melanoma
> 6 months after stopping pembrolizumab
Anti-checkpoint *in transplanted patients*

Cardiac transplants
Tolerability of ipilimumab in a cardiac transplant
Gastman et al., Annals of Oncology (2016).

69 year-old woman cardiac transplant in 2000
receiving 2.5 mg of tacrolimus and 250 mg of mycophenolate mofetil daily

At 12 years: melanoma in situ of the right cheek => surgery

At 14 years: metastatic melanoma (bone and liver)
=> anti-CTLA4 Ipilimumab: 4 doses of 3 mg/kg
 remained on tacrolimus
Toxicity: significant fatigue

Cardiologic evaluations (repeated echocardiograms and cardiac enzyme): stable
Tacrolimus levels during ipilimumab: stable

Melanoma disease remain stable for a number of months
upon progression refused further care and died 11 months after starting ipilimumab
Cardiac allograft rejection as a complication of PD-1 checkpoint blockade for cancer immunotherapy: a case report

Taofeeq K. Owonikoko¹² · Mukesh Kumar¹ · Shu Yang³ · Alice O. Kamphorst³ · Rathi N. Pillai¹ · Rama Akondy³ · Vivek Nautiyal⁴ · Monica S. Chatwal⁴ · Wendy M. Book⁴ · Anurag Sahu⁴ · Gabriel L. Sica²⁵ · Rafi Ahmed²³ · Suresh S. Ramalingam¹²

49-year-old male pt
heart transplant recipient in 1996 (familial dilated cardiomyopathy)
immunosuppressive regimen of low dose prednisone + tacrolimus + sirolimus

At 19 years: anti-PD-1 antibody, nivolumab
49-year-old male pt
heart transplant recipient in 1996 (familial dilated cardiomyopathy)
immunosuppressive regimen of low dose prednisone + tacrolimus + sirolimus

At 19 years: anti-PD-1 antibody, nivolumab
5 days after administration of the 1st dose: progressive cardiac dysfunction,
2 weeks after initiation: cardiogenic shock, EF 25%
=> dobutamine
=> pulsed high-dose intravenous methylprednisolone (500 mg IV Q12 h) for 4 days along with sirolimus and increased dose of tacrolimus

Hemodynamics improved by Day 5 (EF40%)

No donor-specific antibodies were identified.
Endomyocardial biopsy: grade IIIA (acute moderate diffuse) cellular rejection

discharged home in stable clinical condition at day 10
died 8 months after
Anti-checkpoint *in transplanted patients*

Chae et al. (2018). *Cancer Treatment Reviews*

Immune checkpoint blockade regimens with associated risk and timing of allograft rejection based on available reports.

<table>
<thead>
<tr>
<th>Name of agent</th>
<th>Mechanism of action</th>
<th>Organs involved</th>
<th>% of Total rejected</th>
<th>Time until rejection (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab monotherapy</td>
<td>CTLA-4 Inhibition</td>
<td>Kidney: 3 [14,31]Liver: 2 [13,32]Heart: 1 [33]N = 6</td>
<td>Kidney: 1/3 = 33%Liver: 0/2 = 0%Heart 0/1 = 0%Total: 1/6 = ~16%</td>
<td>8 [31]</td>
</tr>
<tr>
<td>Pembrolizumab monotherapy</td>
<td>PD-1 Inhibition</td>
<td>Kidney: 2 [14,34]Liver: 1 [35]N = 3</td>
<td>Kidney: 2/2 = 100%Liver: 0/1 = 0%Total 2/3 = ~66%</td>
<td>6 [34] 8 [15]</td>
</tr>
<tr>
<td>Nivolumab monotherapy</td>
<td>PD-1 Inhibition</td>
<td>Kidney: 3 [36–38]Heart: 2 [16,38]N = 5</td>
<td>Kidney: 2/3 = ~66%Heart 1/2 = 50%Total 3/5 = 60%</td>
<td>Kidney: 6 [36,37]Heart: 2 [16]</td>
</tr>
<tr>
<td><em>Ipilimumab followed by Nivolumab</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(after progression on ipilimumab alone)</td>
<td>CTLA-4 inhibition → PD-1 inhibition (after documented progression)</td>
<td>Kidney: 2 [19,39]N = 2</td>
<td>Kidney: 1/2 = 50%Total: 1/2 = 50%</td>
<td>0.85 [19]</td>
</tr>
<tr>
<td><em>Ipilimumab followed by Pembrolizumab</em></td>
<td>CTLA-4 inhibition → PD-1 inhibition (after documented progression)</td>
<td>Kidney: 1 [2]N = 1</td>
<td>Kidney: 1/1 = 100%Total: 1/1 = 100%</td>
<td>3 [2]</td>
</tr>
</tbody>
</table>

Clinical outcomes of all available cases in which organ transplant recipients received immune checkpoint blockade. These outcomes are organized according to the therapeutic regimen used in each case. Described regimens included monotherapy or combination therapy with CTLA-4 and PD-1 inhibitors.
Anti-checkpoint \textit{in} transplanted patients

Reported cases with combos
anti-PD1 + anti-CTLA4
For metastatic cutaneous squamous cell carcinoma
In a kidney transplanted patient
Miller et al. (2017) JAAD Case Reports

Renal transplant at age 68 (diabetes mellitus complication)
Immunosuppression: mycophenolate and tacrolimus

3 years later developed SCC on his scalp
⇒ treated with surgery
⇒ adjuvant radiotherapy

1 month after radiotherapy: locoregional disease and pulmonary metastases
⇒ resection of locoregional and metastatic nodules
⇒ Mycophenolate lowered, and switch from tacrolimus to sirolimus

1 year later: additional metastases in the lung and intestine
⇒ resection of the small intestinal metastasis
⇒ carboplatin and paclitaxel.

After 2 cycles, new pulmonary nodules
⇒ weekly cetuximab. After 8 doses, new lesions in the peritoneum and descending colon.

Decision to stop immunosuppression
and treat with a combination of ipilimumab and nivolumab
Renal transplant at age 68 (diabetes mellitus complication)
Metastatic SCC (lung, peritoneum and descending colon)

Decision to stop immunosuppression and treat with a combination of ipilimumab and nivolumab

Cycle 1/day 8: fever, nausea and vomiting, abdominal pain, acute kidney injury, hematuria and oliguria
Renal ultrasound: abnormal flow

⇒ started on hemodialysis and methylprednisolone (concern for acute rejection)
anti-PD1 + anti-CTLA4

For metastatic cutaneous squamous cell carcinoma

In a kidney transplanted patient

Miller et al. (2017) JAAD Case Reports

Renal transplant at age 68 (diabetes mellitus complication)
Metastatic SCC (lung, peritoneum and descending colon)

Decision to stop immunosuppression
and treat with a combination of ipilimumab and nivolumab

Cycle 1/day 8: fever, nausea and vomiting, abdominal pain,
acute kidney injury, hematuria and oliguria
Renal ultrasound: abnormal flow

⇒ started on hemodialysis and methylprednisolone (concern for acute rejection)

Cycle 1/day 13: nephrectomy: pathologic analysis confirmed allograft rejection

Patient recovered without complication, cycle 2 of ipi/nivo was administered

Imaging after cycle 2: Partial response:
substantial decrease in the size and number of lung metastases
and complete response of the abdominal lesions
Renal transplant at age 68 (diabetes mellitus complication)
Metastatic SCC (lung, peritoneum and descending colon)

Decision to stop immunosuppression, and treat with ipilimumab and nivolumab combo

Cycle 1/day 8: acute kidney injury, hematuria and oliguria
⇒ started on hemodialysis and methylprednisolone (concern for acute rejection)

Cycle 1/day 13: nephrectomy: pathologic analysis confirmed allograft rejection

Imaging after cycle 2: Partial response:
- substantial decrease in the size and number of lung metastases
- complete response of the abdominal lesions

Pt completed 2 additional cycles of ipi/nivo and remain stable

5 months after starting ipi/nivo: sudden cardiac death of unclear etiology during dialysis.
  Autopsy: myocardial fibrosis, presumed secondary to long-standing diabetes.
  no evidence of myocarditis, acute myocardial infarction, or active malignancy
61-year-old woman with kidney transplantation in April 2008 (diabetes and hypertension)
Immunosuppression: prednisolone, tacrolimus, and mycophenolate mofetil.
Prednisolone discontinued in June 2009

May 2013: urothelial carcinoma
⇒ left nephro-ureterectomy and bladder cuff excision

September 2013 to March 2016: recurrent bladder cancer
repeated transurethral resections of the bladder tumor
and intravesical instillation with pharmarubicin, mitomycin C, and bacillus Calmette–Guerin

July 2016: Major locoregional evolution
(transplanted renal pelvis, urinary bladder, uterine cervix, and vagina)

August 2016: pembrolizumab (1 mg/kg)
and bevacizumab (4 mg/kg), cisplatin (50mg/m2), and gemcitabine (500mg/m2)
Anti-PD-1 with chemotherapy combination
For metastatic urothelial carcinoma
In a kidney transplanted patient
Wu et al. (2017). *Annals of Oncology*

After 4 cycles of therapy
PET-CT scan in October 2016:
significant tumor regression

After 11 cycles
PET-CT in March 2017:
sustained good partial response
Anti-PD-1 with chemotherapy combination
For metastatic urothelial carcinoma
In a kidney transplanted patient
Wu et al. (2017). *Annals of Oncology*

After 4 cycles of therapy
PET-CT scan in October 2016:
significant tumor regression

After 11 cycles
PET-CT in March 2017:
sustained good partial response

Graft function remained stable
with a fixed dose of mycophenolate mofetil (1 g/day)
and mild increase of tacrolimus from 9 to 10 g/day
to maintain serum tacrolimus level
between 5 and 10 ng/ml
Checkpoint Blockade for transplanted patients

Conclusion
Indications for checkpoint inhibitors are expanding and can be highly efficacious in transplant recipients suffering from cancer.
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**Risk of rejection may be greater with allografts**
- that are **less well matched**
- that have been **in situ for a shorter period of time**
- that require **higher doses of immunosuppression**.
PDL1 Is Required for Peripheral Transplantation Tolerance and Protection from Chronic Allograft Rejection

Tanaka et al. (2007). *The Journal of Immunology*

fully MHC-mismatched cardiac transplant model using BALB/c (H-2d) hearts as donors and C57BL/6 (H-2b) mice as recipients
tolerance was induced by CD28-B7 T costimulatory blockade using CTLA4Ig
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Risk of rejection may be greater with allografts:
- that are less well matched
- that have been in situ for a shorter period of time
- that require higher doses of immunosuppression.

Anti-CTLA4
- Appears safer for the risk of rejection
- But other irAEs are more frequent than with anti-PD1

Anti-PD1
- High risk of acute rejection
- But better efficacy

Role of concomitant use of glucocorticoids or mTOR inhibitors to prevent anti-PD1 mediated rejection?

Current data is limited: dedicated studies needed+++
Checkpoint Blockade for transplanted patients

Conclusion

Risks and benefits of anti-checkpoint therapy must be assessed on a case-by-case basis

• Life-dependent transplants vs renal transplants

• Expected response to IO:
  tumor type, PD-L1 status, MSI/mutational load, ...

• Use of single-agent ICB

• Concomitant use of glucocorticoids and mTOR inhibitors?
Anti-checkpoint *in transplanted patients*

**Local IO administration ?**

*Safely and effective administration of T-VEC in a patient with heart transplantation and recurrent locally advanced melanoma*  
Gustavo Schvartsman¹, Kristen Perez², Jill E. Flynn³, Jeffrey N. Myers³ and Hussein Tawbi²,*  
Schvartsman et al. (2017).
ESMO advanced Course on
*Unsolved questions in Immuno-Oncology*

Patients with previous organ transplant

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