Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

# Checkpoint Inhibitors and Solid Organ Transplant

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Section Chief, GI Medical Oncology
Medical Director, Cockrell Center for Advanced Therapeutics – Phase I program
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# Disclosures

- AD board and Speaker Ipsen, AstraZeneca
- I will not be discussing non-FDA approved indications during my presentation.

# Outlines

- CPI in solid organ transplant recipients
- CPI in liver transplant recipients
- Biomarkers for graft rejection
- Toxicity and management
- CPI in liver transplant candidate

# CPI in solid organ transplant recipients

RESEARCH ARTICLE Open Access

Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: an institutional experience and a systematic review of the literature

Noha Abdel-Wahab[1,2], Houssein Safa[3], Ala Abudayyeh[4], Daniel H. Johnson[3], Van Anh Trinh[3], Chrystia M. Zobniw[3], Heather Lin[5], Michael K. Wong[3], Maen Abdelrahim[6], A. Osama Gaber[6], Maria E. Suarez-Almazor[1†] and Adi Diab[3*†]

- 39 patients with transplantation were identified.
  - 62% had metastatic melanoma.
  - 59% had prior renal transplantation.
  - 28% hepatic transplantation.
  - 13% cardiac transplantation.




Abdel-Wahab et al. Journal for ImmunoTherapy of Cancer.2019

# CPI in solid organ transplant recipients

**Table 2** Checkpoint Inhibitor-Induced Allograft Rejection in Patients with Cancer and Prior Solid Organ Transplantation

| Prior organ transplantation | Checkpoint inhibitor | Allograft rejection, no./ reported cases (%) | Median time to rejection, days (range) |
|---|---|---|---|
| All | | 16/39 (41) | 15.5 (5–60) |
| Renal | Ipilimumab | 2/4 (50) | 21 |
| | Nivolumab | 2/5 (40) | 18.5 (7–30) |
| | Pembrolizumab | 4/9 (44) | 21 (5–60) |
| | Ipilimumab + nivolumab | 1/1 (100) | 8 |
| | Ipilimumab followed by nivolumab or pembrolizuamb[a] | 2/4 (50) | 14.5 (8–21) |
| | All | 11/23 (48) | 21 (5–60) |
| Hepatic | Ipilimumab | 1/3 (33) | 13 |
| | Nivolumab | 2/4 (50) | 12.5 (7–18) |
| | Pembrolizumab | 1/3 (33) | 7 |
| | Ipilimumab followed by pembrolizumab[a] | 0/1 (0) | |
| | All | 4/11 (36) | 10 (7–18) |
| Cardiac | Ipilimumab | 0/1 (0) | |
| | Nivolumab | 1/2 (50) | 5 |
| | Pembrolizumab | 0/1 (0) | |
| | Ipilimumab followed by pembrolizumab[a] | 0/1 (0) | |
| | All | 1/5 (20) | 5 |

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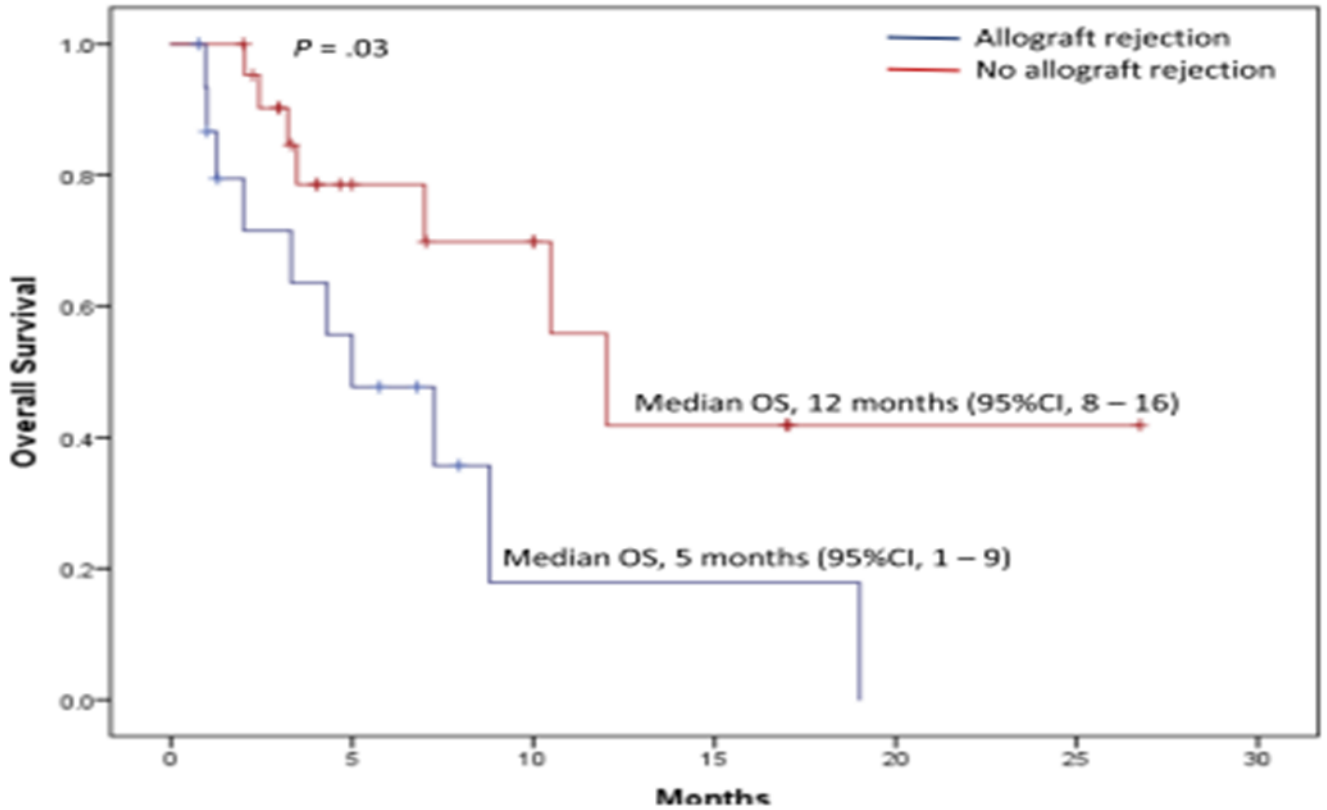
# CPI in solid organ transplant recipients







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# CPI in liver transplant recipients

- Liver transplant (LT) recipients have a 2-fold increased risk of cancer compared to matched general population
  - Cancer associated with oncogenic viruses, sun exposure, smoking and alcohol consumption.

- LT is a curative treatment for HCC
  - Recurrence post LT occurs in up to 15%-20% with mOS only 12 month
  - CPI combination is the preferred first line therapy for HCC

- Is it safe to use CPI post LT?.

# CPI in liver transplant recipients

| Author | Age (years) | Indication for LT | Indication for IO post-LT | Time from LT to ICI (years) | ICI therapy used | Immune suppression given at time of ICI | Graft PDL1 status | Best response to ICI | Liver toxicity | Time to develop toxicity | Treatment of toxicity | Response to treatment of toxicity |
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| Gomez *et al.*[37] 2018 | 61 | HCC | HCC | 2 | Nivolumab | NA | NA | NA | **TCMR** | 1 month | Prednisone | Improvement of rejection |
| Anugwom *et al.*[38] 2020 | 62 | HCC | HCC | 5 | Nivolumab | Tacrolimus | NA | NA | Immune hepatitis | 2 months | Steroids | Worsening of hepatitis |
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| Friend *et al.*[40] 2017 | 20 | HCC | HCC | 3 | Nivolumab | Sirolimus | Pos | NA | **TCMR + AMR** | < 1 month | Pulse high dose steroids, IVIG | No response, death |
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| Al Jarroudi *et al.*[50] 2020 | 70 | HCC | HCC | 3 | Nivolumab | Tacrolimus | NA | NA | Immune hepatitis **vs. graft rejection** | 2 months | High-dose steroids | NA |
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# CPI in liver transplant recipients

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| Lee *et al.*[49] 2019 | 73 | HCC | Cutaneous SCC | 12 | Nivolumab | Everolimus | NA | NA | **TCMR + AMR** | 1 month | High-dose steroids, everolimus, MMF | Improvement in TCMR, but persistent AMR |




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- ~40% ORR and ~15% CR to CPI.
- These response data is similar to data from non-transplant patients.
- In the post transplant setting, CPI can have comparable efficacy to the non-transplant setting. Considering the effect of immunosuppressants .

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# CPI in liver transplant recipients

**Toxicity:**

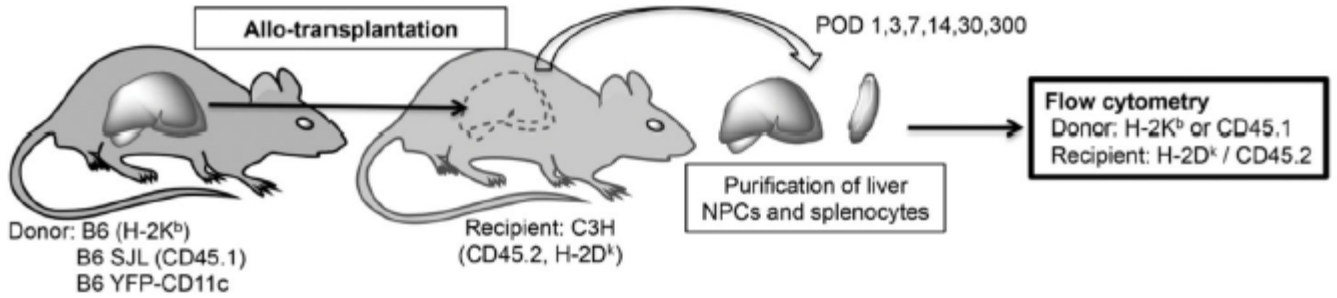
- Safety data from post-transplant patients are limited due to the limited use in this setting.

- It is apparent that the PD-1/PD-L1 and CTLA-4 checkpoint pathways contribute to immune tolerance of a transplanted organ.

- Immunofluorescence analysis of graft biopsies
  - Shows high expression of PD-1/PD-L1 in all grafts
  - Highlights the role of immune checkpoints in graft immune tolerance.

# CPI in liver transplant recipients

**Toxicity:**




- Mouse orthotopic liver transplant model:
  - PD-L1 is expressed by hepatocytes and cholangiocytes of liver allografts
  - PD-1 expression increased on allograft infiltrating T cells.
    - ✓ Raises concern that administration of CPI may increase the risk of T-cell mediated rejection (TCMR).

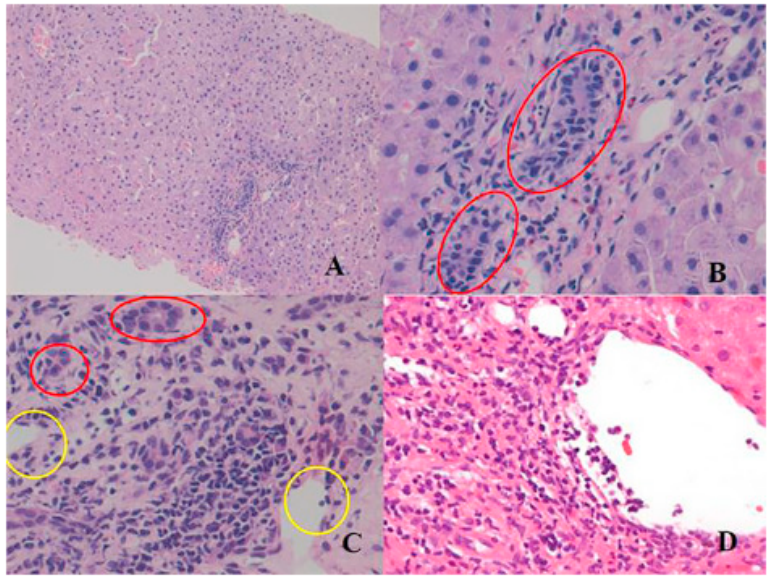



Ono et al. Hepatology. 2018

# CPI in liver transplant recipients

**Toxicity:**

- Graft rejection associated with immunotherapy is an acute process
- Believed to be T-cell mediated given the loss of immune-tolerance from PD-1/PD-L1 or CTLA-4 pathway blockade.
- Histological features of cellular rejection include T-cell infiltration and inflammation of the portal, bile duct, and venous endothelial systems.
- All confirmed cases of graft rejection had component of TCMR, with some AMR




Choudhary et al. J. Cli. Exp. Hepatology. 2017

# CPI in liver transplant recipients

## Toxicity: Markers of CPI safety

**Table 1. Summary of case reports of use of immune checkpoint inhibitors in the post liver transplant setting**

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# CPI in liver transplant recipients

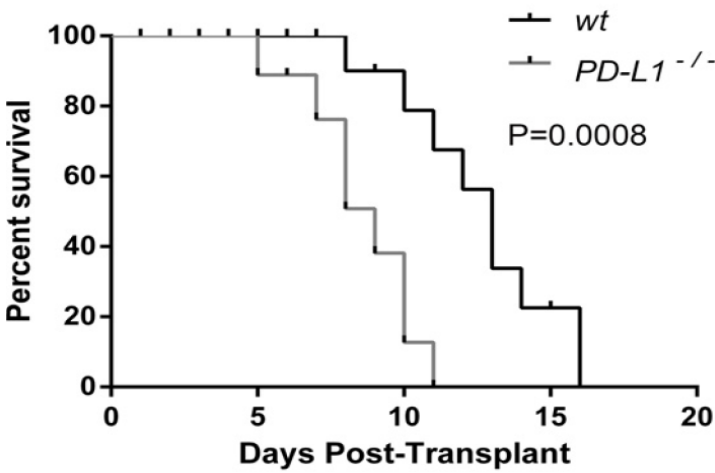
## Toxicity: Markers of CPI safety

PLOS | ONE

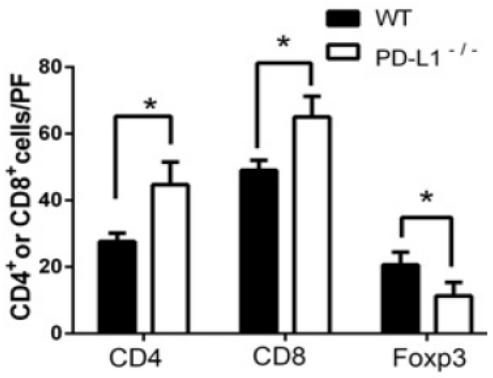
RESEARCH ARTICLE

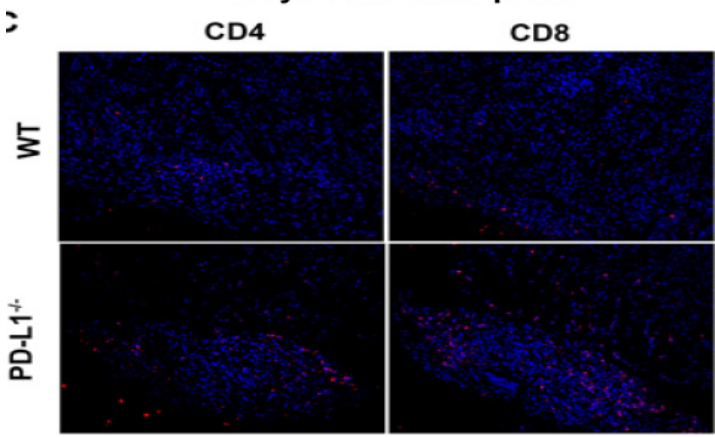
### PD-L1 Deficiency within Islets Reduces Allograft Survival in Mice

Dongxia Ma[1], Wu Duan[2], Yakun Li[1], Zhimin Wang[1], Shanglin Li[1], Nianqiao Gong[1], Gang Chen[1], Zhishui Chen[1], Chidan Wan[3]*, Jun Yang[1]*




- PD-L1 deficiency within islets does not affect islet function.
- However, islet PD-L1 deficiency increased allograft rejection
  - Associated with enhanced inflammatory cell infiltration
  - Recipient T-cell alloreactivity.

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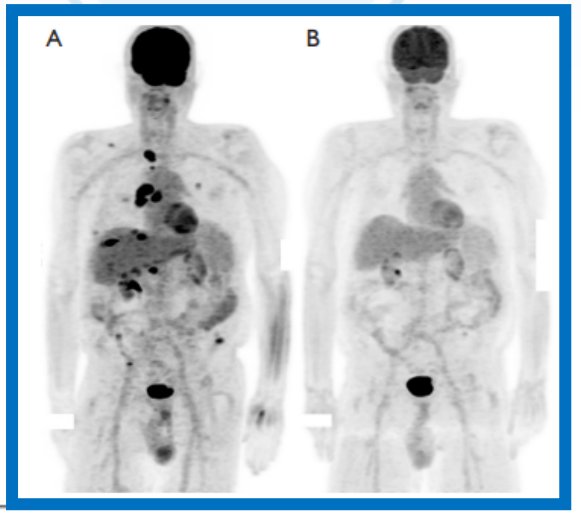
# CPI in liver transplant recipients

## Toxicity: Markers of CPI safety




**Pilot evaluation of PD-1 inhibition in metastatic cancer patients with a history of liver transplantation: the Mayo Clinic experience**

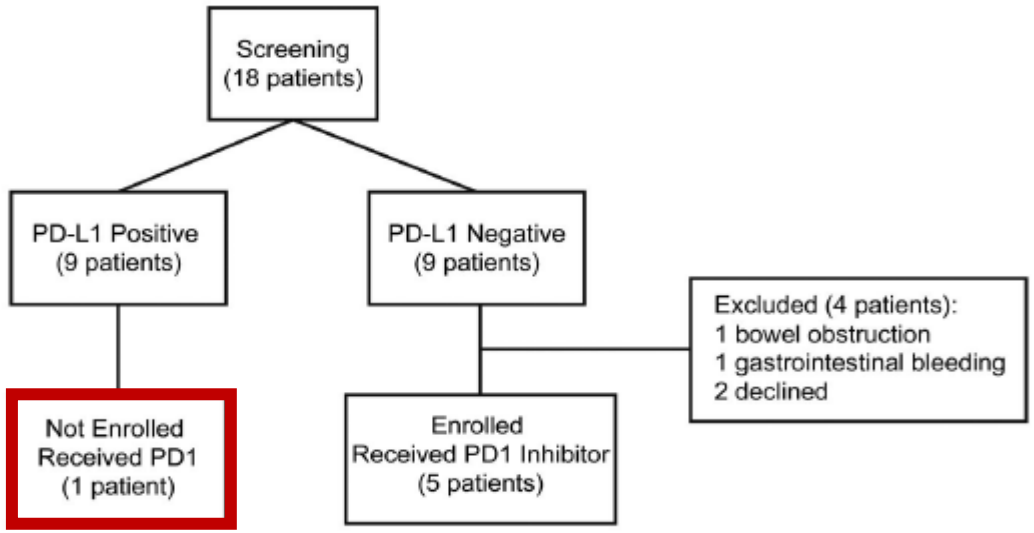
Thomas T. DeLeon[1], Marcela A. Salomao[2], Bashar A. Aqel[3], Mohamad B. Sonbol[1], Raquel T. Yokoda[1], Ahmad H. Ali[3], Adyr A. Moss[4], Amit K. Mathur[4], David M. Chascsa[3], Jorge Rakela[3], Alan H. Bryce[1], Mitesh J. Borad[1,5,6]

| ID | Immunotherapy | Line of therapy | RECISTv1.1 response | DOT (months) | PFS (months) | OS (months) | Reason for stopping therapy | Graft rejection | Allograft PD-L1 staining | PD-L1 tumor staining | TILs | Prior sorafenib therapy | Immunosuppressive agent(s) used |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Nivolumab | 3 | PD | 1.2 | 2.2 | 1.2 | Progression | No | – | 10% | 10% | Yes | Tacrolimus |
| 2 | Pembrolizumab | 2 | CR | 9.5 | 21.1* | 21.1 | Complete response | No | 0% | 5% | 50% | No | Everolimus, mycophenolate mofetil |
| 3 | Nivolumab | 4 | PD | 1.1 | 0.7 | 1.1 | Progression | No | 0% | – | – | Yes | Mycophenolate mofetil, sirolimus |
| 4 | Nivolumab | 5 | PD | 1.3 | 1.3 | 1.3 | Progression | No | 0% | 0% | 5–10% | Yes | Tacrolimus |
| 5 | Nivolumab | 2 | – | 0.3 | – | 0.3 | Multi-organ failure | No | – | 0% | 10% | Yes | Tacrolimus |
| 6 | Nivolumab | 2 | – | 0.9 | – | 0.9 | Graft rejection | Yes | 30% | 0% | – | Yes | Sirolimus |
| 7 | Pembrolizumab | 2 | – | 0.7 | – | 0.7 | Graft rejection | Yes | 25% | – | – | No | Mycophenolate mofetil, prednisone |
| Median | N/A | 2 | N/A | 1.1 | 1.8 | 1.1 | N/A | N/A | 0% | 0% | 10% | N/A | N/A |

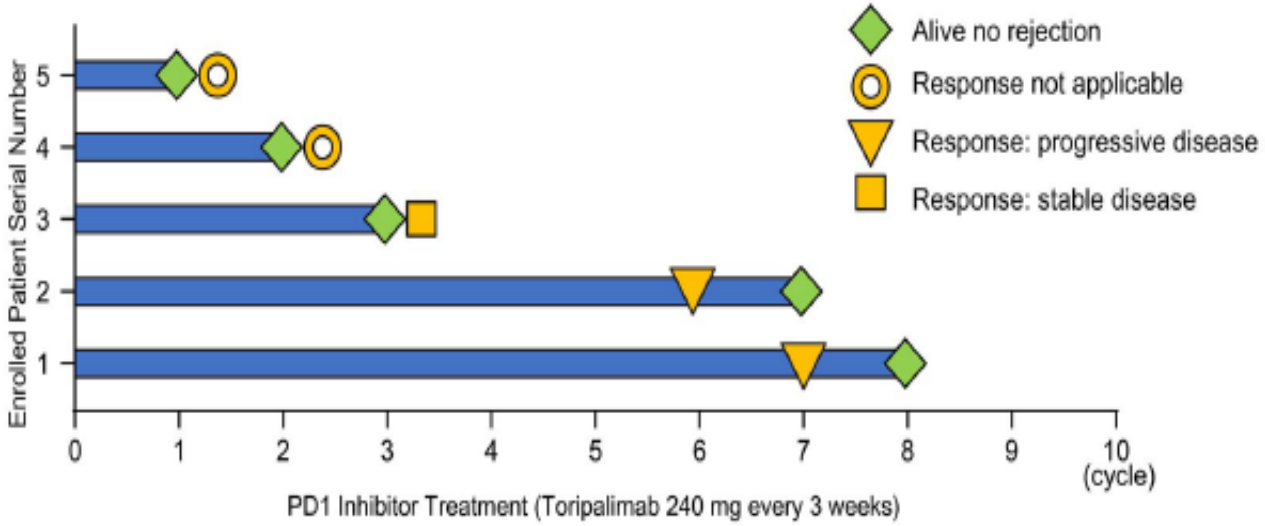
*, denotes ongoing response; –, denotes that data not available for evaluation. ID, patient identification; RECIST, response evaluation criteria in solid tumors; DOT, duration of therapy; PFS, progression free survival; OS, overall survival; PD-L1, programmed death ligand-1; TIL, tumor infiltrating lymphocyte.

# CPI in liver transplant recipients

## Toxicity: Markers of CPI safety




- Among all the screened patients, 50% of patients had positive PD-L1 expression in the graft
- Treated with toripalimab (anti-PD-1) 240 mg of every 3 weeks.




- All patients (100%) with NO graft rejection.
- One patient with positive PD-L1 (not eligible) treated with toripalimab (off protocol).
  - Developed graft rejection 7 days after Rx
  - Died of liver failure 146 days after Rx.

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Shi et al Liver Transpl antation. 2021

# CPI in liver transplant recipients

**Toxicity: Markers of CPI safety:**

- The lack of acute rejection during CPI treatment reflects a predominant role of PD-1 in determining graft tolerance.
- Positive PD-L1 staining in biopsy suggest higher risk of acute rejection. Can initiation of CTLA-1 blocking agents be considered?
- Emerging thought on using PD-L1 expression as a marker of safety for anti-PD1 therapy in transplant patients. Not a guideline yet.

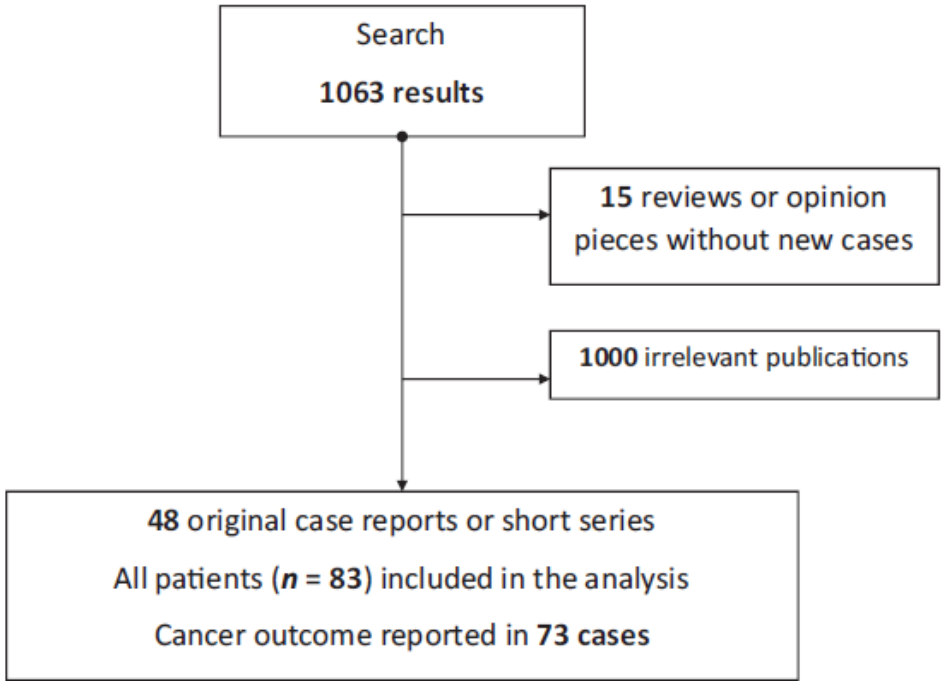



Shi et al Liver Transpl antation. 2021

# CPI in liver transplant recipients

**Toxicity: FACTS**

- Systematic review of 83 patients




| | |
|---|---|
| Patients experiencing allograft rejection—n (%) | 33 (39.8) |
| Kidney recipients | 23/53 (43.4) |
| Liver recipients | 9/24 (37.5) |
| Heart recipients | 1/6 (16.7) |
| Time (weeks) to graft rejection from first CPI use—mean (SD) | 5.6 (7.0) |
| Kidney recipients | 7.3 (7.9) |
| Liver recipients | 2.1 (1.0) |
| Heart recipients | 1 (*NA*) |
| Rejection histology—n (%) | n = 18 |
| T cell–mediated rejection | 11 (61.1) |
| Mixed T cell– and antibody-mediated rejection | 7 (38.9) |
| Positive C4d staining | 4/7 (57.1) |

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# CPI in liver transplant recipients

## Toxicity: Management

- Systematic review of 83 patients

| Immunosuppressive regimen at first CPI use—n (%) | |
|---|---|
| Corticosteroids | 50 (60.2) |
| Calcineurin inhibitors | 34 (41.0) |
| mTOR inhibitors | 30 (36.1) |
| Antimetabolites | 21 (25.3) |
| At least 1 drug other than corticosteroids | 64 (77.1) |
| Modification of immunosuppressive regimen before CPI use | 36/55 (65.5) |

| Overall rejection outcomes—n (%) | n = 31 |
|---|---|
| Complete recovery | 2 (6.5) |
| Partial recovery | 7 (22.6) |
| End-stage organ failure | 22 (71.0) |

| Rejection treatment—n (%) | n = 28 |
|---|---|
| Intravenous corticosteroids | 23 (82.1) |
| Oral corticosteroids | 7 (25.0) |
| Calcineurin inhibitors | 7 (25.0) |
| mTOR inhibitors | 4 (14.3) |
| Antimetabolites | 4 (14.3) |
| Intravenous immunoglobulins | 2 (7.1) |
| Antithymocyte globulins | 1 (3.6) |
| Plasma exchange | 1 (3.6) |
| No treatment | 3 (10.7) |

| End-stage organ failure after rejection—n (%) | |
|---|---|
| In kidney recipients | 16/22 (72.7) |
| In liver recipients | 6/8 (75.0) |
| In heart recipients | 0/1 (0.0) |
| Following anti–PD-1/PD-L1 therapy | 17/24 (70.8) |
| Following anti–CTLA-4 therapy | 2/4 (50.0) |
| Following combination therapy | 3/3 (100.0) |

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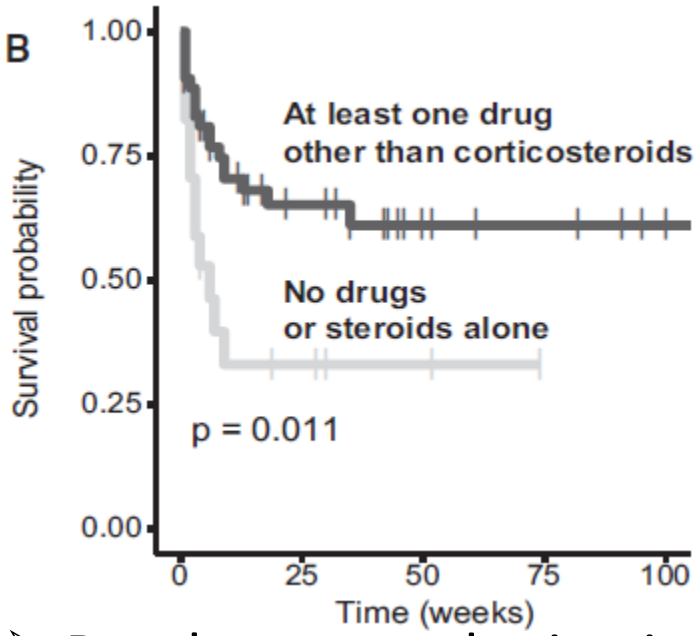
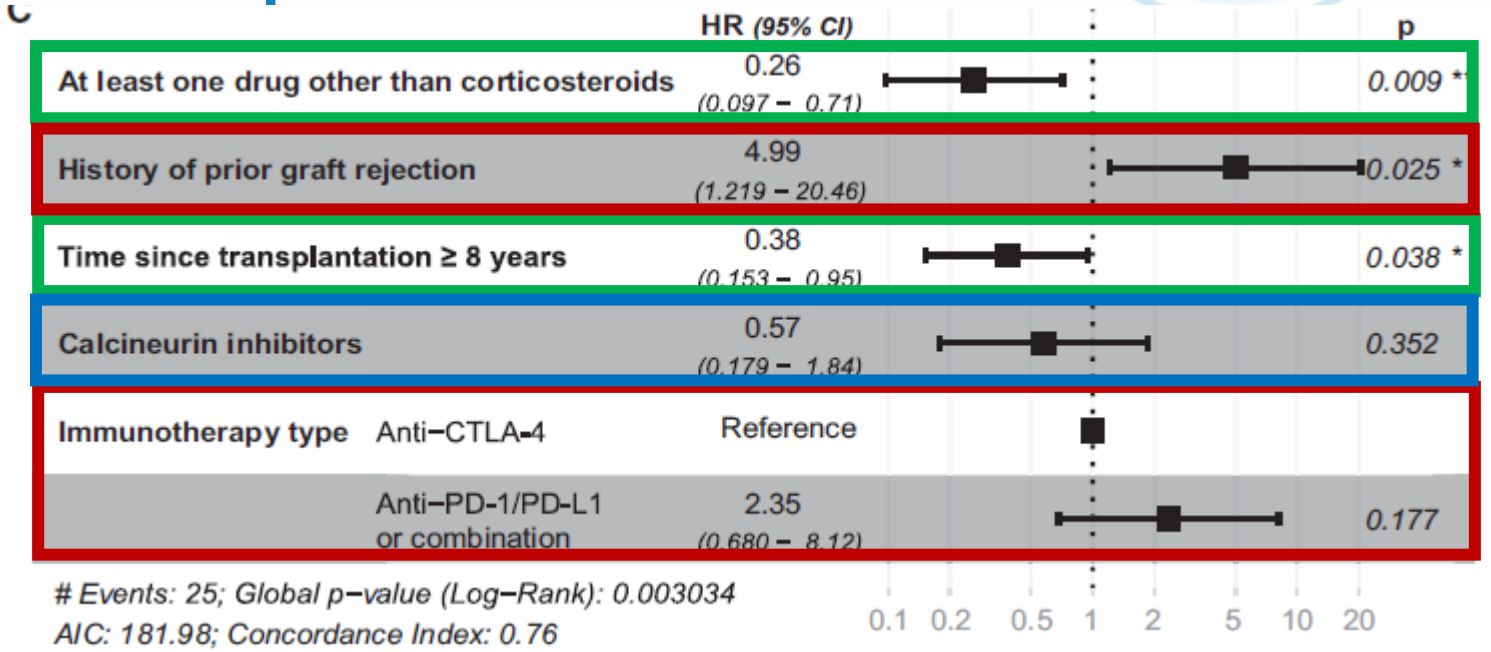
# CPI in liver transplant recipients

## Toxicity: Management




- Death-censored rejection-free survival higher in patients received at least 1 drug other than corticosteroids

- Factors associated with a lower risk of rejection
- Rejection is higher with prior allograft rejection
- Rejection is higher with anti–PD-1 vs CTLA-4(not significant)
- Rejection rates is similar across CPI and IS types.
- No association between allograft rejection and other irAEs.

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# CPI in liver transplant candidate

- Use of CPI in the treatment of liver cancer have evolved rapidly
  - Become the preferred first line of therapy (atezolizumab plus bevacizumab)
  - Durvalumab/tremelimumab (phase 3, HIMALAYA trial) increase OS, pending FDA approval
  - Increase interest in using CPI as bridging/neoadjuvant therapy to liver transplant
  - Is it safe to use CPI before LT?

# CPI in liver transplant candidate

- The clinical outcome of patients receiving immunotherapy before transplant remains unknown.

- Between 2017 and 2020, 9 patients with HCC were successfully transplanted after receiving nivolumab as neoadjuvant/bridging therapy before LT.
  - One transplant (11%) was from a living donor.
  - Nivolumab 240 mg given every 2 weeks.
  - Eight (89%) patients received their last dose within 4 weeks of transplant.




Tabrizian P. Am J Transplant. 2021.

# CPI in liver transplant candidate

- Median follow-up of 16 months post-transplant:
  - ✓ No severe allograft rejections, tumor recurrences, or deaths occurred.
  - ✓ One patient developed mild acute rejection secondary to low tacrolimus level (<6 ng/ml) and responded rapidly to increased dosage.
  - ✓ Explant pathology revealed near complete (>90%) tumor necrosis in one-third of the cases.




Tabrizian P. Am J Transplant. 2021.

# CPI in liver transplant candidate



## Atezolizumab and Bevacizumab Pre-Liver Transplantation for Patients With Hepatocellular Carcinoma Beyond Milan Criteria



ClinicalTrials.gov Identifier: NCT05185505

Recruitment Status ⓘ : Not yet recruiting
First Posted ⓘ : January 11, 2022
Last Update Posted ⓘ : January 11, 2022

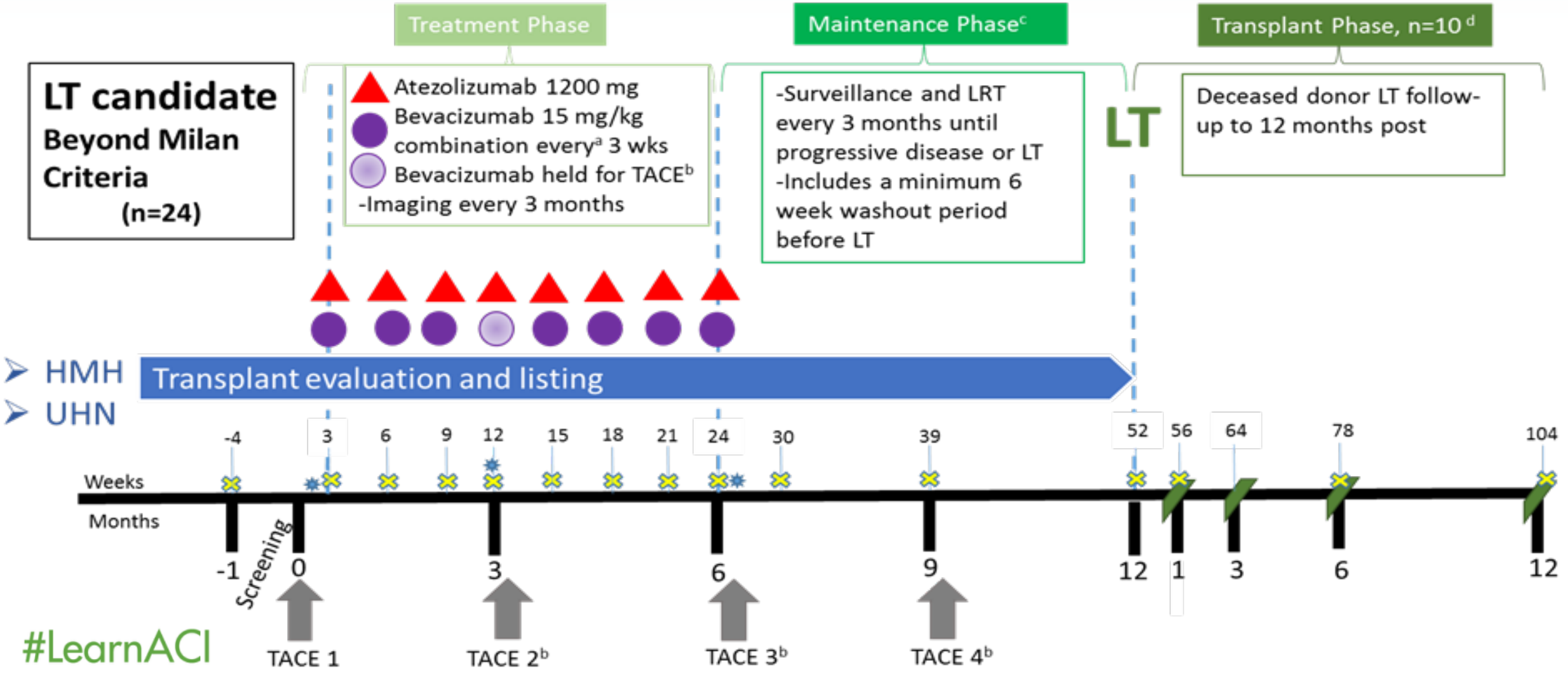
See Contacts and Locations

**Sponsor:**
The Methodist Hospital Research Institute

**Collaborator:**
Genentech, Inc.

**Information provided by (Responsible Party):**
Maen **Abdelrahim**, MD, PhD, Pharm.B, The Methodist Hospital Research Institute

# CPI in liver transplant candidate

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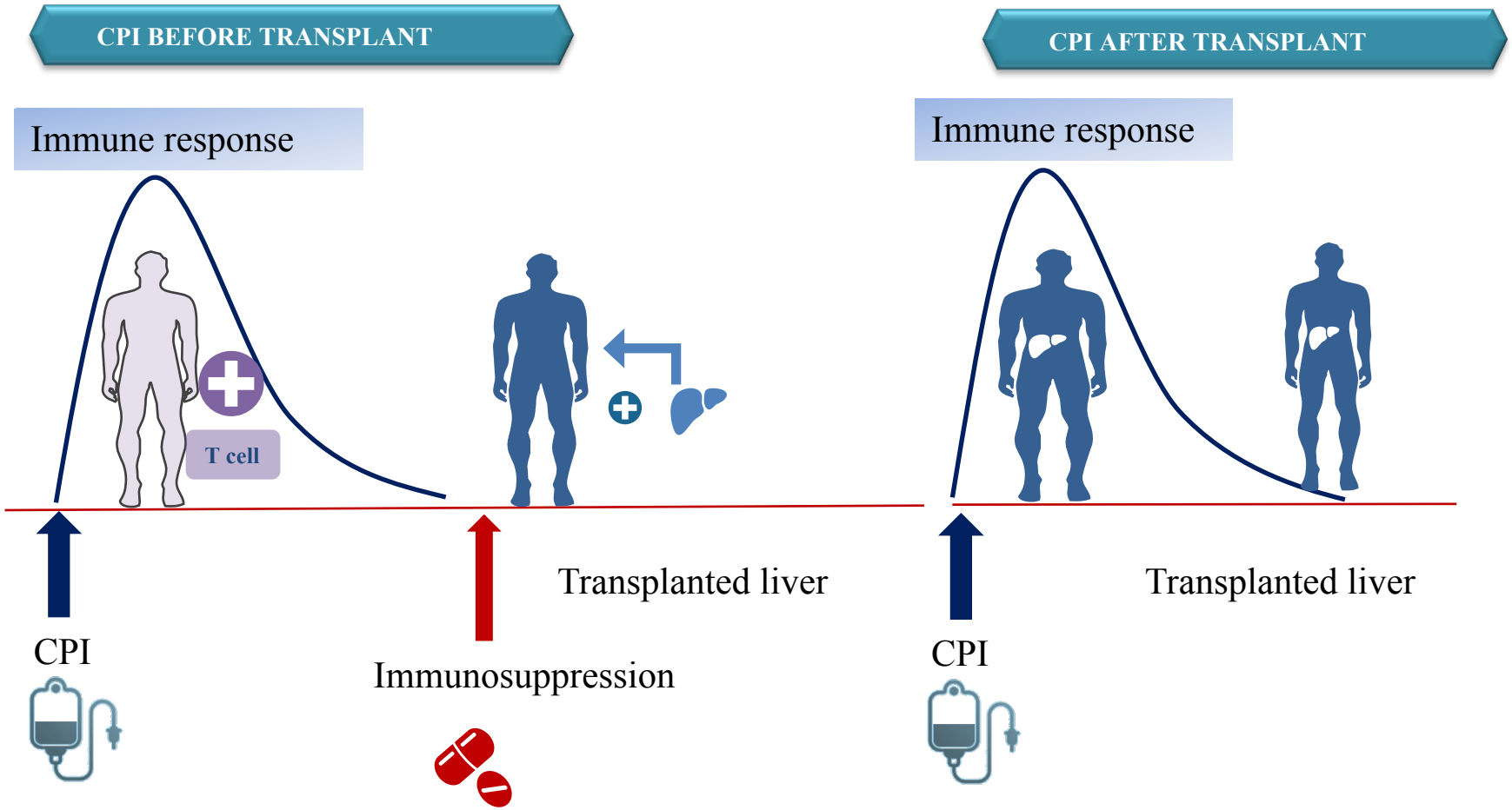
# CPI in liver transplant candidate







Abdelrahim, M et al. Cancers. 2021

# CPI in liver transplant recipients

**Conclusion:**

- The absolute risk of graft rejection with CPI post-transplant is better predicted with strict patient selection criteria and randomized controlled trials.
- PD-L1 expression as a safety marker for CPI therapy in transplant patients is evolving.
- Factors associated with lower risk of rejection is the use of at least one drug other than corticosteroids.
- Use of immunotherapy in liver transplant recipients is promising, prospective clinical trial is ongoing.

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