Urelumab (anti-CD137 agonist) in combination with vaccine and nivolumab treatments is safe and associated with pathologic response as neoadjuvant and adjuvant therapy for resectable pancreatic cancer

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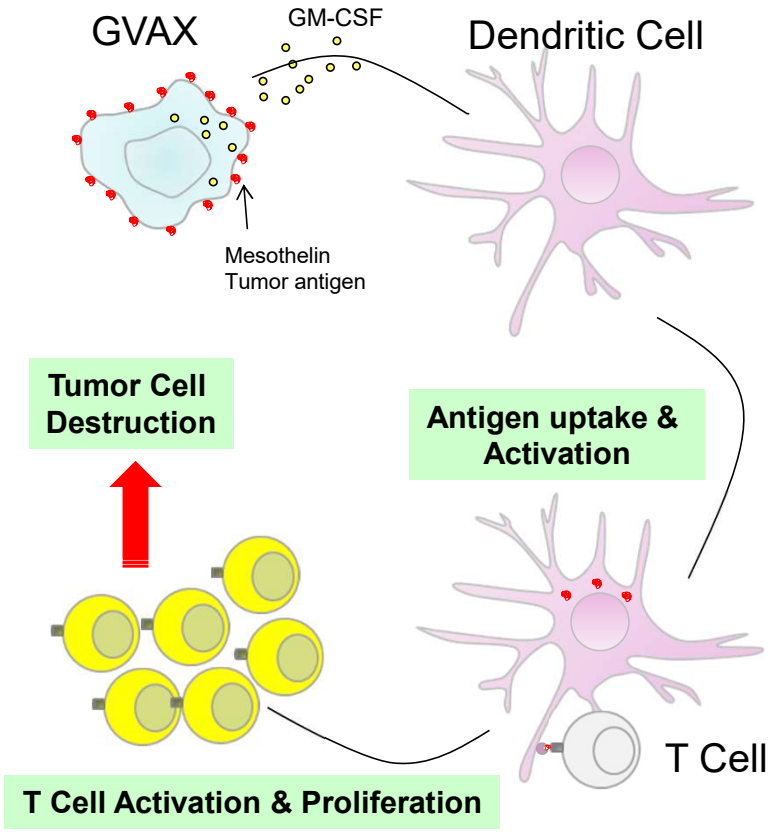
- Aduro: Under a licensing agreement between Aduro BioTech, Inc. and the Johns Hopkins University, the University and investigators are entitled to milestone payments and royalty on sales of the vaccine product.

Can We Convert the Pancreatic Cancer TME from a "Cold" One to a "Hot" One by "Fueling" with T Cells?



- Allogeneic pancreatic cancer cell vaccine expressing GM-CSF
- Off-the-shelf product produced at JHU GMP
- Excellent safety profile
- Limited efficacy as a single agent

Jaffee et al. JCO 2001
Laheru et al. Ann Surg. 2011

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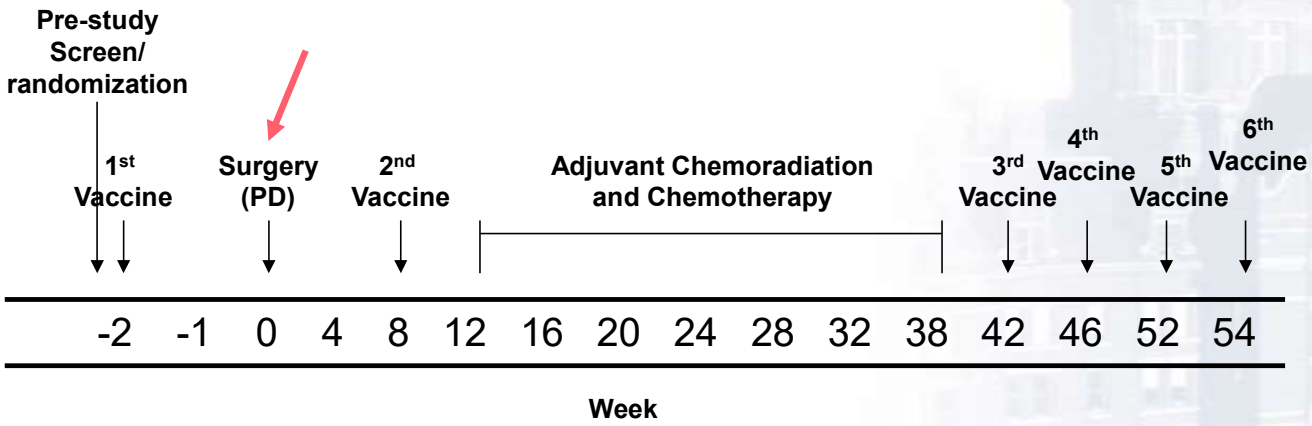
A Prototype Window of Opportunity Neoadjuvant Pancreatic Ductal Adenocarcinoma (PDAC) Vaccine Clinical Trial



Lutz,..Laheru, Jaffee, Zheng et al. Cancer Immunology Research 2014

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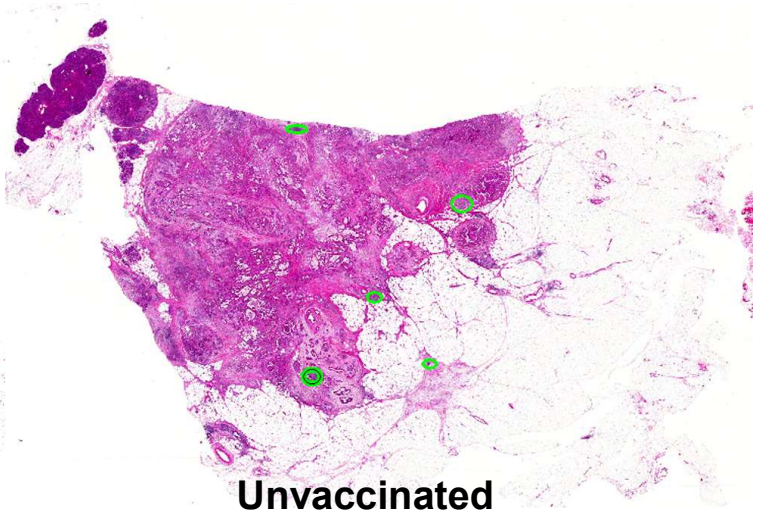
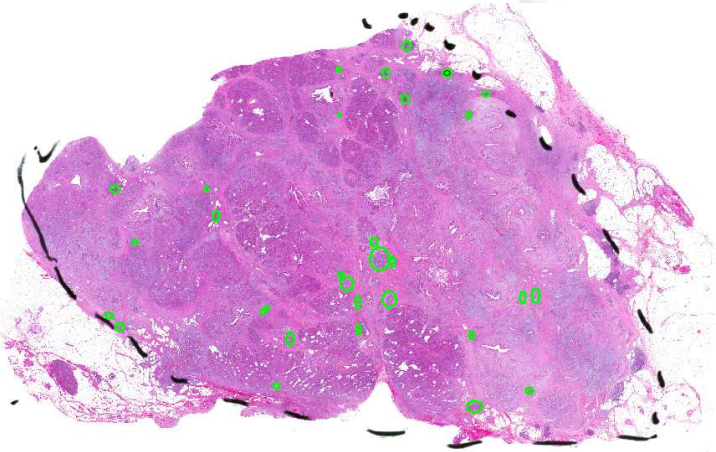
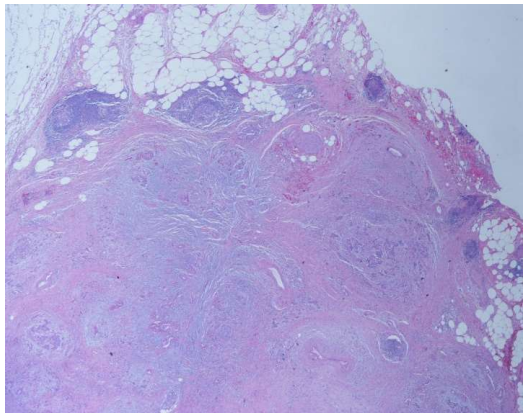
Vaccines are able to induce intratumor lymphoid aggregates



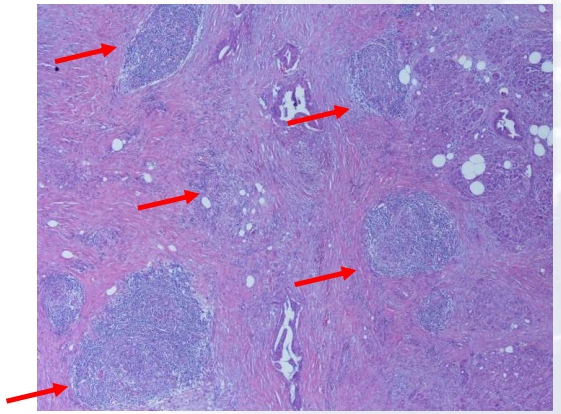
Unvaccinated



Vaccinated



Peri-tumoral



Intratumoral

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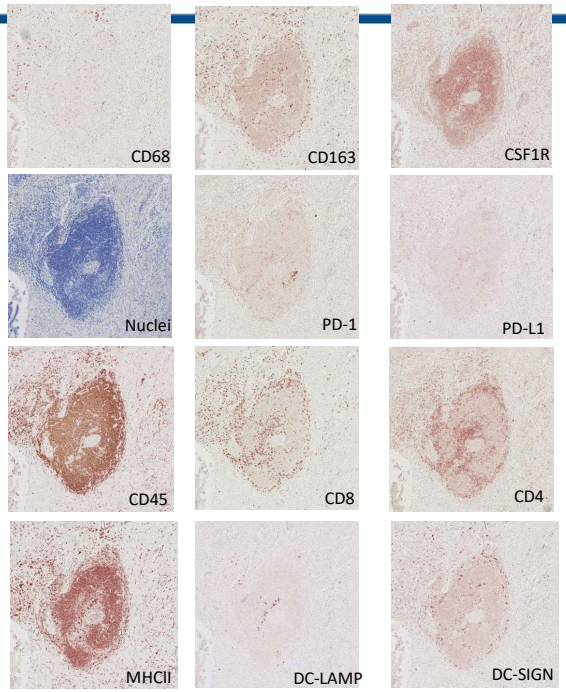
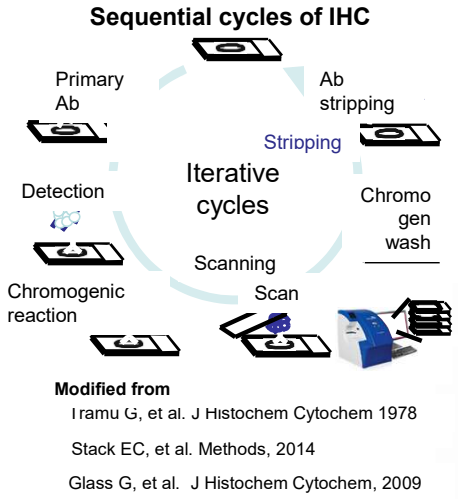
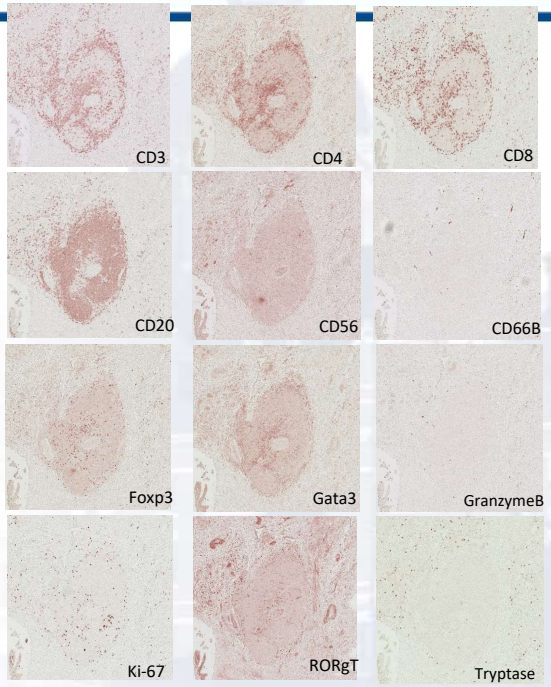
Sequential Multiplex Immunohistochemistry of the Same Lymphoid Aggregates







CD68, PD1, PD-L1, CD163, DC-LAMP, DC-SIGN, TBET, MHCII,CD45,FOXP3, CD4, CD8. TBR2, CSF1R, EpCAM

Myeloid biomarker panel

CD68, PD-L1, GranzymeB, TBET, Gata3, CD3, CD56, CD20, Ki67, FOXP3, CD4, Tryptase, CD8, RORgT, EpCAM

Lymphoid biomarker panel

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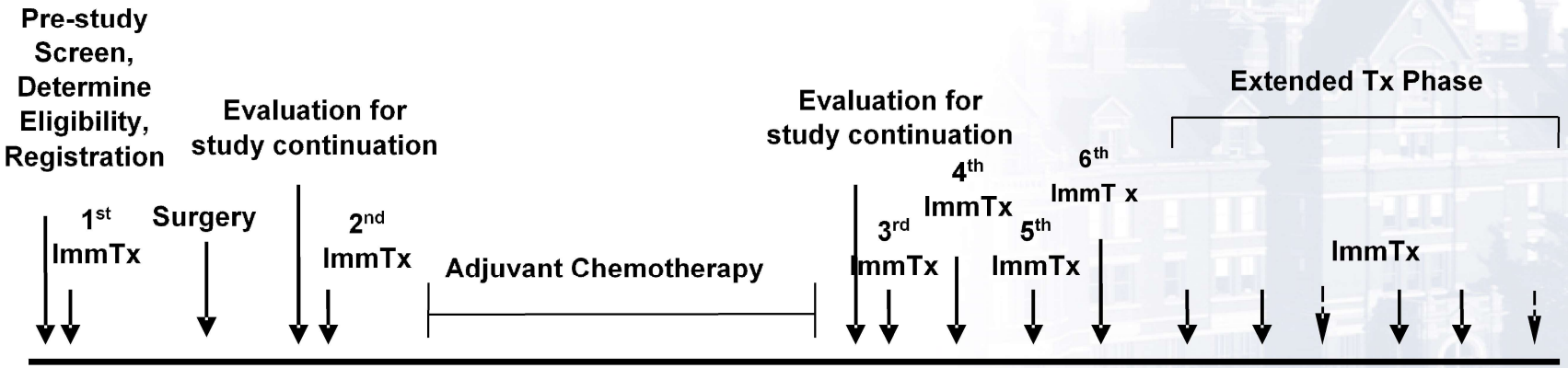
Tsujikawa, Zheng, Jaffee, Coussens, et al. Cell Reports, 2017.

Develop a Neoadjuvant Clinical Trial Platform to Further Delineate the Tumor Microenvironment

Imm Tx:

Arm A: GVAX

Arm B: GVAX+Nivolumab



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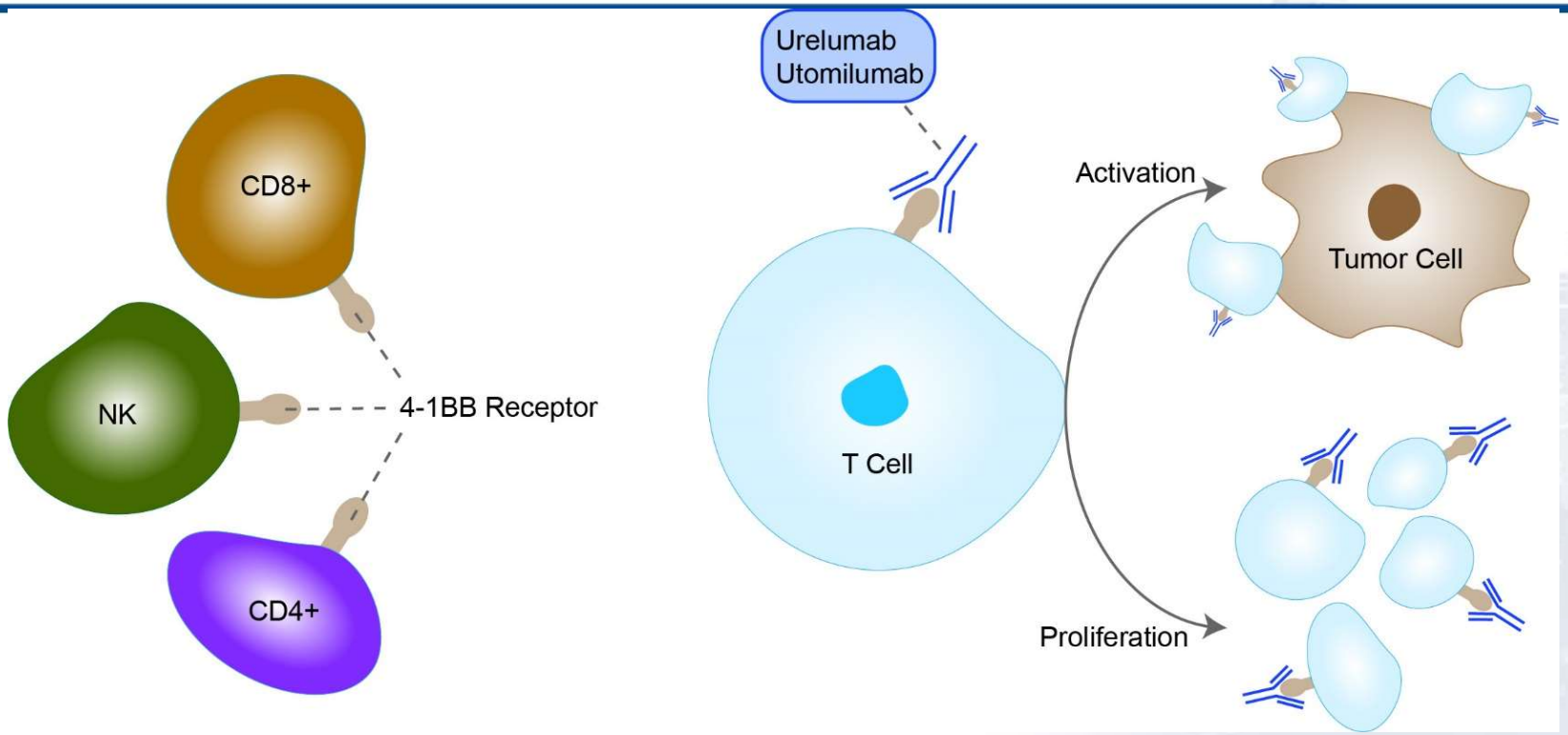
Urelumab is a Fully Human Anti-CD137 Agonist IgG4 Monoclonal Antibody



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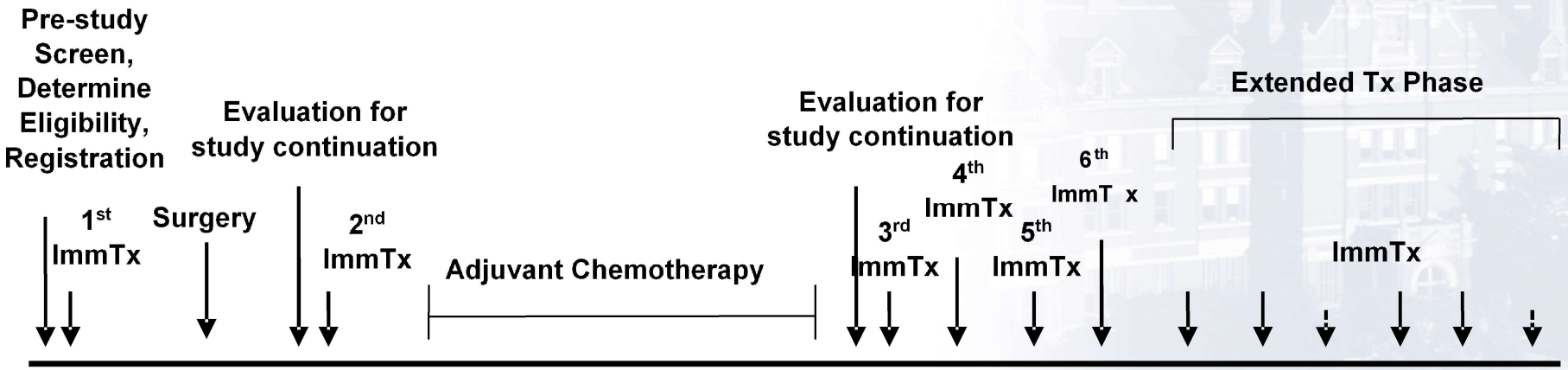
Add a New Arm with Anti-CD137 Antibody Urelumab to the Neoadjuvant Clinical Trial Platform

Imm Tx:

Arm A: GVAX

Arm B: GVAX+Nivolumab

Arm C: GVAX+Nivolumab+Urelumab



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Patient Eligibility

10 evaluable patients (if have R0/R1 resection)

- 18 years old or above
- Radiographic evidence of resectable pancreatic ductal adenocarcinoma (PDAC)
- No prior anti-cancer treatment
- No active autoimmune disease
- Adequate hematologic, renal and hepatic functions.

Study Treatments

- **Dose**
  - Nivolumab 480 mg iv on Day 0
  - Urelumab 8 mg iv on Day 0
  - Cytoxan 200 mg/m2 iv on Day 0
  - GVAX vaccine intradermal

- **Schedule**
  - 2 weeks prior to surgery
  - 6-10 weeks following surgery
  - Following standard of care adjuvant chemotherapy, every 4 weeks for 4 cycles

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Objectives

Primary Objectives

- Evaluate changes in numbers of tumor infiltrating $CD137^{+}CD8^{+}$ T cells.

Secondary objectives

To assess

- Safety
- Overall survival
- Disease free survival
- Other immune parameters.

Results

- Between 2/19-8/20, 10 evaluable patients were enrolled and underwent R0 resection
- All received at least two cycles of study treatments
- No delay of surgery due to the toxicity of study treatments
- Three patients demonstrated CAP grade 2 (moderate) pathologic response
- As of 9/22/20, Nine patients remain disease free after a median follow up of 12 months.

Safety

Adverse Events in Arm C	Grade	N (%)
Abdominal pain	2	1 (10%)
Anorexia	2	1 (10%)
Diarrhea	2	1 (10%)
Nausea	1/2	7 (70%)
Vomiting	1	2 (20%)
Fatigue	1	4 (40%)
Flu-like symptoms (fever, chills, myalgia)	1	2 (20%)
Arthritis	1	1 (10%)
Thyroiditis	2	1 (10%)
Pruritus	2	3 (30%)
Rash	3	2 (20%)
Periorbital edema (w/ pruritus around eyes)	1/2	1 (10%)
Peripheral sensory neuropathy	2	1 (10%)
LFTs increased (ALT, AST, Alk Phos)	2	1 (10%)

- Nausea is the most common adverse event attributed to urelumab.
- 1 patient demonstrated grade 1 arthritis;
- 1 patient demonstrated self-limited, transient grade 2 elevated LFTs;
- 1 patient developed grade 3 rashes, which responded quickly to oral steroid and did not recur after re-dosing.
- Other adverse events and perioperative complication were observed in a type, frequency and degree similar to other treatment arms.

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