# Autoimmune Pancreatitis: Recent Advances

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# Disclosures

- Nestle Health Science, Scientific Advisory Board

- This talk will include discussion of off-label medications and drugs under study

# Objectives

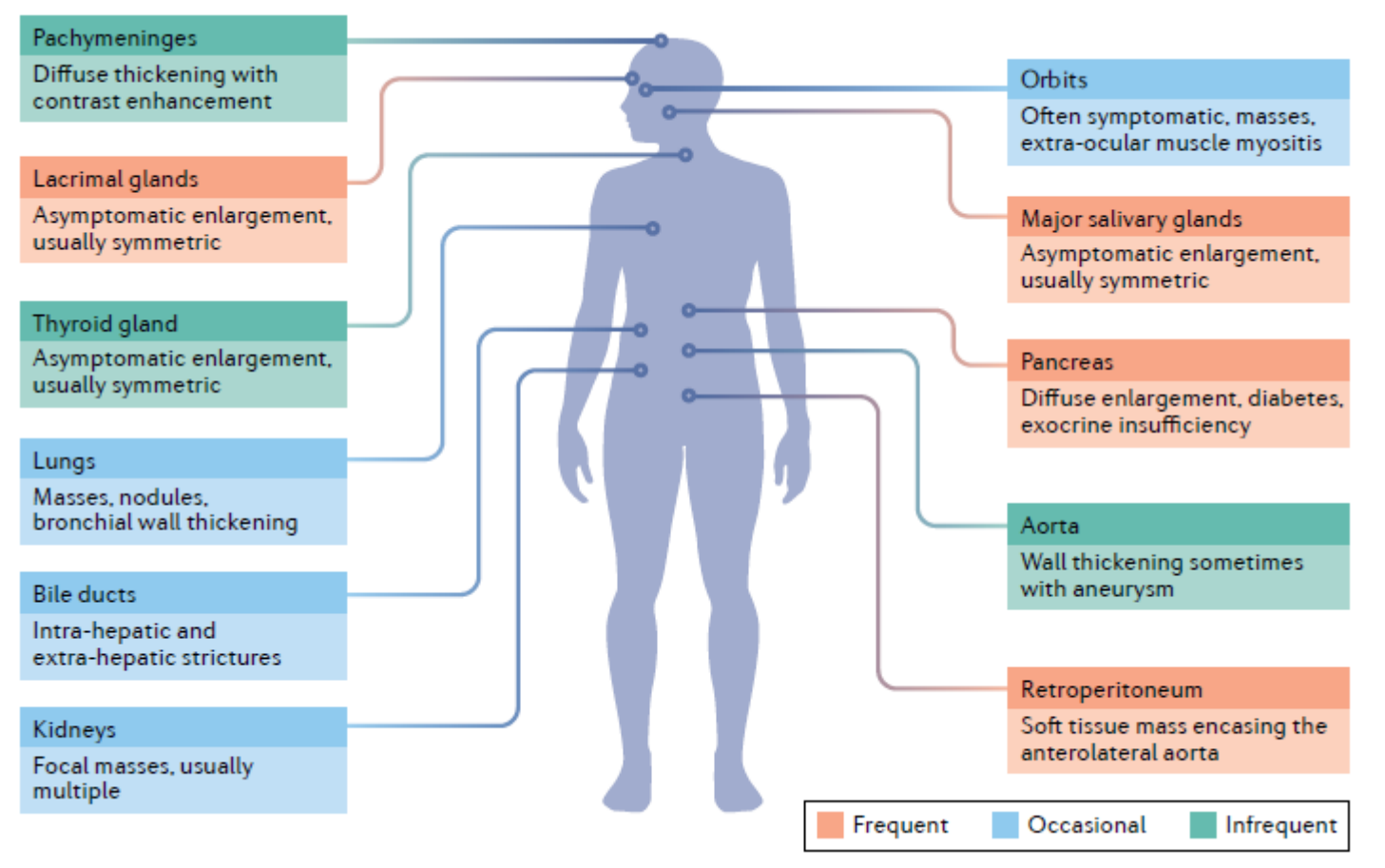
- Provide an overview of the various clinical subtypes of autoimmune pancreatitis
- Review the pathophysiology of IgG4-RD
- Highlight new management strategies on the horizon for Type I AIP

# Type 1 AIP and IDCP (Type 2)

| | Type 1 AIP | IDCP (Type 2) | p-value |
|---|---|---|---|
| Age (years) | 61.8 ± 15.3 | 47.7 ± 18.8 | P<0.0001 |
| Gender (Male %) | 77% | 53.5% | P=0.48 |
| Imaging findings | | | P=0.049 |
| Diffuse swelling | 30 (40%) | 3 (16%) | |
| Other features | 48 (60%) | 16 (84%) | |
| Elevated IgG4 level (>140 mg/dL) | 59 (80%) | 8 (17%) | P=0.004 |
| Other organ Involvement | 47 (60%) | 0 | P<0.0001 |
| IBD Association | 6% | 16% | P=0.37 |
| Relapse rate | 47% | <10% | P<0.0001 |
| | | | |

Chari ST et al, Gastro 2010, 139: 140-8

# Type I AIP is a manifestation of IgG4-RD




- 10-11 organs are primarily affected
- 60% of patients present with irreversible organ damage
- IgG4-RD AIP induced DM, EPI and weight loss

Perugino et al, Nature Review Rheumatology 2020

# The HISORt Criteria

- Histology/immunostaining
- Imaging
- Serology
- Other organ involvement
- Response to steroid therapy
- Best developed for autoimmune pancreatitis and to a lesser extent for IgG4 associated cholangitis

Chari ST et al, Clin Gastroenterol Hepatol 2006

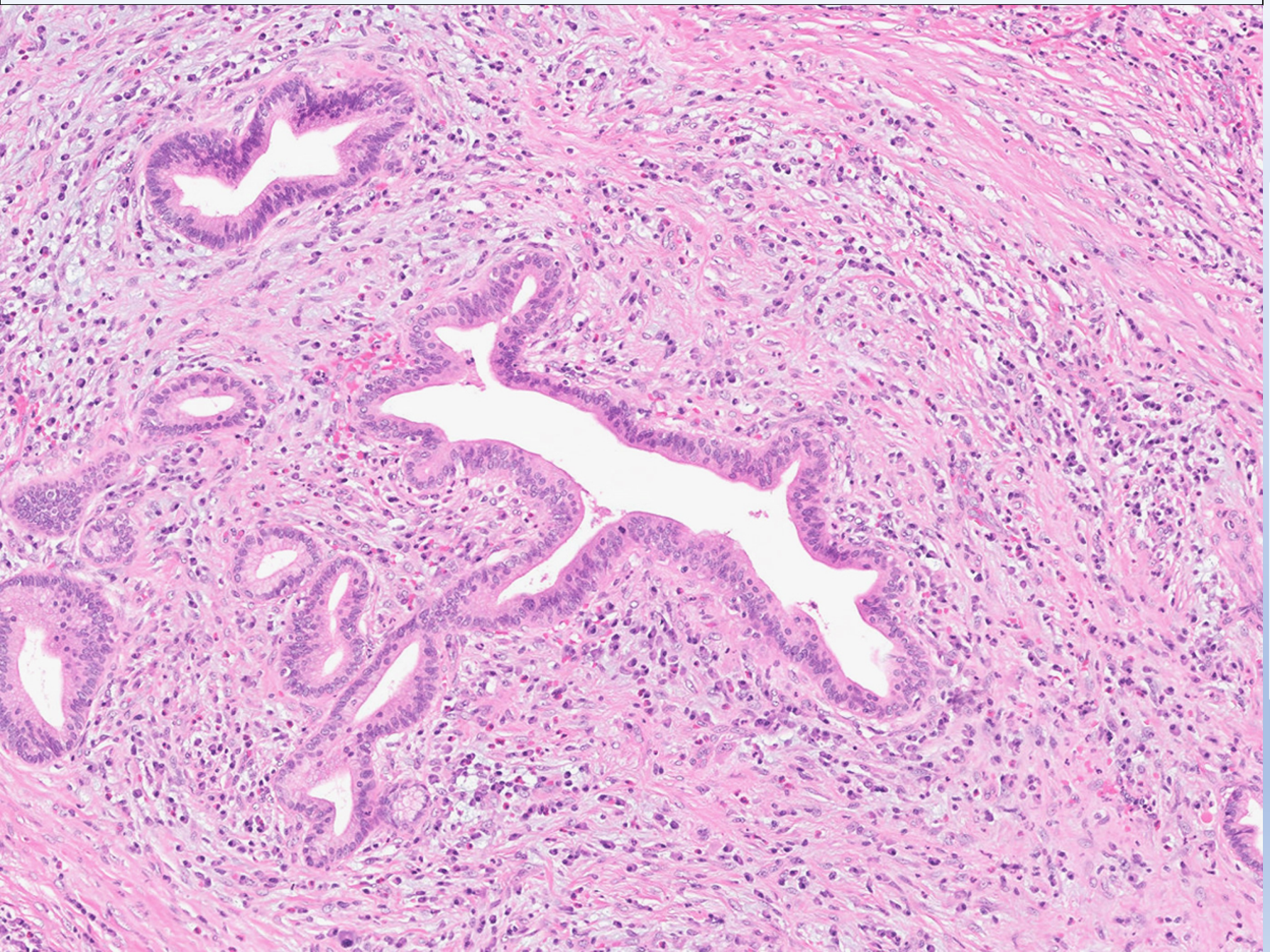
# AIP requires architecture for diagnosis

- EUS-FNB core required for diagnosis because architecture is needed
  - Yields adequate  specimen in 73% of cases
  - 22G needle associated with higher diagnostic yield; 19G does not increase diagnostic yield

- EUS-FNA **inadequate** for diagnosis
  - 30% PDAC have IgG4 in tissue
  - 30% PSC patients have IgG4 in tissue
  - 30% cholangiocarcinoma have IgG4 in tissue
  - Celiac disease >10 IgG4+ cells/hpf

Kanno, Gastrointest Endos 2016; Iwashita et al, Clin Gastroenterol Hepatol, 2012

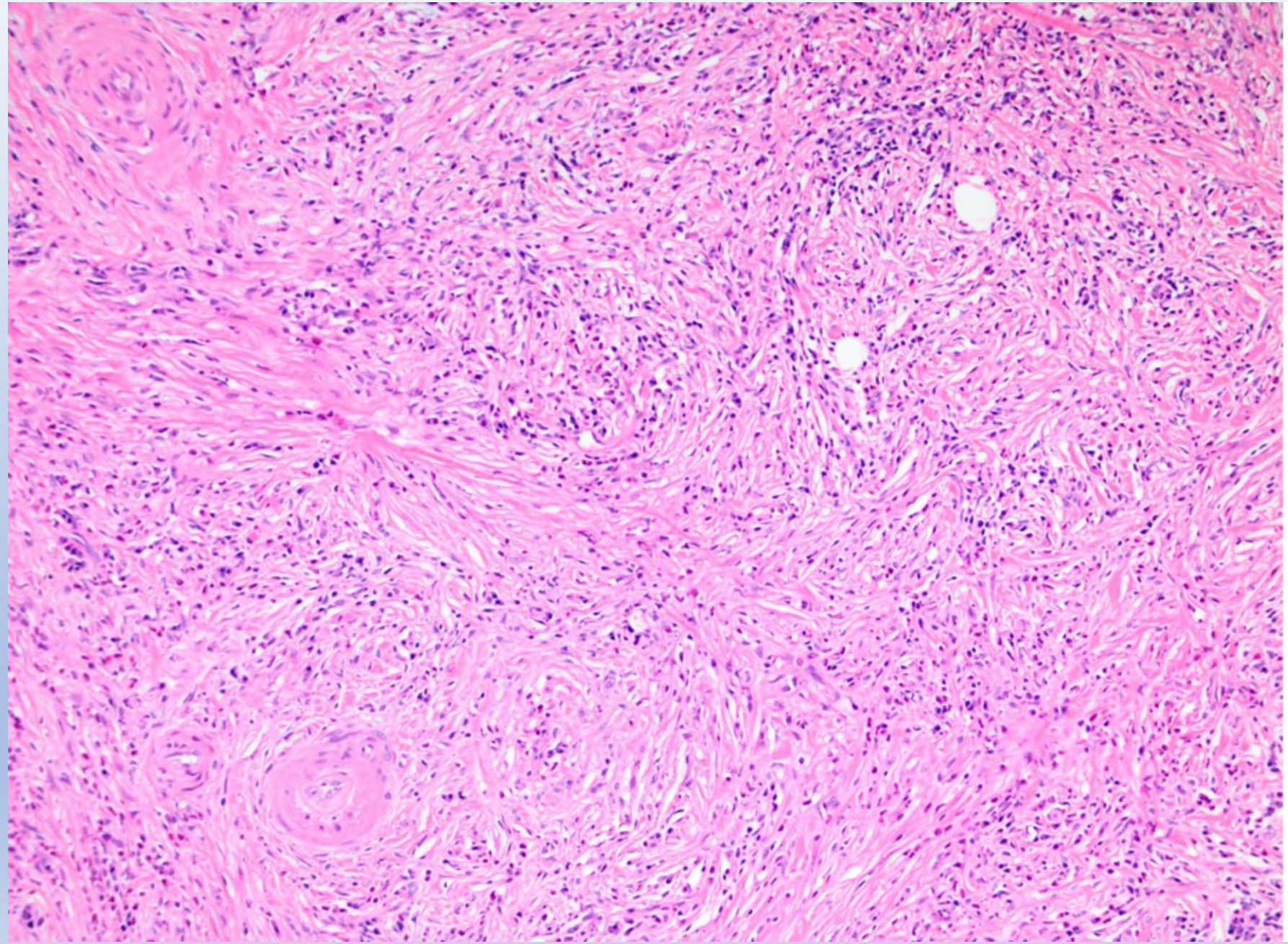
# **Type 1:** Lymphoplasmacytic sclerosing pancreatitis



Diffuse **lymphoplasmacytic infiltrate** centered around pancreatic ducts and ductules

Slides courtesy of Dr. Vikram Deshpande, MGH

# **Type 1:** Lymphoplasmacytic sclerosing pancreatitis



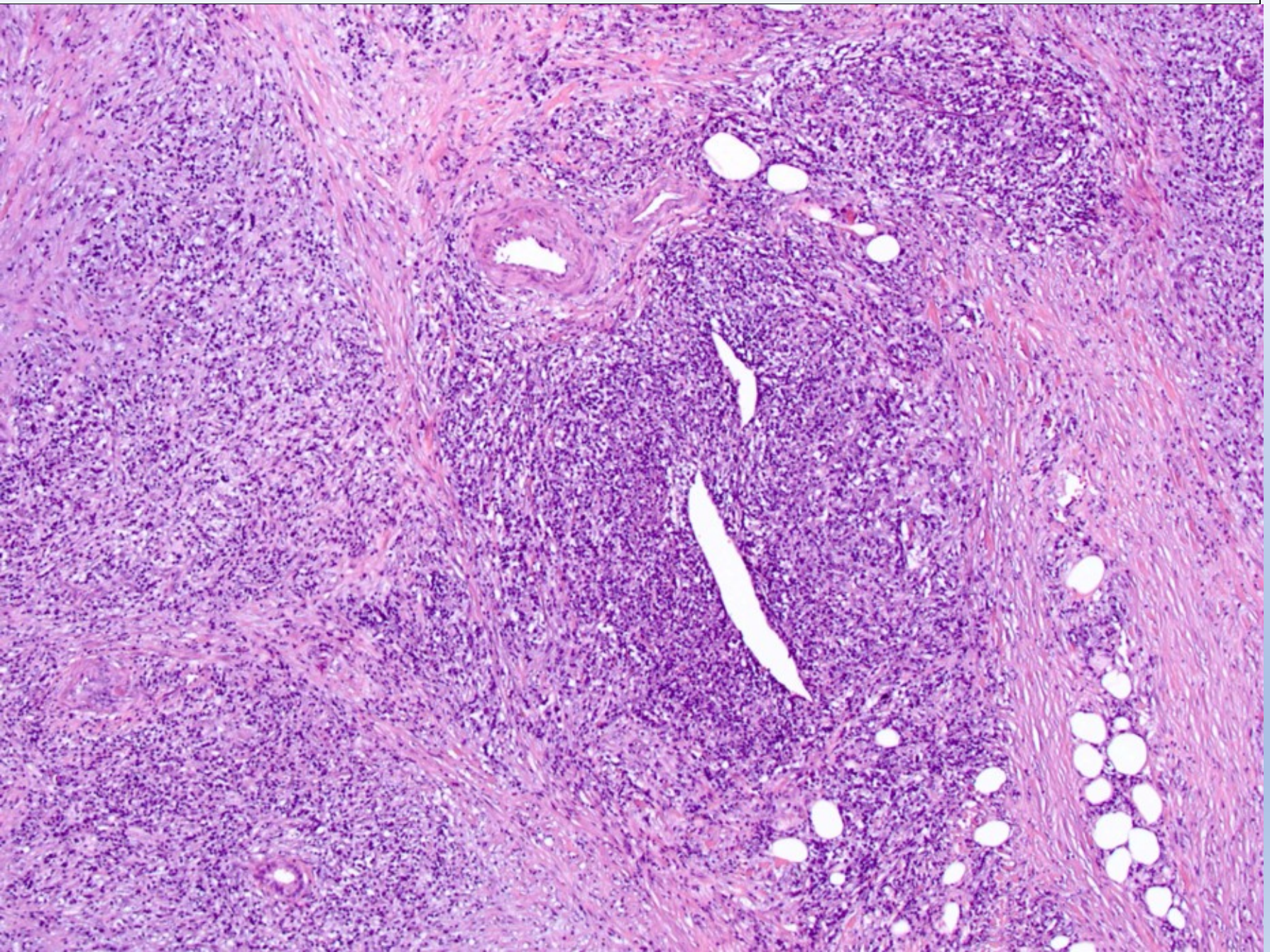
Diffuse fibrosis with **Storiform type** Fibrosis

*woven/cartwheel pattern not seen in other forms of chronic pancreatitis

*Persists after steroid treatment

Slides courtesy of Dr. Vikram Deshpande, MGH

# **Type 1:** Lymphoplasmacytic sclerosing pancreatitis

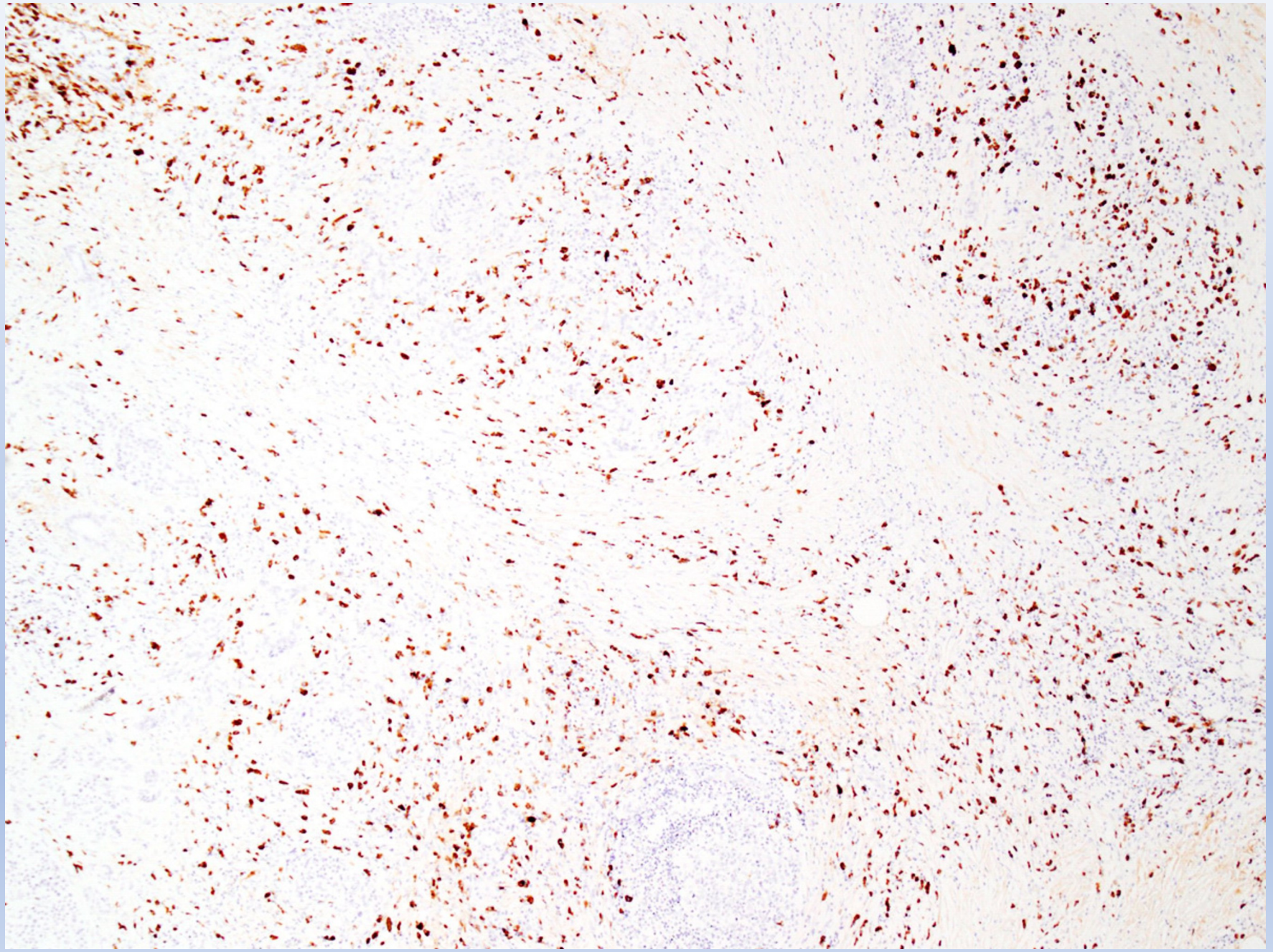


**Obliterative phlebitis**

*sparing of the arteries

Slides courtesy of Dr. Vikram Deshpande, MGH

# **Type 1:** Lymphoplasmacytic sclerosing pancreatitis



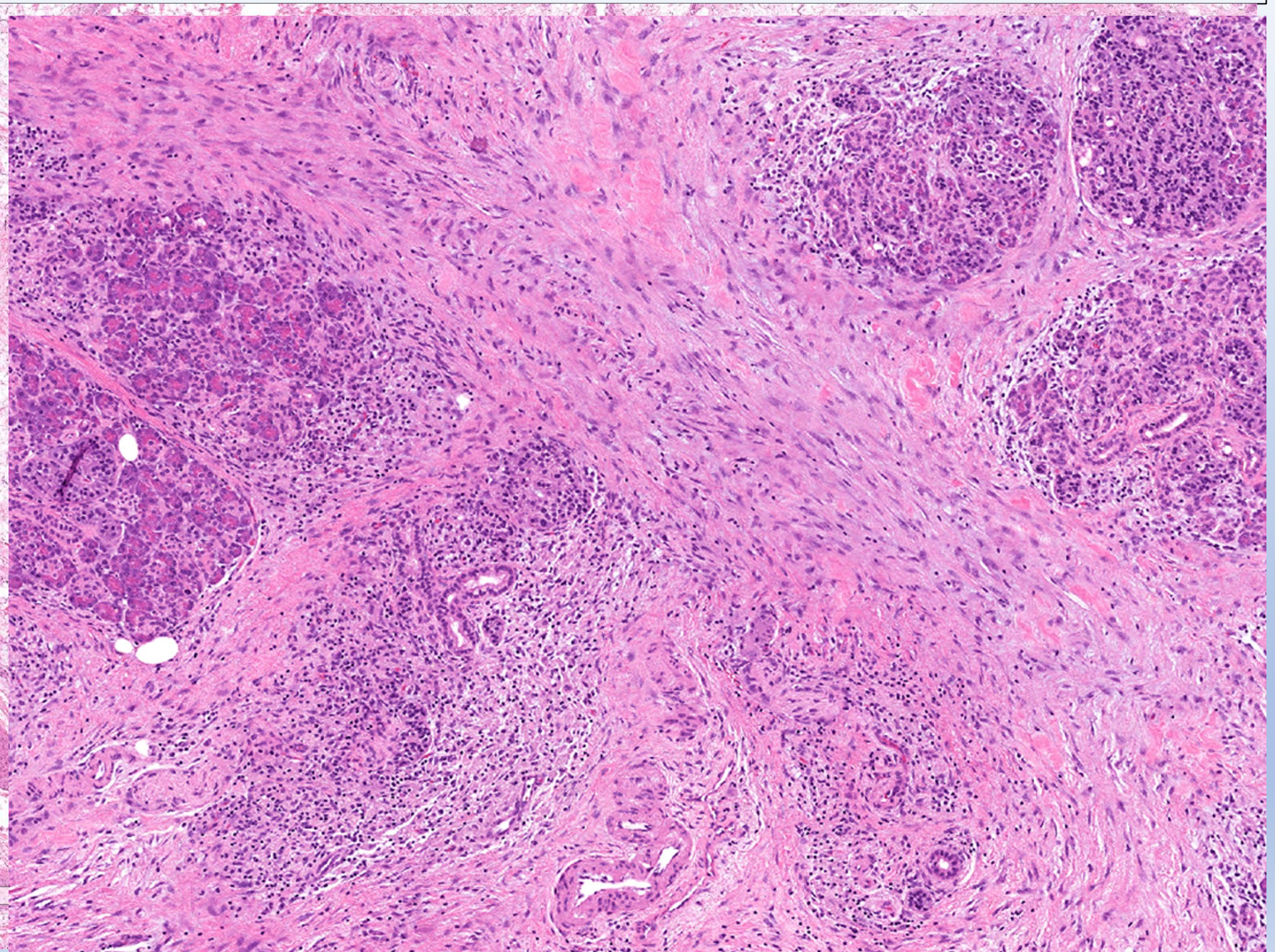
**IgG4+ plasma cells**

>10/hpf

IgG4:IgG >40%

Slides courtesy of Dr. Vikram Deshpande, MGH

# **Type 2:** Idiopathic duct-centric pancreatitis

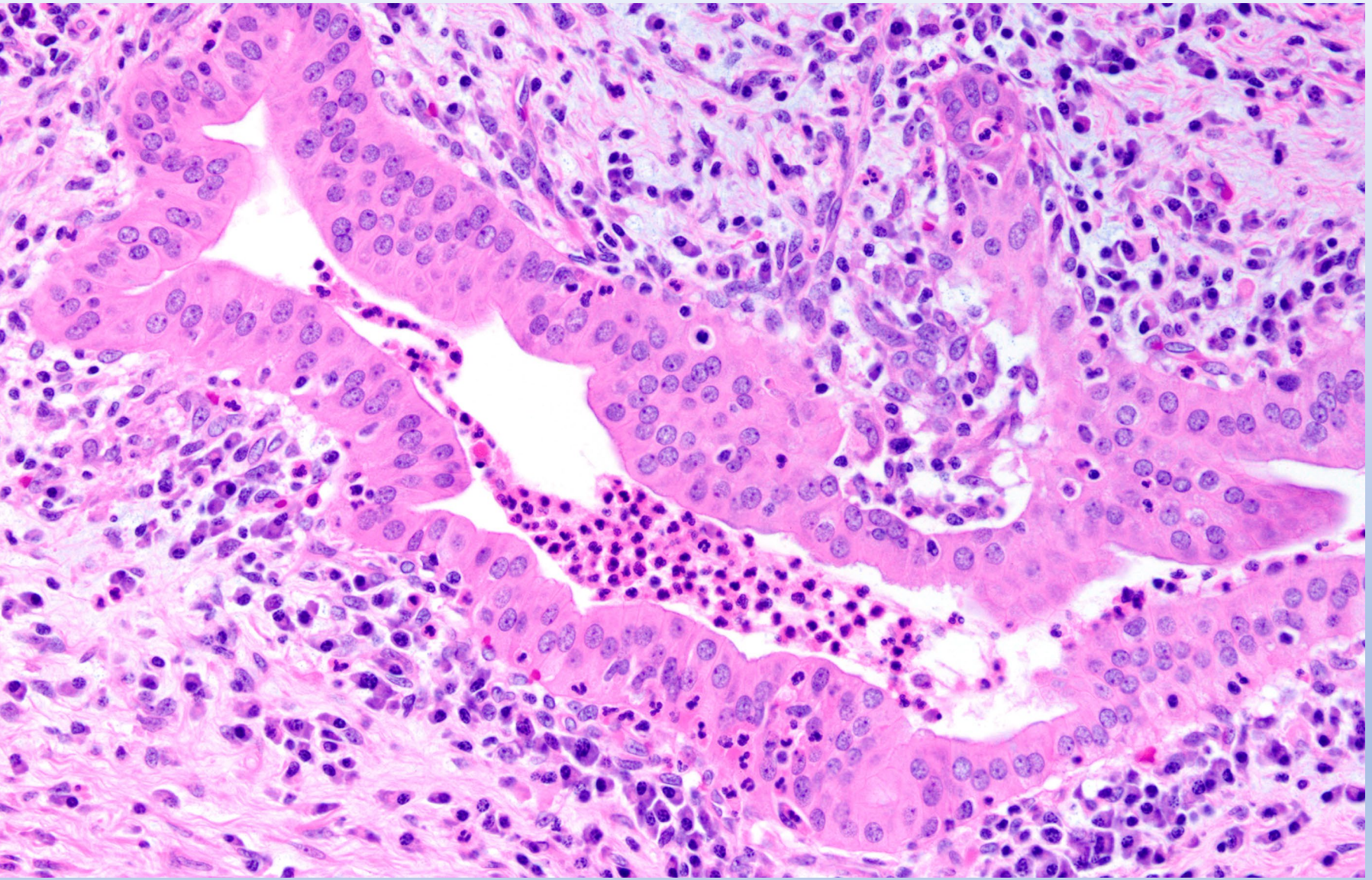


Periductal lymphoplasmacytic and neutrophilic infiltrate

Destruction of small ducts and ductal epithelium

Slides courtesy of Dr. Vikram Deshpande, MGH

# **Type 2:** Idiopathic duct-centric pancreatitis

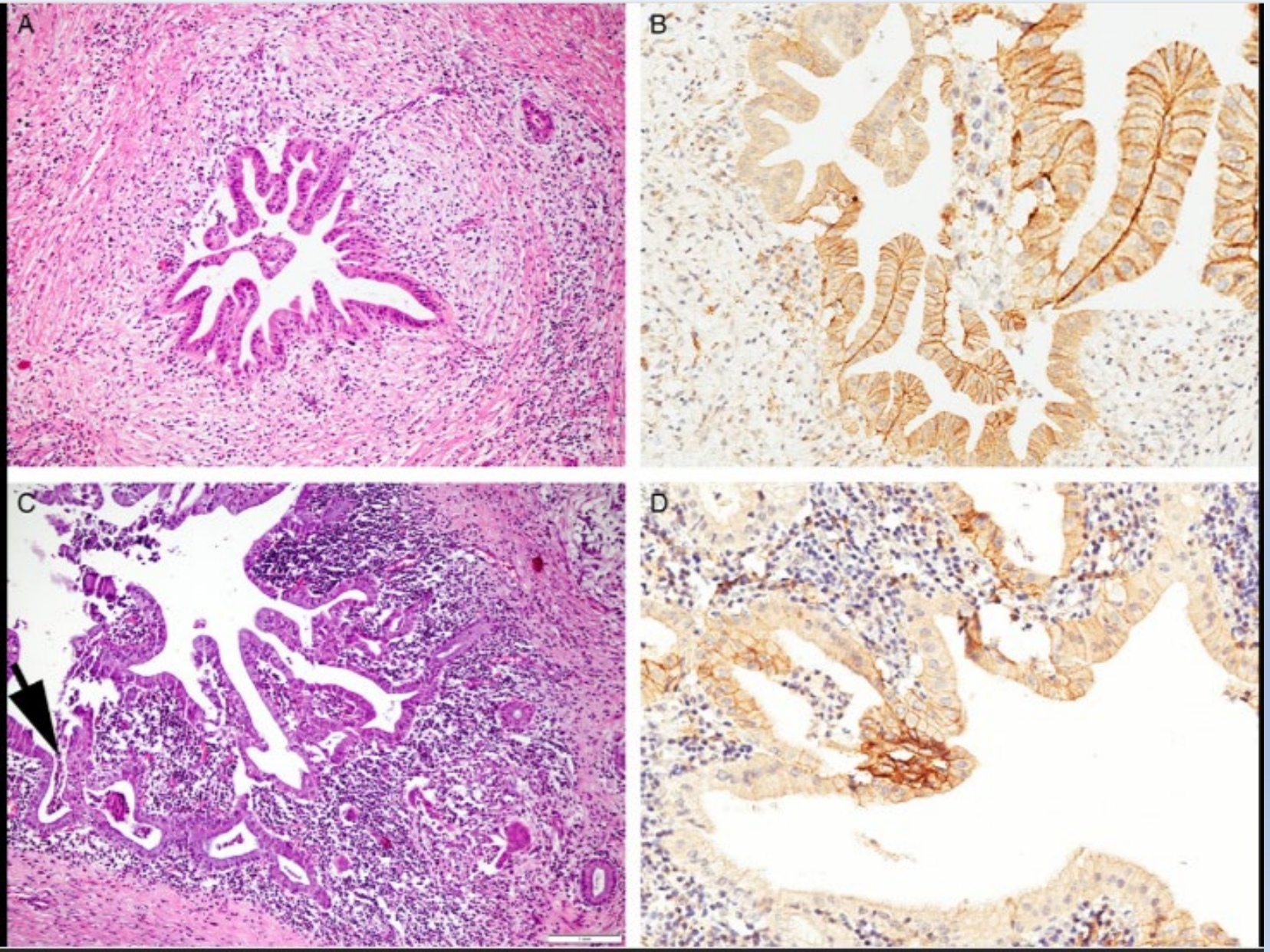


Periductal lymphoplasmacytic and neutrophilic infiltrate

**Granulocytic epithelial lesion (GEL)** positive pancreatitis

Slides courtesy of Dr. Vikram Deshpande, MGH

# **Type 2:** Idiopathic duct-centric pancreatitis




**PD-L1 staining for diagnosis of Type 2 AIP**

Sensitivity – 70%

Specificity – 99%

- 2.5% (6/210) of PDAC positive for PD-L1
- 0 Type I AIP positive for PD-L1

Gupta et al, Am J Surg Pathol, 2019

# Treatment Approach Type I AIP/IgG4-RD

- Induce and maintain remission

- Indications for treatment
  - Symptomatic patients with pancreatic involvement or other organ involvement
  - Persistence of pancreatic mass
  - Persistence of cholestasis in IgG4-RD cholangitis/LFT abnormalities
  - Risk for severe or irreversible organ failure

Hart, Gastro 2015, Lohr et al UEG J 2020

# Therapy - Steroids

- Therapeutic Steroid Trial
  - Prednisone 20-40 mg per day for 4 weeks, tapering by 5 mg/week (North America and Europe)
- 99.6% effective at inducing remission, 40-50% relapse rate
- Risk Factors for relapse:
  - Proximal cholangiopathy
  - Persistent IgG4 elevations despite therapy
  - Multi-organ involvement
- Data suggests you can use steroids for maintaining remission – ~25% relapse rate on low-dose steroids (Japan and Asia)

Chari ST et al, Gastro 2015; Hart, Gut 2013; Okazaki K et al, Pancreatology 2017

# Therapy - Immunomodulators

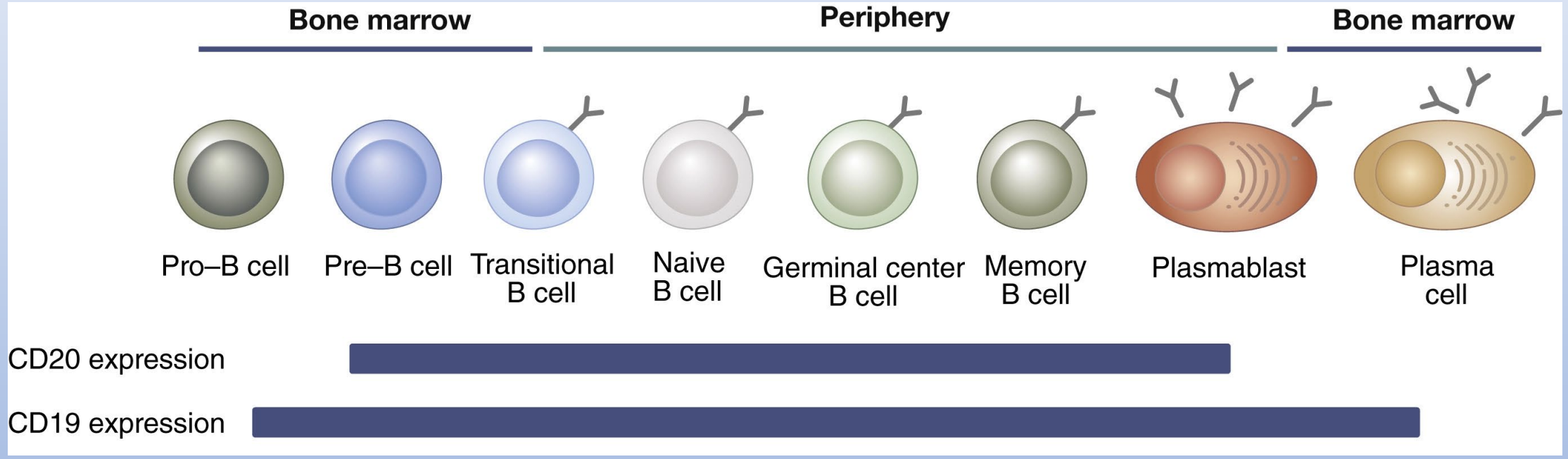
**Table 4** Details of immunomodulator (IM) treatment in patients* treated with azathioprine (AZA), 6-mercaptopurine (6-MP) or mycophenolate mofetil (MMF)

| | AZA (n=31)† | 6-MP (n=6) | MMF (n=11) |
|---|---|---|---|
| Duration from diagnosis to drug initiation (months) | 10.0 (1.1–266) | 9.5 (5.5–37.7) | 11.0 (1.0–55.6) |
| Dose (mg) | 150 (50–200) | 100 (37.5–200) | 1750/day (1000–2000) |
| Dose (mg/kg/day) | 1.9 (0.5–2.5) | 1.5 (0.7–2.6) | – |
| Duration of treatment (months) | 9.8 (0.7–43.9) | 9.0 (0.2–17.5) | 17.4 (3.0–50.8) |
| Indication for drug discontinuation | | | |
| Disease remission | 7/30 (23%) | 3/6 (50%) | 3/11 (27%) |
| Relapse on treatment | 9/30 (30%) | 1/6 (17%) | 3/11 (27%) |
| Side effects | 5/30 (17%) | 2/6 (33%) | 0/11 (0) |
| Continued at follow-up | 9/30 (30%) | – | 5/11 (45%) |

- Azathioprine/6-Mercaptopurine, mycophenolate mofetil (MMP), methotrexate – require IBD dosing
  - Cannot induce remission, but maintain it in about 50-60%
- Should be considered in high-risk individuals or early relapse (<1 year)

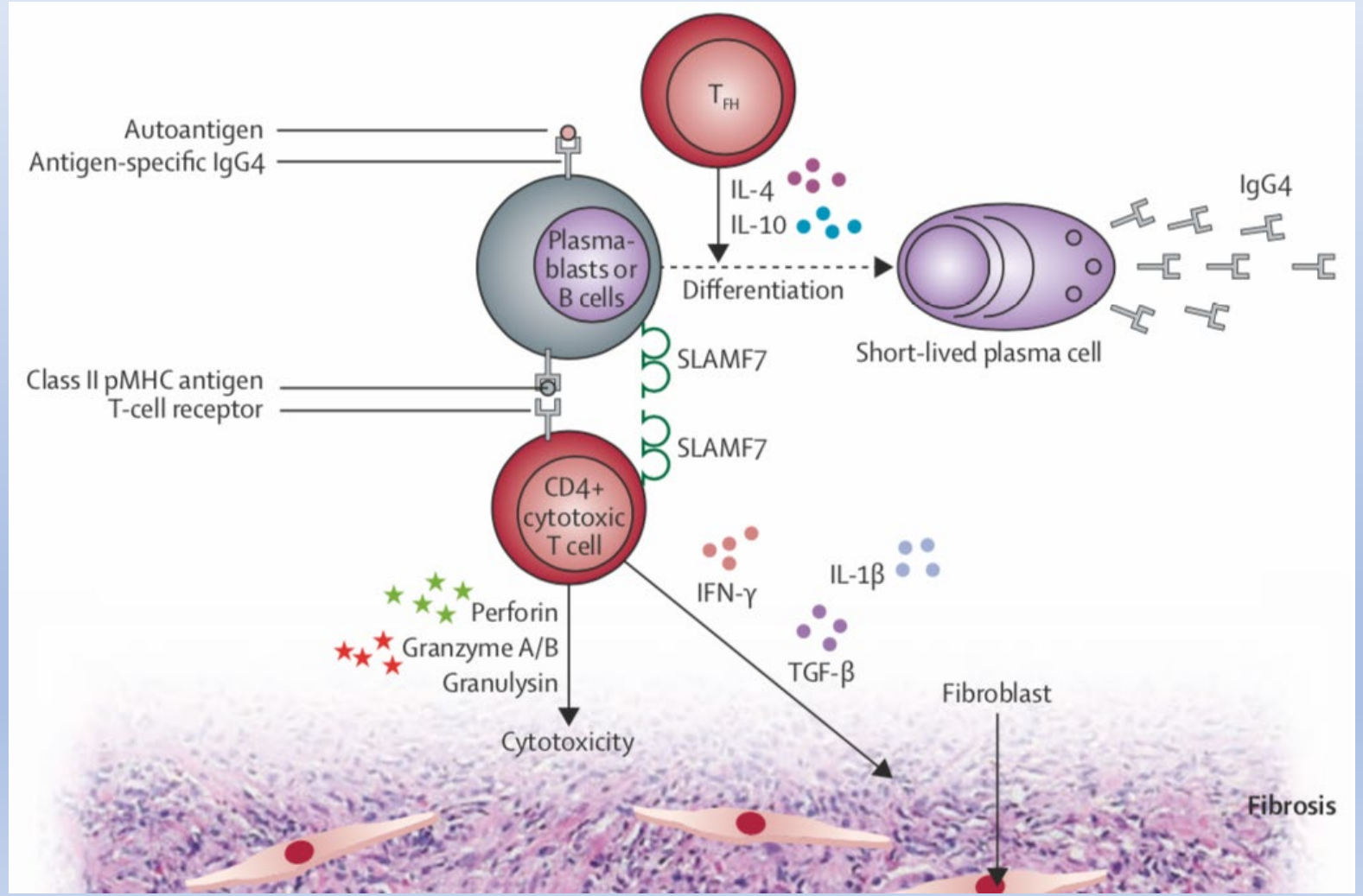
Hart, Gut 2013;

# B cell differentiation and CD19, CD20 expression




Crickx et al, Kidney Int, 2020

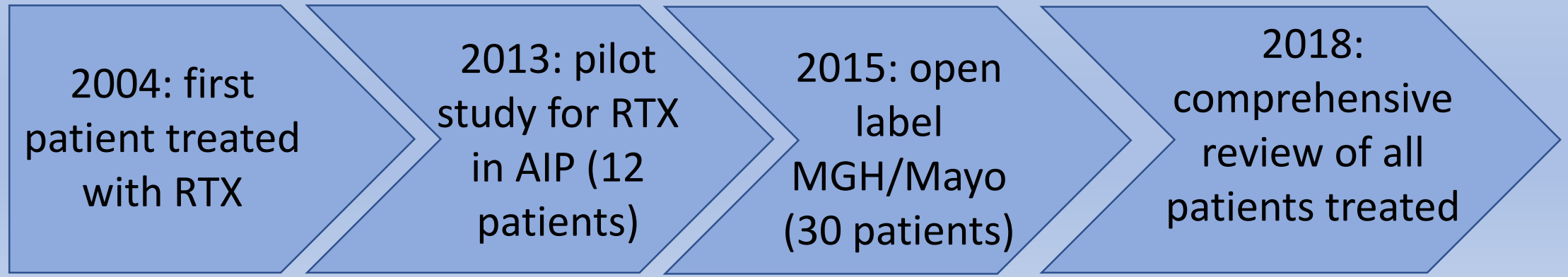
# B-cell antigen presentation to CD4+ CTLs drives IgG4-RD pathophysiology



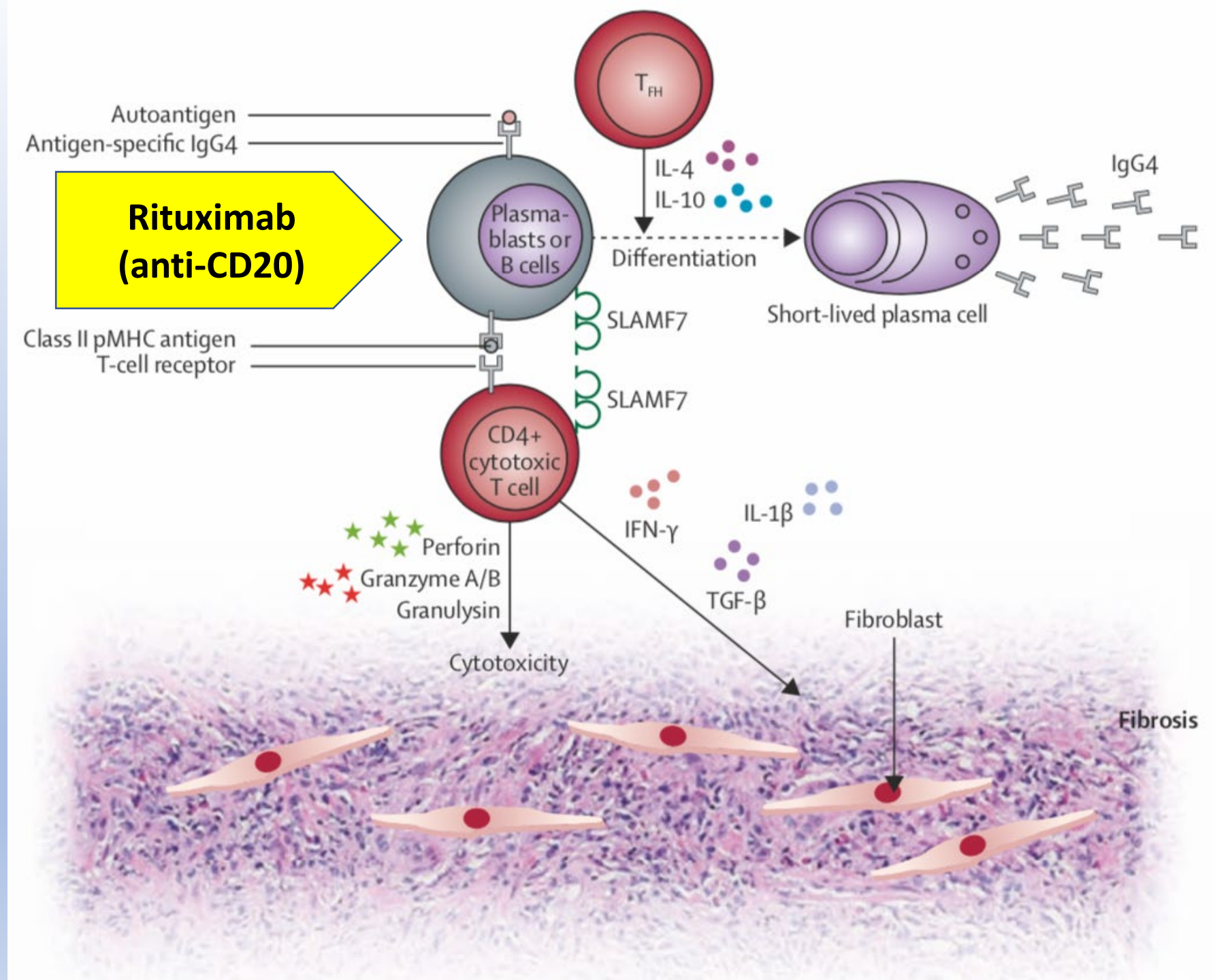

Courtesy of John Stone, MD

# Therapy – Biologics: Rituximab (anti-CD20)

- Chimeric mAb binds to cell surface protein CD20 and decreases B-cell populations
- Single agent given as 2 infusions 2 weeks apart and doses q6 months
- Induces and maintains remission, relapse rate is low
- Appropriate as first line agent if
  - previous serious steroid intolerance
  - Multi-organ involvement




Hart, Gut 2013, Majumder et al, CGH 2018; Carruthers, Ann Rheum Dis, 2015


Autoantigen
Antigen-specific IgG4
Rituximab
(anti-CD20)
Plasma-
blasts or
B cells
Class II pMHC antigen
T-cell receptor
CD4+
cytotoxic
T cell
$T_{FH}$
IL-4
IL-10
Differentiation
IgG4
Short-lived plasma cell
SLAMF7
SLAMF7
Perforin
Granzyme A/B
Granulysin
Cytotoxicity
IFN-γ
IL-1β
TGF-β
Fibroblast
Fibrosis

# RTX induces remission in IgG4-RD AIP

- Induction group – 12 pts
- Induction + maintenance – 29 pts

- Dosing strategy:
  - 375 mg/m2 weekly X4 (lymphoma dose)
  - 1000 mg biweekly X2 (RA dose)

- Response rate 79% measured by steroid-free
- Remission achieved in 98% of patients

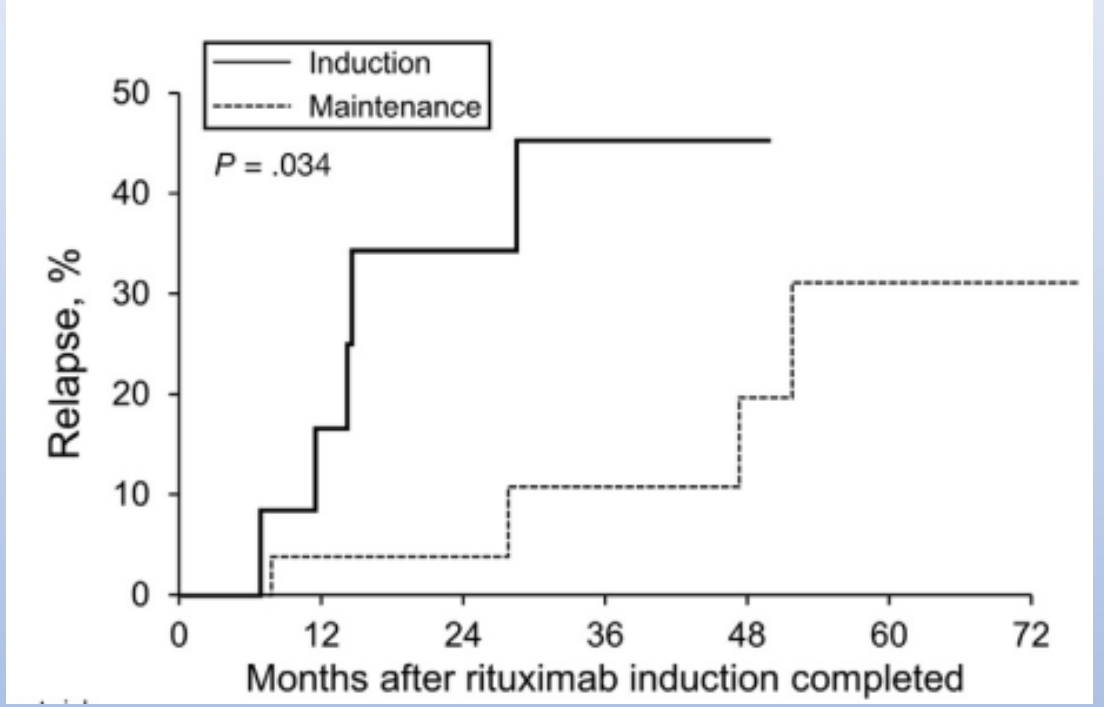
Majumder et al, CGH 2018

# RTX Induction + Maintenance results in significantly improved relapse rates compared to induction alone

- Induction group – 12 pts
- Induction + maintenance – 29 pts

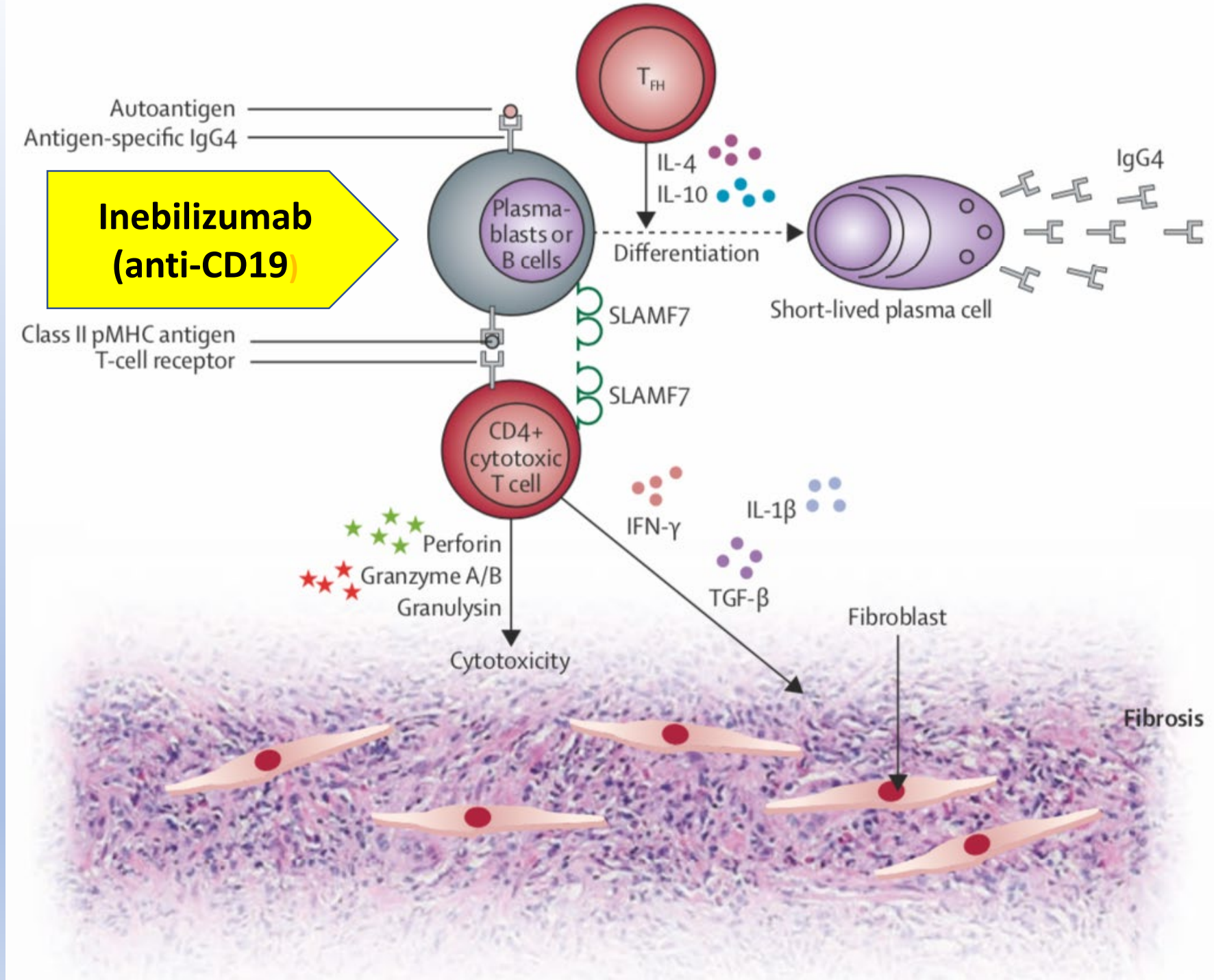
- 3-year event relapse rate 45% versus 11% (p=0.034)

- Majority of relapse occurred once treatment completed




**Median duration for relapse is ~15 months**

Majumder et al, CGH 2018


Inebilizumab
(anti-CD19)
$T_{FH}$
Autoantigen
Antigen-specific IgG4
Plasma-blasts or B cells
IL-4
IL-10
Differentiation
IgG4
Short-lived plasma cell
SLAMF7
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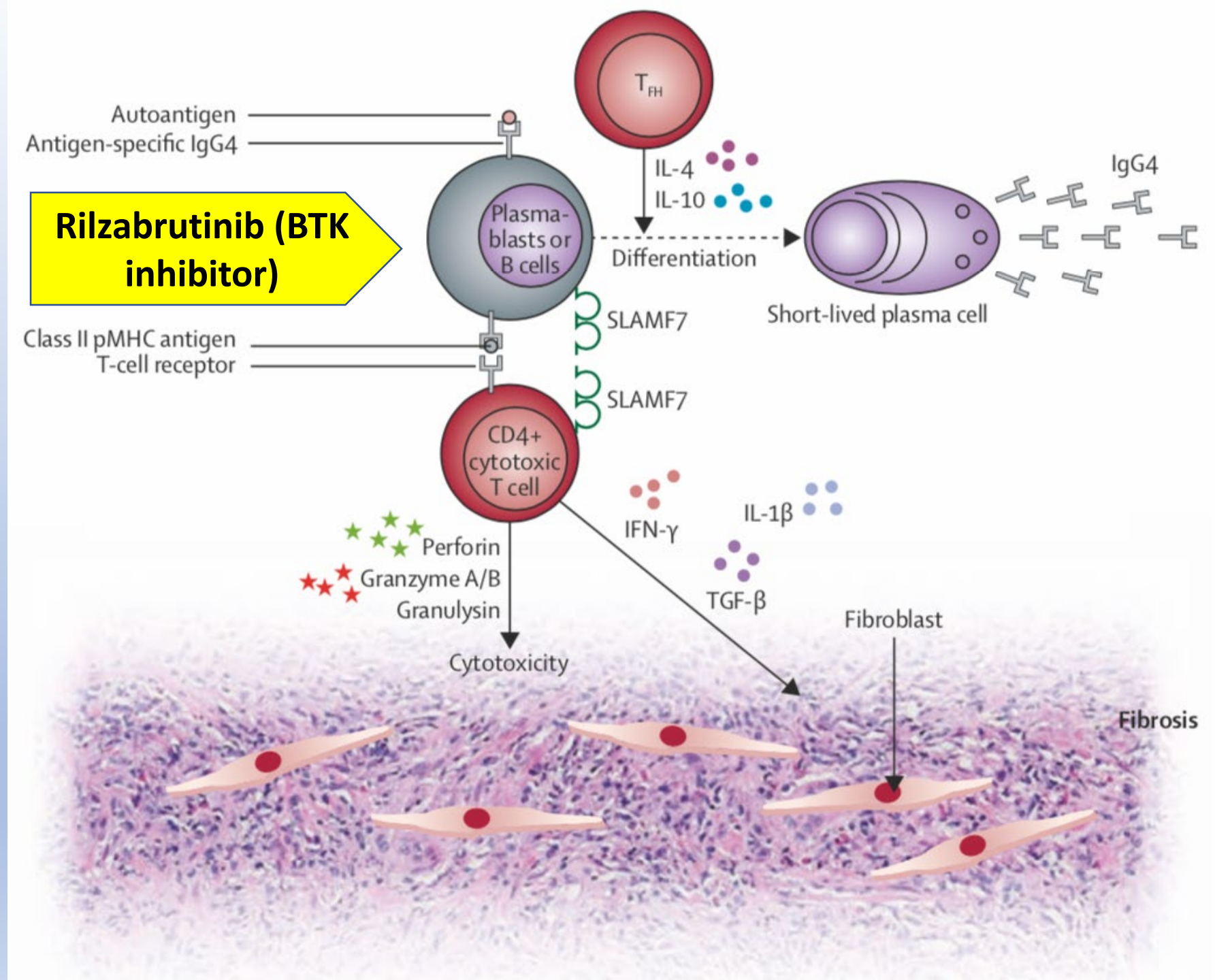
Class II pMHC antigen
T-cell receptor
CD4+ cytotoxic T cell
IFN-γ
IL-1β
TGF-β
Perforin
Granzyme A/B
Granulysin
Cytotoxicity
Fibroblast
Fibrosis

# Therapy on the Horizon: Inebilizumab (anti-CD19)

- Phase 3 randomized, double blinded, multicenter placebo controlled study of Inebilizumab
- Therapy approved for NMOSD (neuromyelitis optica spectrum disorder
- MOA:
  - Humanized anti-CD19 mAb which binds to and deplete CD19+ B cells and plasma cells
- Inclusion:
  - Adults with IgG4-RD
  - Meet 2019 ACR/EULAR classification
  - Recent IgG4-RD flare requiring treatment
  - At least 2 organ systems involved
- Primary outcome: time to flare

NCT04540497


Rilzabrutinib (BTK inhibitor)
$T_{FH}$
Autoantigen
Antigen-specific IgG4
IL-4
IL-10
Plasma-blasts or B cells
Differentiation
IgG4
Short-lived plasma cell
SLAMF7
SLAMF7
Class II pMHC antigen
T-cell receptor
CD4+ cytotoxic T cell
IFN-γ
IL-1β
Perforin
Granzyme A/B
Granulysin
TGF-β
Fibroblast
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# Therapy on the Horizon: Rilzabrutinib (BTK inhibitor)

- Phase 2a multi-center, Open label, two-arm study to evaluate the effect of Rilzabrutinib on safety and Disease Activity in Patients with IgG4-RD

- MOA:
  - BTK (Bruton tyrosine kinase) inhibitor targets multiple pathways in of innate and adaptive immunity

- Primary outcome:
  - Proportion of patients who achieve complete remission at Week 12 with no steroids at week 4 for experimental arm and week 12 for the comparator arm

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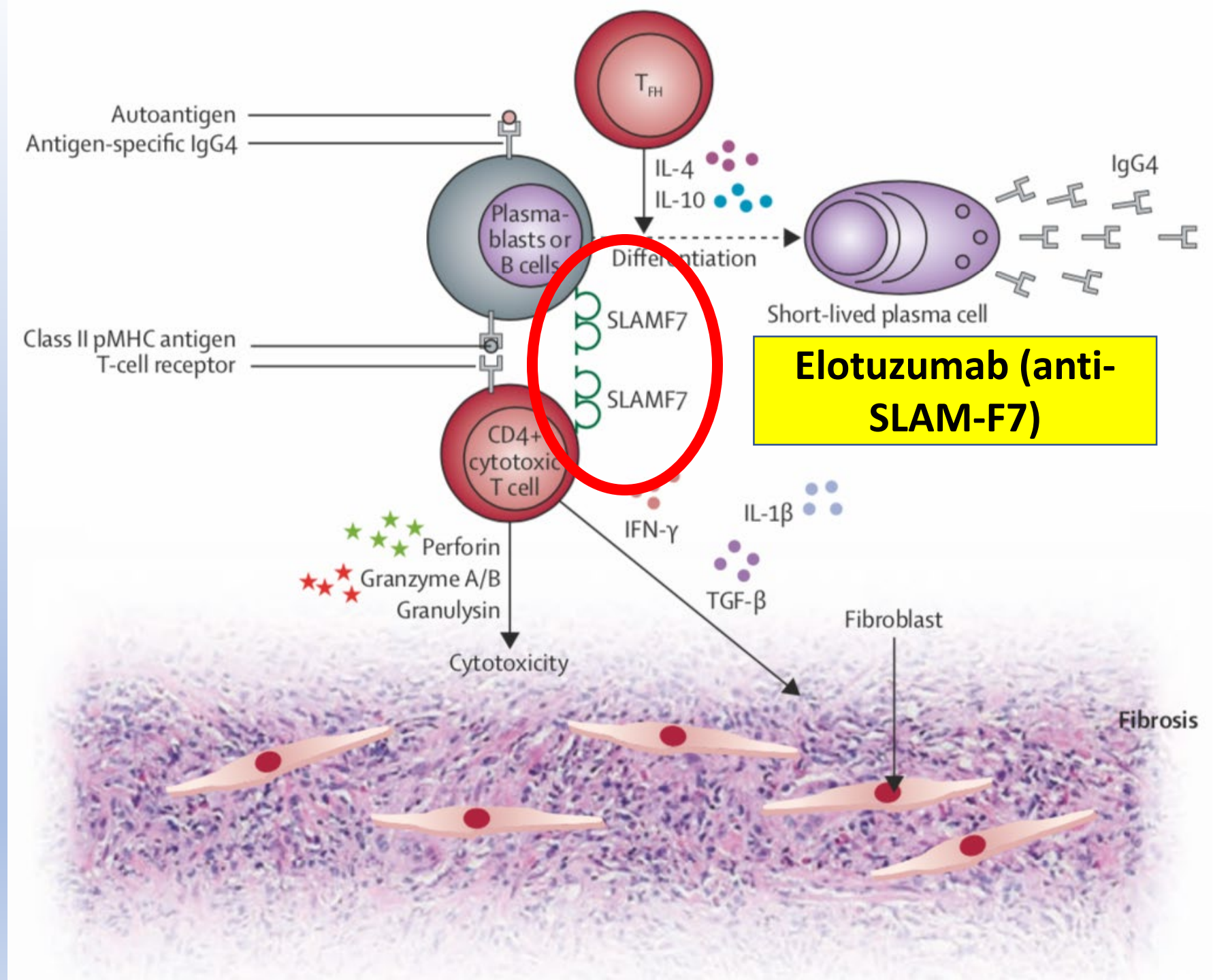
T FH
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SLAMF7
Class II pMHC antigen
T-cell receptor
CD4+ cytotoxic T cell
Elotuzumab (anti-SLAM-F7)
IFN-γ
IL-1β
Perforin
Granzyme A/B
Granulysin
TGF-β
Fibroblast
Cytotoxicity
Fibrosis

# Therapy on the Horizon: Elotuzumab (SLAMF7-i)

- Cohort 1a and 1b: open label, dose escalation phase to determine safety
- Cohort 2: Randomized, placebo controlled double-blinded trial to determine treatment effect

- MOA:
  - Humanized recombinant mAb targeted against SLAMF7, a cell surface glycoprotein

- Current approved for multiple myeloma

- Primary outcome:
  - Safety and Tolerability
  - Compare effect of addition of Elotuzumab to Prednisone

NCT049181447

# Summary Type I AIP

- Type 1 AIP is part of IgG4-RD
- Relapse rates with steroid treatment alone is high
- RTX should be considered in high-risk patients and likely as first line agent for most cases
- When choosing RTX, induction plus maintenance should be the standard of care
- New therapies on the horizon targeted at multiple immunological pathways
- Remember that PDAC is more common that Type I AIP

# Type II AIP:
# Idiopathic Duct-Centric Chronic Pancreatitis

- Exquisitely steroid responsive with <10% recurrence rate
- Treatment at least 20 mg po qdaily for 4 weeks and then taper by 5 mg per week
- PD-L1 can be helpful in the diagnosis
- 35% of patients with AIP have IBD

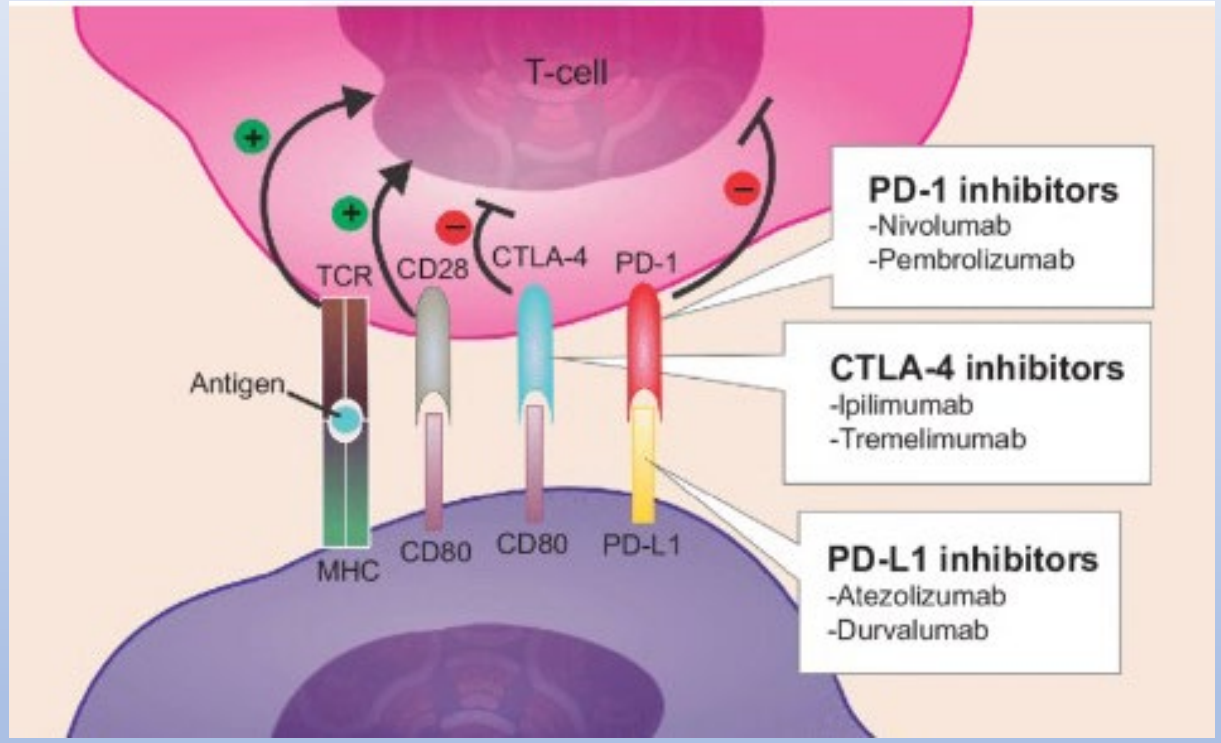
- Can cause endocrine and exocrine dysfunction long term

Gut 1997, Am J Surg Pathol 20023, Gasttro 2010

# Type III AIP – ICI-Pancreatic Injury

- Immune-checkpoint inhibitors revolutionized cancer care
  - Target either PD-1, CTLA-4 or PD-L1 which leads to non-specific augmentation of T-cell tumor immune response
  - Has off-target effects in various organs leading to autoimmune-like phenomenon (30-40% irAE)

- **ICI-pancreatic injury is an Immune mediated phenomenon**




Type 3 AIP credit - Suresh Chari; figure courtesy of Dr. Molly Thomas, MGH

# ICI-mediated pancreatic Injury is rare

- Incidence 0.6-4%
- Asymptomatic lipase/amylase elevations estimated at **2.7%**
- Pancreatitis even more rare 1.9%
- Increased risk in combination therapy or treatment for melanoma
- Typically occurs during treatment though can be seen up to 12 months following discontinuation of therapy
- Imaging findings are rare, but diffuse or focal enlargement, pancreatic masses have been described
- Always need to consider metastatic disease if new mass identified

Abu-Sbeih, J Immunother Cancer 2019; Das, Eur J Radiol, 2020; Johnson Nature Rev cClinical Oncology 2022

# Management of ICI-pancreatic injury

- No treatment indicated for ASYMPTOMATIC enzyme elevations
- Symptomatic pancreatitis
  - Manage as pancreatitis with IVF and pain management
  - Depending on severity, may need to hold ICI-therapy
  - Steroids avoided as can impact oncological outcomes
- Monitor for development of diabetes and EPI as with other forms of pancreatitis

# Part 2 Summary

- Type 2 AIP is rare disorder and almost exclusively steroid responsive
- Always consider pancreatic cancer in the differential as it is more common
- ICI-pancreatic injury is an immune mediated phenomenon and may be classified as Type 3 AIP (Dr. Chari)
- No treatment is indicated in asymptomatic enzyme elevations or mild symptoms
- Avoid steroids and ICI-therapy discontinuation unless severe presentation as oncological outcomes can be negatively impacted

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

# Thank you – Happy to take questions

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**Special Thank you**

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Guy Katz, MD

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Vikram Deshpande, MD

# Supplementary Slides