Steroid-refractory GVHD beyond JAK-inhibition

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GvHD
Graft-versus-Host Disease
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Conflict of Interest

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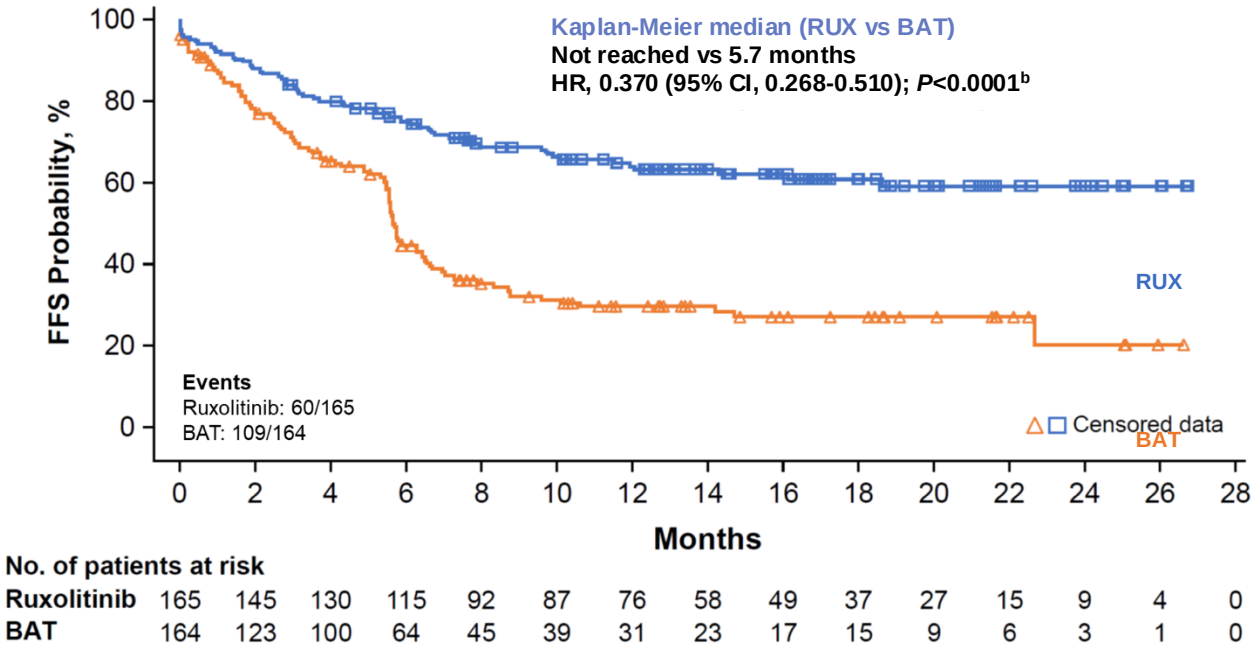
Results from the REACH 3 trial



BAT, best available therapy; cGVHD, chronic graft-vs-host disease; FFS, failure-free survival; HR, hazard ratio; RUX, ruxolitinib.
[a] Defined as time to the earliest of recurrence of the underlying disease, the start of new systemic treatment for cGVHD, or death. [b] Descriptive *P* value at primary analysis (non-US testing sequence only) as the efficacy boundary was crossed at the interim analysis (N=196, hazard ratio, 0.315 [95% CI, 0.205-0.486], *P*<0.0001). For US testing sequence, the hypothesis was retested at the primary analysis following the overall hierarchical testing procedure.

- While ruxolitinib is standard of care in 2nd line treatment at least 40% require an additional treatment
- Problematic are patients with cytopenia, infectious complications (not eligible for ruxo) and sclerosing manifestations lacking inflammation

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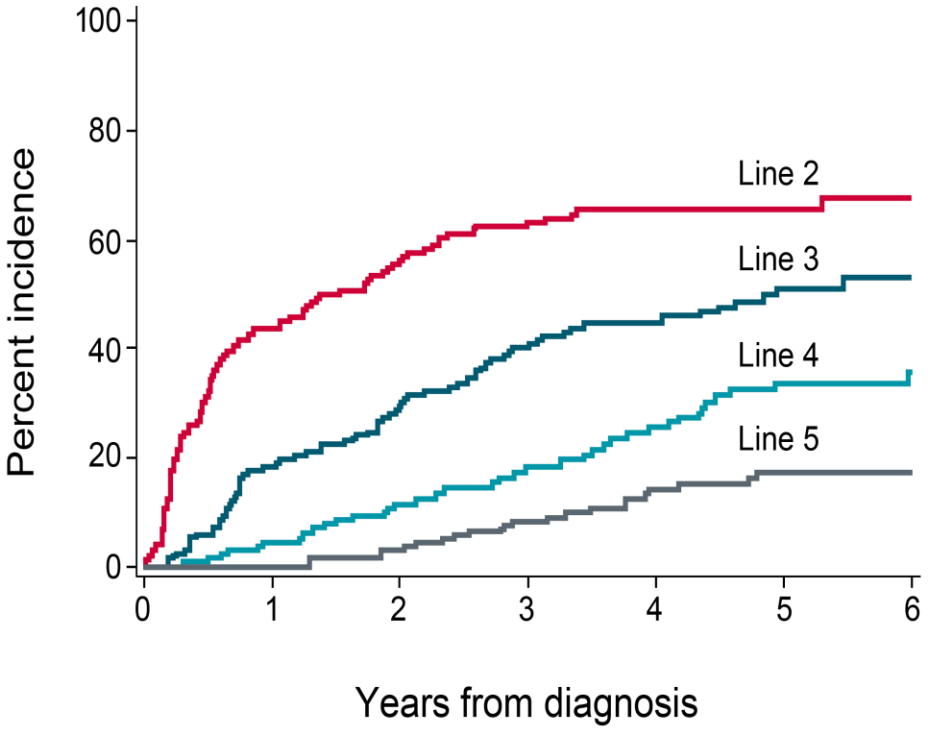
Length of treatment

- More than 50% of patients receive ≥3 therapy lines with decreasing efficacy



Lee et al. Biol Blood Marrow Transplant. 2018;24:555-562

- Stopping immunosuppression is not the primary goal
- Finding the most efficient and least toxic treatment is the goal
- Patient information and framing is crucial
- Capture all symptoms (PFT, Gyn)
- PROs incl. physician and patient Prompt lists may aid

Treatment of cGvHD – 2nd line options

(modified according to Wolff 2011 & 2019 (EBMT Text-Book)

Agent	Reco	Evid.	comments
Steroids	B	III-1	Important, spare steroids due to side effect profile
ECP	C-1	II	spares steroids, no infectious risk
Ruxolitinib	**C-1**	**II**	**risk for infections (FDA & EMA approval)**
mTOR –I.	C-1	III-1	increased risk for TAM in combination with CNI
CNI	C-1	III-1	spares steroids
MMF	C-1	III-1	risk for viral reactivation, spares steroids
Ibrutinib	**C-1**	**III-1**	**risk for infection, bleeding (FDA approval)**
Axatilimab	**C-2**	**III-1**	**effective in advanced line (FDA approval 3rd line)**
MTX	C-2	III-1	best results in mucocutaeous cGVHD
Imatinib	C-2	II	sclerotic skin lesions and mild and moderate BO
Rituximab	C-2	II	most effective in autoAB mediated manifestations
TLI	C-2	III-2	best results in fasciitis or mucocutaneous cGVHD
Pulse steroids	C-2	III-2	rapid control of symptoms

Treatment of cGvHD – 2nd line options

(modified according to Wolff 2011 & 2019 (EBMT Text-Book)

Agent	Reco.	Evid.	comments
IL-2	C-2	III-1	best results in mucocutaneous and liver involv.
Bortezomib / Ixazomib	C-2	III-1	Effective in mucocutanous cGVHD, may be used in myeloma patients
Regulatory T cells	C-3	III-1	Currently explored in a number of trials
Hydroxychlor.	C-2	III-2	best results in mucocutaneous and liver involv.
Tocilizumab	C-3	III-3	best results in sclerotic mucocutaneous cGVHD
Belumosudil	**C-2**	**III-1**	**FDA approval 3rd line treatment of cGVHD**
Pomalidomide	C-2	III-1	Late sclerosing cGVHD (involvement of B cells)
Retinoids	C-3	III-2	effective in sclerotic skin lesion
Cyclophosphamid	C-3	III-3	Either low dose or pulse, most effective in GN
Abatacept	C-3	III-1	Initial data indicate efficacy in lung disease

Treatment of cGvHD – 2nd line options – factors influencing treatment decisions

Relapse risk: high risk of relapse – avoid "overimmunosuppression" and substances known to potentially increase relapse risk (i.e., CNI, MMF)

Infectious disease history: a number of agents are associated with specific infectious risks (i.e., Ruxo: viral + bacterial, Ibru: bact. + fungal, MMF: viral)

Comorbidity: avoid agents with side effects in already impaired organs (i.e., CNI in renal insufficiency, mTOR in uncontrolled hypercholesterinemia, MTX in pleural effusions or renal insufficiency, Ruxo in pancytopenia)

History of applied agents: avoid treatment options already failed or associated with inacceptable side effects, flare after stop?

Biology of disease: overlap symptoms present?, IgG levels (low or high, auto-AB, organ manifestations typical for auto-AB), number of T and B cells (avoid depletive strategies in patients already depleted), organ pattern?

Treatment of cGvHD – 2nd line options – factors influencing treatment decisions

Compliance: avoid substances requiring compliant patients in incompliant (i.e., Tocilizumab), prefer substances given i.v. if patients tend to stop medication, listen to patient´s preferences (the patient is unlikely to be compliant if indicates upfront not to be so)

Steroid-refractory versus dependent: Steroid refractory patients with inflammation need anti-inflammatory agents other than steroids (ruxolitinib, tocilizumab, Tregs, ECP).

Distance to Tx center and availability of treatment: ECP, TNI,

Approval status: Avoid financial toxicity to your dept or the patient´s account

Treatment of cGvHD – 2nd line options – considerations based on patients history and biology I

Ibrutinib (Miklos 2017)

✓ Reversible blockage of B cells and plasmablasts, to some degree also T cells – preferable used with potential autoantibody involvement

– Risk for bacterial and fungal infections

– Anticoagulatory side effects

Rituximab (Arai 2016, Klobuch 2019)

✓ Irreversible depletion of B cells but no plasmablasts

✓ Evaluated even in randomized trial

✓ Preferential <u>early</u> use in autoantibody mediated manifestations, higher efficacy in case of normal B cell counts

– Increased risk for bacterial and possibly viral reactivations especially in non-responder

Treatment of cGvHD – 2nd line options – considerations based on patients history and biology II

ECP (Jagasia 2019, Flowers 2008, Greinix 2011)

- ✓ Low toxicity and low risk for relapse
- ✓ Steroid sparing
- – Requires venous access and center visits
- – Low efficacy in Steroid-refractory cGvHD (compared to Steroid-dependent)

Abatacept (Wertheimer 2021, Koshy 2023, Nahas 2016)

- ✓ Effective in BOS (5/10 PR, 4/10 NC)
- ✓ Relative favorable tox profile
- – Airway infections
- – Infusion related side effects

Treatment of cGvHD – 2nd line options – considerations based on patients history and biology III

Imatinib (Olivieri 2009/2013, Arai 2016)

- ✓ Does not increase infectious risks
- ✓ effective in sclerosing manifestations
- – Oedema, may increase muscle cramping
- – Relatively low response rate ~20%

Belumosudil (Cutler 2021)

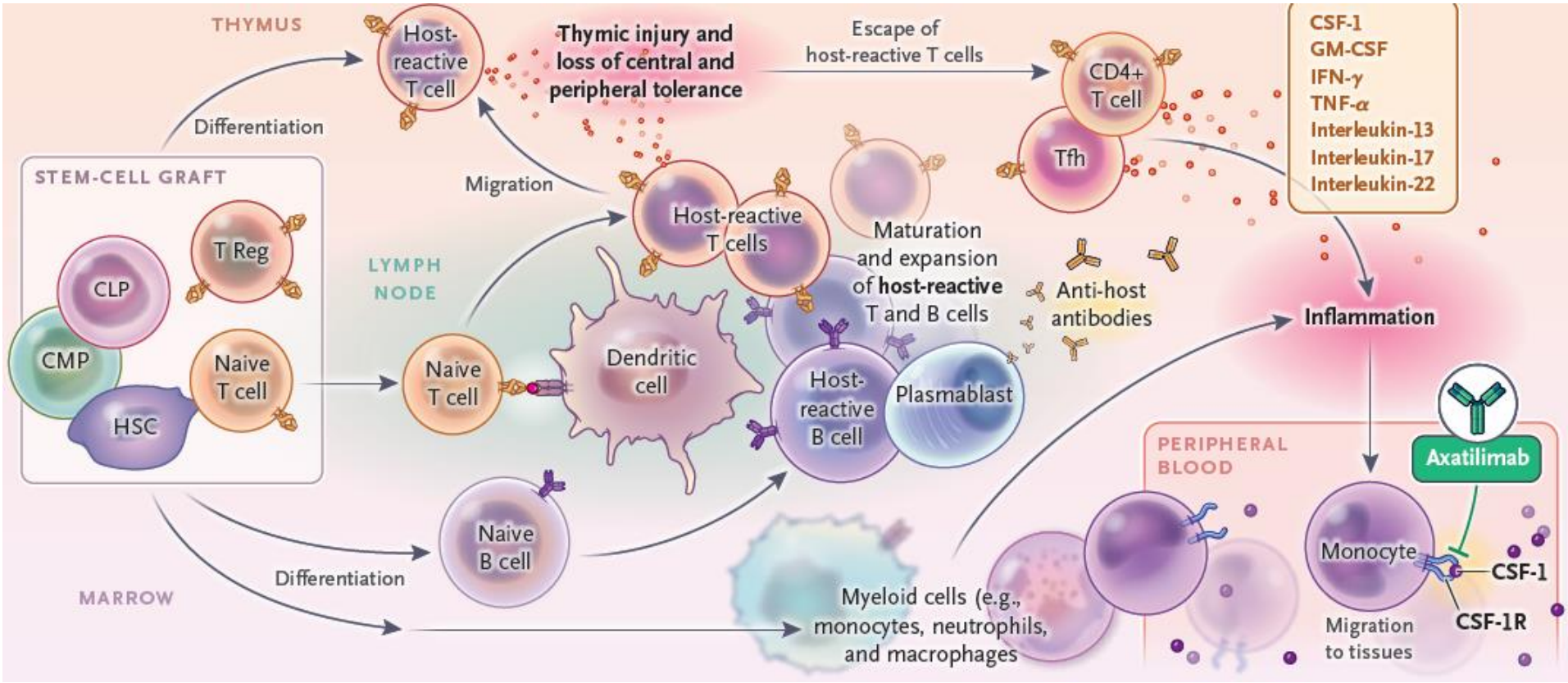
- ✓ Th1 & Th17 inhibition relatively specific for cGVHD
- ✓ Effective in 3rd line treatment including skin sclerosis and BOS
- – Can cause occasional GI disturbance and liver enzyme abnormalities
- – FDA and UK approved

Treatment of cGvHD – 2nd line options – considerations based on patients history and biology V

Axatilimab (Wolff 2024, Kitko 2023)

- ✓ Does not impair GvL nor infectious control (no effect on granulocytes, nor lymphocytes)
- ✓ Rapid relatively high response rate in advanced sclerosing cGVHD
- – i.v. application (s.c. in development)
- – Interferes with assessment of liver enzymes and lipase

Mechanismus of action of Axatilimab



Wolff, D. Editorial: Science Behind the Study.NEJM.2014

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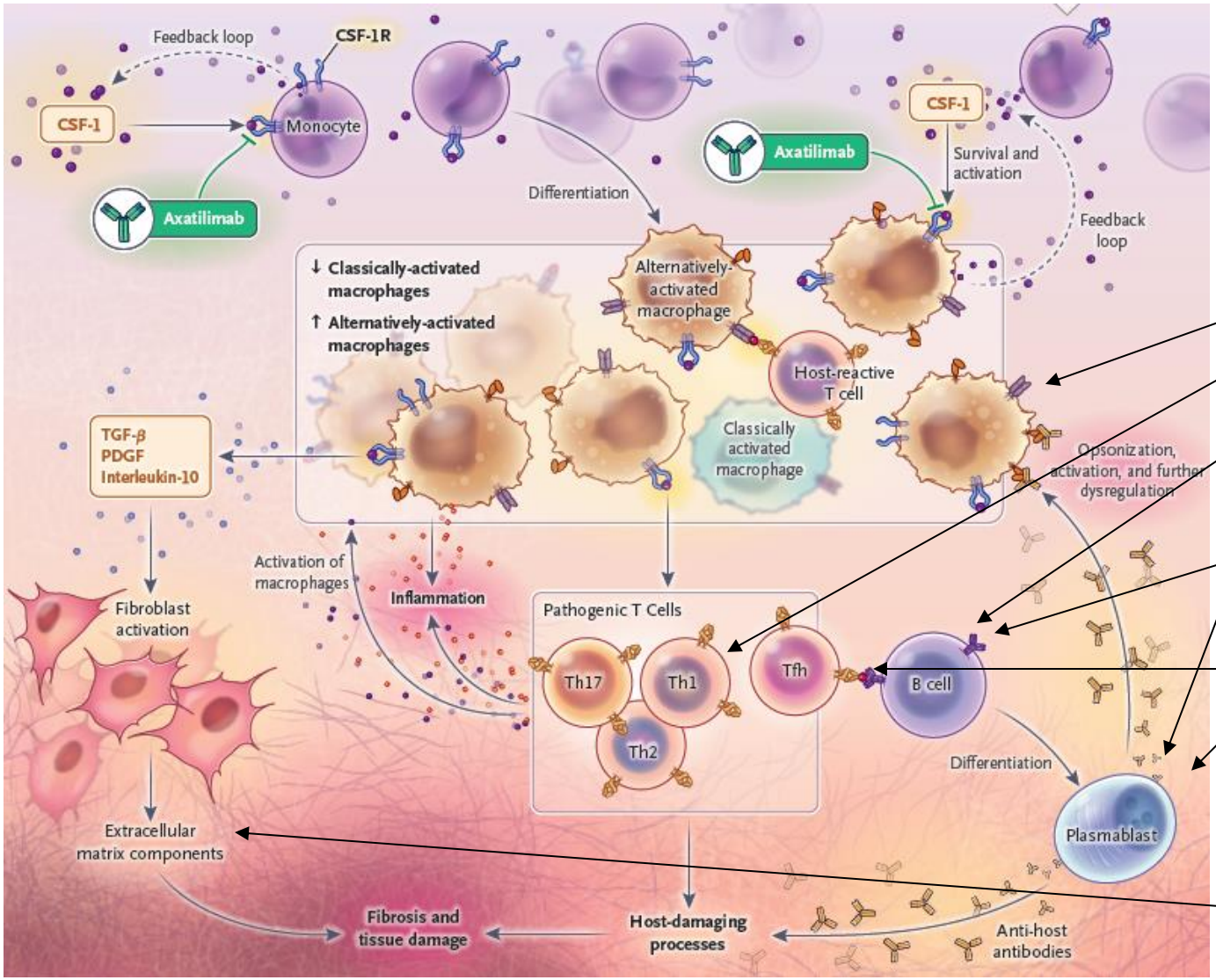


Belumosudil

Rituximab

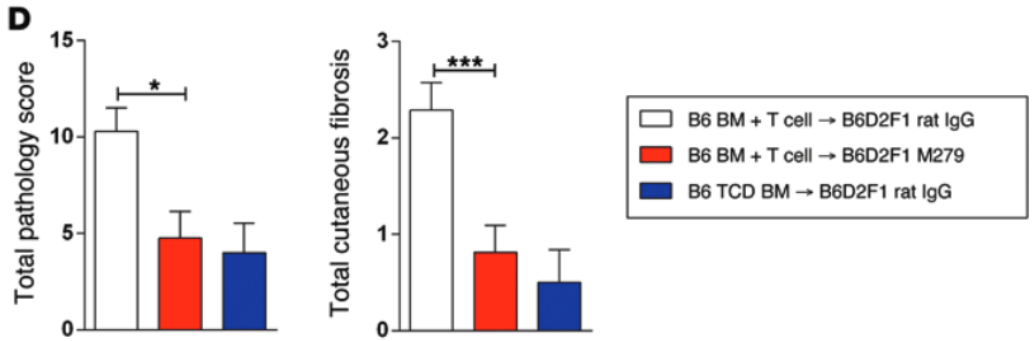
Tocilizumab

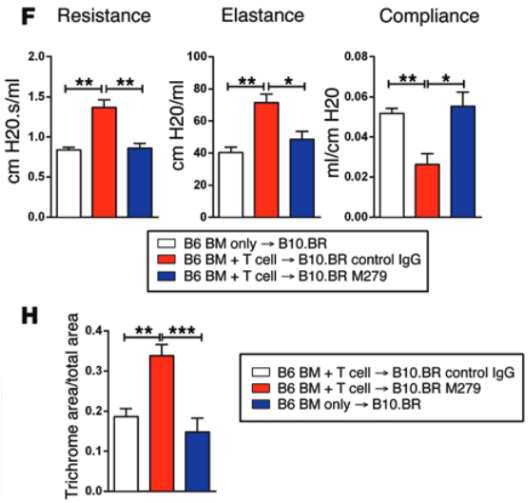
Ibrutinib

Imatinib

Preclinical work targeting CSF1 in cGVHD

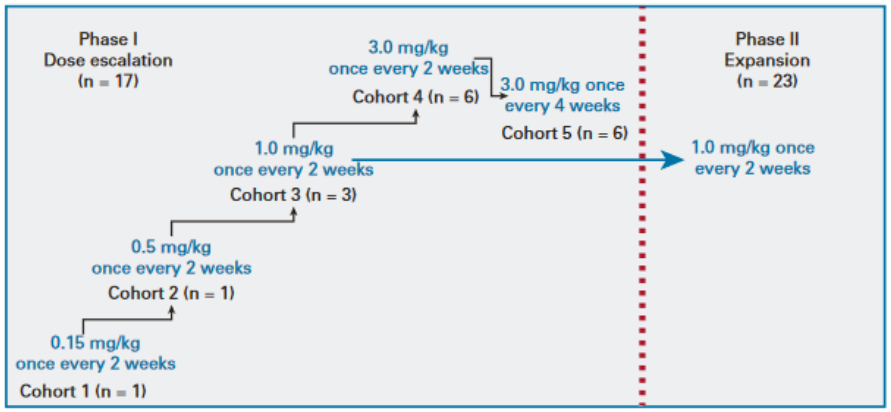
- cGVHD is mediated by CSF1 dependent donor macrophages
- Additional CSF1 exacerbates cGVHD
- Depletion of CSF1-R receptor expressing macrophages with an anti-CSF-1 antibody attenuates skin and lung fibrosis
- Skin is predominately dependent on CSF1 pathway
- The lung is also Th17 and GM-CSF dependent

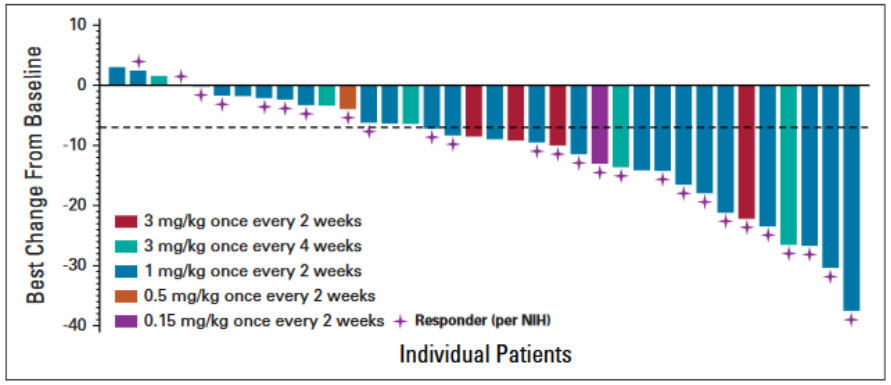


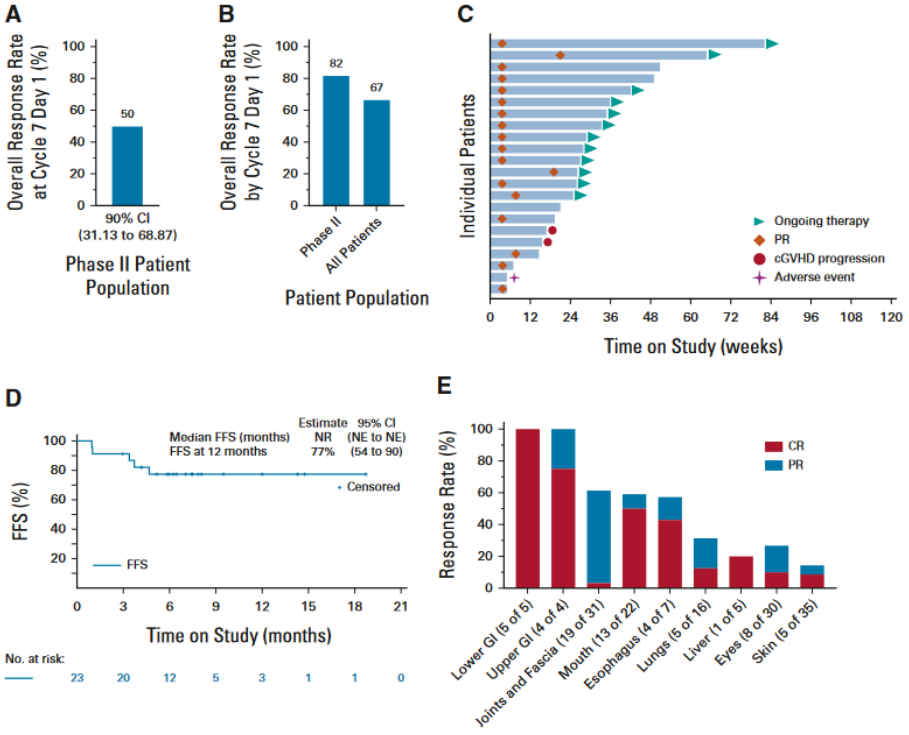


Alexander/MacDonald. J Clin Invest.2014;124(10):4266-4280

Phase I / IIa trial on axatilimab in cGVHD



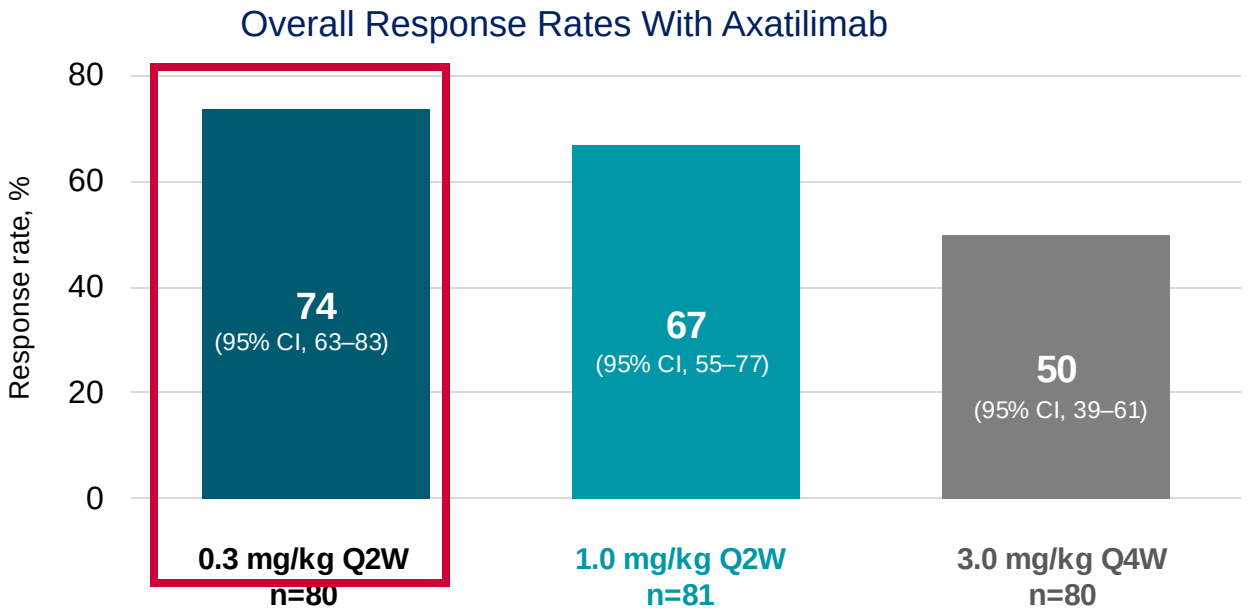




- Axatilimab has a favorable safety and efficacy in refractory cGVHD with an ORR of 67%

Kitko C, et al. J Clin Oncol.2023;41:1864-1875

Results of the AGAVE 201 trial



	0.3 mg/kg Q2W n=80	1.0 mg/kg Q2W n=81	3.0 mg/kg Q4W n=80
Time to response, median months (range)	1.7 (0.9–8.1)	1.9 (0.9–8.6)	1.4 (0.9–5.6)
Response maintained for ≥12 months, % (95% CI)	60 (43–74)	60 (43–74)	53 (30–71)

Q2W, every 2 weeks; Q4W, every 4 weeks.
[a]Primary endpoint was overall response rate in the first 6 cycles as defined by NIH 2014 Consensus Criteria[1]
1. Lee at al. Biol Blood Marrow Transplant. 2015;21:984-999.

Wolff, et al. ASH 2023_oral plenary. Blood.2023;142:1-3
Wolff, et al. NEJM.2024_vSept 19

Conclusions

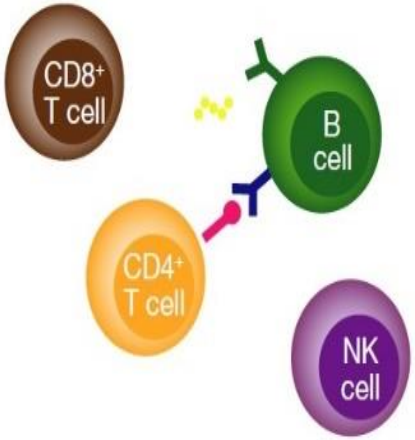
- While the number of treatment options is increasing the individual sequence of applied off label options remains a “trial and error” system
- Avoid prolonged inefficient treatment but also rapid escalation without chance to respond impairs response assessment, cumulation of agents adds to infectious burden
- Safety and evidence of efficacy are important driver (safe and efficient comes first)
- Biomarker to predict response are highly warranted
- Clinical decisions should based on the patients` risk profile, organ manifestations, course of the disease, comorbidities, compliance

chronic GVHD - Pathway (and time) dependent targets

Phase 1
Acute inflammation & tissue injury

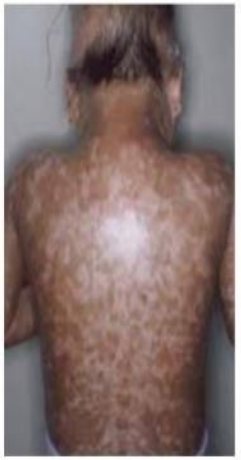
- Cytokines (steroids, etanercept, tocilizumab)
- TLR-Agonists
- Neutrophils (steroids, montelukast)
- Platelets
- Vascular inflammation
- microbiome
- lymphocytes (modulation depletion, migration)

Phase 2
Chronic inflammation & dysregulated immunity



- Thymic injury & dysfunction
- T cells (CNI, mTOR-Inh., MMF, ruxolitinib, baricitinib, cyclo., pentostatin, MTX, abatacept, alefacept, TNI)
- B cells (Ibrutinib, MMF, rituximab, tocilizumab)
- Plasmablasts (proteosome inhibitors, imids)
- Antigen presenting cells (steroids, mTOR-Inhibitors)
- Treg (IL-2, ECP, MSC) & B reg cells

Phase 3
Aberrant tissue repair & fibrosis



- TGFβ (pirfenidon, nintedanib)
- PDGFα (imatinib, nilotinib)
- Fibroblasts (lenabasum)
- TNFα etanercept)
- IL17 (belumosudil)
- Macrophages (axatilimab)

➢ **The future goal is biology-based treatment**

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