Graft-versus-Host Disease: Advances in Prevention and Treatment

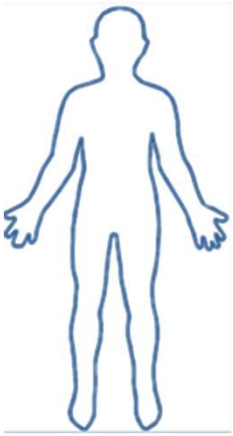
Celebrating a Second Chance at Life Survivorship Symposium

April 29 – May 5, 2023

Marcello Rotta, MD
Colorado Blood Cancer Institute,
part of the Sarah Cannon Cancer Institute at
Presbyterian/St. Luke's Medical Center

Topics We'll Discuss

- Introduction to graft versus host disease
- Discuss new strategies to avoid graft versus host disease
- Discuss new treatments for graft versus host disease
  - Available new drugs
  - Drugs under investigation



Recipient

"Host"

Transplant from donor

Blood forming cells: STEM CELLS

- Replace Host's stem cells

Immune Cells:

- They can attack the recipient

" Graft versus host disease"

- They can destroy cancer cells

"Graft Versus Leukemia"

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Graft-vs-Host Disease (GVHD)

- Biological consequence of the transfer of a donor immune cells into the recipient
- Immunosuppressive medications are necessary to prevent GVHD
- GVHD can be eliminated by removing immune cells (T-cells) from the donor collection

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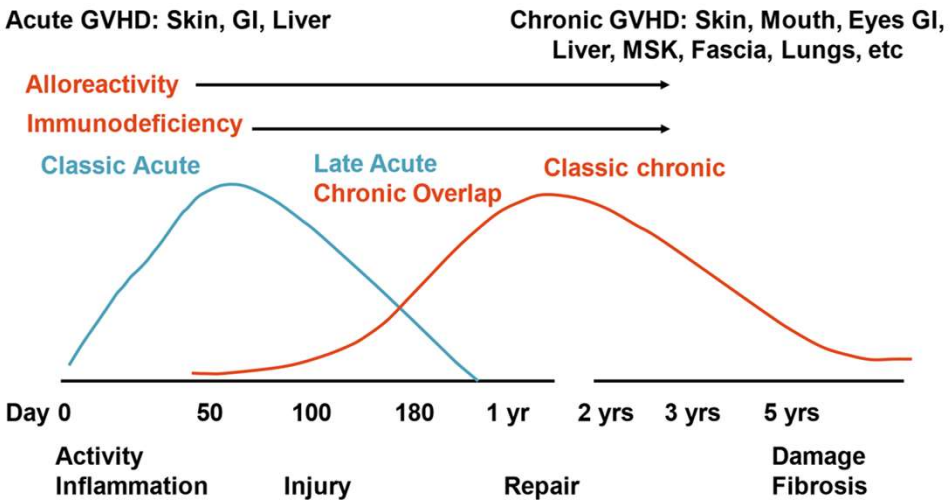
Graft-vs-host disease (GVHD)

- GVHD is associated with anti cancer graft-versus-leukemia (GVL) effect
- If you completely remove the donor immune cells increases risk of disease relapse.

GVHD: Acute and Chronic



Cutler BMTinfo 2020

Acute GVHD

- Leading cause of mortality
- Grade II-IV occurs in ~70% pts
- Grade III-IV occurs in 10-15%
- ~***2-6 weeks after transplant***
- 30-40% refractory to 1st line of treatment

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Chronic GVHD

- Most serious and common long-term complication transplant
- Occurs in ***30% - 55% of patients***
- ~4-6 months after transplant
- 50% of patients have 3 or more involved organs
- On average therapy is required for 2-3 years

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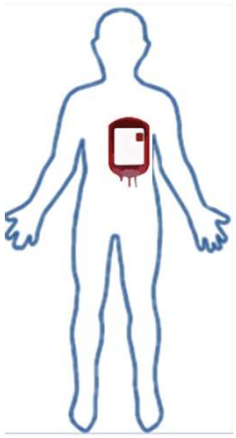
Transplant from donor: How to define success



Tolerance

- Cure the blood cancer
- NO Graft vs Host Disease

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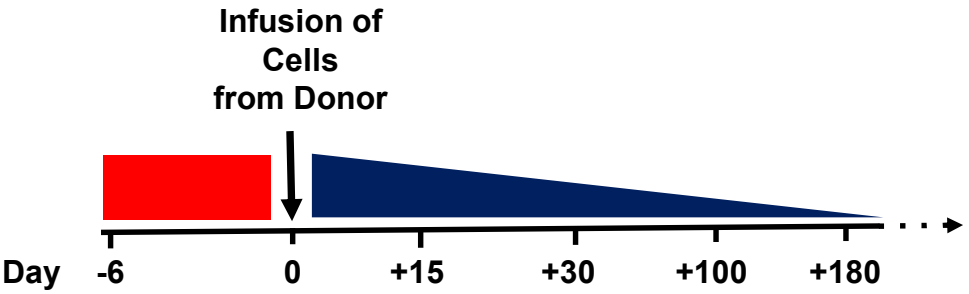
Transplant from Donor: General Schema



CONDITIONING
- Chemo +/- Radiation
- More or less intense
- Prevent Rejection
- Destroy cancer cells

POST TRANSPLANT IMMUNOSUPPRESSION
- Drugs given in vein or pills
- Prevent GVHD

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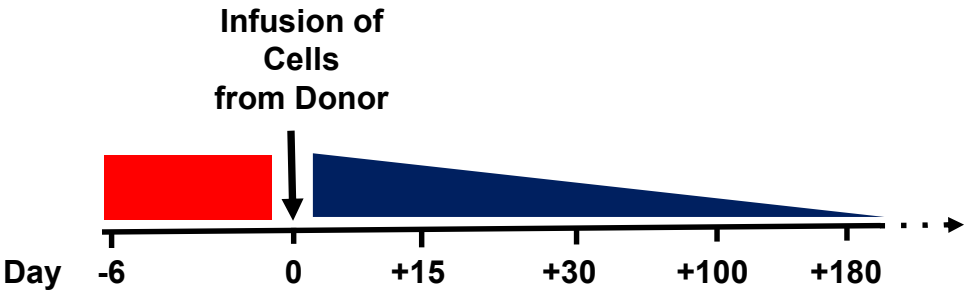
Transplant from Donor: General Schema



CONDITIONING

- Chemo +/- Radiation
- More or less intense
- Prevent Rejection
- Destroy cancer cells

Cyclosporine + Methotrexate

Tacrolimus + Methotrexate

Tacrolimus + MMF

Tacrolimus + Rapamycin + MMF

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Other Ways to Reduce GVHD: Look at the Donation

We collect from donor a mix of many kind of cells:
Stem Cells and LOTS and LOTS of immune cells.

- Some immune cells can induce GVHD (Naïve T-cell)
  - ***ALLOREACTIVE – BAD guys***
- Some immune cells can prevent or reduce GVHD (Regulatory Tcells)
  - ***TOLERANCE – GOOD guys***

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Strategies to Avoid GVHD

- Post-transplant Cytoxan (PTCy)
- Graft manipulation

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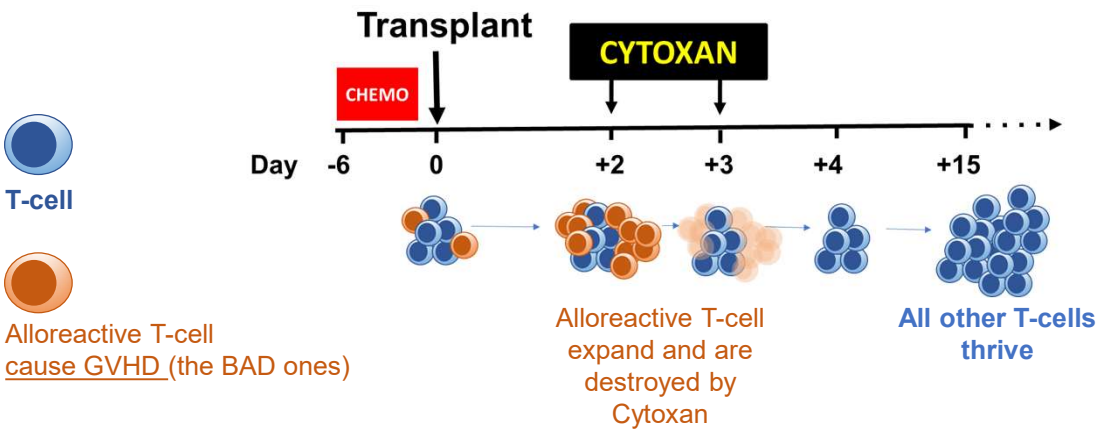
How post-transplant Cytoxan (PTCy) works



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Post transplant Cytoxan (PTCy): Study and Clinical Data

- PTCy (+TAC/MMF) is already used world-wide for transplant from children or parents (Haplo)
- BMT CTN 1203 clinical trial showed promising results in transplant from siblings and unrelated donors.
- **Phase III BMT CTN 1703** study evaluated outcomes post reduced-intensity conditioning transplant in patients randomized to receive PTCy + TAC + MMF vs standard TAC+ MTX

PTCy=post-transplant cyclophosphamide TAC=tacrolimus MMM=mycophenolate mofetil

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Holtan et al ASH 2022

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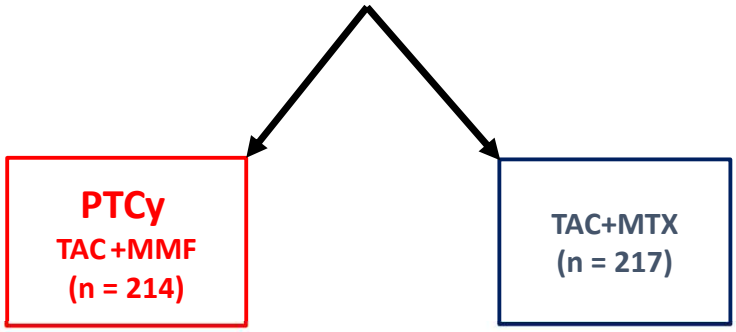
BMT CTN 1703: Study Design

431 Patients received reduced-intensity transplant from well matched donors



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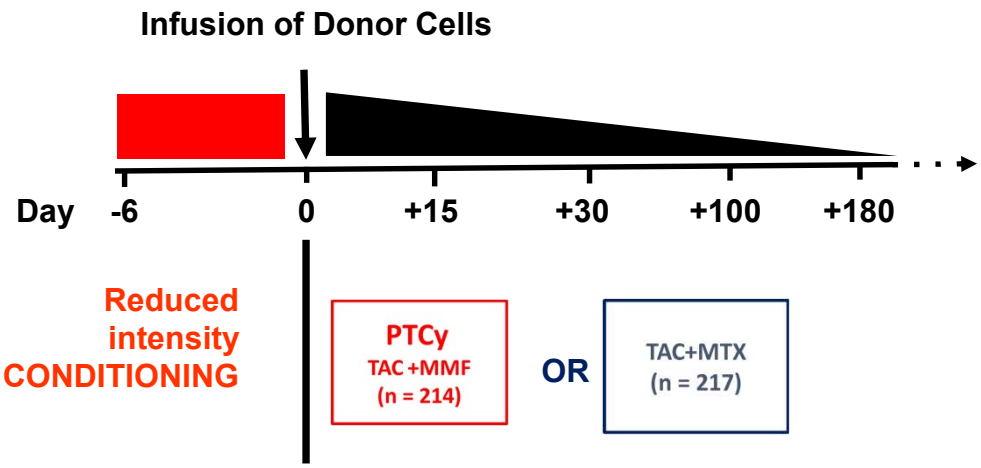
BMT CTN 1703: Study Design



MTX=methotrexate

Holtan et al ASH 2022

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BMT CTN 1703: Patients Transplanted

	PTCy + TAC + MMF (n = 214)	TAC + MTX (n = 217)
Men	63%	58%
Women	37%	42%
Age: average	66 years	66 years
Age: range	21-79 years	26-78 years
Disease		
▪ Leukemia	60%	58%
▪ MDS	29%	30%
▪ Lymphoma	11%	8%
Donor type		
▪ Related	28%	31%
▪ Unrelated	72%	69%

Holtan et al ASH 2022

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BMT CTN 1703: Results

	PTCy + TAC + MMF (n = 214)	TAC + MTX (n = 217)
Patients living without disease and without GVHD 1 year post transplant	53%	35%

Holtan et al ASH 2022

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BMT CTN 1703: Results

	PTCy + TAC + MMF (n = 214)	TAC + MTX (n = 217)
Patients with **acute GVHD** 100 days post transplant	**6%**	**15%**
Patients with **chronic GVHD** 1 year post transplant	**12%**	**25%**
Patients with **Cancer Relapse** 1 year post transplant	**21%**	**20%**
Transplant mortality 1 year post transplant	**12%**	**17%**

Holtan et al ASH 2022

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BMT CTN 1703: Conclusions

PTCy + TAC + MMF:
2023 new standard of care
for GVHD prophylaxis in well-matched donor transplant for adults receiving reduced-intensity conditioning

Holtan et al ASH 2022. Abstr LBA-4.

Other Ways to Reduce GVHD: Look at the Donation

We collect from donor a mix of many kind of cells:
Stem Cells and LOTS and LOTS of immune cells.

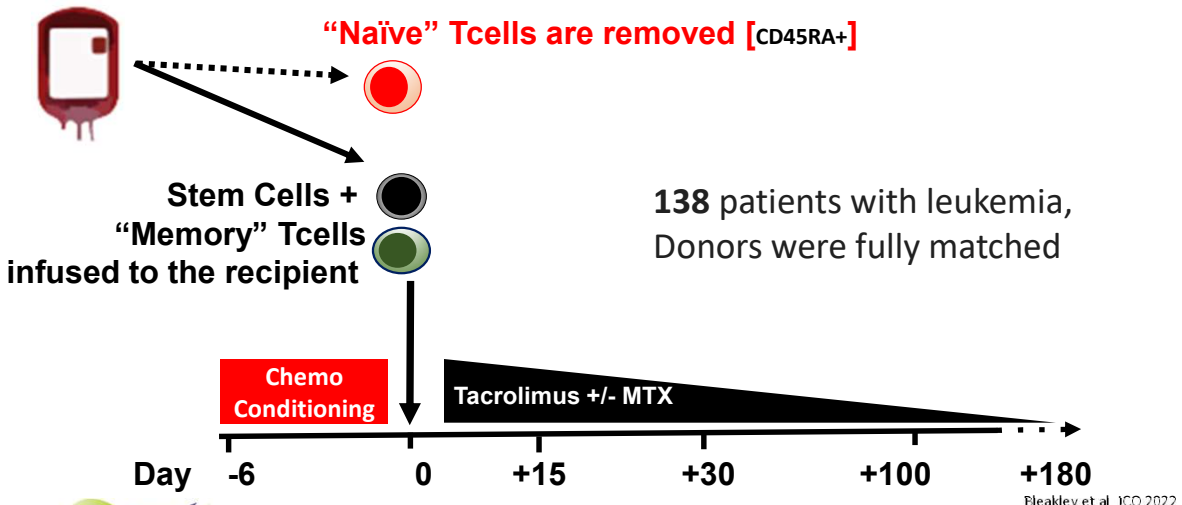
- Some immune cells can induce GVHD (Naïve T-cell)
  - ***ALLOREACTIVE – BAD guys***
- Some immune cells can prevent or reduce GVHD (Regulatory Tcells)
  - ***TOLERANCE – GOOD guys***

Other Ways to Reduce GVHD

Donor collection :

- Let's remove the bad guys
- Let's help the good guys

"Let's remove the BAD guys" approach



"Let's remove the BAD guys" approach

	"Naïve"Tcell depleted (n = 138)
Patients with **acute GVHD g≥3** 180 days post transplant	**4% None severe**
Patients with **chronic GVHD** 1 year post transplant	**7% None severe**
Patients living without disease and without GVHD 3 year post transplant	**68%**
Overall Survival 3 year post transplant	**77%**

Bleakley et al JCO 2022

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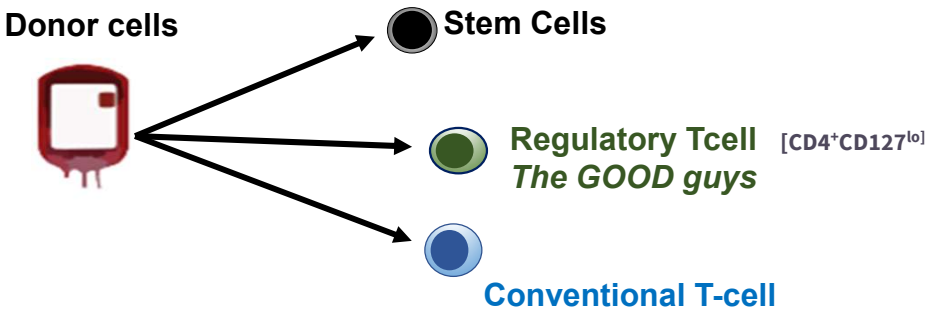
"Let's help the GOOD guys" approach

ORCA-T



Oliai et al, ASH 2022

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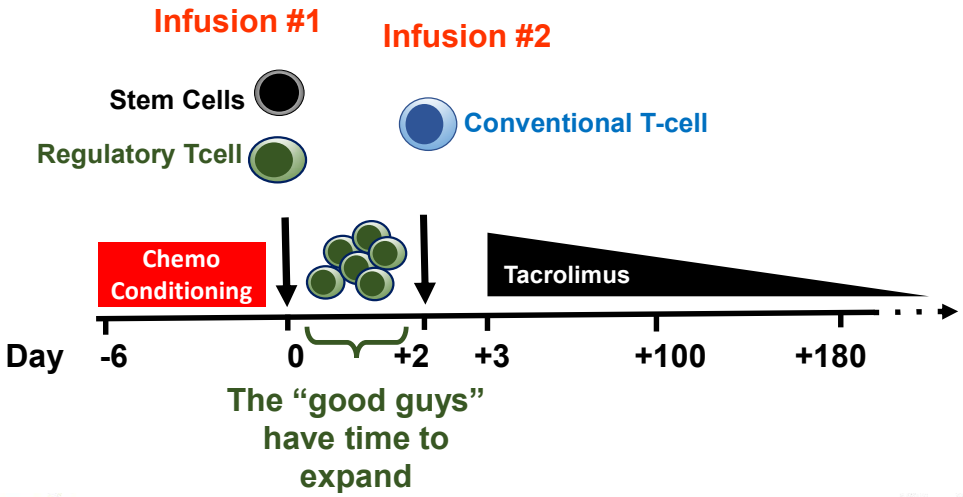
"Let's help the GOOD guys" approach: ORCA-T



Oliai et al, ASH 2022

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ORCA-T: clinical trials

- 127 patients, with high-risk blood cancers
- Donors were fully matched-related (n=66) or unrelated (n=61).
- Transplant was with high-dose chemo or radiation
- Post-transplant single-agent tacrolimus
- Outcomes were compared with 375 matched patients from the CIBMTR registry

NCT04013685
NCT01660607

Oliai et al, ASH 2022

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ORCA-T: Results

	ORCA-T (n = 127)	CIBMTR Control (n = 375)
Patients with **acute GVHD g≥3** 180 days post transplant	5%	16%
Patients with **chronic GVHD** 1 year post transplant	6%	38%
Relapse free survival 1 year post transplant	81%	62%
Non Relapse mortality 1 year post transplant	5%	10%
Overall Survival 1 year post transplant	91%	68%

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Oliai et al, ASH 2022

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ORCA-T: Results

	ORCA-T (n = 127)	CIBMTR Control (n = 375)
Patients living without disease and without GVHD 1 year post transplant	76%	34%

A multi-center randomized controlled phase 3 trial comparing Orca-T to standard of care is currently enrolling across the US (NCT05316701).

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Oliai et al ASH 2022

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GVHD treatment: Principles

- Steroids: mainstay of Systemic Treatment
- Acute: 40-60% response < 5 days
- Chronic: needs long course, combo not better
- When steroids don't work: always poor outcome

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GVHD: CHALLENGES

- No treatment fits all patients
- Largely ineffective treatments
- Treatment is toxic, immunosuppressive, might be needed lifelong
- Impact on quality of life, return to family life, relationships, work

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GVHD: Ideal treatment

- Effective
- Not toxic
  - Does not reduce immune defenses
  - Does not damage organs in the long-run

New drugs approved for GVHD treatment

	Type of GVHD	FDA approved
Ibrutinib (Imbruvica)	Chronic	2/8/2017
Ruxolitinib (Jakafi)	Acute	5/24/2019
	Chronic	9/22/2021
Belomosudil (Rezurock)	Chronic	7/16/2021

Ibrutinib (Imbruvica)

- **Pill:** once a day with water
- Already used for treatment of lymphomas and leukemia
- *How does it work?*
  - Blocks B and T cells responsible for GVHD
  - Stops production of antibodies involved in GVHD
  - Stops production of inflammatory substances (cytokines) involved in GVHD

Ibrutinib

In original study including 42 patients with bad GVHD resistant to steroids:

- In 31% of patients, GVHD went away completely
- 38% of patients had partial resolution of GVHD
- In 55% of patients, the response lasted at least 11 months
- 64% of patients could reduce the usage of steroids like prednisone

- **It works on sclerotic GVHD:**
  - 61% of patients with sclerosis showed improvement and in 39% tightening of the skin went away

Waller EK, BBMT 2019
PCYC-1129-CA

Ibrutinib (Imbruvica)

Adverse effects:

>20%

- Fatigue;
- Bruising
- Low platelets
- Muscle spasm
- Nausea
- Pneumonia
- Mount sore

~5%

- Irregular heartbeat

Ruxolitinib (Jakafi)

- **Pill:** twice a day
- Already used for other blood diseases (myelofibrosis and P.Vera)

- **How does it work?**
  - *Modulates immune system* to switch off GVHD: regulates the development, proliferation, and activation of several immune cell types.

Ruxolitinib

REACH2 Trial : acute GVHD

Randomly assigned 309 patients with severe steroid-refractory acute GVHD to receive ruxolitinib 10 mg twice daily (n = 154) or best available therapy (n = 155)

- The improvement was seen in **62%** of patients compared to 39%.
- GVHD went completely away in **34%** of patients on ruxolitinib vs 19% in the control group
- The good response was maintained after 2 months of treatment in more patients in the ruxolitinib group than in the control group (40% vs. 22%)

Ruxolitinib

REACH3 Trial : chronic GVHD

- Randomly assigned 329 patients with moderate or severe steroid-refractory or dependent chronic GVHD to receive ruxolitinib 10 mg twice daily (n = 165) or best available therapy (BAT; n = 164)
- The improvement was seen in **50%** of patients compared to 26%.
- The responses lasted up to 1 year and 7 months
- **Patients reported improved quality of life and symptoms**

Ruxolitinib (Jakafi)

Adverse effects:

>35%

- Anemia
- Low platelets

>20%

- Infection, fungal, viral
- Liver test go up

Belumosudil (Rezurock)

- **Pill:** once or twice a day with food
- **Totally new drug designed to fight fibrosis (ROCK inhibitor)**

- **How does it work?**
  - Modulates immune system to switch off GVHD, does not depress the immune system
  - **Anti-fibrosis**

Belumosudil

- **77%** of patients treated improved; noted responses in all affected organs
- In 50% of patients the response lasted at least 14 months
- Very well tolerated
- **Signals of response in patients who experienced treatment failure with ruxolitinib and ibrutinib.**

Cutler et al, Blood 2021
Study: ROCKstar

Belumosudil (Rezurock)

Adverse effects:

≥20%

- Fatigue
- Edema, muscular pain
- Liver test go up
- Headache
- GI upset

On the Horizon: DRUG on CLINICAL TRIAL

Axalitimab:

Anti CSF-1R antibody that blocks cells involved in GVHD (macrophage)

- 40 patients with very bad GVHD, received, on average 4 previous therapies: 65% had already ibrutinib, 52% ruxolitinib, 20% belumosudil
- **Infusion IV every 2 weeks**
- **67%** of patients improved, worked in all affected organs
- Responses noted by the **first month** of treatment
- Drug was well tolerated, minimal drug-drug interactions

Ongoing clinical trial AGAVE-201 (NCT04710576)

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Kitko et al. JCO 2022

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Thank you !!!

My Patients!

My Nurses

My colleagues

BMT*Infonet*

Pharmacists
Transplant coordinators
Case managers
Social workers
Administrative staff

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QUESTIONS?

Marcello Rotta, MD
Colorado Blood Cancer Institute, Part of the
Sarah Cannon Cancer Institute at
Presbyterian/St. Luke's Medical Center

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