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2020 NIH Chronic GvHD Consensus Project on Criteria for Clinical Trials

The 2020 Treatment of cGvHD Report

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Treatment of cGvHD WG3

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- **Bruce R. Blazar**
  - Advisor (Magenta Therapeutics, BlueRock Therapeutics); research funding (BlueRock Therapeutics, Rheos Medicines, Childrens' Cancer Research Fund, KidsFirst Fund); co-founder of Tmunity
- **Daniel Couriel**
  - Consultant (Fresenius Inc); research support (Fresenius Inc); non-promotional speaker (Seattle Genetics)
- **Zachariah DeFilipp**
  - Consultant (Syndax Pharmaceuticals, Inc); research support (Incyte, Corp., Regimmune Corp.)
- **Hildegard Greinix**
  - Consultant (Novartis, Sanofi, Therakos); non-promotional speaker (Amgen, Novartis, Roche, Sanofi, Therakos)

Progress in Treatment of cGvHD

- Large, multicenter phase II and phase III clinical trials in upfront or steroid-refractory cGvHD completed:
  - Ibrutinib (NCT02195869, NCT02959944)
  - Ruxolitinib (NCT03112603)
  - Itacitinib (NCT03584516)
  - Belumosudil (KD025) (NCT03640481)
- FDA approval of Ibrutinib for treatment of cGvHD after failure of ≥1 lines of systemic therapy.
- FDA evaluations of other agents ongoing.

Current Status and Areas for Improvement

- First-line therapy of cGvHD has remained corticosteroids.
- Expanded treatment options but persistent chronicity of disease:
  - Long treatment duration with associated serious side-effects.
  - Multiple lines of empirically selected therapies to be given.
  - Progression into irreversible fibrotic manifestations observed.
  - Persistence of immune dysfunction with serious infectious complications for prolonged periods of time.
- No uniform improvement of long-term outcome of patients with cGvHD yet to be seen.

Purpose of this Document

- Setting research priorities and direction in treatment of cGvHD by considering:
  - Pathophysiologic mechanisms of disease
  - Clinical phenotype (inflammatory, fibrotic, and combinations; immune dysfunction)
  - Mechanisms of action of novel agents
- Gaining more and important insights into pathophysiologic mechanisms of cGvHD and clinically investigated novel agents by predefined biosampling and biomarker analysis during future clinical studies.
- Working towards a more biological and individualized strategy for treatment of cGvHD instead of empirical steroid-based approach.

Ultimate Goal for Upfront Treatment of cGvHD Patients

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Instead of **STEROIDS FIT ALL**

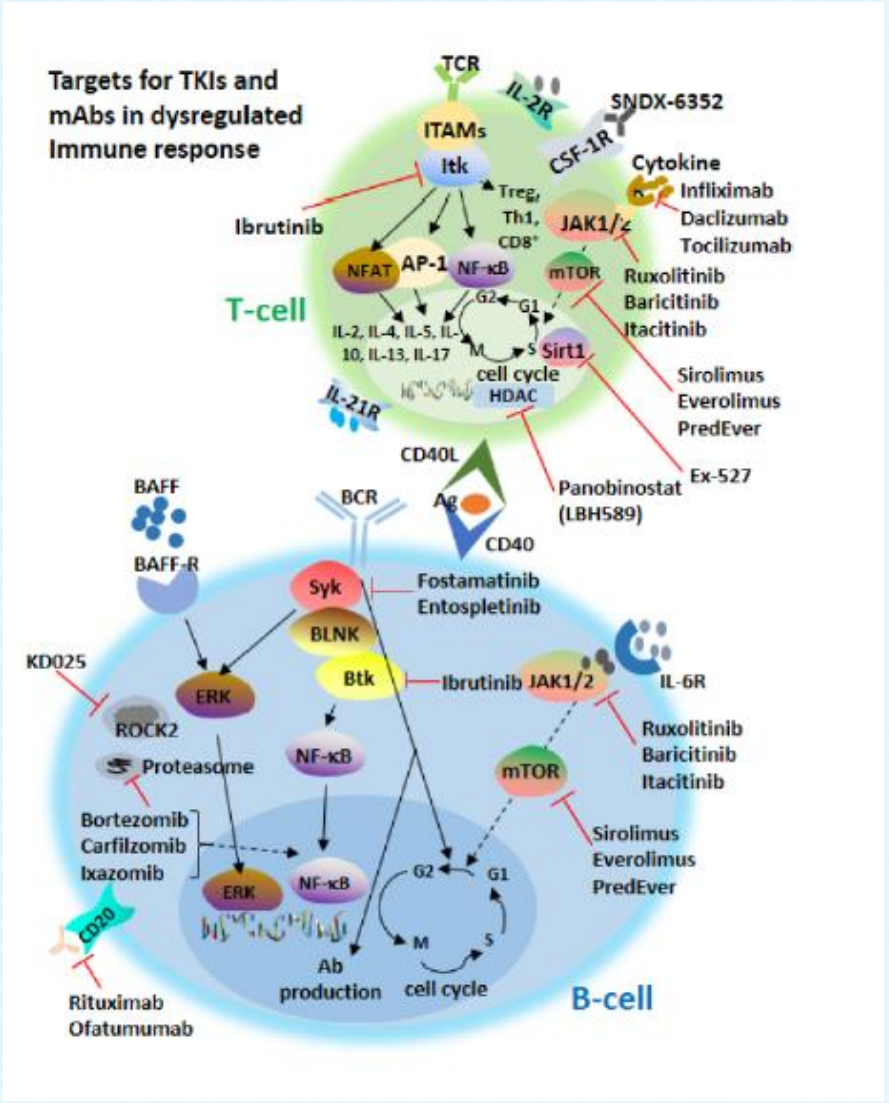
- Improved insights into biology of cGvHD
- Availability of targeted therapies relevant to pathophysiology of cGvHD

Administration of the **RIGHT DRUG TO THE RIGHT PATIENT AT THE RIGHT TIME**

Biological Considerations

- **Biological phenotype**
  - Inflammatory
  - Fibrotic/sclerotic
  - Immune dysfunction
- **Treatment goals of cGvHD**
  - Reduction of activation status of B-and T cells
  - Anti-inflammatory effect
  - Prevention/reduction of fibrosis
  - Repairing/maintaining immune regulation
- **Known targets/signaling pathways** from (pre)clinical studies relevant for pathophysiology of cGvHD

Miriad of Potential Treatment Agents for cGvHD



Saidu NE et al. Front Immunol 2020

Exploring Associations between Clinical Disease Manifestation, Biological Profiles, and Treatment Effect in cGvHD

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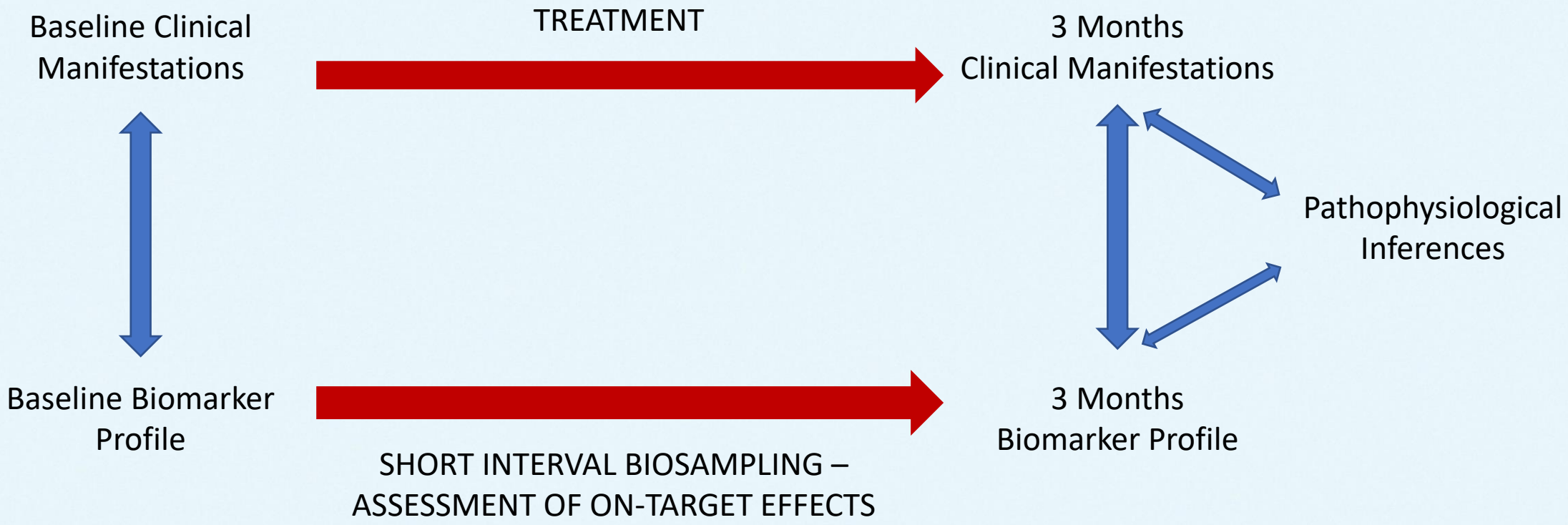

Analyses of Immune Response in cGvHD Pathogenesis and Therapeutic Targets

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	Tier 1 (Core testing)*	Tier 2 (Specialized testing, upfront centralized storage)**
PB cellular specimens	Multiparameter FACS: • T cell and B cell differentiation • Dendritic cells, monocytes, macrophages • Molecules involved in cell migration, positive and negative regulation and cytokine receptors	Multiparameter CyTOF • Intracellular signaling and transcription factor expression High throughput technologies including single cell RNA-sequencing with ATAC-sequencing: chromatin accessibility
Tissue biopsies	Immunohistochemistry	Multiplexed immunofluorescence • Spatial relationships of cells e.g. CODEX
Serum and plasma	ELISA for biomarkers	Mass spectrometry • Proteins or metabolites

*Tests readily available at many study sites, not cost prohibitive. **Tests that require special equipment, sophisticated analytics, complex sample processing or incur high cost.

First-Line Therapy of cGvHD: Steroid-Free

- **Advantages**
  - Test the biological and clinical effects of study drug in absence of confounding by other concurrent treatment.
  - Ability to assess true impact of study drug on pathophysiological pathways of cGvHD in an individual patient.
  - Avoid steroid toxicities.
- **Risks**
  - Rapid progression of cGvHD under study drug – health risk for patient
  - Toxicities and side effects of study drug
  - Lack of efficacy

Clinical Trials for Upfront Treatment of cGvHD

Eligibility criteria

- Broad eligibility to allow assessment of responses in multiple phenotypes
- No corticosteroid treatment

Study endpoints

- **Primary:** safety and feasibility; clinical need for steroid treatment = treatment failure
- **Relevant secondary:** ORR*, organ-specific response rate* and response acccording to clinical phenotype after 3 and 6 months; ORR at 1 year; long-term outcome including OS; correlate biological endpoints

*according to NIH Response criteria Lee SJ 2015

Steroid-Free First-Line Therapy of cGvHD: Safety Considerations

- Excellent **study center infrastructure** required
  - Patient access to OPD on 7/24 basis
  - Continuous patient care
  - Ability to perform Tier 1 and Tier 2 studies
  - Clinical phase 1 experience

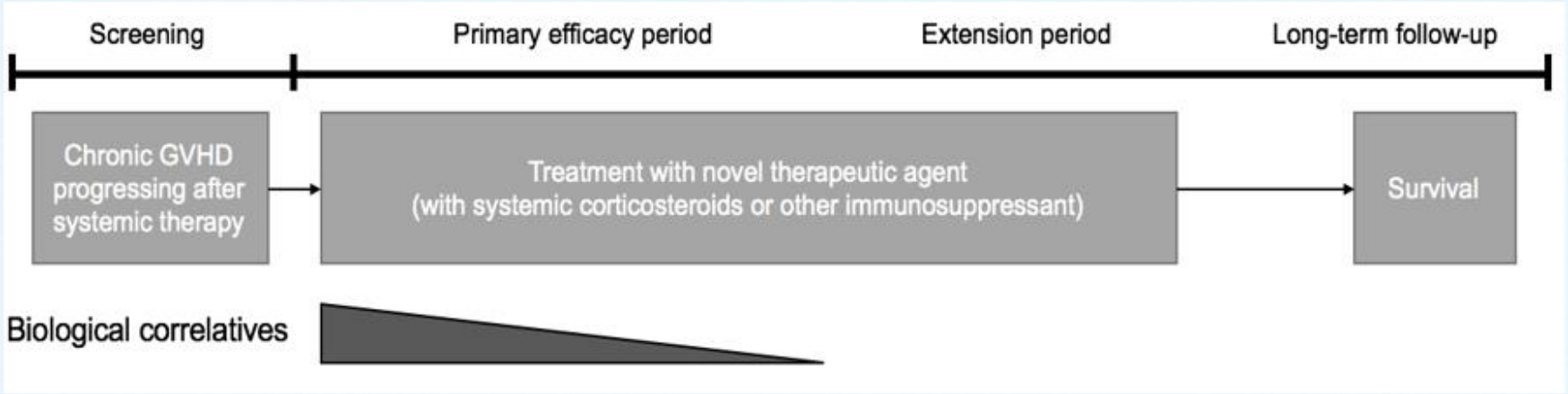
- **Clinical need for corticosteroid therapy during study = treatment failure**
  - Corticosteroid indications
  - Precise documentation of steroid use (dose, duration, time of onset)
  - Stopping rules for phase 1 study

Beyond First-Line Therapy of cGvHD

- **Corticosteroid considerations**
  - Steroid-refractory* and treatment-refractory cGvHD
  - Ongoing steroid therapy at time of study enrollment
- **Disease considerations**
  - Heterogeneity in disease manifestations and treatment history
  - Presence of inflammatory vs fibrotic manifestations
  - Multiple concurrent features of cGvHD
  - Persistent and severe immune dysfunction
- **Study Goals**
  - Broaden understanding of interactions between clinical disease, therapeutic response and disease biology
- Explore **combinations of novel targeted agents** with non-overlapping toxicities to increase efficacy and safety

*according to 2014 NIH Clinical Trial Design WG Report Martin PJ et al 2015

Clinical Trials for Salvage Treatment of cGvHD



Eligibility criteria

- Subjects with shorter disease duration
- All phenotypes and defined manifestations
- Limitations based on steroid exposure (duration, dose, etc)

Study endpoints

- **Primary:** ORR* at 3 and 6 months
- **Relevant secondary:** organ-specific response rate* and response acccording to clinical phenotype after 3 and 6 months; ORR at 1 year; disability and QoL; OS; correlate biological endpoints

*according to NIH Response criteria Lee SJ 2015

Future Directions: Targeted Therapies Based on Biology and Clinical Phenotype Response

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Small and medium sized clinical trials
- Upfront systemic treatment
- Treatment-refractory at early time points

Better understanding of associations between:
- Clinical phenotype
- Pathophysiologic mechanisms of disease
- Biological and clinical effect of novel agents

Alternative study design to
- Consolidate data in different phenotypes
- Investigate more selectively biomarkers
- Perform extension trial

Randomized clinical trials
- Comparison with steroids, specific agents or best available therapy

Summary of Recommendations: Upfront Therapy

- Investigate novel agents for initial systemic therapy in designs without concurrent corticosteroid administration in experienced academic medical centers.

- Evaluate novel agents in correlation with predefined biosampling and biomarker analysis to obtain important insights into pathophysiologic mechanisms of new onset cGvHD and its response to targeted therapies.

Summary of Recommendations: Beyond First-Line Therapy

- Timely initiation of targeted therapies with response assessment according to clinical phenotype and biological study results.
- Drug choice based on preclinical data, mechanism of action, clinical data (cGvHD, autoimmunity and organ transplantation) or correlative biological studies whenever possible.
- Evaluate broad panels in biological correlative studies to inform selection of a narrower panel for subsequent studies.
- Obtain tissue biopsies before and after treatment to enable evaluation of disease involvement, response to therapy and correlation with blood/marrow biomarkers.
- Build an advanced cooperation between academic medical centers, medical societies and industry to support biology-based strategic approach.

Summary of Recommendations III

- Conduct randomized clinical trials with agents demonstrating disease activity in large single arm studies.
- Explore master protocols to enable rapid clinical screening of new treatments in early-phase studies.
- Future goal: work towards algorithms for personalized approach to treatment based on clinical phenotype and biological profile of each patient.

Issues for Discussion

- **Upfront therapy**
  - Steroid-free study design: patient recruitment, safety, stopping rules
- **Salvage therapy**
  - Assessment of mechanisms of action of novel agents when used in combination therapy including steroids
- **Biological sampling**
  - Choice, logistics, funding, qualified infrastructure, governance
- **Future directions of clinical trials**
  - Confirmation of promising initial results in randomized studies:

    ? comparator arm/standard of care
  - Alternative study designs for targeted therapies based on biology and clinical phenotype response

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Reviewer

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Panel Q and A

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Audience Discussion

Steroid-Free First-Line Therapy of cGvHD: Clinical Endpoints for Clinical Studies

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- **Primary endpoint** of phase I study
  - Safety and feasibility
  - Stopping rules for futility and unacceptable toxicity required
  - Clinical need for steroid treatment = treatment failure
- **Secondary endpoints**
  - ORR* at 3 and 6 months
  - Organ-specific response rate* after 3 and 6 months
  - Response acccording to clinical phenotype after 3 and 6 months
  - Biomarker results in correlation with clinical phenotype
  - Biomarker results in correlation with response
  - ORR at 1 year
  - OS at 1 year

*according to NIH Response criteria Lee SJ 2015

Beyond First-Line Therapy of cGvHD: Clinical Endpoints

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- **Efficacy**
  - ORR* after 3 and 6 months of therapy
  - Organ-specific response rate* after 3 and 6 months
  - Response acccording to clinical phenotype after 3 and 6 months
  - Biomarker results in correlation with clinical phenotype
  - Biomarker results in correlation with response
  - Steroid-sparing (magnitude, timing and durability of steroid dose reduction)
  - Discontinuation of steroids and durability
  - Patient-reported outcomes
  - ORR at 1 year – durability of response
  - Discontinuation of study agent and durability
  - OS at 1 year
- **Safety**
  - Treatment-emergent adverse events
  - Defined stopping rules

*according to NIH Response criteria Lee SJ 2015