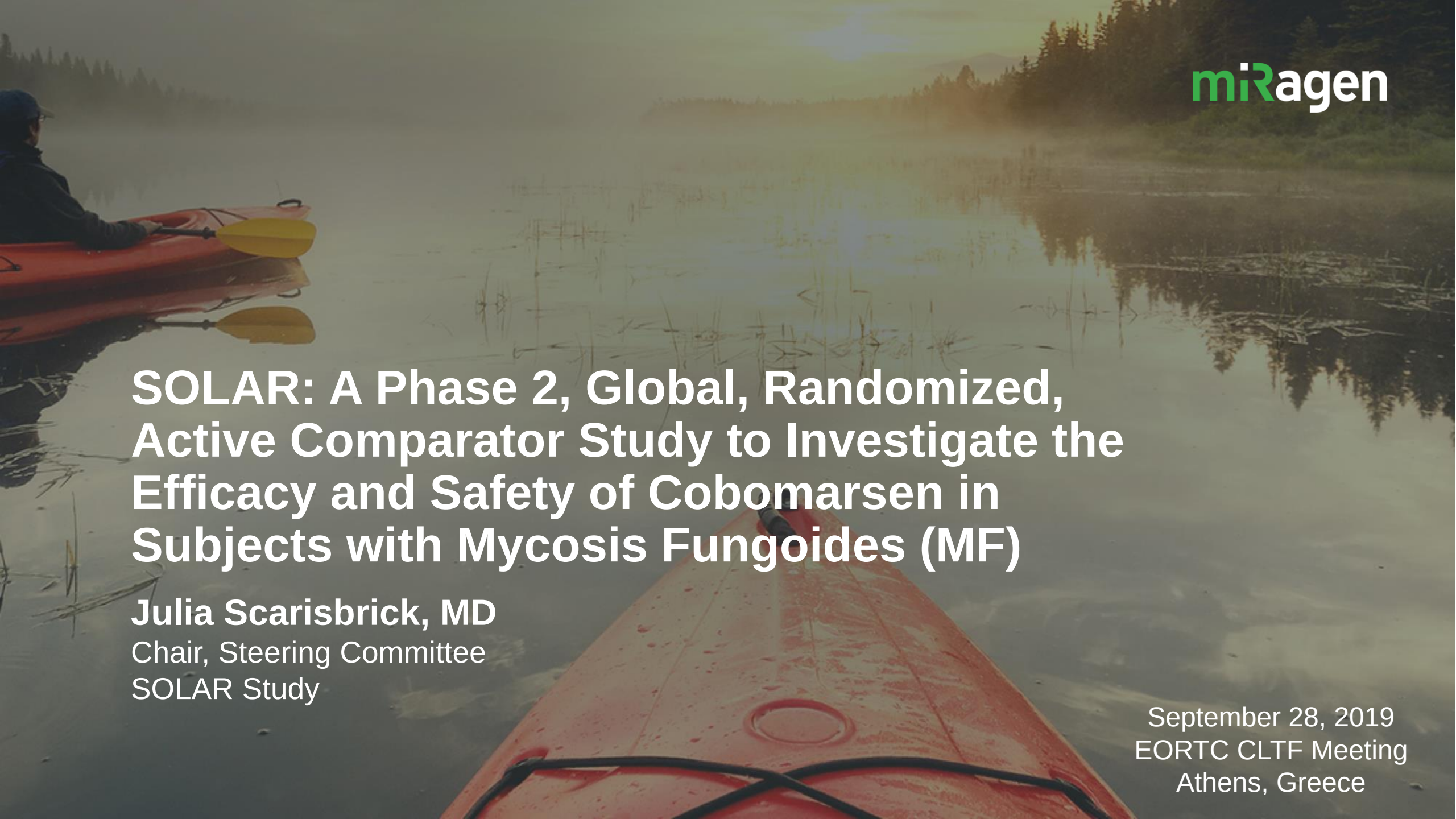


SOLAR: A Phase 2, Global, Randomized, Active Comparator Study to Investigate the Efficacy and Safety of Cobomarsen in Subjects with Mycosis Fungoides (MF)

Julia Scarisbrick, MD
Chair, Steering Committee
SOLAR Study

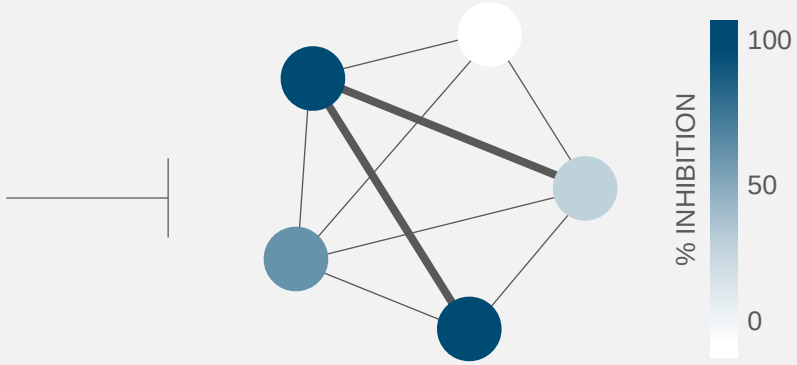
September 28, 2019
EORTC CLTF Meeting
Athens, Greece

microRNAs Regulate Network Biology to Maintain Homeostasis

- microRNAs have been evolutionarily selected to regulate networks of genes
- microRNAs are dysregulated in many diseases
- Dysregulation of microRNAs is associated with alteration of downstream gene networks and disease
- microRNA-targeted therapy is focused on disease modification by restoring homeostasis to dysregulated processes
- microRNA therapeutics are particularly suited for complex, multigenic disorders

Conventional Therapies
(Small molecules, Antibodies, siRNA, etc)
Single molecule as target

microRNA-based Therapies
Network (pathway) as target



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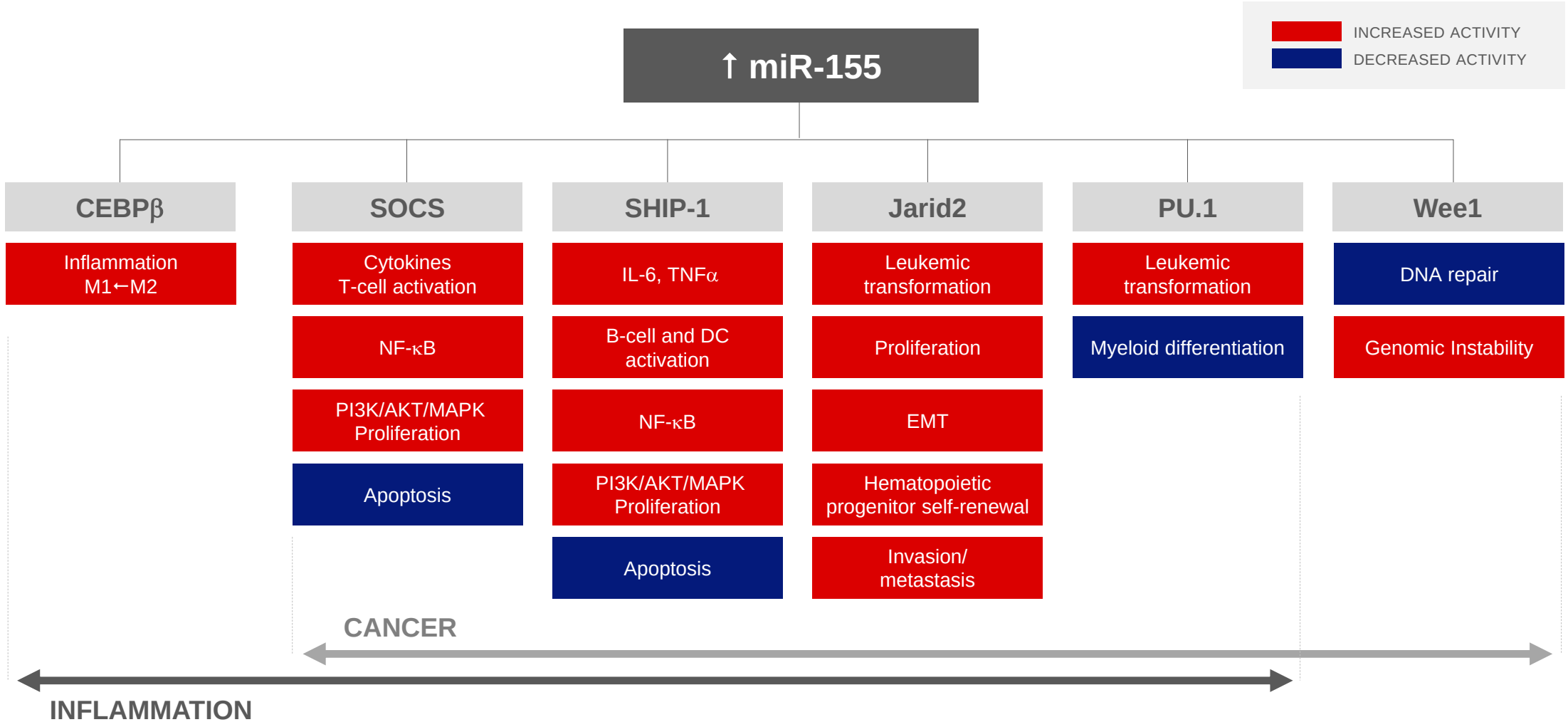
mir-155 Is a Master Regulator of Inflammation and Oncology

Cobomarsen inhibits miR-155



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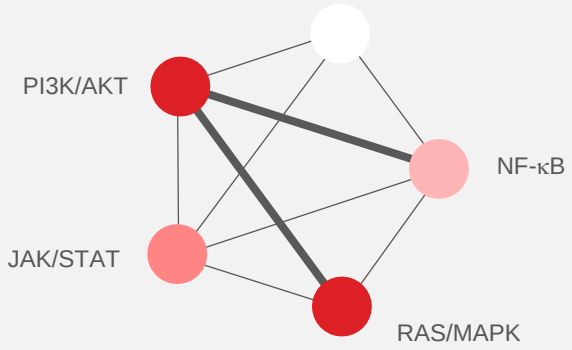
miR-155 Regulates Disease Gene Pathways Implicated in Mycosis Fungoides

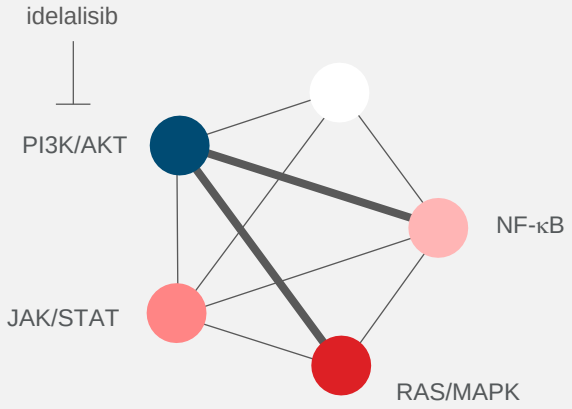
↑ miR-155



Multiple survival and immune pathways activated

- ✓ Proliferation
- × Apoptosis
- ✓ T-cell activation

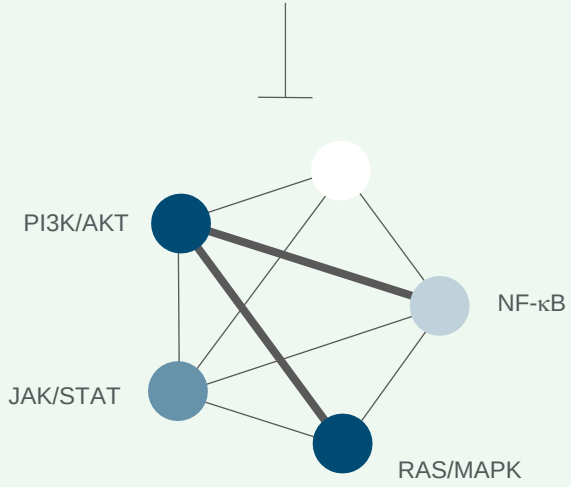
Conventional Therapy (e.g., idelalisib)



One survival pathway inactivated

- ✓ Proliferation
- × Apoptosis
- ✓ T-cell activation

Cobomarsen



Multiple survival and immune pathways inactivated

- × Proliferation
- ✓ Apoptosis
- × T-cell activation

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Cobomarsen Shows Favorable Tolerability

No serious adverse events attributed to cobomarsen in CTCL

No acute inflammatory toxicities

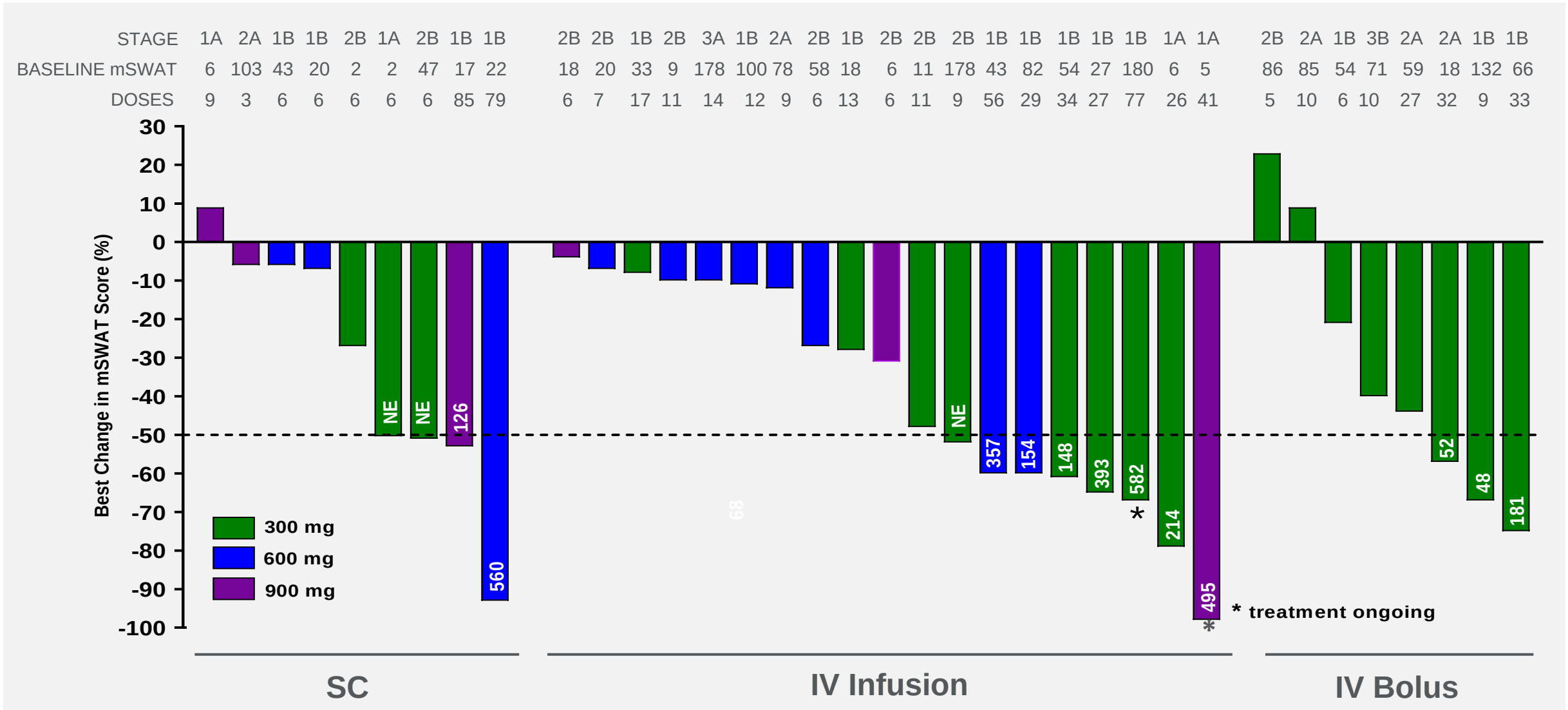
No significant abnormalities found in liver, kidney or blood

+ **COBOMARSEN HAS BEEN GENERALLY SAFE** and well tolerated
  - Multiple patients receiving more than a year of therapy
  - Total of 1254 cumulative doses (across 68 patients)
+ **NO SIGNIFICANT LAB ABNORMALITIES** found in liver function, kidney function, thyroid function and platelet counts
+ **NO EVIDENCE OF METABOLIC** or **HEMATOLOGICAL** toxicities
+ **NO EVIDENCE OF GLOBAL IMMUNOSUPPRESSION**
+ **NOVEL OLIGONUCLEOTIDE** drug class

In Total, **68 Patients** (CTCL, ATLL, DLBCL, and CLL from Ph1 and CTCL SOLAR) **Have Been Exposed To Cobomarsen** For Up To 2.5 Years

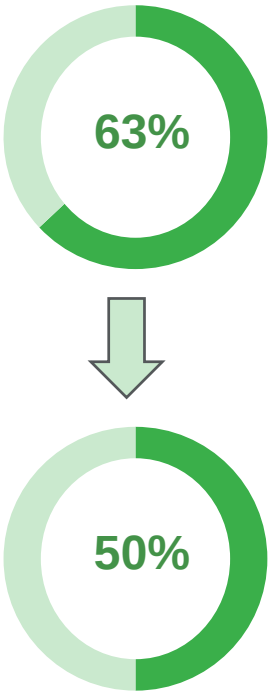
(Data Cutoff July 23, 2019)

Phase I CTCL Thirty-three of Thirty-six Patients (92%) Treated Systemically with Cobomarsen Have Shown mSWAT Score Improvement



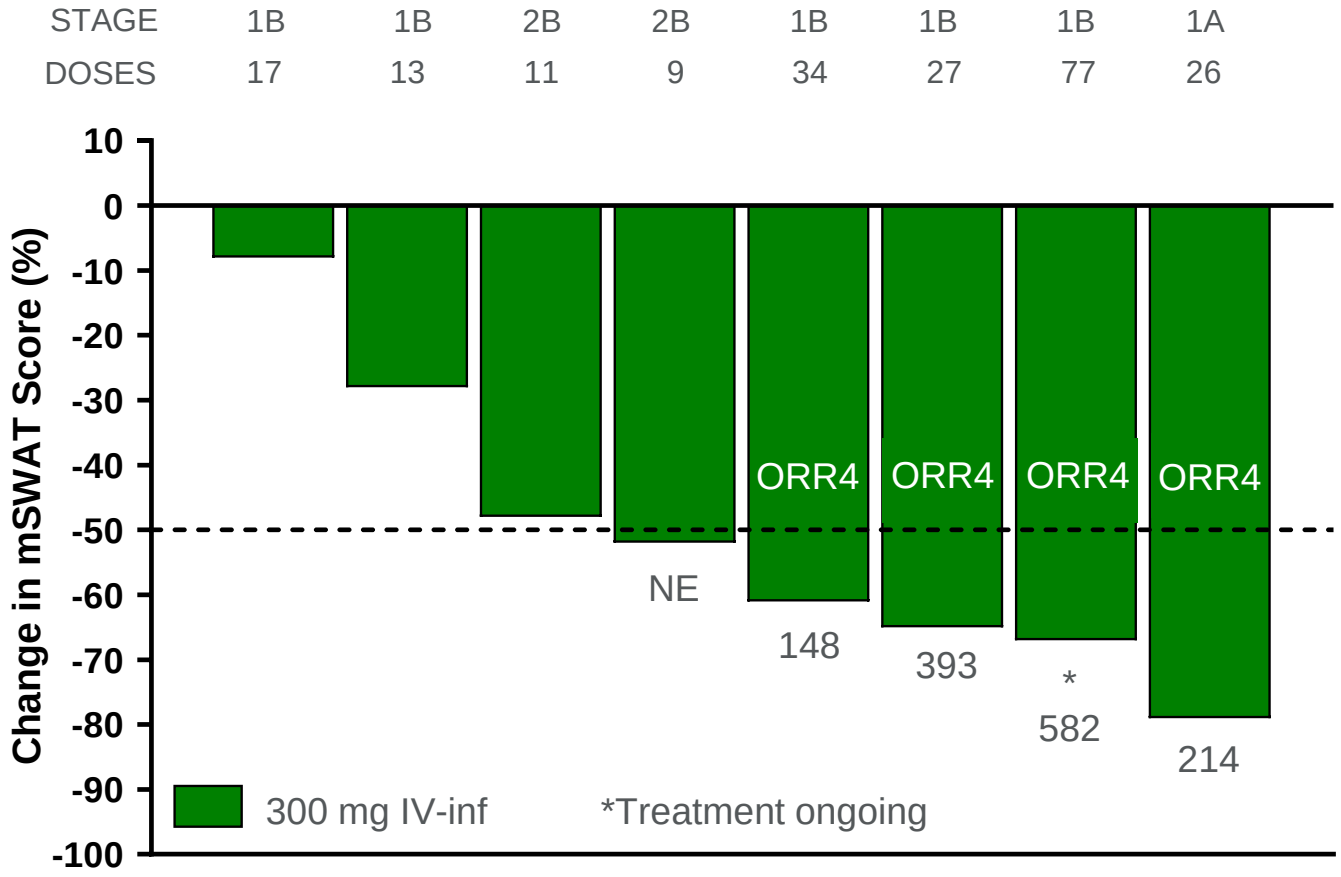
(Data Cutoff January 9, 2019)

Phase I CTCL



Patients Treated with Cobomarsen Administered as a 300 mg IV-infusion Achieved a PR

Reached ORR4



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SOLAR: A Phase II Clinical Trial of Cobomarsen in Mycosis Fungoides

Protocol Overview

SOLAR Phase 2 Clinical Trial

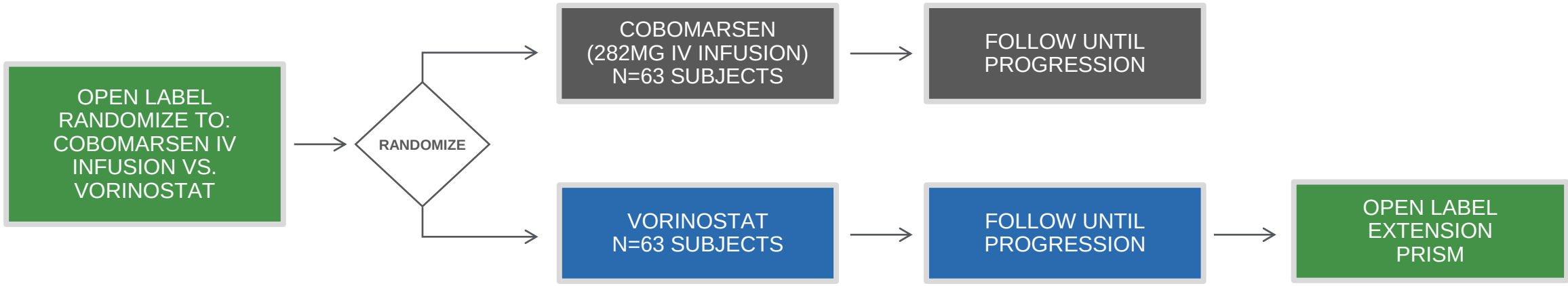
A Randomized, Open-Label, Parallel-group, Active Comparator, Global Trial in Patients with Stage IB-III Mycosis Fungoides (MF)

Primary Endpoint

+ Overall Response Rate of Four Months (ORR4) using Global Response Criteria

Secondary Endpoints

+ Progression-free Survival
+ Patient Reported Outcomes



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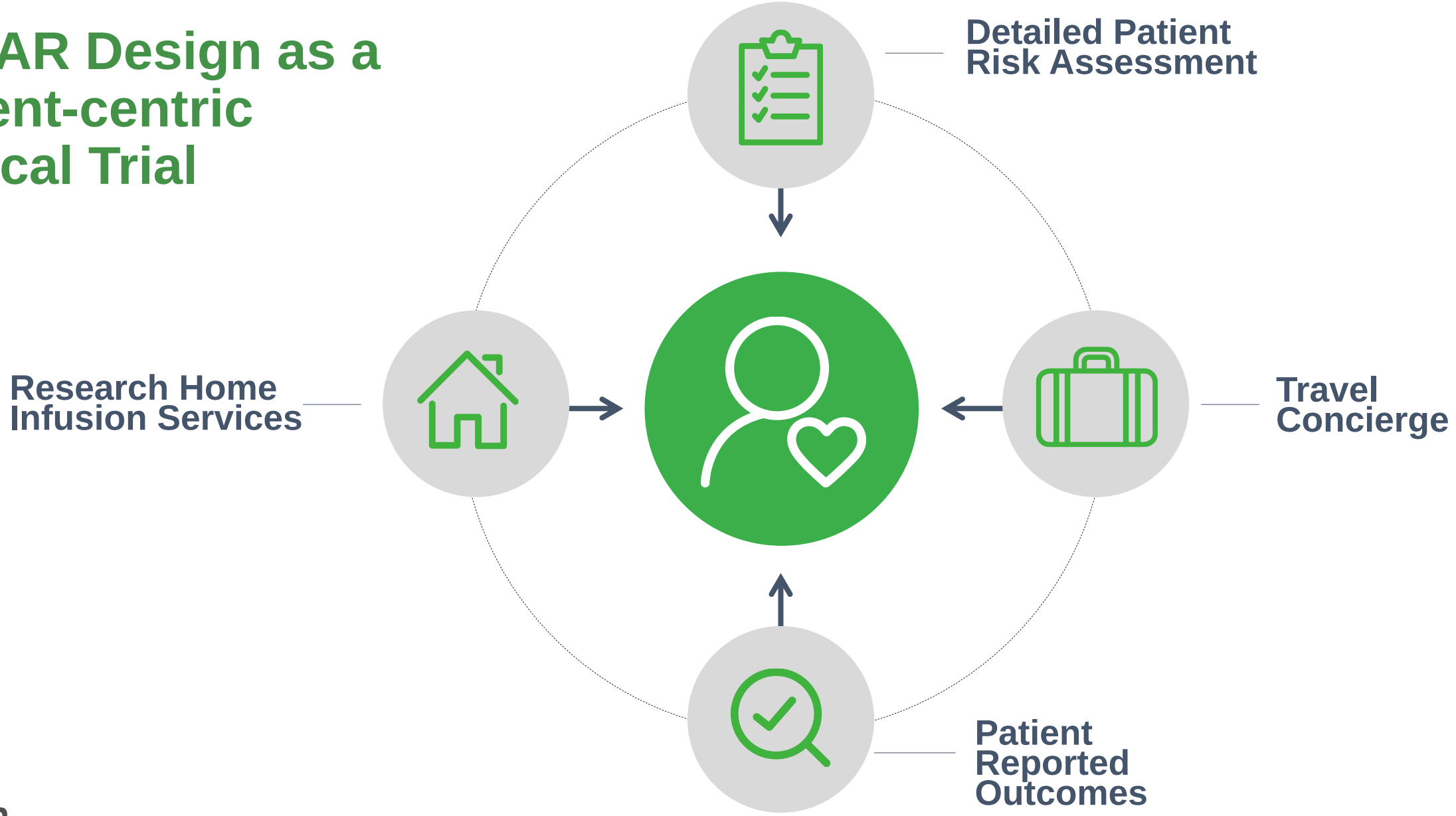
SOLAR Design as a Patient-centric Clinical Trial



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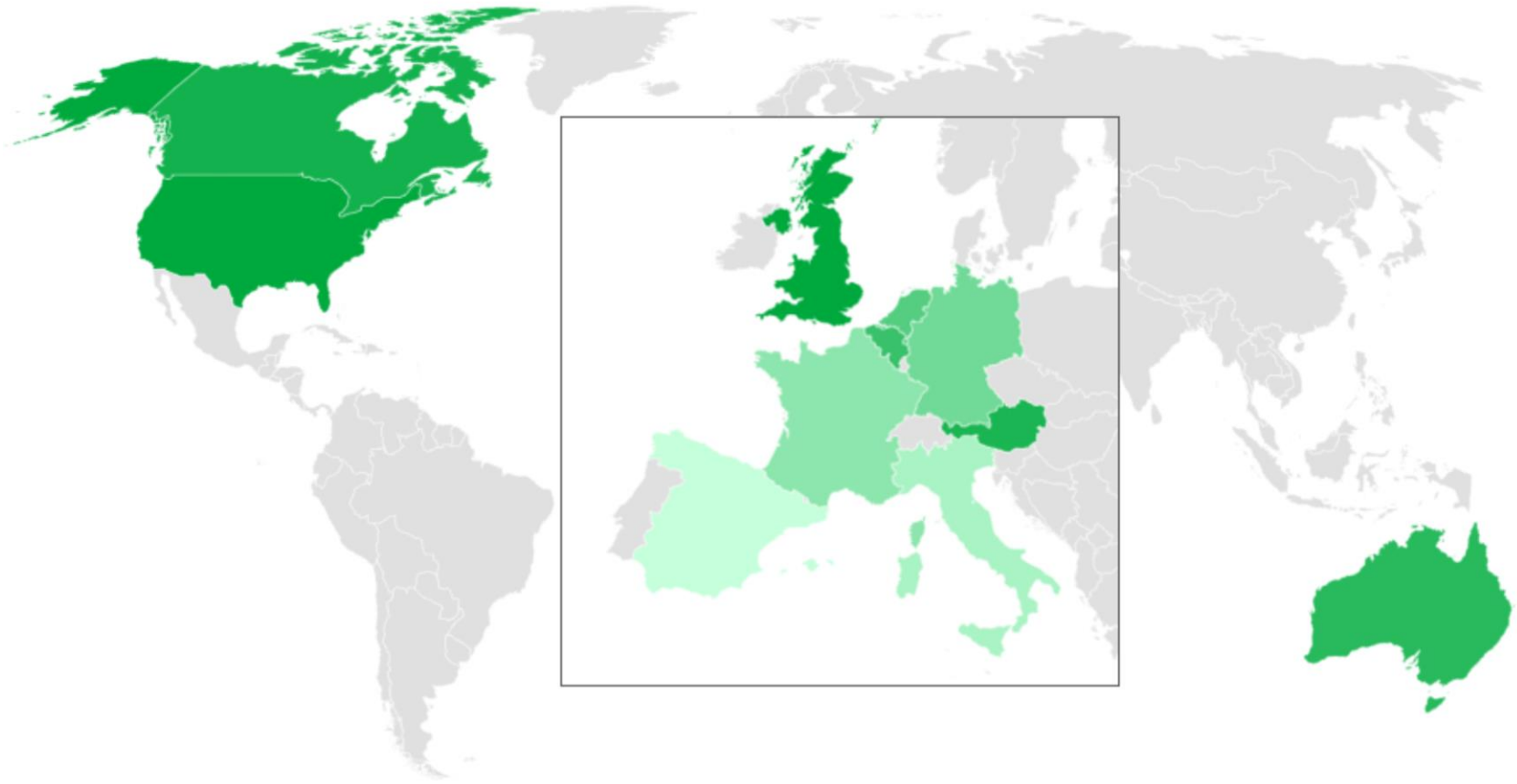
SOLAR Study Participating Countries

126 Subjects at ~60 Sites

Across 11 Countries

- Austria
- Australia
- Belgium
- Canada
- France
- Germany
- Italy
- Netherlands
- Spain
- United Kingdom
- United States



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SOLAR Design

+ **PHASE 2 STUDY:** comparing cobomarsen to vorinostat
    - Up to 126 subjects – 1:1 randomization
    - ~60 sites in US, Canada, EU & Australia
    - Duration of study – up to 36 months
+ **STRATIFICATION FACTORS:**
    - Skin tumors (0 vs 1 or more)
    - Having 0-1 vs 2 of the following prognostic factors:
        - 60 years age at diagnosis
        - LDH level > ULN at diagnosis
+ **DURATION OF TREATMENT:** until progression or study completion
    - 28-day screening period, active treatment period, follow-up for progression and survival
+ **INTERIM ANALYSIS FOR FUTILITY:** after the first 40 subjects followed for at least 6 months
+ **LONG-TERM FOLLOW UP:** every 3 months (phone call) for survival

SOLAR Patient Reported Outcomes

- PROs provide important patient centric outcomes
- Daily Pruritus and Pain
  - Novel information on the fluctuation of these symptoms
  - Effect of drug on the severity and frequency of the symptoms (numeric fluctuation in the rating scales show an actual perception of severity at that time point)
- Weekly PGI-C and PGI-S
  - Patient's impression regarding the importance of daily/weekly changes in pain and pruritus severity
- Monthly Skindex-29 and MF/SS QOL
  - Disease specific QOL instruments which assess the drug impact on other aspects of their disease
  - Provides correlation of mSWAT score change with the actual impact of this change on their QOL (clinical meaningfulness of change in mSWAT)

Patient Reported Outcomes	Daily	Weekly	Every 4 Weeks
Pain Numerical Rating Scale*	✓		
Pruritus Numerical Rating Scale*	✓		
Patient General Impression of Severity (PGI-S)*	✓		
Patient General Impression of Change (PGI-C)		✓	
Patient Impression of Treatment Side Effects		✓	
MF/SS Quality of Life (QOL)			✓
Skindex-29			✓

** Conducted daily for 6 months, then weekly thereafter*

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Selection of the Comparator

- **REGULATORY REQUIREMENT TO HAVE ONLY ONE COMPARATOR**
- **BEXAROTENE OR METHOTREXATE** were not selected (limited patient population naïve to these therapies)
- **LIMITED CONTROLLED TRIALS** in CTCL to gather comparator response rates that can be utilized to calculate sample size
- **HDAC INHIBITOR CONSIDERED A GOOD COMPARATOR** so vorinostat and romidepsin were considered; vorinostat administration is less burdensome on patients (oral medication vs. 4-hour in hospital IV infusion)
- **VORINOSTAT EFFICACY IS SIMILAR TO OTHER CANDIDATE COMPARATORS**

MF PATIENTS	ORR	ORR4	PFS
Vorinostat	7%	N/A	3.1 mos
Methotrexate	16%	7.7%*	3.5 mos
Bexarotene	16%	15.8%*	3.5 mos

Data from Mavoric and ALCANZA trials
* Includes pcALCL and MF patients

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Strategies For Management of Vorinostat Side Effects And Patient Retention Until Progression

- **miRagen PROVIDES** patient and physician guidelines on managing vorinostat side effects
- **MOST COMMON AEs** are gastrointestinal
- **PRACTICAL STRATEGIES**
  - Take vorinostat before bed
  - Remind patients to stay hydrated
  - Popsicles
  - Inform patients of possible side effects of the drug

- **OPTIONS TO MANAGE** side effects:
  - Lowering dose to 300 mg qd
  - Decreasing to 5 days per week
  - Stopping medication (but *continue with follow-up until progression*)
- **CAN PATIENTS WITH STABLE DISEASE OR PR/CR** that discontinue for tolerability cross to PRISM?
  - **No**: patients can discontinue treatment, but they NEED to remain on study UNTIL PROGRESSION to be eligible for PRISM

KEY INCLUSION CRITERIA

- Stages IB, IIA, IIB, III
- Must have received at least one prior therapy for CTCL (per NCCN guidelines for generalized skin involvement)
- mSWAT score ≥ 10

SPAIN	At least 2 prior systemic therapies
ITALY	Prior therapies, at least 1 systemic
FRANCE	Stage IIB or III only; 2 prior therapies, at least 1 systemic

KEY EXCLUSION CRITERIA

- Previous enrollment in a cobomarsen study
- Prior therapy with HDAC inhibitors or contraindication to vorinostat (or HDAC inhibitors)
- Evidence of (current) large cell transformation (LCT)
- Prior or current Sézary syndrome or mycosis fungoides with IIB
- Extensive nodal involvement with complete or partial effacement of LN (i.e., N3) or visceral involvement
- Unresolved toxicities from prior therapy
- Other medical conditions such as bleeding diathesis, prolonged QT syndrome or previous or concurrent malignancies

Protocol V3.0

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Treatment Washout Requirements (Prior to Screening)

5 Half Lives

Investigational Small Molecule Drug

Investigational Biologic Drug

8 Weeks

Systemic corticosteroid prednisone equivalent > 10 mg per day[1]

- Chronic use, more than 20 days total
- More than 3 short courses of 7 days

Immune therapy

- Antibody-directed
- Immunoglobulin-based
- Other monoclonal antibody therapies

4 Weeks

Macrolide or tetracycline antibiotics

Total skin electron beam (TSEB) therapy

Phototherapy

High potency topical corticosteroids (chronic use, more than 20 days total)[2]

Other topical MF treatments (chronic use, more than 20 days total)

Previous systemic MF treatments

Day -28

Screening Begins

[1] Stable regimen of **systemic** prednisone equivalent to **≤ 10 mg** per day is permitted

[2] Stable doses of **low to medium potency topical** corticosteroids are permitted

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Concomitant Steroid and Anti-pruritic Agent Guidance

NEW SYSTEMIC TREATMENT FOR CTCL WILL BE PROHIBITED DURING THE STUDY

Patient may *continue on*:

- ✓ Stable regimens of systemic prednisone equivalent to ≤10mg per day
- ✓ Stable dose of medium or low potency topical corticosteroids for the treatment of pruritus
- ✓ Stable dose of systemic anti-pruritic agents (not used for prophylaxis)
- ✓ Topical moisturizers

Patient may *start new*:

- ✓ Short courses (≤ 7 days) of low- and medium-potency topical corticosteroids
- ✓ Short courses of systemic or high-potency topical corticosteroids for non-CTCL indications
- ✓ Short courses (≤ 7 days) of systemic corticosteroids for CTCL indication allowed in exceptional cases
- ✓ Short courses (≤ 7 days) of oral antihistamines for symptomatic pruritus
- ✓ Short courses of other anti-pruritic agents for symptomatic pruritus are allowed in exceptional cases

Patients may not:

- ✗ Start new prophylactic systemic anti-pruritic agents
- ✗ Increase corticosteroid dose for CTCL-related symptoms
- ✗ Start new chronic courses of topical or systemic agents for pruritus or CTCL-related symptoms

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PRISM Overview

Open Label PRISM Study

For patients that have progressed

on the vorinostat arm in SOLAR

+ **TO BE ELIGIBLE FOR PRISM,** SOLAR patients on vorinostat must have **confirmed progression**
+ **ADDITIONAL THERAPIES** for MF **should not be initiated between SOLAR and PRISM**
+ **INCLUSION CRITERIA:** allows patients with **nodal progression** (N3)
+ **EXCLUSION CRITERIA:** patients with **blood progression** (B2)
+ **PRISM SCREENING ASSESSMENTS will not need to be repeated** if rolling directly from SOLAR

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For the most up to date study information,
please visit
miRagen.com/clinicians