COBOMARSEN (miR155 INHIBITOR) IN MYCOSIS FUNGOIDES

Christiane Querfeld, MD, PhD

2015... 2018 T-Cell Lymphomas: we are close to the finalization

Bologna, IT May 9, 2018

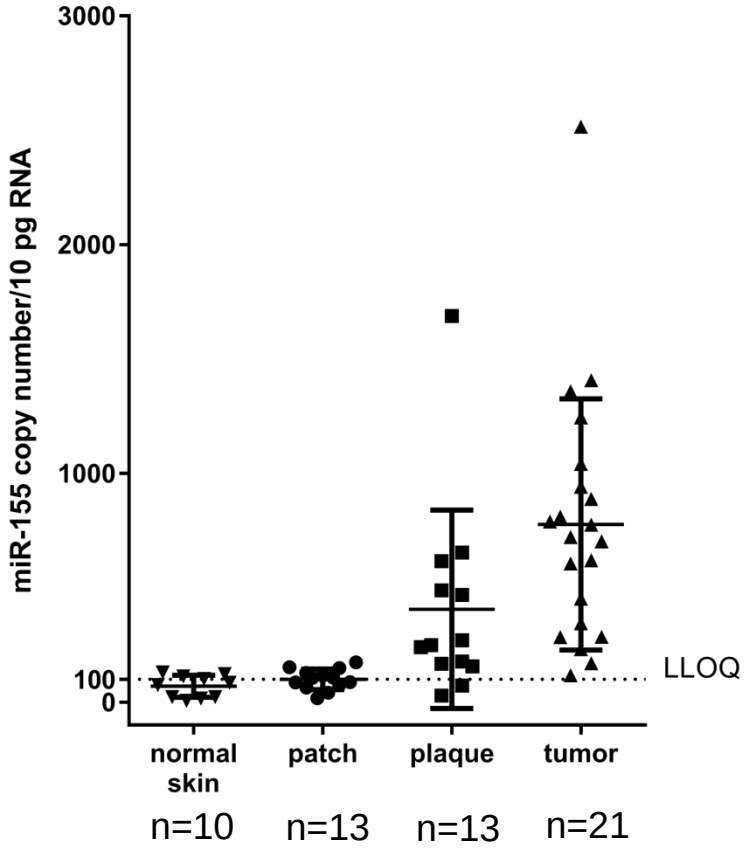
MICRORNA-155 IS ABNORMALLY ELEVATED IN CTCL AND REGULATES KEY PATHOGENIC PATHWAYS

- Epigenetic alterations have been implicated in the pathogenesis of lymphomas and leukemias including CTCL
- miRNA profiling and RT-PCR discriminate CTCL and non-malignant inflammation with a high accuracy
- miR-155 is overexpressed in CTCL skin
- JAK/STAT, NFkB and PI3K pathways are activated in CTCL and regulated by miR-155 that lead to uncontrolled clonal cell expansion

Ralfkiaer et al. Blood 2011; Netchiporouk et al. Cell Cycle 2014; Van Kester et al. 2011; Maj et al. Br J Derm 2012; Kopp et al. APMIS 2013; Kopp et al. Cell Cycle 2013; Moyal et al. Exp Derm 2013; Moyal et al. Br J Derm 2017

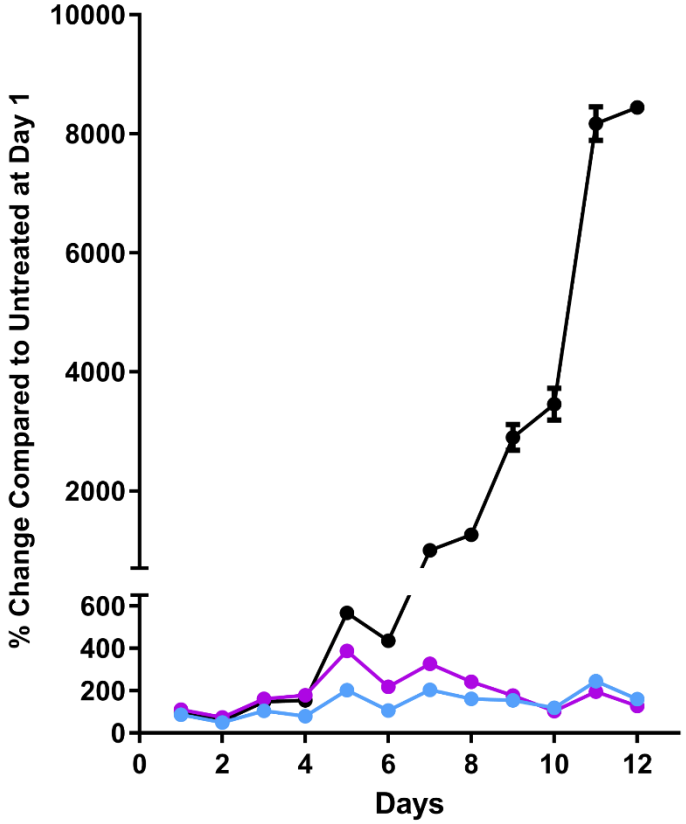
MIR-155 IS UPREGULATED IN MF LESIONS AND INHIBITION AFFECTS CELL GROWTH & APOPTOSIS

Lesion Type vs miR-155 Copy-Number

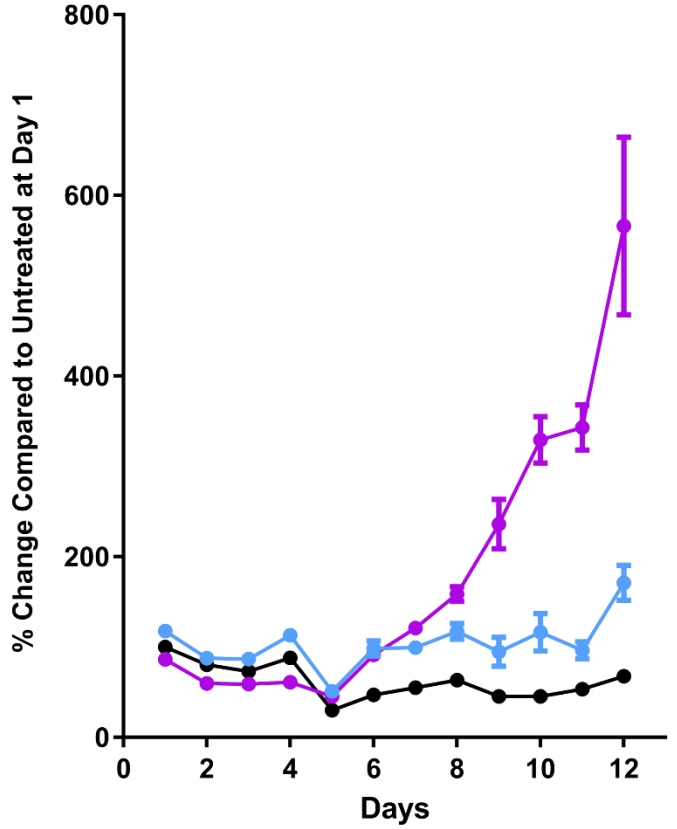


Archived tissue provided by Madeleine Duvic (MD Anderson)

Cell Proliferation of HuT102 Cells



Apoptosis Pathway Activation in HuT102 Cells



Untreated
Bexarotene
miR-155 Inhibitor (MRG-106)

PHASE 1 COBOMARSEN OPEN LABEL STUDY IN CTCL DESIGN AND INTERIM RESULTS

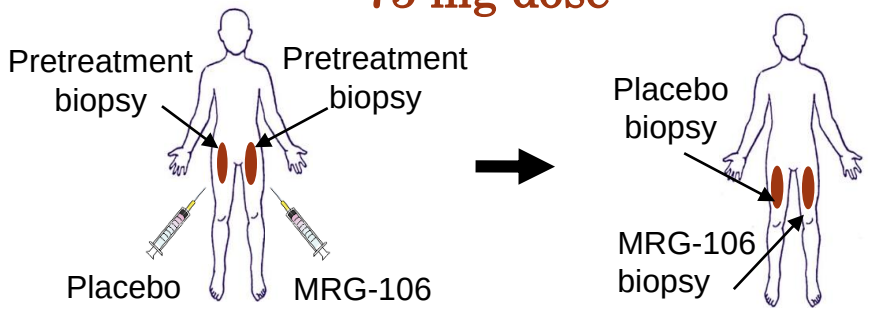
Safety and efficacy

COBOMARSEN: FIRST-IN-HUMAN PHASE 1 STUDY OF MRG-106 IN PATIENTS WITH MYCOSIS FUNGOIDES TWO-PART PHASE 1 CTCL STUDY

Part A

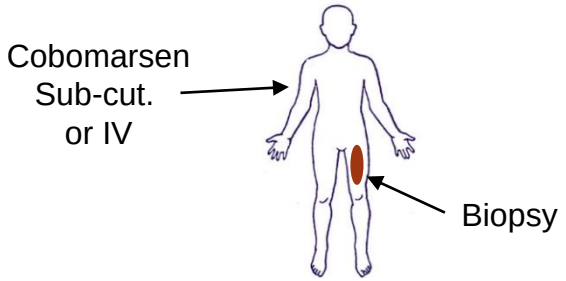
Intra-tumoral delivery of cobomarsen.

75 mg dose



Part B

Systemic SC or IV delivery to determine optimal potential dose. **300, 600 and 900 mg dose**



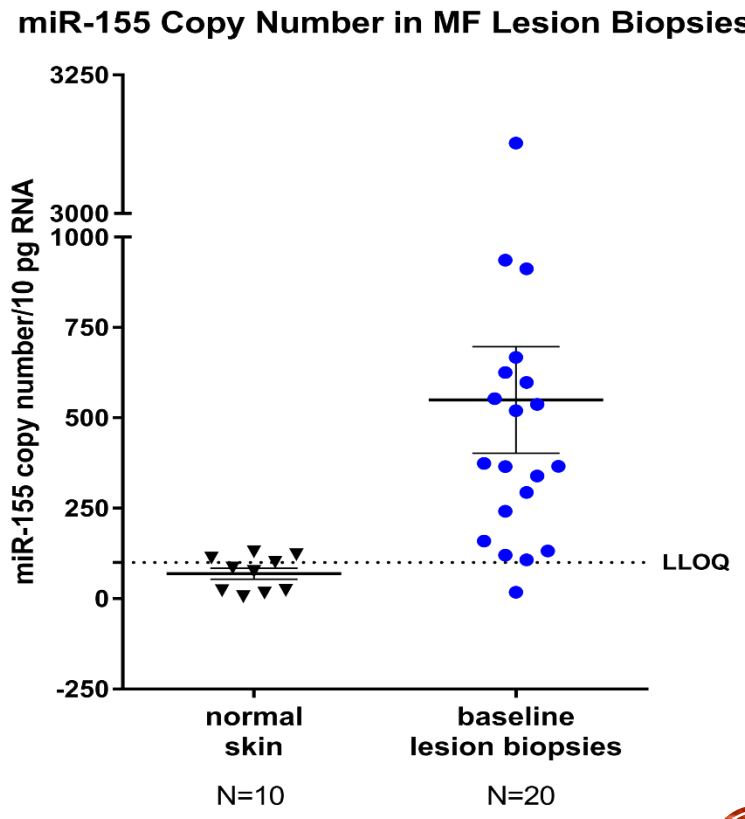
Objectives:

- **Primary**: Investigate safety & tolerability of multiple injections
- **Secondary:** Characterize the pharmacokinetic profile
- **Exploratory**:
  - Pharmacodynamic profile
  - Gene expression alterations
  - Histopathology of lesion biopsy
  - Imaging of tumor morphology

BASELINE CHARACTERISTICS

Demographic	Part A n = 6	Part B n = 30	Total n = 36
Sex			
Male (n, %)	5 (83%)	20 (67%)	25 (69%)
Age			
Median years (range)	61 (50-64)	63 (21-85)	63 (21-85)
Race			
White/Caucasian	4 (67%)	24 (80%)	28 (78%)
Black	1 (17%)	3 (10%)	4 (11%)
Asian	0 (0%)	1 (3%)	1 (3%)
Other	0 (0%)	2 (7%)	2 (6%)
Not reported	1 (17%)	0 (0%)	1 (3%)
Disease Stage at Screening			
Stage IA	0 (0%)	6 (20%)	6 (17%)
Stage IB	1 (17%)	8 (27%)	9 (25%)
Stage IIA	2 (33%)	3 (10%)	5 (14%)
Stage IIB	3 (50%)	9 (30%)	12 (33%)
Stage IIIA	0 (0%)	1 (3%)	1 (3%)
Stage IIIB	0 (0%)	3 (10%)	3 (8%)
Prior Systemic Therapies			
Number of Patients Reporting	6	25	31
Median # (range)	4 (1-6)	3 (1-13)	4 (1-13)
Prior Skin Directed Therapies			
Number of Patients Reporting	6	26	32
Median # (range)	4 (1-6)	3 (1-8)	3 (1-8)
Baseline mSWAT per Subject			
N	3	30	33
Median (range)	23 (3-96)	45 (2-180)	43 (2-180)

- Balanced across stages
- Patient population failed many prior therapies
- miR-155 elevated in most enrolled patient's lesions



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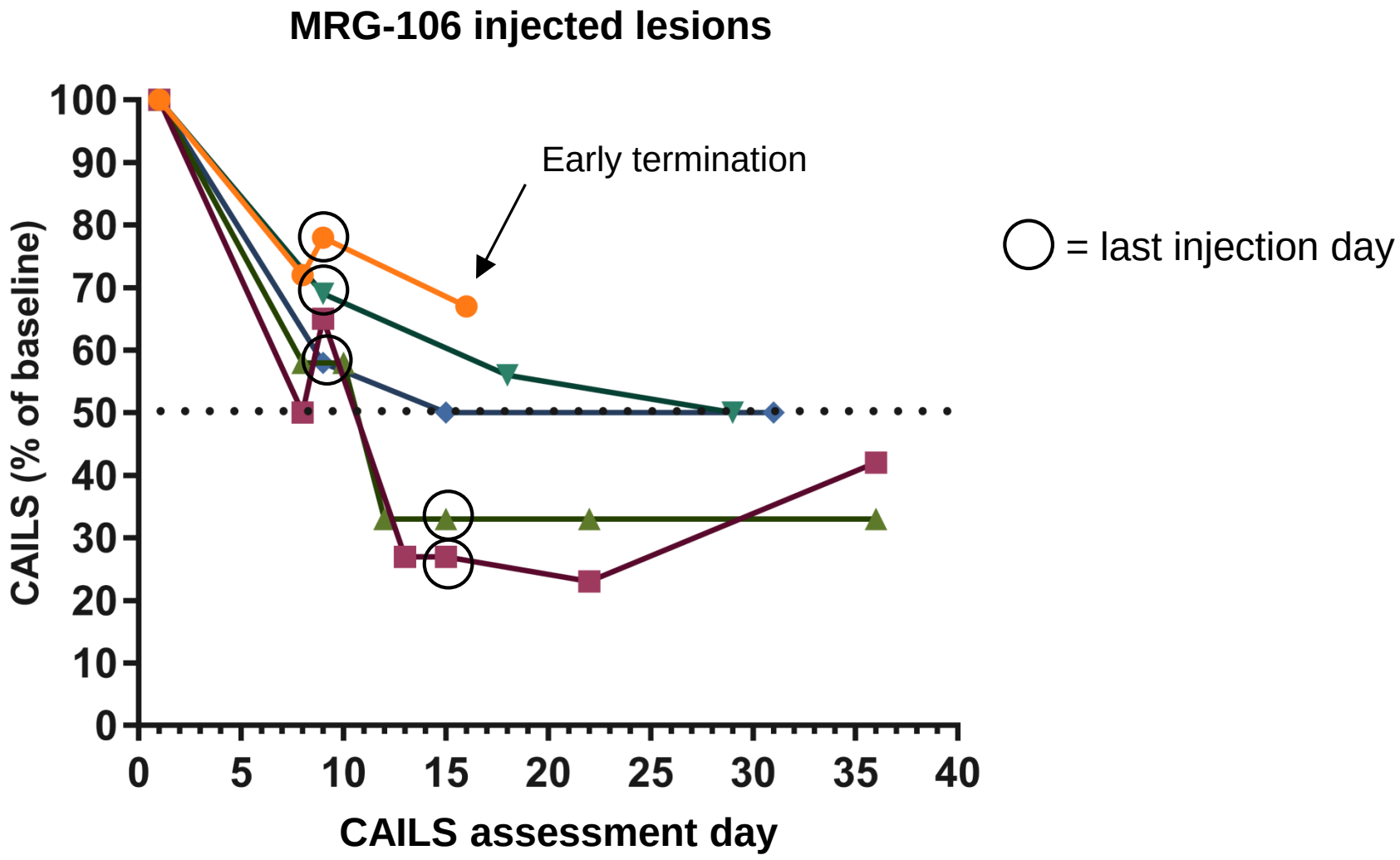
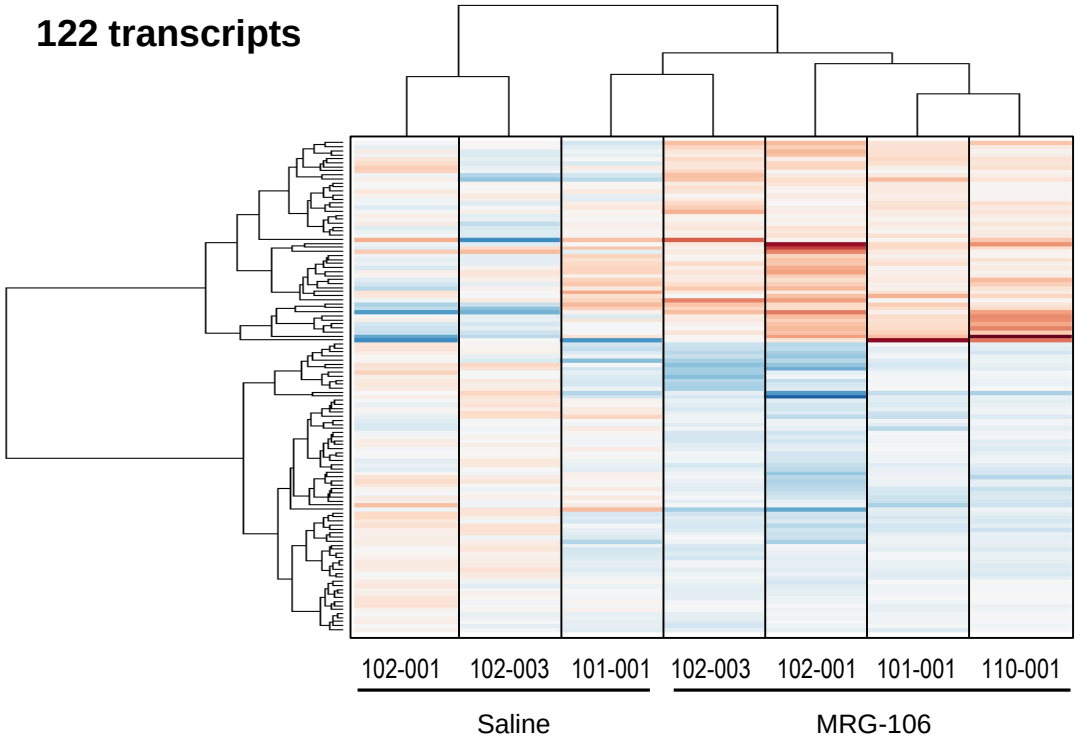
COBOMARSEN IMPROVED CAILS WITH INTRALESIONAL INJECTION (PART A)

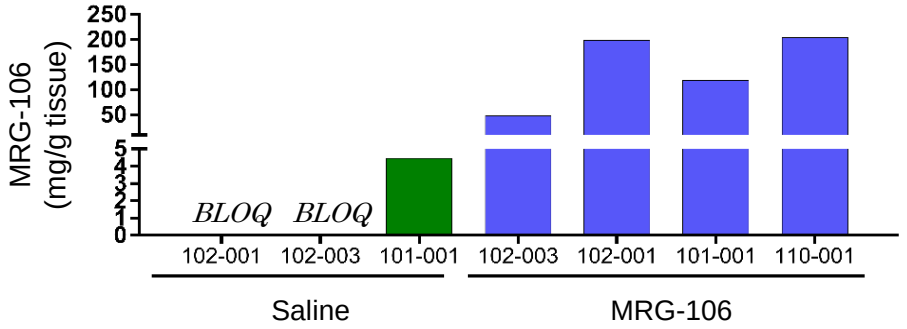


GENE EXPRESSION CHANGES WITH INTRALESIONAL INJECTION OF COBOMARSEN CORRELATE TO DRUG LEVELS IN MF LESION BIOPSIES (PART A)

Cobomarsen Decreases Key CTCL Pathways:

- **STAT**
- **PI3K/AKT**
- **NFkB**





Up-regulated vs. untreated
Down-regulated vs. untreated

COBOMARSEN SHOWS FAVORABLE SAFETY AND TOLERABILITY

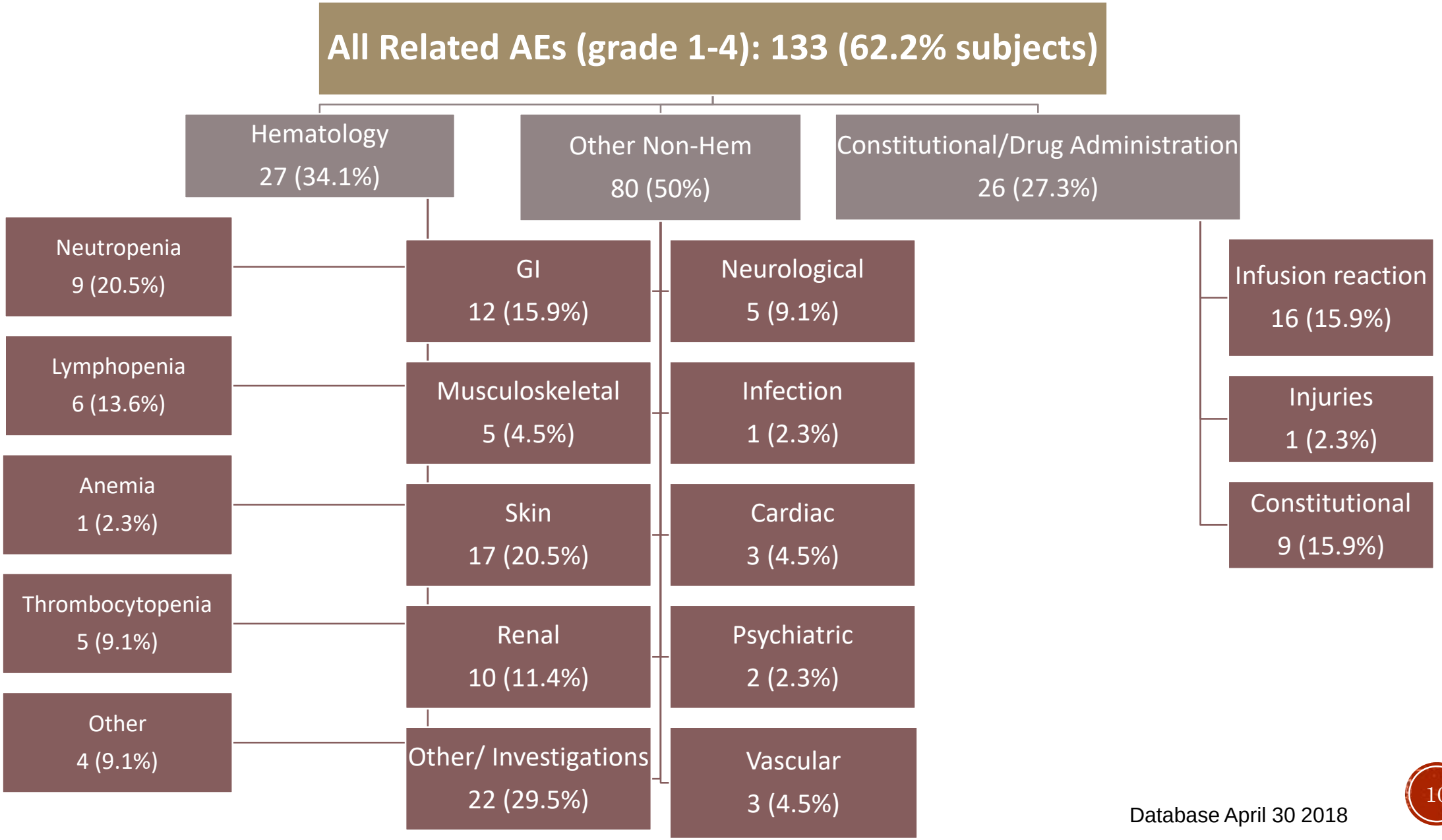
No Serious Adverse Events attributed to cobomarsen

No acute inflammatory toxicities

No significant abnormalities found in liver, kidney or blood

- Cobomarsen has been safe and generally well tolerated at all doses tested
  - Multiple patients receiving more than a year of therapy (up to 39 grams cumulative dose) with no serious adverse events attributed to cobomarsen
- No significant abnormalities found in liver or kidney function, no abnormalities in platelet counts
- No acute inflammatory toxicities
- No SAEs attributed to cobomarsen
- Two Dose-Limiting Toxicities:
  - Grade 3 worsening pruritus, possible tumor flare, occurred twice in one patient at 900 mg SC and 300 mg IV infusion
  - Grade 3 tumor flare (300 mg IV bolus)
- Novel oligonucleotide drug class
  - Elimination of “gap” reduces chemical class based toxicity
  - Short length minimizes heparin mimetic activity

COBOMARSEN HAS BEEN WELL TOLERATED



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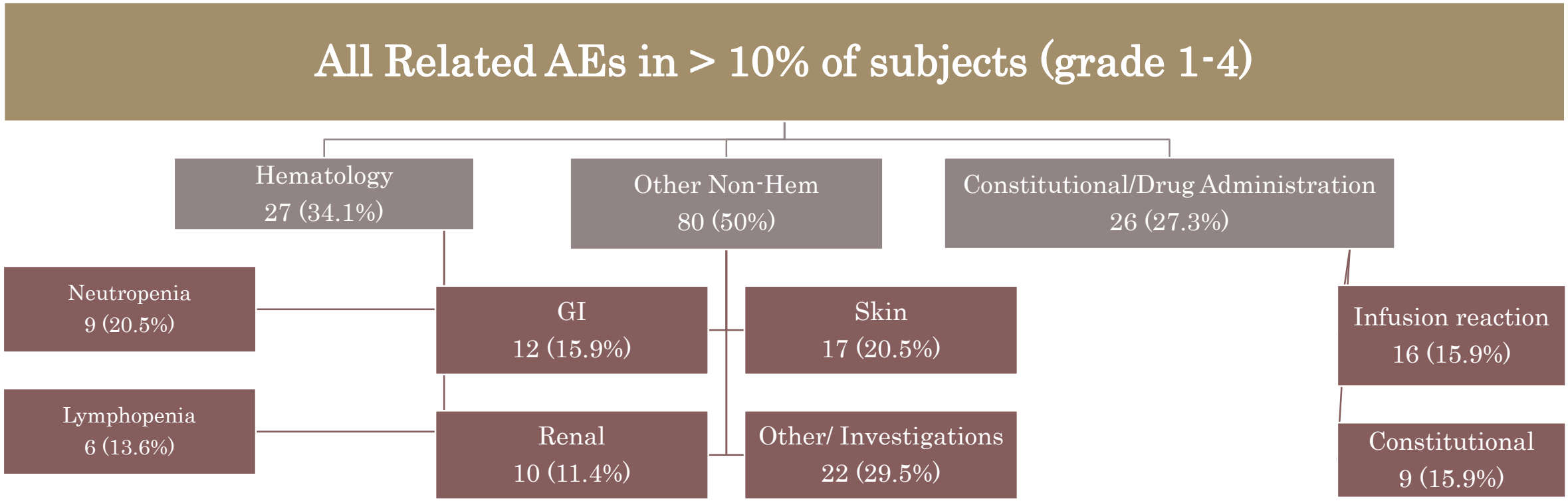
COBOMARSEN HAS BEEN WELL TOLERATED



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COBOMARSEN- A FAVORABLE SAFETY PROFILE

13 GRADE 3 AND 4 EVENTS WERE POSSIBLY RELATED TO COBOMARSEN ACROSS 45 SUBJECTS

	Part B SQ	Part B (IV, 2 hr infusion)			Part B (IV Bolus)	
System Organ Class	900mg	300mg	600mg	900mg	300mg	Total
Preferred Term						n=45
Hematology						4 (8.9%)
Neutrophil count decreased		1	1		1	3 (6.7%)
White blood cell count decreased		1			1	2 (4.4%)
Lymphocyte count decreased		1				1 (2.2%)
Skin						2 (4.4%)
Pruritus	1	1				2 (4.4%)
Rash		1				1 (2.2%)
Metabolism and nutrition disorders						1 (2.2%)
Hyperuricaemia		1				1 (2.2%)
Neoplasms						2 (4.4%)
Tumour flare			1		1	2 (4.4%)
Vascular						1 (2.2%)
Hypertension					1	1 (2.2%)

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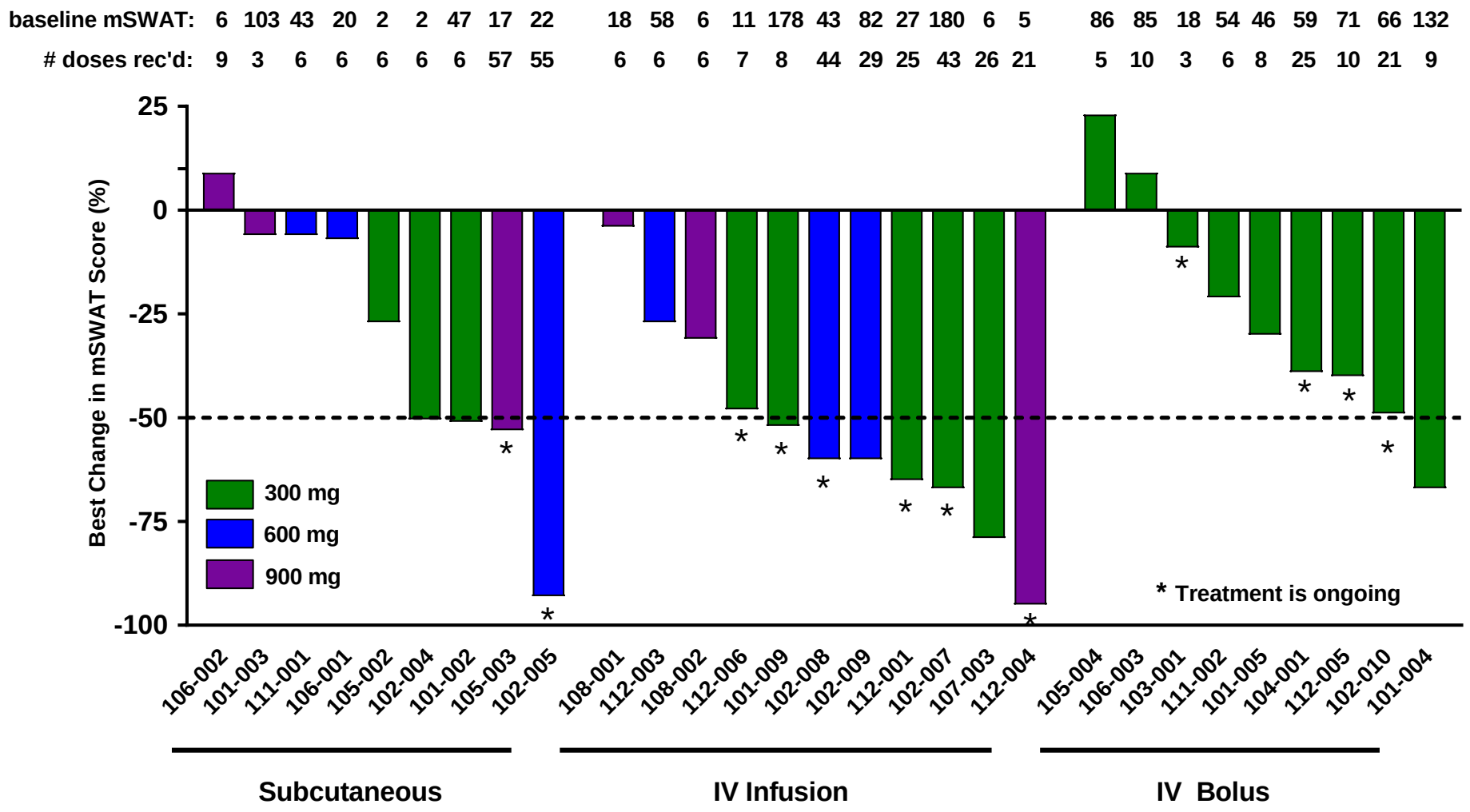
26 OF 29 SUBJECTS TREATED SYSTEMICALLY WITH COBOMARSEN SHOWED mSWAT SCORE IMPROVEMENT



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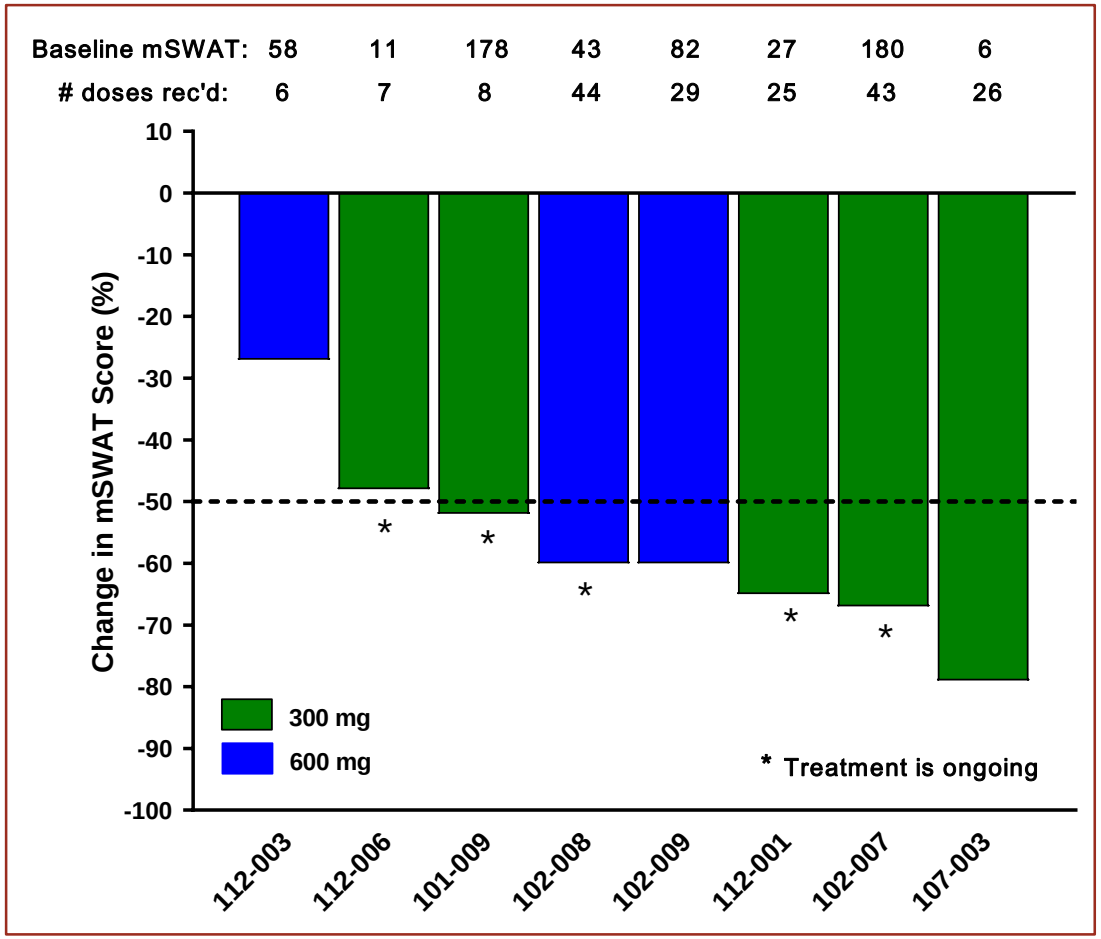
IV infusions showed the most consistent response

6 OF 8 (75%) PATIENTS ELIGIBLE FOR MORE THAN 1 MONTH OF 300MG AND 600MG IV DOSING OF COBOMARSEN ACHIEVED ≥50% mSWAT REDUCTION



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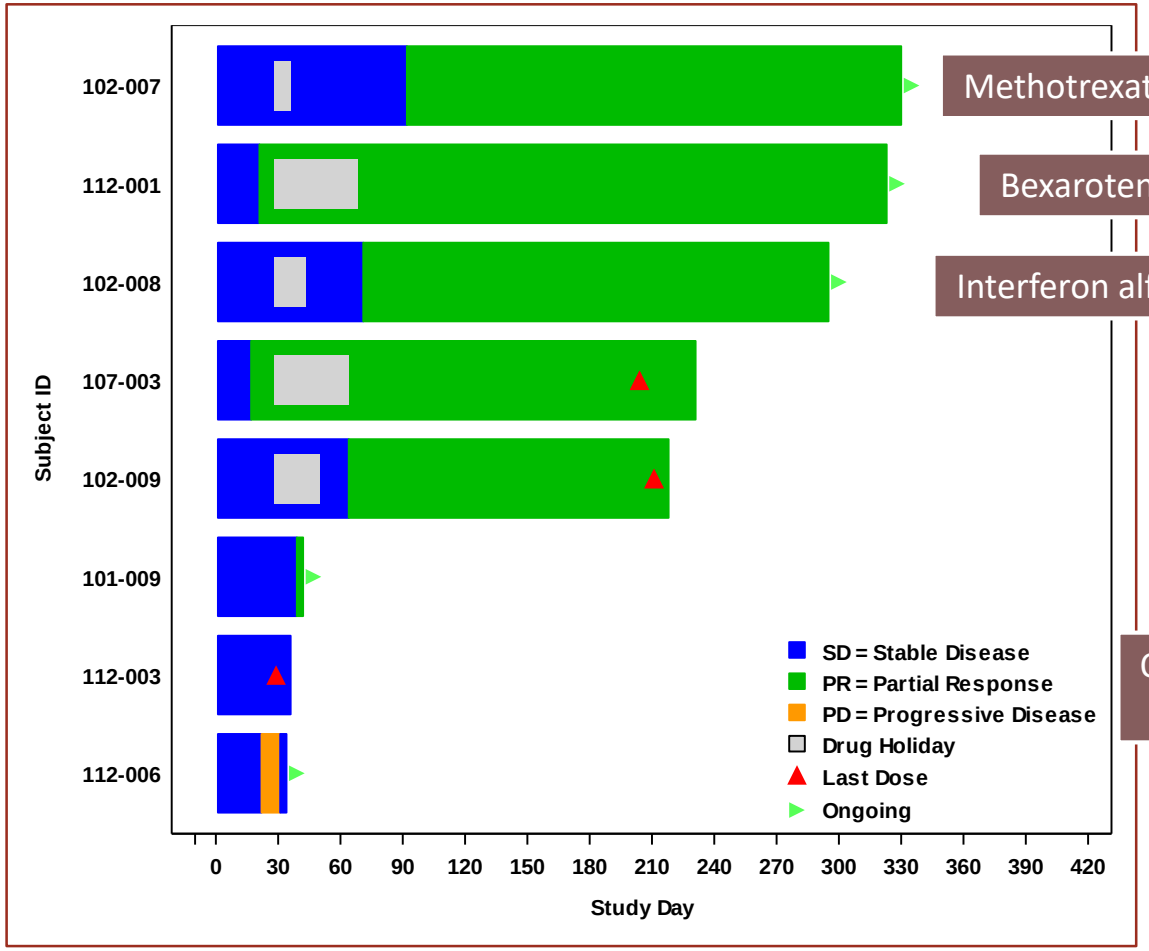
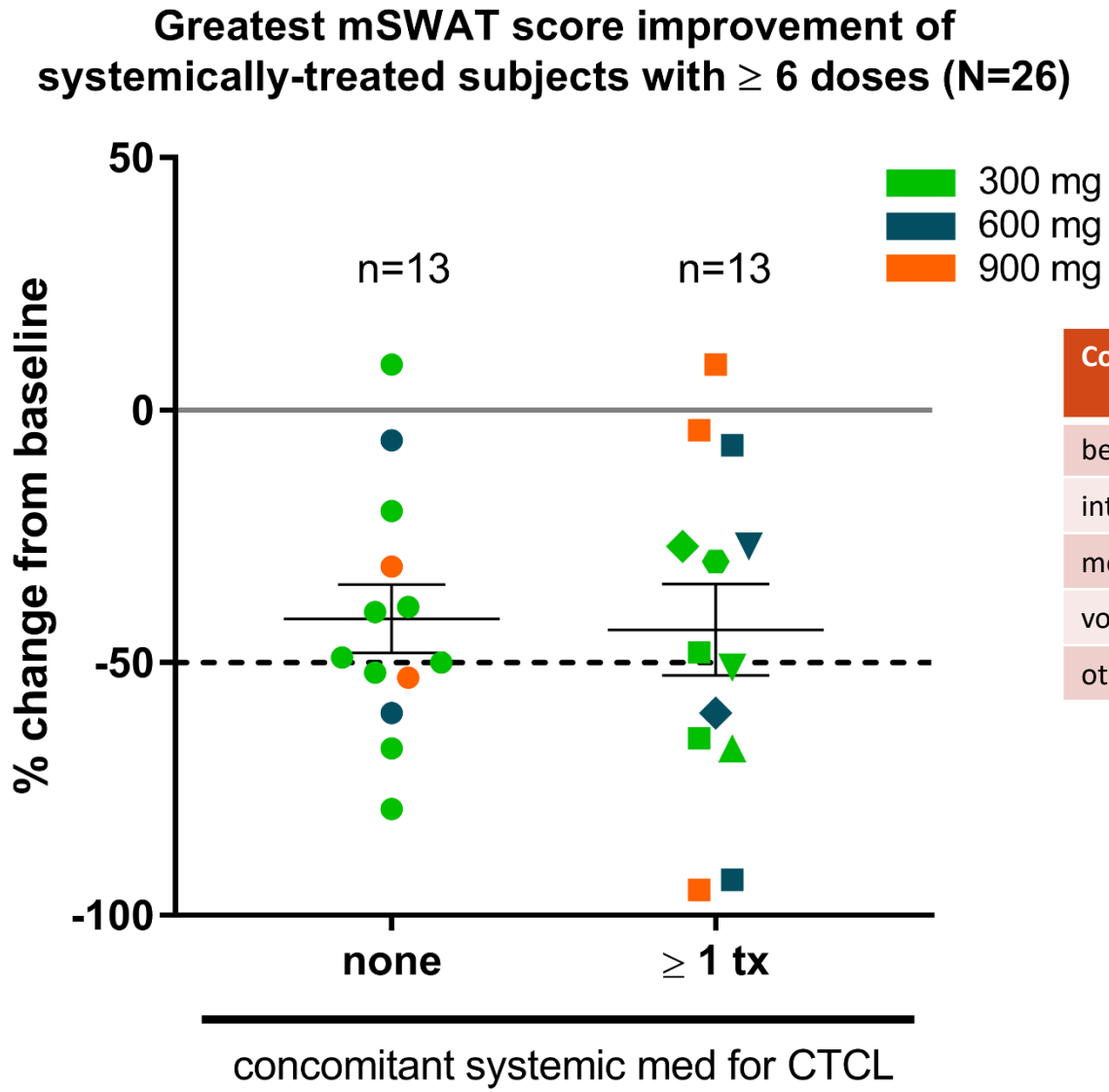


300mg Dose Selected for Phase 2 in MF

Response and durability observed independent of concomitant medication

BEST mSWAT IMPROVEMENT WITH COBOMARSEN INDEPENDENT OF ADMINISTRATION AS MONOTHERAPY OR COMBINATION WITH ANOTHER CTCL THERAPY



Concomitant med	N	Median time (min, max) on therapy prior to study day 1
bexarotene □	7	16 months (2, 26)
interferon-alfa ◇	2	26 months (17, 34)
methotrexate △	1	22 months
vorinostat ⬡	1	4 months
other ▽	2	21 months (3, 45)

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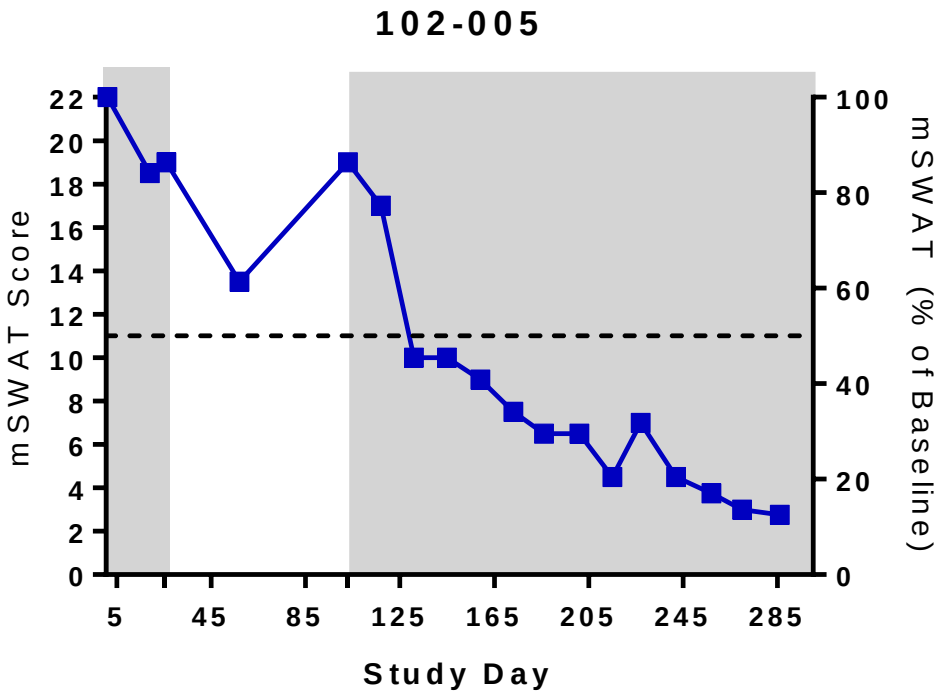
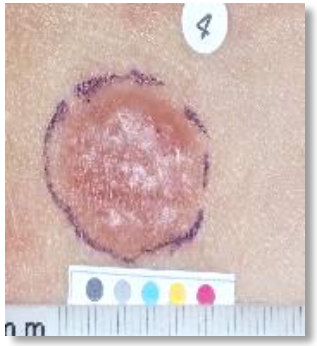
PART B: CASE STUDY IMPROVEMENT IN TOTAL SKIN DISEASE SCORE CORRELATES WITH COBOMARSEN TREATMENT



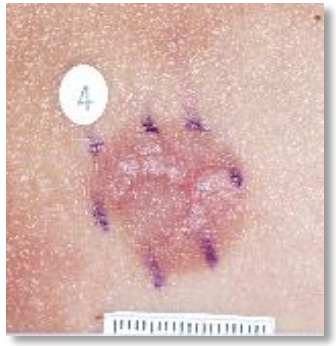
Note: **Grey shading** = drug administration period, **White Shading** = pause in drug administration

- There is continued improvement that extended beyond discontinuation of the first 4 weeks of dosing that eventually dissipated during the drug holiday
- Patient responded with re-initiation of therapy

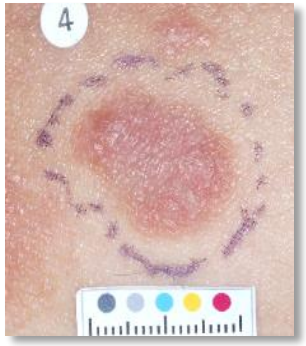
Day 1
CAILS: 13



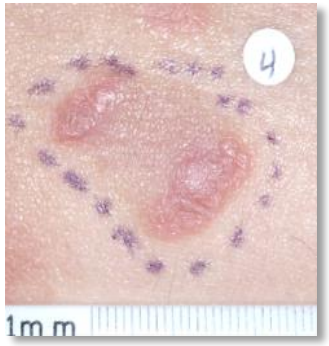
Day 19
CAILS: 10



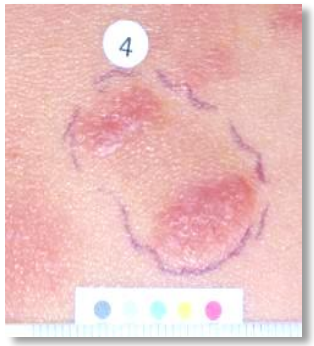
Day 27
CAILS: 8



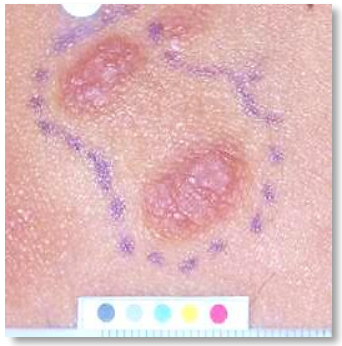
Day 57
CAILS: 5



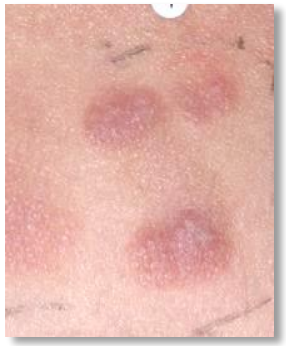
Day 103
CAILS: 10



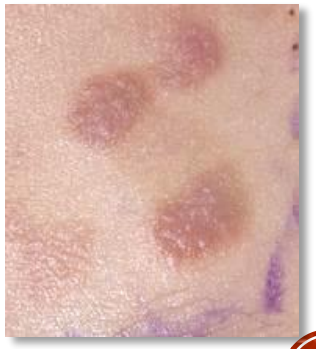
Day 131
CAILS: 8



Day 159
CAILS: 7



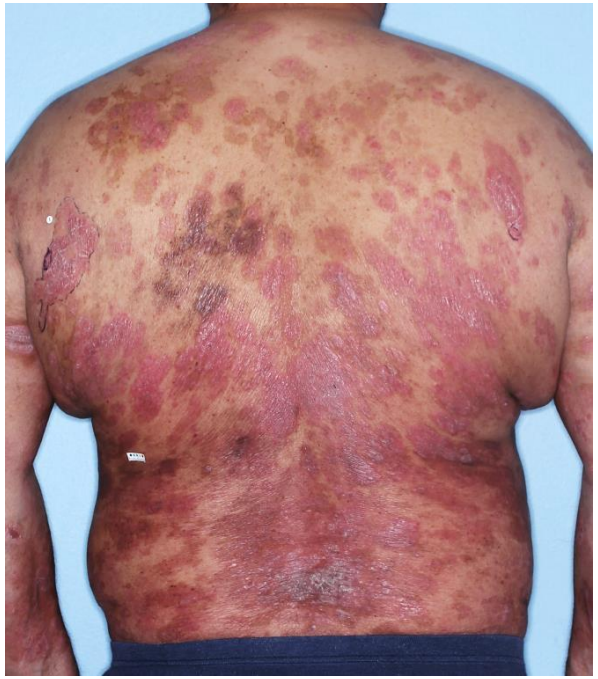
Day 186
CAILS: 6

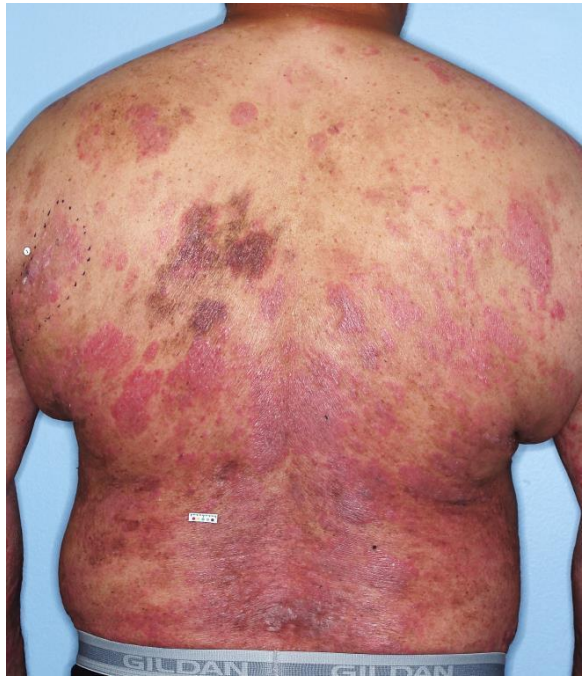


CASE EXAMPLE (102-007): 300 MG IV INFUSION COHORT

- Age: 51; Sex: Male
- Date of diagnosis: 2013
- CTCL stage at screening: IB
- Baseline mSWAT: 180
- Concomitant systemic therapy: Methotrexate (started June 2015)
- Has skin (mSWAT) PR lasting > 4 months

Day 1
mSWAT: 180





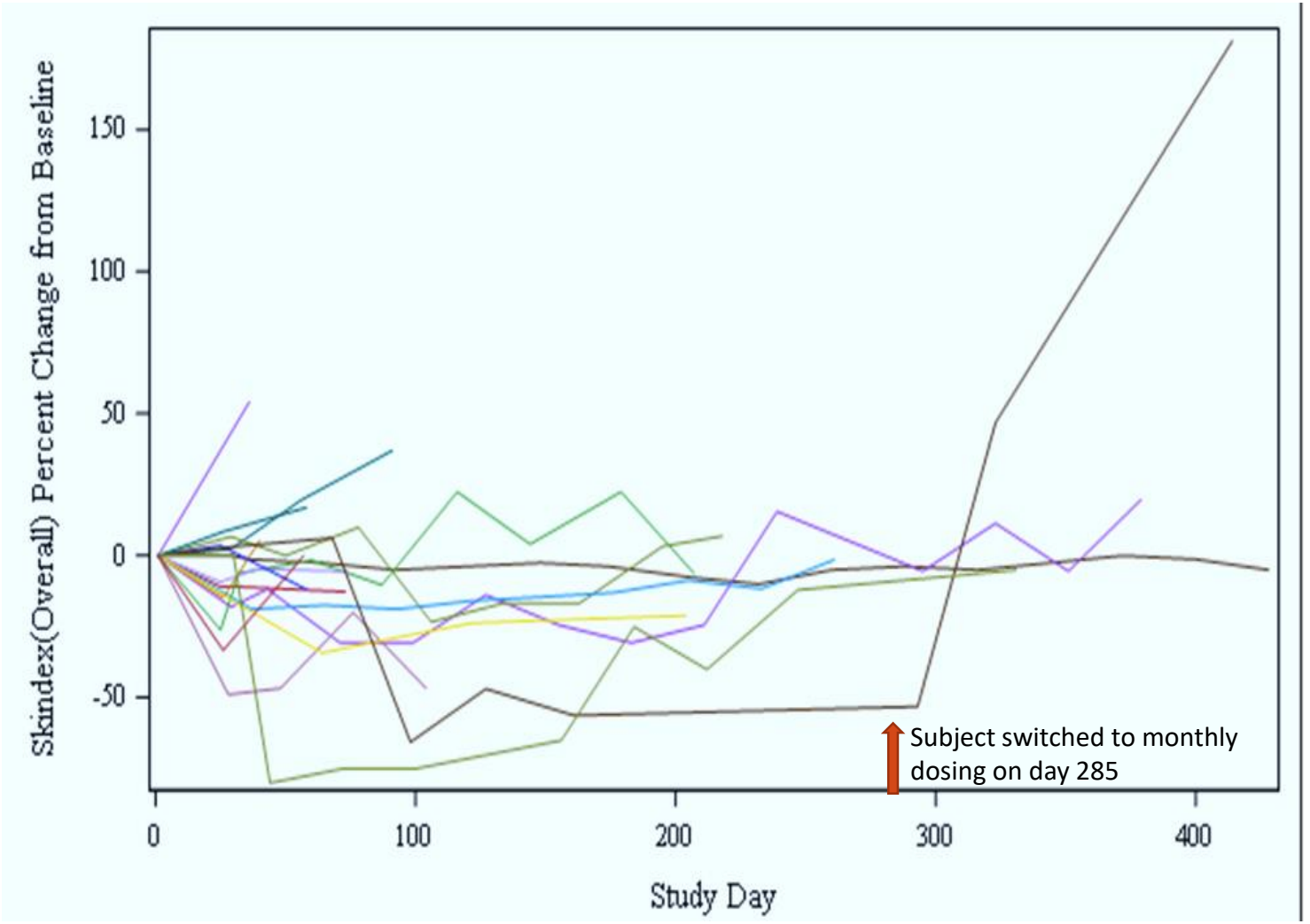
Day 93
mSWAT: 68
(62% reduction)

Database Dec. 4, 2017

DISEASE IMPROVEMENT RESULTS IN IMPROVED QUALITY OF LIFE

SKINDEX 29 TOTAL SCORE SHOWS IMPROVEMENT OR STABILIZATION IN MOST PATIENTS

- 13 of 18 subjects show a significant improvement over the first 100 days on study drug
- Improvement and stabilization seem durable, in 4 subjects for up to one year and one subject is stable after 400+days on study drug
- Subject 112-001 (300 mg IV infusion) worsen Skindex 29 and mSWAT response after switched to monthly dosing on day 285.



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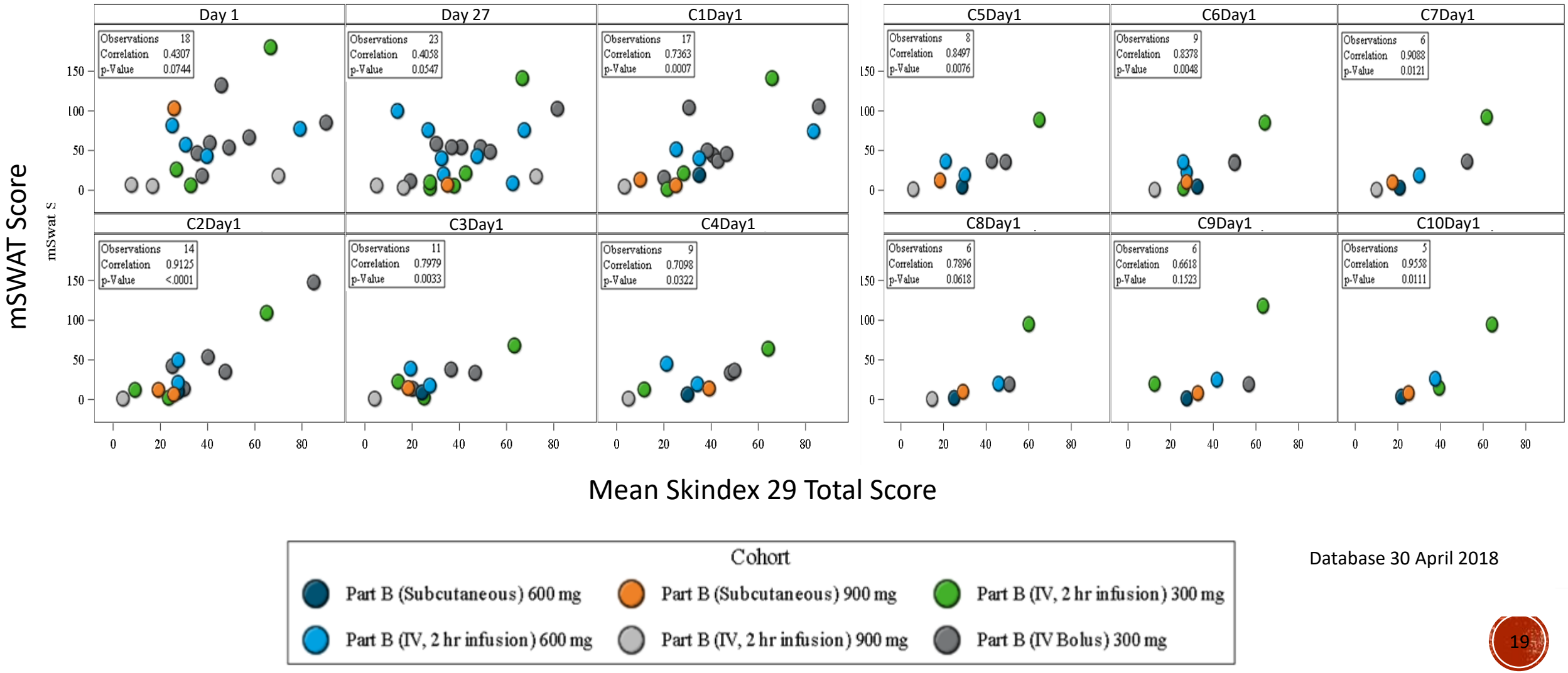
QOL CORRELATES WITH DISEASE SEVERITY AT EACH POINT OF THE STUDY

SKINDEX 29 TOTAL SCORE HIGHLY CORRELATES WITH mSWAT SCORE THROUGHOUT THE STUDY DURATION



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DOSE SELECTION FOR PHASE II STUDY

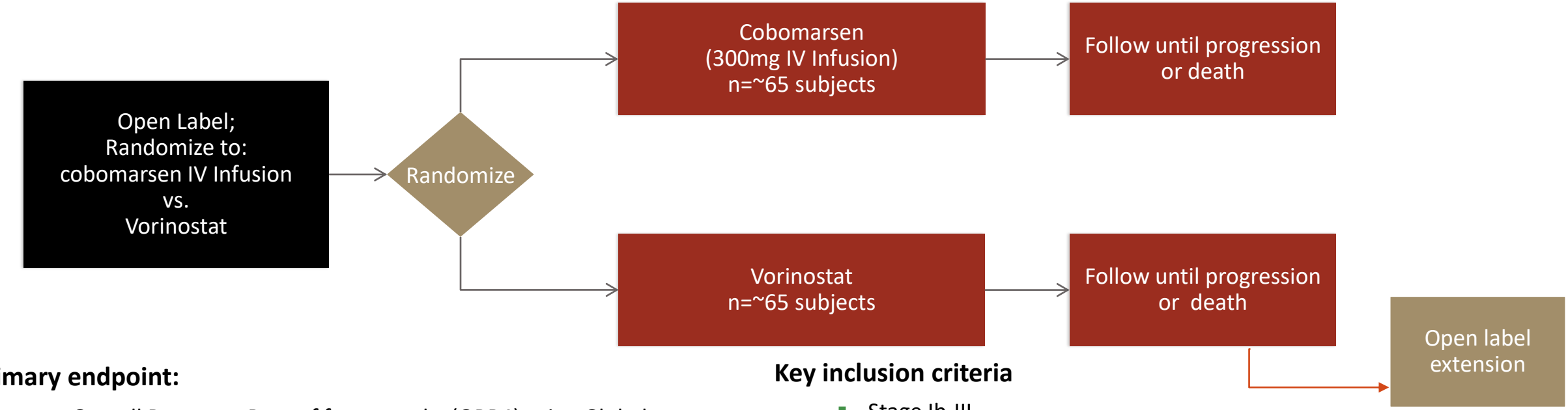
- Durable partial responses have been achieved at all dose levels
  - 300-900 mg appear to represent the top of the dose response curve
- 300 and 600 mg IV-infusions had similar efficacy and tolerability, offering the most consistent response rate based on skin mSWAT scores
- 6 of 8 (75%) patients (initially assigned to 300 or 600 mg dose level) achieved skin PR

SUMMARY

- Cobomarsen is generally well-tolerated to date
  - No SAEs deemed related to study drug
  - Two Dose-Limiting Toxicities:
    - Grade 3 worsening pruritus, possible tumor flare, occurred twice in one patient (900 mg SC cohort, 300 mg IV-infusion)
    - Grade 3 tumor flare in 300 mg iv bolus patient
- 6 of 8 (75%) patients treated for > 1 month with 300 or 600 mg systemically had ≥ 50% mSWAT score reduction
- Best improvement in mSWAT score appeared to be seen after 1 or more months of dosing
- Cobomarsen treatment resulted in durable improved quality of life, as measured by the Skindex 29 Total Score
- This improvement parallels improvements in disease, as measured by the mSWAT score, in most subjects, even if the patients achieve less than a defined PR
- Study in CTCL is on-going (enrollment closed)
- Study has expanded to include patients with CLL, DLBCL, and ATLL, diseases in which miR-155 expression is increased

SOLAR PHASE 2 CLINICAL TRIAL ANTICIPATED TO INITIATE IN 2H18

A RANDOMIZED, PARALLEL, OPEN LABEL, ACTIVE CONTROL, GLOBAL TRIAL IN PATIENTS WITH STAGE IB-III MYCOSIS FUNGOIDES



Primary endpoint:

- Overall Response Rate of four months (ORR4) using Global Response

Key Secondary endpoints:

- Progression-free survival
- Patient reported outcomes
  - Pain, itching

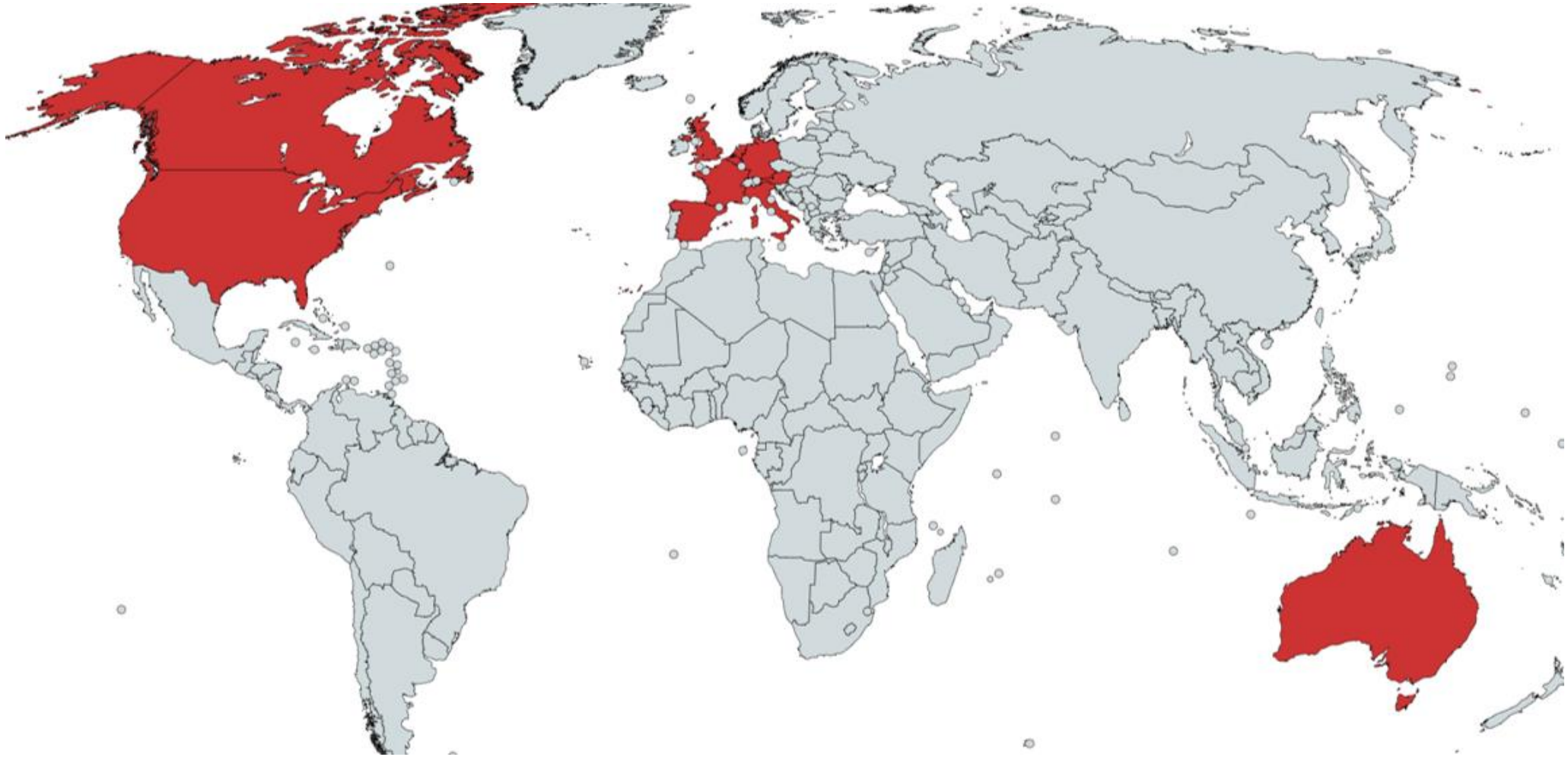
Key inclusion criteria

- Stage Ib-III
- Must have received at least one prior therapy for CTCL (per NCCN guidelines for generalized skin involvement)
- mSWAT score ≥ 10
- No concurrent systemic therapy

Stratification factors

- Stage (Ib-IIa vs IIb-III)
- Prior Therapies (1-2 vs. 3 or more)

SOLAR STUDY LOCATIONS



THANK YOU!

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