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Phase 1 Study of the Safety and Efficacy of MRG-106, a Synthetic Inhibitor of microRNA-155, in CTCL Patients

Christiane Querfeld, Francine M. Foss, Lauren Pinter-Brown, Pierluigi Porcu, Basem M. William, Theresa Pacheco, Bradley Haverkos, Youn Kim, Joan Guitart, Ahmad Halwani, Jennifer DeSimone, Anita Seto, Linda Pestano, Aimee Jackson, Paul Williams Jr., Brent Dickinson, Judy Ruckman, Gilad Gordon, Paul Rubin, William Marshall

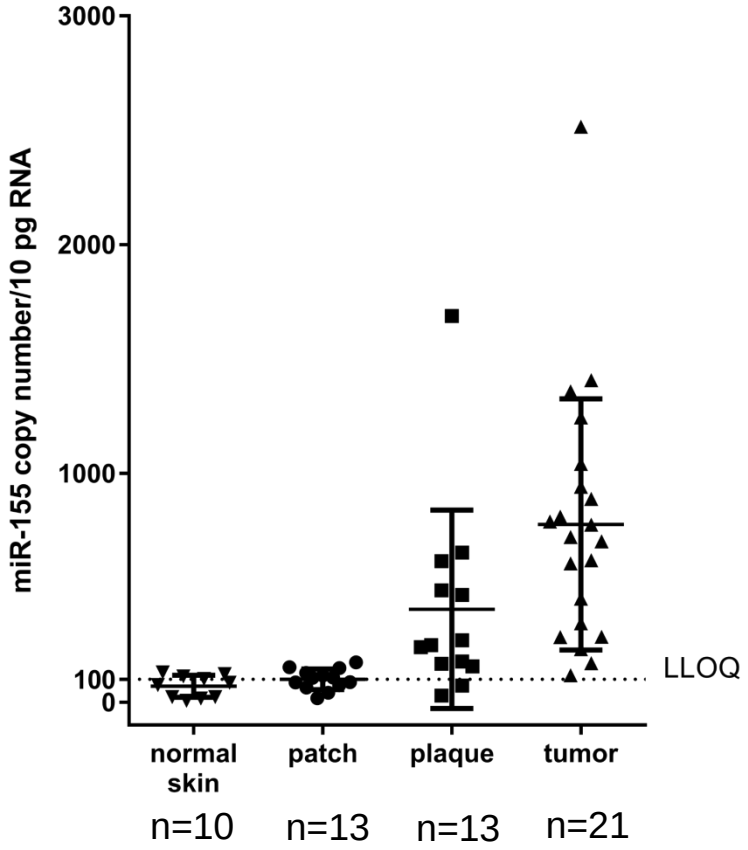
MicroRNA-155 Regulates Key Pathogenic Pathways in CTCL

- 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; miR-203 & miR-205 are decreased in CTCL skin
- JAK/STAT 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

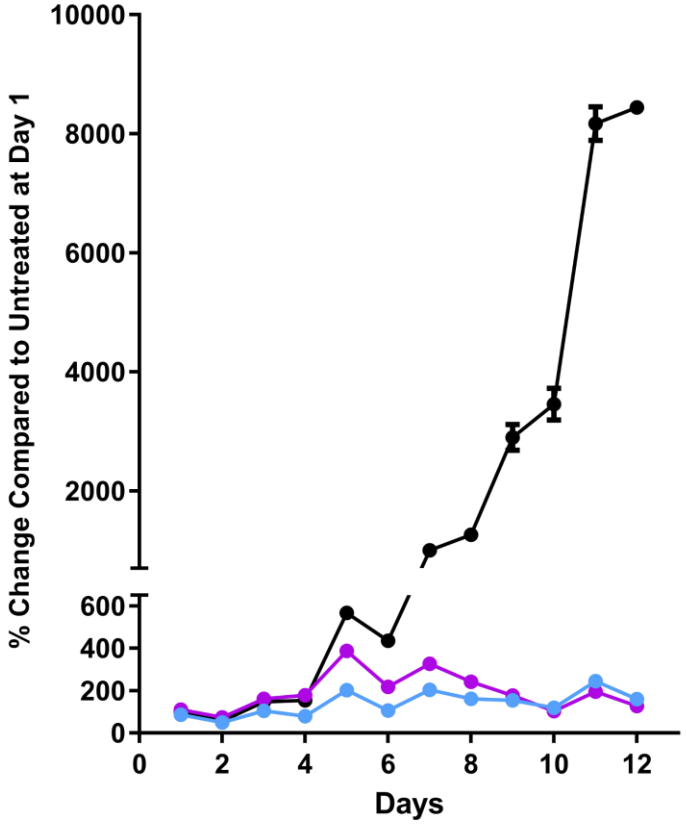
Preclinical Data:
miR-155 is Upregulated in MF Lesions and Inhibition Affects Cell Growth & Apoptosis

Lesion Type vs miR-155 Copy-Number

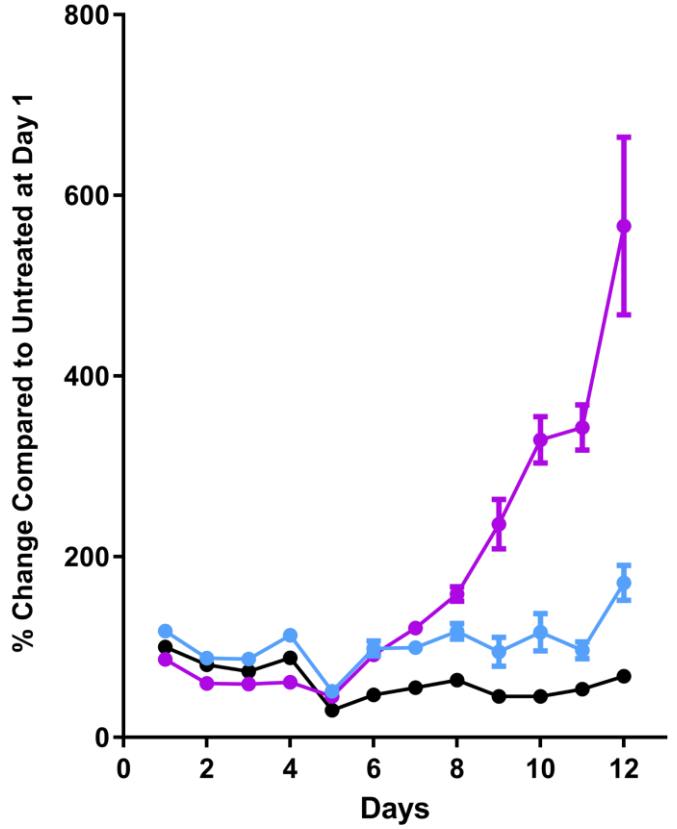


Archived tissue provided by
Madeleine Duvic (MD Anderson)

Cell Proliferation of HuT102 Cells



Apoptosis Pathway Activation in HuT102 Cells



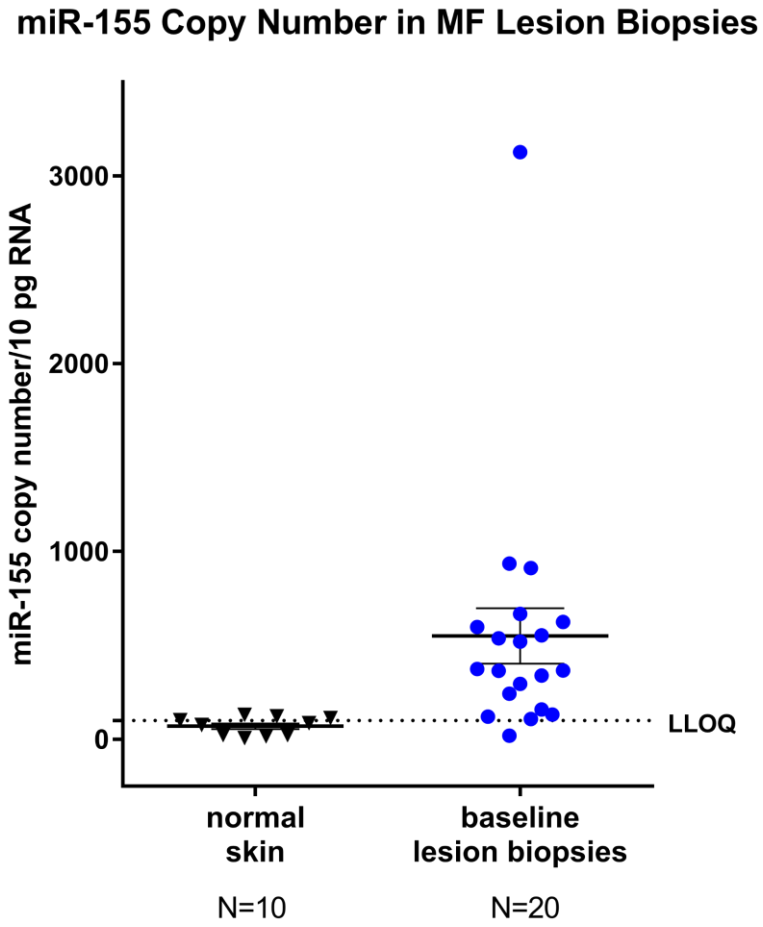
Untreated
Bexarotene
miR-155 Inhibitor (MRG-106)

First-In-Human Phase 1 Study of MRG-106 in Patients with Mycosis Fungoides

- MRG-106 is an optimized oligonucleotide inhibitor of miR-155 formulated in saline
- Study objectives:
  - Primary objective: Safety and tolerability
  - Secondary objectives: PK profile, efficacy, recommended Phase 2 dose and route of administration
- Study design:
  - Subjects permitted to continue CTCL therapy if stable dose $\geq$ 4 weeks prior to MRG-106 administration
  - Part A: Activity of MRG-106 through intralesional injection
  - Part B: Dose-escalation by systemic administration (subcutaneous or I.V.)
    - Dose schedule: Three doses in the first week followed by weekly doses
    - Five subjects were eligible for only 4 weeks of treatment due to original protocol version

Patient Characteristics:

Demographic	Part A Intralesional (N=6)	Part B Systemic (N=27)	Total (N=33)
Sex			
Female	1 (17%)	8 (30%)	9 (27%)
Male	5 (83%)	19 (70%)	24 (73%)
Age Range (Years)			
18 - 45	0 (0%)	3 (11%)	3 (9%)
46 - 65	6 (100%)	15 (56%)	21 (64%)
> 65	0 (0%)	9 (33%)	9 (27%)
Race			
Asian	0 (0%)	1 (4%)	1 (3%)
Black	1 (17%)	2 (7%)	3 (9%)
Not reported	1 (17%)	0 (0%)	1 (3%)
Other, specify	0 (0%)	2 (7%)	2 (6%)
White/Caucasian	4 (67%)	22 (81%)	26 (79%)
Ethnicity			
Hispanic	1 (17%)	2 (7%)	3 (9%)
Non-Hispanic	5 (83%)	25 (93%)	30 (91%)
Disease Stage at Diagnosis			
Stage IA	0 (0%)	5 (19%)	5 (15%)
Stage IB	1 (17%)	7 (26%)	8 (24%)
Stage IIA	2 (33%)	3 (11%)	5 (15%)
Stage IIB	3 (50%)	7 (26%)	10 (30%)
Stage IIIA	0 (0%)	2 (7%)	2 (6%)
Stage IIIB	0 (0%)	3 (11%)	3 (9%)
Prior Therapies			
IV	3 (30%)	9 (28%)	12 (29%)
ORAL	6 (60%)	20 (63%)	26 (62%)
OTHER	1 (10%)	3 (9%)	4 (10%)
Baseline mSWAT			
N	3	26	29
Median (Min-Max)	23 (3-96)	45 (2-186)	43 (2-186)



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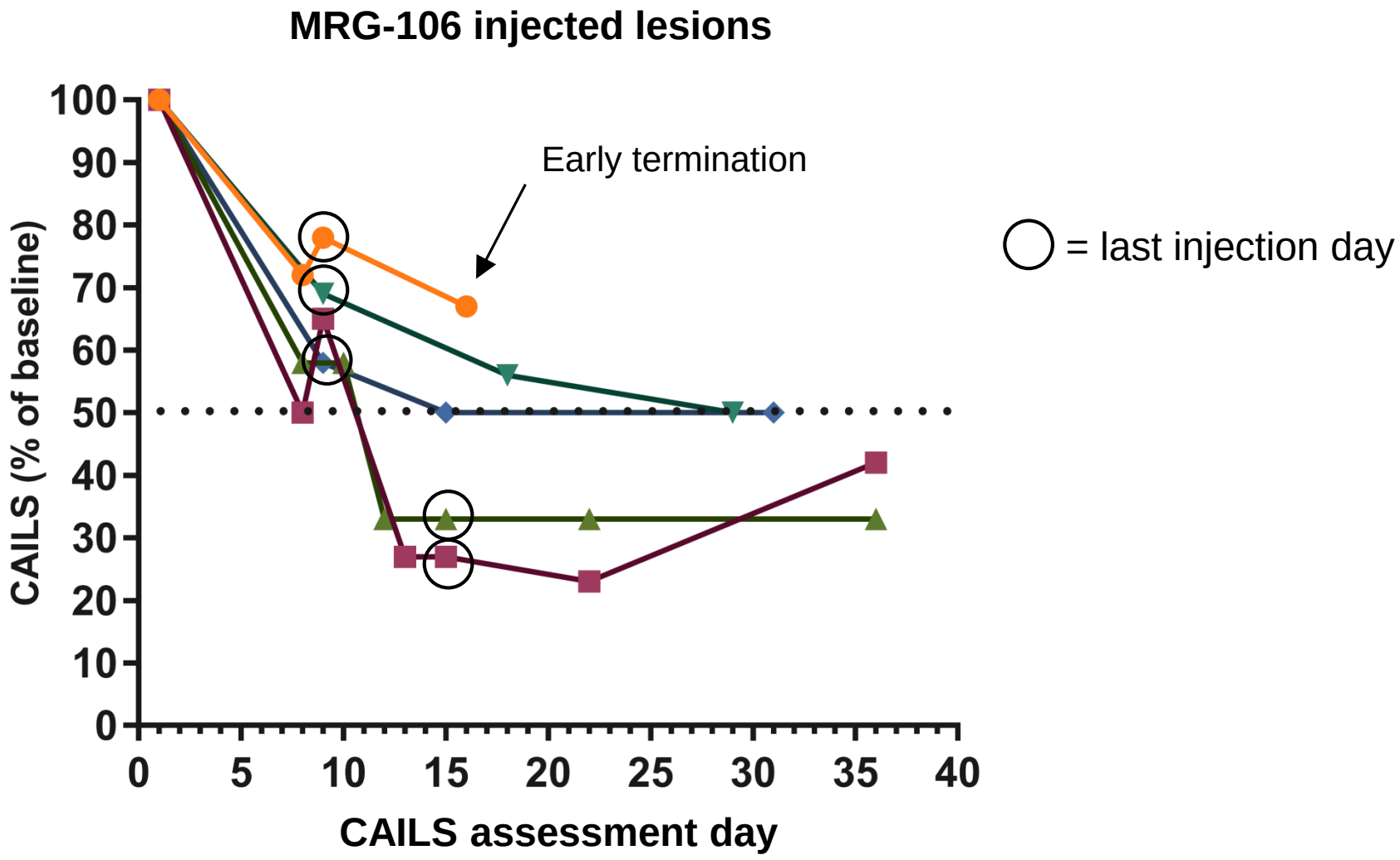
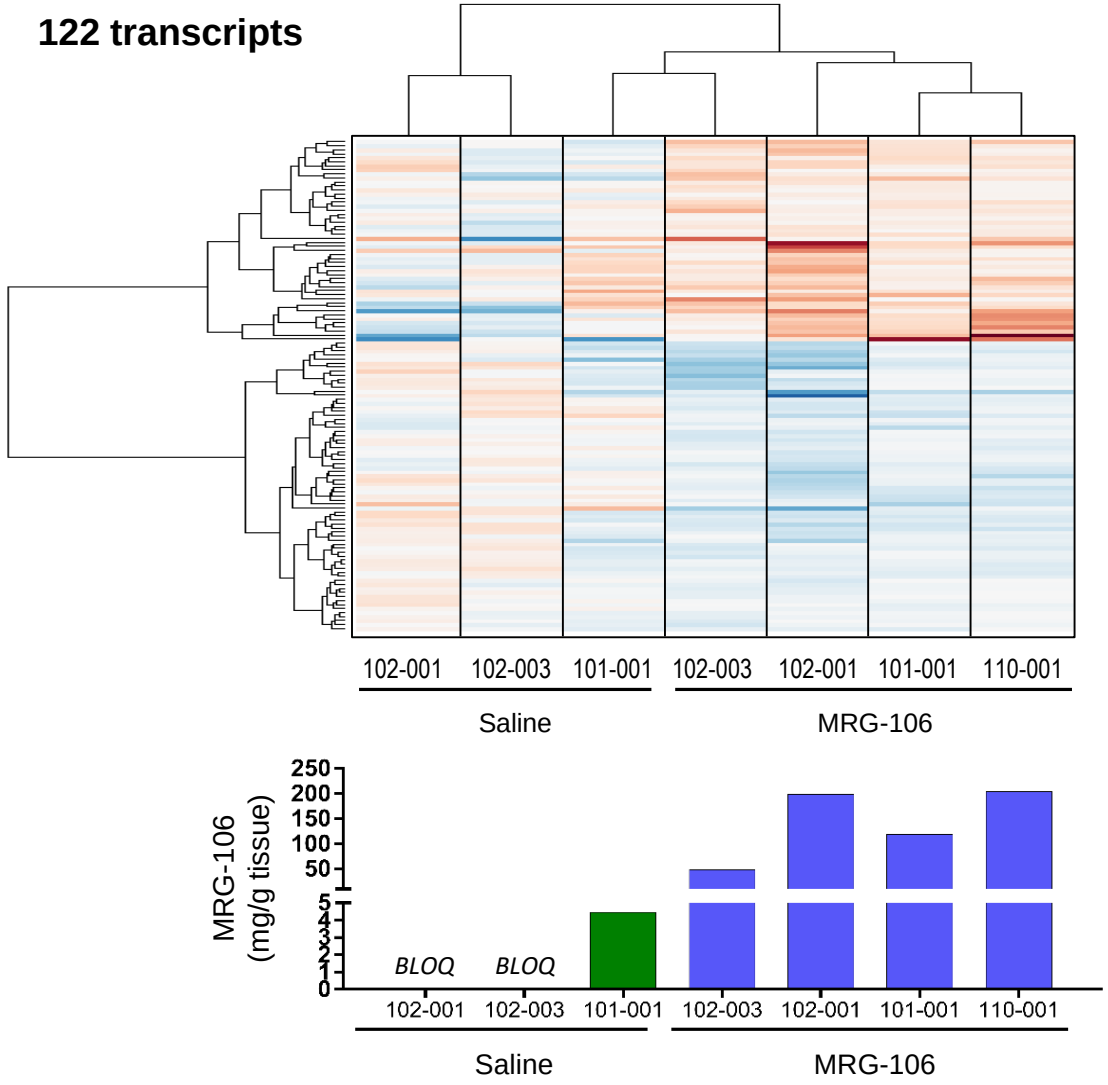
Improvement of CAILS with Intralesional Injection of MRG-106 (Part A)

MRG-106 was well-tolerated with generally minor injection site reactions

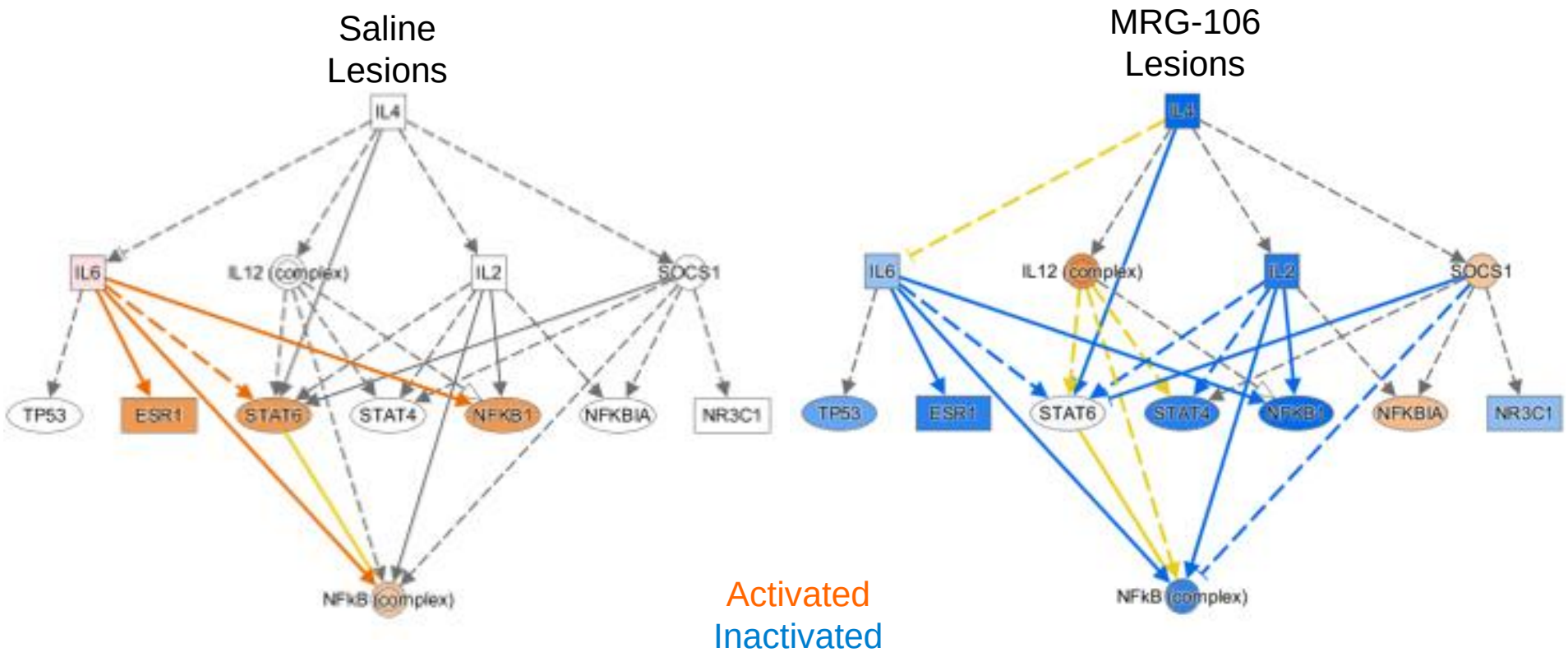


Gene Expression Changes with Intratumoral Injection of MRG-106 Correlate to Drug Levels in MF Lesion Biopsies (Part A)



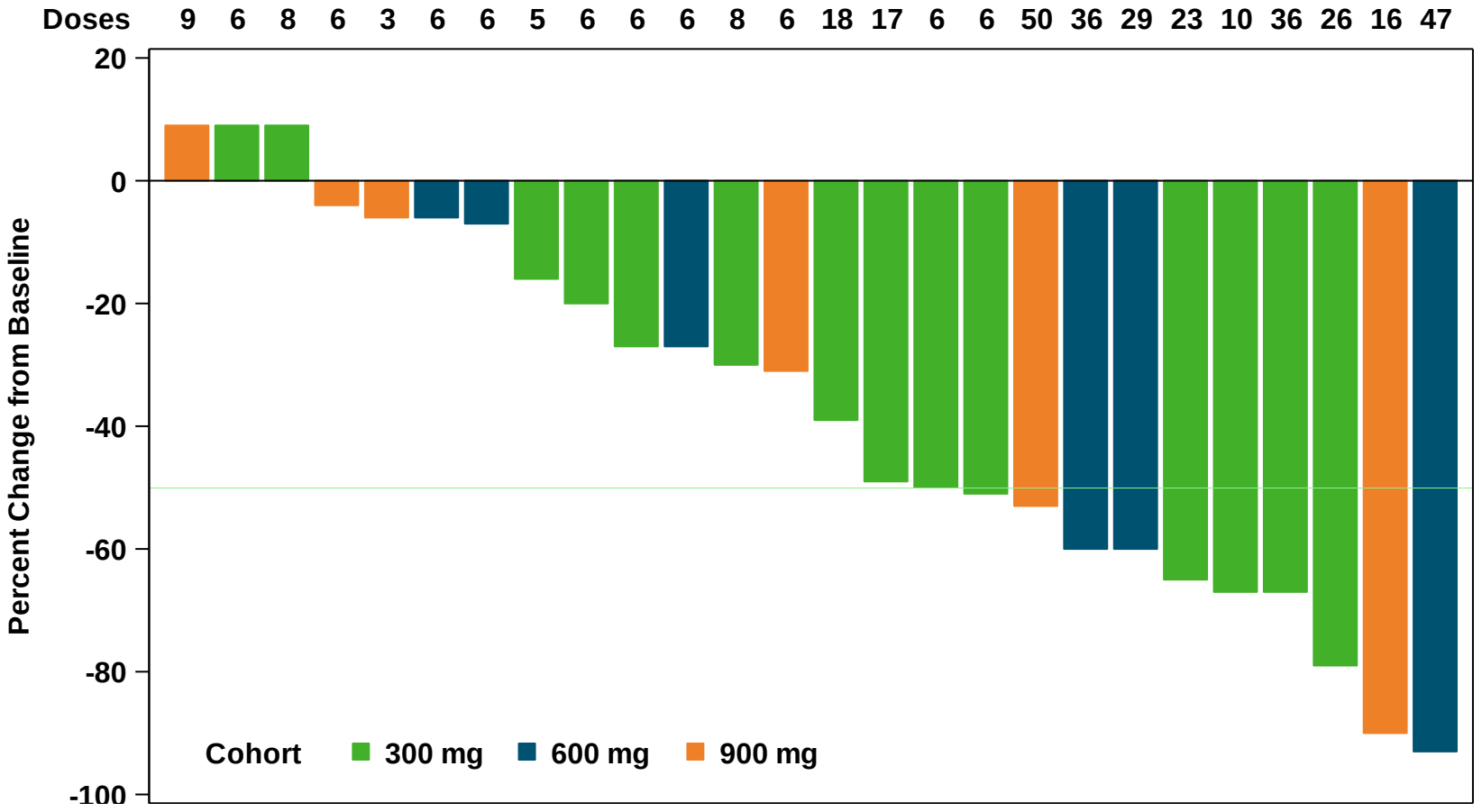
Up-regulated vs. untreated
Down-regulated vs. untreated

MRG-106 Treatment Decreases Key CTCL Disease Pathways Including STAT and NFκB Pathways (Part A)



23/26 (88%) Patients Treated Systemically with MRG-106 Have mSWAT Score Improvement Independent of Treatment Duration (Part B)

- 21 subjects were eligible for > 1 month of treatment
- 15 subjects chose to continue with additional months of treatment



6 doses = initial cycle
4 doses in subsequent cycles

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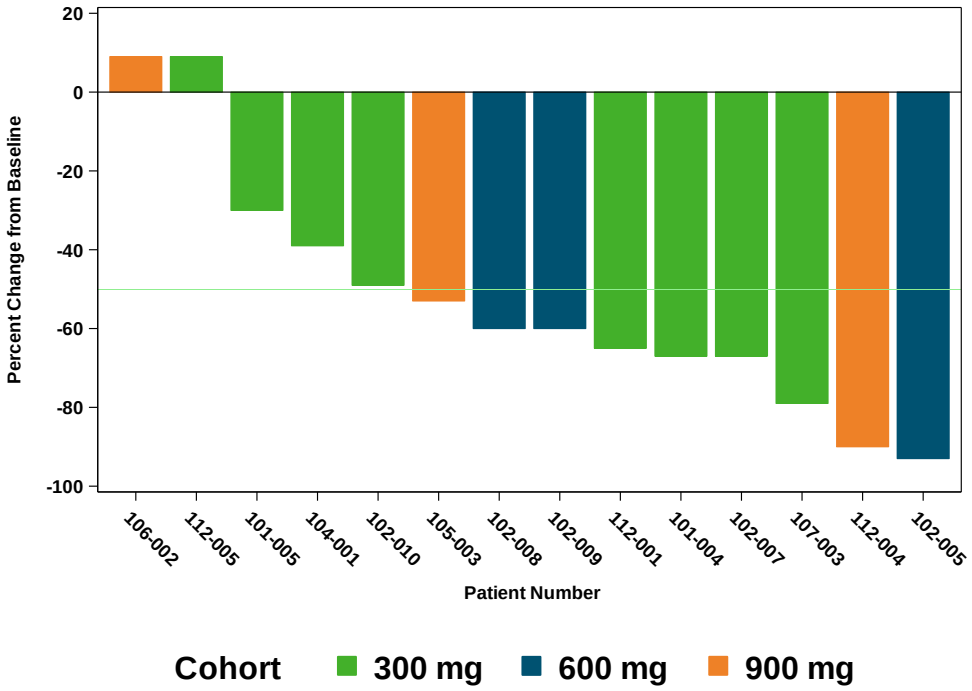
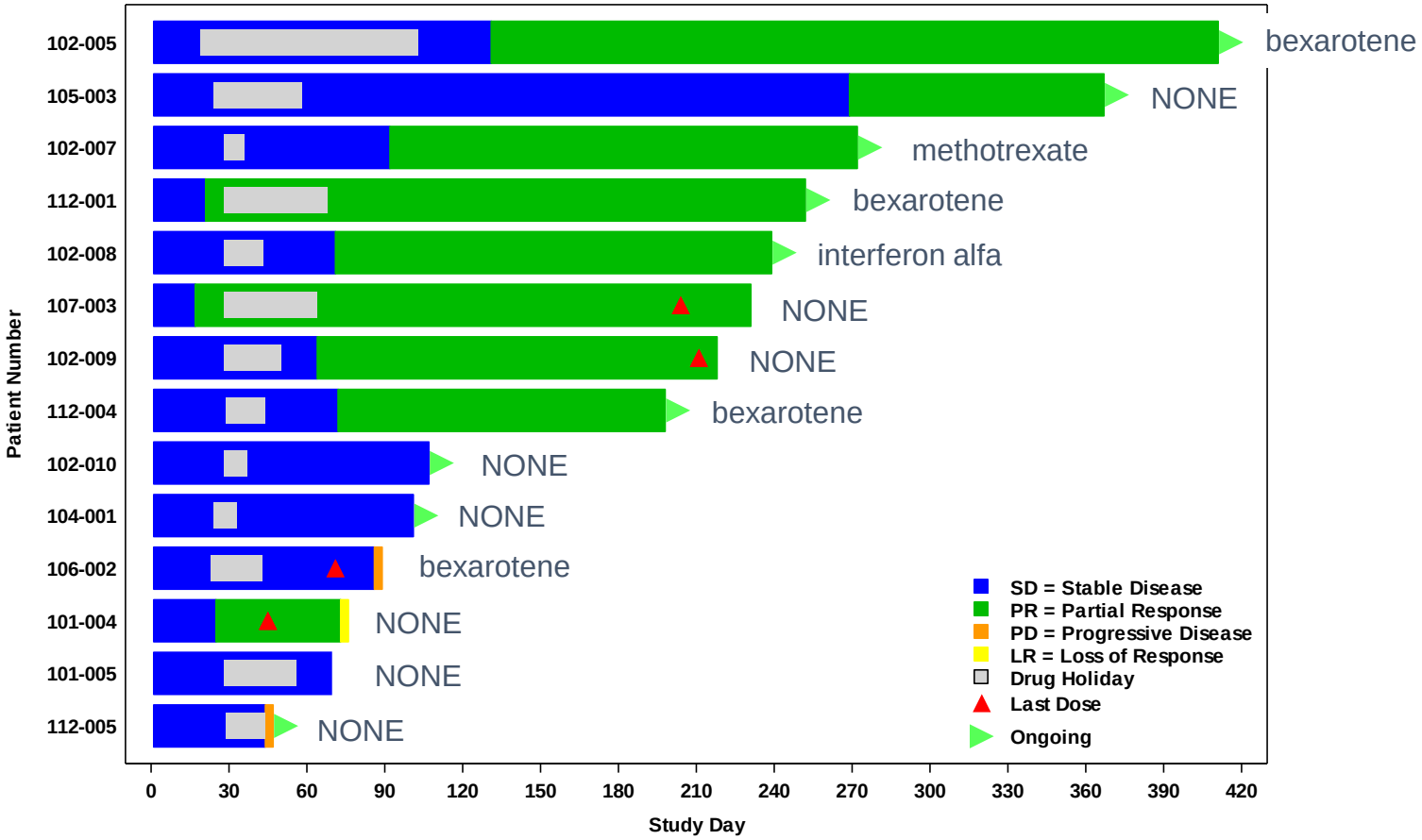
9/14 (64%) Pts Treated for > 1 Month Show ≥ 50% mSWAT Score Improvement

Once 50% mSWAT PR is achieved, response is durable





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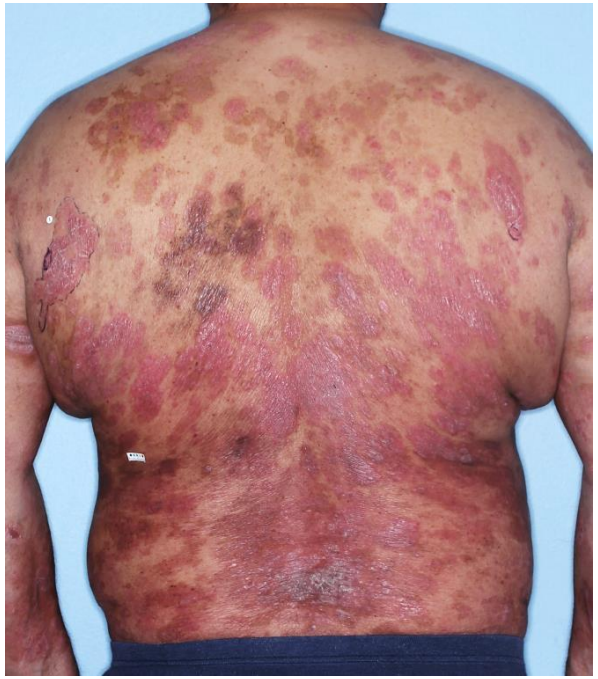
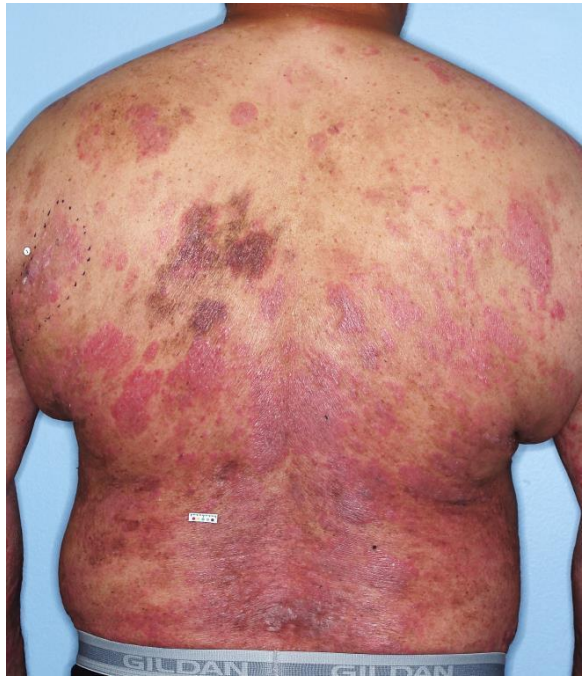
Case Example (102-007): 300 mg IV Infusion Cohort

- 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)

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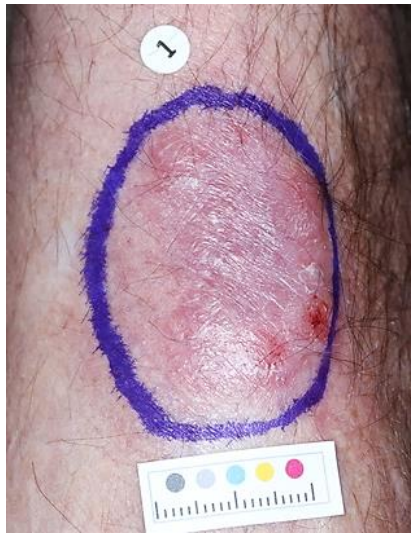
Case Example (112-001): 300 mg IV Infusion Cohort

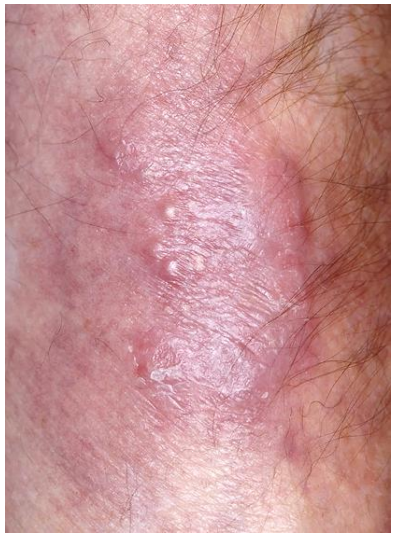
- Age: 63; Sex: Male
- Date of diagnosis: 2015
- CTCL stage at screening: IIB
- Concomitant systemic therapy: Bexarotene (started 2015)
- Has skin (mSWAT) PR lasting > 4 months

Day 1



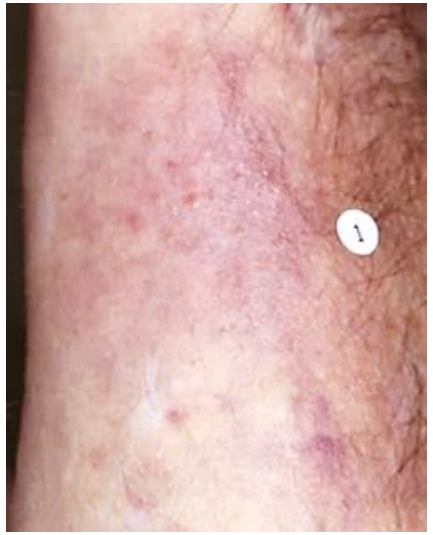
CAILS: 12

Day 29



CAILS: 9

Day 127



CAILS: 3

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MRG-106 Has a Favorable Safety Profile

AEs by preferred term, N (%)	Any grade*	Grade 3-4
Fatigue	6 (17)	
Injection site pain	6 (17)	
Neutropenia	5 (14)	2 (6)
Nausea	4 (11)	
Pruritus	4 (11)	1 (2)
Erythema	4 (11)	

* Coded AEs occurring in ≥ 10% of subjects

- No SAEs attributed to MRG-106
- No Grade 4 Adverse Events attributed to MRG-106
- Two Dose-Limiting Toxicities:
  - Grade 3 worsening pruritus, possible tumor flare, occurred twice in one patient
  - Grade 3 tumor flare

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MRG-106 Has a Favorable Safety Profile

All coded Grade 3 or 4 Adverse Events

	Part A (Intra-tumoral)	Part B (Subcutaneous)			Part B (IV, 2 hr infusion)			Part B (IV Bolus)	
System Organ Class ***Preferred Term***	**75mg (6)**	**300mg (3)**	**600mg (3)**	**900mg (3)**	**300mg (6)**	**600mg (3)**	**900mg (3)**	**300mg (8)**	**Total (35)**
Blood and lymphatic system disorders			1 (33.3%)	1 (33.3%)					2 (5.7%)
Neutropenia			1 (33.3%)	1 (33.3%)					2 (5.7%)
Leukopenia				1 (33.3%)					1 (2.9%)
Investigations	2 (33.3%)								2 (5.7%)
Blood creatine phosphokinase increased	1 (16.7%)								1 (2.9%)
Lymphocyte count decreased	1 (16.7%)								1 (2.9%)
Metabolism and nutrition disorders	1 (16.7%)	1 (33.3%)							2 (5.7%)
Hypercalcaemia	1 (16.7%)								1 (2.9%)
Hyponatraemia		1 (33.3%)							1 (2.9%)
Infections and infestations	1 (16.7%)								1 (2.9%)
Cellulitis	1 (16.7%)								1 (2.9%)
Skin and subcutaneous tissue disorders				1 (33.3%)					1 (2.9%)
Pruritus				1 (33.3%)					1 (2.9%)
Vascular disorders				1 (33.3%)					1 (2.9%)
Hypertension				1 (33.3%)					1 (2.9%)

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Conclusions

- MRG-106 is generally well-tolerated to date
  - No SAEs or Grade 4 AEs deemed related to study drug
  - Two Dose-Limiting Toxicities:
    - Grade 3 worsening pruritus, possible tumor flare, occurred twice in one patient
    - Grade 3 tumor flare
- 9 of 14 (64%) patients treated for > 1 month have ≥ 50% mSWAT score reduction
- mSWAT improvement is durable in all patients, who continued on treatment
- mSWAT improvements correlate with time on MRG-106 treatment
- Efficacy appears similar across dose range tested (300-900 mg/dose)
- Study in CTCL is on-going
- Study is expanded to enroll patients with DLBCL, CLL, and ATLL

MRG106-11-101 CTCL Investigators

Jennifer DeSimone (Inova)

Herbert Eradat (UCLA)

Francine Foss (Yale)

Joan Guitart (Northwestern)

Ahmad Halwani (Huntsman)

Youn Kim (Stanford)

Theresa Pacheco (University of Colorado)

Lauren Pinter-Brown (UC Irvine)

Pierluigi Porcu (Thomas Jefferson)

Christiane Querfeld (City of Hope)

Basem William (The Ohio State University)