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

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# MicroRNA-155 Regulates Key Pathogenic Pathways in CTCL

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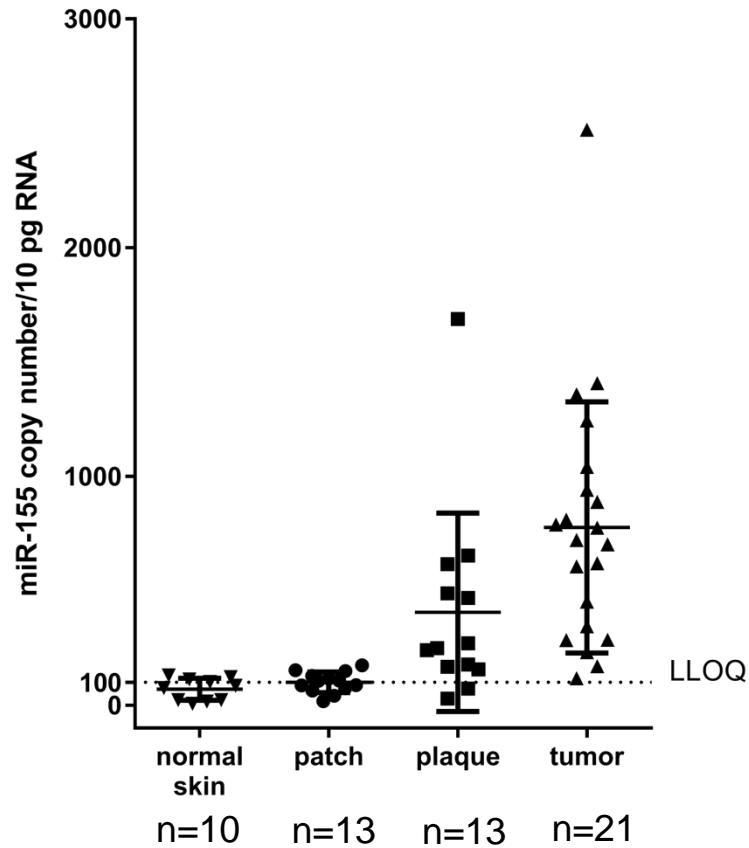
- Epigenetic alterations have been implicated in the pathogenesis of lymphomas and leukemias including CTCL
- miRNA profiling and RT-PCR discriminate CTCL and non-malignant inflammation with a high accuracy
- miR-155 is overexpressed; miR-203 & miR-205 are decreased in CTCL skin
- JAK/STAT and PI3K pathways 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:

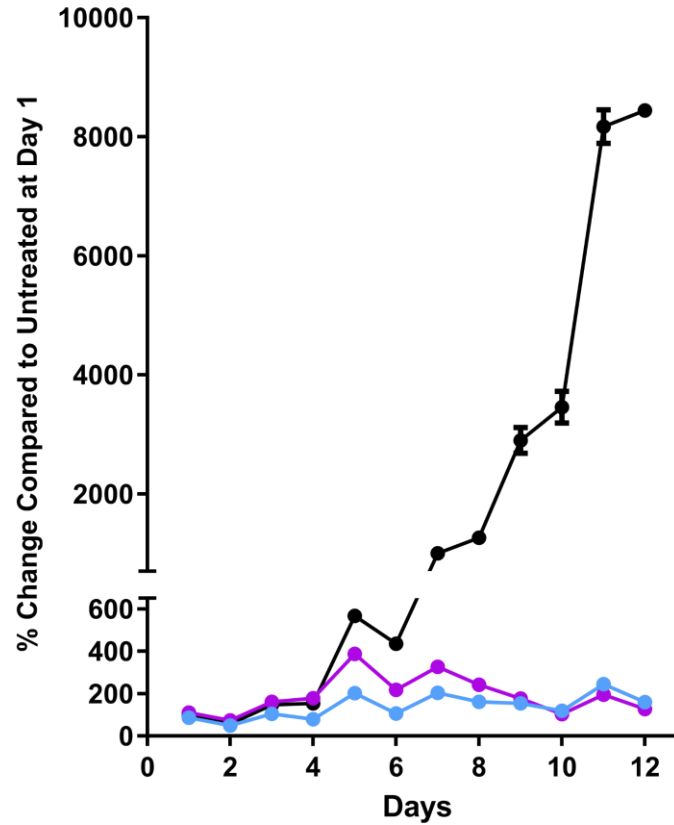
## miR-155 is Upregulated in MF Lesions and Inhibition Affects Cell Growth & Apoptosis

### Lesion Type vs miR-155 Copy-Number

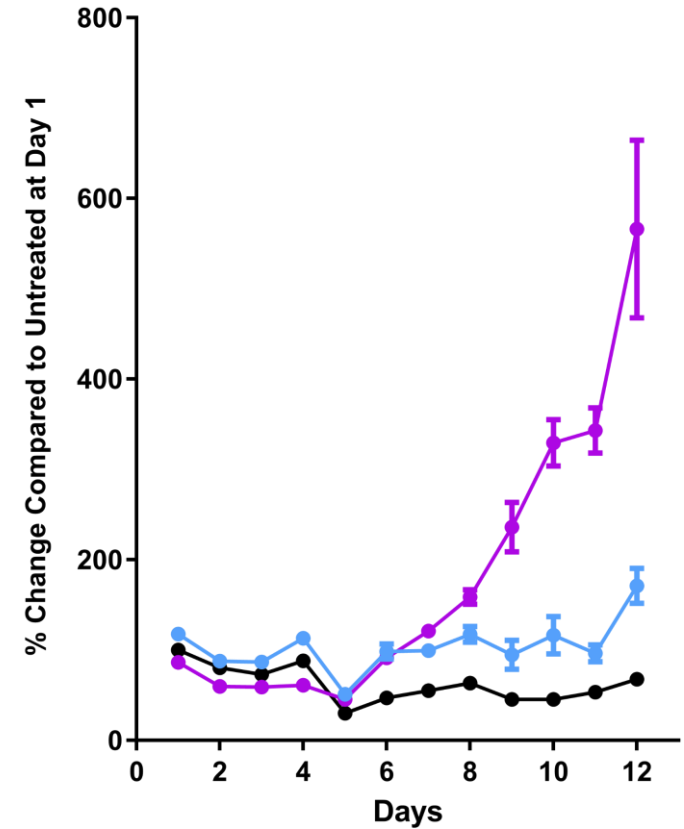


Archived tissue provided by Madeleine Duvic (MD Anderson)

### 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

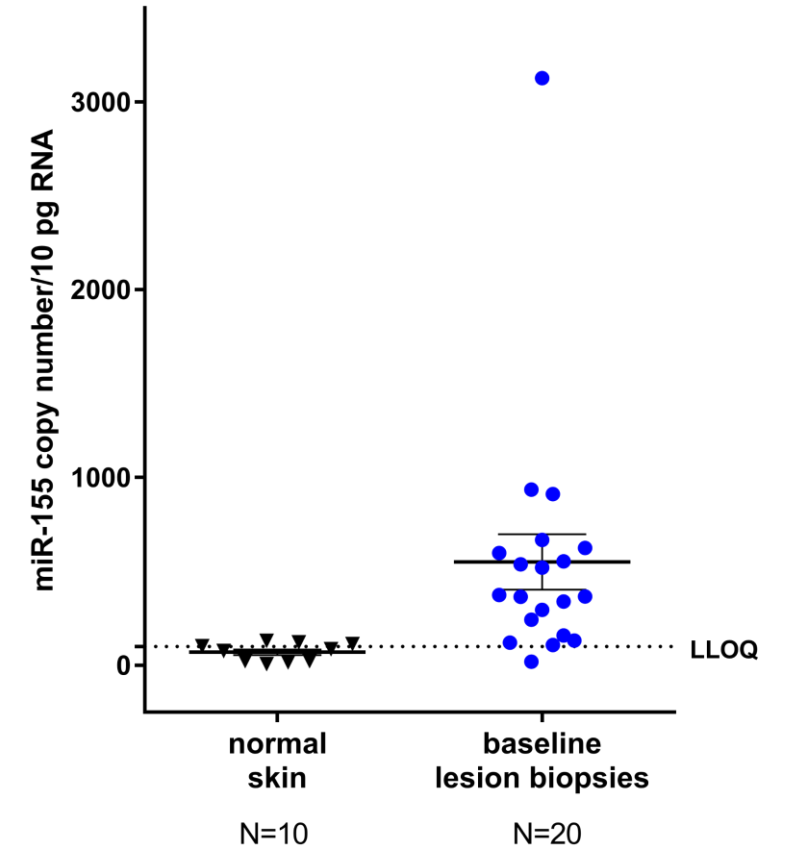
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- MRG-106 is an optimized oligonucleotide inhibitor of miR-155 formulated in saline
- Study objectives:
  - Primary objective: Safety and tolerability
  - Secondary objectives: PK profile, efficacy, recommended Phase 2 dose and route of administration
- 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:

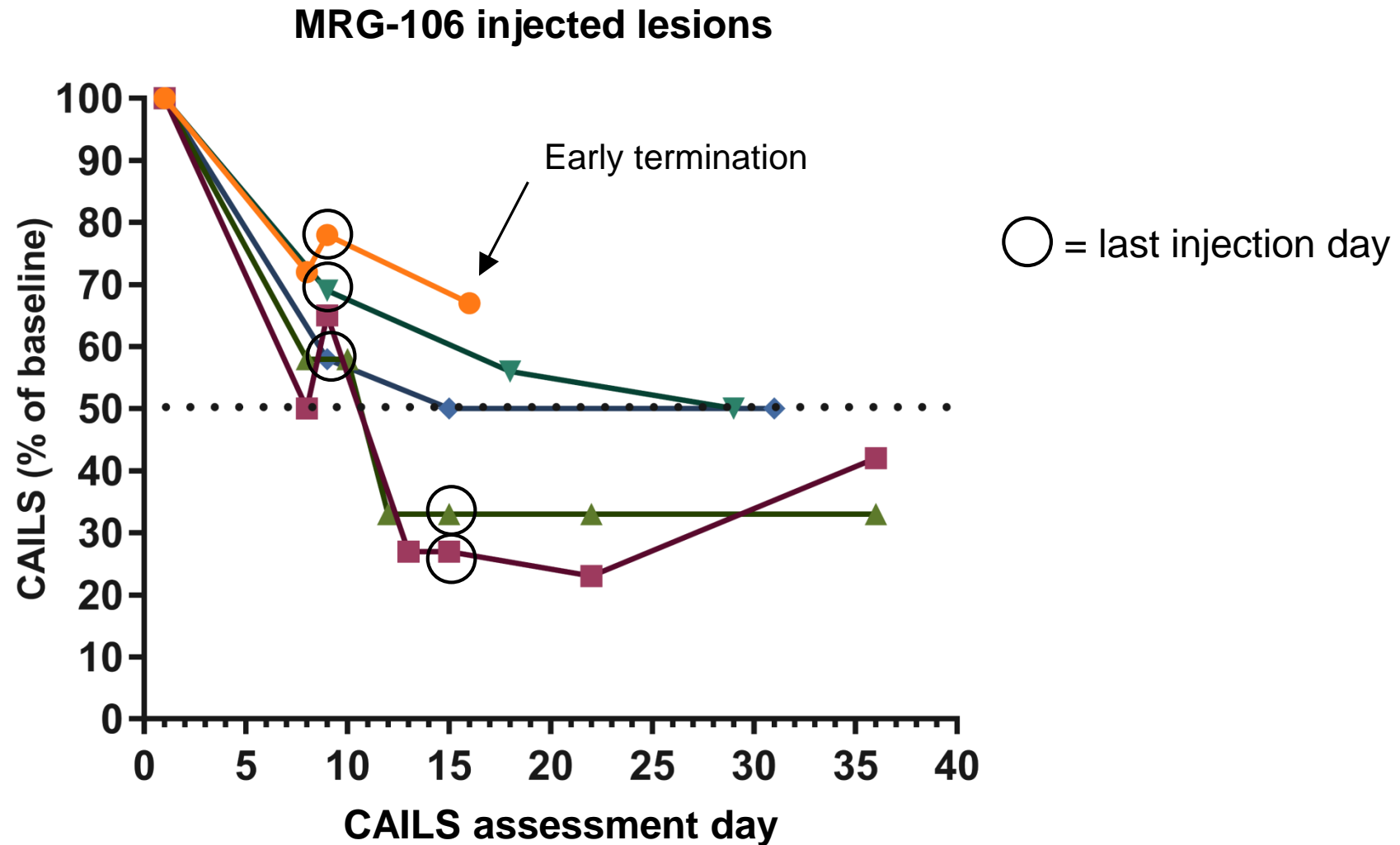
Demographic	Part A Intralesional (N=6)	Part B Systemic (N=27)	Total (N=33)
Sex			
Female	1 (17%)	8 (30%)	9 (27%)
Male	5 (83%)	19 (70%)	24 (73%)
Age Range (Years)			
18 - 45	0 (0%)	3 (11%)	3 (9%)
46 - 65	6 (100%)	15 (56%)	21 (64%)
> 65	0 (0%)	9 (33%)	9 (27%)
Race			
Asian	0 (0%)	1 (4%)	1 (3%)
Black	1 (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)

miR-155 Copy Number in MF Lesion Biopsies

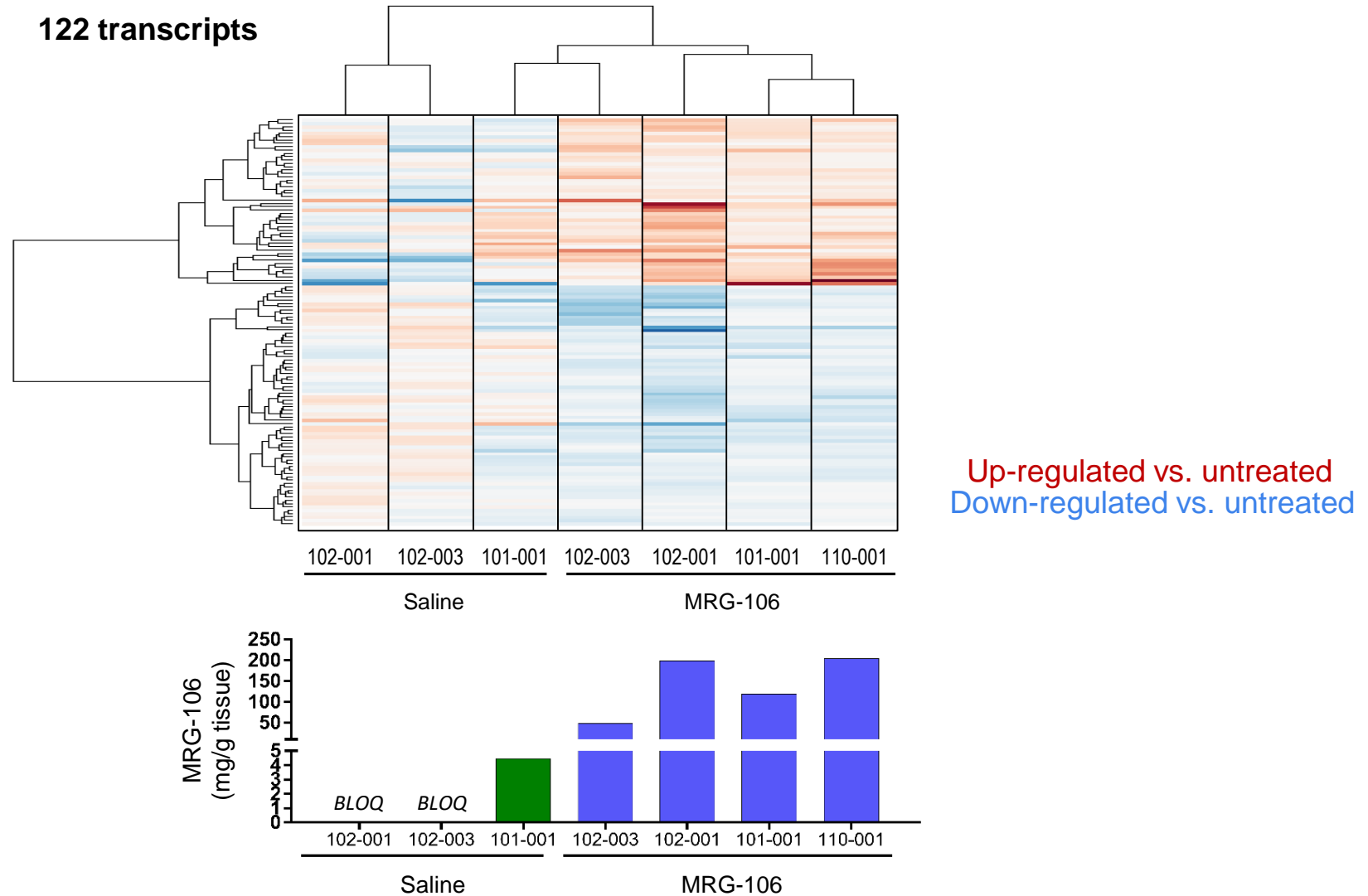


# Improvement of CAILS with Intralesional Injection of MRG-106 (Part A)

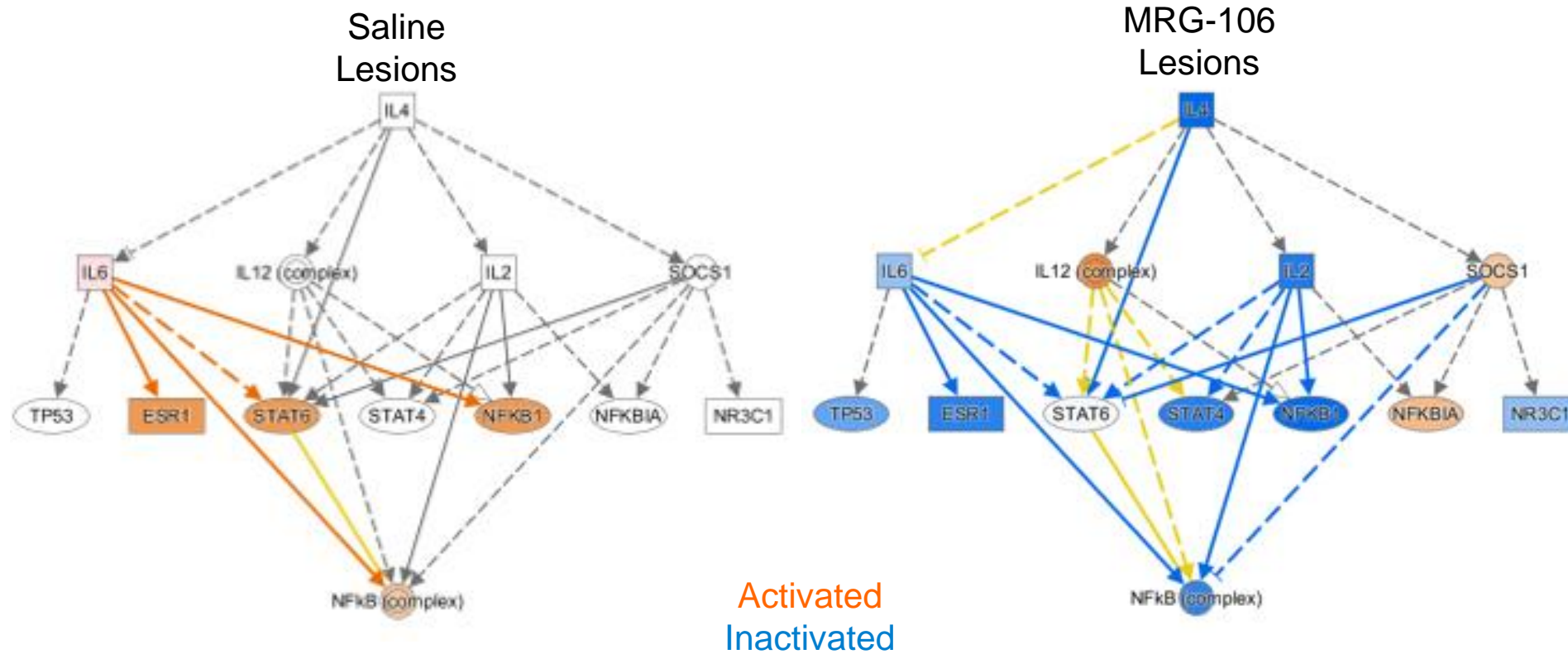
MRG-106 was well-tolerated with generally minor injection site reactions



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



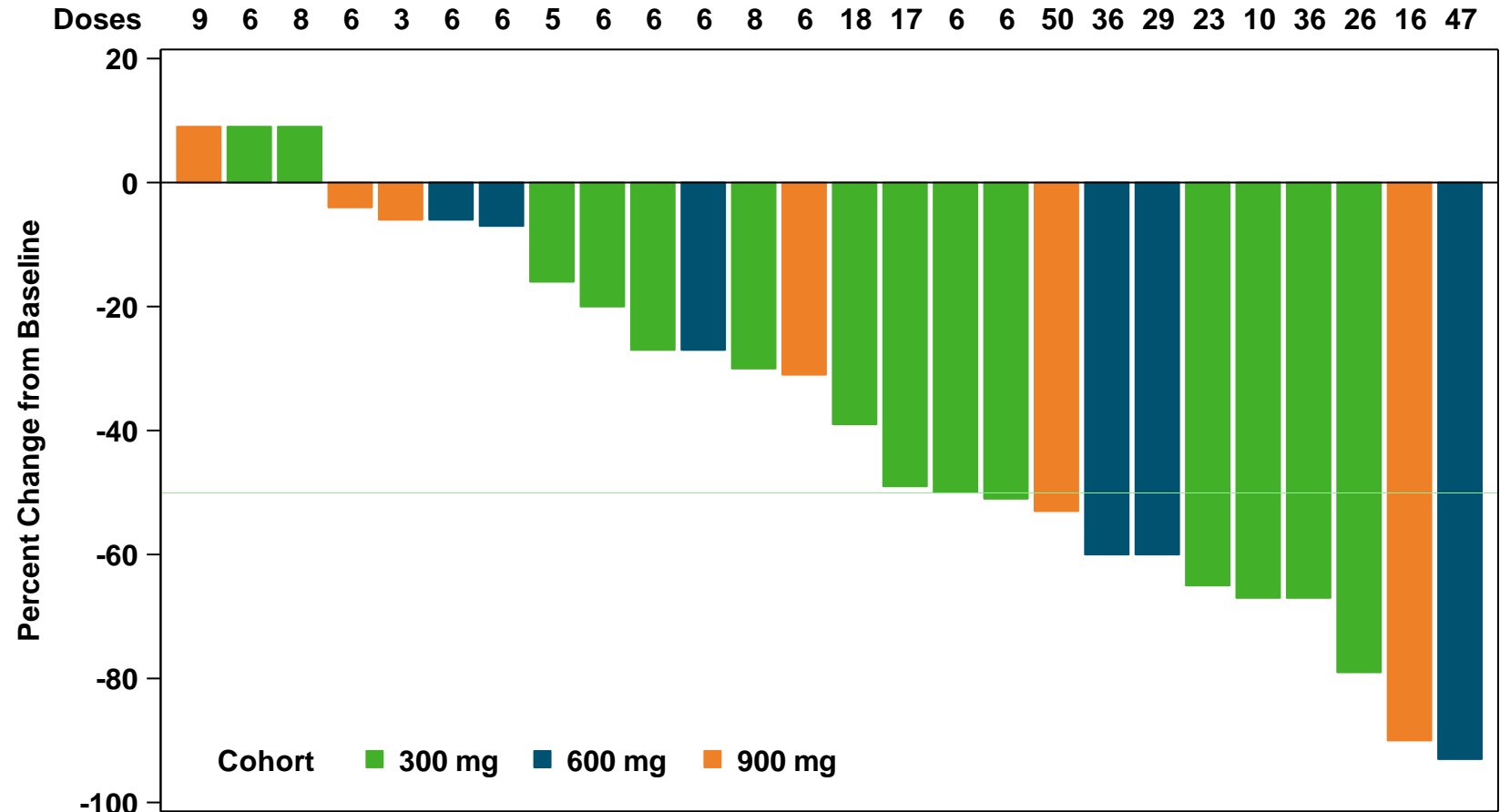
# MRG-106 Treatment Decreases Key CTCL Disease Pathways Including STAT and NFκB Pathways (Part A)





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

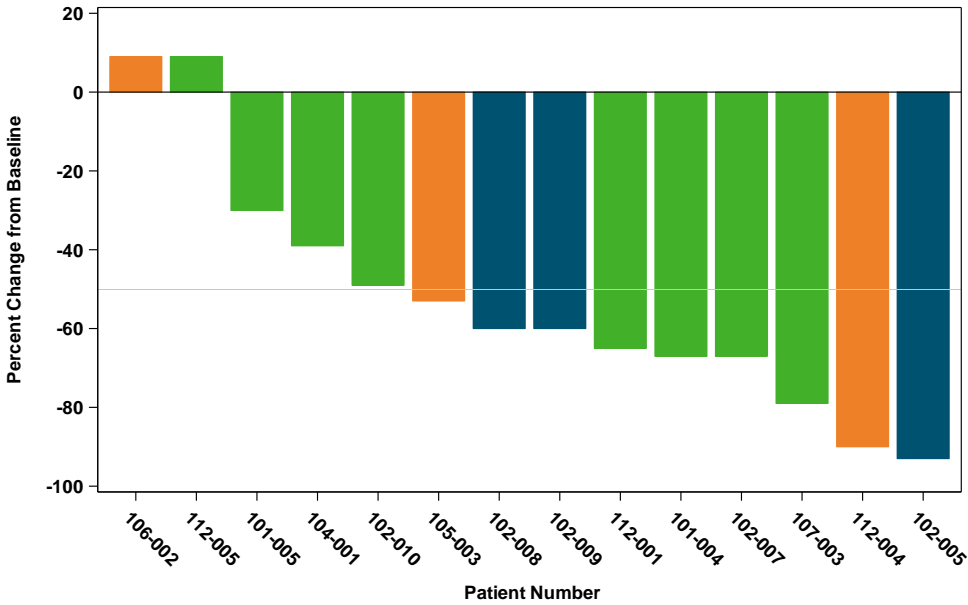
- 21 subjects were eligible for > 1 month of treatment
- 15 subjects chose to continue with additional months of treatment



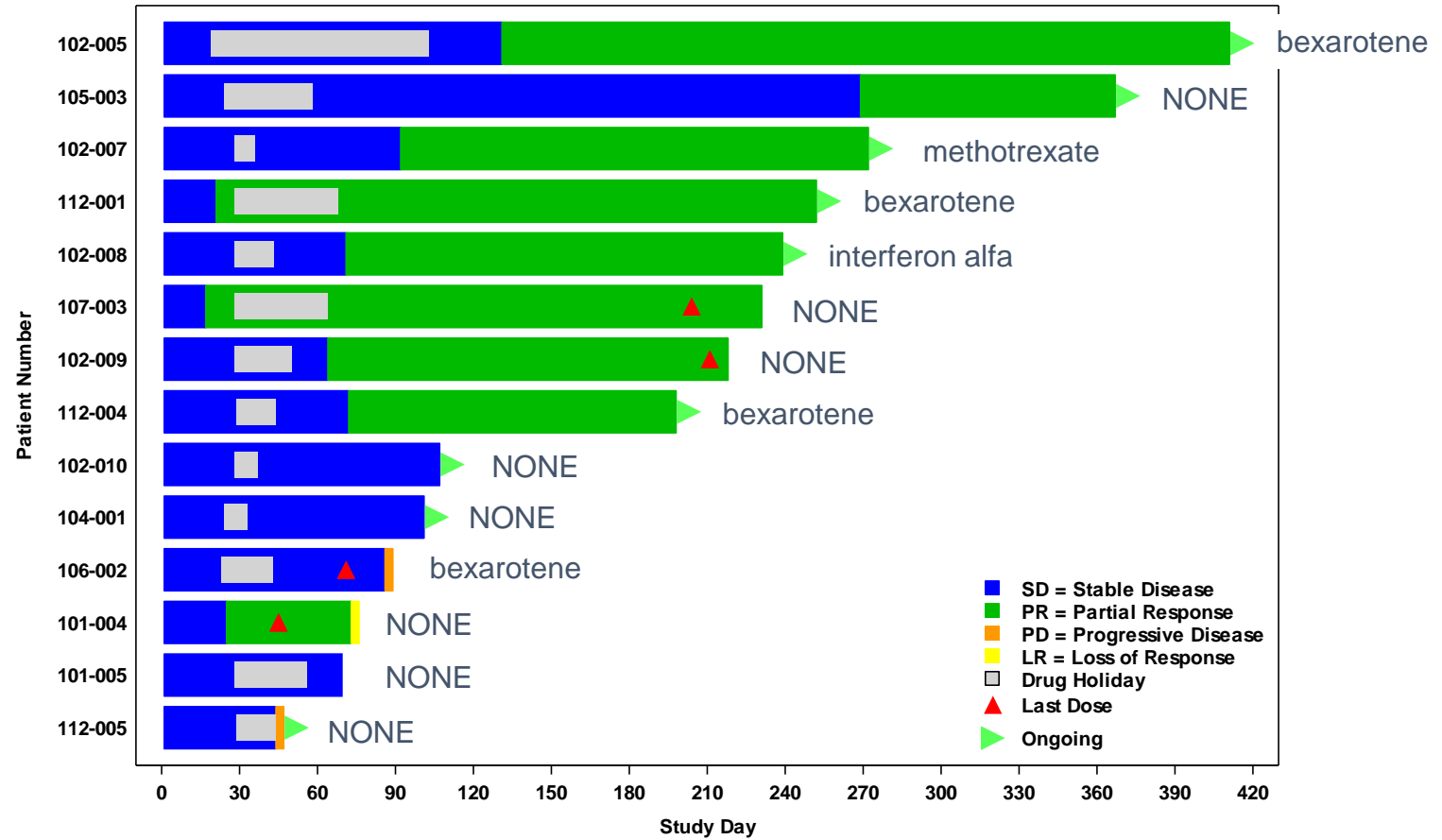
6 doses = initial cycle  
4 doses in subsequent cycles

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

Once 50% mSWAT PR is achieved, response is durable



Cohort    300 mg    600 mg    900 mg



# 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)



# 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

# 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  $\geq 10\%$  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

# MRG-106 Has a Favorable Safety Profile

## All coded Grade 3 or 4 Adverse Events

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

# Conclusions

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- 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  $\geq 50\%$  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

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