Characterisation of the oncolytic kinetics of the immunotherapeutic agent, CAVATAK™, delivered intratumorally in patients with advanced malignant melanoma.

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OVC
Boston, MA
June 16, 2015

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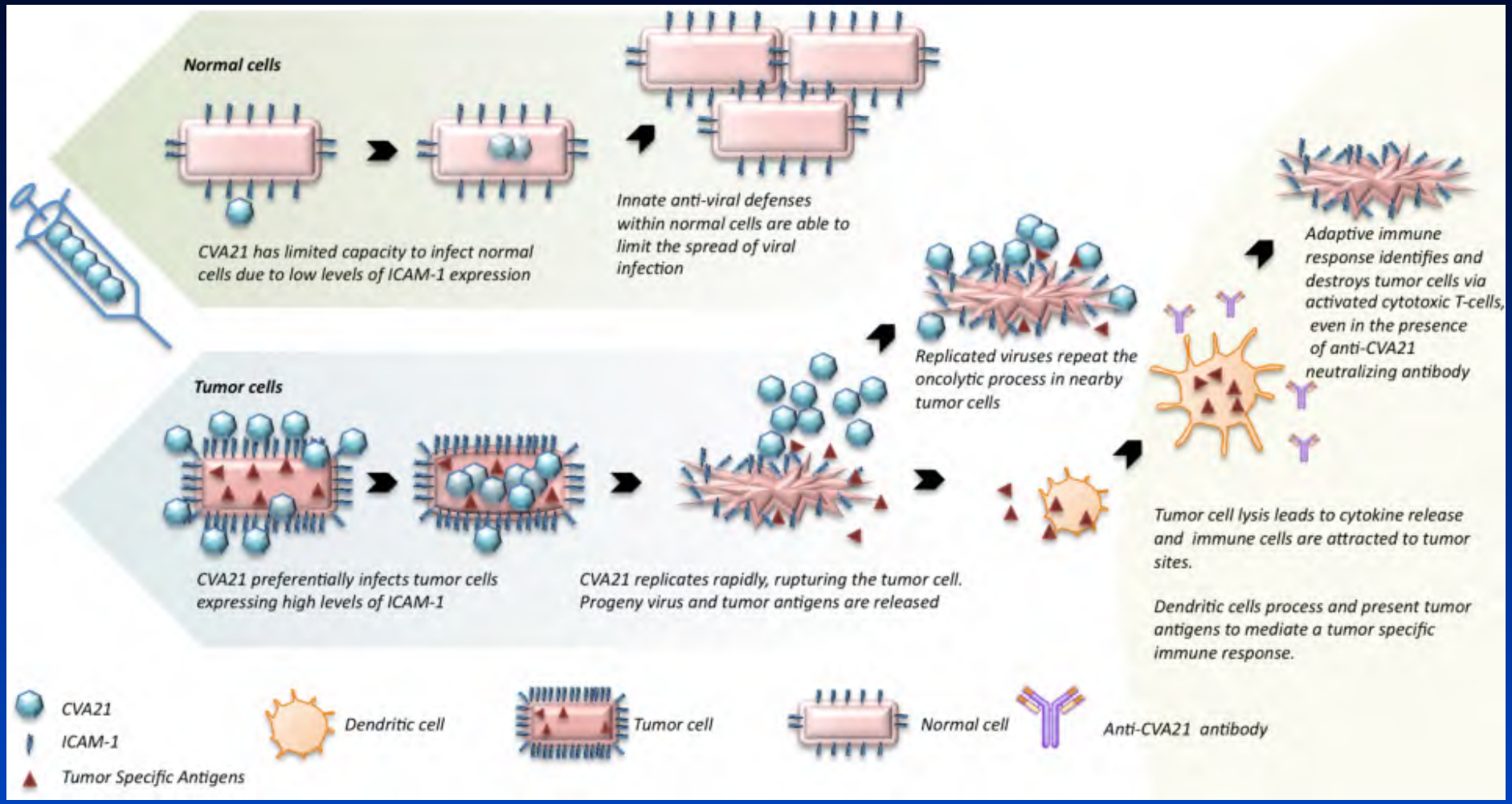
CAVATAK™ (Coxsackievirus A21) an oncolytic immunotherapeutic agent

- Proprietary formulation of the oncolytic virus, Coxsackievirus A21
- Targeted to specific receptor over expressed on cancer cells (ICAM-1)
- Kills local and metastatic cells by oncolytic and immunotherapeutic activity
- Potential application across a range of cancer types
  - Prostate, lung, melanoma, bladder and others
- Well tolerated in patients - to date no treatment-related grade 3 or 4 adverse events
- Potential intravenous as well as intratumoural use
- Potential application as monotherapy or in combination
- Manufactured under cGMP at SAFC, California

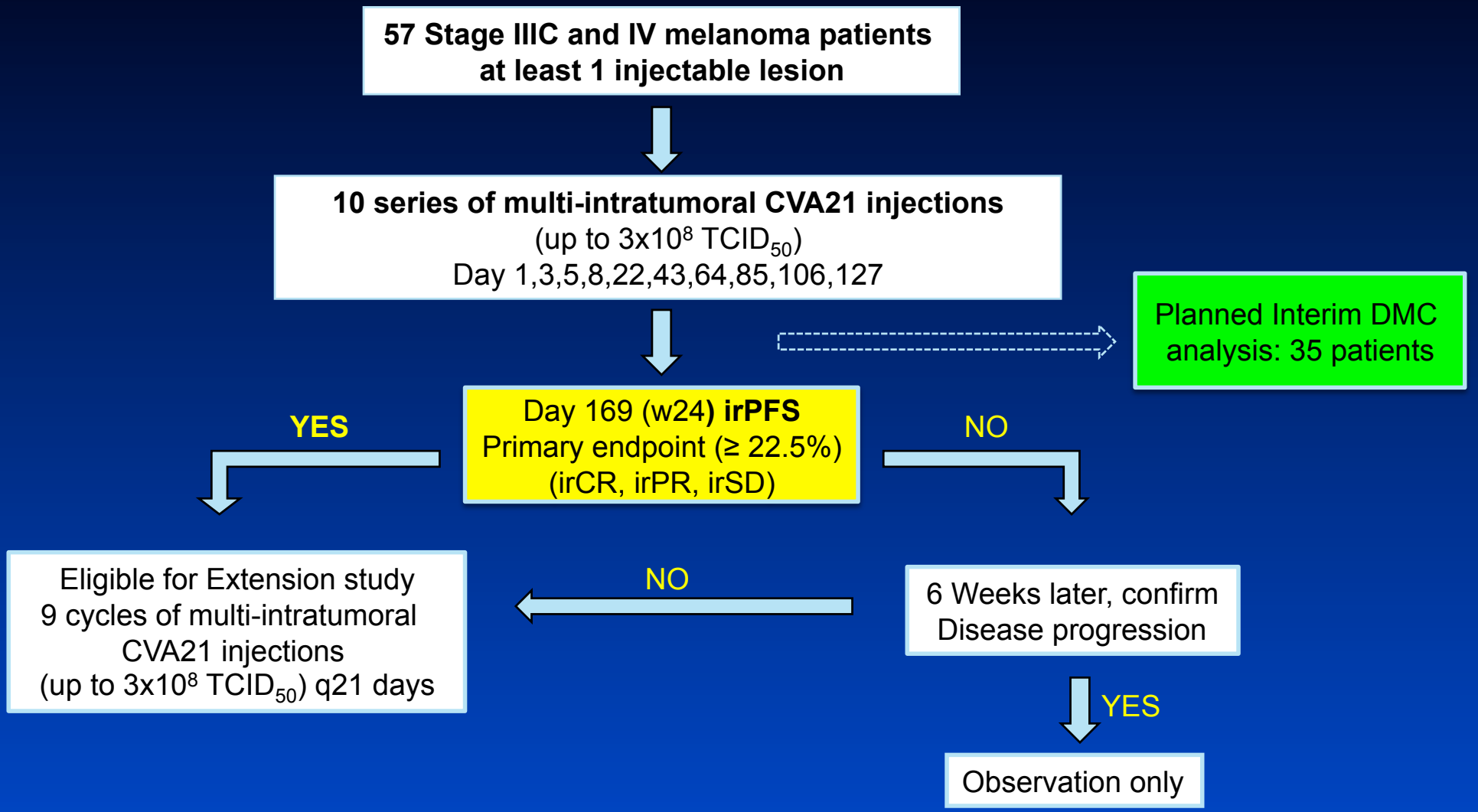
Coxsackievirus A21(CVA21)

Oncolytic immunotherapeutic modes of action



CALM Phase II

CAVATAK in Late stage Melanoma study design



CALM Phase II trial (VLA-007)

Safety and toxicity¶

Adverse Event[1]	Grade 1* n (%)	Grade 2 n(%)	Grade 3 n(%)	Grade 4 n(%)
Injection site pain	16 (28%)	2 (4%)		
Tiredness (fatigue)	15 (26%)	2 (4%)		
Chills	15 (26%)			
Pyrexia	7 (12%)			
Injection site erythema	7 (12%)			
Pain	6 (11%)	1 (2%)		
Myalgia	6 (11%)			
Headache	6 (11%)			
Hyperhidrosis	5 (9%)			
Peripheral edema		1 (2%)		
Erythema		1 (2%)		
Musculoskeletal stiffness		1 (2%)		
Rash		1 (2%)		

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- only Grade 1 adverse events occurring in 5 or more patients are listed
- [1] AE coded using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

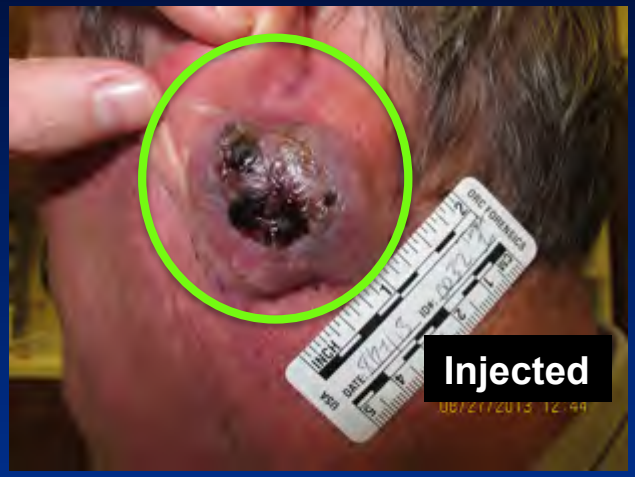
CALM Phase II trial (VLA-007)

Response data

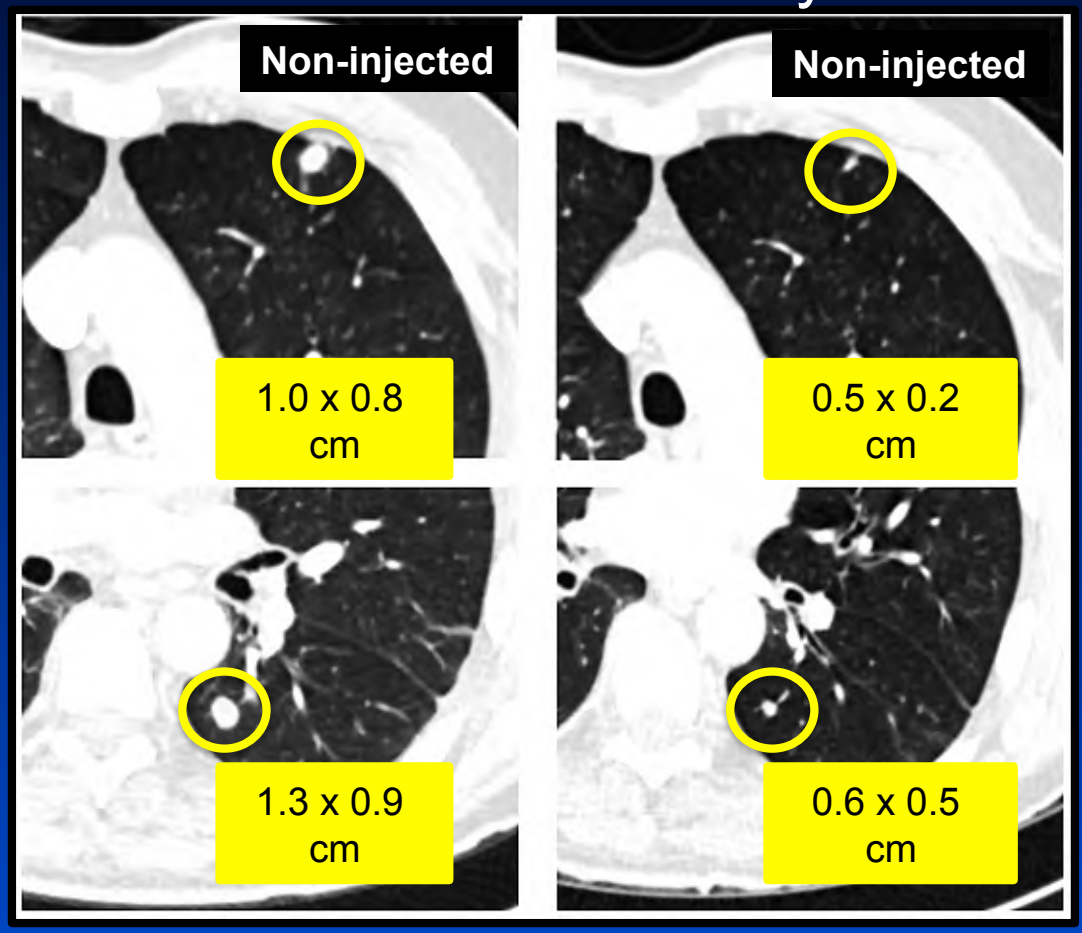
Primary endpoint (≥ 10 pts with irPFS 6 months from 54 evaluable pts)	
irPFS 6 months (CR+PR+SD)	38.6% (22 / 57 pts)

Secondary endpoints	
Overall response rate (CR+PR, irRECIST 1.1)	28.1% (16 / 57 pts) [8 CR+ 8 PR]
Median time to response	3.4 months (95% CI: 1.5, 4.2)
Median irPFS	5.7 months (95% CI: 2.8, 11.1)
Median Overall Survival	26 months (95% CI: 16.7, NR^{+})
1-year survival rate	75.4% (43 / 57 pts)

Pt 03-032: Non-injected distant visceral lesion response



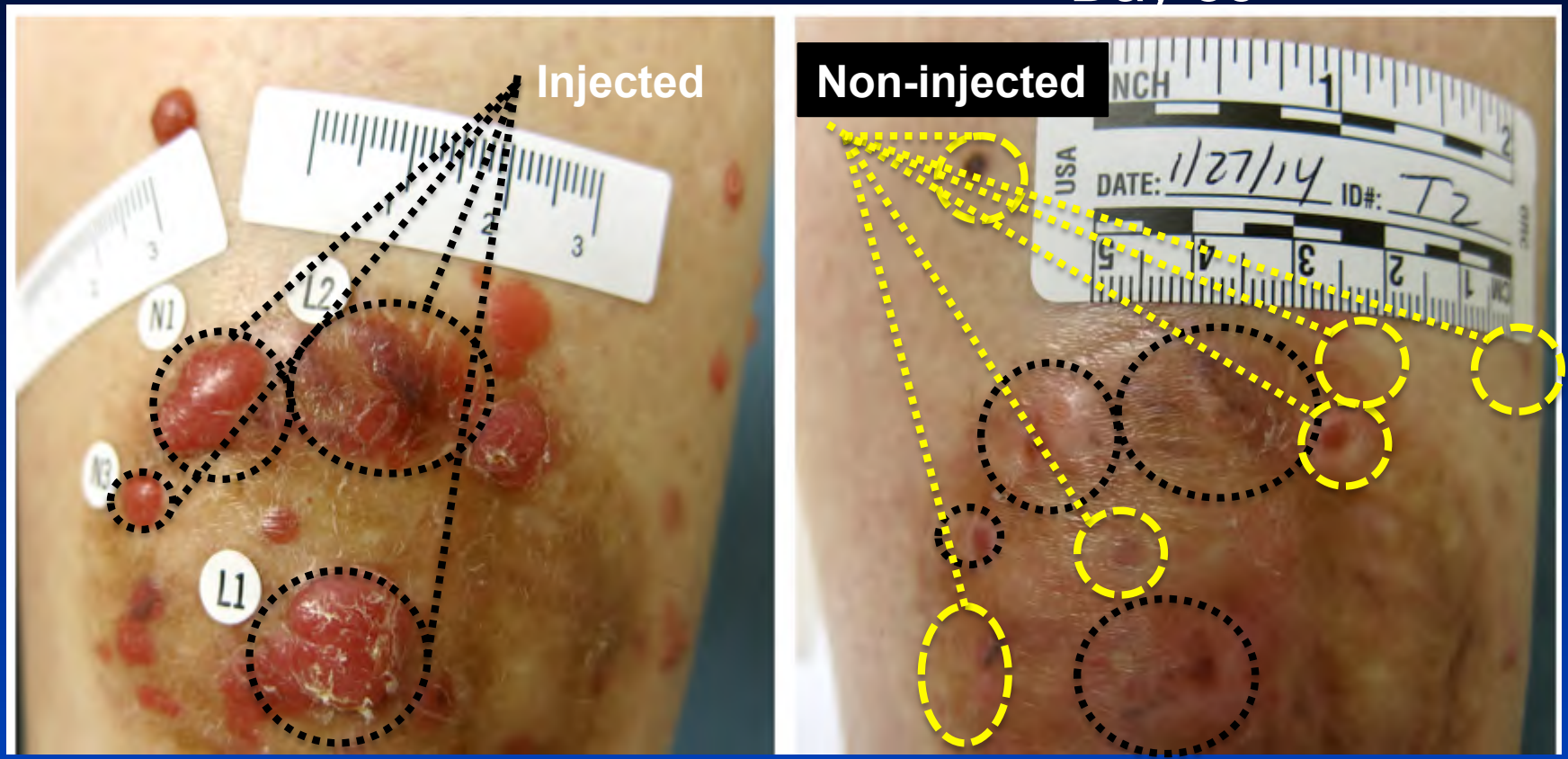
Male with metastatic melanoma to left neck and lungs. Injection in left neck.



Pt 12-002: Local injected and non-injected lesion responses

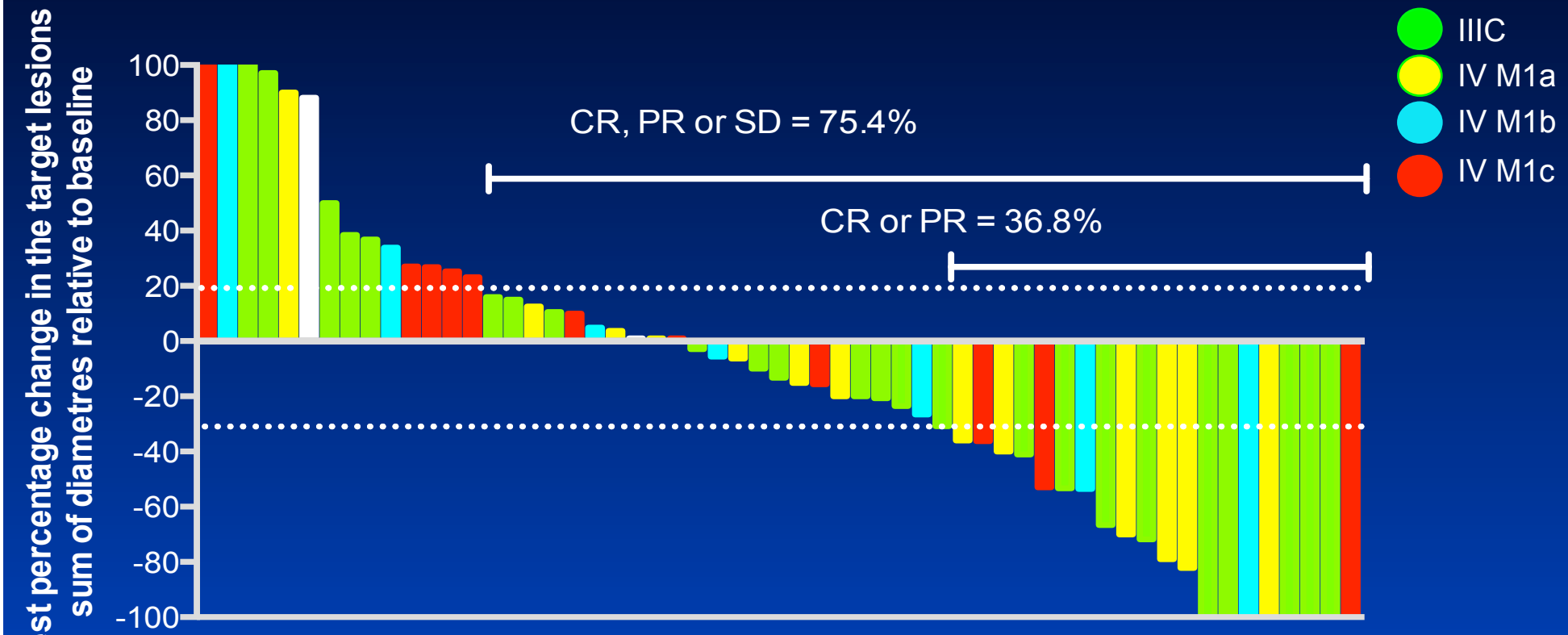
Baseline

Day 85



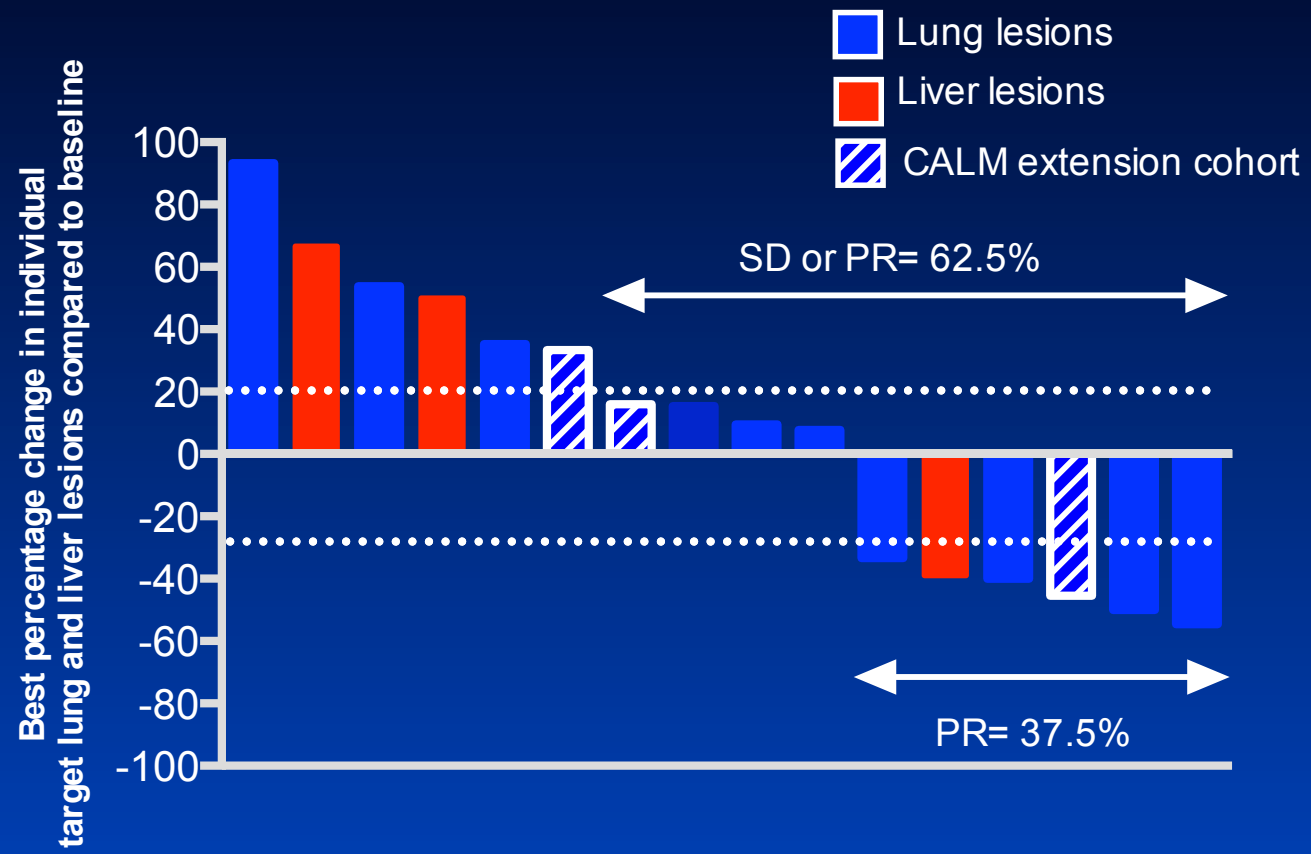
Male with metastatic melanoma to the leg. Injection in leg lesions .

VLA-007 (CALM study): Best Percentage changes in Target lesions

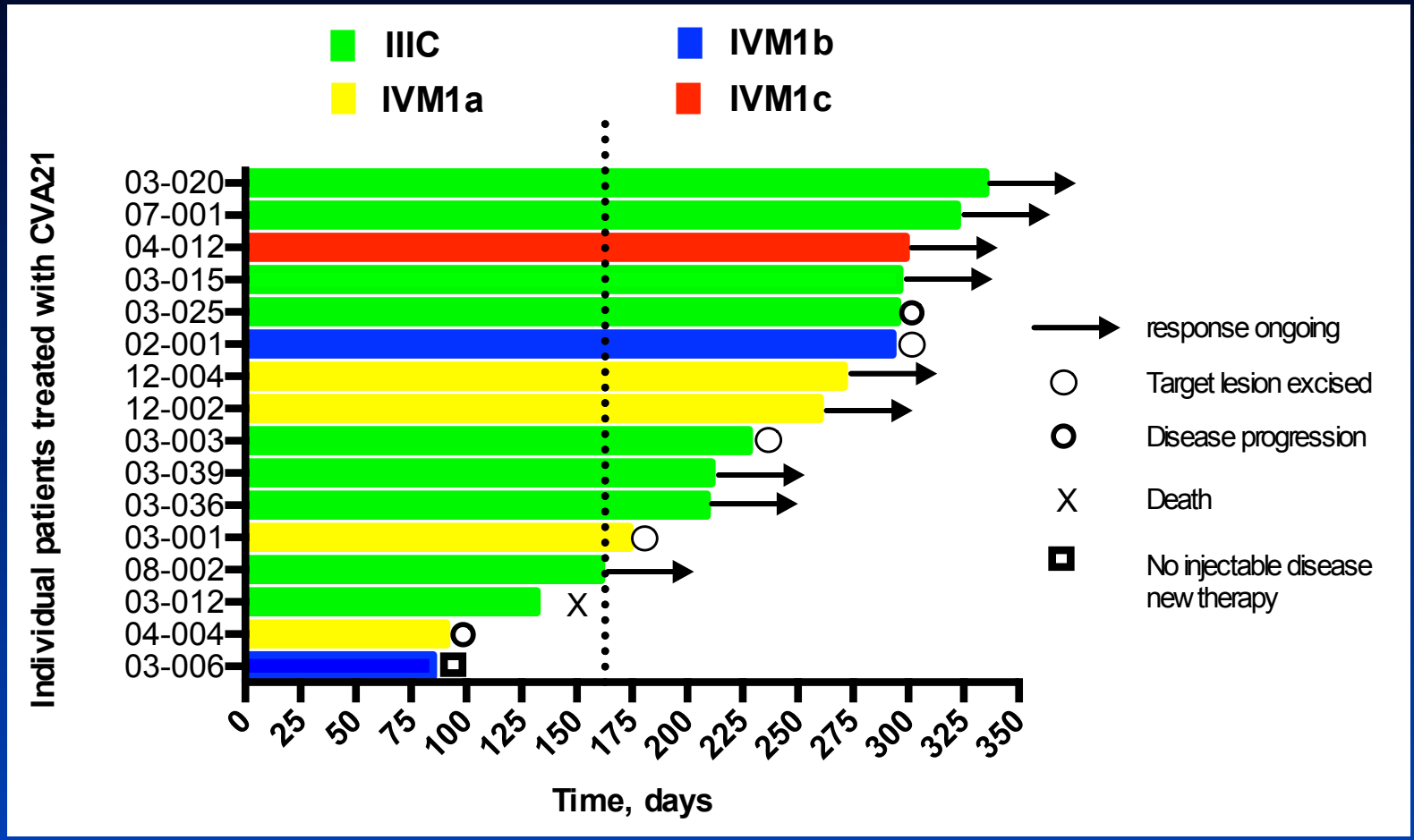


• Analysis excludes patients satisfying protocol criteria but not on study long enough for 6 week tumor response assessment; CR=Complete response, PR= Partial response, SD= Stable disease and PD= Progressive disease

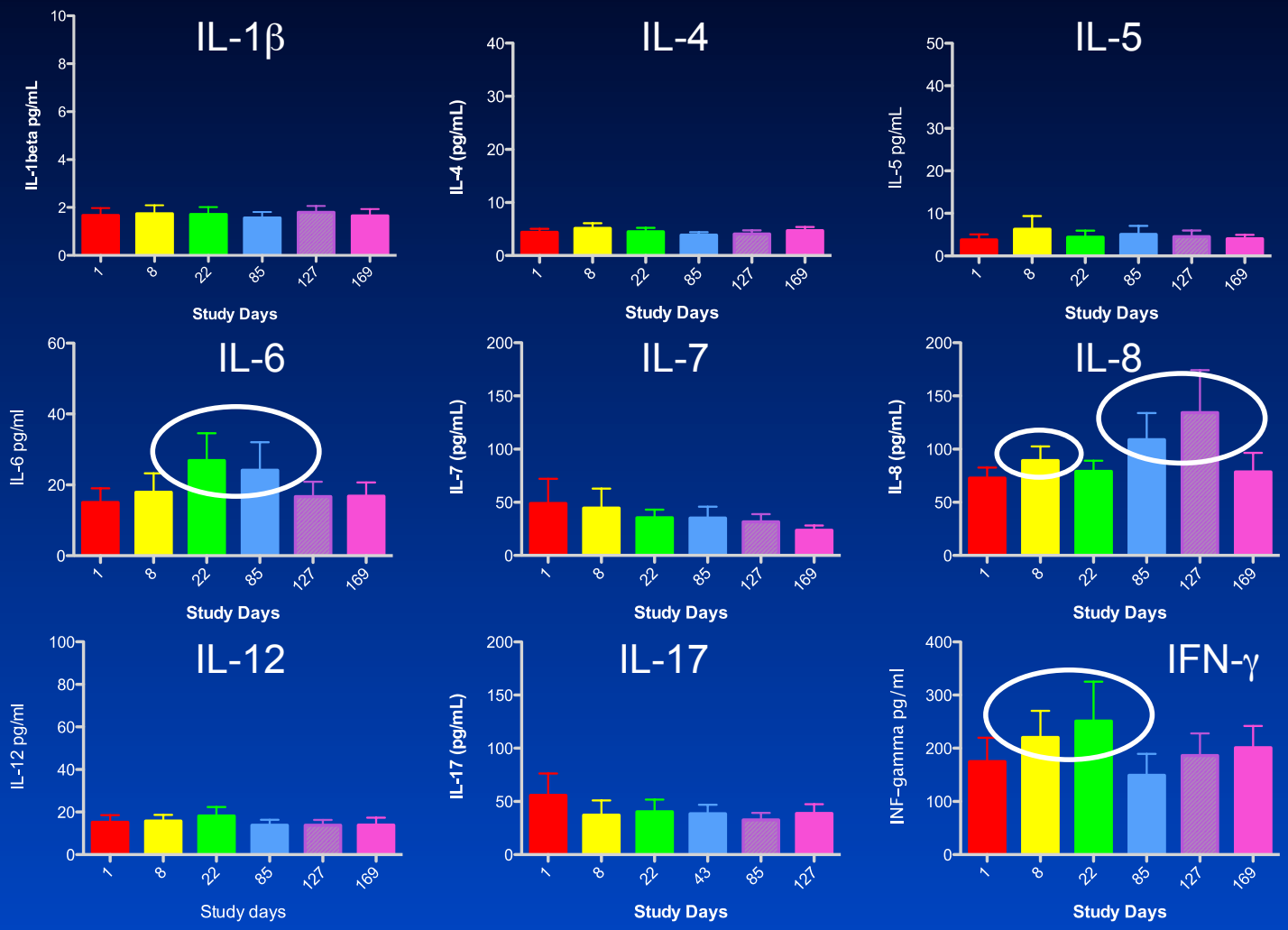
VLA-007 (CALM study): Best Percentage change in non-injected lung and liver lesions



VLA-007 (CALM study): Duration of Response



VLA-007 (CALM study): Patient Serum Cytokine levels. Anti-viral / anti-tumor immune response ?



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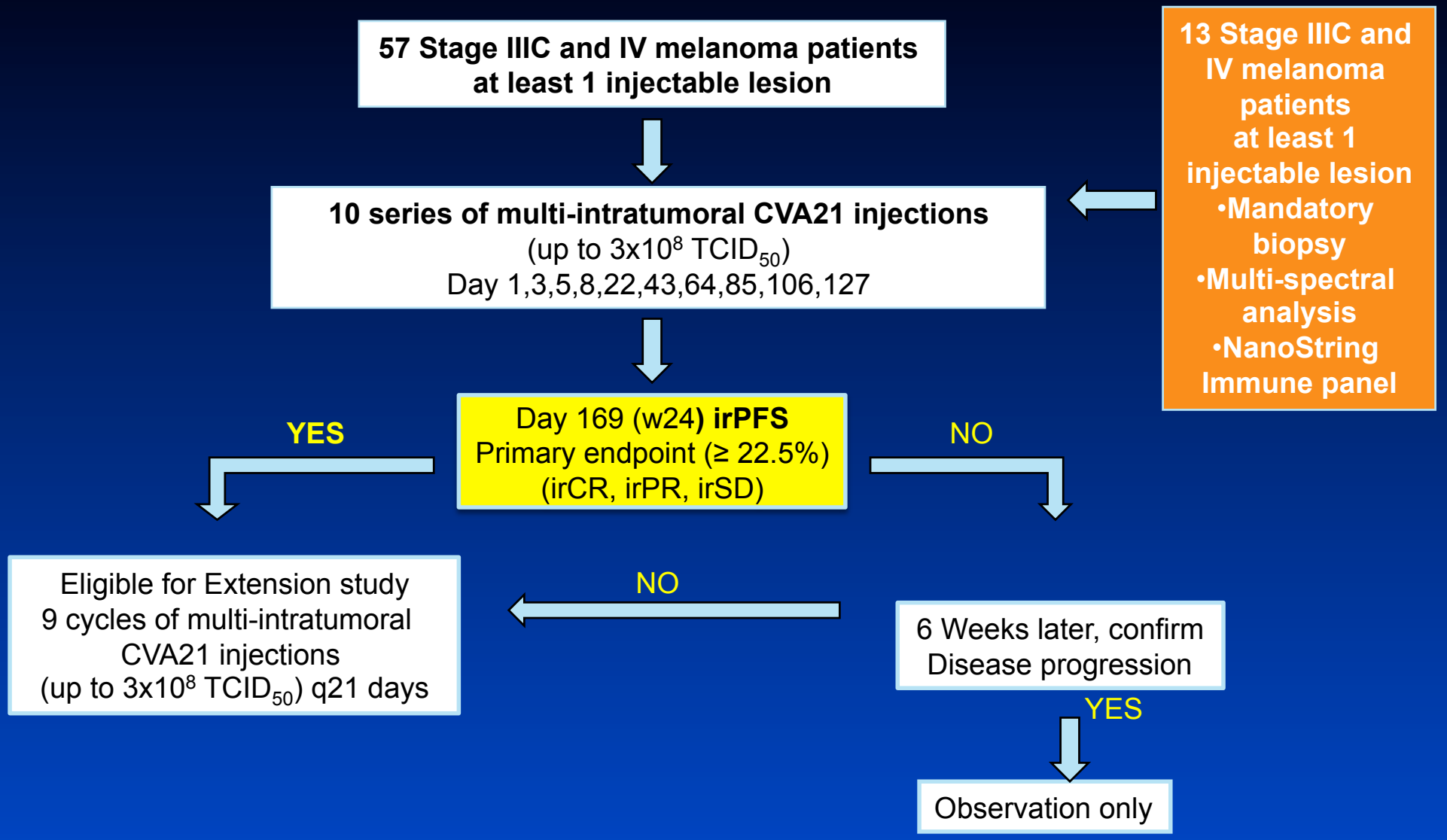
+ Serum prior to CAVATAK injection from patients with CR, PR or SD

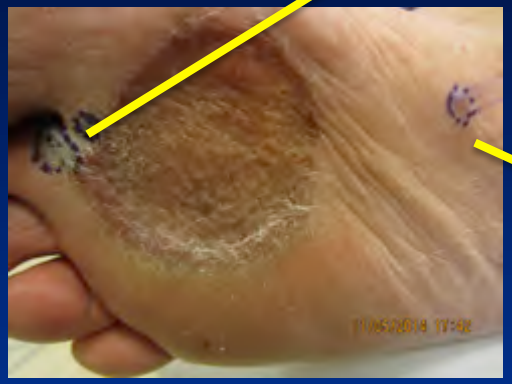
* Preliminary on-going analysis

CALM Phase II: Extension Cohort



Pt 03-043

- *Male: Stage IIIC with melanoma to the feet*
- *Prior treatment with surgery*

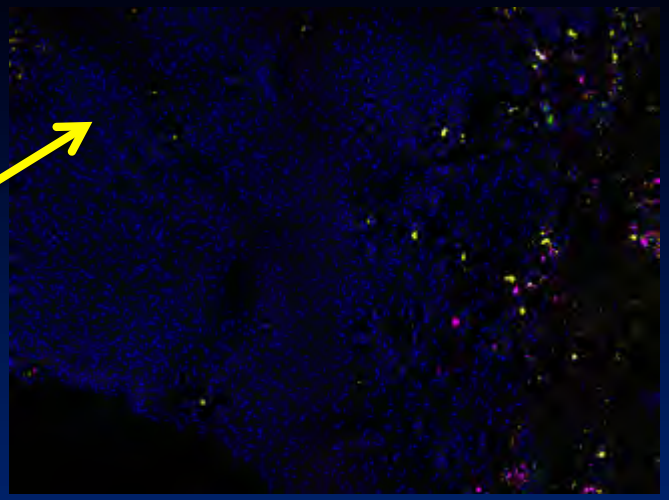


FoxP3
CD163
DAPI
PD-L1
CD3
CD8

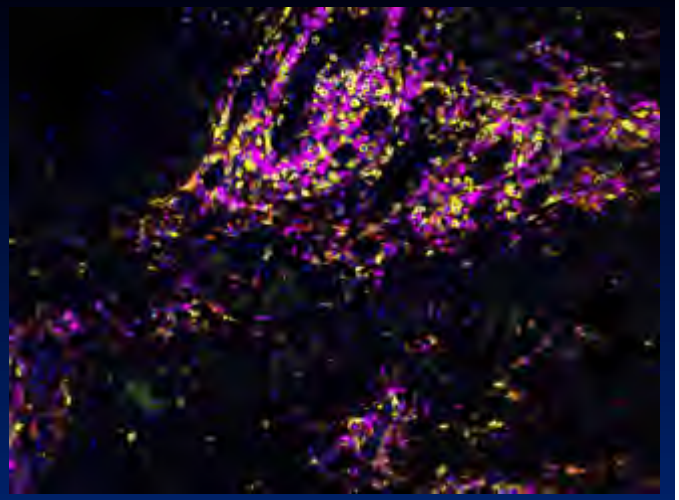
Injected

Non-injected

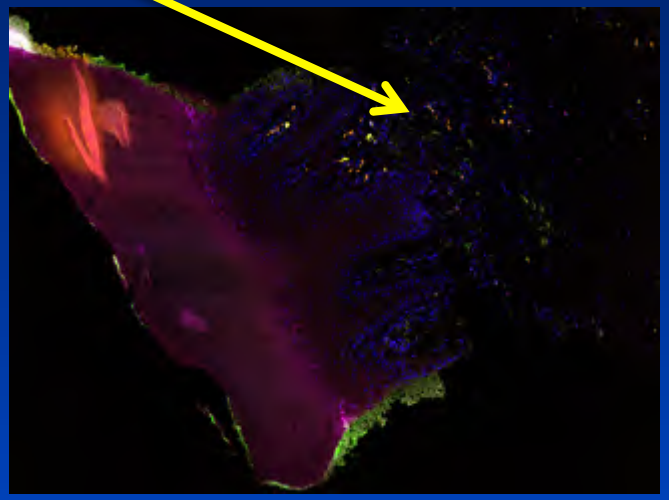
Day 0 (pre-treatment)



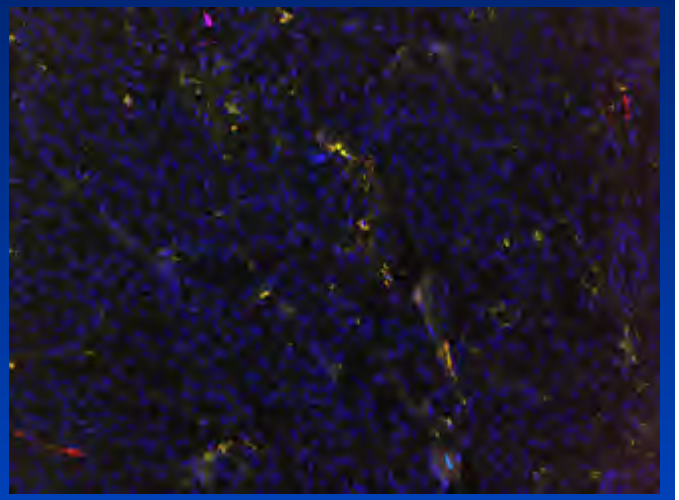
Day 8 (post-treatment)



Day 0



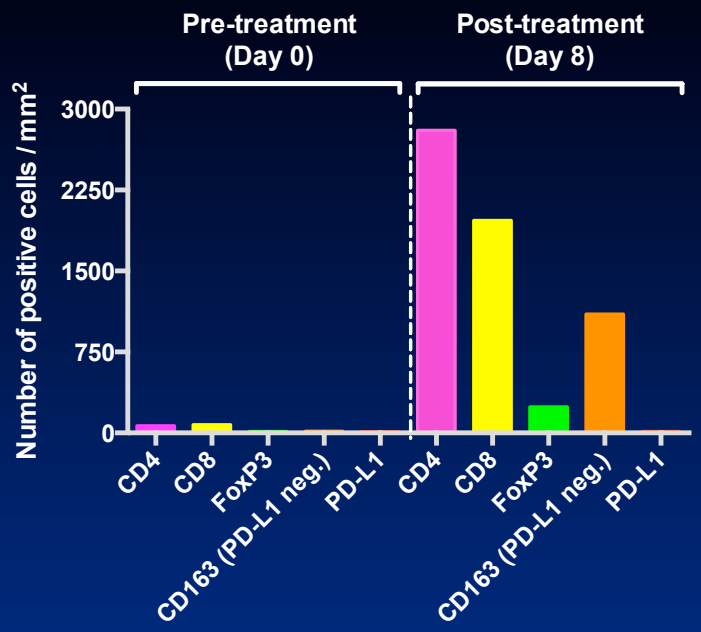
Day 8



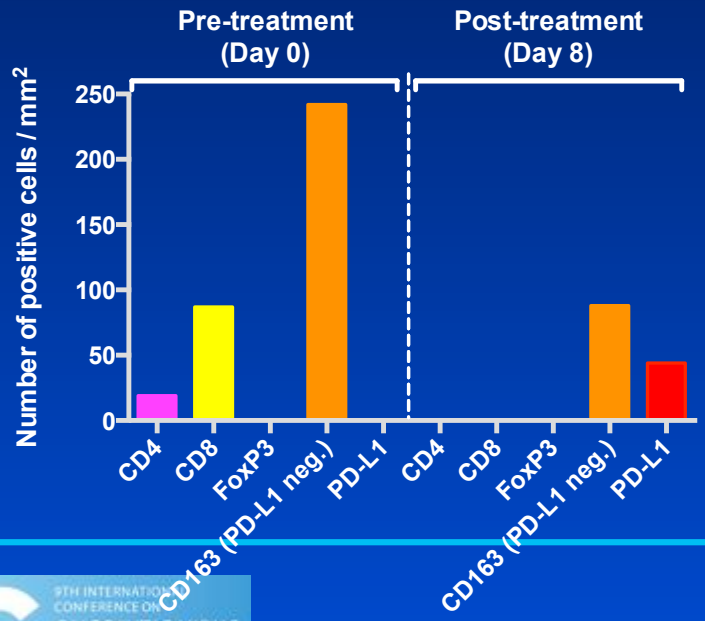
Pt 03-043

Multi-spectral analysis

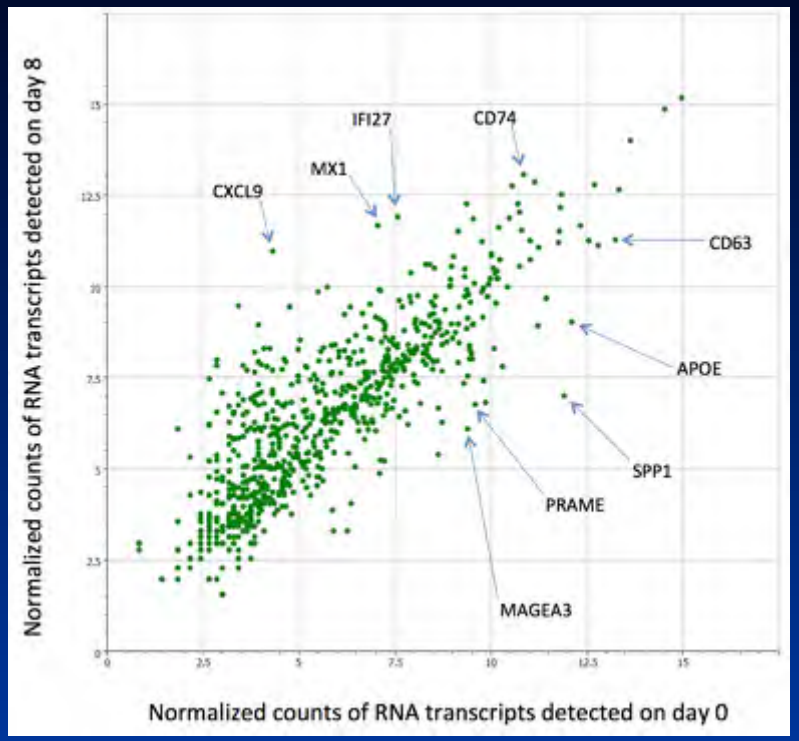
Injected



Non-injected

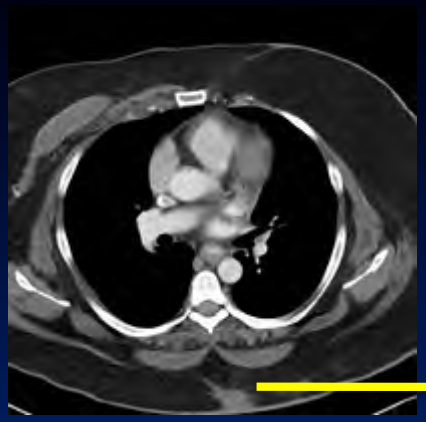


NanoString analysis: Immune profiling panel



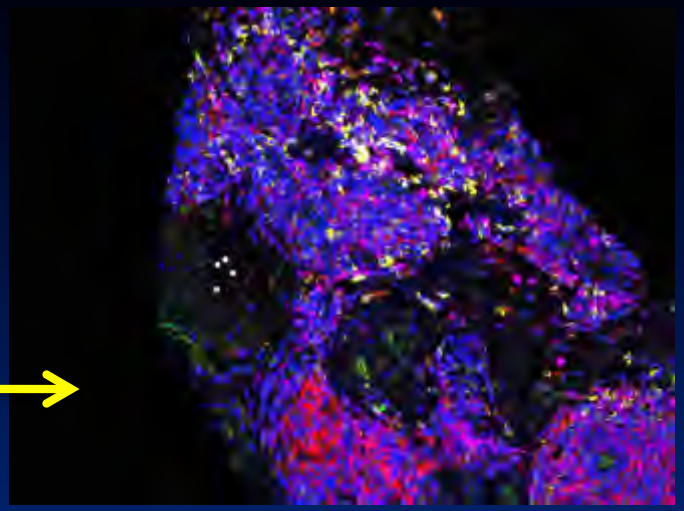
This patient's treated lesion exhibited a Th1-shift, with interferon-induced (CXCL9, MX1 and IFI27) and antigen presentation (CD74) genes upregulated by day 8 and Th2/regulatory associated transcripts (CD63 and APOE) down-regulated by day 8. Notably, transcripts for CT antigens MAGEA3 and PRAME were also less plentiful by day 8.

Pt 03-044

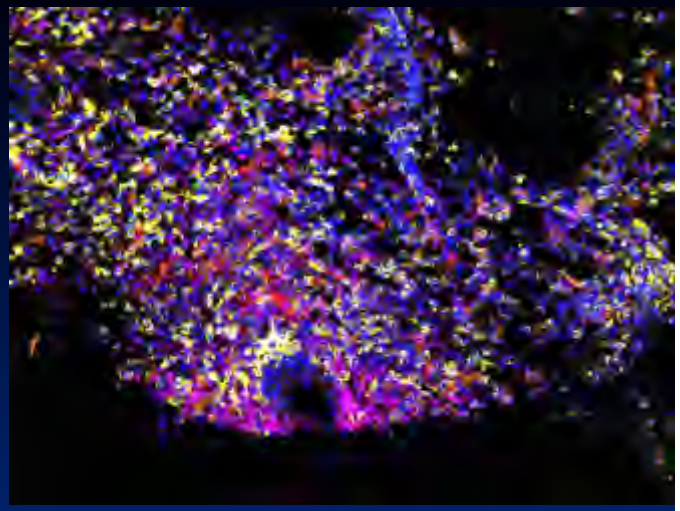


Injected

Day 0 (pre-treatment)



Day 8 (post-treatment)

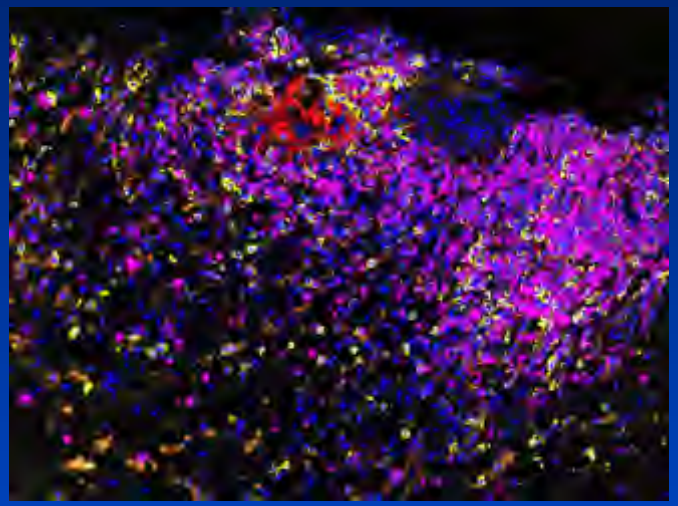


- *Female: Stage IIIC with melanoma to back*
- *Prior treatment with ipilimumab and talimogene laherparepvec*

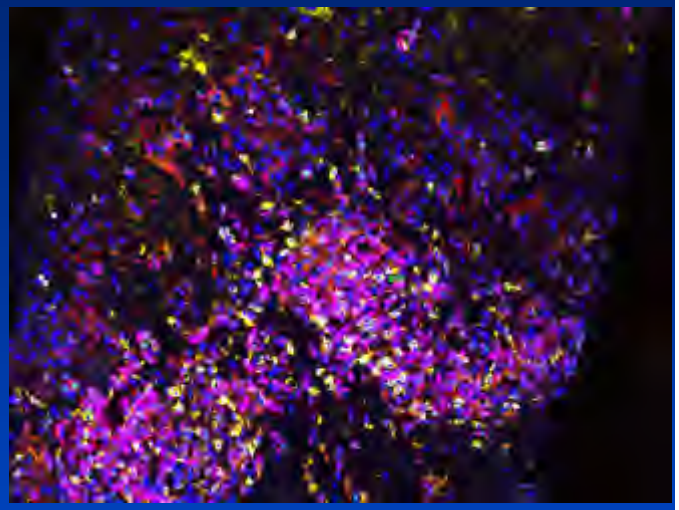
FoxP3	PD-L1
CD163	CD3
DAPI	CD8

Non-injected

Day 0



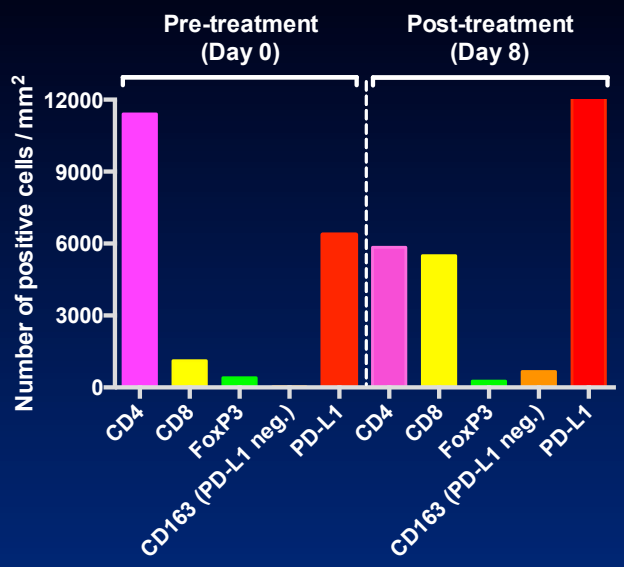
Day 8



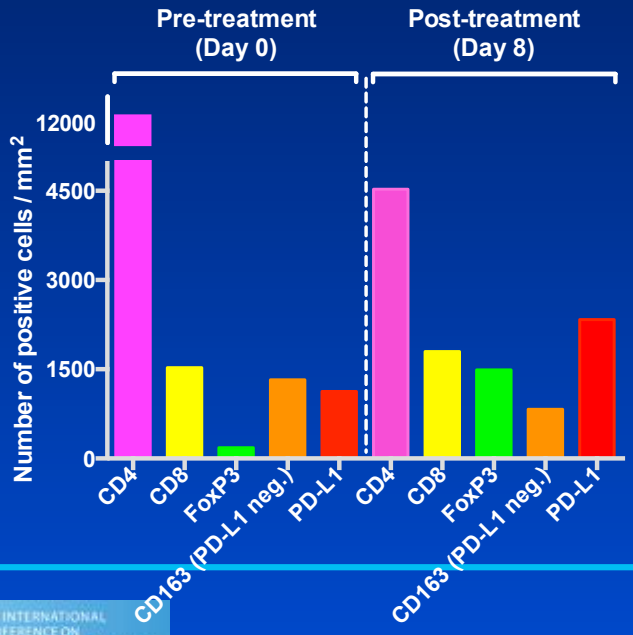
Pt 03-044

Multi-spectral analysis

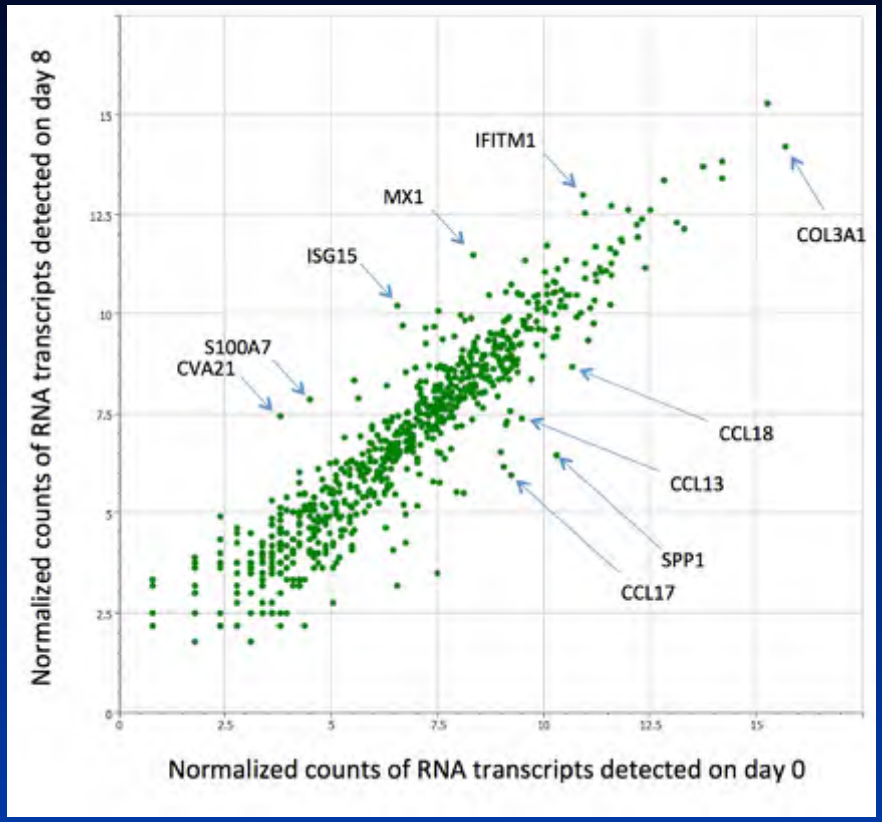
Injected



Non-injected



NanoString analysis: Immune profiling panel



This patient's treated lesion exhibited a Th1-shift, with interferon-induced genes (ISG15, MX1 and IFITM1) upregulated by day 8 and Th2/regulatory associated transcripts (CCL13 and CCL18) down-regulated by day 8.

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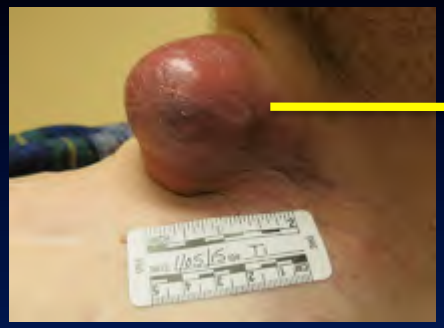
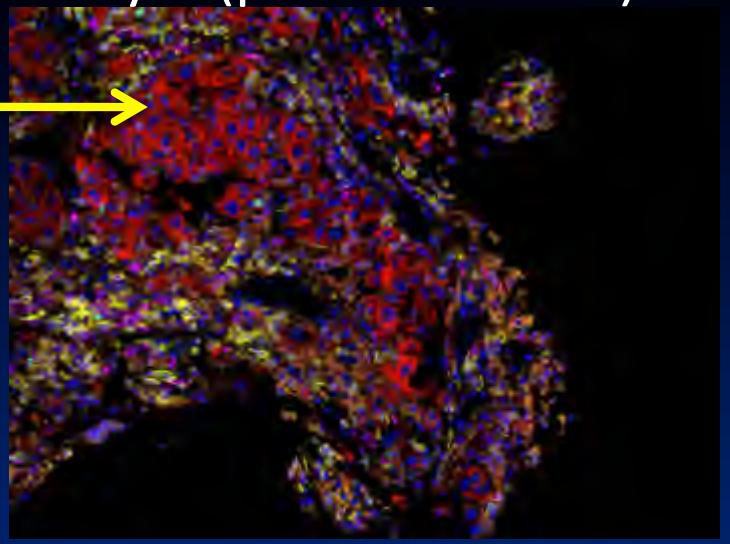
Pt 12-010

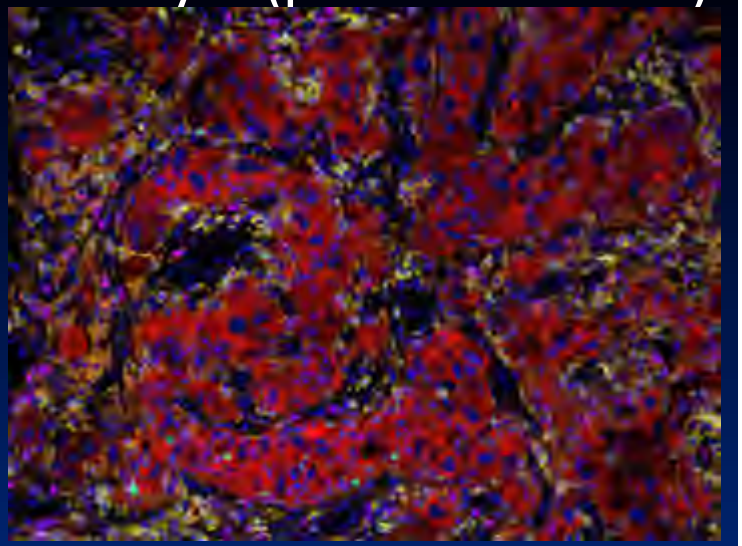


- *Male: Stage IV M1a with melanoma to neck*
- *Prior treatment with ipilimumab and talimogene laherparepvec*

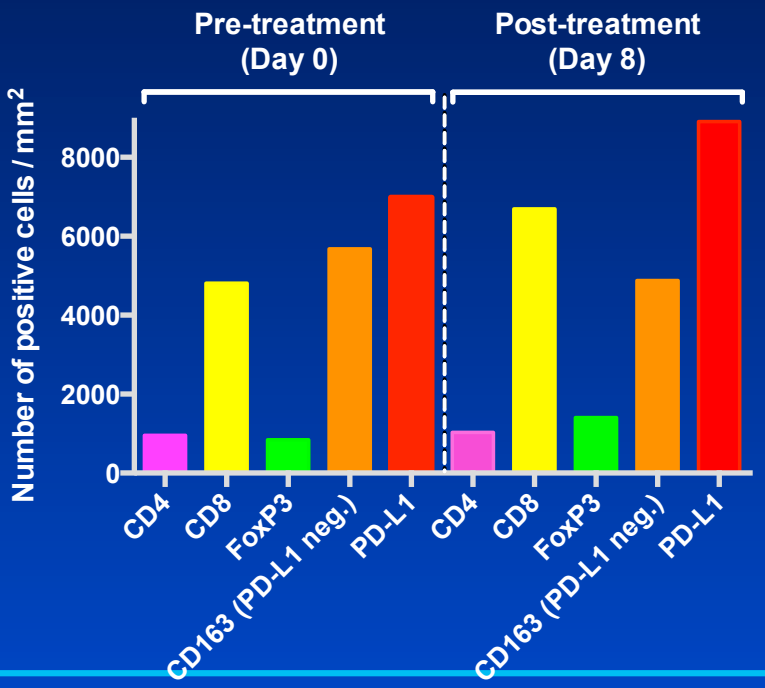
Day 0 (pre-treatment)



Day 8 (post-treatment)



FoxP3 PD-L1
CD163 CD3
DAPI CD8



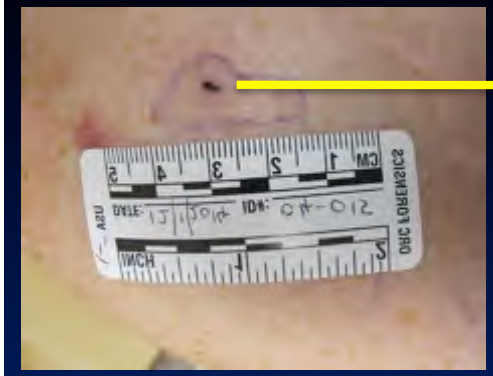
When treatment with immune checkpoint inhibitors fail

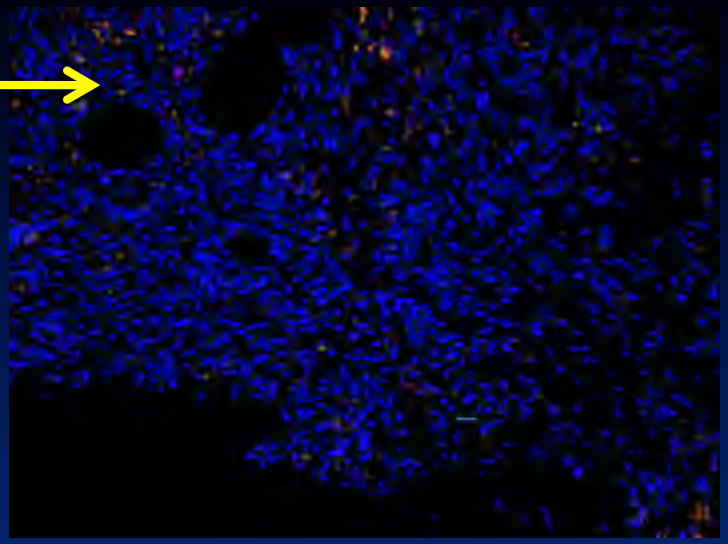
- Reconstitution of the tumour micro-environment with immune cell infiltrates

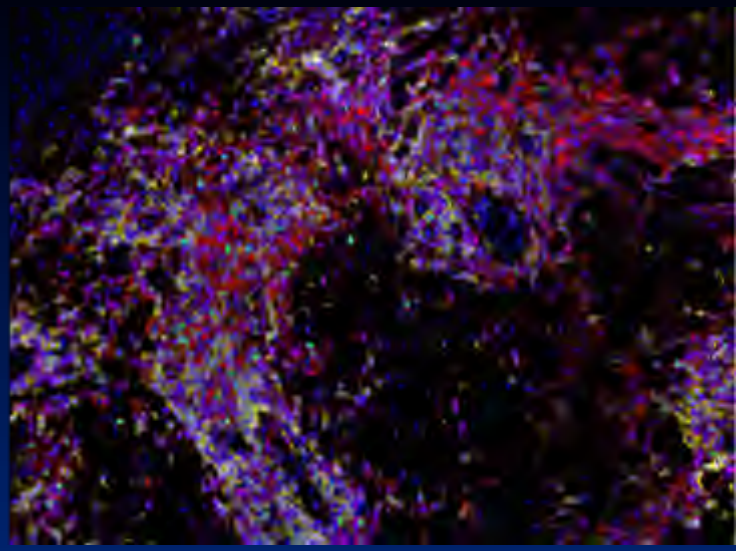
Pt 04-015

Day 0 (pre-treatment)

Day 8 (post-treatment)

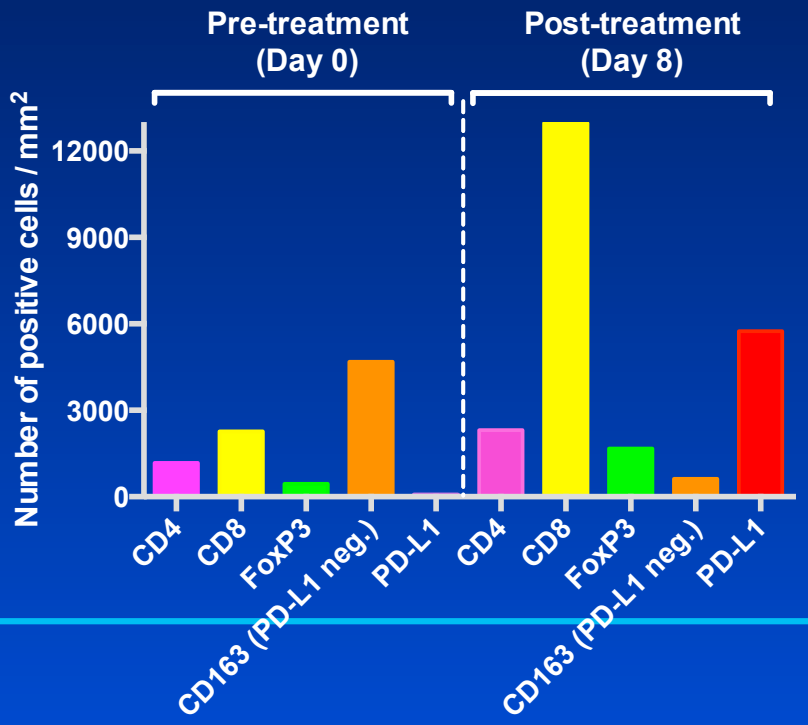






- *Female: Stage IIIC with melanoma to legs*
- *Prior treatment with ipilimumab and pembrolizumab*

FoxP3
CD163
DAPI
PD-L1
CD3
CD8



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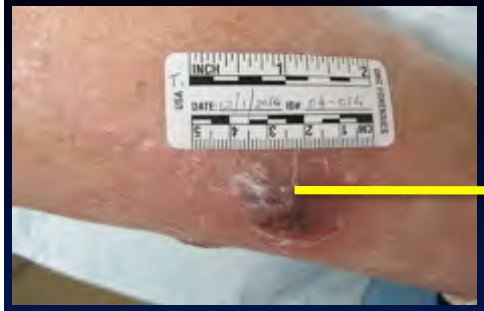
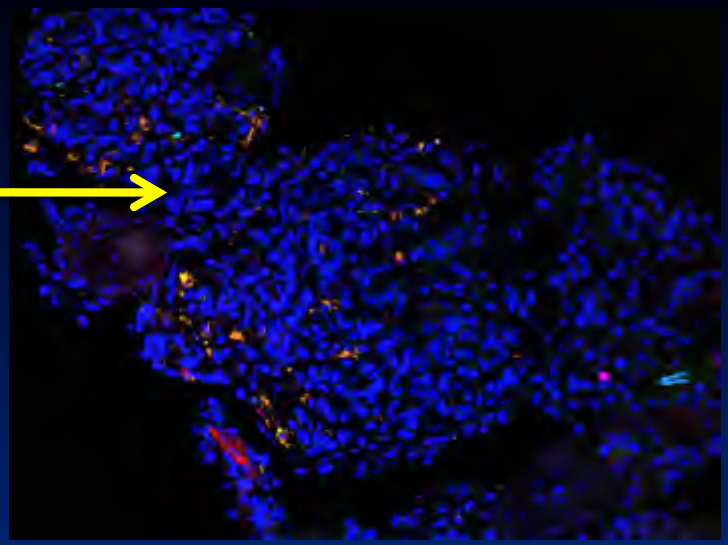
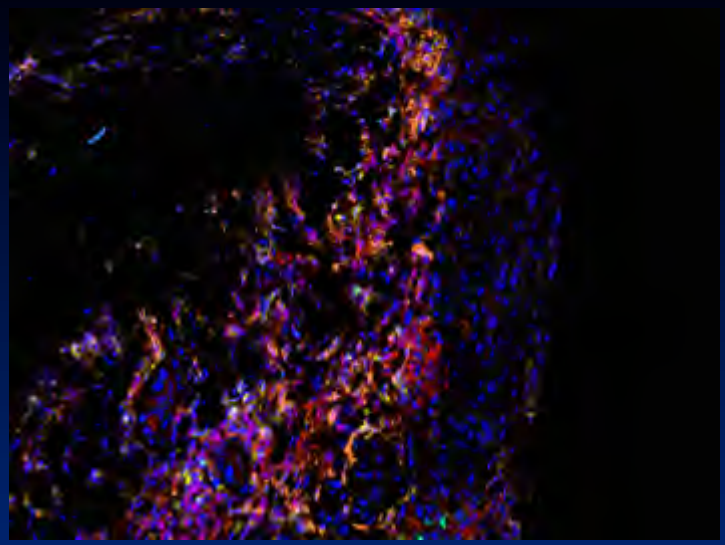
Pt 04-014

Day 0 (pre-treatment)

Day 8 (post-treatment)

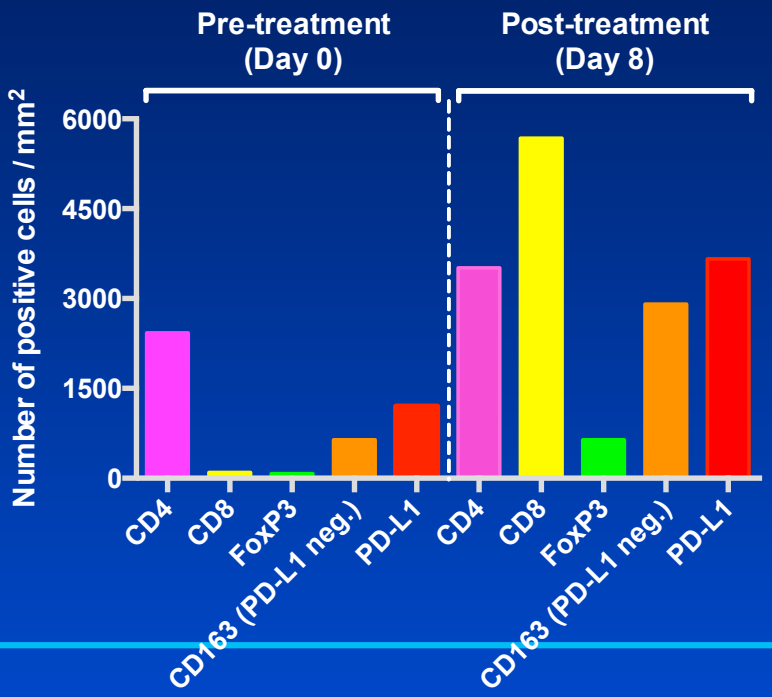






- *Male: Stage IV M1c with melanoma to the leg and lungs*
- *Prior treatment with ipilimumab*
- *and pembrolizumab*

FoxP3 PD-L1
CD163 CD3
DAPI CD8



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CALM Phase II trial: Conclusions

- The CALM study achieved its primary endpoint with 22/57 pts (38.6%) irPFS at 6 months
- Multi-dose intralesional therapy with CVA21 was generally well tolerated (*No Grade 3 or 4 treatment related AEs*
- Responses were observed in injected lesions, non-injected non-visceral lesions and in distant non-injected visceral lesions
- CVA21 treatment induced notable changes within the tumor microenvironment by inducing increases in immune cell infiltrates and expression of PD-L1
- CVA21 treatment induces a Th1-gene shift, with increases in interferon-induced genes

Future Directions

- CVA21 treatment may be used to in combination with immune checkpoint blockade
- CVA21 treatment may be used in a rescue strategy to reconstitute the immune cells within the tumor microenvironment of lesions resistant to immune checkpoint blockade

Acknowledgements

Many thanks to:

- The CALM study patients and families
- CALM study investigators
- CALM study Clinical Trials Research Staff
- Viralytics Clinical Development team

Roberta Karpathy
Leanne Stootman
Bronwyn Davies
Gough Au
Jackie Burgess
Rebecca Ingham
Erin Green
Susanne Johansson
Penny Yates
Robert Herd
Eric Chan
Min Quah
Yvonne Vern Vee
Richard Barry