Presenter Disclosure:
John Nemunaitis, MD

The following relationships exist with this disclosure.

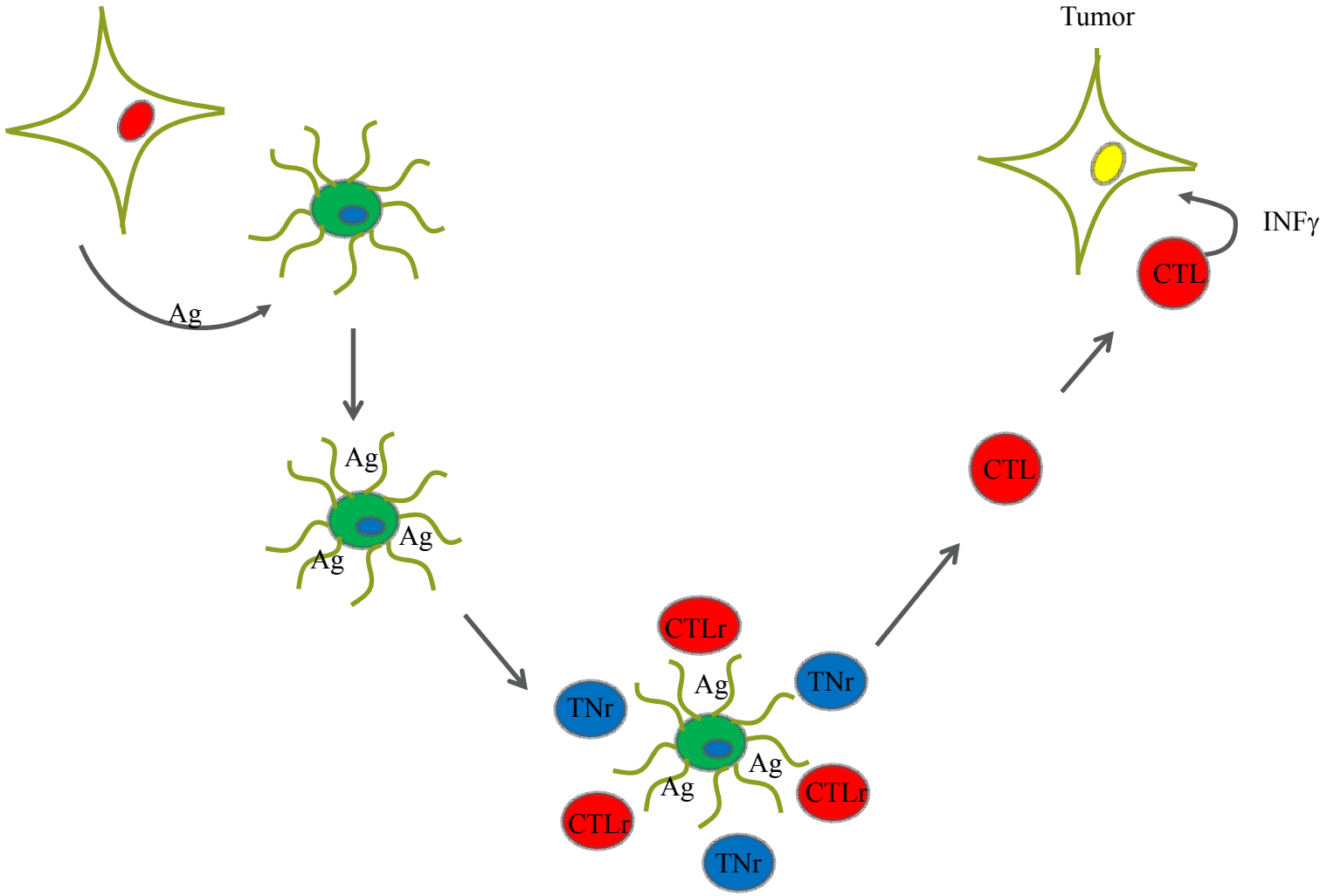
Gradalis, Inc. - shareholder

MARY CROWLEY
CANCER RESEARCH CENTERS
HOPE LIVES HERE.

Clinical Update of bi-shRNA furin/GMCSF DNA Transfected Tumor Vaccine: FANG™ in Cancer Patients

gradalis

Adaptive Cancer Immune Mechanism



Concept: "Triad" Immunotherapy

Construct a DNA based immunotherapy that addresses the key elements necessary for an effective immune attack against cancer

1) Patient Tumor Antigen matrix
2) Immune Activation
3) Inhibition of Afferent Immune Suppressors

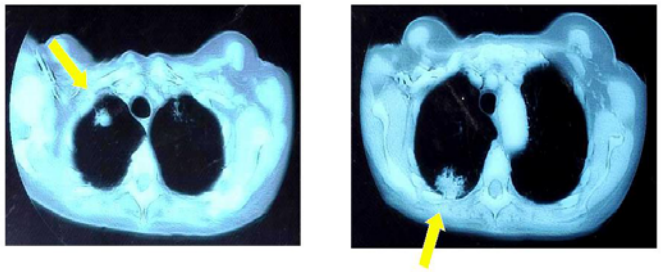
Identify biorelevant surrogate of activity correlating with survival

Key Gene-Based Vaccines in IIIB/IV NSCLC ("not melanoma/renal cell")

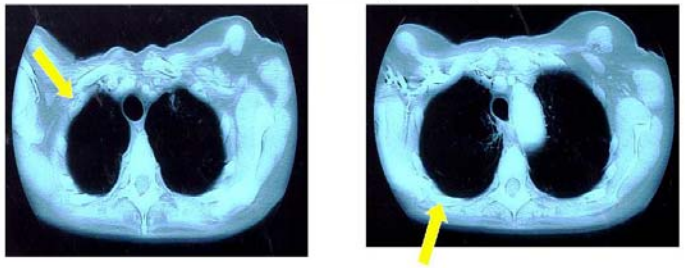
Vaccine	Stage	# Pts	Median Survival	Reference
GMCSF gene vaccine	IV	35	Not done	Salgia, R. et al; 2003
GMCSF gene vaccine	IIIB/IV	33	12 months (44% 1yr)	Nemunaitis, J. et al; 2004
GMCSF gene vaccine - bystander	IIIB/IV	49	7 months (31% 1 yr)	Nemunaitis, J. et al; 2006
Lucanix	IIIB/IV	61	14.4 months (56% 1 yr)	Nemunaitis, J. et al; 2007
Lucanix	IIIB/IV	21	15.5 months (72% 1 yr)	Nemunaitis, J. et al; 2009
TG4010	IIIB/IV	65	14.9 months (60% 1 yr)	Ramlau, R. et al.; 2008
TG4010	IIIB/IV	48	17.1 months	Quoix E et al; 2011

Targeted Immune Activation Tumor Responses to GMCSF Gene Vaccine

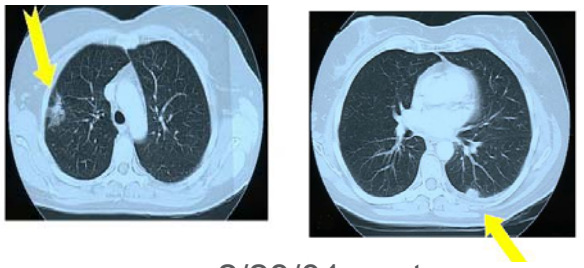
3/10/00 baseline



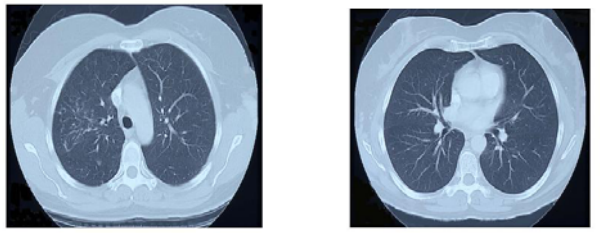
8/2/00 post*



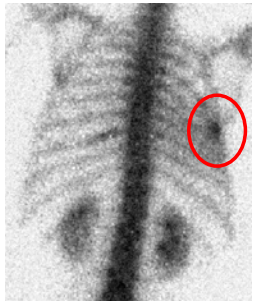
9/20/00 baseline



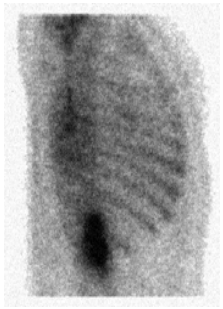
2/28/01 post



5/19/00 baseline



1/22/01 post*



* Still alive/no recurrence

Nemunaitis J, et al. *J Natl Ca Inst.* 2004; 96(4):326-331.

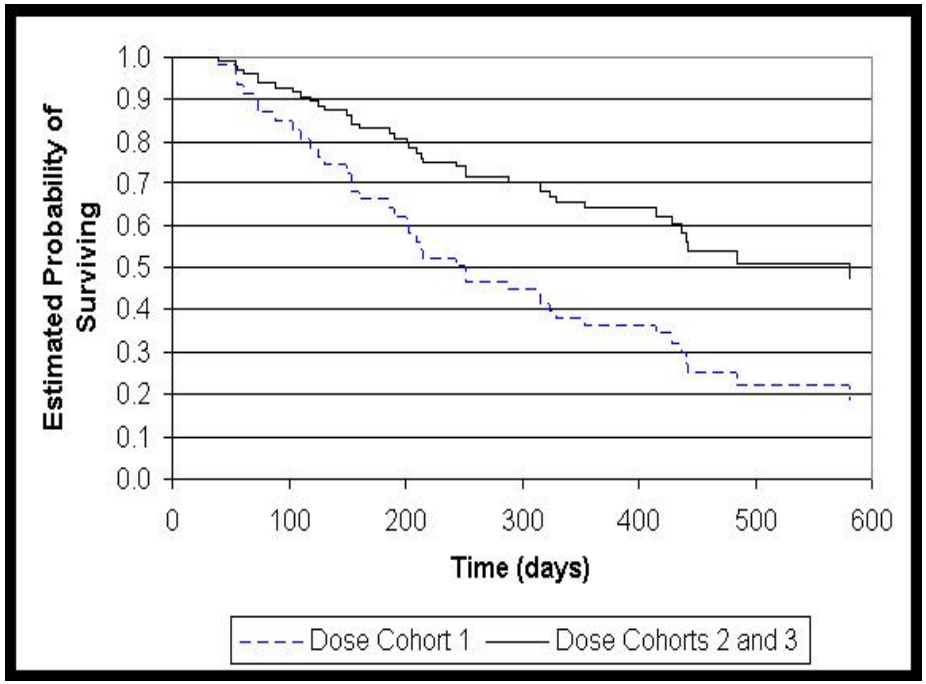
So what did we learn with GVAX

- Clinically relevant immune mediated activity can be observed (limited degree)
  - Antigen (autologous cells despite “tolerance” can provide immunogenic stimulus)
  - Benefit of GMCSF DNA activation
- No surrogate measure of activity

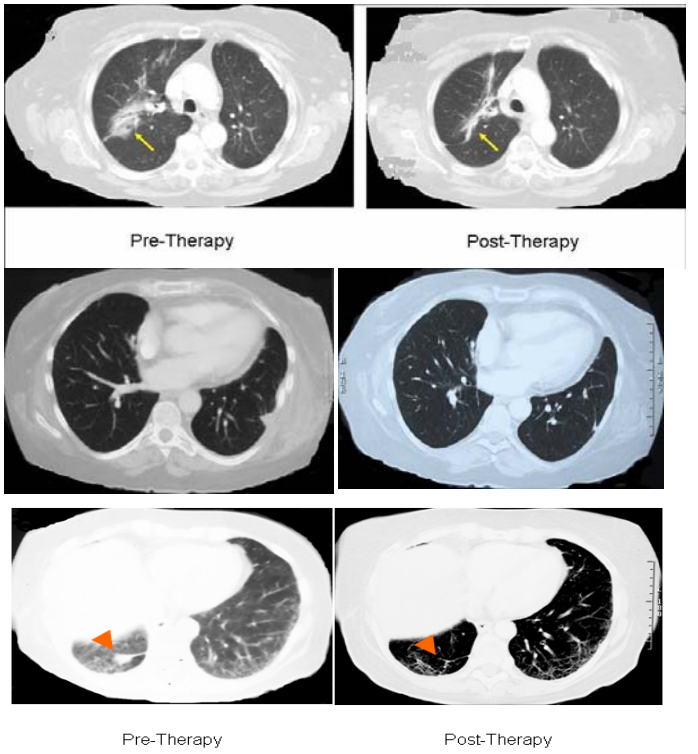
Inhibition of Intrinsic Tumor Immunosuppressors

(4 allogeneic NSCLC lines / TGFβ_2 AS transfection)

Overall survival for cohorts 1 vs. 2 and 3 for advanced stage patients (n=61, p=0.0186)



Radiographic evidence of response (3 of 6) comparing week 16 assessment (post therapy) to baseline



Nemunaitis et al. JCO 2006 10; 24(29):4721-4730.
Nemunaitis et al. CGT 2009; 16(8):620-624.

Allogeneic TGFβ_2 AS transfection: Belagenpumatucel-L

- Preliminary results of Belagenpumatucel-L Phase III testing in front line NSCLC were negative.
  - Subset analysis underway by NovaRx

So What Did We Learn With Belagenpumatucel-L?

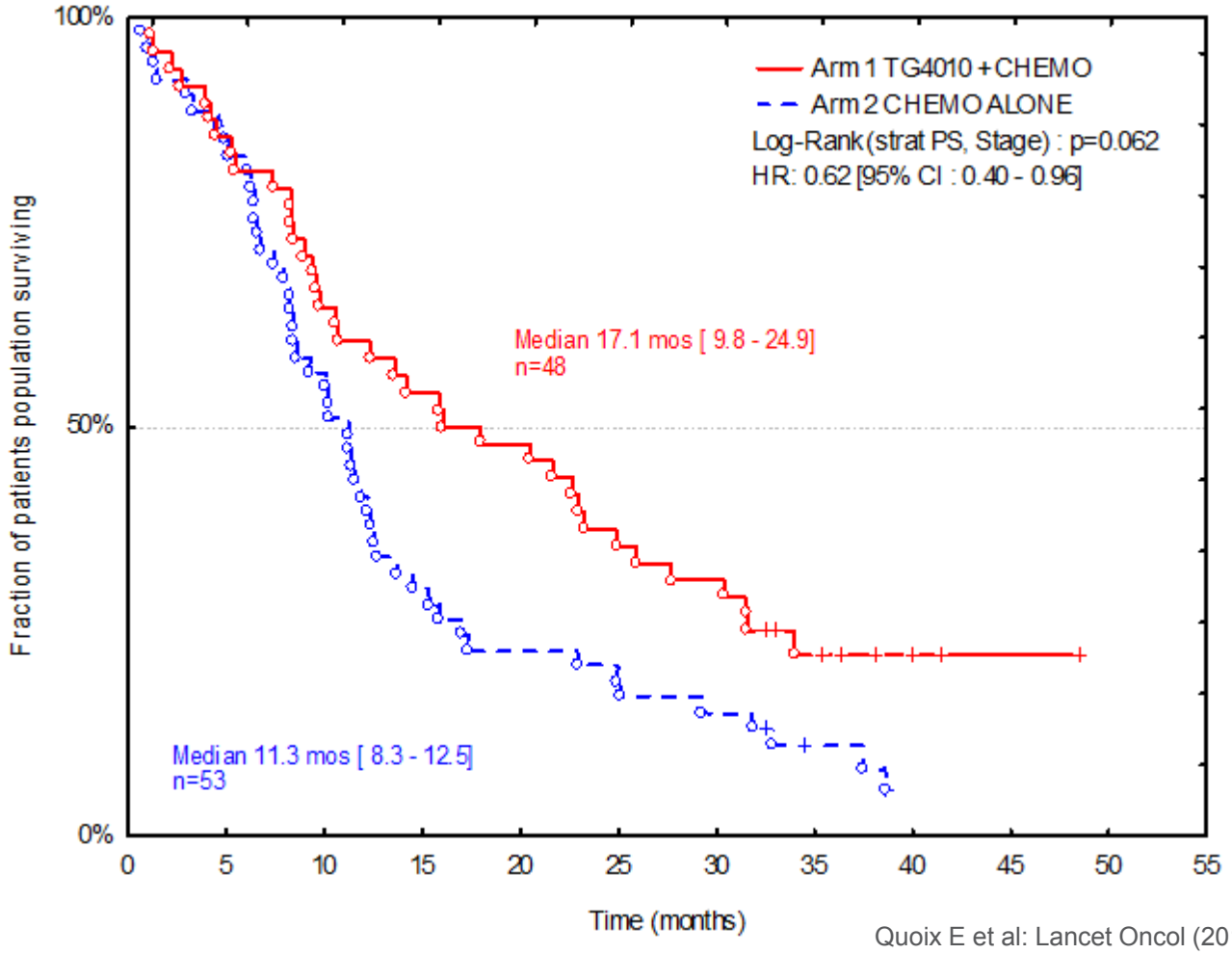
- Phase II trials suggested evidence of clinical benefit in subsets of patients with ≥ 2nd line NSCLC
- Phase III trial suggests insufficient clinical response in front line NSCLC
  - ➢ But Why?

    Allogeneic tumor antigens less efficient then autologous tumor antigen?

    $TGF\beta_2$ knockdown insufficient (TGFβ1 is dominant TGFβ cancer immunosuppressor)

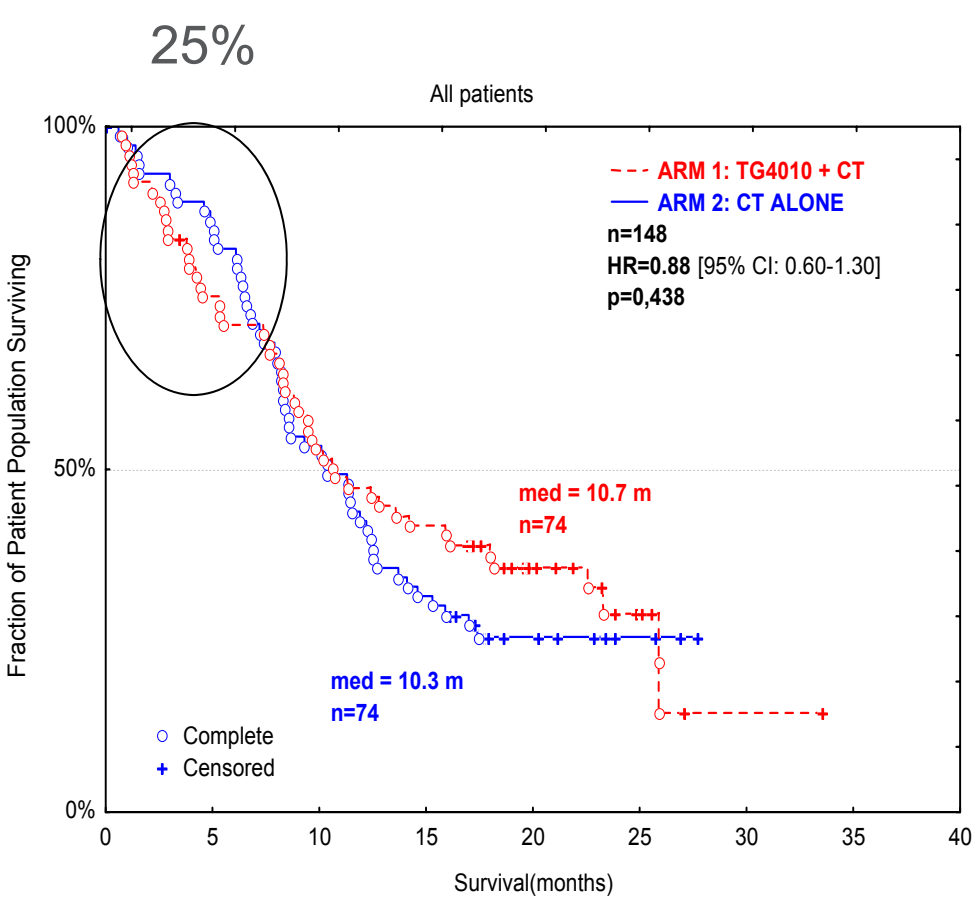
    Level of Knockdown insufficient (35-50%)?
- No Surrogate measure of activity

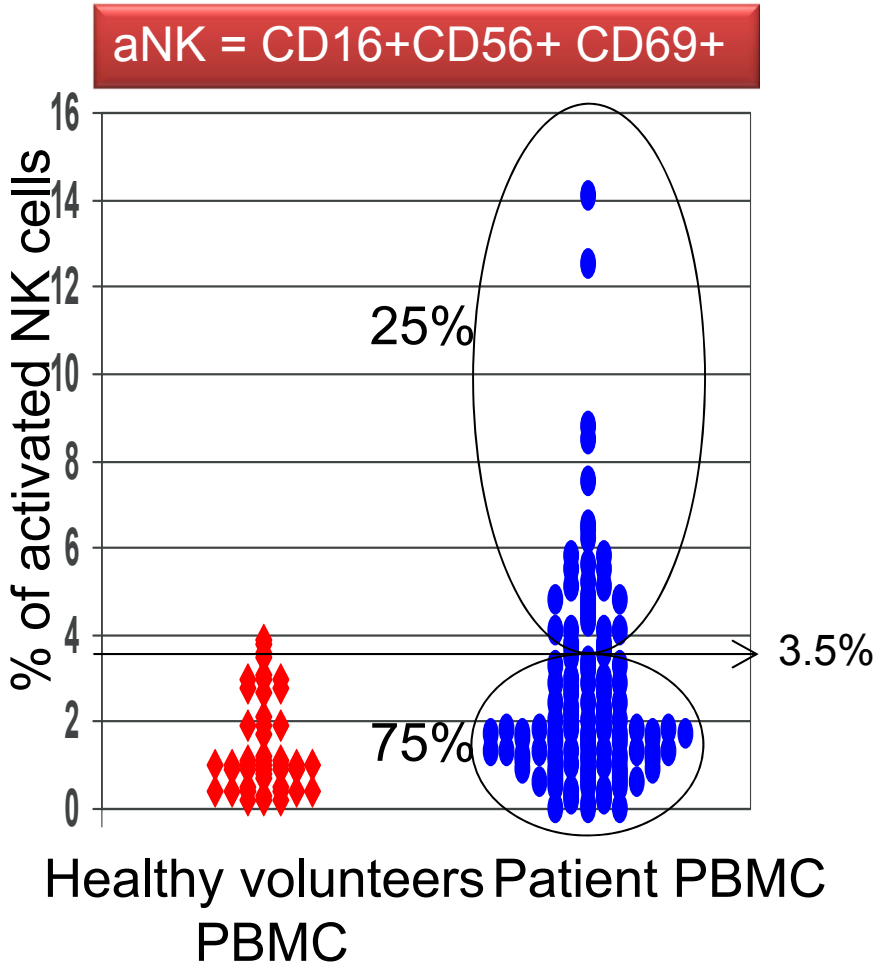
TG4010 (Recombinant Vaccinia Virus/MUC1 Antigen IL2 Transgene) Overall Survival in Patients with Normal Level of Activated NK Cells in Advanced NSCL



Quoix E et al: Lancet Oncol (2011) 12(12): 1125-33

Early safety signal: correlation with aNK cells level





What Did We Learn From TG4010?

- Subsets of patients may benefit from relevant tumor antigen education
- Immune function enhancement may contribute to clinical benefit
- Identification of predictor biorelevant measures of activity may be feasible
  - Level of Activated NK cell activity affects outcome: possible predictive marker

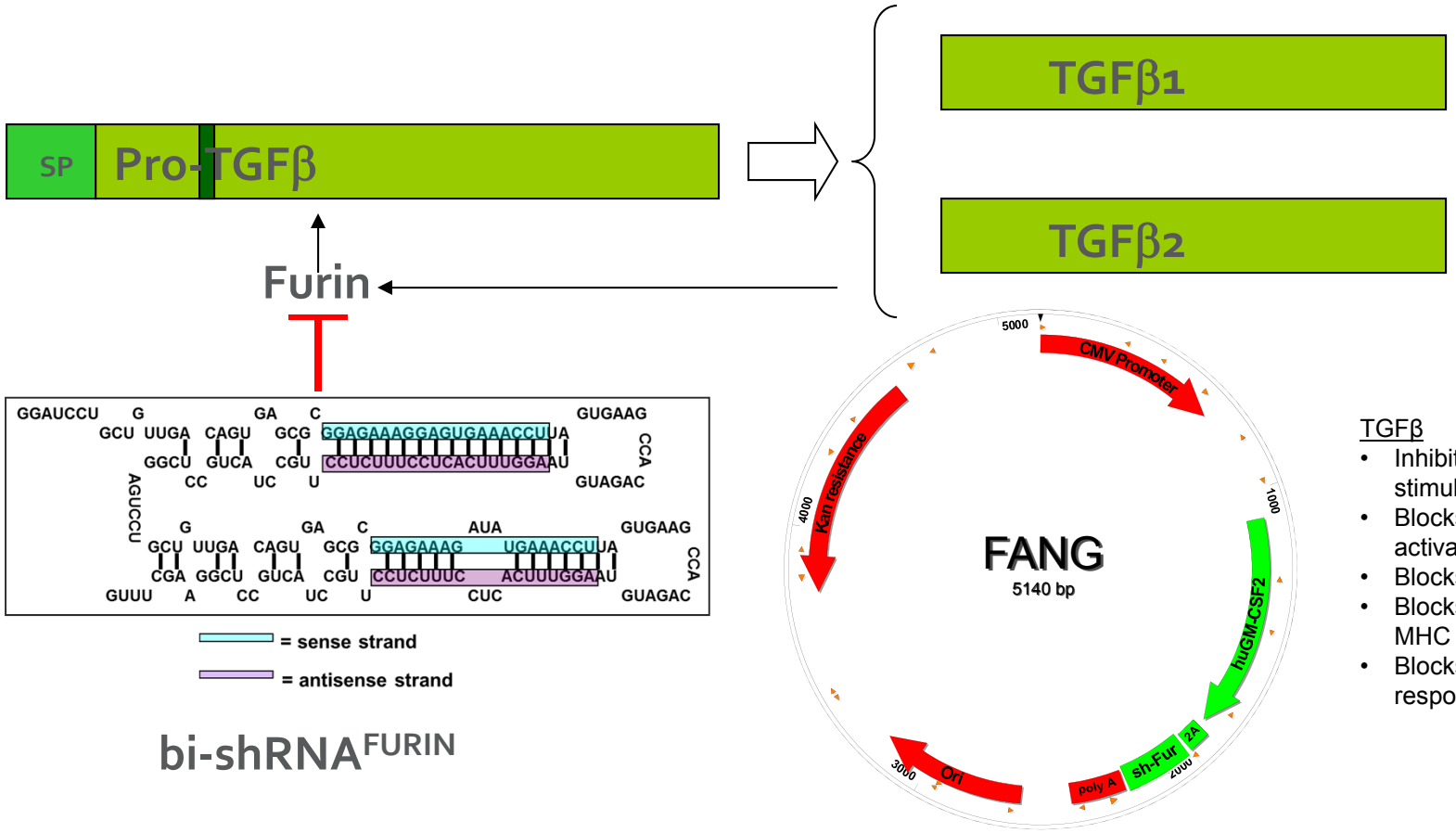
Could "Triad" Approach provide a greater activity

- Patient/tumor-specific antigen education
- Enhanced afferent immune activation
- Blockade of intrinsic immune suppressors

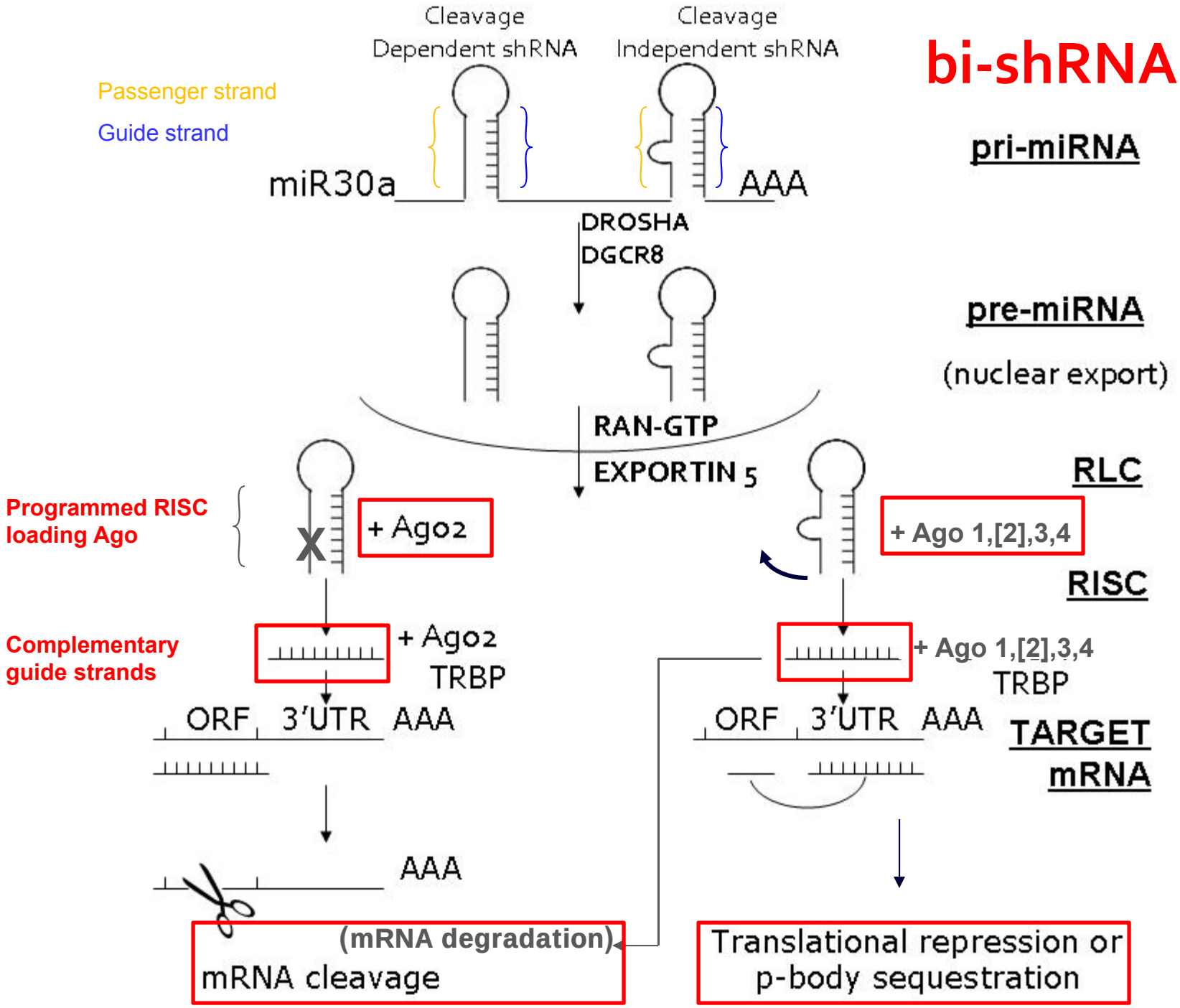
  - ➢ Identify surrogate measure of biorelevant activity

Nemunaitis. Expert Review of Vaccines 2011; 10(6):713-715

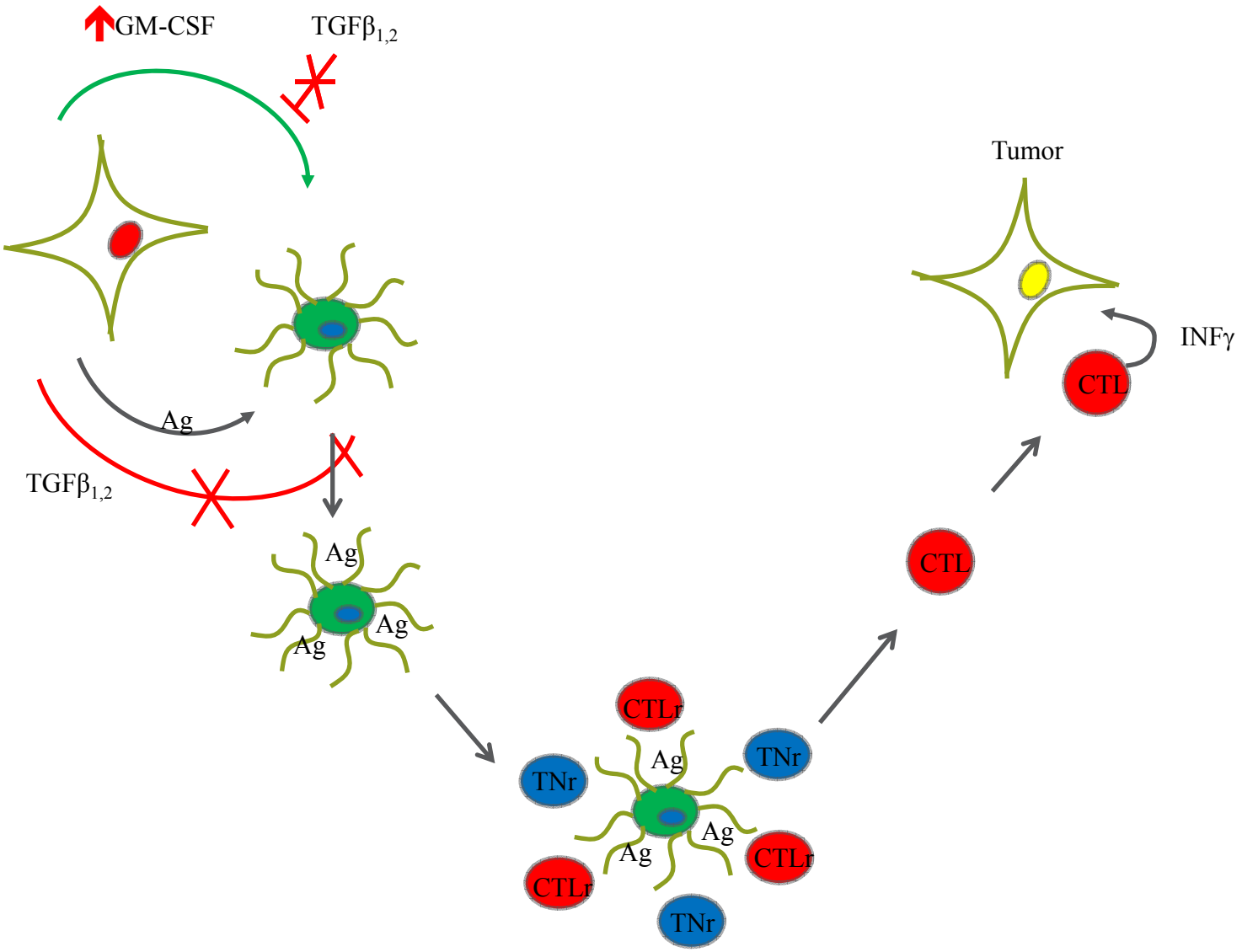
Furin pro-protein convertase – immunomodulatory TGFβ_1, β_2
(Gradalis, Inc., Dallas, TX)



TGFβ
- Inhibits GMCSF stimulation
- Blocks macrophage activation
- Blocks Ag presentation
- Blocks expression of MHC class II
- Blocks dendritic cell response


bi-shRNA
Cleavage Dependent shRNA
Cleavage Independent shRNA
Passenger strand
Guide strand
miR30a
AAA
pri-miRNA
DROSHA
DGCR8
pre-miRNA
(nuclear export)
RAN-GTP
EXPORTIN 5
RLC
Programmed RISC loading Ago
+ Ago2
+ Ago 1,[2],3,4
RISC
Complementary guide strands
+ Ago2
TRBP
+ Ago 1,[2],3,4
TRBP
ORF
3'UTR
AAA
TARGET mRNA
AAA
(mRNA degradation)
mRNA cleavage
Translational repression or p-body sequestration

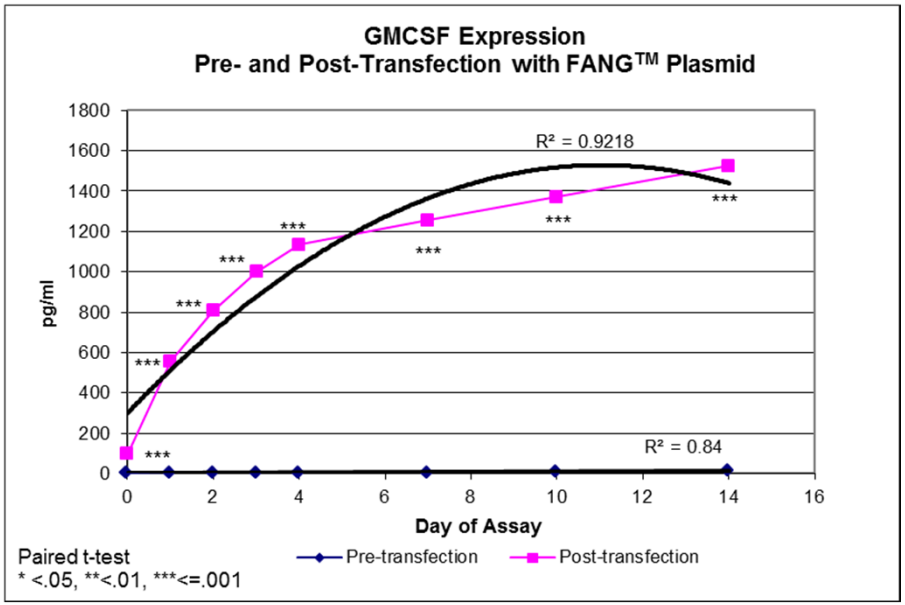
Triad Vaccine Mechanism



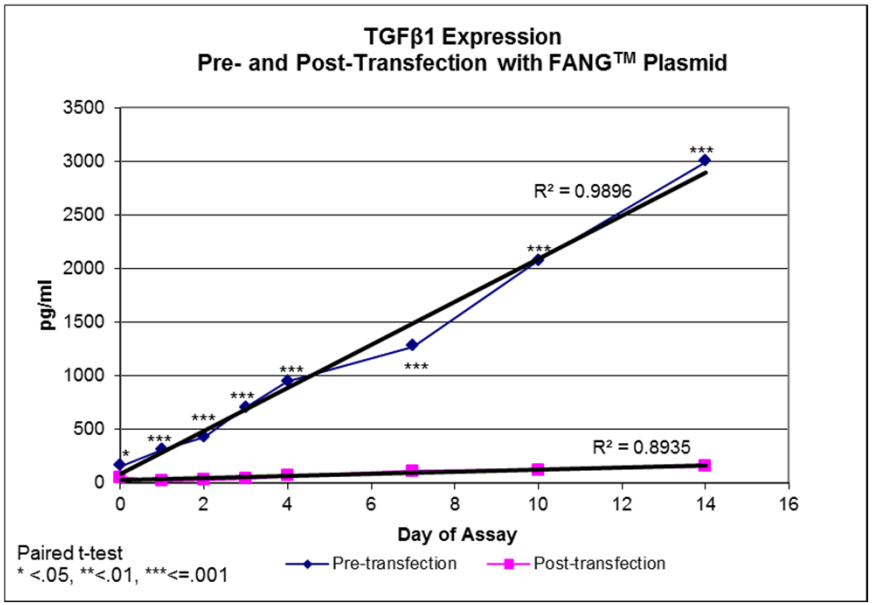
FANG™ Phase I Trial
6/8/09

- Vaccine constructed following autologous tissue harvest and electroporated transfer of bi-shRNA^{furin} GMCSF vector
- 2 dose levels ($1x10^7$ / $2.5x10^7$ cells/inj)
- Monthly ID injection (maximum of 12 months)
- Two groups of patients: other options prior to FANG™ vs. no options → FANG™
- ELISPOT for T cell activation at baseline and follow up timepoints

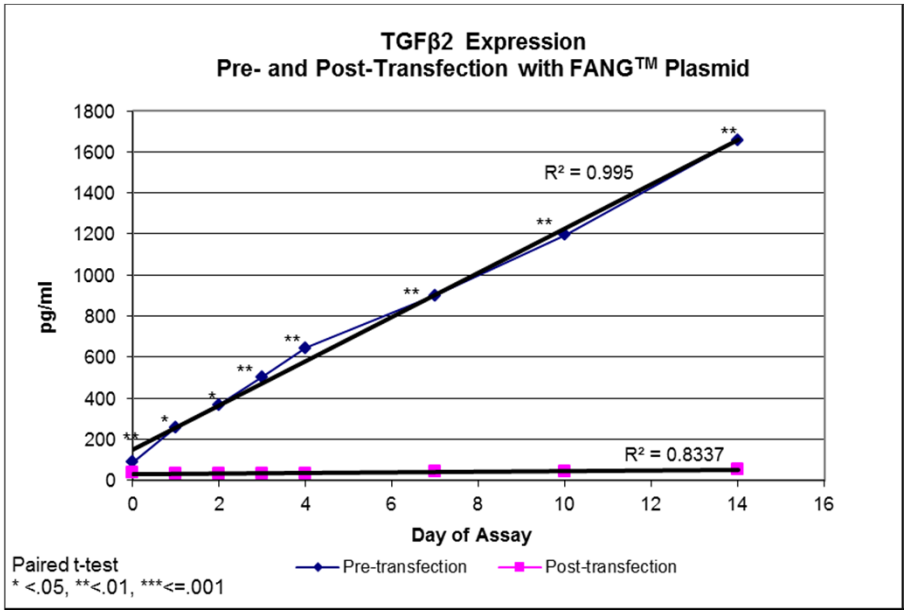
a


GMCSF Expression
Pre- and Post-Transfection with FANG™ Plasmid
pg/ml
R² = 0.9218
R² = 0.84
Day of Assay
Paired t-test
* <.05, **<.01, ***<=.001
Pre-transfection
Post-transfection

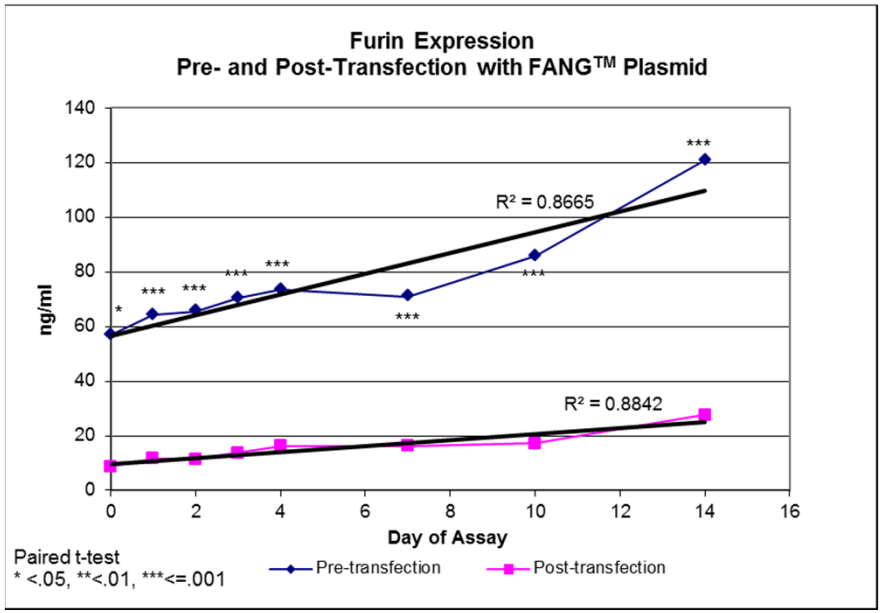
b


TGFβ1 Expression
Pre- and Post-Transfection with FANG™ Plasmid
pg/ml
R² = 0.9896
R² = 0.8935
Day of Assay
Paired t-test
* <.05, **<.01, ***<=.001
Pre-transfection
Post-transfection

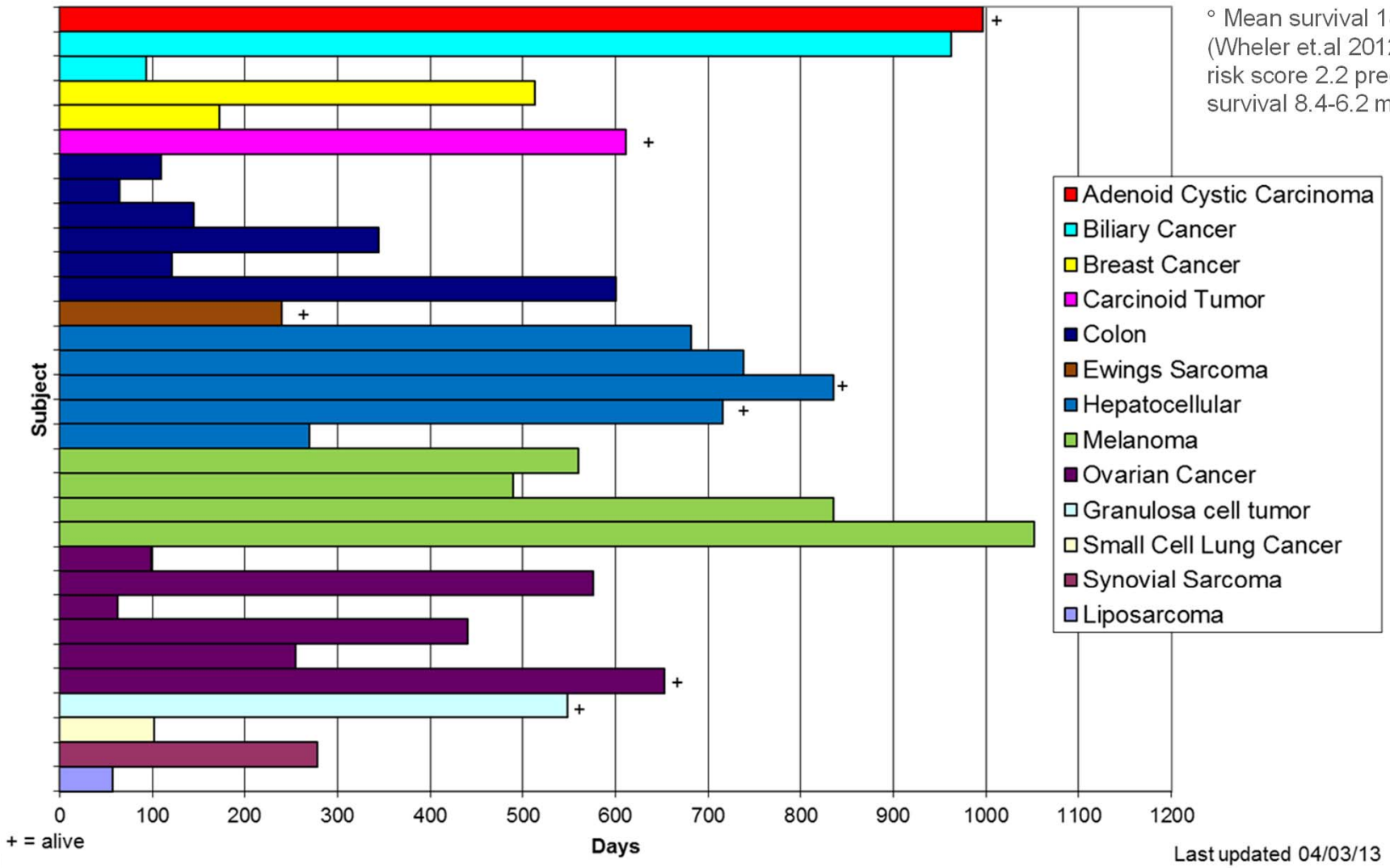
c


TGFβ2 Expression
Pre- and Post-Transfection with FANG™ Plasmid
pg/ml
R² = 0.995
R² = 0.8337
Day of Assay
Paired t-test
* <.05, **<.01, ***<=.001
Pre-transfection
Post-transfection

d

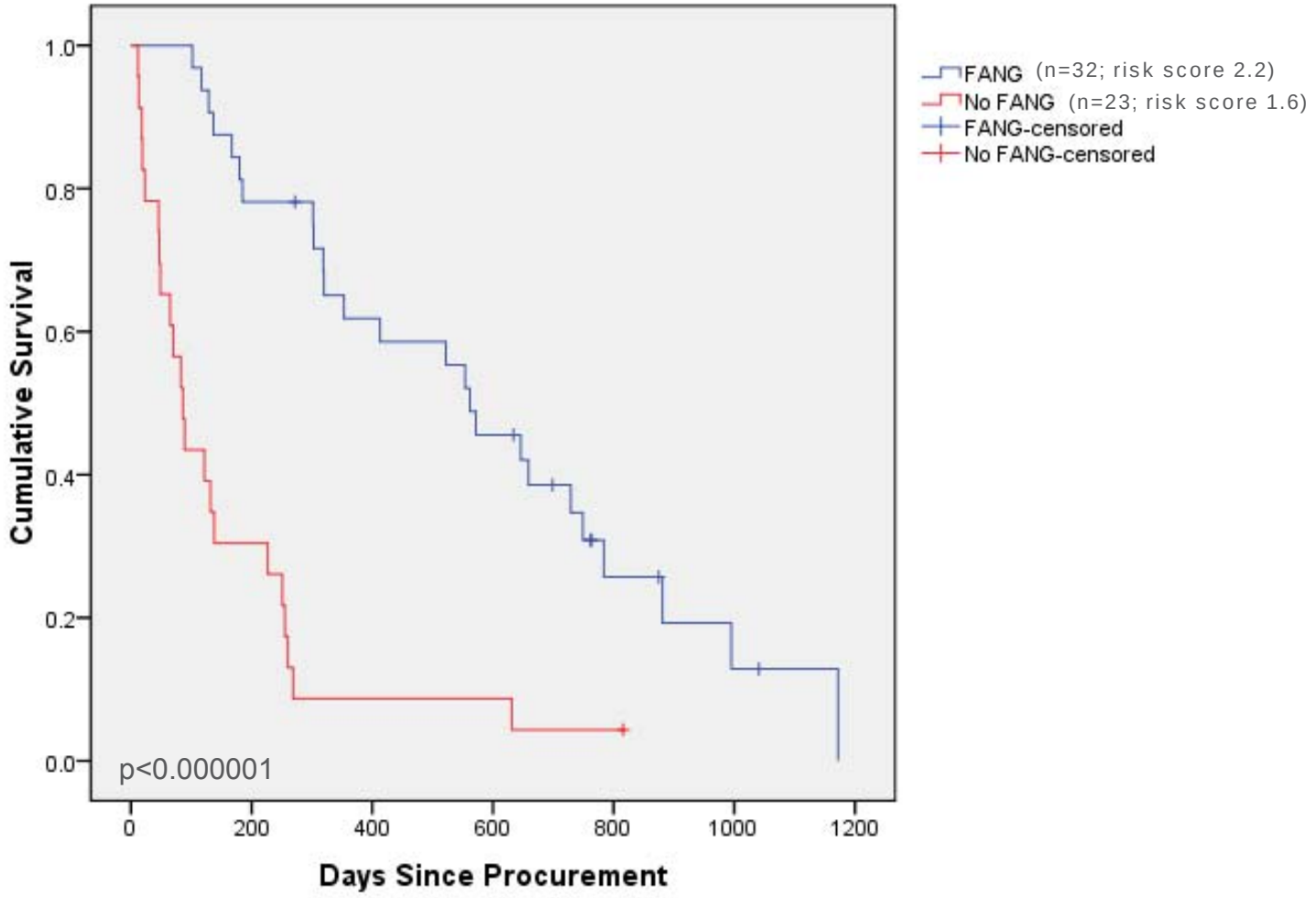

Furin Expression
Pre- and Post-Transfection with FANG™ Plasmid
ng/ml
R² = 0.8665
R² = 0.8842
Day of Assay
Paired t-test
* <.05, **<.01, ***<=.001
Pre-transfection
Post-transfection

Survival of Treated Patients Since Treatment Start on FANG™ Phase I Protocol°



° Mean survival 18.7 months (Wheler et.al 2012) Phase I risk score 2.2 predicated survival 8.4-6.2 months.

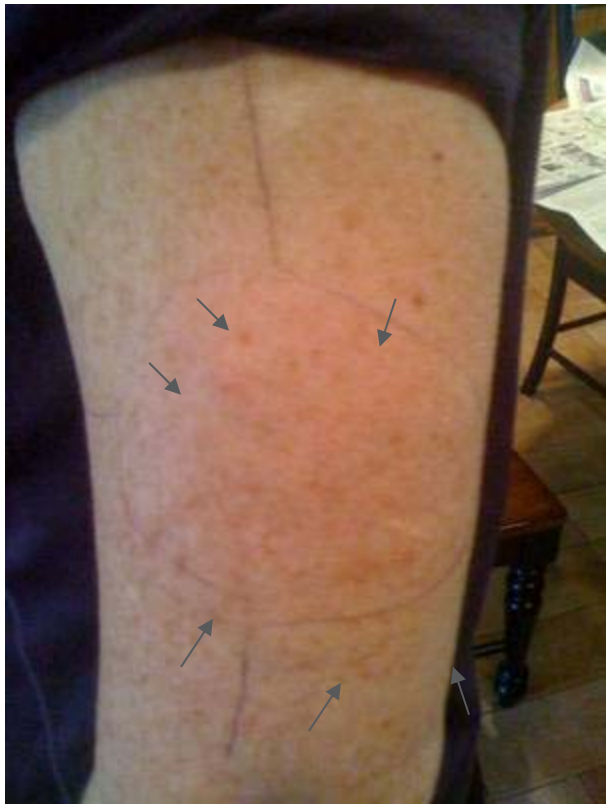
Survival of Treated Patients Since Procurement on FANG™ Phase I Protocol



Data as of 04/26/13

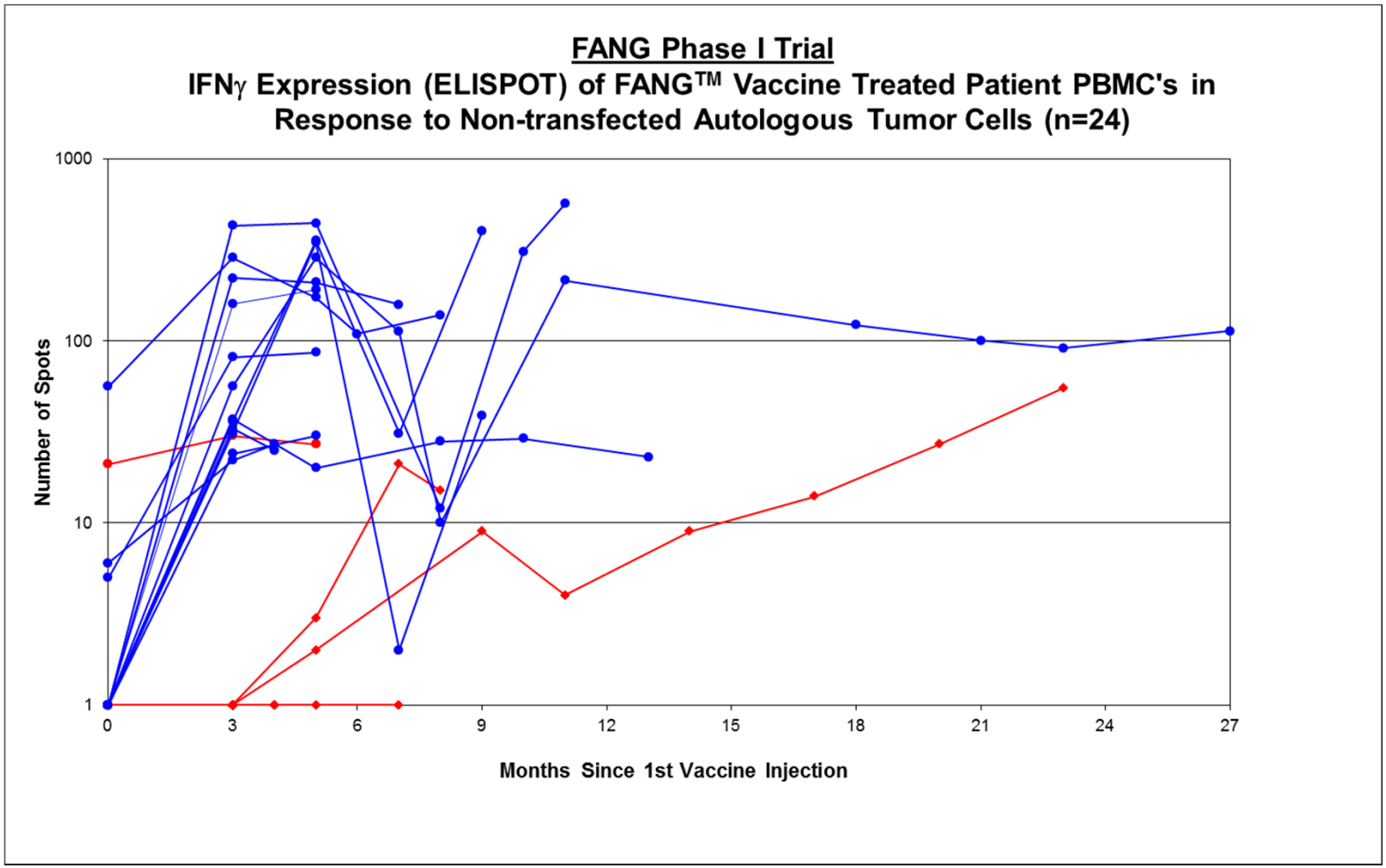
FANG Vaccine: Toxicity

Patient #018
Colon Adenocarcinoma

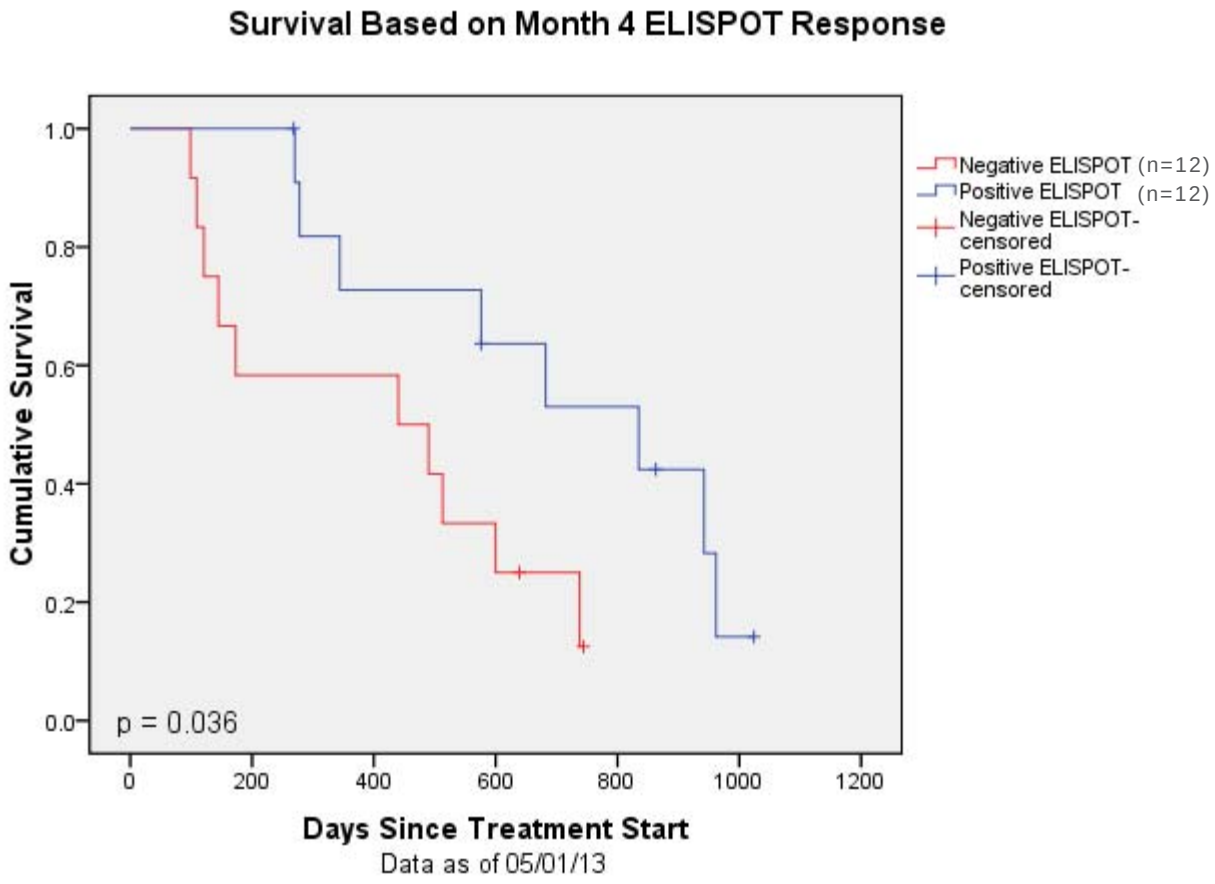


(C1D2)

- No treatment related Grade 3, 4 toxic events
- Minor low grade events such as injection site irritation, fatigue observed


FANG Phase I Trial
IFNγ Expression (ELISPOT) of FANG™ Vaccine Treated Patient PBMC's in Response to Non-transfected Autologous Tumor Cells (n=24)
Number of Spots
1000
100
10
1
0
3
6
9
12
15
18
21
24
27
Months Since 1st Vaccine Injection

FANG Phase I Survival Relationship to Immune Response



Moved into Phase II Trial Program*

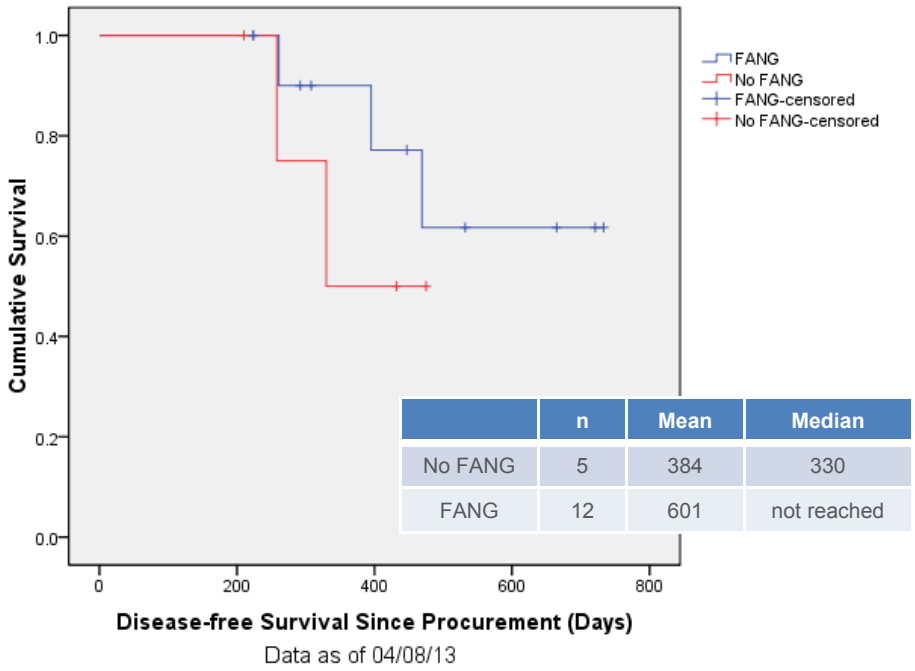
CL-PTL-105*	Randomized Phase II Trial of Adjuvant bi-shRNA^{furin} and GMCSF Augmented Autologous Tumor Cell Vaccine (FANG™) for High Risk Stage IIIc Ovarian Cancer *(Adjuvant)*
CL-PTL-107	Randomized Phase II Trial of Post-operative Adjuvant Chemotherapy ± FANG™ Autologous Tumor Cell Vaccine in Colorectal Carcinoma with Liver Metastases *(Concurrent chemotherapy)*
CL-PTL-114*	Phase II Trial of FANG™ Autologous Tumor Cell Vaccine in Advanced Melanoma *(Correlate Intratumoral/serologic immune markers)*

* Secured orphan product designation in Stage III/IV melanoma and ovarian cancer

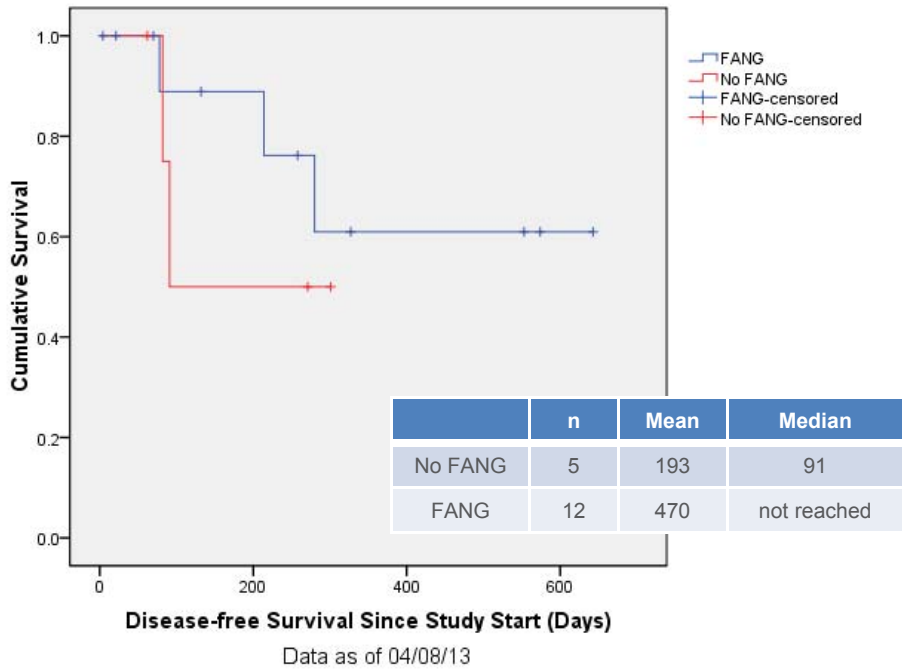
Phase II Ovarian (III/IV)Trial Design

- 2:1 randomized trial
  - FANG vs. No FANG (n=60 treated/evaluable)
- $1x10^7$ cells/inj 2 month (max 12/minimum 4)
- Standard of care (debulking surgery $\rightarrow$ 6 cycles carboplatin/taxol$\pm$IP) prior to FANG
- Crossover if PD (FANG/Avastin)

Disease-Free Survival Interval: Preliminary Analysis



	n	Mean	Median
No FANG	5	384	330
FANG	12	601	not reached



	n	Mean	Median
No FANG	5	193	91
FANG	12	470	not reached

Successful Vaccine Construction Rate

21%

Protocol	Successful Vials Manufactured	Successful Patient Samples Manufactured	Insufficient Patient Samples	Failed Patient Samples	Vaccines Administered
Phase I CL-PTL 101	559	60*	7	5	174
Phase II OV CL-PTL 105	501	52	4	10	89
Phase II CLM CL-PTL 107	21	2	0	0	14
Phase II Mel CL-PTL 114	66	7	3	5	70
TOTAL	**1147**	**121**	**14**	**20**	**347**

*including 2 pre-clinical and 1 benign

Conclusion

- Overall clinical benefit is demonstrated using DNA based technology as Immunotherapy
- More specifically,
  - FANG vaccine is well tolerated and evidence of benefit is demonstrated in advanced cancer.
- Considering Breakthrough Application process of FANG vaccine in ovarian cancer with FDA