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Vaccines Insights from Ongoing Trials

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Results of Non-Gene-Based Vaccines in IIIB/IV NSCLC

Vaccine	Stage	# Pts	Median Survival	Reference
SRL172	IIIB/IV	210	7.3 months	O'Brien et al; 2004
CIMAvax EGF	III, IV	80	11.7 months (GAR*) vs. 3.6 months (PAR*)	Neninger, V. et al; 2008
CIMAvax EGF	IIIB, IV	43	Low dose: 6.43 months; High does: 8.4 months	Ramos, T.C. et al; 2006
Telomerase peptide	IIIB, IV, (I,III A)	26	8.5 months (36% 1yr)	Brunsvig, P.F. et al; 2006
BLP25[x]	IIIB	88	17 months	Butts, C. et al; 2005
BLP25[x]	IIIB/IV	171	3 year OS 31% for BLP25 / 17% for BSC (p=0.035)	Butts, C. et al; 2011
EP2101	IIIB/IV	135	17 months	Barve, M.; 2008
1E10	IIIB/IV	71	9.9 months	Alfonso et al.; 2007
1E10	IIIB/IV	20	10.6 months	Hernandez et al.; 2008
CEA pulsed DC's	IIIB/IV	14	22 months (64% 1 yr)	Zhang et al; 2011
Talactoferrin	IIIB/IV	110	RR° 47% (+Cb/Tx) vs. 29% (+Cb/Tx); p=0.05	Digumarti, R. et al. 2011
Ipilimumab	IIIB/IV	204	PFS 5.7 months (+Cb/Tx) vs. 4.6 (+Cb/Tx); p=0.05	Lynch, T. et al; 2012

* GAR = Good Antibody Response

* PAR = Poor Antibody Response

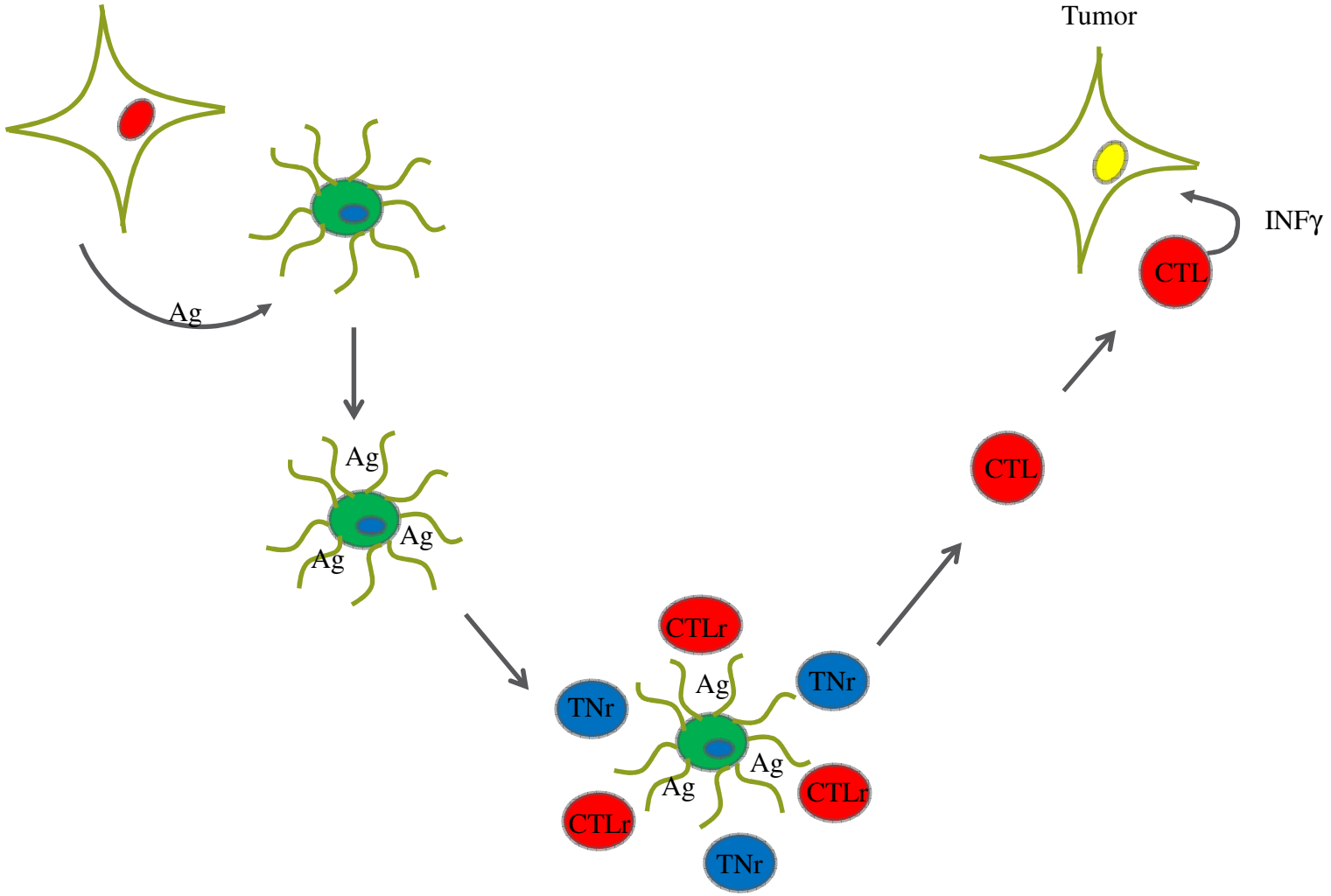
°RR=Response Rate

[x] Phase III trial involving 1,500 patients negative overall

Results of Gene-Based Vaccines in IIIB/IV NSCLC

Vaccine	Stage	# Pts	Median Survival	Reference
Allogenic Ad B 7.1	IIIB/IV	19	18 months (52% 1yr)	Raez, L.E. et al; 2004
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
Galactosyltransferase	IV	7	Not done	Morris, J.C. et al; 2005
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; 2008
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

Adaptive Cancer Immune Mechanism



Concept: “Triad” Immunotherapy

Immunotherapy that addresses the key elements necessary for an optimal 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)

BLP25

MUC1 antigen specific cancer immunotherapy advanced unresectable stage III NSCLS s/p so with concurrent or sequential XRT/chemo

START:

- 1,239 patient Phase III trial (2:1 randomization)
- Median OS 25.6 mo. BLP25
- AE's >10% include cough, dyspnea, fatigue, nausea, headache, arthralgia
- No treatment unique grade 3, 4 toxicity

Subset Analysis START Trial

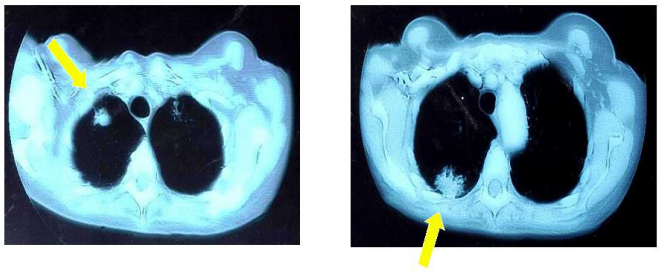
- Concurrent XRT/chemo group (n=806)
- Median OS 30.8 mo. BLP25 vs. 20.6 mo. BLP25 p=0.016

What Did We Learn From BLP25

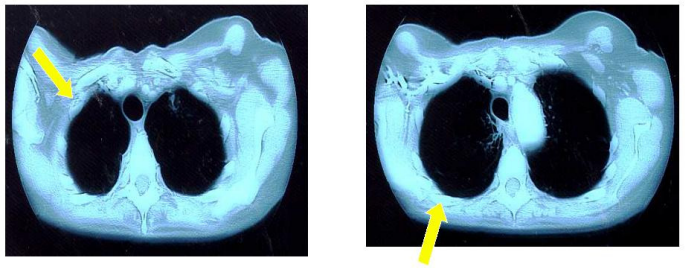
- Single antigen immunotherapy can be well-tolerated
- Suggestion of relevant activity survival advantage in a large sub population
- Unclear why concurrent vs. sequential XRT/chemo different
- No surrogate measure of activity

Targeted Immune Activation Tumor Responses to GMCSF Gene Vaccine

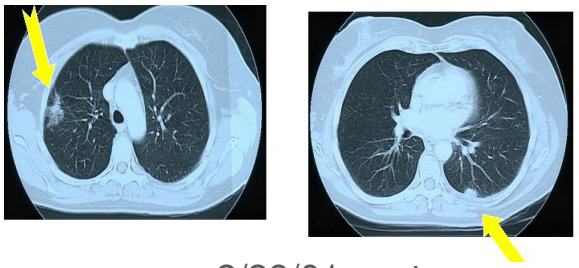
3/10/00 baseline



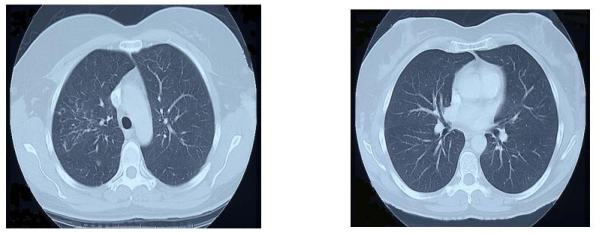
8/2/00 post*



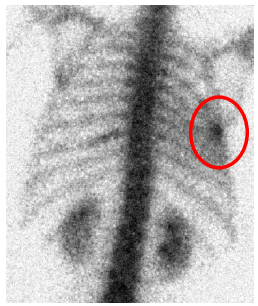
9/20/00 baseline



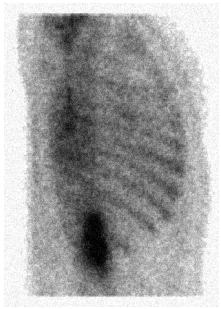
2/28/01 post



5/19/00 baseline



1/22/01 post*



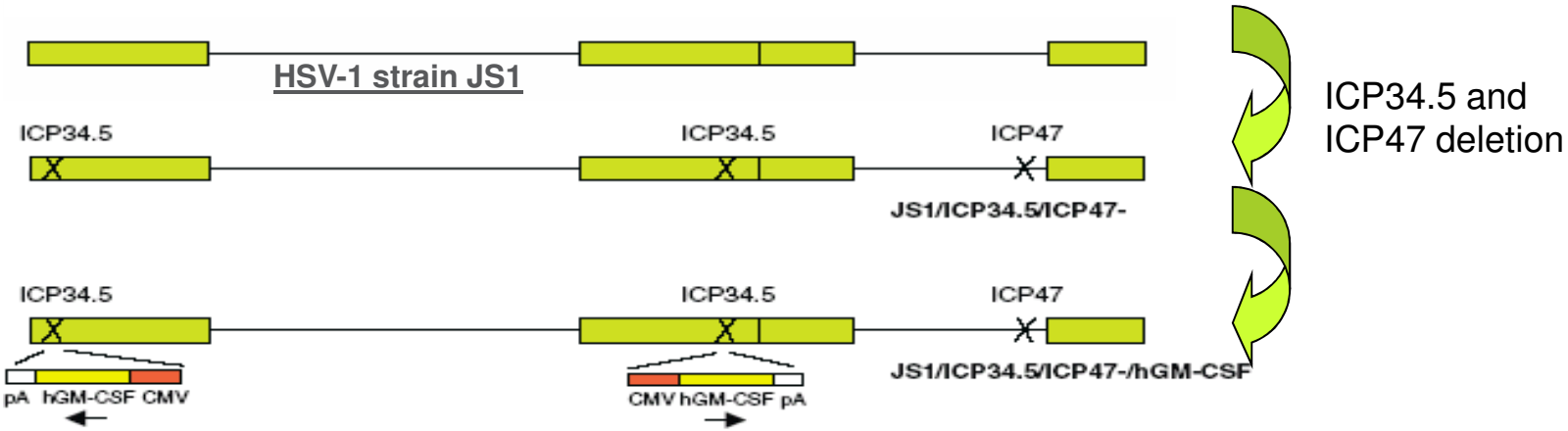
* Still alive/no recurrence

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)
  - Multi-antigen autologous cells despite "tolerance" can also provide immunogenic stimulus
  - No significant toxic effect was observed
  - Beneficial results can be prolonged (>10 year)
- No surrogate measure of activity

Vector/Effector –T-VEC



Modes of Action

1.Oncolytic (tumor specific)

a.-ICP34.5 (decreased normal tissue virulence)

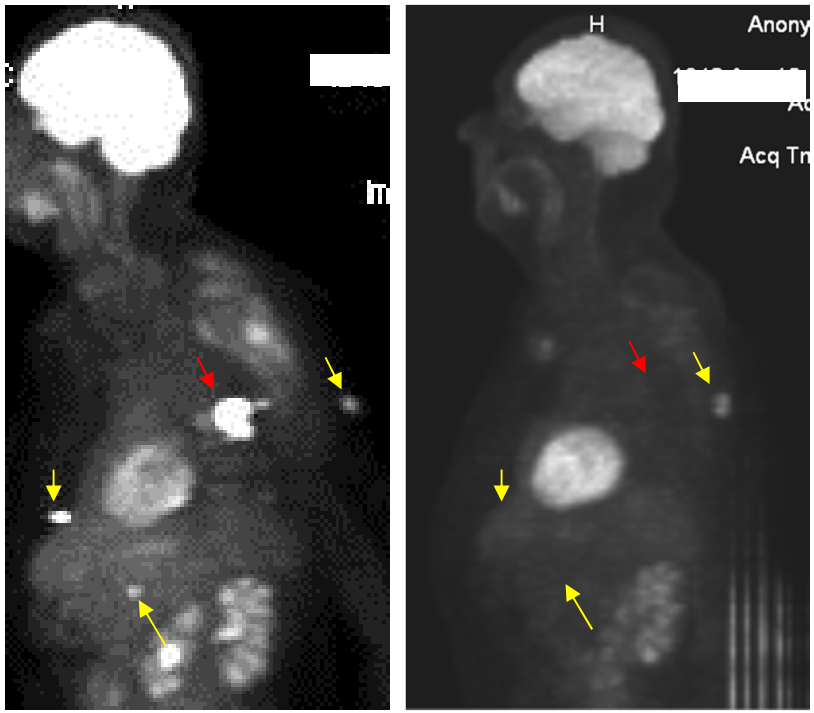
b.L→IE US11 (enhanced oncolytic cytotoxicity)

2.Immunogenic

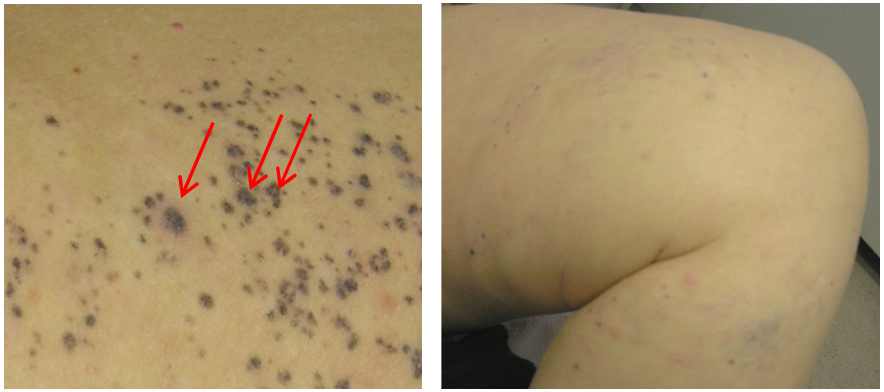
a.-ICP47 (enhanced antigen presentation; increased levels class I MHC confirmed by FACS analysis)

- RECIST response was 26% (8CR, 5PR) and regression of local injected and distal (non injected) lesions were observed

PET



Patient 1502
Axillary injection of T-VEC (red↓) metastatic (yellow↓) disease regression shown by PET 16 months later



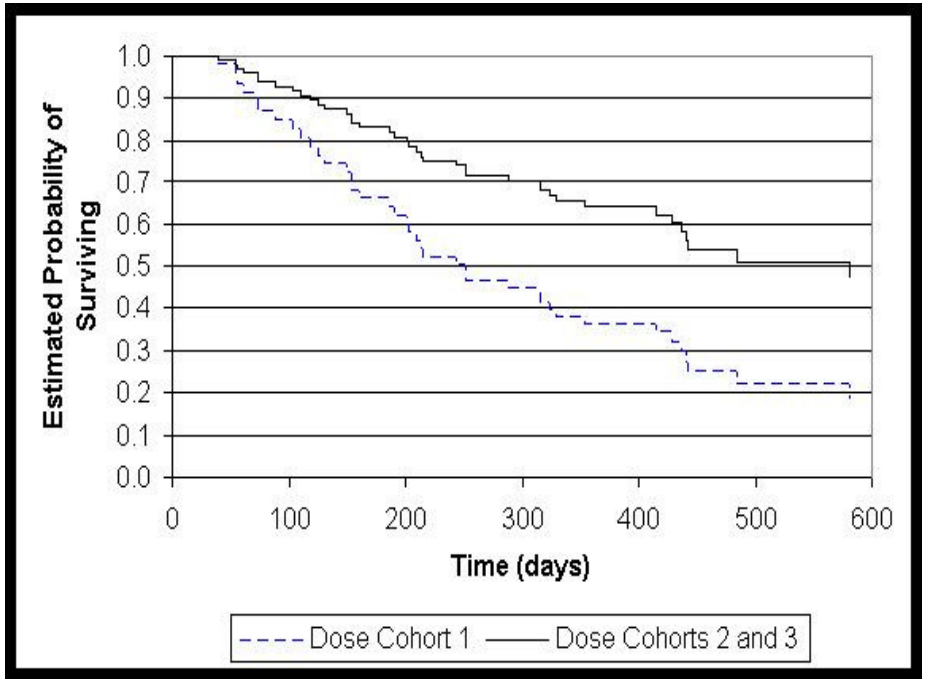
Patient 603: Baseline (red↑) and at 4 months.

(Senzer et.al. JCO 2009; 27(34):5763-5771)

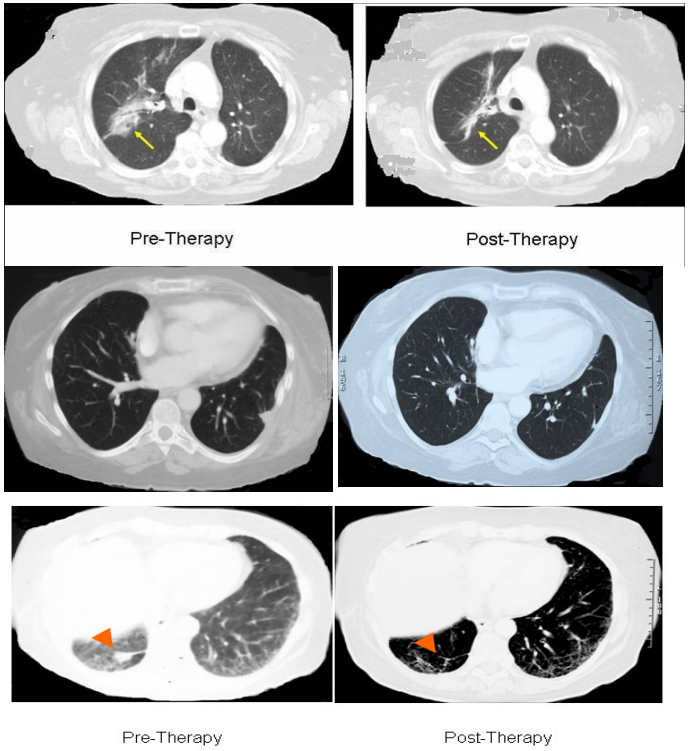
Belagenpumatucel: Inhibition of Intrinsic Tumor Immunosuppressors

(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

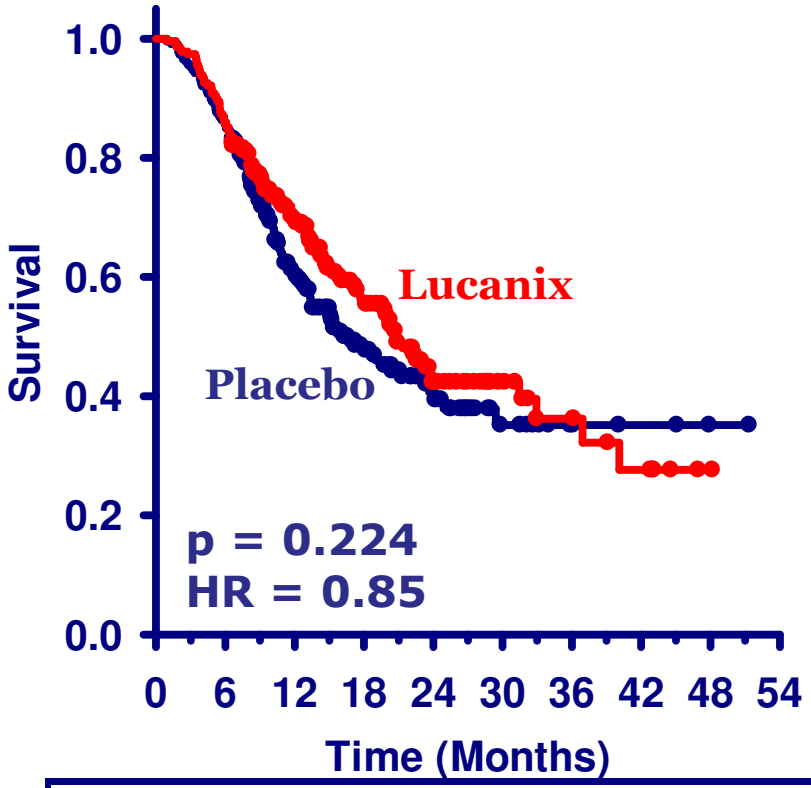


Nemunaitis et al. JCO 2006 10; 24(29):4721-4730.
Nemunaitis et al. CGT 2009; 16(8):620-624.

Belagenpumatucel: Phase III (STOP Trial) Results

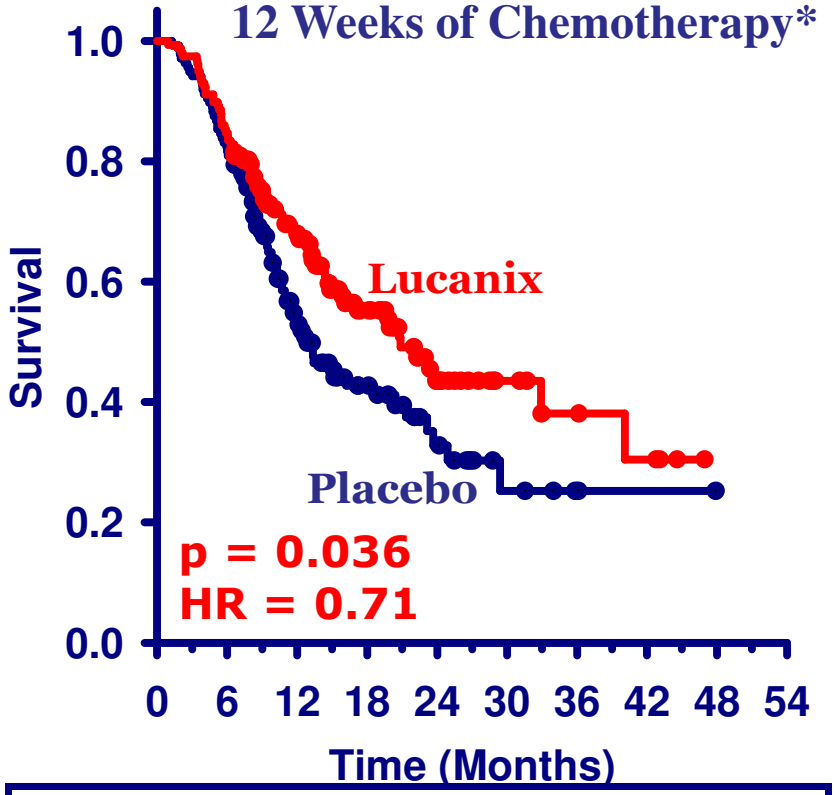
- Phase III testing in front line NSCLC were negative.
  - Subset analysis by NovaRx suggestive of benefit

IIIB/IV Subjects



Cohort	Median Survival	N	Percent Censored
Lucanix	20.9	229	55%
Control	16.7	226	50%
Difference	4.2		

IIIB/IV Subjects Enrolled Within 12 Weeks of Chemotherapy*



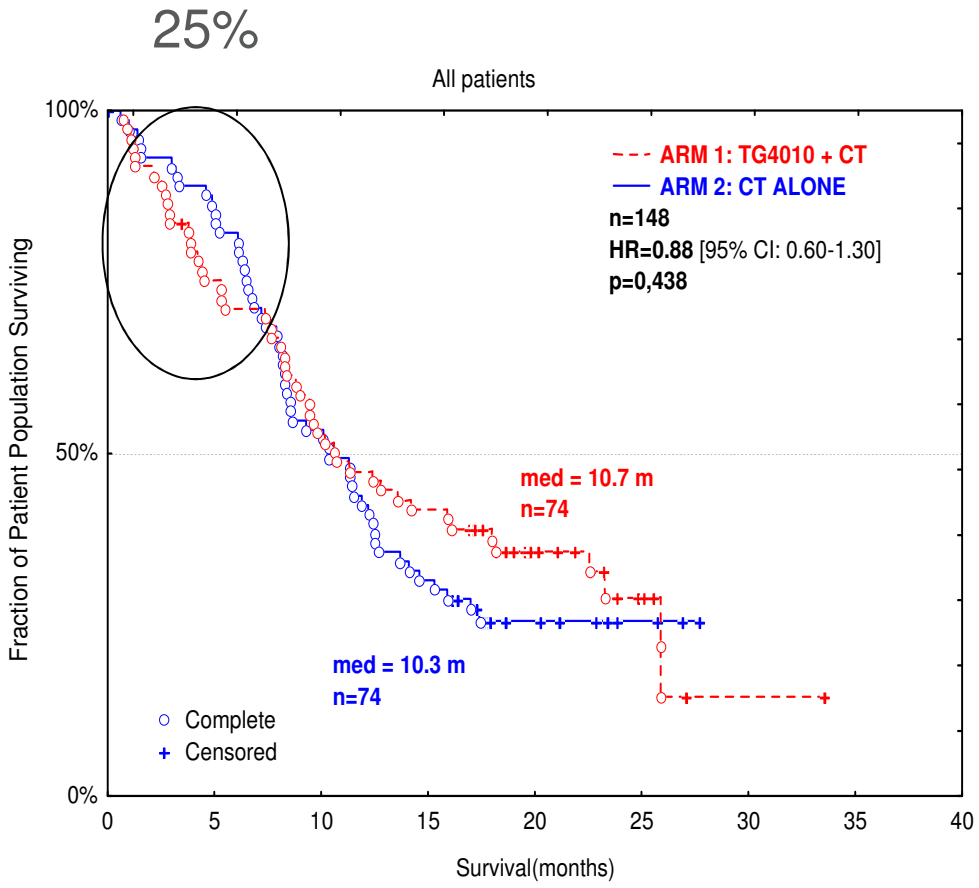
Cohort	Median Survival	N	Percent Censored
Lucanix	20.9	157	56%
Control	12.9	136	45%
Difference	8.0		

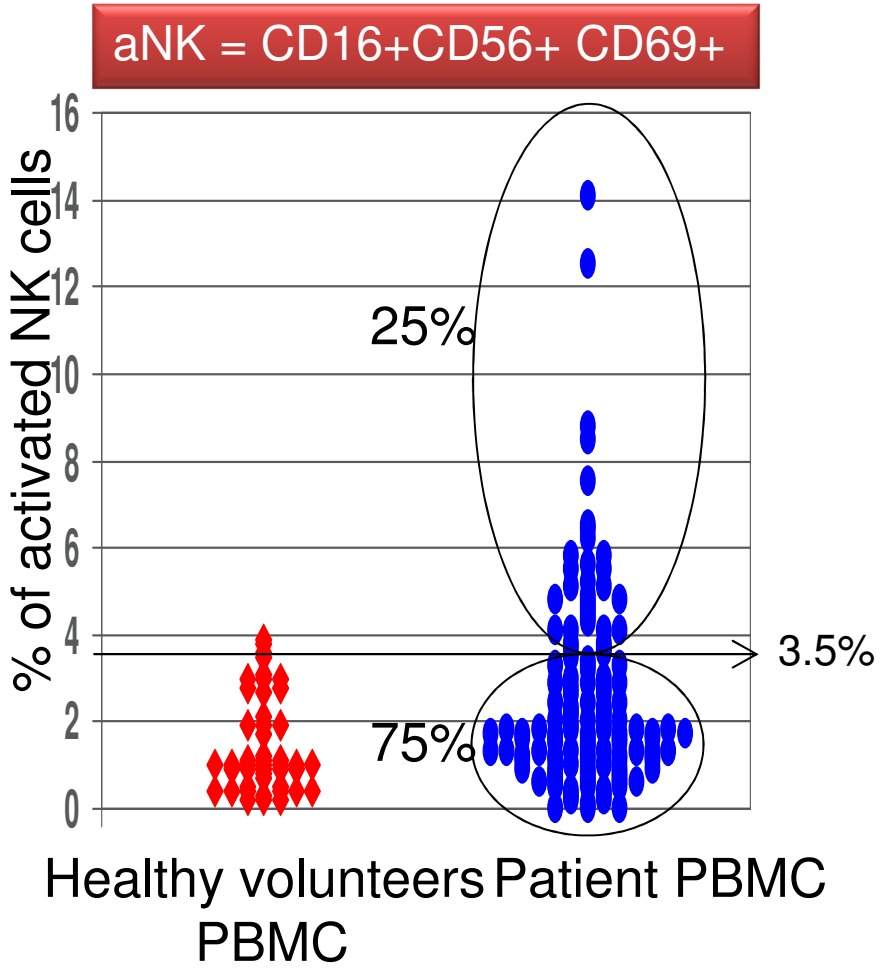
* *Data from all clinical sites except one with significant compliance issues*

So What Did We Learn With Belagenpumatucel?

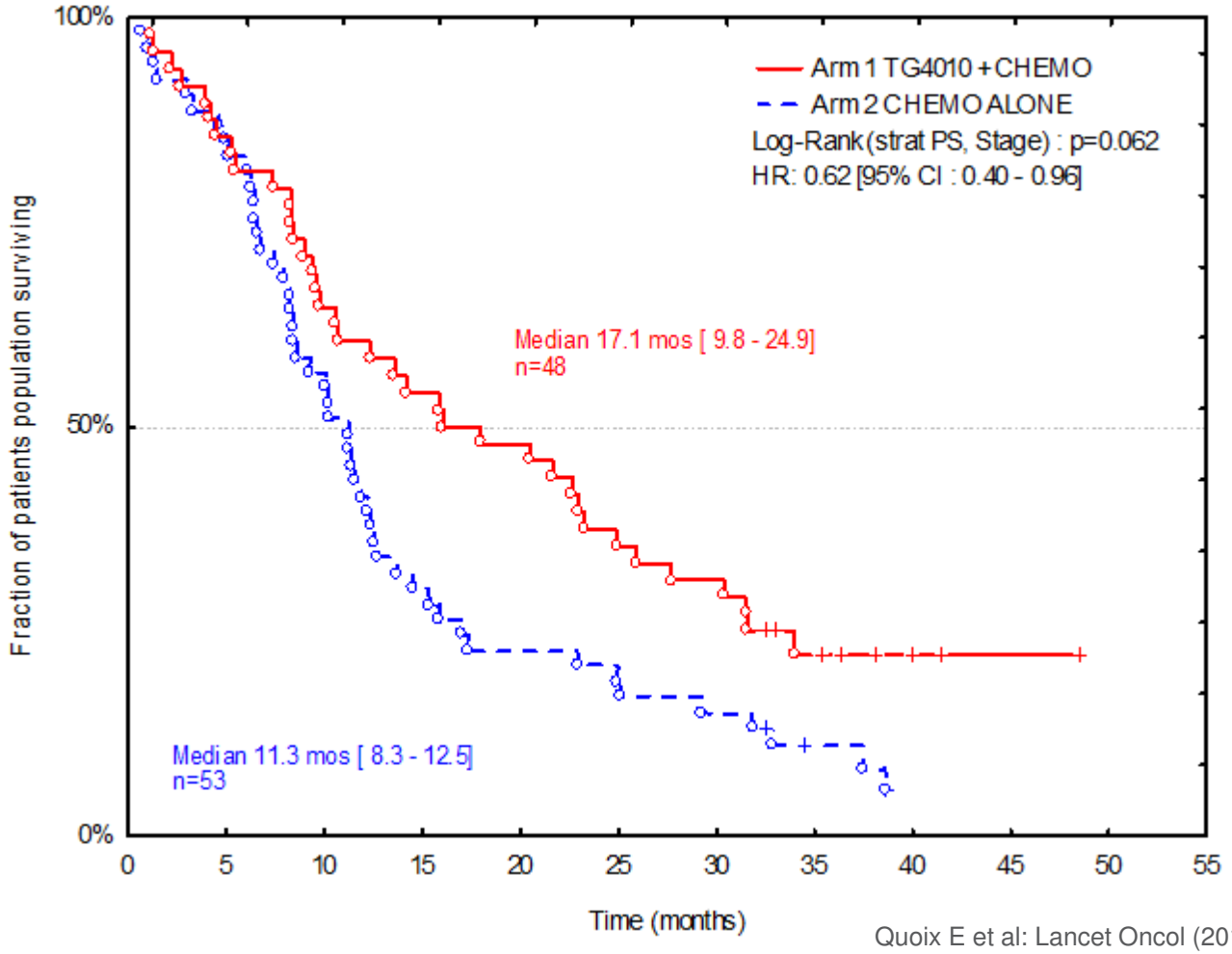
- Phase II trials suggested evidence of clinical benefit in subsets of patients with ≥ 2nd line NSCLC
- Phase III trial suggests insufficient clinical response in front line NSCLC
  - But Why?
    - Allogeneic tumor antigens less efficient then autologous tumor antigen?
    - $TGF\beta_2$ knockdown insufficient (TGFβ1 is dominant TGFβ cancer immunosuppressor)
    - Level of Knockdown insufficient (35-50%)?
    - Physiologic effects related to subset sensitivity/resistance
- No Surrogate measure of activity

TG4010 (Recombinant Vaccinia Virus/MUC1 Antigen IL2 Transgene) Early Safety Signal: Correlation with aNK Cells Level





TG4010 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

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

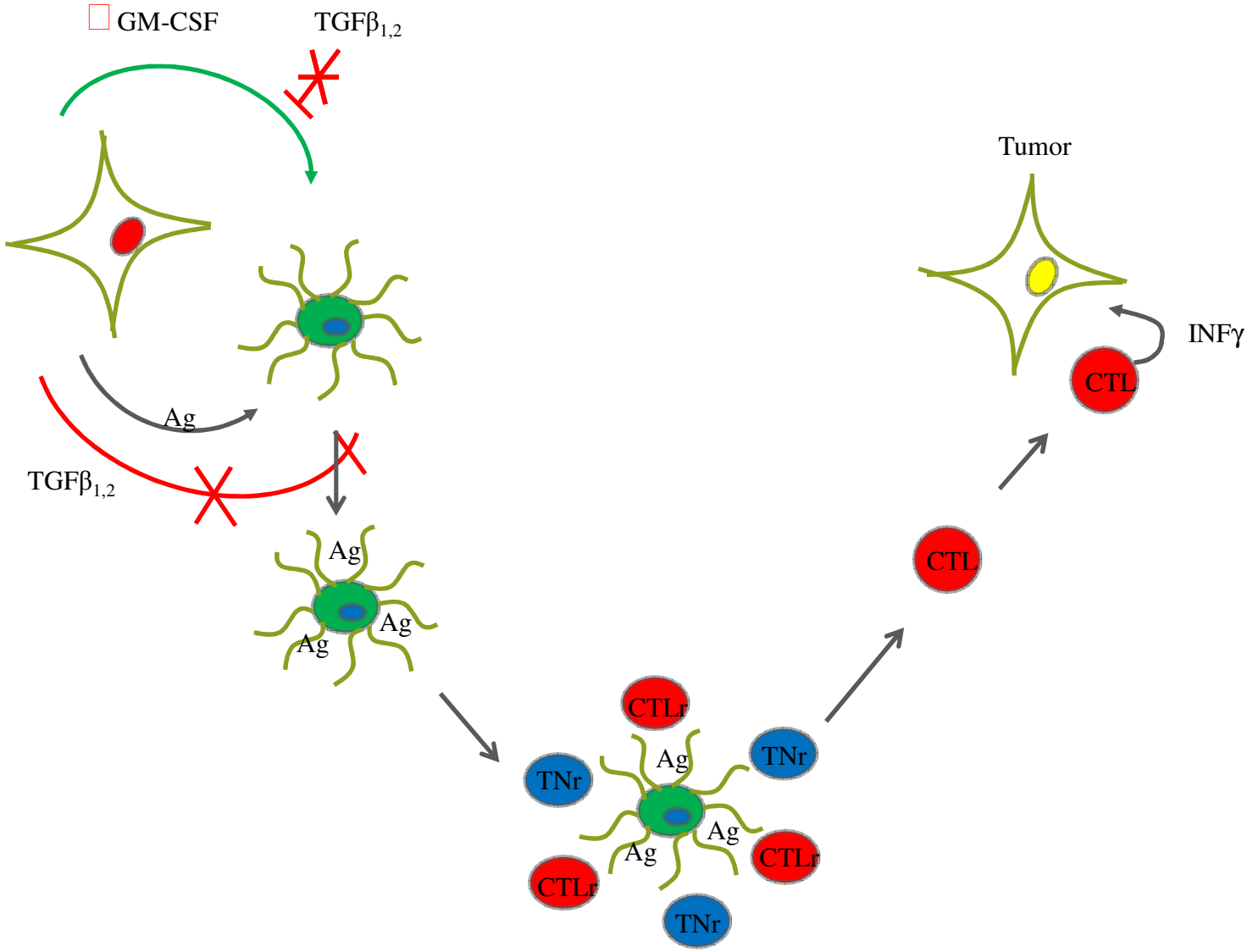
Could "Triad" Approach Provide a Greater Activity

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

  - Identify surrogate measure of biorelevant activity

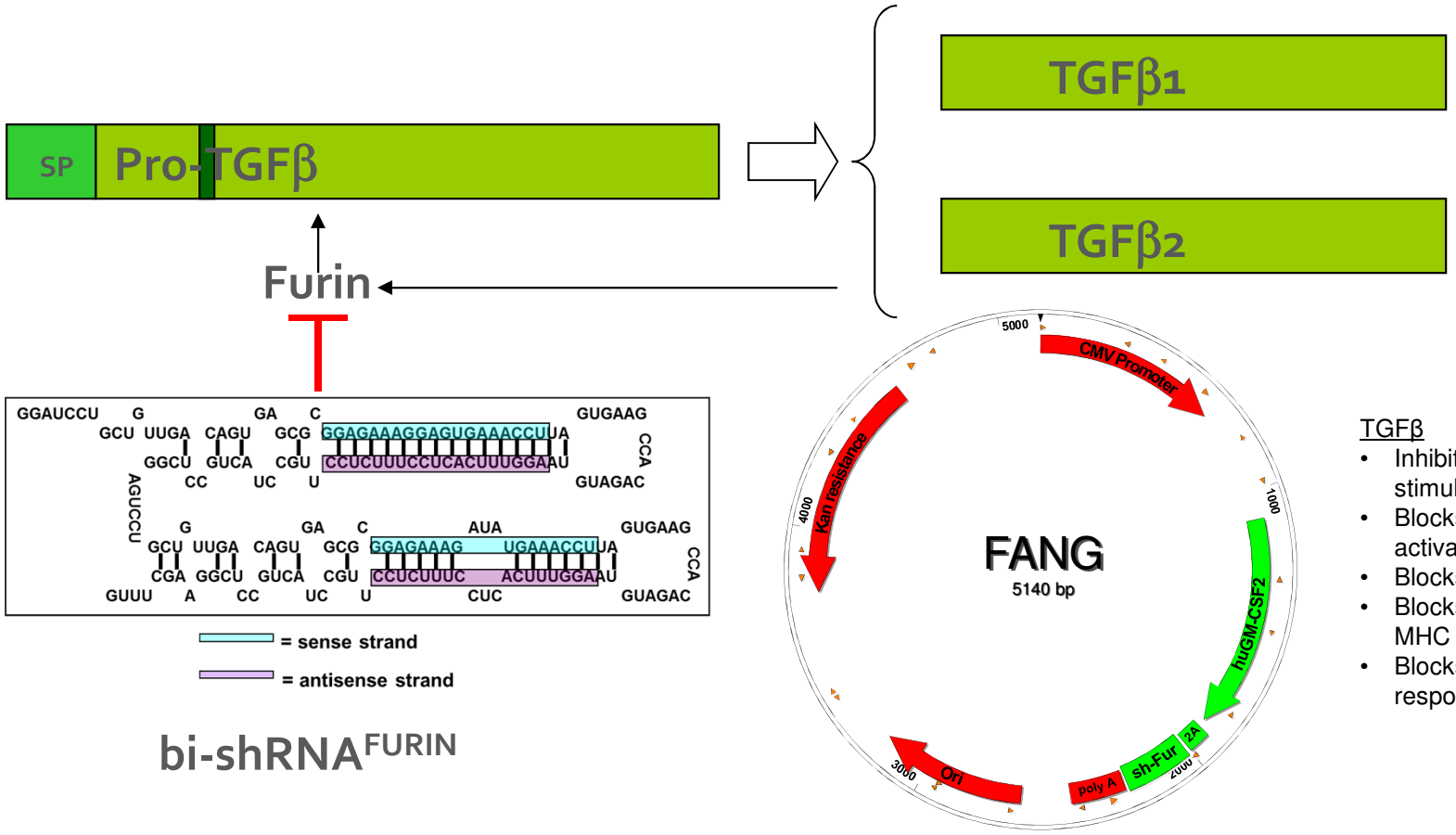
Nemunaitis. Expert Review of Vaccines 2011; 10(6):713-715

Triad Vaccine Mechanism



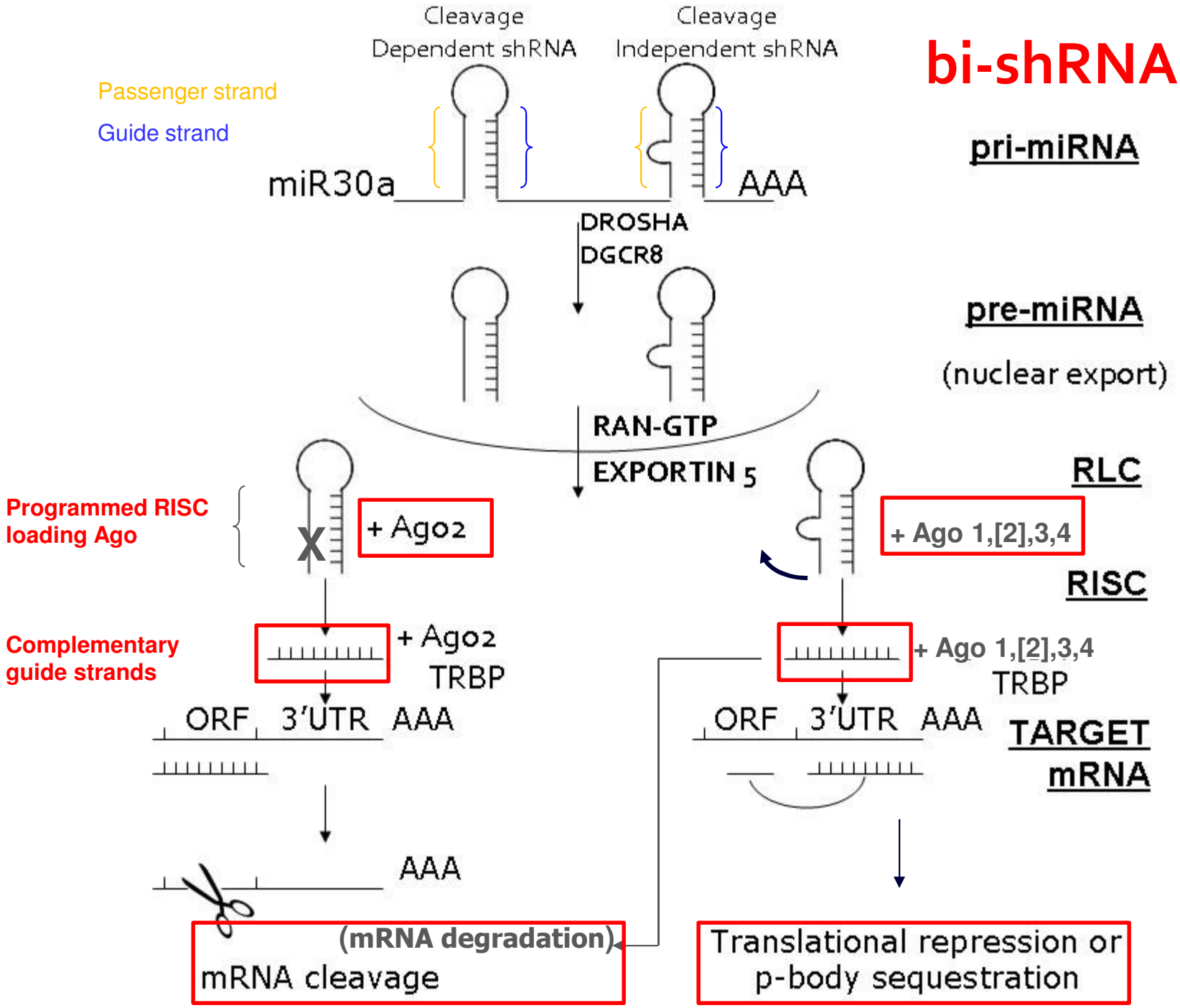
Furin pro-protein convertase – immunomodulatory TGFβ_1, β_2

(Gradalis, Inc., Dallas, TX)



TGFβ

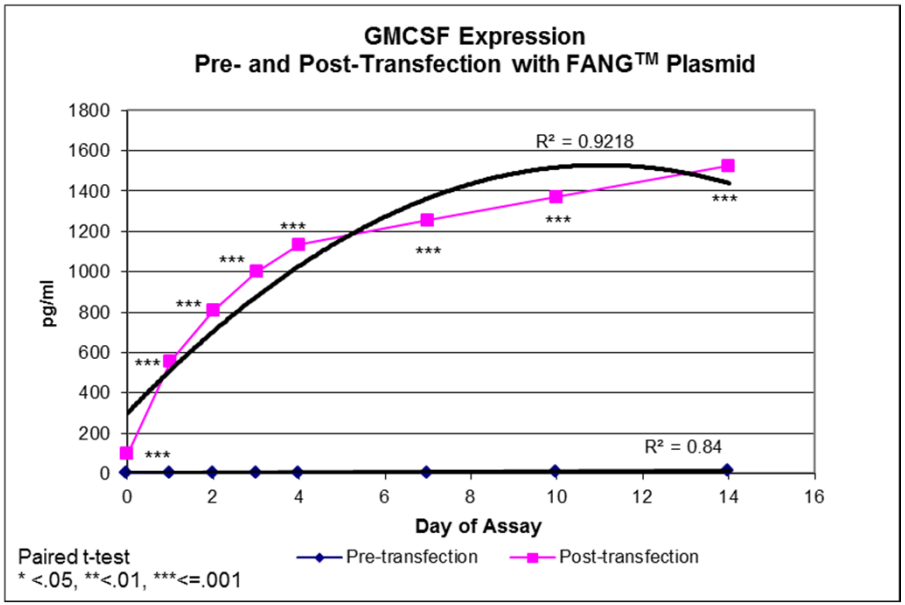
- Inhibits GMCSF stimulation
- Blocks macrophage activation
- Blocks Ag presentation
- Blocks expression of MHC class II
- Blocks dendritic cell response


Cleavage
Dependent shRNA
Cleavage
Independent shRNA
bi-shRNA
Passenger strand
Guide strand
pri-miRNA
miR30a
AAA
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
ORF
3'UTR
AAA
TARGET
mRNA
AAA
(mRNA degradation)
mRNA cleavage
Translational repression or
p-body sequestration

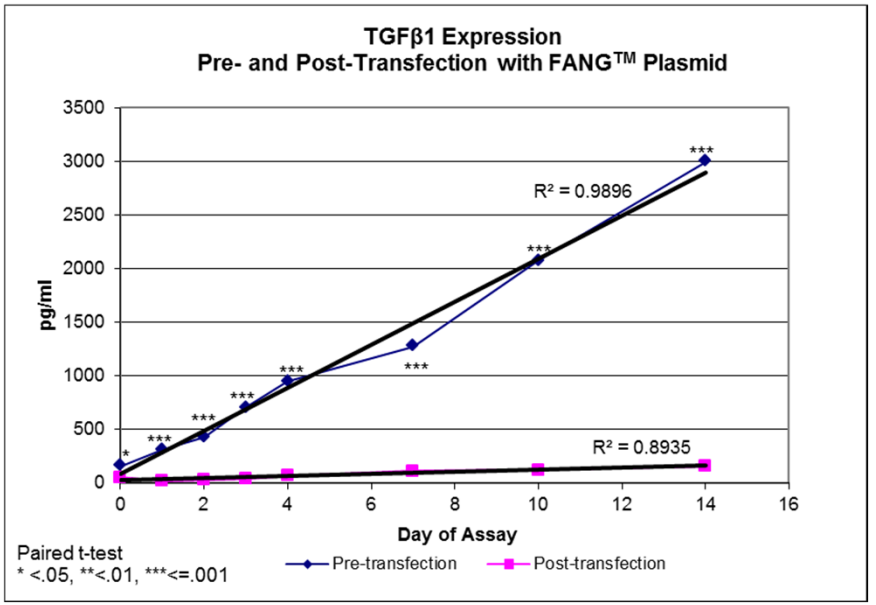
FANG™ Phase I Trial
6/8/09

- 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

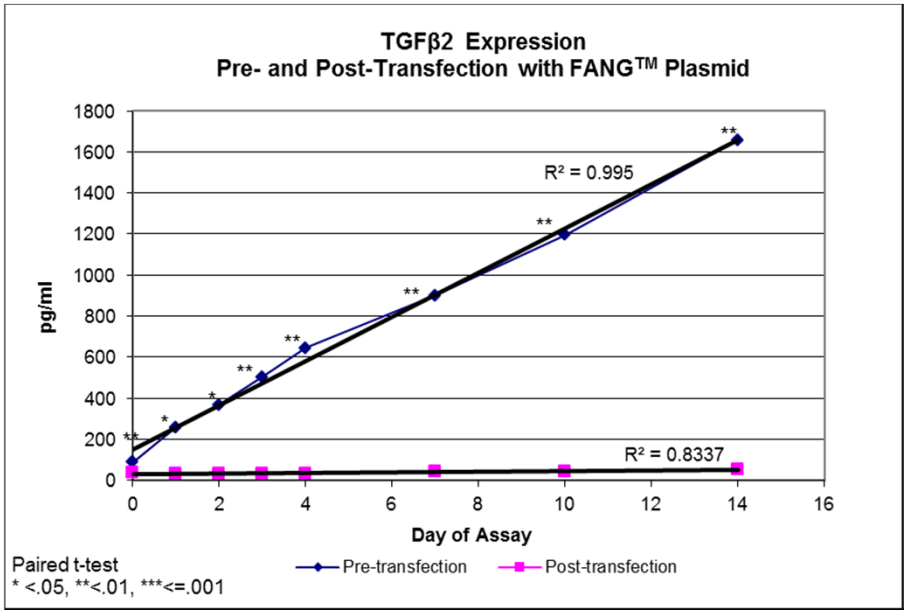
a


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

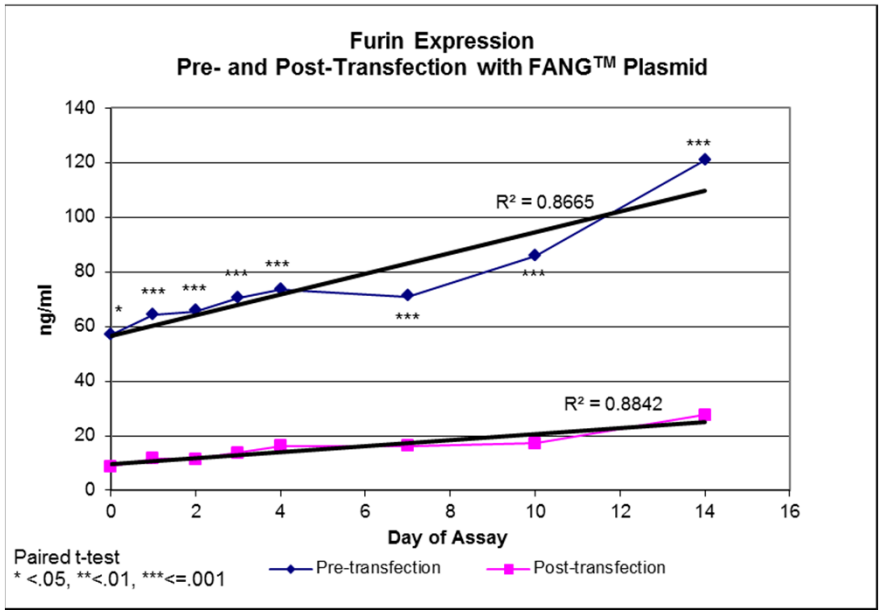
b


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

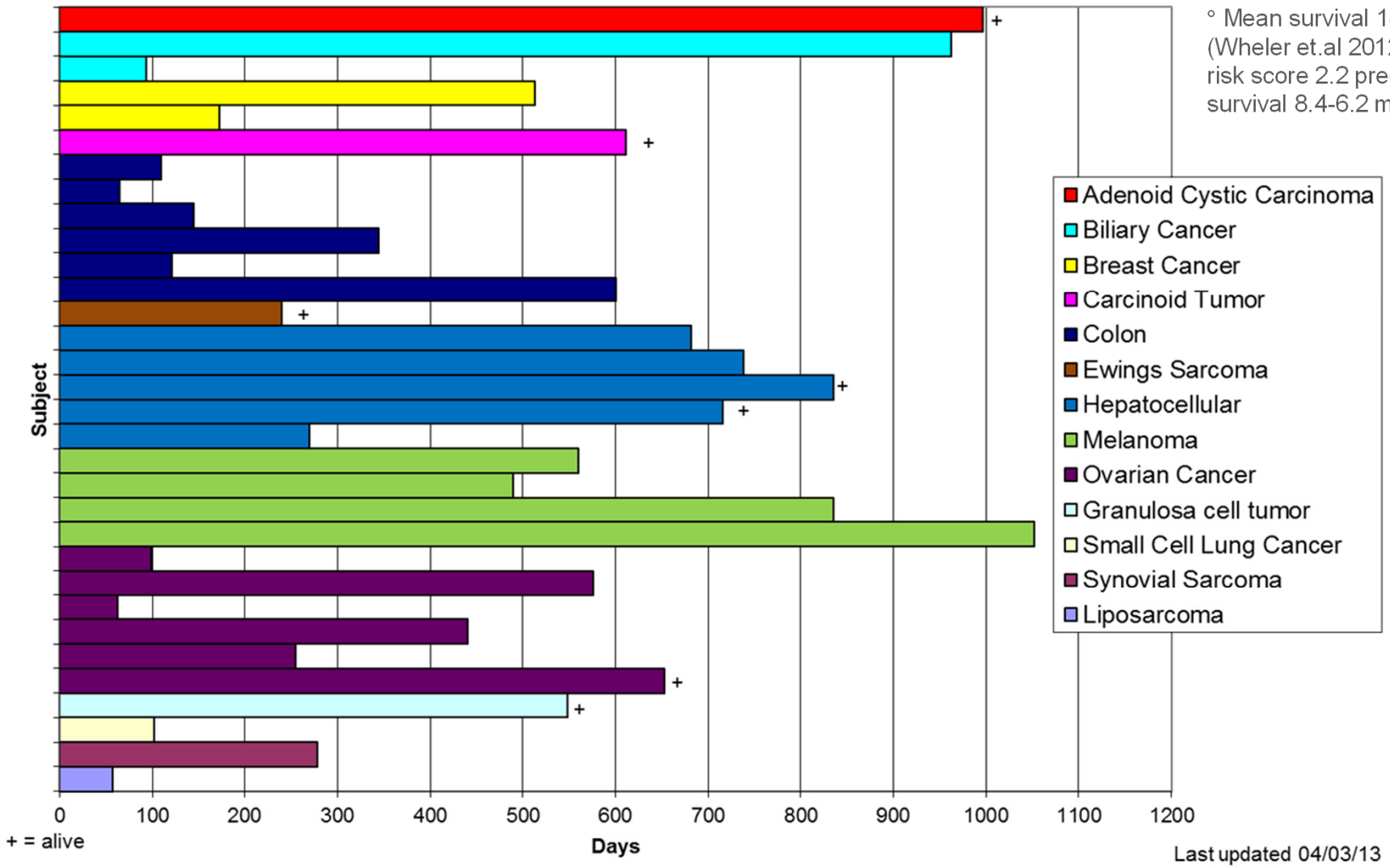
c


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

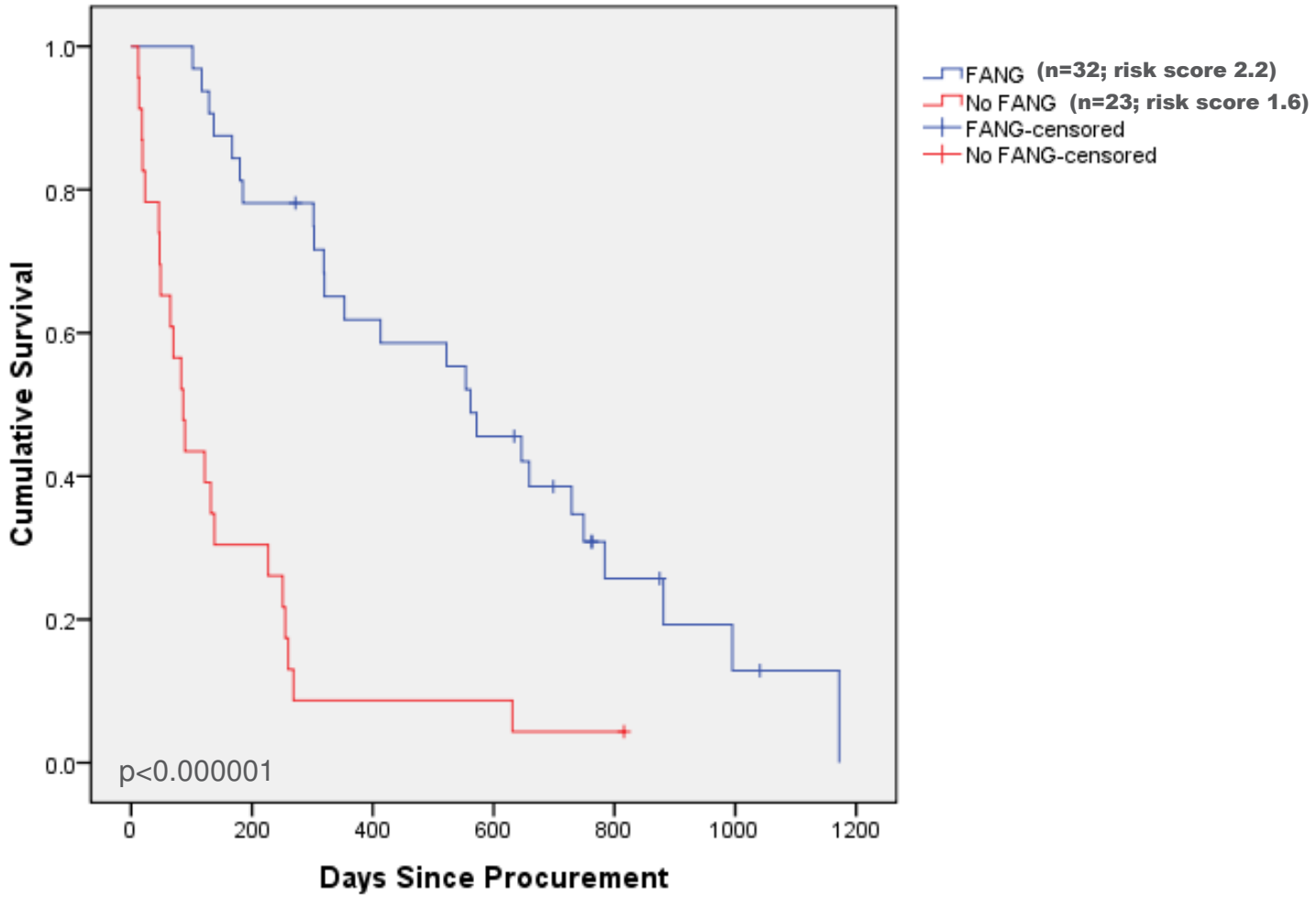

Furin Expression
Pre- and Post-Transfection with FANG™ Plasmid
ng/ml
R² = 0.8665
R² = 0.8842
Day of Assay
Paired t-test
* <.05, **<.01, ***<=.001
Pre-transfection
Post-transfection

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.

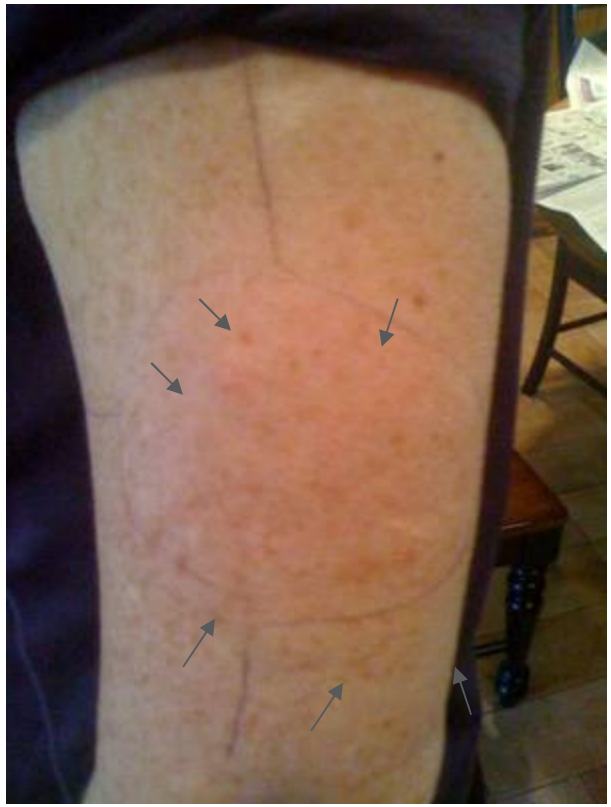
Survival of Treated Patients Since Procurement on FANG™ Phase I Protocol



Data as of 04/26/13

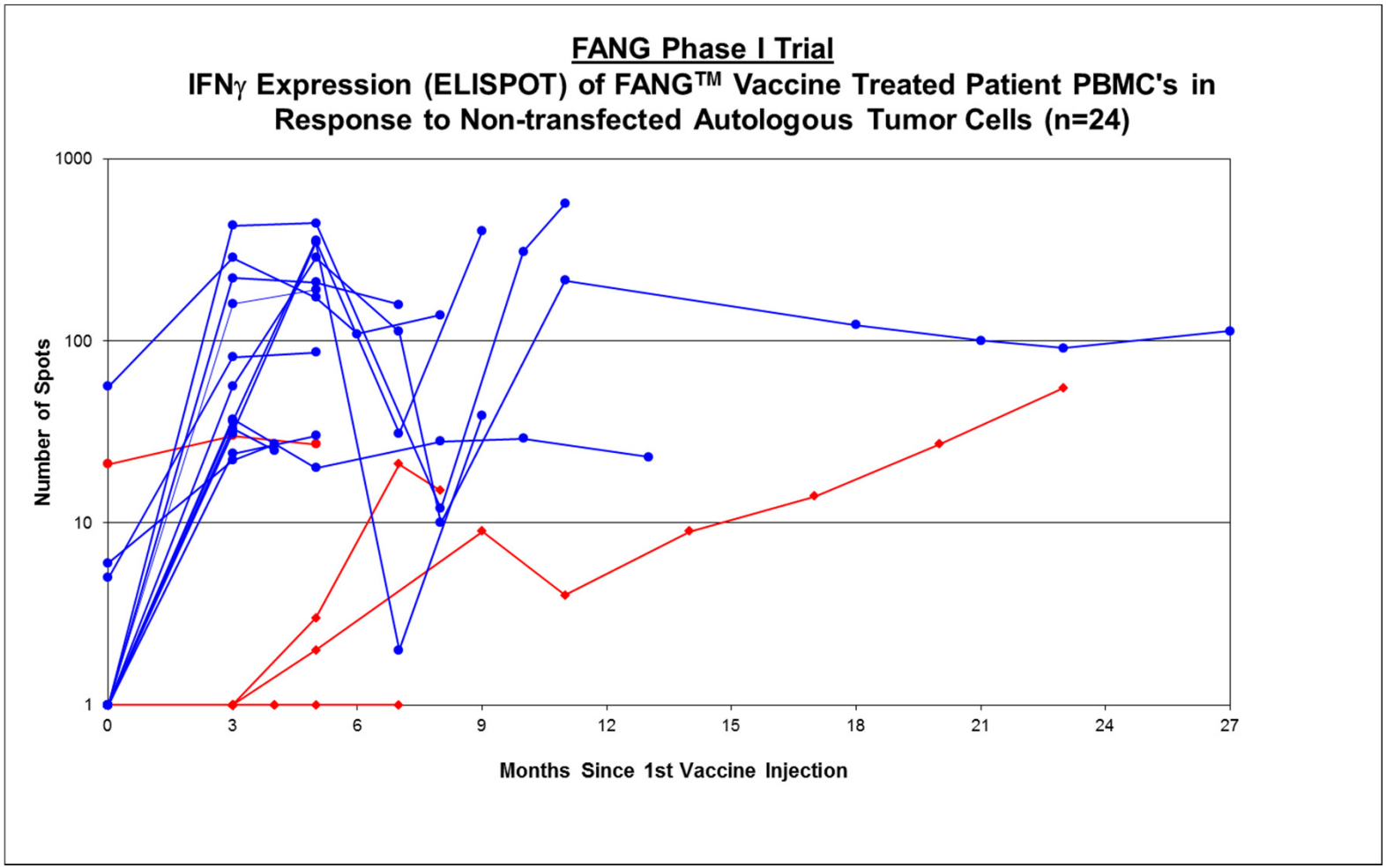
FANG Vaccine: Toxicity

Patient #018
Colon Adenocarcinoma

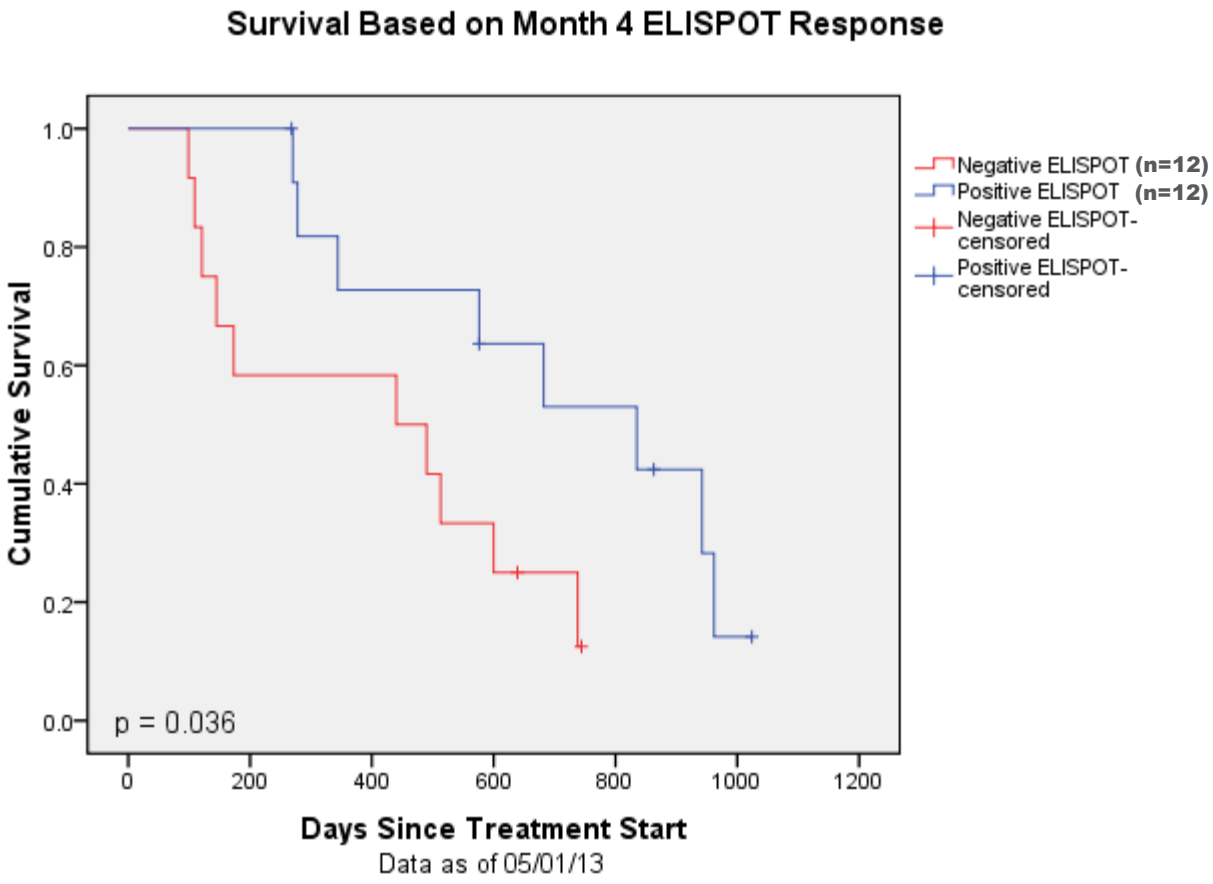


(C1D2)

- 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 I Expansion Phase II Trial Program*

CL-PTL-101	Phase I Trial of FANG Expansion of NSCLC, Hepatocellular, Renal, Ewings, Thyroid
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

Successful Vaccine Construction Rate

21%

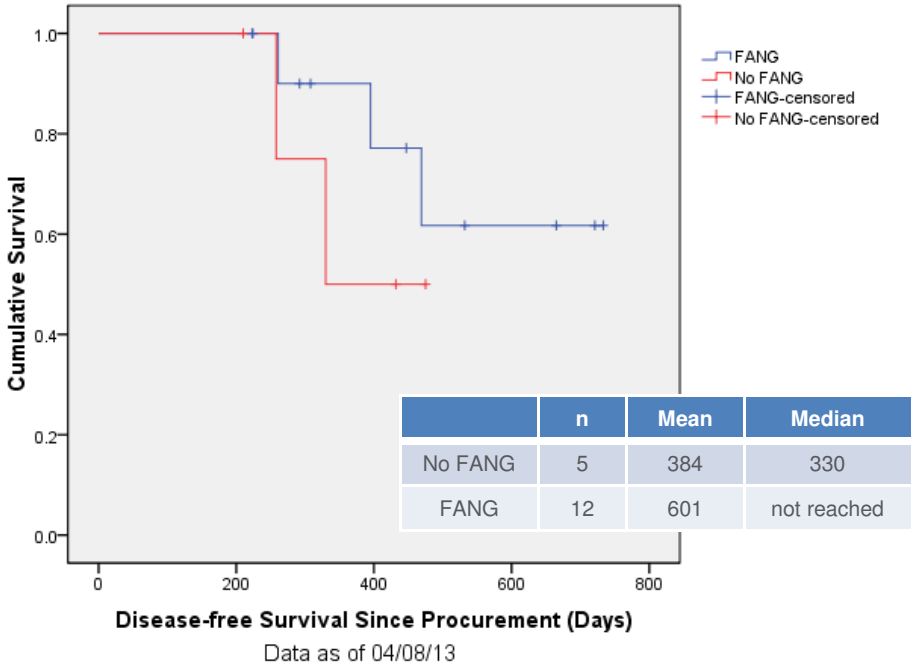
Protocol	Successful Vials Manufactured	Successful Patient Samples Manufactured	Insufficient Patient Samples	Failed Patient Samples	Vaccines Administered
Phase I CL-PTL 101	559	60*	7	5	174
Phase II OV CL-PTL 105	501	52	4	10	89
Phase II CLM CL-PTL 107	21	2	0	0	14
Phase II Mel CL-PTL 114	66	7	3	5	70
TOTAL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

*including 2 pre-clinical and 1 benign

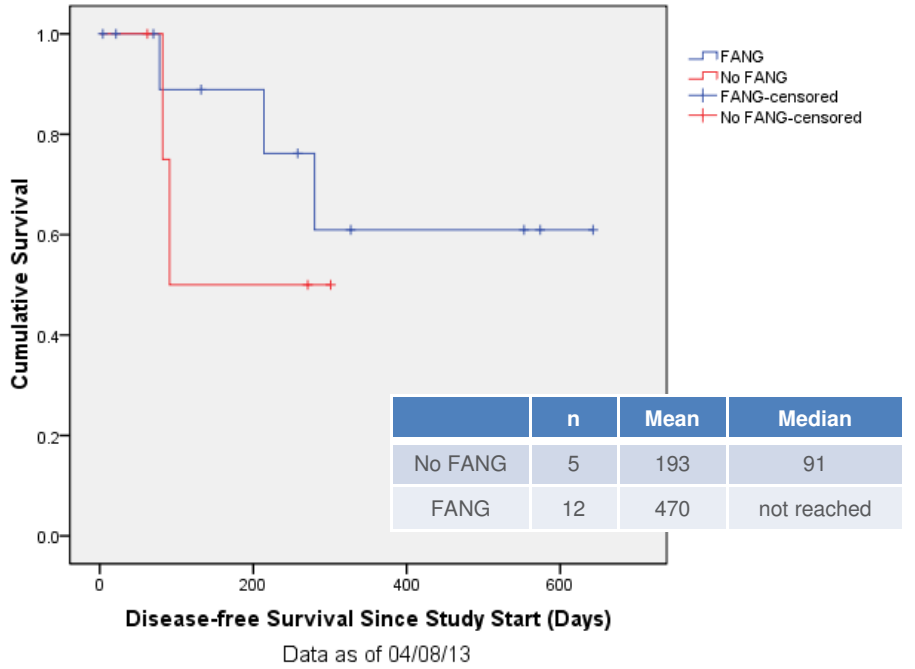
Phase II Ovarian (III/IV)Trial Design

- 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

Conclusion

- Evidence of increasing beneficial and safe immune modulatory activity is observed in advanced NSCLC to novel targeted immunotherapies
- Employment of “Triad” functions to vaccine effect should be considered (multi vaccines/single “triad” therapeutics)
- Surrogate biomarkers correlating response/survival to mechanism facilitate immunotherapy development