Experimental Therapeutics Committee Meeting

Saturday, May 10, 2014

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

- Status update on activated current trials

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

A091104

(permanently closed to enrollment)

Phase II MK-2206 in Patients with Progressive Recurrent/Metastatic Adenoid Cystic Carcinoma

A. Ho

Alliance A091103: A Phase II Study of the Angiopoietin-1 and -2 Peptibody AMG 386 for the Treatment of Angiosarcoma

Study Chair: Sandra P. D'Angelo, MD

- This is a phase II study in patients with AS who have progressed after prior systemic treatments or who are unresectable.
  - **Primary endpoint:** ORR
  - **Secondary endpoints:** PFS and OS

- An optimal Simon two-stage design with an early stopping rule will be used.
  - 1 confirmed response in 12 treated patients expands enrollment to 37.
  - Study will be deemed positive if 4/37 confirmed responses are observed. (Type I error=Type II error=0.1)

- Patients treated with AMG-386 30mg/kg weekly and each cycle will consist of 28 days

- Correlatives
  - Tumor biopsies pre/post treatment (MSKCC patients) 3/4 patients paired biopsies
  - Baseline Ang2/Tie2 expression by IHC
  - Mutational status of VEGFR-2 and amplification of MYC/FLT4
  - Serum Ang1/2 levels

Alliance A091103: A Phase II Study of the Angiopoietin-1 and -2 Peptibody AMG 386 for the Treatment of Angiosarcoma

Study Chair: Sandra P. D'Angelo, MD

- First-stage accrual complete (12 patients)

- Active patients to date:
  - 16 registered and treated (MSKCC 4, Wash U 9, Carle 1, MC Rochester 1, George DC 1)
  - Gender: 10 female, 6 male
  - Primary site of disease (head & neck, cardiac pericardium/muscle, extremity, breast, scalp)
  - Average number of prior therapies: 2 per patient (range 1-7)
  - Median number cycles of treatment: 2 per patient (range 1-6)
  - No tumor responses were observed
  - Clinical activity (4 patients had SD for at least 3.5 months, 6 progressed, 4 non-evaluable)
  - All patients are off-treatment, 13 have progressed, and 6 are alive
  - Biopsies (Obtained in 3/4 MSKCC patients, omitted in 1 patient to maintain measurable disease)

Alliance A091102: Phase II Study of MLN8237 (Alisertib) in Advanced/Metastatic Sarcoma

Study Chair: Mark A. Dickson, MD

Primary endpoint: ORR

Secondary endpoints: PFS and OS

Patients enrolled in 5 separate cohorts:

- Cohort 1: liposarcoma
- Cohort 2: leiomyosarcoma
- Cohort 3: undifferentiated sarcoma
- Cohort 4: malignant peripheral nerve sheath tumor
- Cohort 5: other sarcomas

Simon two-stage design for each cohort:

- Treat 9 patients. If ≥ 1 response, enroll additional 16.

- Treatment: Alisertib 50mg PO bid x 7 days, every 21 days
- Correlatives:
  - Pre- and on-treatment tumor biopsies
  - Pre- and on-treatment FLT-PET scans
- Study activation 8/22/2012

Alliance A091102: Phase II Study of MLN8237 (Alisertib) in Advanced/Metastatic Sarcoma

Study Chair: Mark A. Dickson, MD

Total accrual: 72 patients

Cohort	N
1: Liposarcoma	12
2: Leiomyosarcoma (non-uterine)	10
3: Undifferentiated Sarcoma	13
4: Malignant Peripheral Nerve Sheath Tumor	10
5: Other Sarcomas	27

First-stage accrual complete for each cohort. Based on 1 confirmed PR in angiosarcoma, cohort 5 was expanded to second stage accrual.

Toxicity: Principally neutropenia, mucositis, hand-foot

Paired FLT-PET scans on 7 patients and paired biopsies on 6

Results to be reported at ASCO 2014

Induction chemotherapy and ABT-888 in SCCHN – Alliance Update

Jonas de Souza, MD
Assistant Professor of Medicine
The University of Chicago

THE UNIVERSITY OF CHICAGO

SCHEMA for Phase 1 Combination Study

Dose Cohort	ABT-888 (veliparib) (mg), twice daily, PO day 0 to 6	Docetaxel (mg/m^2)	Cisplatin	5- Fluorouracil (mg/m^2)
- 2	10	75	75	750 mg/m^2 on days 1 – 5
- 1	20	75	75	750 mg/m^2 on days 1 – 5
0	30	75	75	750 mg/m^2 on days 1 – 5
1	50	75	75	750 mg/m^2 on days 1 – 5
2	100	75	75	750 mg/m^2 on days 1 – 5
*Doses are stated as exact dose in units (e.g., mg/m^2, mcg/kg, etc.) rather than as a percentage.				

TAX 324 **TPF: Docetaxel 75_{D1} + Cisplatin 100_{D1} + 5-FU 1000 $_{CI\text{-}D1\text{-}4}$ Q 3 weeks x3**

Schema:

Phase 1 - Locally Advanced Head and Neck

(TPF)
Docetaxel 75 mg/m^2 D1
Cisplatin 75 mg/m^2 D1
5- Fluorouracil 750 mg/m^2 D1-D5

+

Veliparib escalating dose cohorts
D0 – D6:
30mg PO bid
50mg PO bid
100mg PO bid

2 cycles

Resume chemotherapy for cycle 2 on Day 22

Target Population – Phase 1

- Oropharyngeal Cancer (OPC) HPV-negative, IVa-b
- Stage III (hypopharynx or nasopharynx) or IVa-b SCC other than OPC

↓

Determine maximum tolerated dose (MTD) of combined therapy → **Response Assessment & Concomitant Chemoradiotherapy (see below)**

Phase 1 Portion

- TPF + veliparib 30mg bid x 7 days, dose level 0

- 3 treated patients = 3 DLT's
  - 2 neutropenic fevers, 1 prolonged neutropenia
    - Unclear if related to TPF and/or interaction with veliparib

- Current veliparib doses in other trials > 100 mg bid

- CTEP agreed to proposed change of induction regimen to carboplatin/paclitaxel x 2 cycles

  - Based on GOG trial with carboplatin and paclitaxel on metastatic ovarian cancer, currently at carboplatin AUC 6/paclitaxel 80mg/m2 and veliparib 200mg bid, likely MTD
  - Amendment under review at CTEP

Phase 1 Portion

Planned Dose Scheme			
Dose Cohort	**ABT-888**	Paclitaxel	Carboplatin
- 2	**50 mg BID x 7 days**	100 mg/m^2	AUC 6
-1	**100 mg BID x 7 days**	100 mg/m^2	AUC 6
*0	**150 mg BID x 7 days**	100 mg/m^2	AUC 6
1	**200 mg BID x 7 days**	100 mg/m^2	AUC 6
2	**250 mg BID x 7 days**	100 mg/m^2	AUC 6
3	**300 mg BID x 7 days**	100 mg/m^2	AUC 6

Phase 1 Portion

Phase A (First de-escalation will result in reduction to Paclitaxel to 80mg/m2 at any dose level)

Dose Cohort	**ABT-888**	Paclitaxel	Carboplatin
-1	**Current Veliparib dose**	80 mg/m^2	AUC 6
*0	**Current Veliparib dose**	100 mg/m^2	AUC 6

Phase B (After first dose de-escalation, further changes will only affect veliparib dose)

Dose Cohort	**ABT-888**	Paclitaxel	Carboplatin
- 2	**50 mg BID x 7 days**	80 mg/m^2	AUC 6
-1	**100 mg BID x 7 days**	80 mg/m^2	AUC 6
*0	**150 mg BID x 7 days**	80 mg/m^2	AUC 6
1	**200 mg BID x 7 days**	80 mg/m^2	AUC 6
2	**250 mg BID x 7 days**	80 mg/m^2	AUC 6
3	**300 mg BID x 7 days**	80 mg/m^2	AUC 6

To Watch

Randomized, Double-Blind, Multicenter, Study Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Previously Untreated Advanced or Metastatic Squamous Non-Small Cell Lung Cancer

This study is currently recruiting participants.

Verified April 2014 by AbbVie

Sponsor:
AbbVie

Information provided by (Responsible Party):
AbbVie

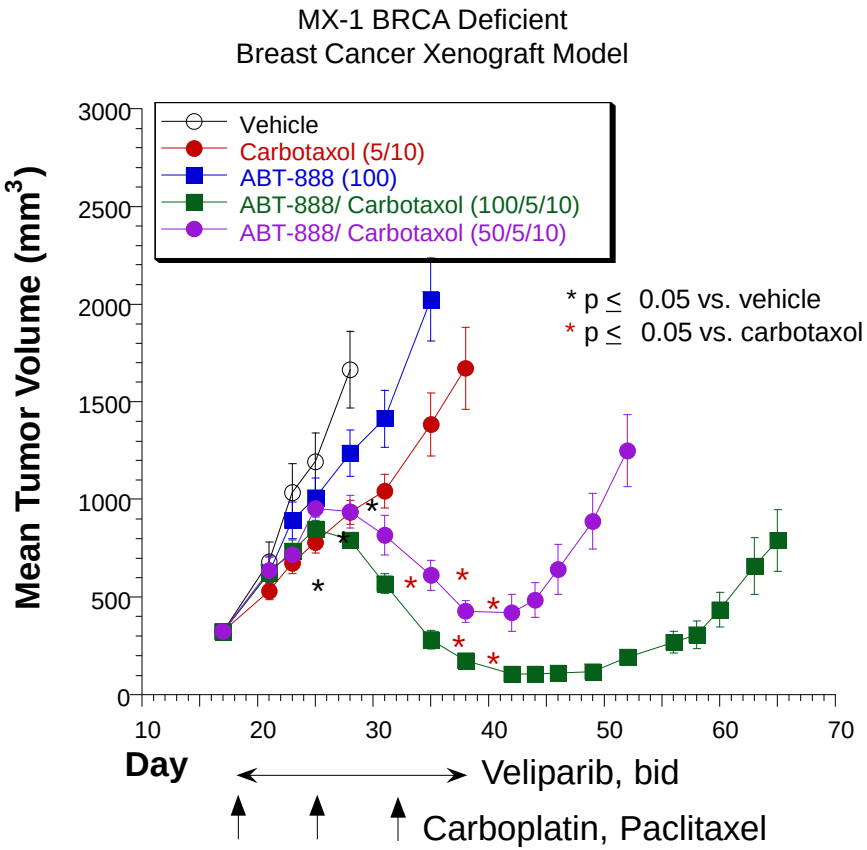
ClinicalTrials.gov Identifier:
NCT02106546

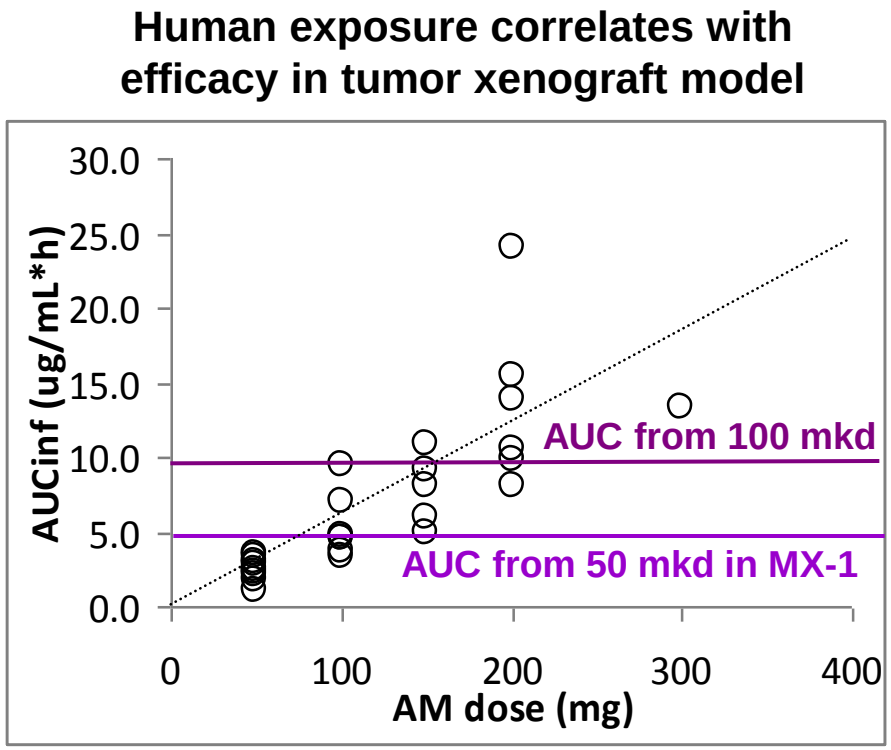
First received: April 4, 2014
Last updated: NA
Last verified: April 2014
History: No changes posted

Estimated Enrollment:	900
Study Start Date:	March 2014
Estimated Study Completion Date:	March 2016
Estimated Primary Completion Date:	March 2016 (Final data collection date for primary outcome measure)

Veliparib Potentiates Carboplatin/Paclitaxel Combination:

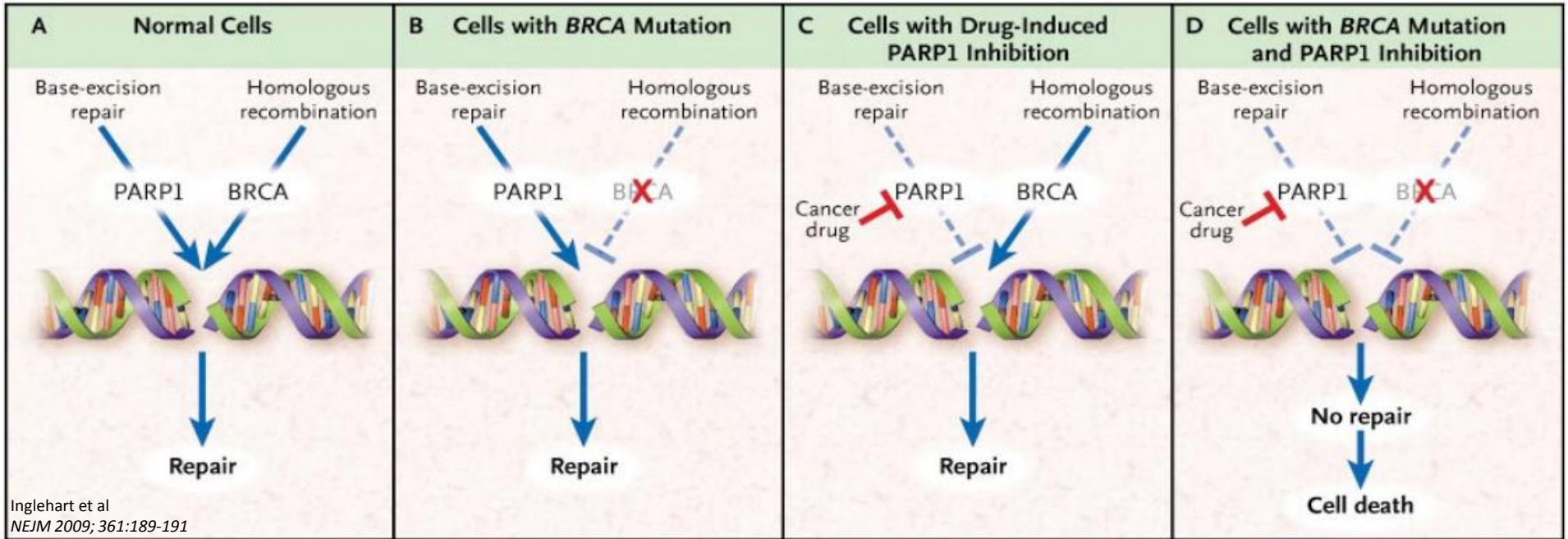
BRCA Deficiency Enhances Sensitivity to PARP Inhibition





Synthetic lethality

- First described by Dobzhansky in the 1940's to describe the exploitation of a potent and lethal synergy between two otherwise non-lethal events
- In other words, if two genes can be targeted in a pathway in which both are key, or if these genes function in co-operating pathways, lethality of cells can occur → PARP inhibition + BRCA deficiency



Inglehart et al
NEJM 2009; 361:189-191

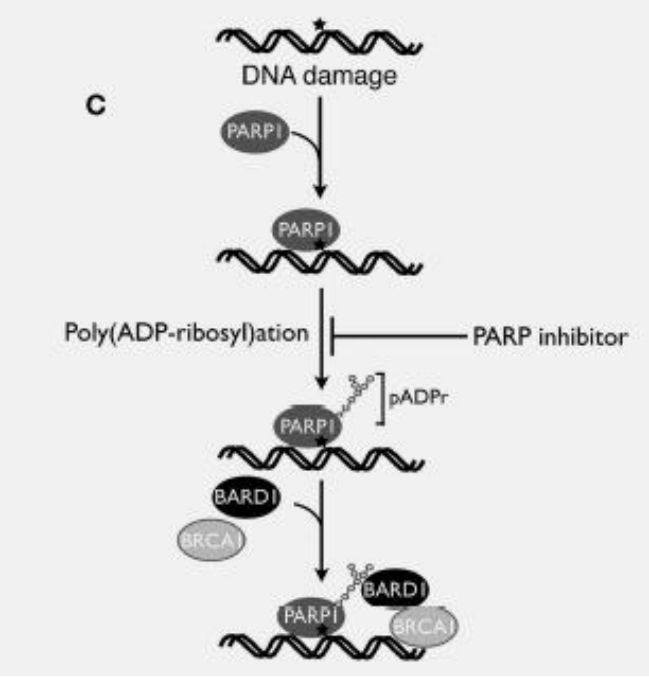
PARP inhibition leading to cell death

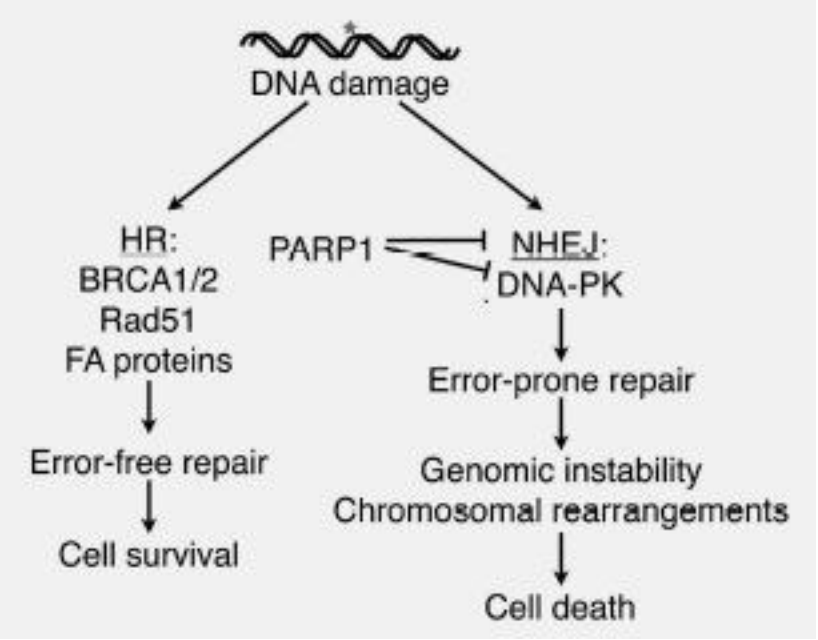
- Both BRCA1 and BRCA2 are involved in double-strand breaks (DSBs) repair by HR
- In wild-type and heterozygous BRCA cells, even with ineffective BER (as caused by PARP inhibition), HR repair will correct the DSBs
- In BRCA homozygous mutated cells, the ineffective BER (caused by PARP inhibition) and defective HR pathway will lead to cell death

Martin Forster
Current Pharmaceutical Design, 2012, Vol.18, No. 34

PARP inhibition leading to cell death

- Failure to initiate HR by poly(ADP-ribose) polymer-dependent BRCA1 recruitment
- Activation of the NHEJ pathway, which selectively induces error-prone repair in HR-deficient cells





Martin Forster
Current Pharmaceutical Design, 2012, Vol.18, No. 34

BRCA mutation and Head and Neck Cancer?

The "HR deficiency/BRCAness" concept

- Yes, you are right:
  - HNC is not known to be associated with germline BRCA 1 or 2 mutations
  - Somatic BRCA1/2 mutations are exceedingly rare in squamous cell cancers (TCGA/ Chicago Genomics Cohort)
- HR pathway encompasses proteins beyond BRCA1/2
- The HR deficiency / BRCAness concept defines characteristics that some sporadic cancers share with BRCA1 or BRCA2 cancers:
  - DNA repair defect with a loss of HR

The "BRCAness" concept Applied to HNC

- Epigenetic hypermethylation has been reported to induce HR deficiency:
  - FANCF (gene F of Fanconi anemia)

Table 2 | **Frequency of BRCA/FA-pathway inactivation in sporadic cancers**

Cancer type	Somatic *BRCA* mutations	*BRCA1* methylation	*FANCF* methylation	*EMSY* amplification
Breast	Very rare[7,8]	11–14%[26–28]	17%[45]	13%[49]
Ovarian	< 5%[29,48,71]	5–31%[26,28–30]	21%[44]	17% of high-grade cancers[49]
HNSCC	ND	0%[34]	15%[34]	ND
NSCLC	ND	4%[34]	14%[34]	ND
Cervical	ND	6.1%[35]	30%[35]	ND

FA, Fanconi anaemia; HNSCC, head and neck squamous-cell carcinoma; ND, not determined; NSCLC, non-small-cell lung cancer.

Nicolas Turner
Nature Reviews, Volume 4, October 2004

ORL J Otorhinolaryngol Relat Spec. 2010 May; 72(1): 44–50

The “HR deficiency/BRCAness” concept
Dysfunctional HR repair

- HR process can be interrupted at many points
- HR fails to occur if genes encoding components of the MRN complex, ATM, MDC-1, H2AX, PALB2, BRCA1, BRCA2 or Rad51 are silenced or mutated

The “HR deficiency/BRCAness” concept Applied to HNC

- The phosphatase and tensin homolog (PTEN) is a tumor suppressor gene that inhibits the oncogenic phosphoinositide 3-kinase (PI3K)–AKT–mTOR pathway downstream of epidermal growth factor receptor (EGFR) signaling
  - Cells lacking PTEN were shown to be deficient in Rad51, also leading to HR dysfunction and PARP inhibitor sensitivity
    - Counterpoint: recent study on prostate cancer has weakened the relationship PTEN-Rad51

- e. N1153 Phase I/II Study of Sorafenib+TH302 in HCC and RCC (M. Borad)

N1153 – Phase IB/II Study of Sorafenib + TH-302 In HCC/RCC

- Sorafenib + TH-302 (hypoxia activated prodrug)
- **Primary Objective :** MTD/DLT Assessment (Phase I); mRECIST Response Rate (Phase II)
- **Secondary Objectives :** Overall Toxicity; AFP Response; RECIST Response Rate; PFS; OS
- **Phase IB/II Design :** "3+3" in Phase IB portion; HCC/RCC
- **Phase II Portion HCC Only :** N = 24 (90% power to detect response rate of 25% vs null of 5% at significance level of 0.09)

- f. N0871 A Phase II Study of Taxol+Carboplatin+RAD001 (M. Goetz)
  - Trial completed accrual and manuscript is in preparation

N0879 A Randomized Phase II Trial of Carboplatin, Paclitaxel, Bevacizumab, with or without Everolimus for Therapy of Metastatic Malignant Melanoma

PI: Robert McWilliams, MD

Mayo Clinic

Dosing schedule

- Carboplatin AUC 5, day 1
- Paclitaxel 80 mg/m2, day 1,8,15
- Bevacizumab 10 mg/kg, day 1,15
- +/-Everolimus 5 mg MWF weekly
  - 28 day cycle
- Primary endpoint PFS

N0879

- 145 of 148 slots accrued
- Can have had prior ipilimumab, vemurafenib (no limit on prior biologics), 1 prior cytotoxic chemo allowed
- BRAF wt or mutant, ocular or unknown primary OK

Update on A091201:

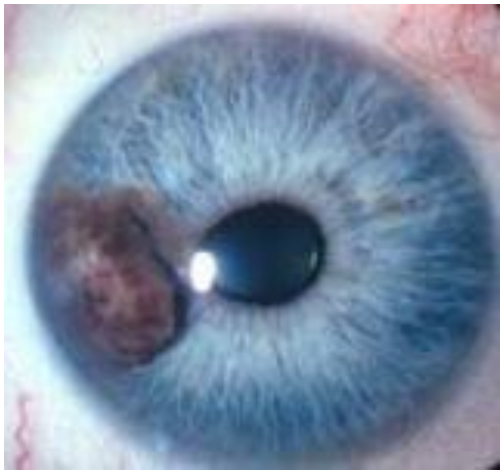
Randomized Phase II Study Comparing the MET inhibitor Cabozantinib to TMZ/DTIC in Ocular Melanoma

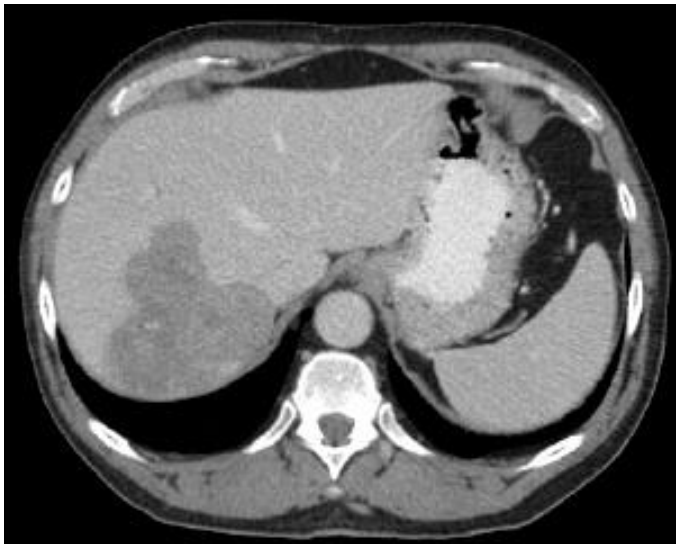
Jason J. Luke, MD

Melanoma Disease Center

Dana-Farber Cancer Institute

Ocular Melanoma





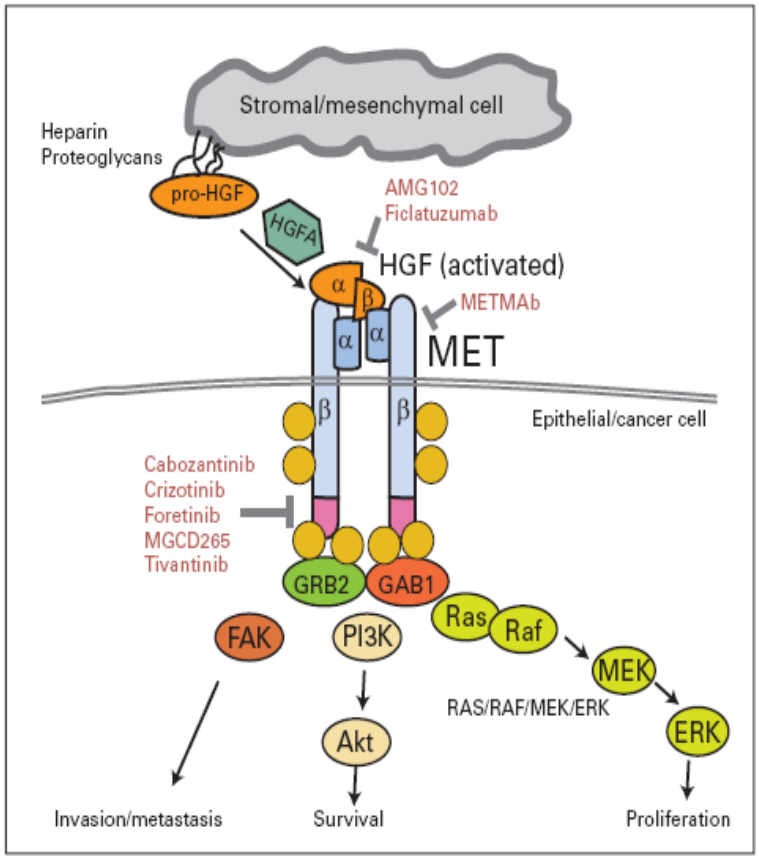
- Rare disease
  - 7 cases per million annually
- Most common intra-ocular cancer
- 50% metastasize
  - Liver tropism
- No standard systemic treatments

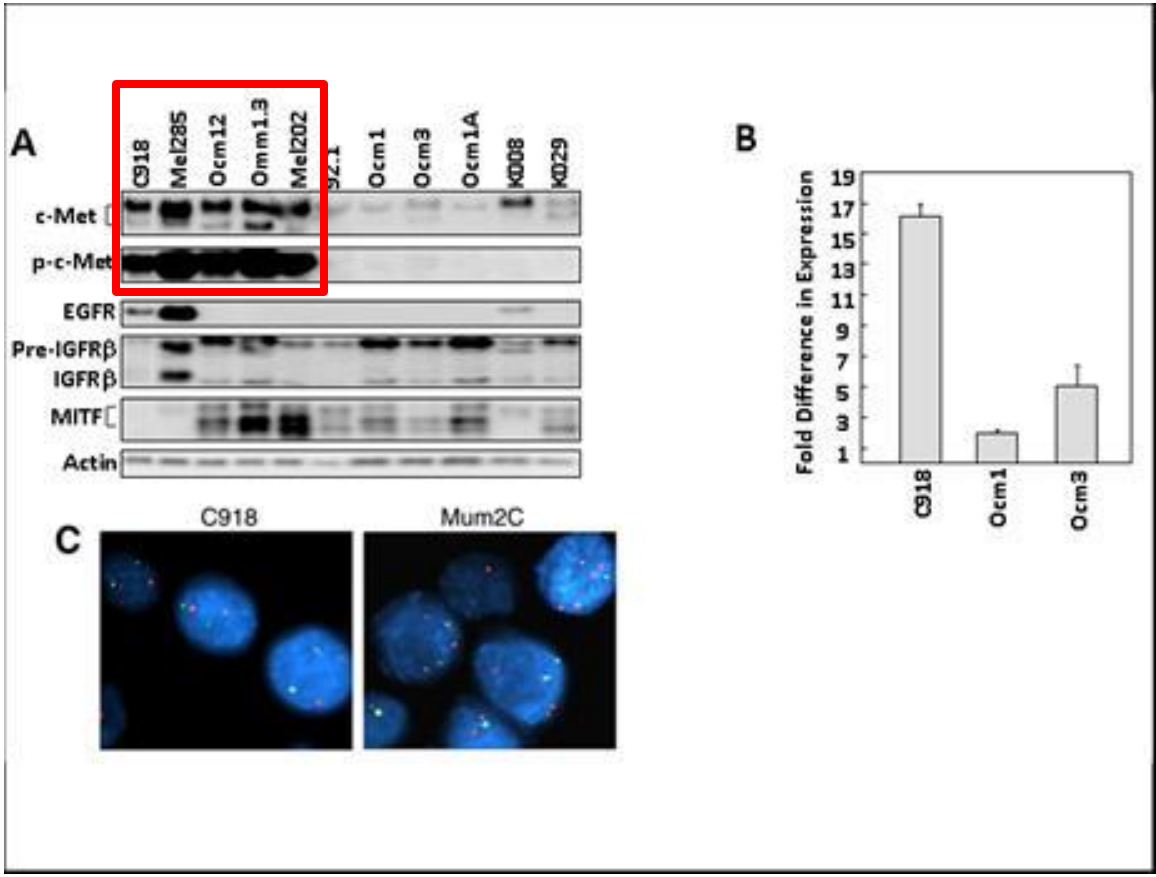
Bakalian *et al.*, Clin Cancer Res 2008

First Author	Intervention	n	RR	OS/PFS
Kivelä, 2003	BOLD + IFN	22	**0%**	1.9 mo PFS
Bedikian, 2004	Temozolomide	14	**0%**	1.8 mo TTP
Schmidt-Hieber, 2004	Bendamustine	9	**0%**	NR
Schmittel, 2005	Gem/Cis/Treosulfan	17	**0%**	3 mo PFS
O'Neill, 2006	DTIC/Treosulfan	15	**0%**	3 mo PFS
Schmittel, 2006	Gem/Treosulfan vs Treosulfan	48	**2%**	2-3 mo PFS
Penel, 2008	Imatinib	10	**0%**	10.8 mo OS
Homsi, 2010	DHA-Paclitaxel	22	**4%**	9.8 mo OS
Mahipal, 2012	Sunitinib	20	**5%**	4.2 mo PFS, 8.2 mo OS
Leyvraz, 2012	Fotemustine (IV vs HAI)	171	**6%**	4.5 mo PFS, 14.6 mo OS
Sacco, 2013	Sunitinib vs DTIC	74	**4%**	2.8 mo PFS, 6.4 mo OS

Courtesy of Rich Carvajal and Alex Shoushtari, MSKCC

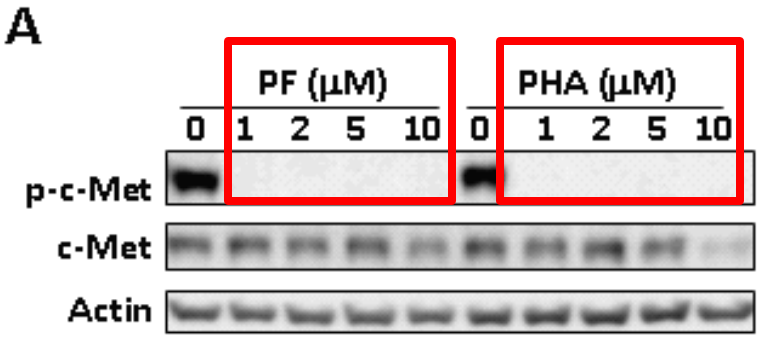
MET in Ocular Melanoma

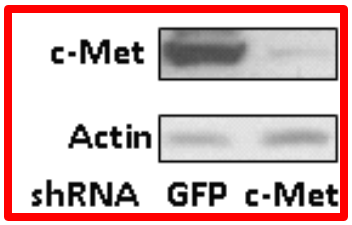


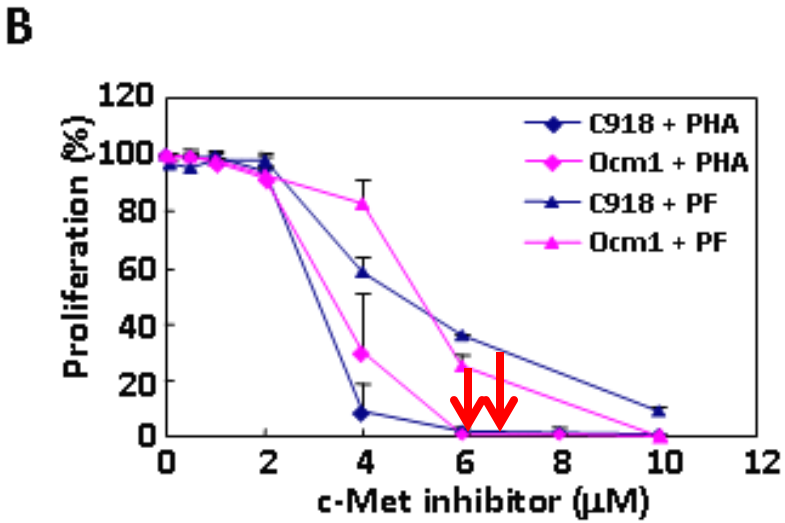


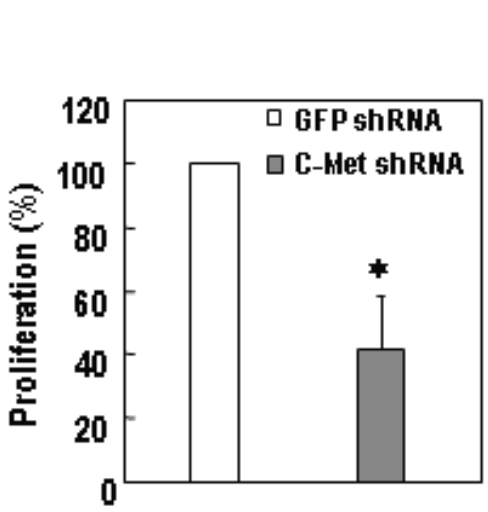
Appleman, JCO 2011
Wu et al, Melanoma Res 2012

MET Inhibition Blocks Proliferation in OM







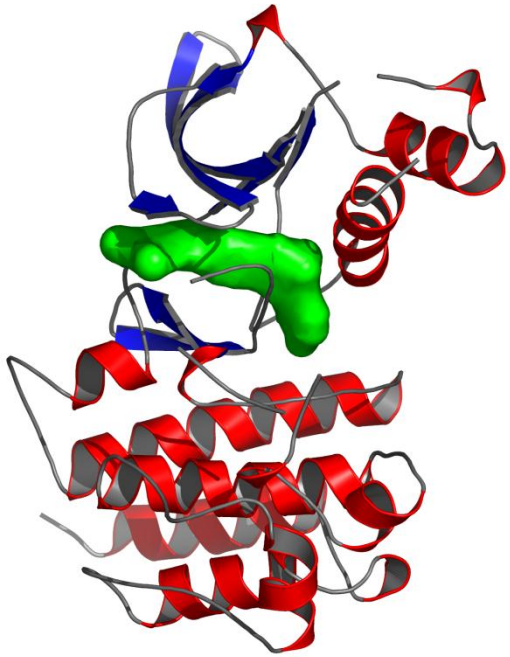


Wu *et al*, Melanoma Res 2012

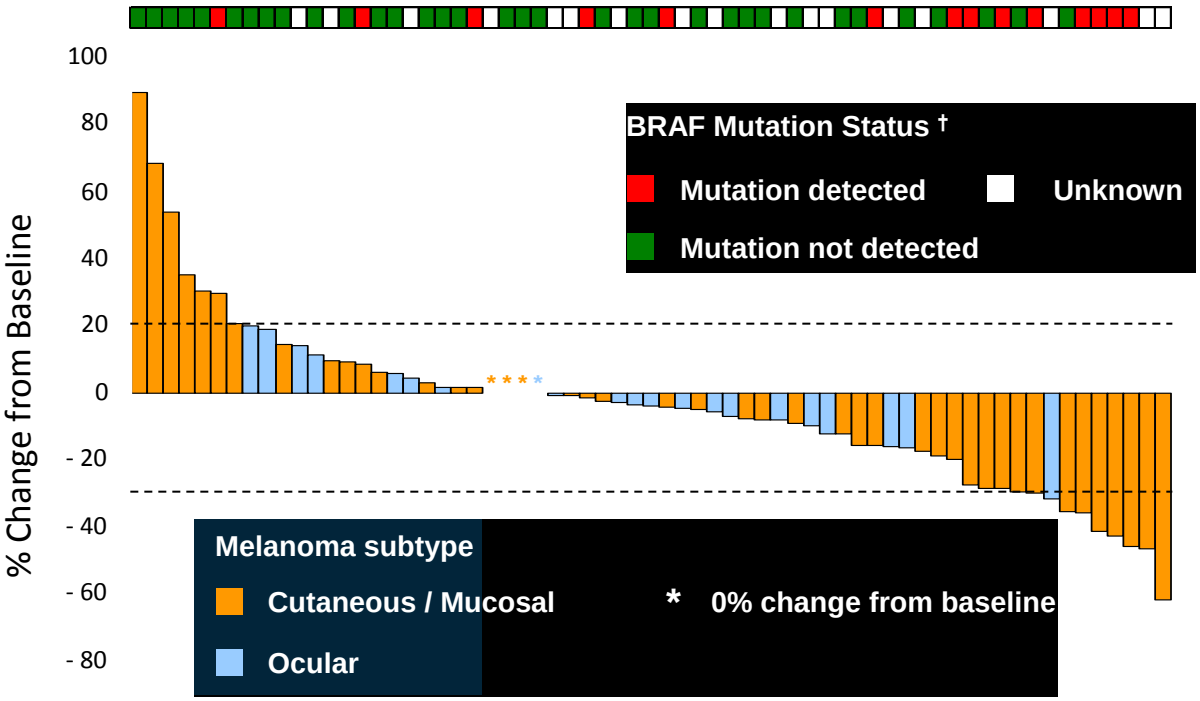
Cabozantinib (XL184) Target Profile

Kinase	IC_{50} (nM)
MET	1.8
VEGFR2	0.035
RET	5.2
KIT	4.6
AXL	7.0
TIE2	14
FLT3	14
S/T Ks (47)	>200

RTK	Cellular IC_{50} (nM) Autophosphorylation
MET	8
VEGFR2	4

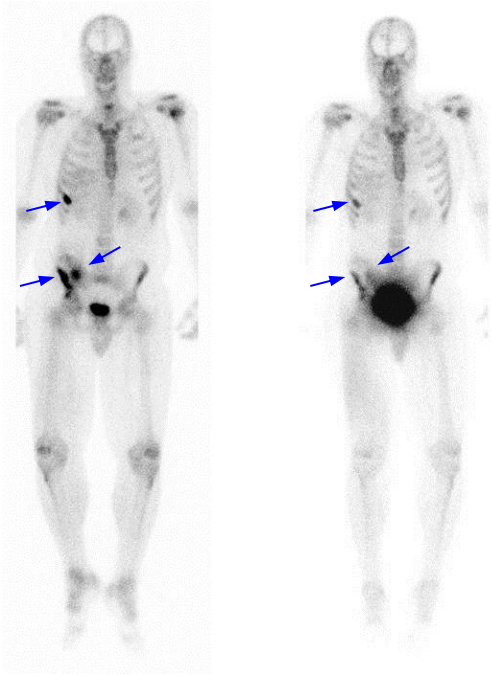


ATP competitive, reversible



Pt with OM and Symptomatic Bone Metastases Treated at DFCI

Baseline Bone Scan	Follow-up Bone Scan



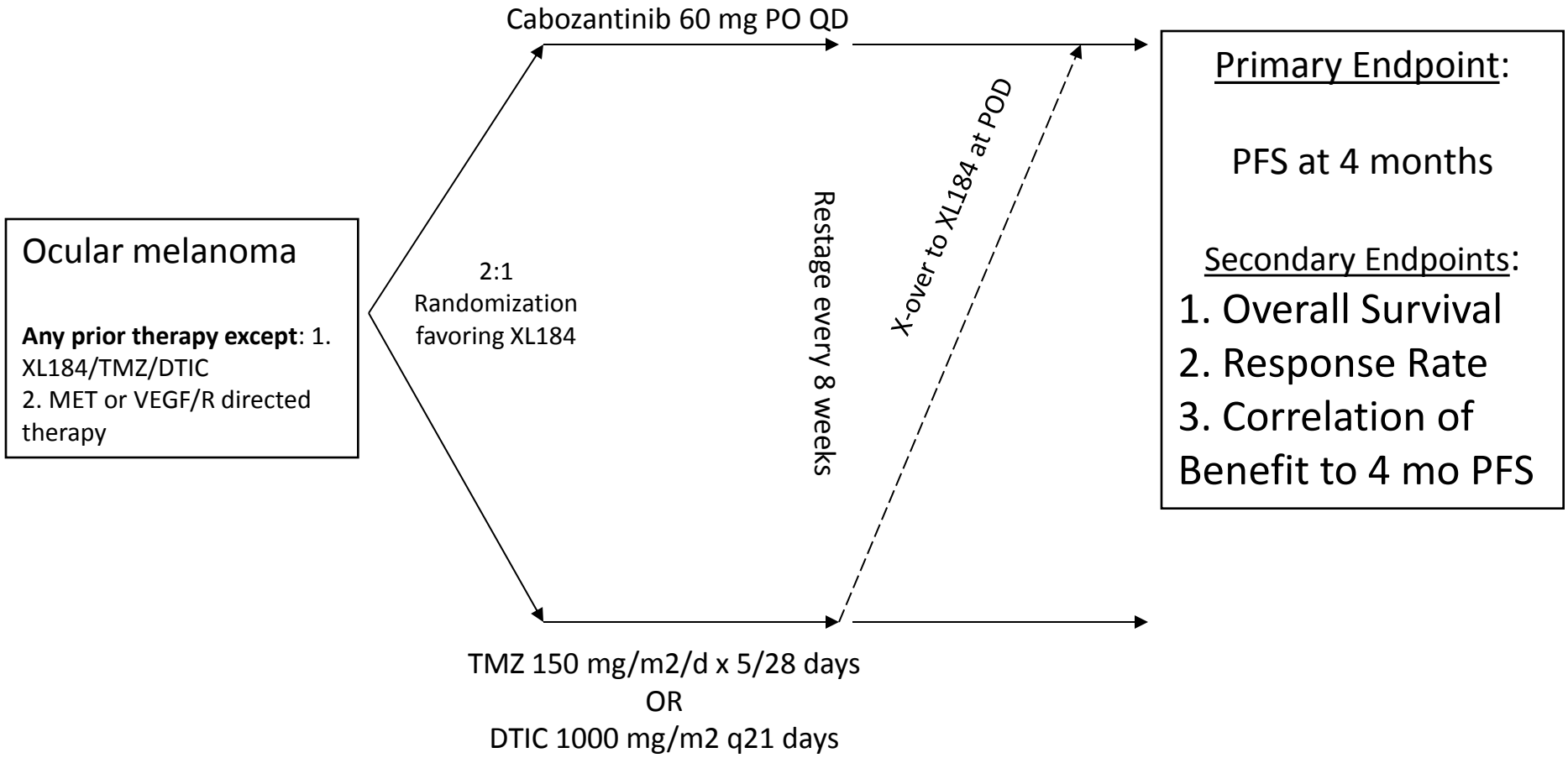
- Objective tumor shrinkage observed in 39/65 (60%) of patients
- 2/2 patients experienced partial resolution on bone scans‡

Patient experienced pain relief

(Stayed on drug 53 weeks with RECIST stable disease)

Courtesy of Geoff Shapiro, MD, PhD

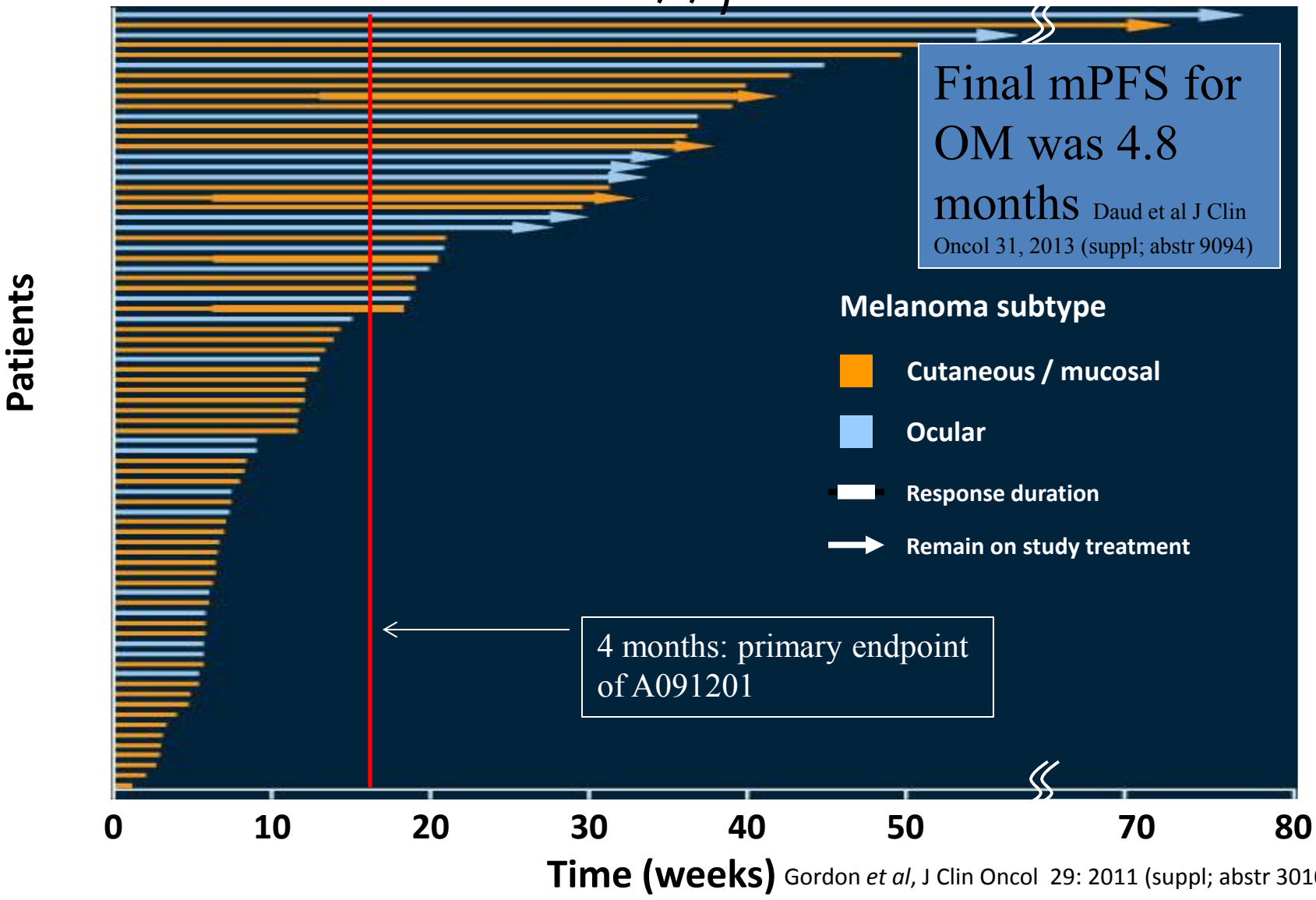
Adapted from Gordon *et al*, J Clin Oncol 29: 2011 (suppl; abstr 3010) 2011



NCI 9287 and Alliance A091201

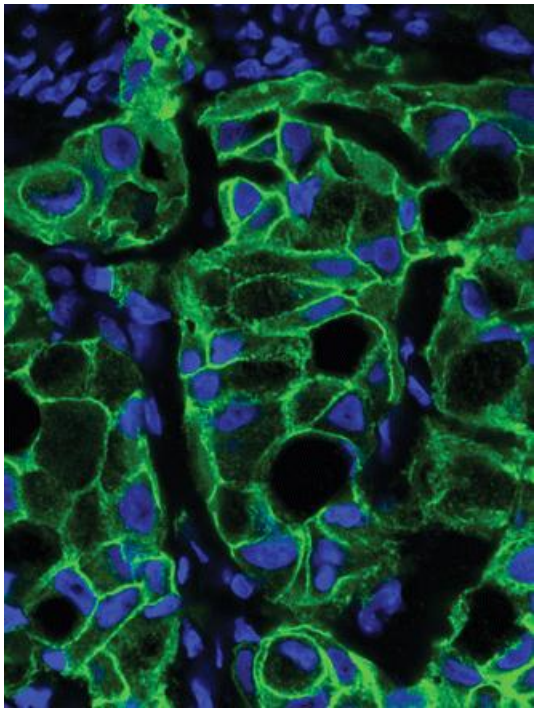
Principal investigator and National Study Chair: Jason Luke, MD

Melanoma Cohort from XL184-203: Time on Study (N = 77)



Gordon *et al*, J Clin Oncol 29: 2011 (suppl; abstr 3010) 2011

MET analysis



Yu *et al*, Clin Can Res 2009

- Pre-treatment tissue on all patients
  - total MET
  - phospho-MET
  - HGF
- DFCI Center for Molecular Oncologic Pathology
  - Massimo Loda, MD, PhD
- Correlate IHC with 4 mo PFS

Trial Status Update

- Number of open sites:
  - 31 PI's at 96 hospitals
- Several larger sites just opened the study:
  - Mayo, Ohio State, Duke, Miami
- Accrual 7/63

Accrual and Sites To Date

Obs	EXTREFID	ARM	DATE_ON	RND_LOC
1	ex177030	1	09/18/2013	Trinity Med.
2	ex177427	1	10/22/2013	Dana-Farber/Partners site
3	ex177476	2	10/28/2013	Froedtert WI
4	ex178622	2	01/09/2014	PrvdncPrtlndMed
5	ex178885	2	01/24/2014	Mercy MO043
6	ex178975	1	01/31/2014	Froedtert WI
7	ex181456	1	04/18/2014	Duke

Related AE summary

- DTIC / TMZ AEs all as expected
  - Decrease blood counts, fatigue
- Cabozantinib expected:
  - HTN, fatigue
- Cabozantinib unexpected:
  - Anaphylaxis

Next Steps

- Highlighted the trial at CURE OM scientific meeting 5/1/14
  - Working with CURE OM to increase awareness
- Engaging ECOG and SWOG
  - ECOG: Tara Gangadhar, MD – Penn
  - SWOG: Sapna Patel, MD - MDACC

A091105 A Phase III, Double Blind, Randomized, Placebo-Controlled Trial of Sorafenib in Desmoid Tumors or Aggressive Fibromatosis (DT/DF)

Study Chair: Mrinal Gounder
Alliance Protocol Chair: Elise Horvath

UPDATE(s):

Study currently activated on March 21, 2014

Available to all sites on CTSU

19 sites have IRB approval on 4/24.

MSKCC approved by IRB. Budget pending.

No patients have accrued at this time.

Study Chair has reached out to individual PIs to discuss study design.

Will reassess accrual and intervention in 3 months.

- Status update on current trials in development

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Proposed Randomized Phase II study in RAI-refractory Hurthle Cell Thyroid Cancer: Sorafenib vs Sorafenib/Everolimus

Eric Sherman, MD

Memorial Sloan-Kettering Cancer Center

Hurthle Cell Thyroid Cancer

- 3-10% of differentiated thyroid cancer
- More aggressive than other DTC
  - 5-year mortality 8%
  - 5-year mortality 65% if distant mets present
- Genomic data suggest Hurthle Cell different than Follicular/Papillary thyroid cancers
  - Common mutations seen in Papillary and Follicular cancers not seen in Hurthle Cell
  - Gene amplification for activation of PI3K-AkT-mTOR pathway

Ganly, I., et al. (2013). J Clin Endocrinol Metab.

Sorafenib

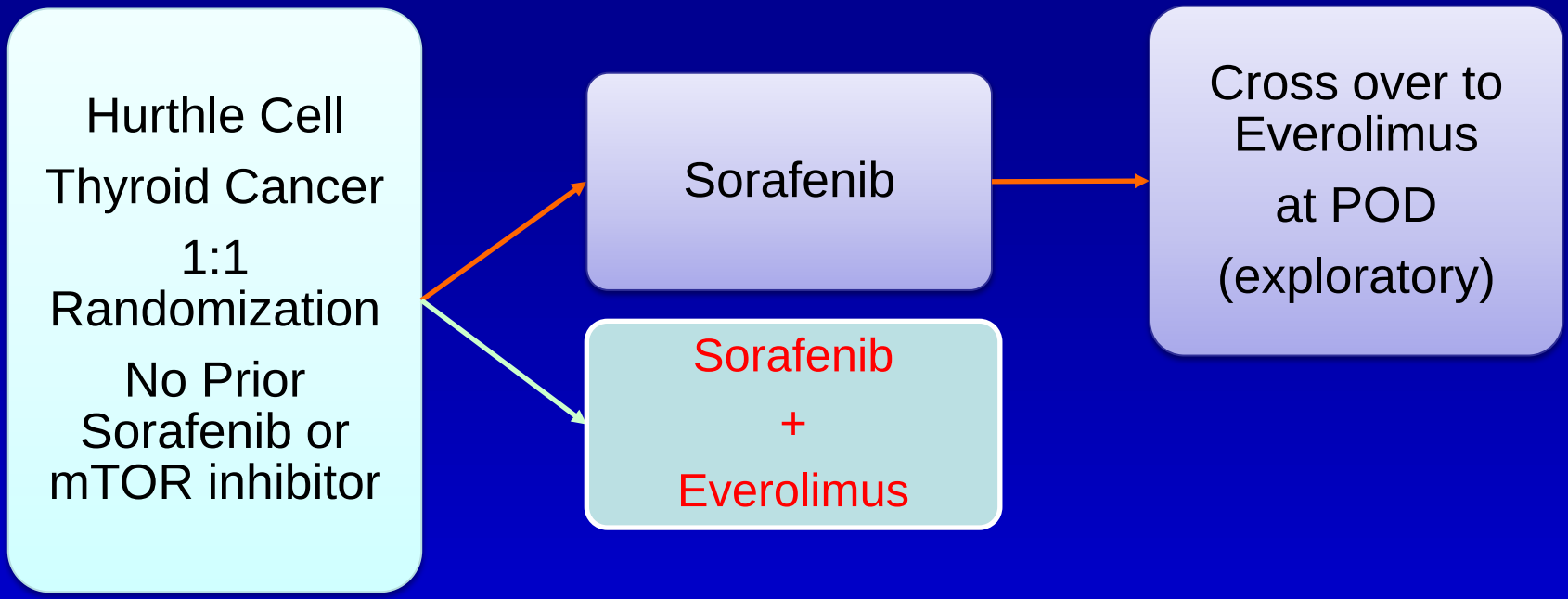
- Kinase Inhibitor
  - Target VEGF-R 1 to 3, PDGF receptor, RET
  - RAF inhibitor
- Several phase II studies have been completed with single agent sorafenib
- Phase III study (vs Placebo) recently completed
  - FDA-approved, but response rates overall are low
- Due to the data with sorafenib, MSKCC recently completed a phase II study in DTC with the combination of sorafenib and everolimus, an mTOR inhibitor

Response Rates

	Ohio State Study – Sorafenib Alone			Sorafenib + Everolimus
	PTC, chemo-naïve (33 pts)	PTC, prior chemo (n=8)	HTC/FTC (n=11)	Hurthle Cell (n=9)
Partial Response	5 (15%)	1 (13%)	**0**	**7 (78%)**
Stable Disease	19 (57%)	6 (75%)	**9 (82%)**	**2 (22%)**
Progressive Disease	4 (12%)	1 (12%)	**1 (9%)**	**0 (0%)**
PFS, median, months	16	10	**4.5**	**17.3* (2.5-26.4)**
OS, median, month	23	37.5	**24.2**	

* 5 patients are still on active treatment

Hurthle Cell Proposal



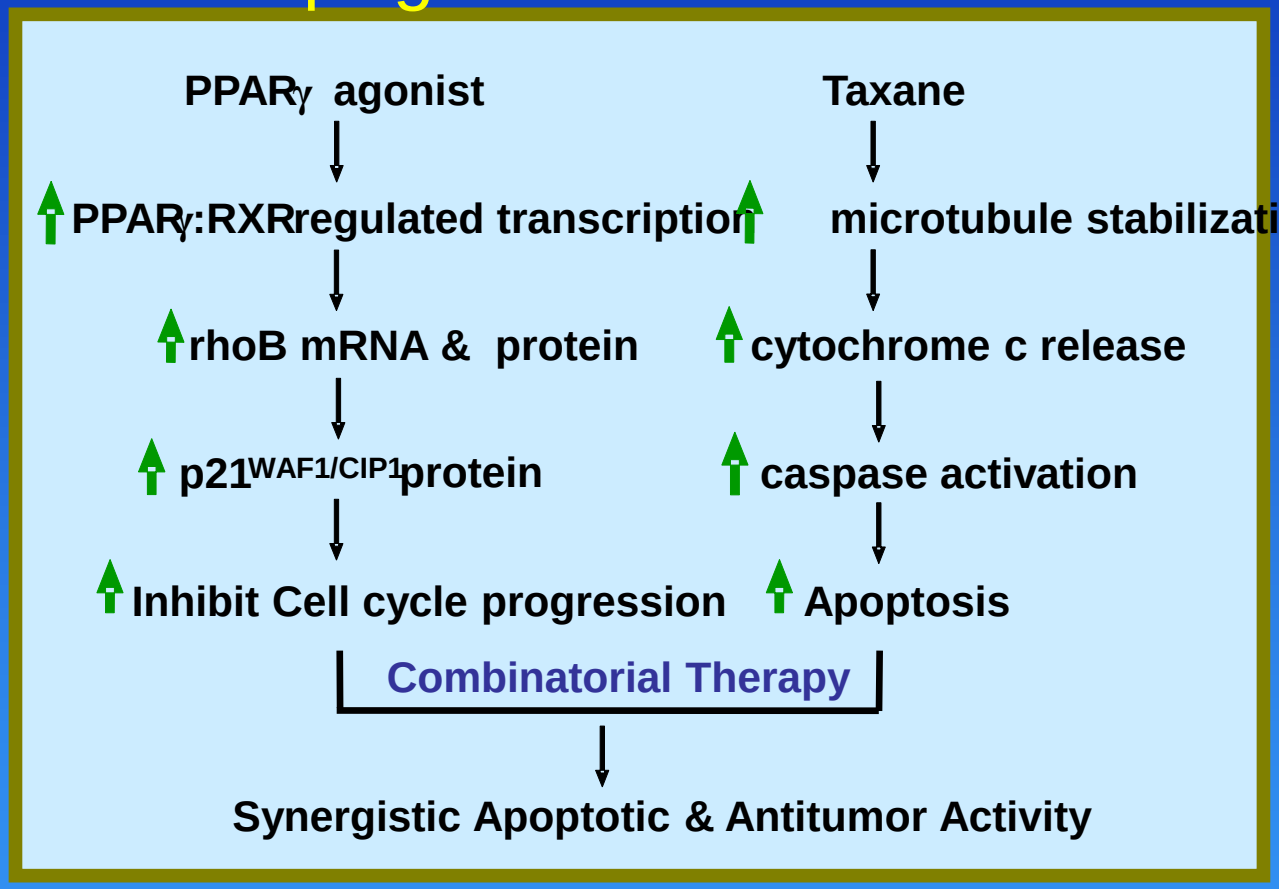
Total Number: 56 Patients (28 in each arm)
Objective: Increase in median PFS 4.5 to 9 months with addition of Everolimus to Sorafenib compared to Sorafenib alone
Power 80%; p=0.05 (1-sided)

Secondary Endpoints:
Response Rate, Overall Survival, Adverse Events

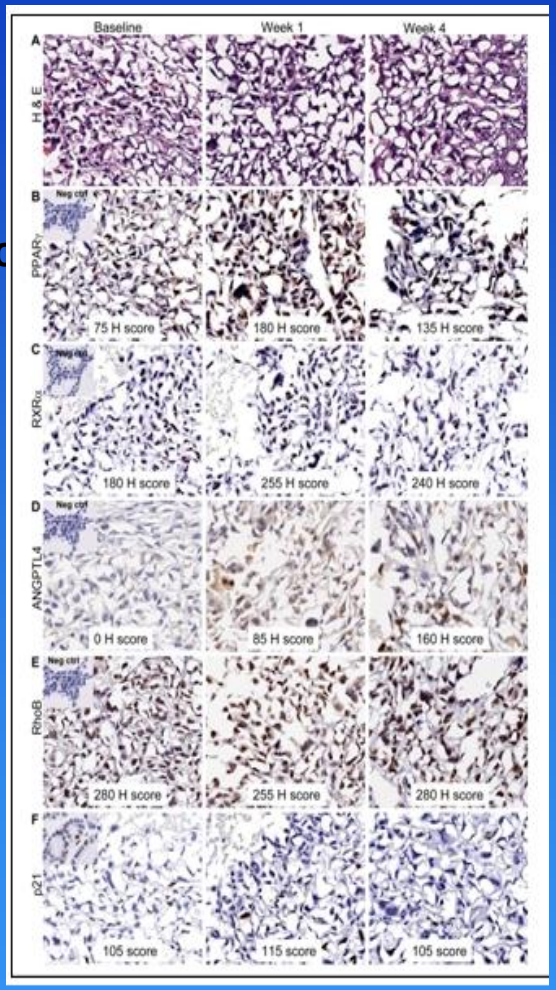
A Phase 2 Randomized Study of Efatutazone, an Oral PPAR-gamma Agonist, in Combination with Paclitaxel versus Paclitaxel Alone in Patients with Advanced Anaplastic Thyroid Cancer

Robert C. Smallridge, MD (Study Co-Chair)
Michael Menefee, MD (Study Co-Chair)
Balkrishna Jahagirdar, MD (Community Oncology Co-Chair
John A. Copland, PhD (Correlative Study Co-Chair)
Nate Foster (Study Statistician)
Mayo Clinic

Synergistic antitumor activity of PPARγ agonist and taxane



Tissue Angiopoeitin-like



Copland JA et al. Oncogene 2006; 25:2304
Marlow LA. Cancer Res 2009; 69:1536

mayo

Phase 1: Efatutazone & Paclitaxel
(Smallridge RC et al, J Clin Endocrinol Metab 2013; 98:2392)

Hypotheses: At least one dose level of the combination efatutazone & paclitaxel would be safe and well tolerated

Objectives: Determine safety, tolerability, recommended phase 2 dose, pharmacokinetics, biomarkers

Design: Phase 1, open label, multicenter

Adverse Events: Any AE (14); Any ≥ grade 3 AE (10)

No dose limiting toxicities (DLTs)

Durable RECIST partial response in one IVC patient

Study Design (1)

Primary Objective:

Determine if combination of paclitaxel and efatutazone increases overall survival compared to paclitaxel alone.

Secondary Objectives:

Determine confirmed response rate and duration

Determine progression-free survival

Evaluate the safety profile

Exploratory

Evaluate biomarker changes relative to response

Study Design (2)

Treatments

Efatutazone (0.5 mg) po q 12h [↓ to 0.3 mg if needed]

Paclitaxel (175 mg/m^2) – 3 hrs iv, q 3 wks

Endpoints

Efficacy; Biomarkers; Serum – adiponectin

Tissue – PPARγ, RXRα, RhoB, p21, ANGPTL-4

Design

Phase 2 randomized study 23 patients per arm; interim futility analysis after 21 events observed

mayo

Study Benefits

Pre-clinical science developed by Dr. Copland (Co-I)

Phase 1 multicenter trial designed by Dr. Smallridge (Co-PI)

Supports NCI R01 (Drs. Copland and Smallridge, Co-PIs)

Supports career development of Dr. Menefee (Co-PI)

Supports NCI mandate to study rare tumors

mayo

Protocol Update

Final approval from CTEP is pending. All comments have been addressed.

Case Report Forms have been finalized.

Study should be ready for activation soon.

A Phase II Randomized Study of the Peroxisome Proliferator-Activated Receptor Gamma Agonist, CS-7017 (Efatutazone) vs. Placebo in Patients with Previously Treated, Unresectable Myxoid Liposarcoma

Study Chair: **Michael Pishvaian, MD, PhD**
Lombardi Comprehensive Cancer Center,
Georgetown University

Study Co-Chairs: **Dennis Priebat, MD, PhD – community oncology co-chair**
Medstar Washington Hospital Center
Priscilla Furth, MD – correlative science co-chair
Lombardi Comprehensive Cancer Center,
Georgetown University
Christopher D.M. Fletcher MD FRCPath – study pathologist
Brigham & Women's Hospital

Study Statistician: **Nathan Foster, MS**
Mayo Clinic

Summary of Phase II Trial

- Advanced, unresectable MLS
- 2nd line (and beyond) therapy
- Disease progression
- PS 0-2
- Normal hepatorenal function

- Randomized
- Placebo controlled

Monitoring and Evaluation
- Fluid retention – reflexive use of diuretics
- Triglycerides and cholesterol
- CT q 6 weeks to asses for rapid progression
- Q3 month CTs after 6 months

R a n d o m i z e

CS-7017 0.5mg PO BID
21 day cycles

Biopsies Pre-Tx and C2, D1

MLS with confirmed t(12;16)(q13;p11) translocation = 20% of LPS patients
34 evaluable patients total (17 CS-7017, 17 placebo)
Power=80%, alpha=15% to detect an improvement from 3 to 6 months HR=0.5
Interim analysis after 15 events (est 21 patients) - HR ≥ 1.0658 for CS-7017/placebo
Accrual = 1 patient/month

Biopsies Upon Progression and C2, D1 of CS-7017

Placebo Tablet PO BID
21 day cycles

Crossover

CS-7017 0.5mg PO BID
21 day cycles

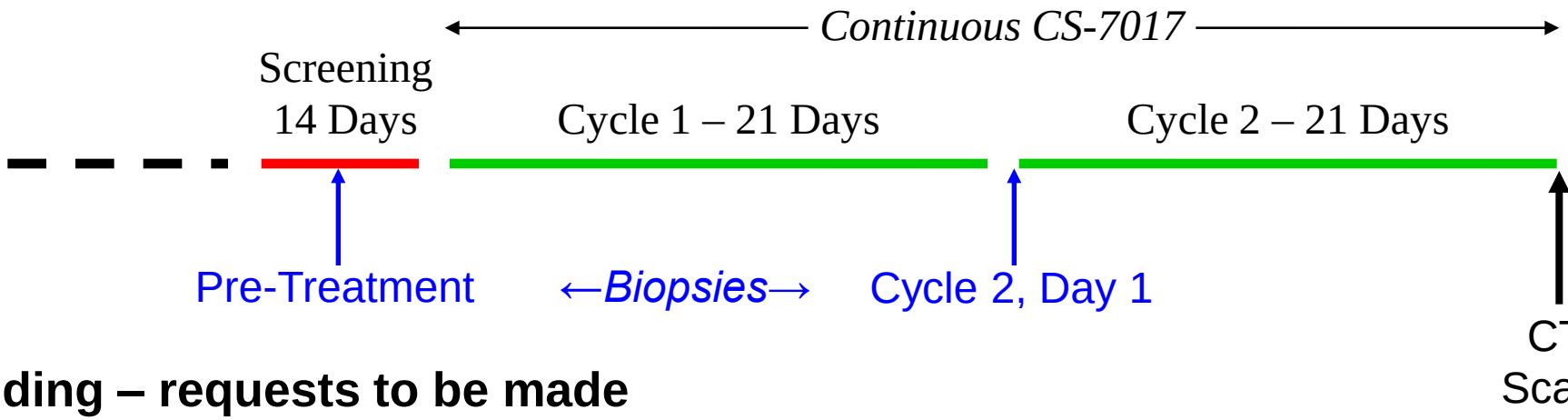
Endpoints and Statistics
- 1^0 endpoint progression free survival
  - CS-7017 vs. placebo
- Hypothesized PFS ≥ 6 months
  - Historical comparison < 3 months
- 2^0 endpoints
  - Response rate
  - Overall survival
  - Adverse events

Feasibility
- 36 patients total, anticipated accrual = 36 months
  - 5% dropout
- 100 advanced unresectable MLS/year in the US
- Necessity of cooperative group setting
- Expected accrual rate = 1 patient/month
- Translocation assessment – commercially available and appropriate standard of care
- Serial tumor biopsies before and after treatment
  - Daiichi-Sankyo to support

Scientific Correlates - PPARγ Function

PPARγ affects:

- Cell cycle
  - Upregulation of cyclin-dependent kinase inhibitors ($p16^{INK4,}$ $p18^{INK4c}$, $p21^{CIP1,}$ $p27^{KIP1)}$
  - Reduced expression of Cyclin D1, c-myc, CDK4, CDK3, Cyclin E, PhosphoRb
- Induction of differentiation
  - aP2, Adiponectin, Adipsin, Snail
- Predictive markers of response
  - PPARγ and RXR tumor expression



Funding – requests to be made

- Daiichi-Sankyo
- NIH funding

Grommes, et al, Lancet Oncol 2004; 5: 419–29; Theocharis, et al, Can Treat Rev 2004; 545–554; Kohno, et al, BMC Cancer 2005; 5:46; Kopelovich, et al, Mol Can Ther 2002; 1:357–363; Kersten, et al, Nature 2000; 421-424; Demetri, et al, PNAS, USA 1999; 96:3951-3956

Trial Updates 05-09-2014

- Final draft reviewed by CTEP
  - Final version to be submitted very soon
  - Anticipate final approval in weeks
  - Activation in summer, 2014
- No funding for serial biopsies
  - Per discussion with CTEP – serial biopsies removed
  - Correlative science of predictive markers (only) on archived specimens
  - Added Dr. Fletcher for central path review and confirmation of FUS-DDIT3 translocation
- NIH R01 submitted, 02-2014
  - To support correlative science

- Status of concepts

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Randomized Phase 2 Study of Chemotherapy versus Androgen Ablation in Salivary Gland Cancer (EORTC 1206)

Alan L. Ho MD, PhD
Memorial Sloan Kettering Cancer Center
Head/Neck Medical Oncology Service

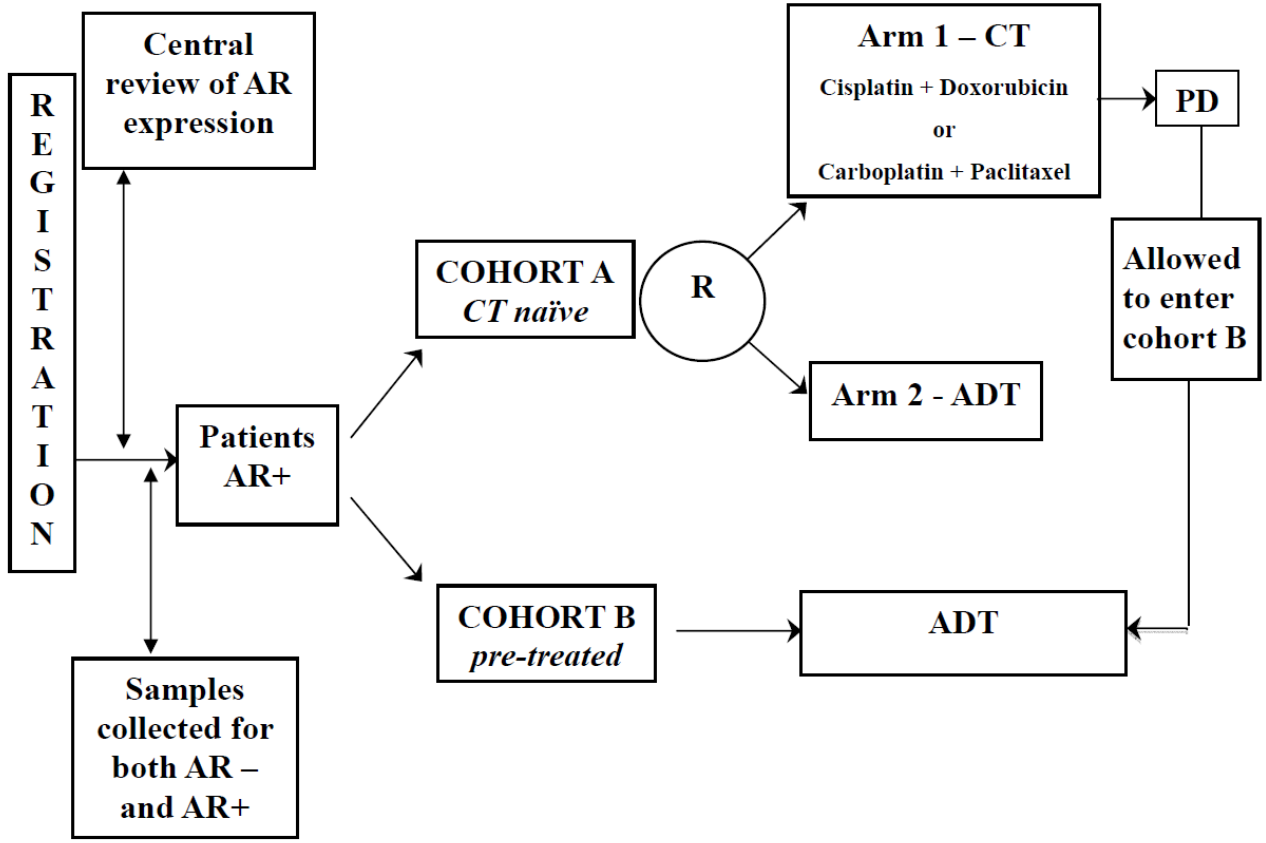
International Clinical Trials in Rare Cancers Initiative

Head/Neck rare tumor focus: Salivary Malignancies

Chairs: Kevin Harrington MD (ICR, UK)
Lisa Licitra MD (Istituto Nazionale dei Tumori, Milan, Italy)
Alan L. Ho MD, PhD (Memorial Sloan-Kettering Cancer Center, USA)

Goal: Develop a biology/target-driven international clinical trial concept for a salivary malignancy

Study Design



AR= androgen receptor, CT = chemotherapy, R= randomization, ADT=Androgen Deprivation Therapy, PD = Progressive disease.

COHORT A

Primary endpoint: Progression-free survival at 6 months

Secondary endpoints: Response rate, overall survival, toxicity, bone lesion assesment according to Prostate Cancer Clinical Trials Working Group 2 recommendations

COHORT B

Primary endpoint: Best overall response

Protocol Development Update/To Do List

- CTEP Head and Neck Steering Committee review (including Rare Tumors Task Force).
- BIQSFP application for funding to conduct AR integral marker testing has been submitted.
- Drug supply issues, awaiting Activas approval to provide triptorelin in the EU.

A Randomized Phase II Study of MLN-0128 vs. Pazopanib in Patients with Locally Advanced (Unresectable) and /or Metastatic Sarcoma

William D. Tap

Chief, Sarcoma Medical Oncology Service

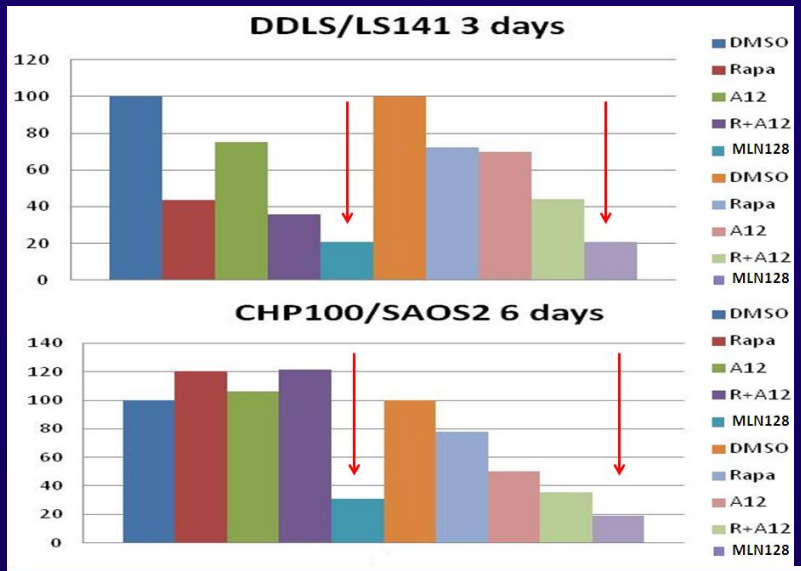
Memorial Sloan Kettering Cancer Center

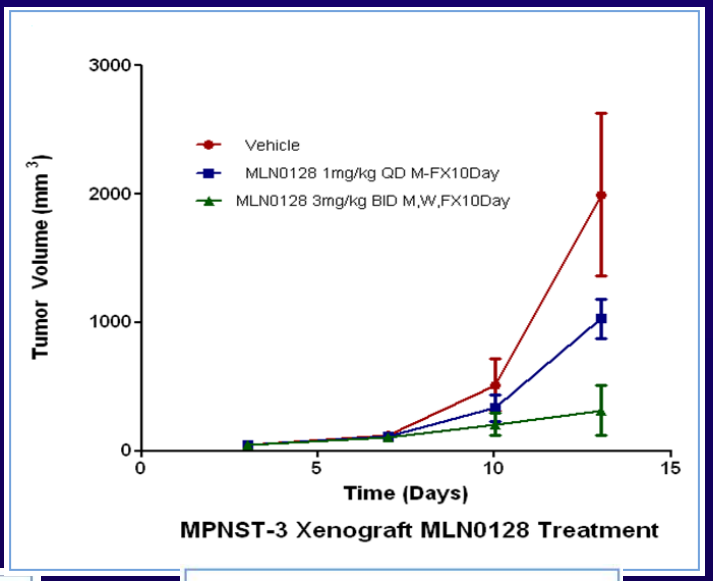
Alliance for Clinical Trials in Oncology May 2014 Committee Meetings

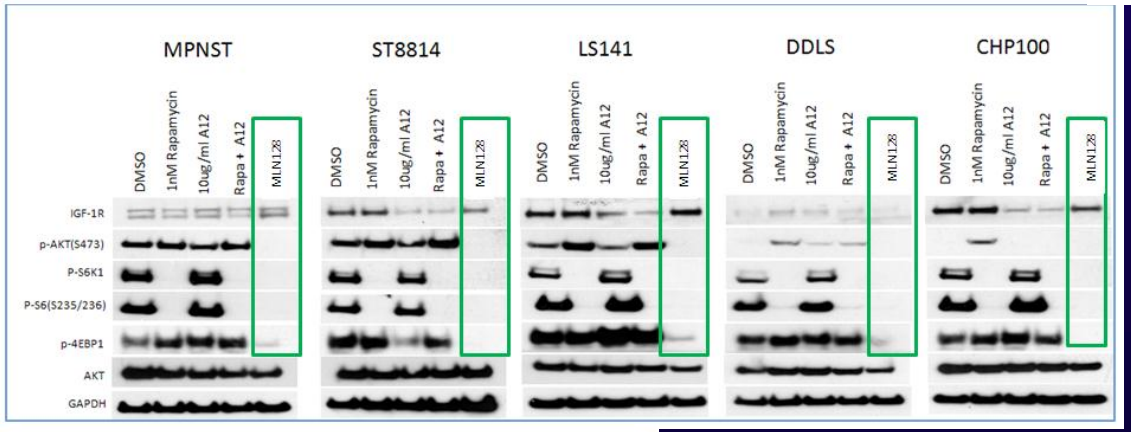
PAN-mTOR INHIBITORS

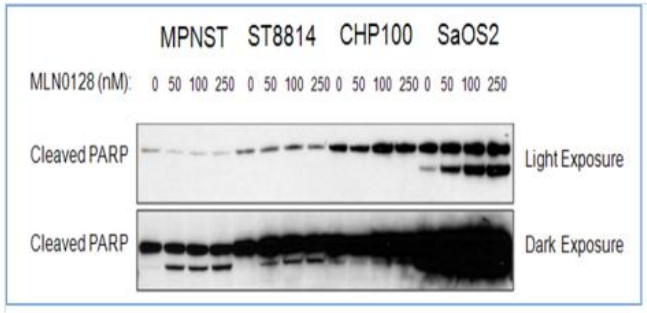
- MLN-128 is a selective and highly potent ATP competitor/inhibitor of both mTORC1 and mTORC2
  - target the PI3K/AKT/mTOR pathway while suppressing de novo and secondary resistance (AKT activation)
  - potential of providing complete and sustained pathway inhibition
  - target PI3K/AKT/mTOR signaling at a single critical point
    - decreases likelihood of aberrant input from the numerous effectors involved in this complex pathway.

MLN-128 Pre-Clinical Investigations





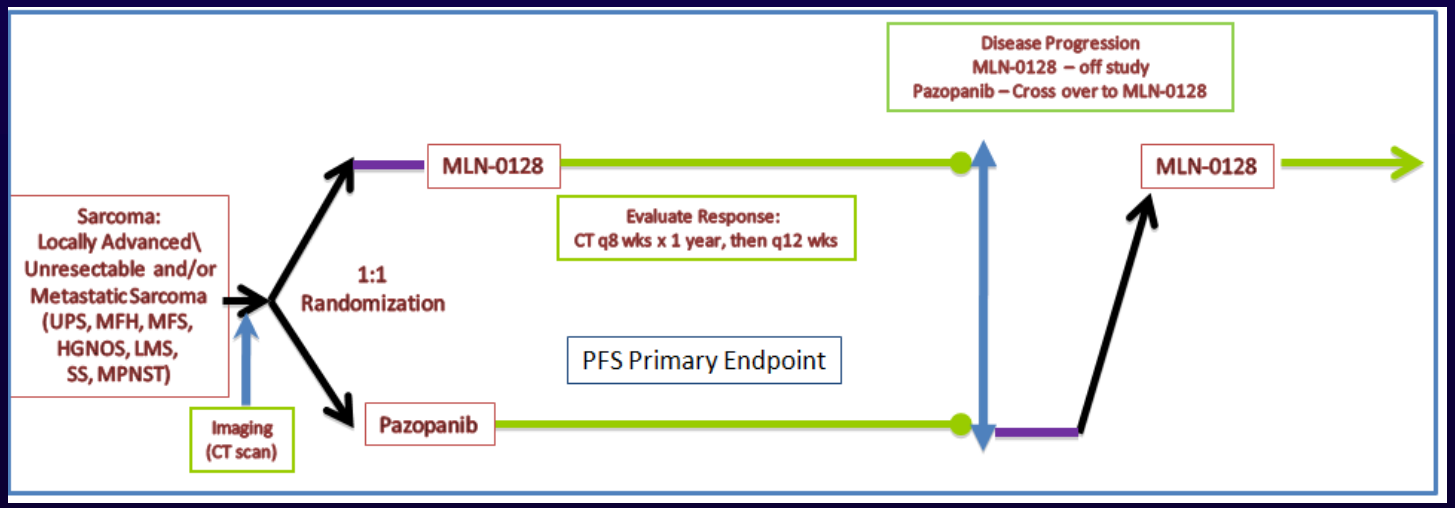




Schwartz, Tap unpub data

Study Overview

- Preclinical data reveal broad range of activity in the various sarcoma subtypes.
- Open label randomized phase II study of MLN-0128 vs. pazopanib for patients with Undifferentiated Pleomorphic Sarcoma (UPS/MFH), Leiomyosarcoma, MPNST, Synovial Sarcoma.
- Age 18 or older; Randomized 1:1 fashion
  - Stratified by number priors and sarcoma subtype
    - UPS/MFH v. LMS v. Other (MPNST/Synovial Sarcoma)
  - Cross over to MLN-0128 upon disease progression on pazopanib



Trial Objectives + Statistics

- Primary Objective: Differences in Progression Free Survival in patients with advanced sarcoma who receive MLN-0128 as compared to pazopanib.
  - Secondary Objective: Evaluate adverse events; Overall Response Rate; Clinical Benefit Rate; Duration of Response; Time to Progression and Overall Survival
  - Exploratory objective(s): Evaluate PFS and secondary endpoints within patients crossing over to MLN-0128, upon disease progression during treatment with pazopanib; Evaluate the 4 month CBR observed within patients treated with MLN-0128 and grouped by histologically defined Cohorts.

- Median PFS of 7 months MLN-0128 will be considered promising, relative to 4.6 months for pazopanib (HR 0.66; one-sided statistical test overall alpha of 0.15.)
  - Planned accrual 98 patients
  - Futility interim analysis

Thank You

tapw@mskcc.org

Phase Ib/II Study of anti PD-1 Antibody MK-3475 In Combination With Ziv-aflibercept For The Treatment Of Metastatic Melanoma

Study Chair: Arkadiusz Z. Dudek, MD,PhD

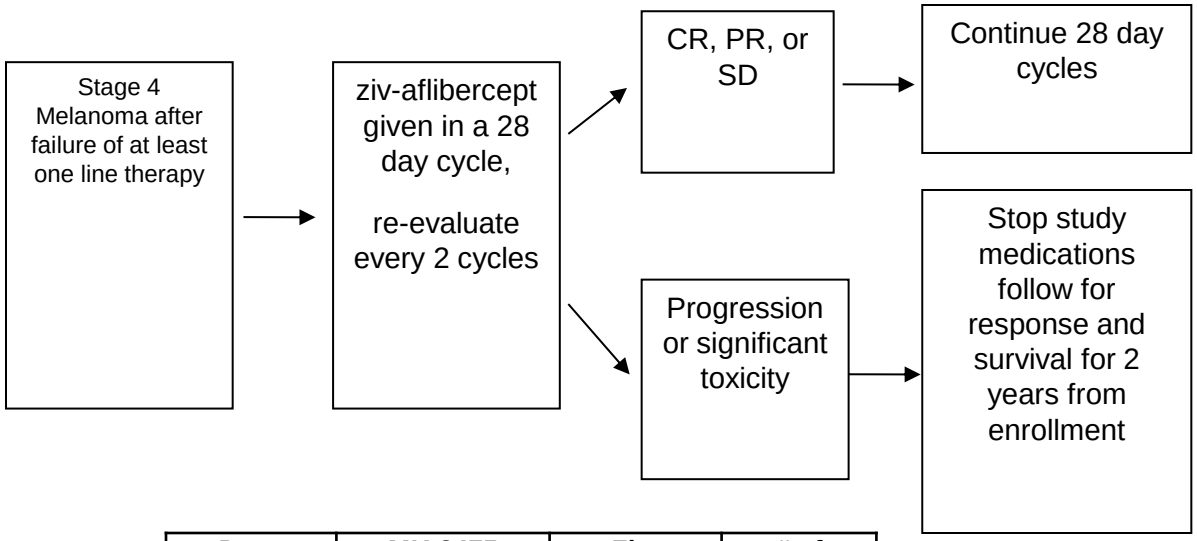
Study Statistician: Jacob Allred, MS

Background

- Study is in response to CTEP solicitation for MK-3475.
- An interaction between immune responses and tumor angiogenesis was recognized in recent years.
- VEGF is known to suppress the maturation of immune cells and their antitumor responses, and evidence points toward an association between high serum VEGF levels and poor prognosis in melanoma patients
- Among patients with advanced melanoma, presence of higher levels of the protein vascular endothelial growth factor (VEGF) in blood was associated with poor response to treatment with ipilimumab.
- We hypothesize that by using anti-PD1 agent (MK-3475) with anti VEGF (Ziv-aflibercept) strategy we will be able to increase immune infiltration of metastatic melanoma tumors and enhance clinical activity of anti-PD1 strategy.

Study Schema Phase 1

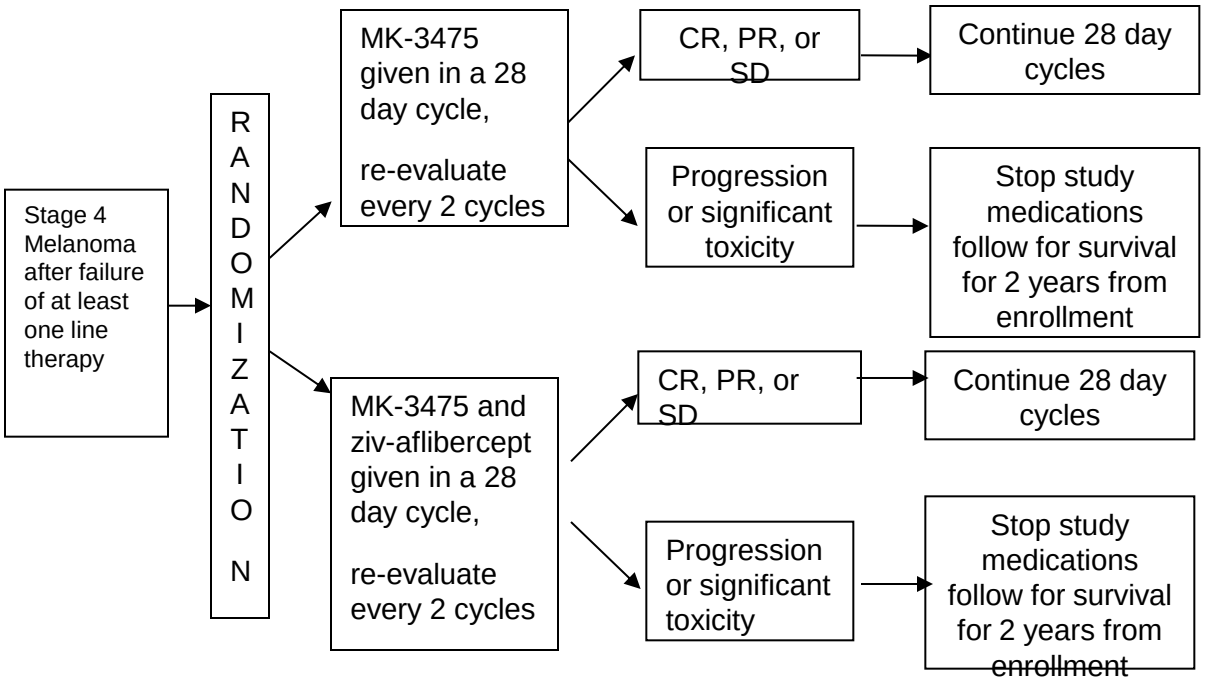
- Phase 1b Dose Escalation and Confirmation (University of Illinois at Chicago and selected Alliance Centers):
- MK-3475 at assigned dose* IV given on Day 1 and 15,
- Ziv-aflibercept at assigned dose* IV given on Day 1 and 15.



Dose Cohort	MK-3475 (mg/kg)	Ziv-aflibercept (mg/kg)	# of Patients
-1	1	4	3-6
1	3	4	3-6
2	10	4	3-6
3	10	6	3-6

Study Schema Randomized Phase 2

- **Arm A; MK-3475** 10* mg/m^2 IV given over 30 minutes given on Day 1 and 15,
- **Arm B; MK-3475** 10* mg/m^2 IV given over 30 minutes given on Day 1 and 15,
- **Ziv-aflibercept** 6 mg/kg* given over 60 minutes given on Day 1 and 15.
- *if the dosing confirmation indicates a lower dose of one or both drugs should be used during phase II, the study will be revised to reflect this prior to affiliate enrollment



Statistical Consideration

- Phase I: A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease or disease progression that occurs within the first cycle of treatment. Toxicities and lab values will be graded according to the NCI Common Toxicity Criteria for Adverse Events (v4.0).
- Dose escalation will occur using a standard '3+3' dose escalation approach, beginning in dose level 1, with standard rules for escalation. The tolerability assessment will be based on cycle 1 alone. The maximum tolerated dose (MTD) is defined as the highest dose level at which 0 or 1 of six patients has experienced a DLT.

Statistical Consideration

- Phase II: The primary endpoint for the phase II portion is Confirmed Response Rate (CRR). A patient will be classified as a confirmed responder if they have a partial or complete response for 2 consecutive evaluations at least 4 weeks apart. The proportion of patients with a confirmed response will be calculated and compared between the 2 arms using a 1-sided Chi-square test to determine if the combination arm is superior to the MK-3475 alone arm.
- Prior studies have shown that single arm MK-3475 produced RR of 52% (52%; 95% CI, 38 to 66)[3]. It is hoped that the combination arm of MK-3475 and aflibercept will improve CRR by 50% to 77%.

Analysis Plan

- Phase II primary endpoint: To evaluate CRR of MK-3475 and ziv-aflibercept compared to MK-3475 alone, 34 evaluable patients will be enrolled in each arm using a 1:1 randomization scheme (68 evaluable patients total). If the p-value for a 1-sided Chi-square test is less than 0.2000, then the null hypothesis will be rejected in support of evidence that the combination arm is superior to the MD-3475 alone arm in terms of overall RR. This analysis will occur after all patients' response classification can be ascertained.
- The accrual time of the phase II portion is expected to be approximately 9 months based on an estimated 8 patients per month accrual rate. All patients who meet the eligibility criteria, sign the consent form, and are randomized will be considered evaluable for this endpoint.

Correlative Studies

To evaluate imaging correlate biomarkers in regards to tumor response by:

- FDG-PET to evaluate metabolic response

To evaluate correlate biomarkers in regards to tumor response evaluated by imaging:

- PD-L1 expression by tumor at baseline “M” and at 3 months “O”.
- Tumor Vascular Density at baseline “M” and at 3 months “O”.
- CD4(+) and CD8(+) T-cell tumor infiltration at baseline “M” and at 3 months“O”..
- Regulatory T-cells number (Treg: defined as CD4+CD25+CD127lowFoxP3+)“M”.
- Cytotoxic T cell (CTL) assays will be at the following time intervals: at baseline, day 28, and every 2 months until progression. Specifically, CTL activity will be assessed using tetramers for NY-ESO-1-137-165, MART-126-35, tyrosinase, survivin, gp100 (all HLA-A2 cognant peptides). In cases where we have >1% of tetramer positive CTL, we will stain for intracellular IFNgamma in order to differentiate active versus tolerant CTL. Tetramer activity will be quantified as percent positive IFNgamma positive T cells. Tetramer activity will be compared within each patient at each time point and a 4-fold increase tetramer activity will be considered clinically significant“M”.
- Circulating melanoma cells enumeration“M”.
- PD-L1 expression on circulating melanoma cells in at baseline and during therapy“M”.
- BRAF, NRAS mutation status in at baseline“M”.
- Melanoma specific miR “M”.
- Measurement of soluble PD-1“M”.

Blood will be collected at baseline, day 28, and every 2 months until progression.

A phase II study of nivolumab with or without ipilimumab in patients with metastatic or advanced sarcoma

Study Chair: Sandra P. D'Angelo
Study Statistician: Michelle Mahoney
Committee Chair: Gary K. Schwartz

Sarcoma & Immunotherapy

- 13,000 cases of soft tissue and bone are diagnosed annually in the US.
- Median survival in the metastatic setting is 10-15 months. Billingsley et al. Ann Surg 1999, Van Glabbeke et al. JCO 1999.
- Standard cytotoxic chemotherapy agents have response rates 10-30%. Brennan et al. Management of STS 2012
- Wilhelm Busch observed tumor regressions after postoperative wound infections. Cancer Immunotherapy 2012
- Coley described a dramatic response in a patient with small cell sarcoma after an erysipelas infection. Coley Ann Surg 1891
- Sarcoma is more common in patients that are immunosuppressed. Gatti et al. Cancer 1971
- A tissue microarray from 249 patients with STS evaluated CD3+, CD4+, CD8+ and CD20+ lymphocytes.
  - CD20+ infiltration was found to be an independent positive prognostic factor in patients that underwent surgical resection and had wide resection margins, (HR=5.5, CI 95% 1.6-18.6, p=0.006.) Sorbye et al. PLOS One 2011
- **Manipulating the immune system in sarcoma may prove to be an effective therapeutic intervention.**

Nivolumab and PD-L1 expression

- Programmed death-1 (PD-1) is a member of the CD28 family of T-cell costimulatory receptors that attenuates immune responses by negatively regulating T-cell proliferation and function

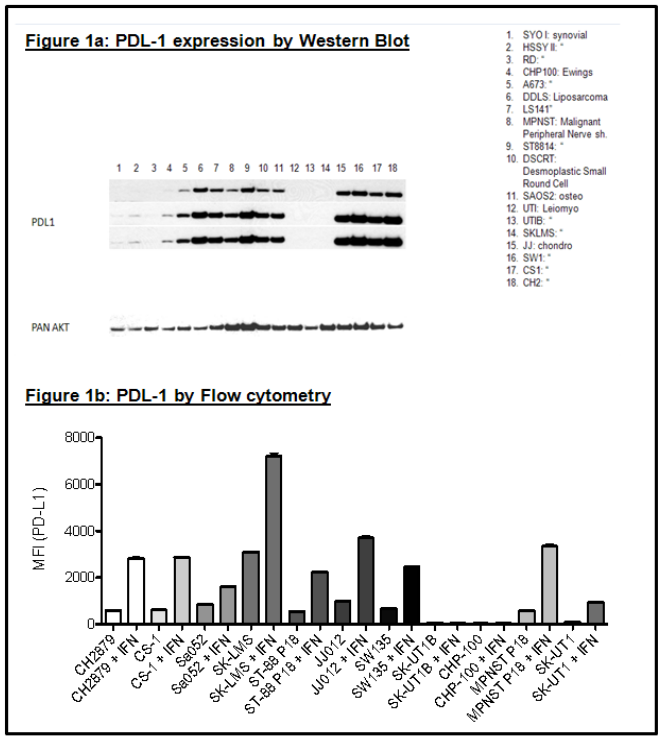
- 296 patients were treated with nivolumab, an antibody to PD-1, response rates were 18%, 28% and 27% in patients with non-small cell lung cancer, melanoma and renal cell carcinoma, respectively.
  Topalian et al. NEJM 2012

- A phase I study of nivolumab and ipilimumab in patients with advanced melanoma demonstrated objective response rates of 40%.
  - Patients that received combination therapy, responses were seen both in patients with PD-L1 expression (6/13) or those without PD-L1 expression (9/22.)
  - For those that received sequential therapy, there appeared to be higher number of responses in those with PD-L1 expression (4/8) versus those without PD-L1 expression (1/13.)

- PD-L1 expression remains a dynamic marker, that can change over time and under different conditions in the microenvironment.
  - Tumor heterogeneity can contribute to varied PD-L1 expression. Merelli et al. Crit Rev Oncol Hematol 2012.
  - PD-L1 expression may change as a result of therapy with checkpoint blockade such as ipilimumab or nivolumab.

- **PD-L1 expression is not an established biomarker predictive of response.**

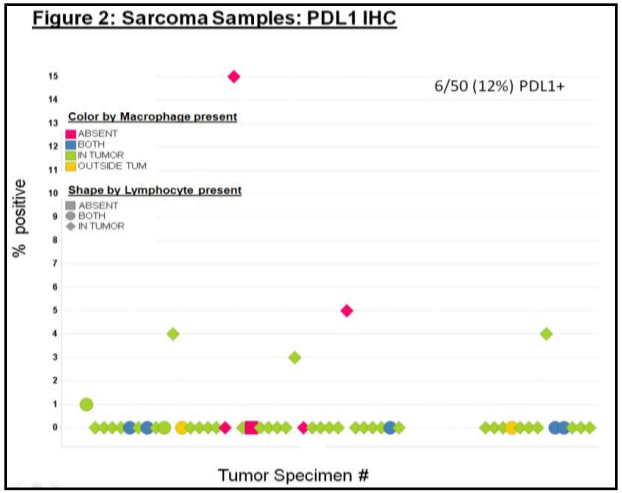
Preliminary data: PD-L1 expression



-Western blot **(Figure 1a)** and by flow cytometry **(Figure 1b)** that is also induced by interferon

- Expression in 65% of the cell lines including synovial sarcoma, Ewing sarcoma, rhabdomyosarcoma, liposarcoma, malignant peripheral nerve sheath tumors, desmoplastic small round cell, osteosarcoma and chondrosarcoma.

Histology	n	% Tumor PD-L1 +	% Lymphocyte PD-L1 +	% Macrophage PD- L1 +
Angiosarcoma	3	0	100	100
GIST	14	27	100	100
Leiomyosarcoma	4	0	0	25
Liposarcoma	5	0	20	60
Synovial Sarcoma	3	0	33	0
Radiation associated pleomorphic sarcoma	1	100	100	100
Other	20	5	10	70
Overall	50	12	30	58



- IHC staining of tumor specimens with a rabbit monoclonal antihuman PD-L1 antibody (clone 28-8)

->1% PDL-1 expression in 6/50 (12%) of samples. **(Figure 2)** As demonstrated in the scatter plot, there was evidence of macrophagic and lymphocytic infiltration both inside and outside of the tumor.

-Tumor, lymphocyte and macrophage PD-L1 expression was noted in 12%, 30% and 58%, respectively.

- Lymphocyte and macrophage infiltration was present in 98% and 90%, respectively.

Endpoints

- **Primary Endpoint**: Clinical Benefit Rate (CBR) of single agent nivolumab (Study Component A), as well as dual agent nivolumab+ipilimumab (Study Components B.1 & B.2).
  - CBR is defined proportion of patients having either achieved a Complete Response, Partial Response, or Stable Disease, at 4 months (16 weeks)
  - Hypotheses for the dual agent evaluations depend on the results of the single agent
- **Secondary Endpoints:**
  - Adverse event rates (NCI CTCAE v4.0).
  - Time to progression, progression-free survival, and overall survival.
  - Immune Response using irRC (Immune Response RECIST), relative to disease measurements collected using RECIST v1.1
- **Exploratory Objectives**: To evaluate the associations between the following and within each Component:
  - PD-L1 expression (by IHC) and clinical outcome
  - Selected biomarker measured in serial peripheral blood and with clinical efficacy
  - Selected biomarker measured in tumor tissue with clinical efficacy
  - Baseline tumor mutational burden and neoantigen production with clinical efficacy

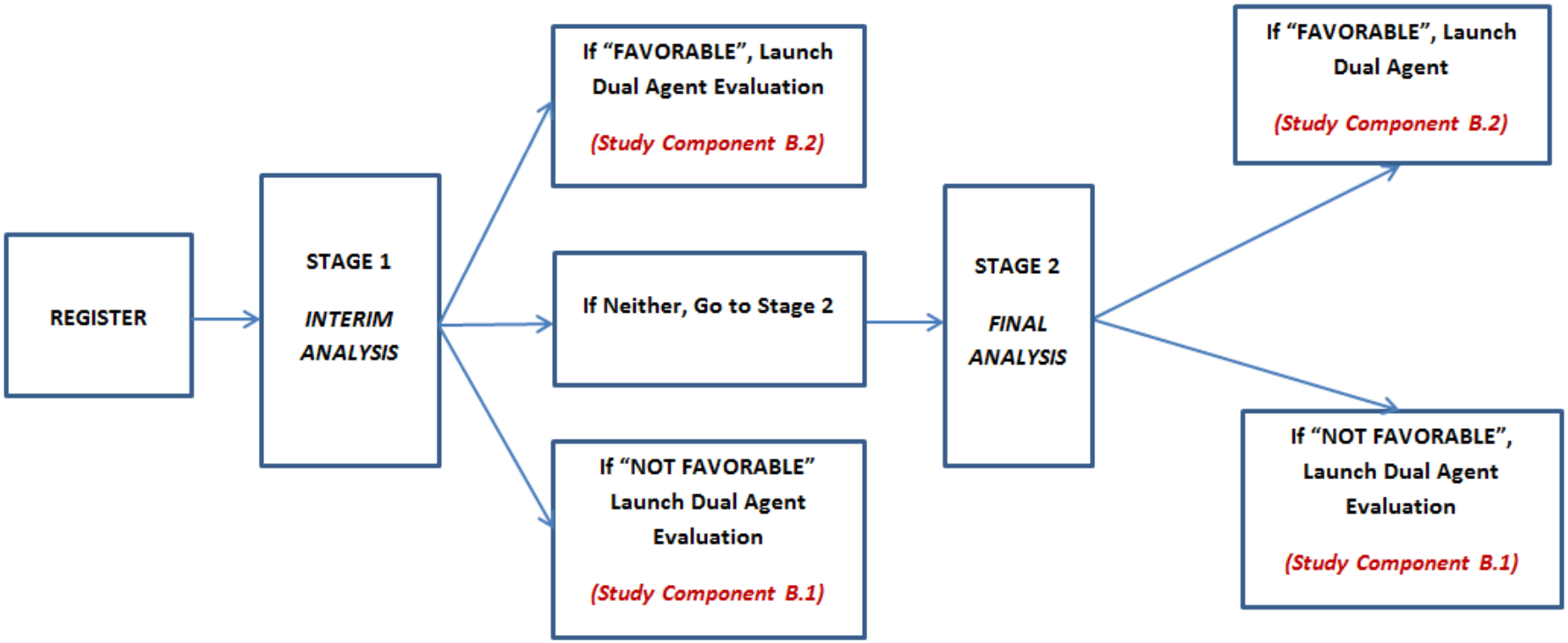
Statistical Design

- **Single Agent (A)** Ho: CBR ≤ 10% vs Ha: CBR ≥ 30%
  - Uses either 11 or 26 patients, in 2 stages.
  - Enroll 11 patients.
    - 1 in 11 launches B.1
    - ≥ 4 in 11 launches B.2
    - Otherwise, enroll 15 more patients
      - ≤ 5 in **26** launches B.1
      - ≥ 6 in **26** launches B.2
  - 85% power at 0.09 alpha level

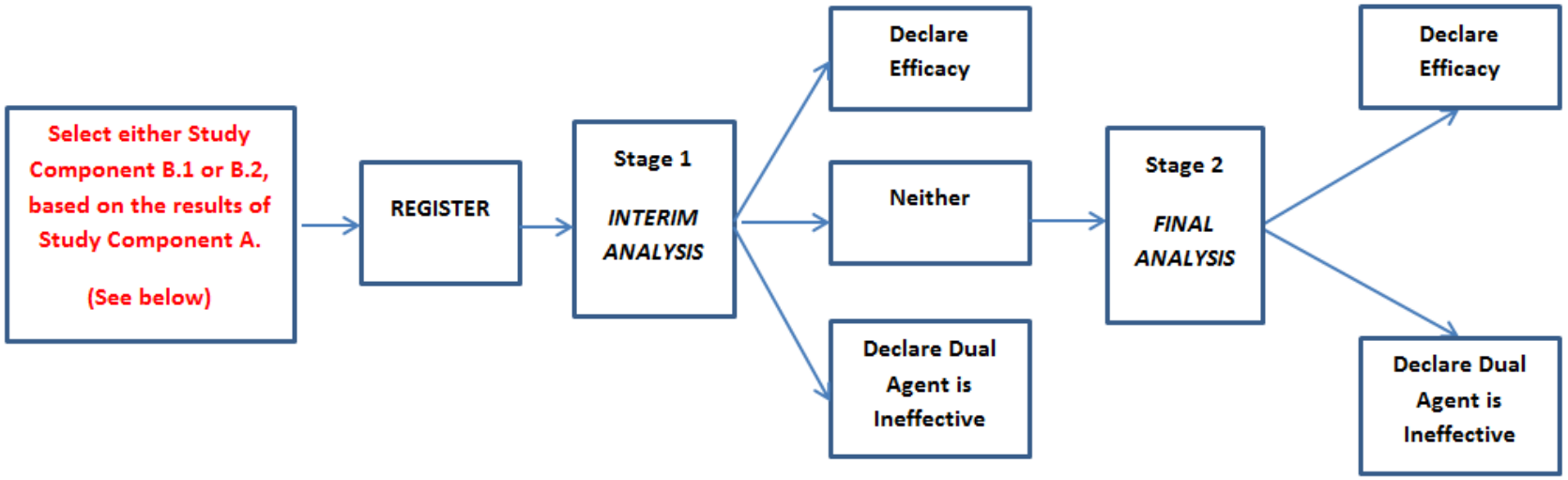
- ***Dual Agent (B.1)*** *– Same as Single Agent design*

- **Dual Agent (B.2)** Ho: CBR ≤ 25% vs Ha: CBR ≥ 45%
  - Uses either 22 of 57 patients, in 2 stages.
  - Enroll 22 patients
    - ≤ **6** in 22 - inactive
    - ≥ **10** in 22 – promising, complete enrollment to gain precision
    - Otherwise, enroll 35 more patients
      - ≥ 20 in 57 is promising activity.
  - 90% power at 0.06 alpha level

Study Design/Schema
(Single Agent - Component A)



Study Design/Schema
(Dual Agent, B.1/B.2)



Study Component B.1 - Use Ho: CBR $\leq$ 10% vs Ha: CBR $\geq$ 30%

Study Component B.2 - Use Ho: CBR $\leq$ 25% vs Ha: CBR $\geq$ 45%

DANA-FARBER CANCER INSTITUTE

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Phase I/II study of BRAF-MEK-Hsp90 inhibition by vemurafenib, cobimetinib and ganetespib in *BRAF* mutant melanoma

Study Concept: A091402

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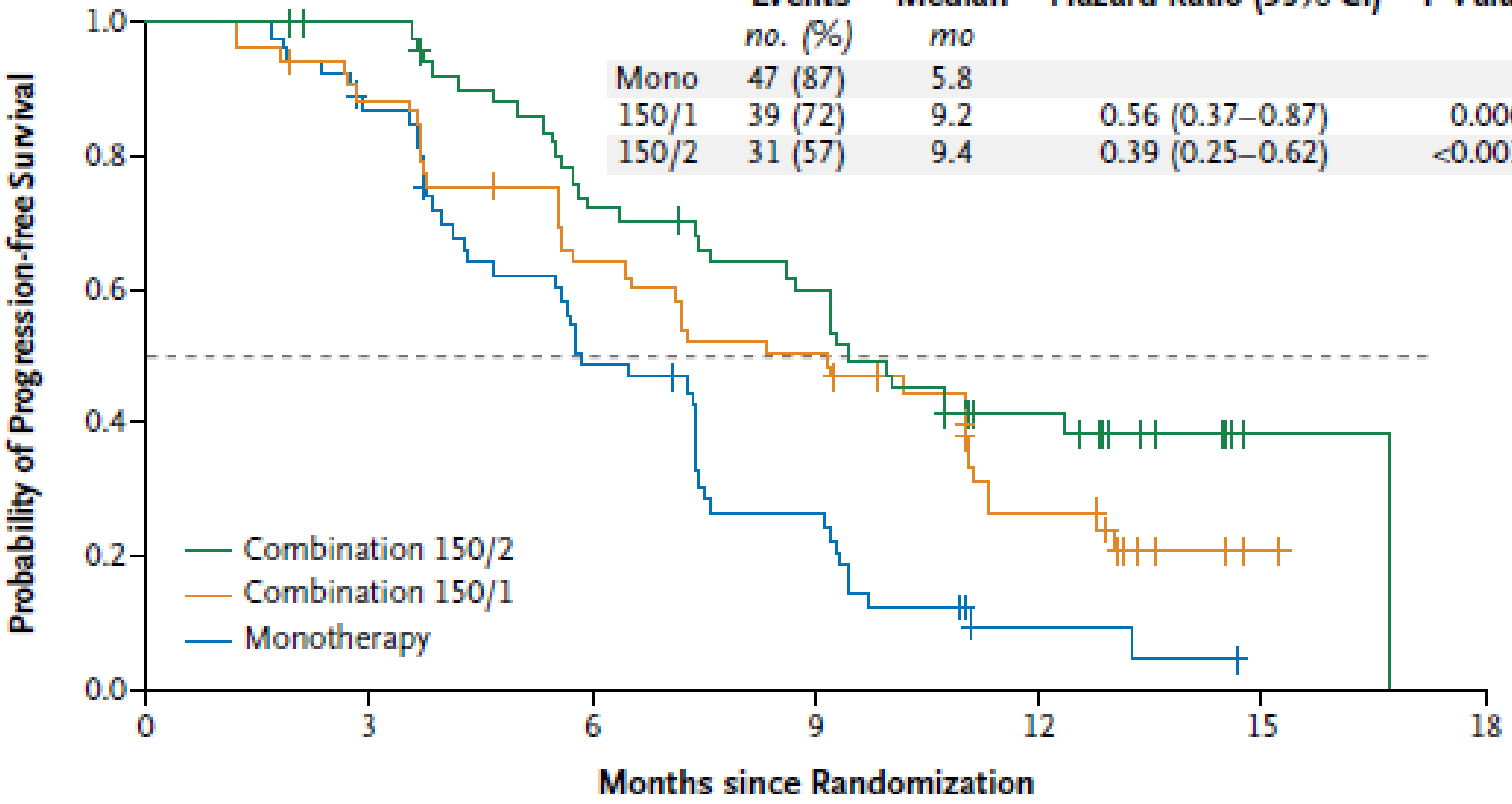
BRAF-MEK in BRAF Melanoma

A Progression-free Survival

	Events no. (%)	Median mo	Hazard Ratio (95% CI)	P Value
Mono	47 (87)	5.8		
150/1	39 (72)	9.2	0.56 (0.37–0.87)	0.006
150/2	31 (57)	9.4	0.39 (0.25–0.62)	<0.001



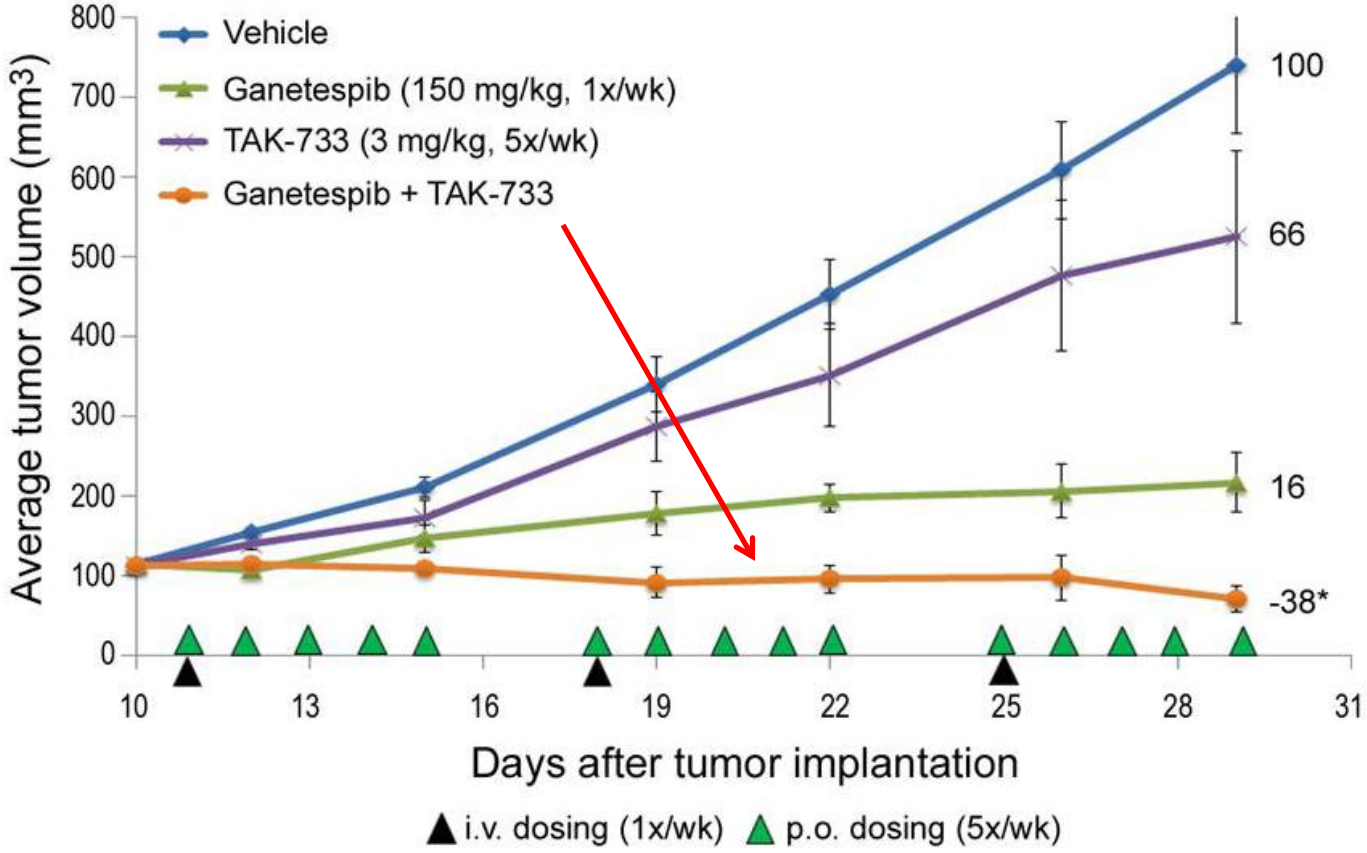
No. at Risk						
Monotherapy	54	46	25	13	2	0
Combination 150/1	54	47	33	26	11	1
Combination 150/2	54	52	36	29	15	1

Flaherty *et al*, NEJM 2012

Mechanisms of resistance to BRAF-MEK and MAPK feedback are diverse but most are Hsp90 client proteins

- BRAFi resistance
  - MAPK: BRAF splice varients, BRAF amplification, MEK / COT / NRAS mutations
  - Non-MAPK: IGF-1R, PDGFR, AKT
- Feedback
  - RTKs (MET, EGFR, FGFR, HER3)
  - ARAF / CRAF / BRAF dimers

Hsp90i+MEKi overcomes RAF resistance *in vivo*



Mice bearing established A375-VR xenografts (n=5 mice/group) were i.v. dosed with ganetespib (150 mg/kg) once weekly and TAK-733 (3 mg/kg) administered p.o. 5x/week, either alone or in combination, as indicated (arrowheads).

DANA-FARBER CANCER INSTITUTE | BRIGHAM AND WOMEN'S HOSPITAL | HARVARD MEDICAL SCHOOL

Phase I/II Study of combination BRAFV600, MEK1/2 and Heat Shock Protein 90 Inhibition by Vemurafenib, Cobimetinib and Ganetespib in BRAFV600 mutant melanoma.

Phase I

Dose Level	Vemurafenib	Cobimetinib	Ganetespib
-1	960 mg BID	60 mg daily (3 wks on, 7 days off)	80 mg/m^2 weekly (3/4 wks/month)
1	960 mg BID	60 mg daily (3 wks on, 7 days off)	110 mg/m^2 weekly (3/4 wks/month)
2	960 mg BID	60 mg daily (3 wks on, 7 days off)	150 mg/m^2 weekly (3/4 wks/month)

Phase II

Randomization 1:1

<u>Stratified by</u>:
1. LDH
2. Prior anti-PD1/L1 or CTLA-4 Ab

Vemurafenib-Cobimetinib

Vemurafenib-Cobimetinib-Ganetespib

Primary Endpoint: PFS

Secondary Endpoint: RR, Safety, OS, PK, PD

Phase I (3+3 escalation)

- Objectives / Endpoints
  - Define Safety and RP2D
    - Secondary: PK, PD in 10 pt expansion cohort
    - Accrual: 6-28 pts
- Correlates
  - PK Analysis of Ganetespib
  - PD of Hsp90 Client Proteins and phopho-ERK
  - Inter-Patient Pathway Adaptation after Hsp90i added to BRAF-MEK Inhibition
- Eligibility:
  - BRAFV600 , ECOG 0-1, standard organ criteria, brain mets stable 1 month
  - QTc $\geq$ 480 ms, Standard BRAFi/MEKi CV, retinal and GI exclusions
  - Phase I: any prior Rx, Expansion/Phase II: No prior BRAFi, MEKi or Hsp90i

Phase II

- Primary Objective: PFS VC vs VCG
  - Secondary: OS, RR, Safety
  - 1' endpt: 80% power, 50% ↓ hazard rate VCG vs VC with 1-sided α=0.20 logrank test
    - (PFS: 10 ->15 mo w 1 interim futility analysis)
  - Accrual: 100-130 pts (possible 30 pt confirmatory expansion)
    - Total accrual 6-158 pts
  - Alliance and will offer to SWOG through Moffitt
  - Secondary Accrual Phase:
    - If study "negative", but VCG shows PFS > 20% vs VC then will accrue 30 further to VCG to confirm PFS
- **Projected Accrual Dates**: **Start** 09/2014 **End**: 05/2016

B SMART:

Biomarker driven therapy for Sarcoma via Molecular pathways, Angiogenesis, Receptors, Translocations, and Novel therapies

- Mission:
- To develop targeted therapy in sarcoma based on pathogenesis of the individual tumor rather than sarcoma histologic subtype.

B SMART:

Biomarker driven therapy for Sarcoma via Molecular pathways, Angiogenesis, Receptors, Translocations, and Novel therapies

- Rationale:
- Current lack of effective treatments for sarcoma
- Model of GIST as a success story
- Multiple other examples with promise (eg ALK/IMT case example, CDK4/LPS)

B SMART:

Biomarker driven therapy for Sarcoma via Molecular pathways, Angiogenesis, Receptors, Translocations, and Novel therapies

- Rationale:
- Lowered success with targeted agents utilized without biomarker positivity (eg SUCCEED trial)
- Molecular pathogenesis does not always correlate with histologic subtype
- Enriching population with biomarker positive patients has been proven in some situations, but not all biomarkers work out cross malignancies

B SMART:

Biomarker driven therapy for Sarcoma via Molecular pathways, Angiogenesis, Receptors, Translocations, and Novel therapies

- Method:
- Patients are fed into the trial by having a biomarker panel tested on their tumor tissue, and treatment is determined by the biomarker testing.

B SMART:

Biomarker driven therapy for Sarcoma via Molecular pathways, Angiogenesis, Receptors, Translocations, and Novel therapies

- Design
- Multi-cohort screening trial (pre-reg/reg)
- 3 major differences between each cohort: drug given, drug specific registration eligibility, and accrual rate (based on % frequency of biomarker).
- Could be a “plug and play” trial (completion of a cohort followed by addition of a new biomarker)

B SMART:

Biomarker driven therapy for Sarcoma via Molecular pathways, Angiogenesis, Receptors, Translocations, and Novel therapies

- Design:
- Pre-reg step: central pathology review and biomarker panel at 1 lab with biomarker chair
- 1 cohort = 1 study chair (drug toxicity expertise)
- Biomarker negative cohort (eg epigenetic, novel anti-angiogenic) so all patients have access to treatment (no screen failures)

B SMART:

Biomarker driven therapy for Sarcoma via Molecular pathways, Angiogenesis, Receptors, Translocations, and Novel therapies

- Design:
- Each cohort has same primary endpoint
- integrated correlative science in cohort as appropriate
- Residual tissue bank (possible PG/PD component)

B SMART:

Biomarker driven therapy for Sarcoma via Molecular pathways, Angiogenesis, Receptors, Translocations, and Novel therapies

- Infrastructure:
- NCI sponsored, BIQSFP for biomarker
- NCTN wide
- Industry collaborations through Alliance Foundation

B SMART:

Biomarker driven therapy for Sarcoma via Molecular pathways, Angiogenesis, Receptors, Translocations, and Novel therapies

- Questions?

Health Outcomes Committee (HOC)

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HOC Liaison to Experimental Therapeutics Committee

2014 Spring Group Meeting
Chicago, IL
May 7-10, 2014

Health Outcomes Committee (HOC)

Chairs: Ethan Basch MD; Jeff Sloan PhD
Vice-Chairs: Michele Halyard MD; Michelle Naughton PhD; Amylou Dueck PhD
Contacts: Jackie Lafky MS, Diana Mehedint, MD

2014 Spring Group Meeting
Chicago, IL
May 7-10, 2014

HOC Mission

- To improve understanding of the patient experience with disease, treatment, and survivorship through the use of patient-reported outcomes (PROs)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Areas of Focus

- Aim 1: To embed PROs in Alliance clinical trials
- Aim 2: To conduct primary PRO methodology research
- Aim 3: To study relationships of genetic/biological mechanisms with PROs
- Aim 4: To evaluate the use of PROs to improve care delivery and quality

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FOR CLINICAL TRIALS IN ONCOLOGY

Alliance Concept Submission Instructions

7. “…if a QOL component, sign-off from the Health Outcomes committee”
8. “It is not currently mandatory to get sign-off from committees that do not have a planned component of the study. However it is STRONGLY SUGGESTED that all concepts be discussed with the … Health Outcomes committee … to see if the concept would be strengthened by such collaborations.”

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FOR CLINICAL TRIALS IN ONCOLOGY

How Can HOC Work with Your Committee?

We will assign an experienced HOC team member to:

- Take the lead to develop PRO correlatives
- Assist or pair up with a member of your committee to develop PRO correlatives
- Review and provide sign-off of your concept prior to SCRC submission

We encourage collaborations with interested investigators!

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HOC Review Timing

- Engage HOC as early as possible to avoid delays - the more we know ahead of time, the faster we can turn things around for review.
- For most studies, we would appreciate at least 2 weeks for review of concept or protocol. For more complicated studies, it may require an extra week or two.

Note: If concept is not reviewed prior to SCRC submission, concept approval by the SCRC may be delayed.

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Alliance QOL/PRO Resources

- Alliance website → Education & Training → Resources → Health Outcomes Resources: https://www.allianceforclinicaltrialsinoncology.org/main/member/standard.xhtml?path=%2FMember%2FHealth-Outcomes-Resources
  - Forms Bank & QOL Brochure
  - Publications
  - Organization Links
  - Questions? QOL@allianceNCTN.org

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Applying QOL Assessments: Solutions for Oncology Clinical Practice and Research

Current Problems in Cancer, 26:265-351, Nov 2005 & 2006

Partial Table of Contents

- Optimal timing for QOL assessments
- Combining information across symptom studies
- Presenting longitudinal data
- Incorporating clinical significance into a study
- Handling missing data
- Can we believe the patient?
- The patient's perspective of QOL assessment
- Future directions in QOL research

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HOC Ongoing Protocols

- 28 HOC liaisons to other committees
- Clinical trials
  - 19 Open studies
  - 6 Protocols in development
  - 30 Concepts in development
  - 45 Closed studies

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Current Trial with ETC: A091105

- *A Phase III, double blind, randomized, placebo-controlled trial of sorafenib in desmoid tumors or aggressive fibromatosis (DT/DF)* (PI: Gounder)
  - Activated 3/21/14; Accrual goal = 83
  - Primary objective
    - To compare the progression-free survival rates
  - Secondary objectives
    - To assess toxicity
    - To assess time to surgical intervention or radiotherapy
    - To assess tumor response rates and survival

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Companion Study: A091105-HO1

- Evidence suggesting that sorafenib improves pain
  - 70% DT/DF patients reported decreased pain and analgesic use (Gounder)
  - However, pain measures were not validated
  - Sample size rather small (*n* = 22)
- Evidence that fatigue and QOL predict survival
- E. Basch (HOC Chair); A. Dueck (HOC Statistician)

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Companion Study: A091105-HO1

- Study aims:
  - To assess pain palliation and time to pain progression
    - The Brief Pain Inventory Short Form (3 items)
    - Pain Medication Diary
  - To assess patient-reported adverse events and QOL
    - The PRO-CTCAE (19 items); The single-item overall LASA
- Timing of assessments:
  - Prior to randomization
  - Every 4 weeks up to Week 32
  - At the end of randomized treatment

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Any Questions, Contact:

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HOC Liaison to Experimental Therapeutics Committee

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Central Protocol Operations Office Updates

- Personnel Changes:
- Retirement of Linda Bressler, PharmD
- Addition of Yujia Wen, PhD, Director of TRP Operations

Central Protocol Operations Office Updates

- Accrual Task Force Changes:
- Disbanding of formal task force
- Continuation of prior AEPs and AAPs
- Continuation of accrual monitoring

Central Protocol Operations Office Updates

- SCRC Changes:
- Change in mission from scientific review to operational review (feasibility)
- Scientific evaluation at Alliance committee level and NCI review
- Weekly meetings

Central Protocol Operations Office Updates

- NCTN Transition:
- Final mergers: 4 adult, 1 pediatric, 1 Canadian
- New membership categories (LAPS, CCOP, network groups) with component tiers
- Funding changes at sites, New grants released
- CIRB utilization
- IROC
- Systems changes (CTSU, Alliance website)

Central Protocol Operations Office Updates

- Questions?