# Experimental Therapeutics Committee Meeting

Saturday, November 8, 2014

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FOR CLINICAL TRIALS IN ONCOLOGY

- Status update on activated current trials

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# A091104: Phase II MK-2206 in Patients with Progressive, Recurrent/Metastatic Adenoid Cystic Carcinoma

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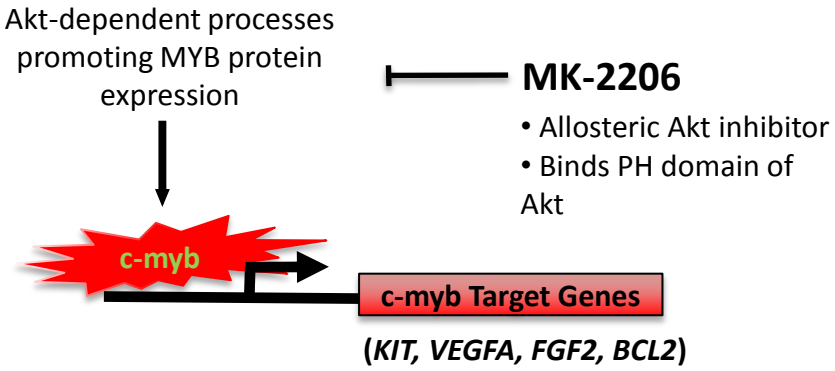
Memorial Sloan Kettering Cancer Center


Memorial Sloan Kettering Cancer Center™

# A091104: Study Rationale/Design




*NCI/CTEP Phase II Study*

Patients with progressive, recurrent/metastatic adenoid cystic carcinoma (ACC)

**MK-2206 150 mg oral weekly**
(w/ possible dose escalation to 200 mg)

RECIST evaluation every 2-3 cycles

Primary endpoint: Objective response rate

Two-stage design : Needed 1 response in the first stage to complete accrual (within the first 8 cycles)

Secondary endpoint: PFS

# A091104: Updated Results

- Enrollment Period: 7/23/12 to 2/15/13
- 16 patients enrolled; 2 ineligible
- 1 patient remain on treatment
- Median follow-up: 16.2 months (range: 9-16 months)
- 0 PRs, 13 SD (11 SD > 2 cycles)
- Median PFS: 9.2 months (95% CI: 3.8-11.0)
- Median OS: 13.7 months (95% CI: 11.8-no upper)
- Correlative tissue studies ongoing

# 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

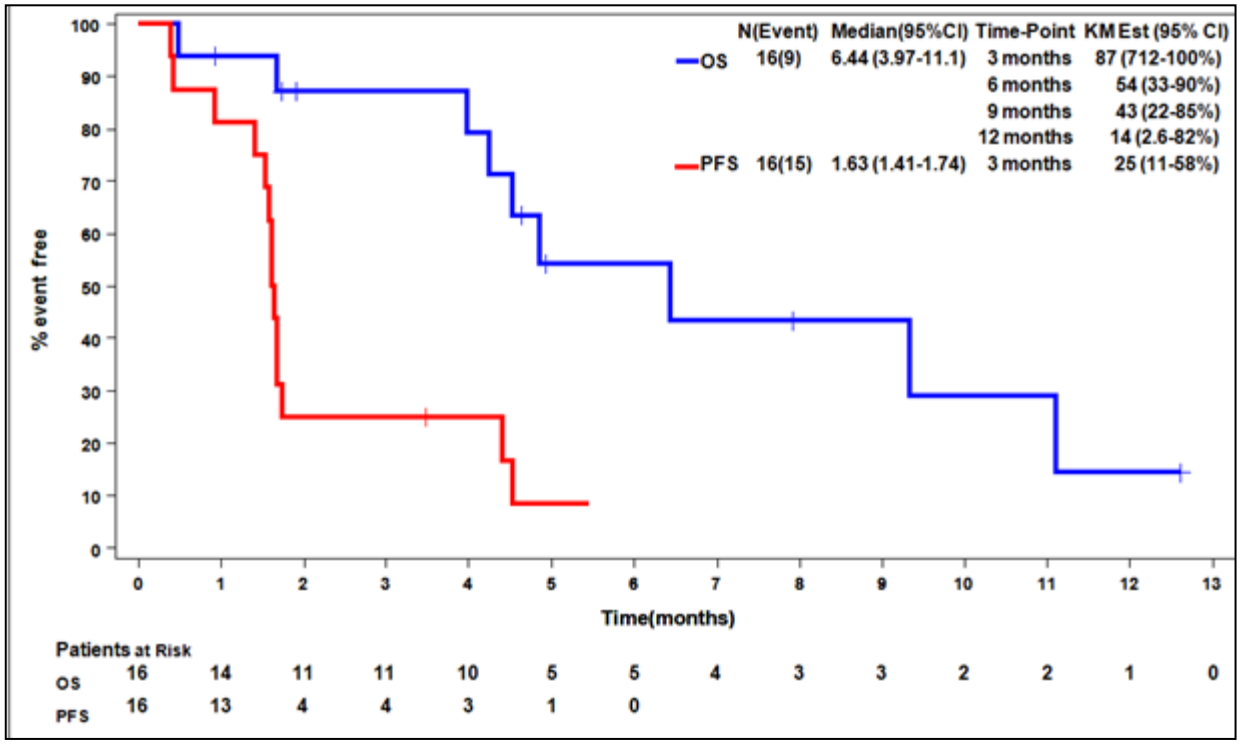
- An optimal Simon two-stage design with an early stopping rule will be used.
  - 1 confirmed response in 12 treated patients expands enrollment to 37.
  - Study will be deemed positive if 4/37 confirmed responses are observed. (Type I error=Type II error=0.1)

- 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**




- No responses seen in the 12 evaluable patients, study closed.
- Manuscript submitted to British Journal of Cancer

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

**Dickson MA[1], Mahoney MR[2], Tap WD[1], D'Angelo SP[1], Keohan ML[1], Van Tine BA[3], Agulnik M[4], Horvath LE[5], Schwartz GK[6]**

**Memorial Sloan-Kettering Cancer Center, New York, NY (1); Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN (2); Washington University, Saint Louis, MO (3); Northwestern University, Chicago, IL (4); Alliance for Clinical Trials in Oncology, Chicago, IL (5); Columbia University Medical Center, New York, NY (6)**



ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

# MLN8237 (Alisertib)

- ATP-competitive and reversible inhibitor of Aurora Kinase A (AURKA)
- Phase I trial:
  - DLT: Grade 3 and 4 neutropenia with stomatitis
  - Recommended phase II dose was 50 mg BID.
  - PR in a patient with pleomorphic liposarcoma lasting > 1 year

    (Cervantes et al. Clin Cancer Res 2012)

# Objectives of Phase 2 Study

- **Primary: To determine the confirmed response rate (RR), within each cohort**
- **Secondary:**
  - **To estimate PFS and OS, within each cohort**
  - **To assess the adverse events observed, within each cohort**
- **Correlative:**
  - **To correlate potential clinical benefit with markers of aurora kinase inhibition in pre- and post-treatment tumor biopsies**
  - **To correlate clinical outcome with change in FLT-PET uptake at baseline vs. after one week of treatment**

# Methods and Statistical Considerations

**Key eligibility criteria:**

- Age > 18 years
- Measurable disease (RECIST 1.1)
- Any number of prior therapies is permitted
- ECOG PS ≤ 2
- Adequate hematologic, renal and hepatic function
- Enrolled into 1 of 5 histologically defined cohorts

**Treatment: Alisertib 50mg PO BID d1-d7, repeated 21 days**

**Statistical Design:**

- Evaluate confirmed RR (CR + PR, lasting 6 weeks), within each Cohort
- A confirmed RR of 25% is considered clinically promising
- Simon two-stage phase 2 study design
  - 1 confirmed response in 9 patients expanded enrollment to 24 patients
  - 3 confirmed responses in 24 patients warranted larger studies
- Power 90%; alpha level 0.10
- Minimum enrollment: 45
- Maximum enrollment: 135

# Patient Characteristics

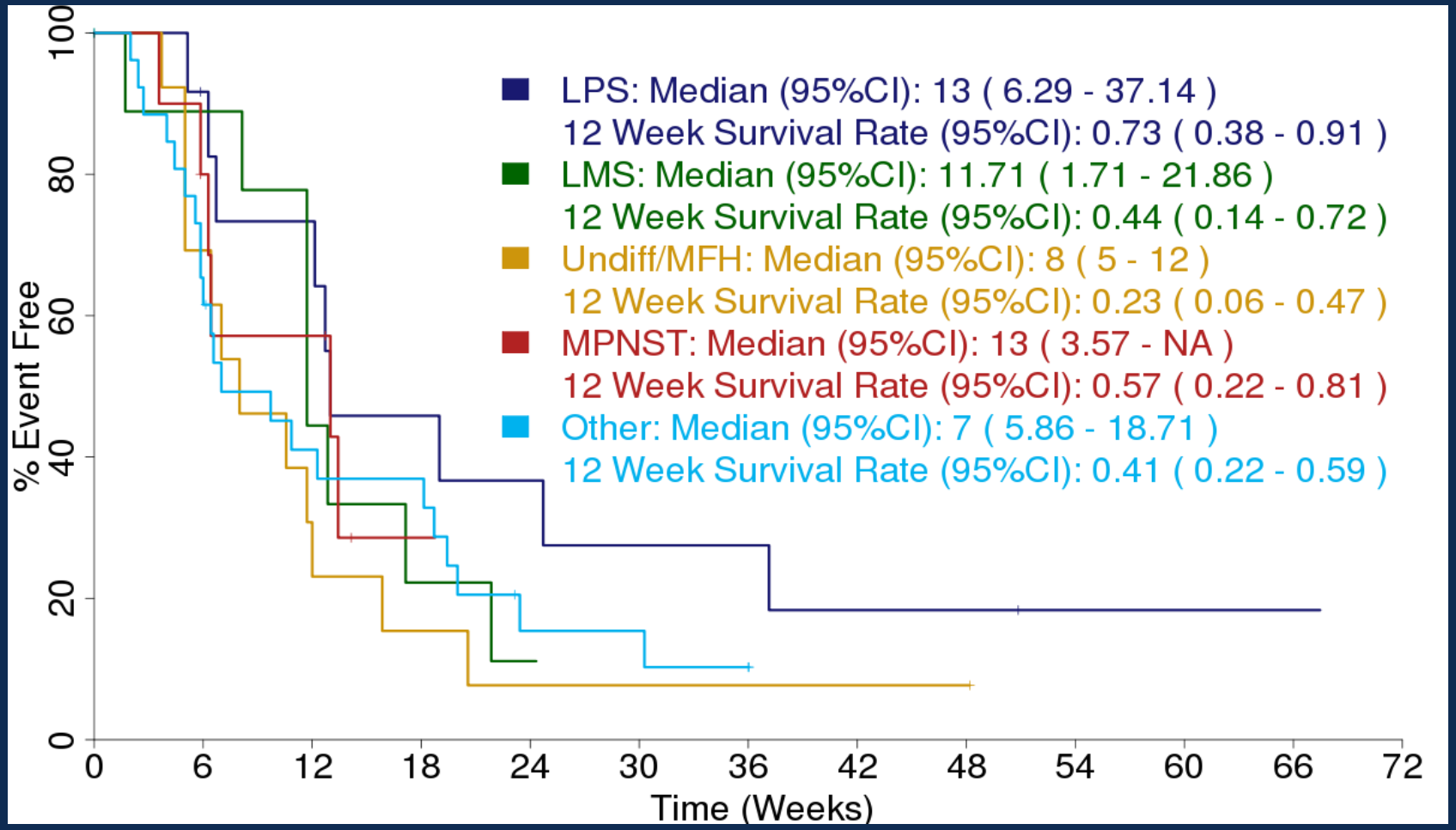
| Characteristic | Frequency (%) |
|---|---|
| Age - Median (Range) | 54.5 (20-84) |
| Male | 54% |
| ECOG PS | |
| 0 | 42 (58%) |
| 1 | 27 (38%) |
| 2 | 3 (4%) |
| Histology | |
| Liposarcoma | 12 (17%) |
| Leiomyosarcoma (non-uterine) | 10 (14%) |
| Undifferentiated Sarcoma[1] | 13 (18%) |
| Malignant Peripheral Nerve Sheath Tumor | 10 (14%) |
| Other[2] | 27 (37%) |

1) Including pleomorphic undifferentiated sarcoma/MFH and myxofibrosarcoma
2) including osteosarcoma (7), chondrosarcoma (5), synovial sarcoma (3), angiosarcoma (2) and 1 each rhabdomyosarcoma, alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, epithelioid sarcoma, DSRCT, GIST

# Results

- **Response:**
  - **1 confirmed PR in a patient with angiosarcoma cohort 5 (other) led to expansion of that cohort to 2nd stage accrual**
  - **Total of 2 confirmed partial responses in cohort 5 (both angiosarcoma)**
  - **1 unconfirmed partial response (dedifferentiated chondrosarcoma) also in cohort 5**
- **Disease Stability > 6 months achieved in 7 patients**
  - **3 Liposarcoma**
  - **1 Undifferentiated sarcoma**
  - **3 Other**

# Progression-free survival



# Adverse Events

| | Grade 3 | | Grade 4 | |
|---|---|---|---|---|
| Neutrophil Count Decreased | 13 | *18%* | 15 | *21%* |
| Anemia | 9 | *13%* | 0 | *0%* |
| White Blood Cell Decreased | 9 | *13%* | 6 | *8%* |
| Mucositis - Oral | 8 | *11%* | 1 | *1%* |
| Lymphocyte Count Decreased | 7 | *10%* | 0 | *0%* |
| Platelet Count Decreased | 4 | *6%* | 5 | *7%* |
| Febrile Neutropenia | 4 | *6%* | 3 | *4%* |
| Fatigue | 3 | *4%* | 0 | *0%* |
| Palmar-plantar Erythrodysesthesia Syndrome | 3 | *4%* | 0 | *0%* |
| Leukocytosis | 1 | *1%* | 0 | *0%* |
| Anal Mucositis | 1 | *1%* | 0 | *0%* |
| Diarrhea | 1 | *1%* | 0 | *0%* |
| Nausea | 1 | *1%* | 0 | *0%* |
| Typhlitis | 1 | *1%* | 0 | *0%* |
| Vomiting | 1 | *1%* | 0 | *0%* |
| Lung infection | 1 | *1%* | 0 | *0%* |
| Alanine Aminotransferase Increased | 1 | *1%* | 0 | *0%* |
| Aspartate Aminotransferase Increased | 1 | *1%* | 0 | *0%* |
| Skin/Subcutaneous Disorder | 1 | *1%* | 0 | *0%* |
| Hypertension | 1 | *1%* | 0 | *0%* |
| Sepsis | 0 | *0%* | 1 | *1%* |

Incidence of Grade 3-4 AE's considered at least possibly related to treatment.

Hematologic toxicity was the most common.

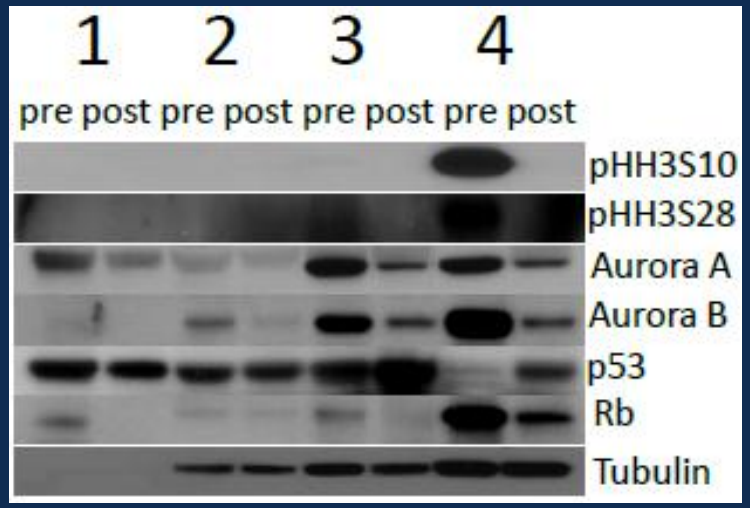
# Correlative Studies (1)

- **FLT-PET Scans**
  - **Preclinical xenograft data show that decrease in SUV on FLT-PET scan is a pharmacodynamic marker for AURKA inhibition (Manfredi et al. Clin Cancer Res 2011)**
  - **3 patients had paired pre- & post-treatment scans**
    - **Dedifferentiated liposarcoma, extraskeletal myxoid chondrosarcoma, leiomyosarcoma**
  - **There was no significant change in SUV uptake**

# Correlative Studies (2)

Paired tumor biopsies were performed on 4 patients and analyzed by Western blot for markers of AURKA inhibition

- #1 - Osteosarcoma
- #2 - Dedifferentiated LPS
- #3 & 4 – LMS
- Unfortunately all progressed
  - < 12 weeks on study




- Decrease of phospho-histone H3 indicates AURKB inhibition.
- Preclinical data suggest that at high dose, alisertib may inhibit AURKB which dominates any AURKA effect
- Thus, at this dose, alisertib may act as AURKB inhibitor
  - In contrast to published phase I study (Cervantes, et al. Clin Cancer Res 2012)

# Conclusions

- Alisertib is generally well tolerated in this population.
- Although the study did not observe the necessary number of confirmed responses, alisertib was associated with prolonged stable disease lasting 7-15.5 months, especially with liposarcoma.
- PFS at 12-weeks was promising compared to historical clinical trial (>40% for several cohorts).
- A phase 2 study in angiosarcoma should be considered given PR in 2 of 2 patients
- A phase 2 study in liposarcoma should be considered given 12-week PFS of 73%

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Head & Neck Cancer Program

# Alliance A091101 (re-opened in October 2014)

- Multi-institutional Alliance Clinical Trial
  - Phase 1/Randomized Phase 2 trial of veliparib added to carboplatin and paclitaxel induction chemotherapy for high-risk locally advanced HNC
    - Stage IVa-b SCC
    - If OPC HPV positive, only high-risk groups (>10 pack smoking history and/or N2b-N3 disease)
- Positive data in squamous cell carcinoma of the lung
- Leverage from GOG clinical trial using carboplatin/paclitaxel/veliparib experience

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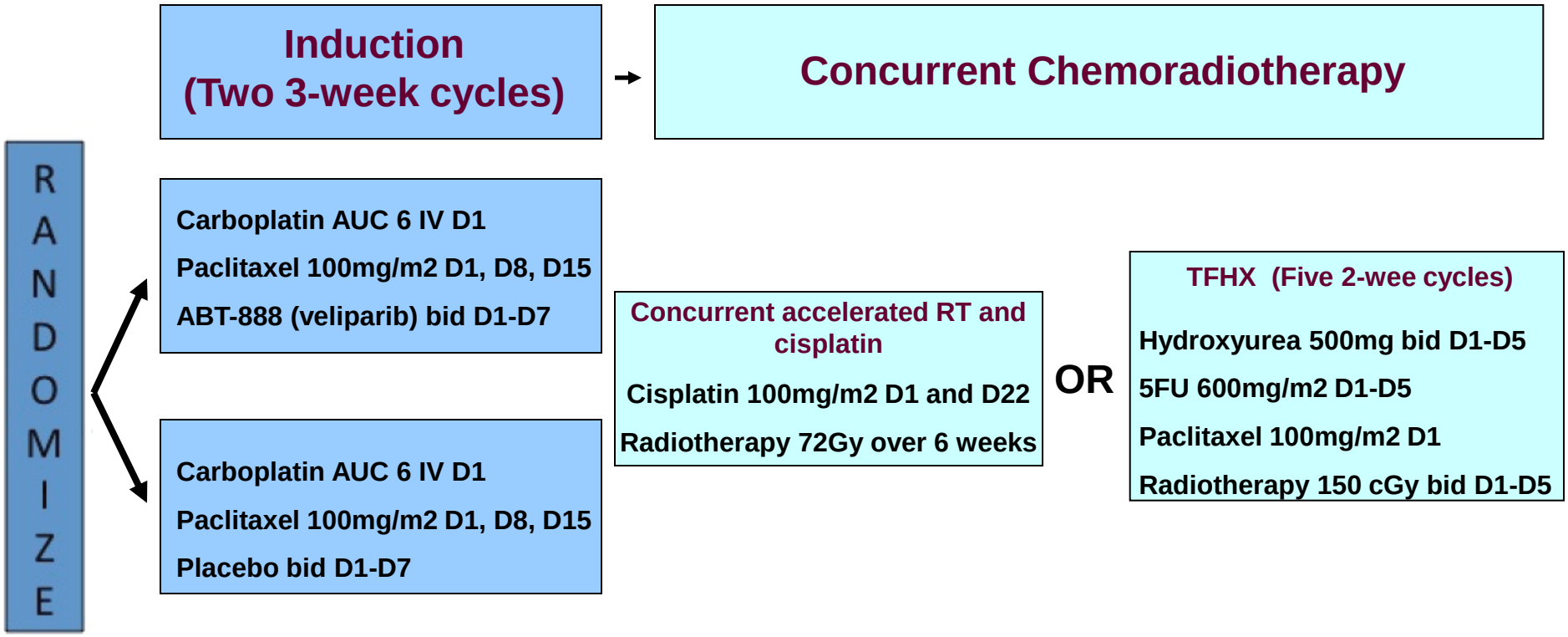
Head & Neck Cancer Program

# Alliance A091101




Primary Endpoint: Response to induction chemotherapy measured as magnitude of tumor shrinkage.

Veliparib starting dose in Phase 1 is **200mg** bid x 7 days

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# Alliance A091101

- Correlative studies with pre and post biopsies in Phase 2
- Open to interested sites
  - PI: Jonas de Souza, MD

    jdesouza@bsd.uchicago.edu

# 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

- 148 of 148 slots accrued, closed Feb 2014
- Primary analysis pending Nov 2014
- Planning ASCO 2015 submission
- Translational studies ongoing
  - Serum assessment of activity on mTOR pathway
  - Genetic studies ongoing

# 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/mRECIST 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)
- Dose Levels : DL1 (sorafenib 200 mg PO bid/TH-302 240 mg/m2 D 8,15,22; cycles every28 days), DL1a (sorafenib 200/TH-302 340), DL2 (sorafenib 200, TH-302 480)
- Currently at DL1a; No DLTs; Enrollment N=16

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

| DOSE LEVEL | SORAFENIB (MG) | TH-302 (MG/M2) |
|---|---|---|
| 2** | 200 BID | 480 D 8,15,22 |
| 1a* | 200 BID | 340 D 8,15,22 |
| 1 | 200 BID | 240 D 8,15,22 |

*CURRENT DOSE LEVEL, INTRODUCED AS NEW INTERMEDIATE DOSE LEVEL DUE TO INTOLERANCE AT DL2

**NOT TOLERATED : DLT = 2

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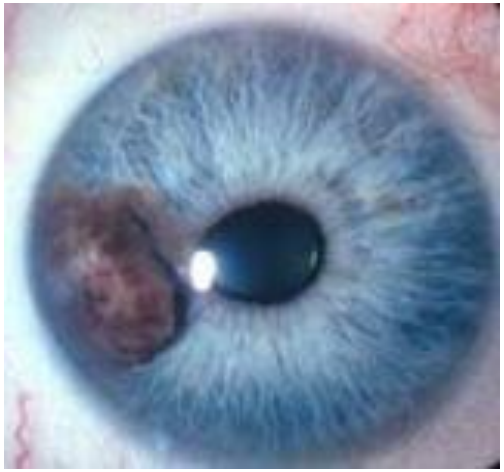
# Update on A091201: Randomized Phase II Study Comparing the MET inhibitor Cabozantinib to TMZ/DTIC in Ocular Melanoma

Jason J. Luke, M.D.

Nov 8, 2014

# Ocular Melanoma

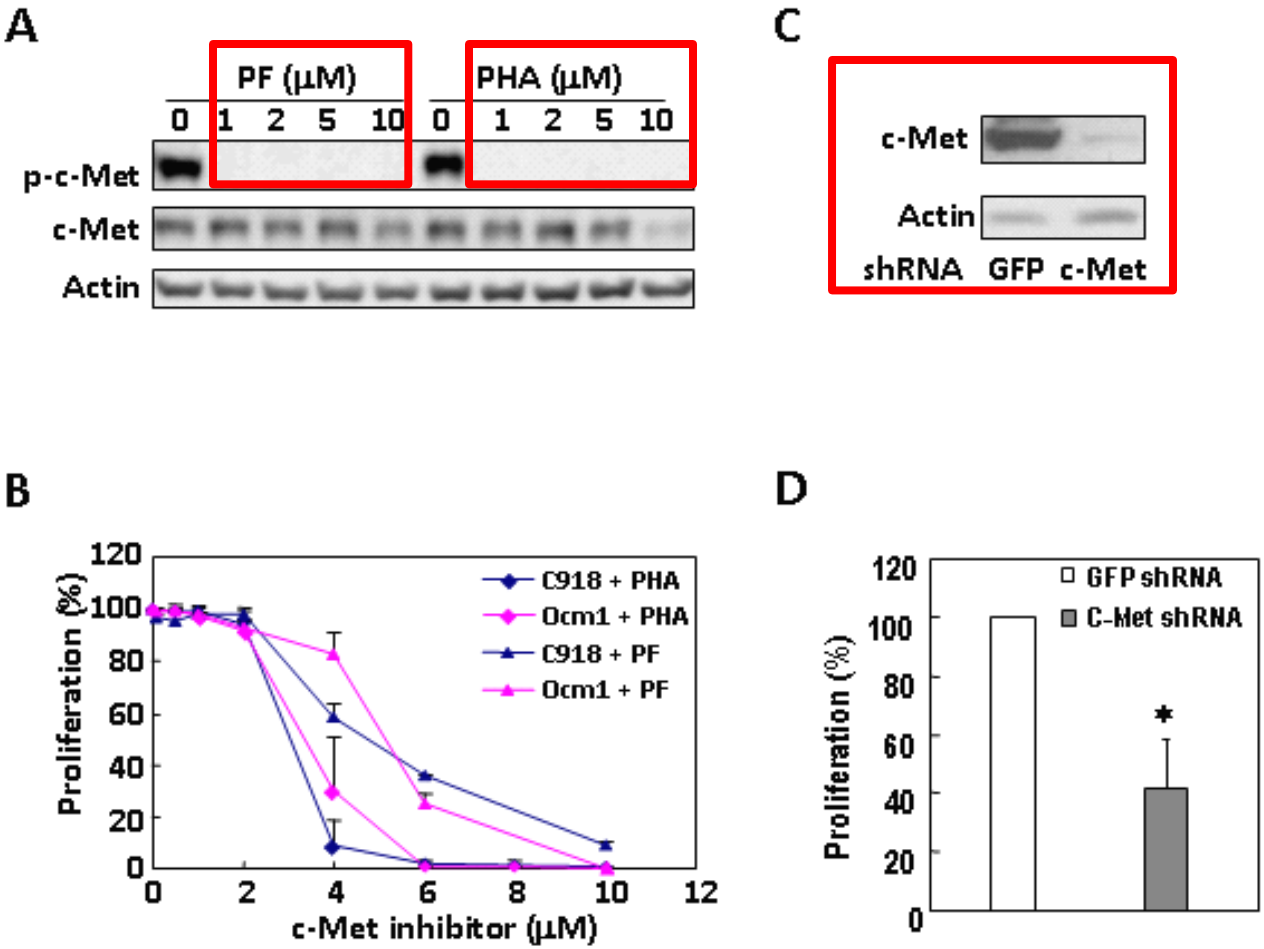


- Rare disease
  - 7 cases per million annually
- Most common intra-ocular cancer
- 50% metastasize
  - Liver tropism
- No standard systemic treatments



Bakalian *et al*., Clin Cancer Res 2008

# MET Inhibition Blocks Proliferation in OM

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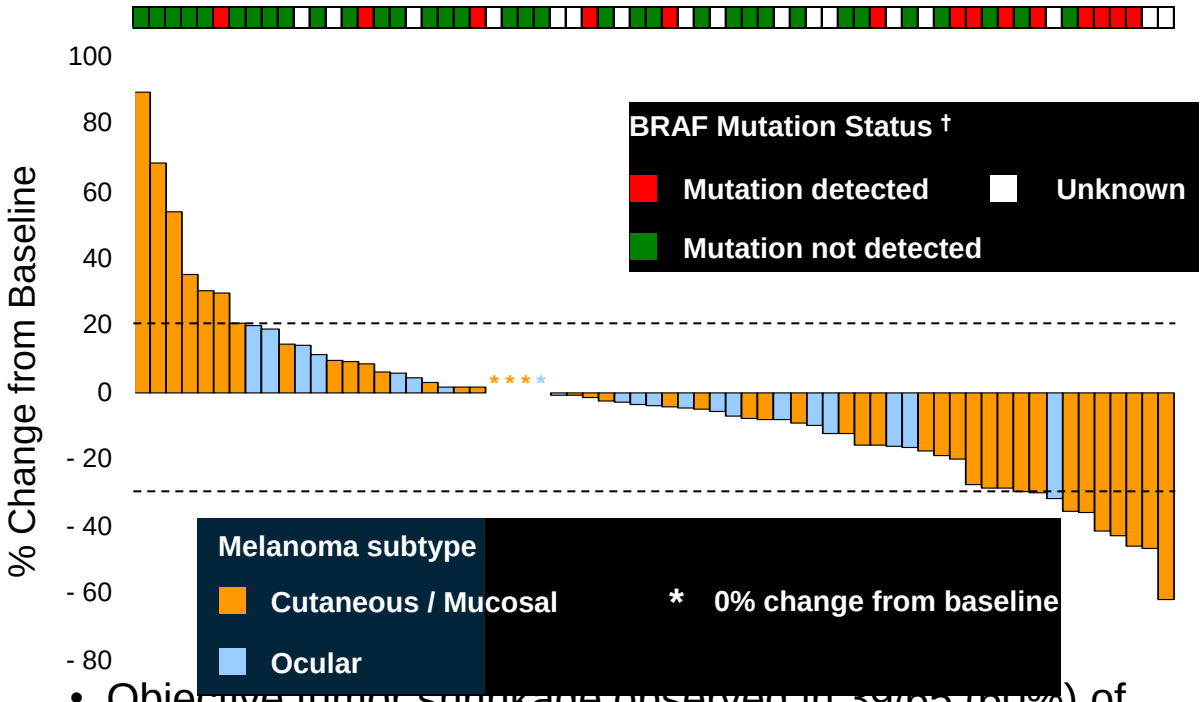
Wu *et al*, Melanoma Res 2012

# Melanoma Cohort: Phase 2 Randomized Discontinuation Trial of Cabozantinib in Patients w/ Advanced Solid Tumors

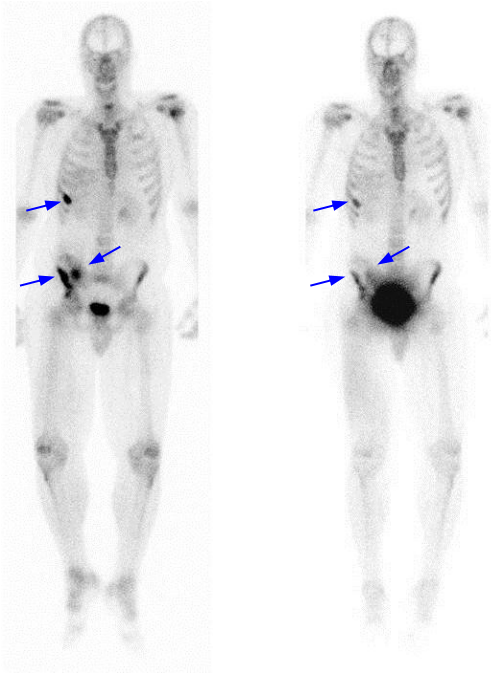
Effects on Measurable Lesions and Bone Metastases (N = 65)‡




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

**Pt with OM and Symptomatic Bone Metastases Treated at DFCI**

| Baseline Bone Scan | Follow-up Bone Scan |
|---|---|



Patient experienced pain relief

(Stayed on drug 53 weeks with RECIST stable diseas

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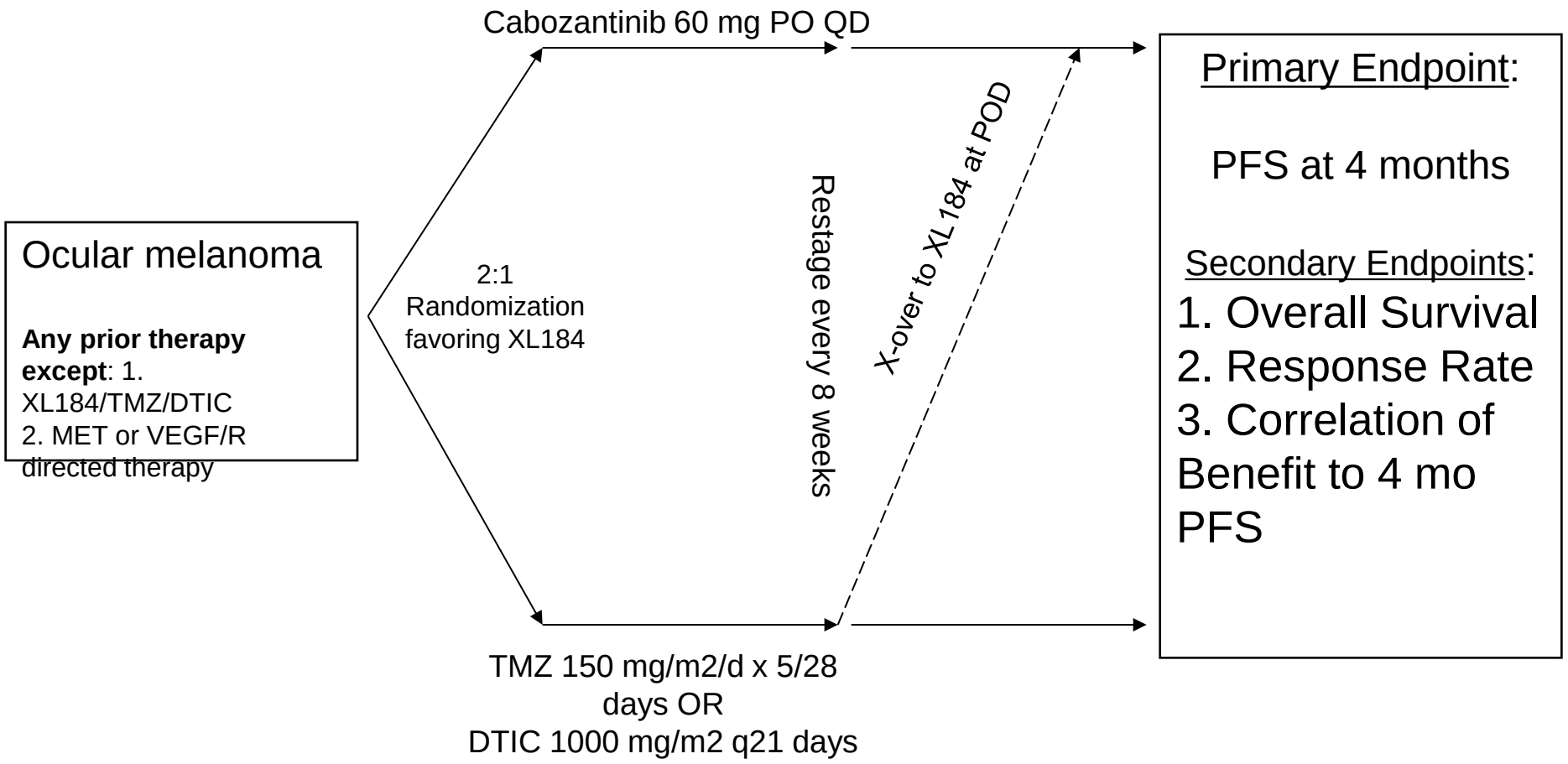
Courtesy of Geoff Shapiro, MD, PhD

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

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



# Trial Status Update

- Number of open sites:
  - 31 PI's at 117 hospitals
- Accrual 15/63
- Limited in number of large volume centers that have opened the study
  - DFCI, Mayo, Ohio State so far
  - Moving through IRB at UPenn

# Accrual and Sites To Date

| Obs | EXTREFID | ARM | DATE_ON | CURR_ARM | RND_LOC | ENDAT_DT |
|---|---|---|---|---|---|---|
| 1 | ex177030 | Cabo | 09/18/2013 | Cabo | Trinity Med. | 11/19/2013 |
| 2 | ex177427 | Cabo | 10/22/2013 | Cabo | Dana-Farber/Partners site | 11/10/2013 |
| 3 | ex177476 | TMZ | 10/28/2013 | CrOver | Froedtert WI | 07/17/2014 |
| 4 | ex178622 | TMZ | 01/09/2014 | TMZ | PrvdncPrtlndMed | 04/07/2014 |
| 5 | ex178885 | TMZ | 01/24/2014 | CrOver | Mercy MO043 | 08/03/2014 |
| 6 | ex178975 | Cabo | 01/31/2014 | Cabo | Froedtert WI | 04/02/2014 |
| 7 | ex181456 | Cabo | 04/18/2014 | Cabo | Duke | 06/16/2014 |
| 8 | ex181595 | TMZ | 04/29/2014 | CrOver | Mount | |
| 9 | ex182172 | Cabo | 06/02/2014 | Cabo | Dana-Farber/Partners site | |
| 10 | ex182345 | Cabo | 06/10/2014 | Cabo | WakeForest | 08/17/2014 |
| 11 | ex182628 | Cabo | 06/25/2014 | Cabo | Dana-Farber/Partners site | |
| 12 | ex183086 | Cabo | 07/22/2014 | Cabo | OSU Med Ctr | |
| 13 | ex183931 | TMZ | 09/08/2014 | TMZ | OSU Med Ctr | |
| 14 | ex184329 | Cabo | 10/01/2014 | Cabo | Froedtert WI | |
| 15 | ex184436 | TMZ | 10/07/2014 | TMZ | Froedtert WI | |

# Related AE summary

- DTIC / TMZ AEs all as expected
  - Decrease blood counts, fatigue
- Cabozantinib expected:
  - HTN, fatigue
- Cabozantinib significant AE's
  - (2 of first 3/10 against toxicity assessment rule):
    - G3 Anaphylaxis
    - G3 HTN

# Current Status and Next Steps

- Trial opened on CTSU to ECOG and to be highlighted at ECOG melanoma meeting
- Have reached out to NCIC Clinical Trials Group
  - To date SWOG has not shown interest
  - Interest from sites in Israel but no mechanism yet to open the study
- Have reached out to CURE OM and MRA to try to generate awareness in patient community

## 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

125 sites have IRB approval on 10/2014.

5 patients have accrued at this time (expected 24 given 4/month).

Given slow accrual an Accrual Enhancement Plan has been formulated. CIRB has provided guidance on submitted patient material documents which will be revised and resubmitted. We will reassess accrual after three months. 1st DSMB report submitted.

# 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

# 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)

Edema most common and serious

# 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 (Beta=18%;power=82%; 1-sided Alpha=10%)

mayo

# Protocol Update

| | |
|---|---|
| CTEP approval | May 16, 2014 |
| Activation | September 2, 2014 |
| IRB approvals | 39 |
| Accruals | 0 |

# 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

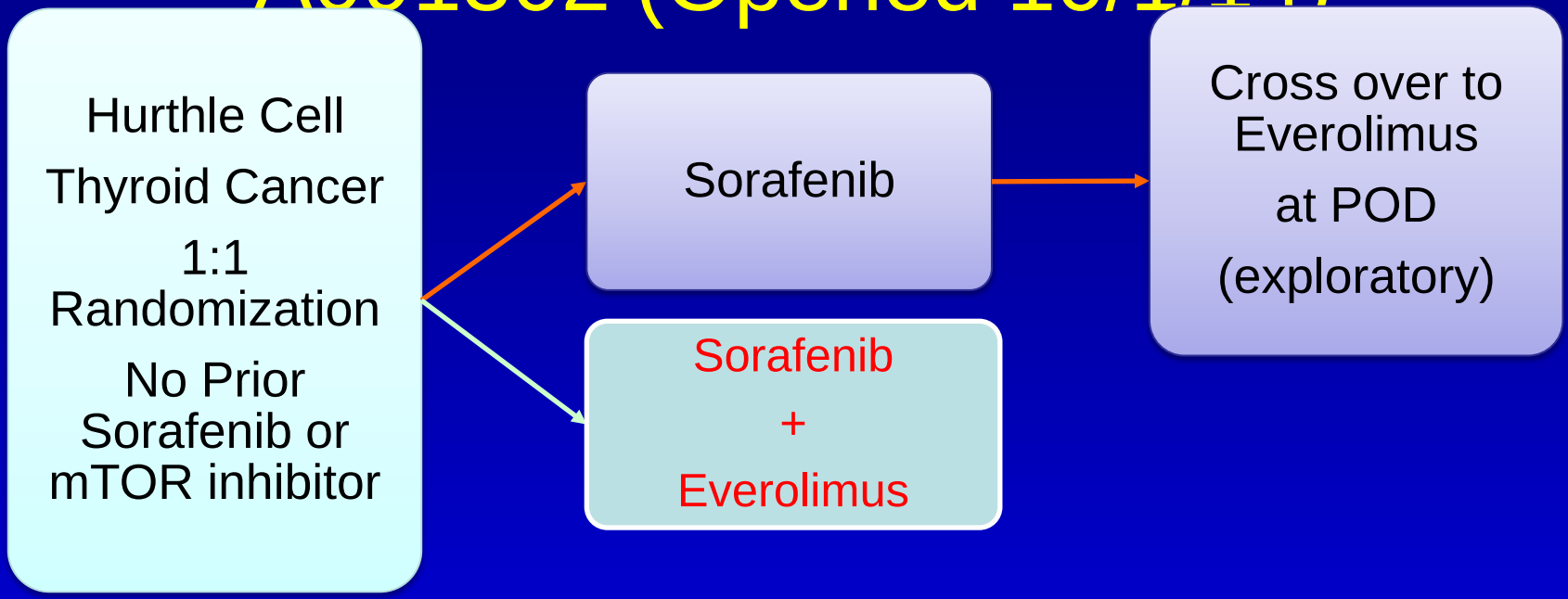
- Kinase Inhibitor
  - Target VEGF-R 1 to 3, PDGF receptor, RET
  - RAF inhibitor
- Several phase II studies have been completed with single agent sorafenib
- Phase III study (vs Placebo) recently completed
  - FDA-approved, but response rates overall are low
- Due to the data with sorafenib, MSKCC recently 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 Study
## A091302 (Opened 10/1/14)




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

- Status update on current trials in development

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# 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*

# Trial Updates 11-08-2014

- Final version approved by CTEP
- Final version in last stages of review by NCI CIRB
- Awaiting submission at Georgetown, then Nationally
  - Hope to be activated by ?January, 2015
- No funding for serial biopsies
  - Per discussion with CTEP – serial biopsies removed
  - Correlative science of predictive markers (only) on archived specimens
- NIH R01 not scored – to be resubmitted, 02-2015
  - To support correlative science

# Summary of Phase II Trial

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

- Randomized
- Placebo controlled
- Stratification
  - Prior anthracycline
  - Prior trabectedin

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

**Randomize**

**CS-7017 0.5mg PO BID**
21 day cycles

**Placebo Tablet PO BID**
21 day cycles

**Crossover**

**CS-7017 0.5mg PO BID**
21 day cycles

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

**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

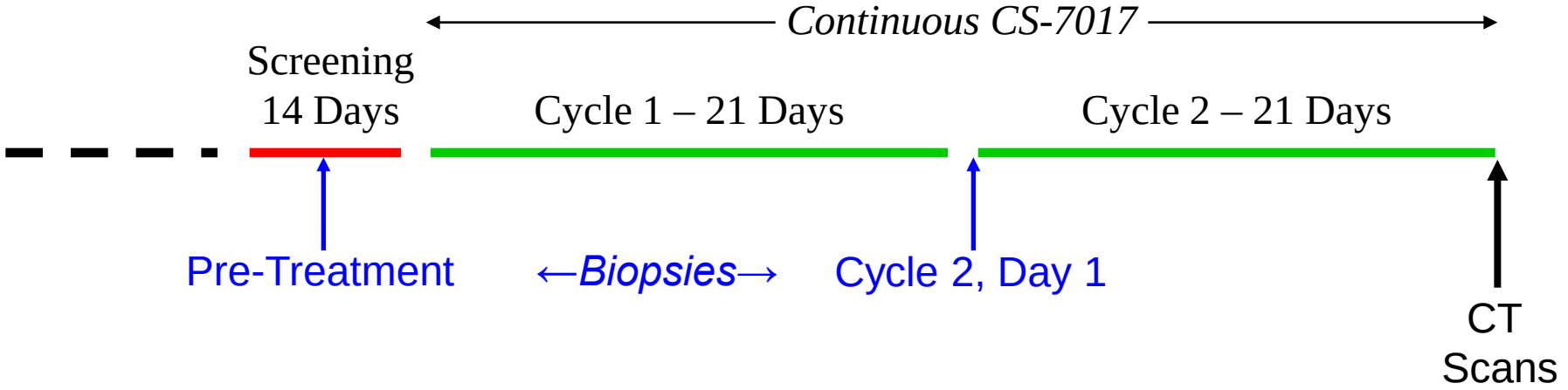
***Archived tumor specimens only***

**PPARγ affects:**

- Cell cycle
  - Upregulation of cyclin-dependent kinase inhibitors ($p18^{INK4c}$, $p21^{CIP1,}$ $p27^{KIP1)}$
  - Reduced expression of Cyclin D1
- Induction of differentiation
  - aP2, Pdhk4, Adfp, E-cadherin, β-catenin, Snail
- Predictive markers of response
  - PPARγ and RXR tumor expression

***Funding – requests to be made for serial biopsies***

- NIH RO1 resubmission 02-2015




*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*

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

William D. Tap

Alliance for Clinical Trials in Oncology

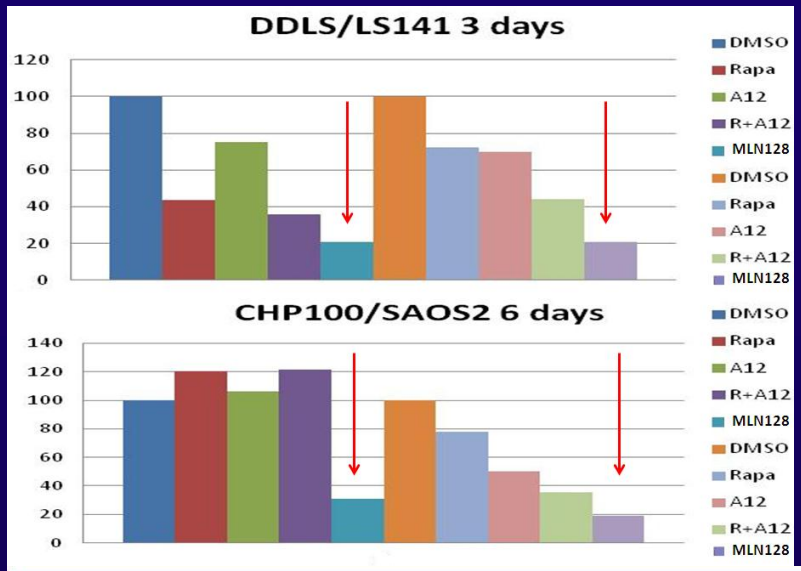
November 2014 Committee Meetings

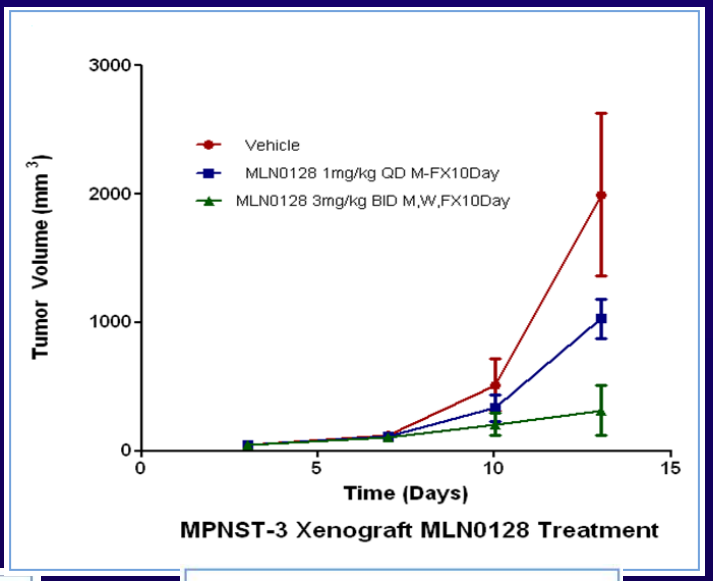
ETC

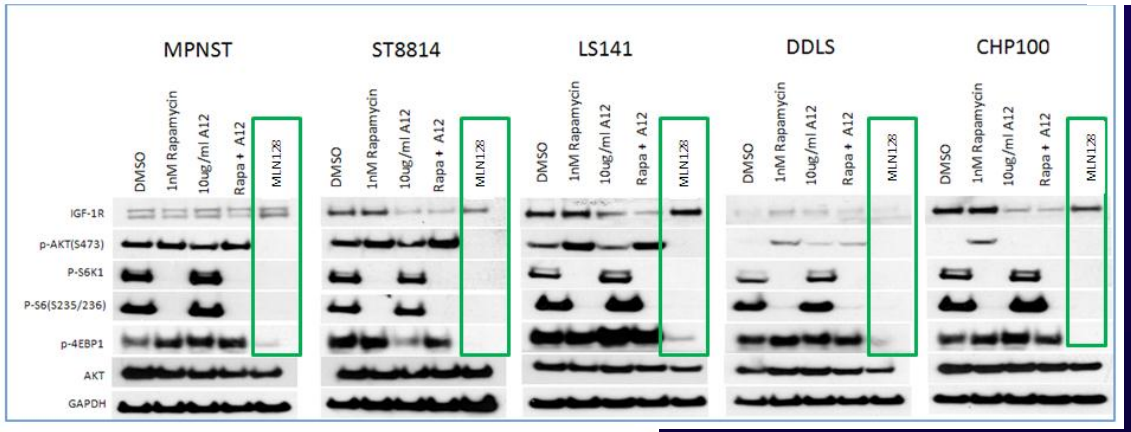
# PAN-mTOR INHIBITORS

- 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.

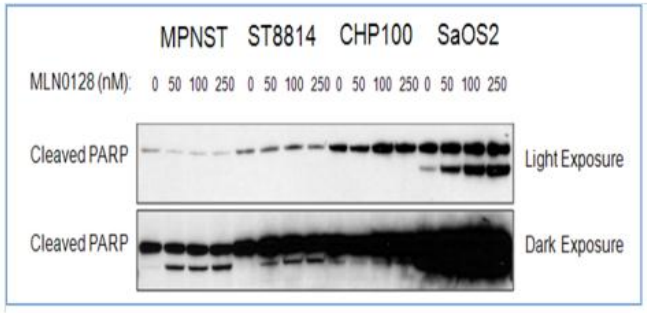
# MLN-128 Pre-Clinical Investigations



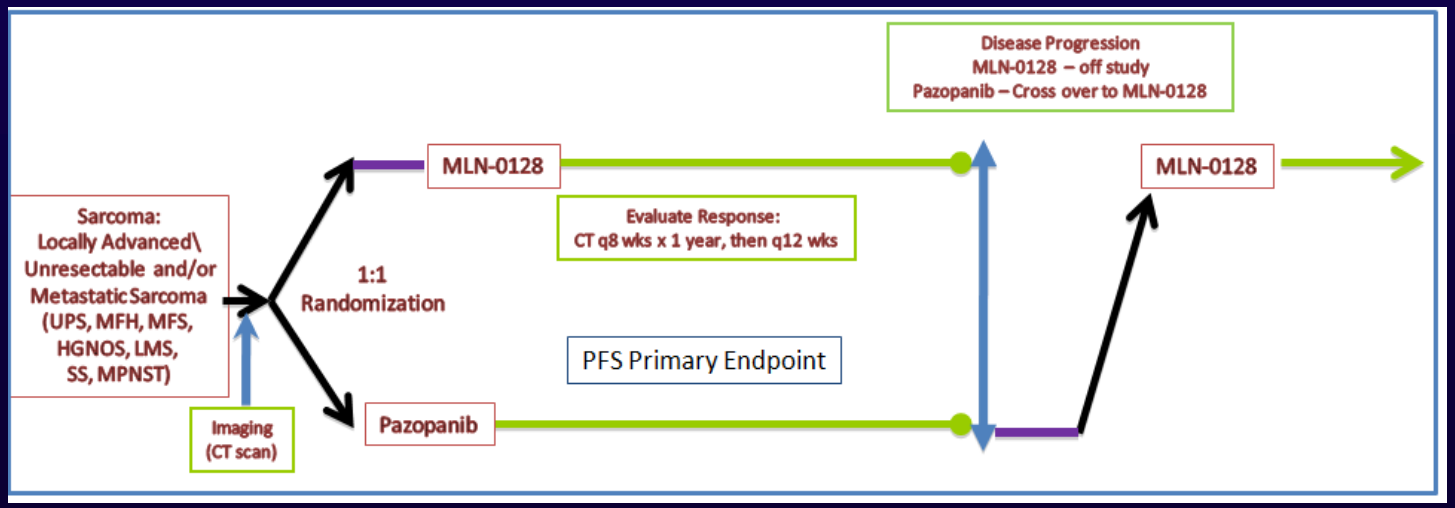





Schwartz, Tap unpub data

# 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/MFX), Leiomyosarcoma, MPNST, Synovial Sarcoma.
- Age 18 or older; Randomized 1:1 fashion
  - Stratified by number priors and sarcoma subtype
    - UPS/MFH/MFS 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

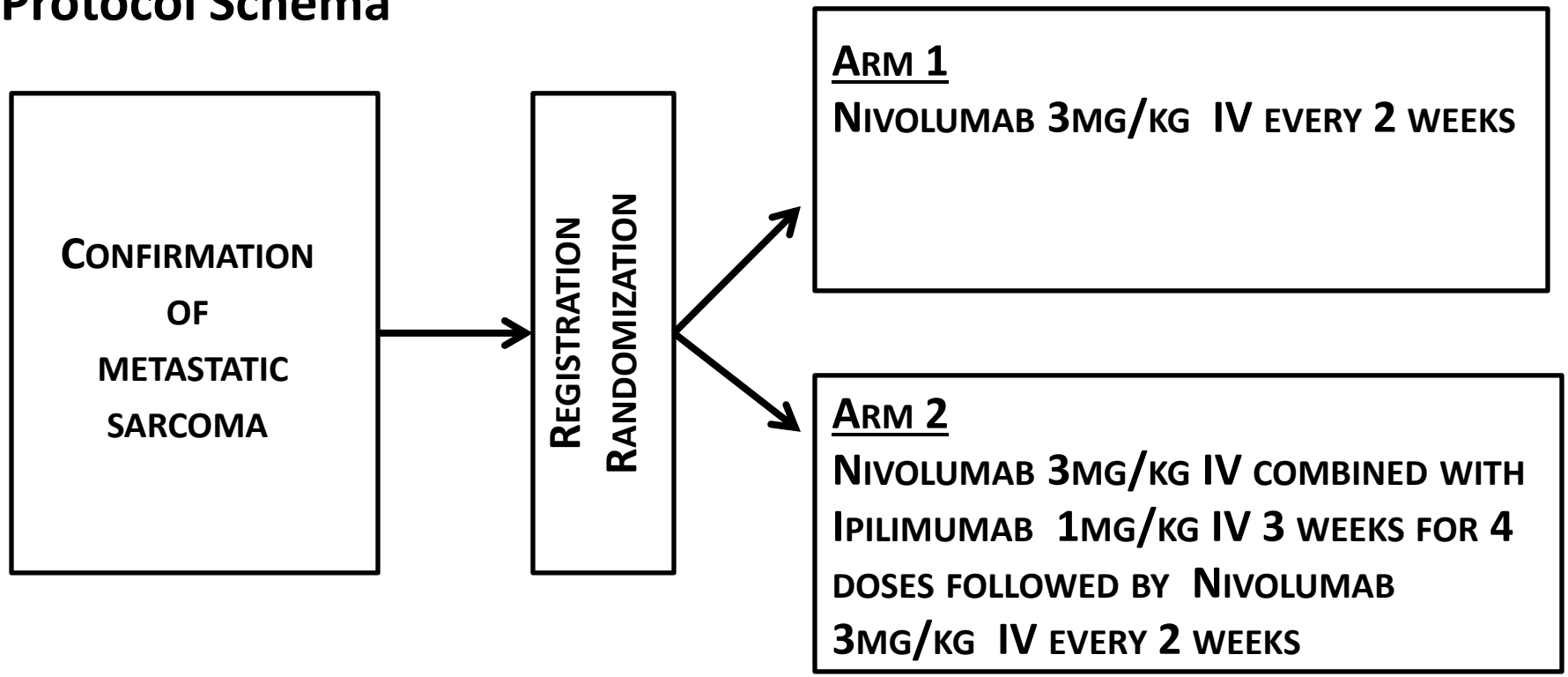
# Thank You

tapw@mskcc.org

# A091401: 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: Nathan Foster

## Protocol Schema



# A091401: A phase II study of nivolumab with or without ipilimumab in patients with metastatic or advanced sarcoma

**Primary Endpoint**

- To evaluate the confirmed response rate of single agent nivolumab and dual agent nivolumab plus ipilumumab in patients with locally advanced/unresectable or metastatic soft tissue sarcoma.

**Secondary Endpoint**

- To evaluate adverse event rates (NCI CTCAE v4.0) within each treatment arm.
- To evaluate duration of response, clinical benefit rate, time to progression, progression-free survival, and overall survival within each treatment arm.
- To evaluate Immune Response using irRC (Immune Response RECIST), relative to disease measurements collected using RECIST v1.1 and within each treatment arm.
- To assess the potential association between PD-L1 expression (by IHC) and clinical outcome, within each treatment. (integral biomarker)

**Correlative Endpoint**

- To evaluate the association between baseline tumor mutational burden and neoantigen production with clinical efficacy within each treatment.
- To evaluate associations between selected biomarker measured in serial peripheral blood and tumor tissue and with clinical efficacy, within each treatment.

# A091401: A phase II study of nivolumab with or without ipilimumab in patients with metastatic or advanced sarcoma

- Two independent phase II studies will be conducted concurrently and patients will be randomized to receive one of the two treatments.

- A confirmed response rate being at most 5% (clinically inactive) versus a confirmed response rate of at least 20% (clinically active). The confirmed response rate will be estimated as the number of patients having a best objective tumor status of CR or PR lasting at least 4 weeks, divided by the number of evaluable patients.

- *Study Design for both treatment arms:*
  - Stage 1: Enroll 18 patients to each arm. If no confirmed responses are observed in 18 evaluable patients for a given treatment arm, stop accrual to that treatment arm for inactivity. Otherwise, proceed to Stage 2 for that treatment arm.
  - Stage 2: Enroll an additional 20 patients to each treatment arm that passed the stage 1 criteria. If at least 3 of 38 evaluable patients have a confirmed response for a given treatment arm, we will declare that treatment arm as promising and recommend larger studies.
  - This design yields 94% power to detect a true confirmed response rate of at least 20%, with a 10% significance level if the true confirmed response rate is 5%. There is a 70% chance of stopping early for “non-favorable” results if the true confirmed response rate is at most 5% and a 40% chance of stopping early for “favorable” results if the true rate is at least 20%

**A091401: A phase II study of nivolumab with or without ipilimumab in patients with metastatic or advanced sarcoma**

- Current status
  - CTEP approved
  - Current in protocol development

- Status of concepts

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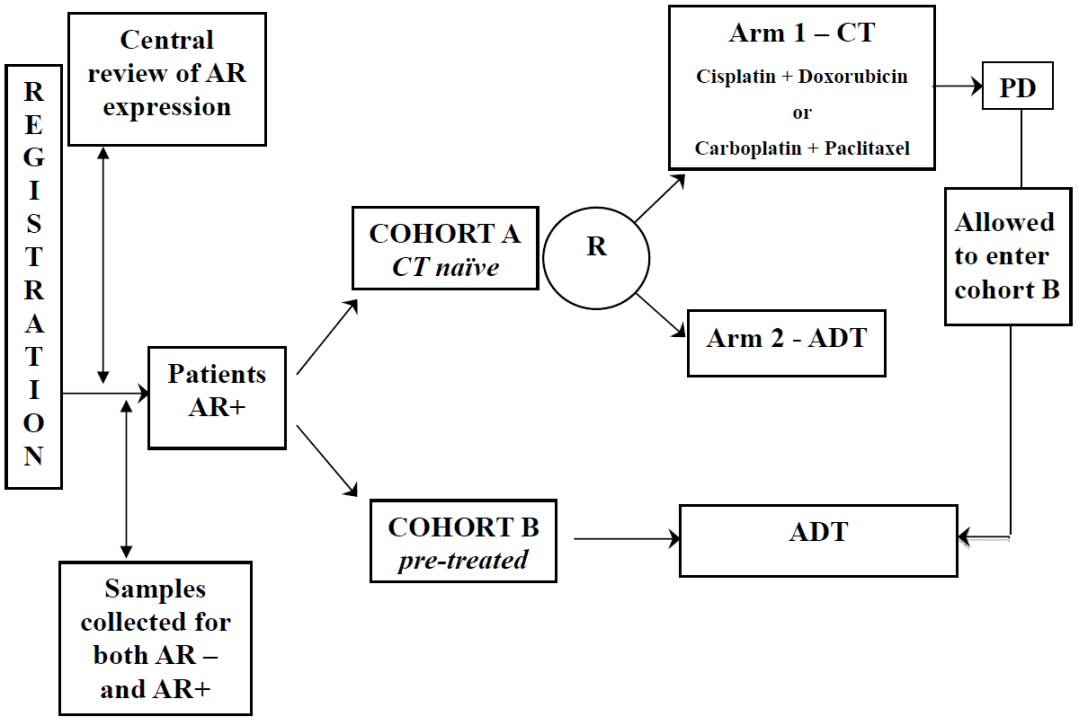
# A091306/EORTC 1206: Androgen Receptor Targeting in Salivary Cancers (IRCI)

Alan L. Ho M.D., Ph.D.
Head and Neck Medical Oncology Service
Memorial Sloan Kettering Cancer Center


Memorial Sloan Kettering Cancer Center™

# A091306/EORTC 1206: 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

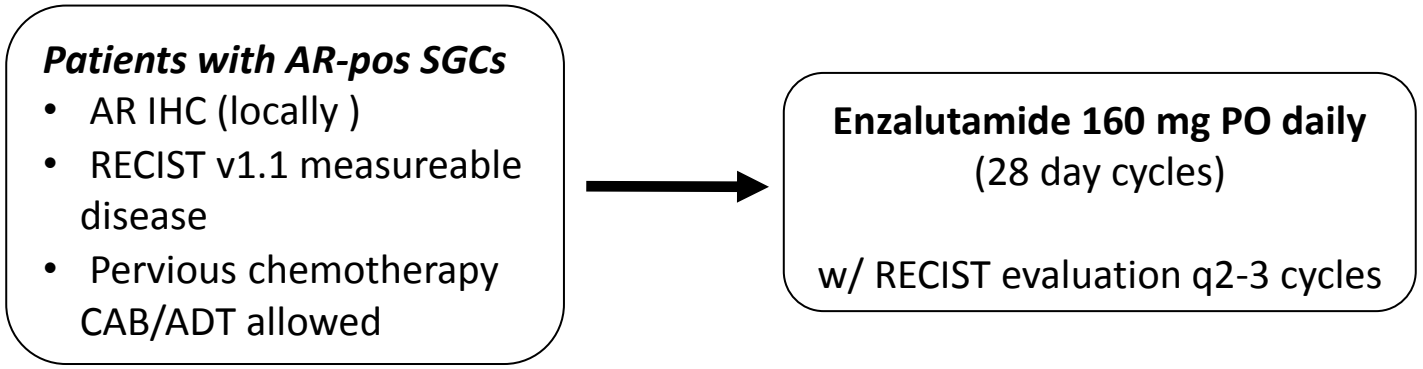
**COHORT B**

**Primary endpoint:** Best overall response

# Obstacles to International Collaborations

- EORTC is currently unwilling to make changes to the protocol and study design required by the NCI Head and Neck Steering Committee and the Rare Tumors Task Force.
- The NCI currently has an active and open-ended moratorium on all international collaborations.
- Drug supply and distribution issues remain a challenge.

# A Phase II Study of Enzalutamide for Patients with AR-Positive Salivary Cancers (Astellas)




Primary Endpoint: Rate of best overall response (BOR)

Optimal 2-stage design: $H_0$= 5%, $H_1$= 20% ; Type 1= 5% and Power= 90%
Need 1 response in the first 20 patients to enroll an additional 21 patients (Total n = 41)
Goal: 5 responses out of the total 41

Secondary Endpoint: PFS, OS, safety/tolerability

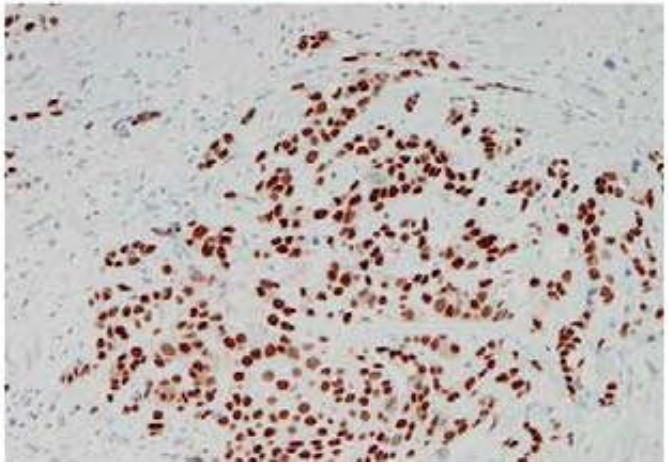
# Androgen Receptor Expression in Salivary Cancers

Significant AR expression is high in salivary duct carcinomas (SDC) and adenocarcinoma NOS subtypes (not in normal salivary tissue)

- 43-100% positivity in SDC
- 21-29% in adenocarcinoma NOS

(also carcinoma ex pleomorphic adenoma, basal cell adenocarcinomas)

***AR IHC in SDC***



**56/84 (67%) AR positivity in salivary duct carcinoma (SDC)**

*Williams, MD, et. al. Am J. Surg. Pathol. 31(11): 1645-1652, 2007.*

# Therapeutic Approaches to Targeting AR in Cancer

***Androgen Deprivation Therapy (ADT):*** *Suppress circulating androgens*

<u>To suppress gonadal sources</u>
- Surgical castration (bilateral orchiectomy)
- Medical castration (LHRH agonists/antagonists)

<u>To suppress non-gonadal sources (adrenals, tumor)</u>
- Ketoconazole, aminoglutethimide. etc..
- Abiraterone (irreversible inhibitor of CYP17)

***AR-antagonists (antiandrogens):*** *Bind AR directly to block ligand binding*

<u>1st generation drugs</u>
flutamide, bicalutamide, nilutamide, cyproterone acetate

# Androgen Deprivation Therapy (ADT) for AR positive Salivary Cancers


- 7 AR-positive salivary cancer patients treated with combined androgen blockade (GnRH agonist + antiandrogen (bicalutamide or cyproterone))
  - 3 adenoca; 3 SDC; 1 mucoepidermoid (?)
  - **1 CR, 4 PRs, 1 SD, 1 PD**
  - Unpublished update of the data with now 16 patients with **3 CRs/4 PRs (RR of 44%) and median TTP of 12 months** (range 2-43 mos)
- 10 SDCs treated with ADT (bicalutamide +/- GnRH agonist)
  - **2 PRs, 3 SD, 5 PD**
  - Median PFS of 12 months
  - 1 response was seen in a female patient
- Two case reports of response to abiraterone in AR + salivary adenocarcinoma NOS (one responder tumor was Her2 amplified).

*Locati et. al., Ann Oncol., 2003.*
*Locati et. al., Ann Oncol., 2003.*
*Jaspers et. al., J. Clin. Oncol., 2011.*
*Locati et. al., Cancer Biol Ther, 2014.*

# Enzalutamide (MDV3100): A second-generation AR-antagonist (Astellas)

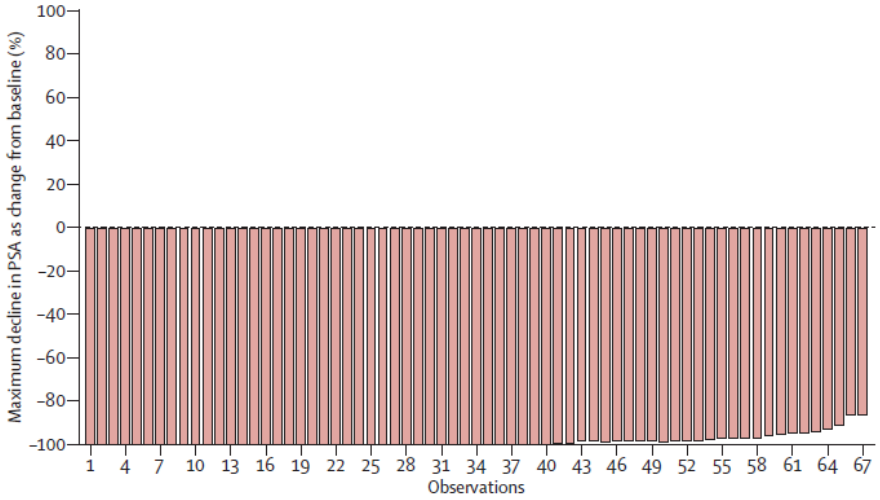
Mechanisms of Action

Rationally designed based upon structure-activity analysis
5-8 fold greater affinity for AR compared to bicalutamide
Blocks AR nuclear translocation
Interferes with the recruitment of AR transcriptional co-activators
Induces AR conformational changes to prevent binding to target DNA sequences

Clinical Data

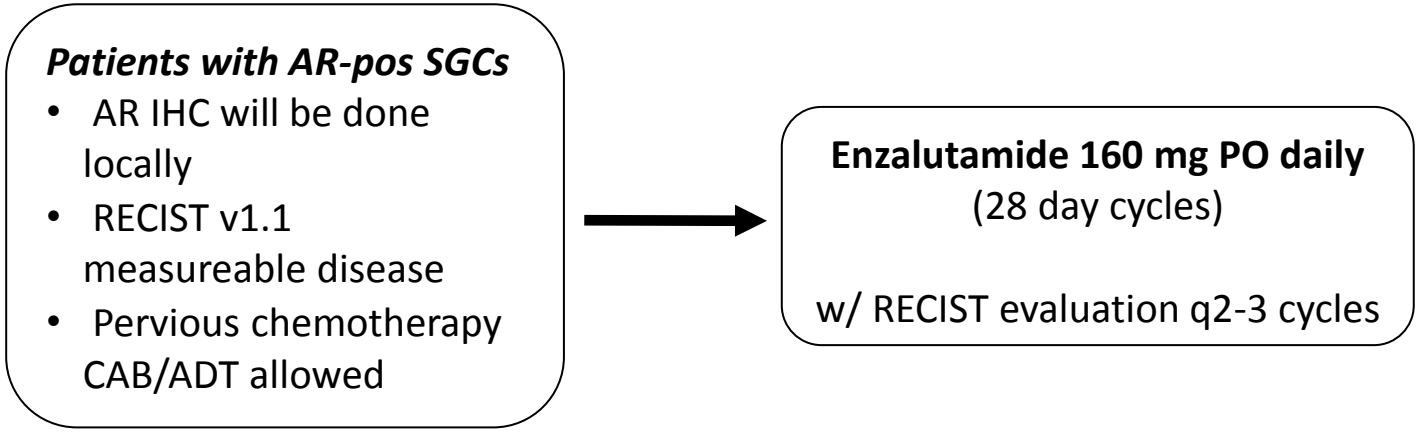
Two positive phase III trials demonstrated that enzalutamide improves OS over placebo in patients with castration-resistant prostate cancer when given either before or after chemotherapy.

One phase II trial demonstrated that enzalutamide was also efficacious for hormone-naïve prostate cancer patients.




Tombal et. al., Lancet Oncol, 2014

# A Phase II Study of Enzalutamide for Patients with AR-Positive Salivary Cancers




Primary Endpoint: Rate of best overall response (BOR)

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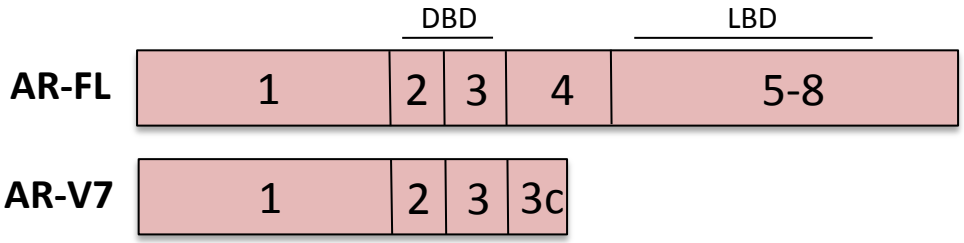
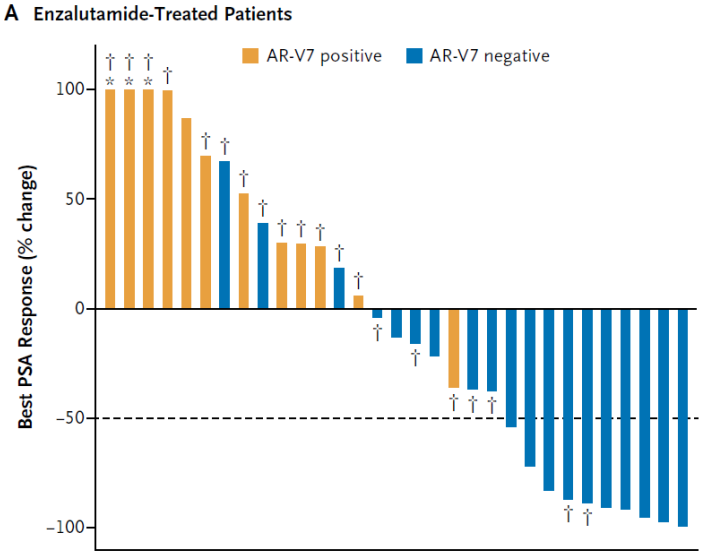
Need 1 response in the first 20 patients to enroll an additional 21 patients (Total n = 41)
Goal: 5 responses out of the total 41

Secondary Endpoint: PFS, OS, safety/tolerability

# Mechanisms of Resistance to AR-Targeting

AR gene amplification
AR gene missense mutations
Tumoral production of androgens
Cross talk with parallel signaling pathways (Her2, PI3k/Akt, etc…)
AR splice variants




Antonarakis, *NEJM*, 2014

Mitani et. al., *Clin Cancer Res*, 2014 (35 salivary duct carcinomas (SDCs))
77% SDCs positive for AR by IHC
13/35 possessed AR-V7 variants

# Proposed Correlative Tissue Analyses

2 Research Biopsies: Pre-therapy and at time of progression

Whole exome analysis
(*AR mutations, amplifications, parallel pathway analysis*)

RNAseq
(*AR variants, AR target genes*)

If fresh tumor biopsies not performed, archival tissue will be used to prioritize AR gene and transcript analysis

# Next Steps

- NCI/CTEP approval of concept
- Protocol development
- Identify funding for correlative studies

# B SMART

BIOMARKER DRIVEN THERAPY FOR SARCOMA VIA MOLECULAR PATHWAYS, ANGIOGENESIS, RECEPTORS, AND NOVEL THERAPIES

***Mission:***

- **Develop targeted therapy in sarcoma based on pathogenesis of the individual tumor rather than the standard model of sarcoma histologic subtype**

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# B SMART

BIOMARKER DRIVEN THERAPY FOR SARCOMA VIA MOLECULAR PATHWAYS, ANGIOGENESIS, RECEPTORS, AND NOVEL THERAPIES

## *Rationale:*

- **Current lack of effective treatments for sarcoma**
- **Model of GIST as a success story**
- **Lowered success when targeted agent is studied without biomarker positivity**
- **Biomarkers cross sarcoma histologic subtypes**
- **Not all biomarkers work across malignancies.**
- **Sarcoma differs biologically from epithelial malignancies**

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***Method:***

- **Patients have a multi-biomarker panel tested on their tumor tissue, and treatment is determined by the results.**
- **Upon progression, biopsy performed to investigate resistance mechanisms**

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***Design:***

- **Multi-cohort trial:**
  - **Biomarker positive drug cohorts**
  - **Biomarker negative drug cohort**
- **Primary Endpoint:**
  - **Progression free survival (16 week)**
- **Secondary Endpoints:**
  - **Response Rate**
  - **Overall Survival**
  - **Toxicity**
  - **Correlative Science**

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## *Key Eligibility:*

- **Locally advanced or metastatic sarcoma**
- **Measurable disease**
- **Adequate performance status (0 or 1), normal organ function, toxicity recovery (grade 0 or 1)**
- **Any number of prior lines of therapy**

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| Drug | Biomarker |
|---|---|
| mTOR inhibitor | PTEN mutation, PTEN loss, cMET phosphorylation |
| $PI_3K$ inhibitor, Akt inhibitor, $TORC_{1,2}$ inhibitor | PTEN loss, $PI_3K$ mutation |
| PARP inhibitor | PTEN loss, BRCA mutation |
| CDK Inhibitors | $CDK_1$, $CDK_4$ amplification, $CDKN_2A$ |
| $MDM_2$ antagonist or $HDM_2$ antagonist | $Tp_{53}$ mutation or loss, $MDM_2$ amplification |
| MET inhibitor | cMET upregulation |
| MEK inhibitor | MEK, $NF_1$ mutation, $MAP_3K_5$ amplification, BRAF mutation, $FLT_4$ amplification, Ras mutation, c-myc overexpression |
| AURK A,B inhibitor | AURK amplification |

**Biomarker positive cohorts**

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BIOMARKER DRIVEN THERAPY FOR SARCOMA VIA MOLECULAR PATHWAYS, ANGIOGENESIS, RECEPTORS, AND NOVEL THERAPIES

| Drug | Biomarkers |
|---|---|
| $IDH_{1/2}$ inhibitor | $IDH_{1/2}$ |
| $CSF_1R$ inhibitor | $CSF_1R$ , $FLT_3$ |
| FGFR inhibitor | FGFR mutation or overexpression |
| Wnt inhibitor | Wnt/beta-catenin: overexpression |
| SMO inhibitor | Hedgehog overexpression |
| $IGF_1R$ inhibitor | $IGF_1R$ upregulation |
| RAR modulator | RAR expression |

**Additional potential biomarker positive cohorts**

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# B SMART

BIOMARKER DRIVEN THERAPY FOR SARCOMA VIA MOLECULAR PATHWAYS, ANGIOGENESIS, RECEPTORS, AND NOVEL THERAPIES

| Drug | Biomarker |
|---|---|
| ALK inhibitor | ALK mutation |
| Bcl2 inhibitor<br>NOTCH inhibitor | NOTCH mutation |
| TERT vaccine | TERT mutation |
| PDK1 inhibitor | PDK1 |
| PDGFR inhibitor | PDGFR |
| KDR inhibitor | KDR (VEGFR2) |
| antiER, antiAR | Steroid receptors |
| Her2 Inhibitor | Her2 expression |
| Doxorubicin | TOPO2 overexpression |
| CDK4/6 inhibitor | RB decreased expression |
| EGFR inhibitor | SMAD loss, EGFR overexpression |

**Additional potential biomarker positive cohorts**

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## Biomarker Negative Cohorts:

| Generalized Mechanism | Specific Pathway |
|---|---|
| Immunotherapy | PD1<br>PDL1 |
| Epigenetics | HDAC<br>Methylation |
| Antiangiogenesis | |

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BIOMARKER DRIVEN THERAPY FOR SARCOMA VIA MOLECULAR PATHWAYS, ANGIOGENESIS, RECEPTORS, AND NOVEL THERAPIES

## *B SMART SCIENTIFIC STUDY TEAM:*

- **Global Study Chair: Dr. Gary Schwartz, Columbia University Medical Center**
- **Committee Chairs: Dr. Charles Erlichman, Mayo Clinic, and Dr. Gary Schwartz**
- **Statistician: Dr. Lindsay Renfro, Mayo Clinic**
- **Executive Officer: Dr. Elise Horvath**

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## *B SMART SCIENTIFIC STUDY TEAM:*

- **Drug Cohort Study Chairs:**
  - **Dr. Bob Maki, Mt. Sinai**
  - **Dr. Bill Tap, MSKCC**
  - **Dr. Mark Dickson, MSKCC**
  - **Dr. Suzanne George, DFCI**
  - **Dr. Richard Riedel, Duke University**
  - **Dr. Steve Robinson, Mayo Clinic Florida**

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BIOMARKER DRIVEN THERAPY FOR SARCOMA VIA MOLECULAR PATHWAYS, ANGIOGENESIS, RECEPTORS, AND NOVEL THERAPIES

## *B SMART SCIENTIFIC STUDY TEAM:*

- **Drug Cohort Study Chairs:**
  - **Dr. Brian Van Tine, Washington University**
  - **Dr. Mark Agulnik, Northwestern (ECOG)**
  - **Dr. Scott Okuno, Mayo Clinic Rochester**
  - **Dr. Chris Ryan, OHSU (SWOG)**
  - **Dr. Robin Jones, University of Washington (SWOG)**
  - **Dr. Bartoz Chmielowski, UCLA**

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BIOMARKER DRIVEN THERAPY FOR SARCOMA VIA MOLECULAR PATHWAYS, ANGIOGENESIS, RECEPTORS, AND NOVEL THERAPIES

## *B SMART SCIENTIFIC STUDY TEAM:*

- **Biomarker Chair: Dr. Mark Ladanyi, MSKCC**
- **Pathology Chair: Dr. Christina Antonescu, MSKCC**
- **Radiology Chair: Dr. Larry Schwartz, Columbia University Medical Center**
- **Global Correlative Science Chair: TBD**
- **Community Oncology Chair: Dr. Samir Undevia, Edward Hospital/University of Chicago**

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# B SMART

**BIOMARKER DRIVEN THERAPY FOR SARCOMA VIA MOLECULAR PATHWAYS, ANGIOGENESIS, RECEPTORS, AND NOVEL THERAPIES**

## Questions?

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# Reversing Resistance to Pazopanib with Histone Deacetylase Inhibition

Study Chair: Pamela Munster, MD

Co-PI: Rahul Aggarwal

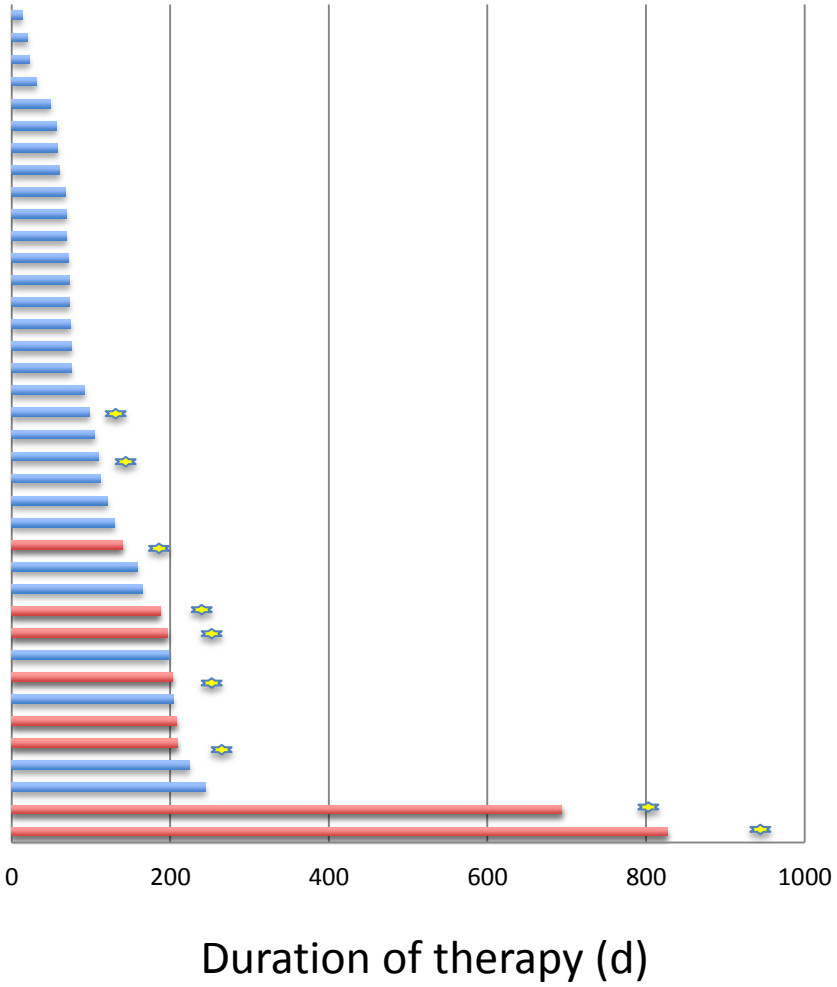
# Background

- Pazopanib has broad activity across multiple solid tumors
  - Renal cell – FDA approved, first-line treatment
  - Sarcoma – FDA approved, second+ line
  - Pancreatic NET – investigational, preliminarily efficacious
- However disease resistance is universal
  - Median PFS in front-line RCC is ~ 11 months
  - tumor responses are infrequent
- Rebound tumor growth may occur following cessation of VEGF-directed therapies
  - Treatment beyond progression clinically validated treatment strategy
    - E.g. bevacizumab in colon cancer

# HDAC inhibition may reverse resistance to VEGF-directed therapy

- Pre-clinical models suggest epigenetic modulation with HDACi may reverse resistance to VEGF inhibitors

- Phase 1 study of pazopanib in combination with pan-HDACi abexinostat
  - Tumor shrinkage observed in pts with prior progression on VEGF-targeting drugs including pazopanib
  - Prolonged disease stabilization in subset of pts
  - Well tolerated using 3 weeks/ on/ one week-off HDACi dosing schedule



# Proposed Study

- Phase 1b/2 study of pazopanib in combination with panobinostat in advanced solid tumor after progression on VEGF inhibitors

Rationale/Hypothesis:

- epigenetic modulation with a histone deacetylase inhibitor (HDACi) prevents outgrowth of resistant phenotype and reverse resistance to PAZ monotherapy
- Histone acetylation in PBMCs ex vivo is a predictor for response
- Panobinostat is more potent with better characterized safety profile than abexinostat

# Study Population

- Phase 1b (N = 3-12)
  - Any solid tumor histology with biologic rationale for targeting VEGFR and/or HDAC
  - No limit on number of prior therapies including pazopanib monotherapy
- Phase 2 (N = 29)
  - Patients with prior resistance to pazopanib monotherapy across multiple solid tumor malignancies with known response to VEGFR inhibition
    - Includes renal cell, sarcoma, and other emerging tumor types including PNET
  - Must have had radiographic progression on pazopanib monotherapy as most recent systemic anti-cancer therapy prior to study enrollment

# Study Endpoints

- Primary:
  - Phase 1b: MTD of panobinostat in combination with pazopanib
  - Phase 2: Objective response rate
- Secondary:
  - Safety profile by CTC version 4.0
  - Median progression-free survival
  - Clinical benefit rate (ORR + SD >24w)
- Correlative studies:
  - Association between acetylation status in PBMCs with subsequent clinical outcomes on pazopanib + panobinostat
  - Ex vivo assessment of Histone acetylation
  - Changes in VEGF expression

# Study Design – Phase 1b

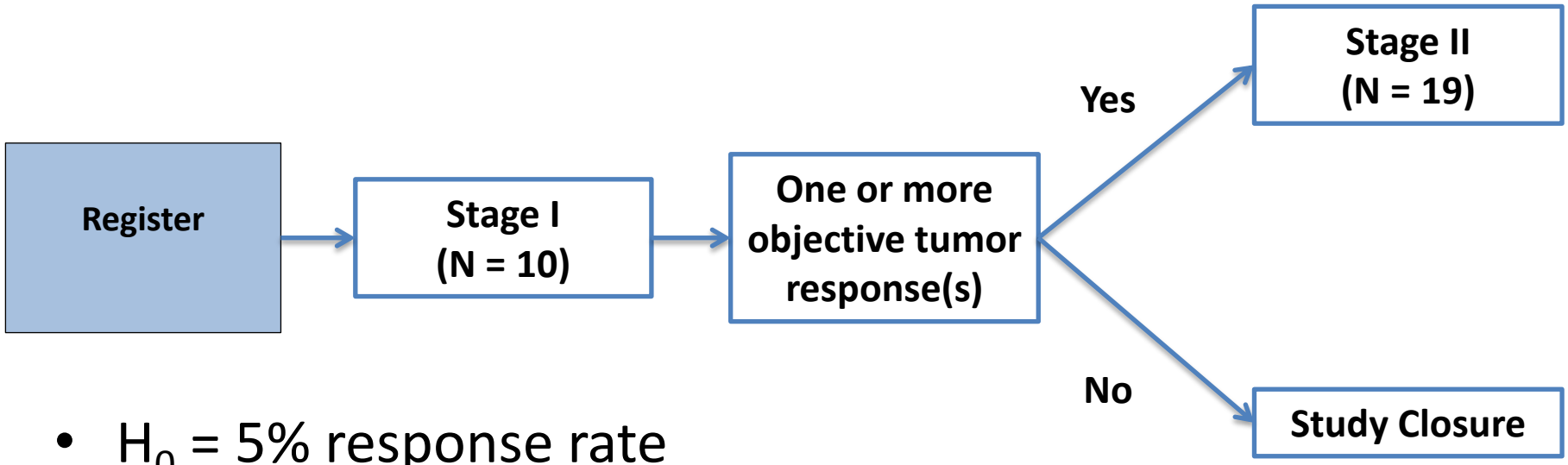
- 3+3 dose escalation
- Dose levels

| Cohort | Panobinostat TIW 2/3 weeks | Pazopanib (mg) Daily |
|---|---|---|
| -1 | 20 | 600 |
| 1 | 20 | 800 * |
| 2 | 30 | 800 * |
| 3 | 40 | 800 * |
| expansion | MTD | 800 * |

* Or most recent individual patient dose of pazopanib

# Study Design – Phase 2

- Single arm, open-label, Simon two stage optimal design




- $H_0$ = 5% response rate
- $H_A$ = 20% response rate
- If 4 or more pts out of 29 evaluable experience tumor response, null hypothesis rejected with power 0.80 and unidirectional level of significance = 0.05

Thank you

# A phase II study of cetuximab and lapatinib in patients with metastatic/recurrent Head and Neck Squamous Cell Carcinoma

John Deeken, M.D.

Inova Health System

# Head and Neck SCC

- Incidence in US, 2014 (oral cavity, pharynx, larynx):
  - 55,070 new cases (up from 38,530 in 2004)
  - 12,000 deaths
  - 6th most common cancer world-wide
- Metastatic/recurrent disease
  - Median survival is 6 – 11 months
  - Treatment is salvage surgery if localized and cure possible
  - Palliative chemotherapy options:
    - 1st line: platinum + taxane or 5-FU + / - cetuximab
    - 2nd/3rd lines: cetuximab (single agent), methotrexate, taxanes, etc
  - Currently open clinical trials in US for met/recur patients:
    - Only 1 open NCI cooperative group study (ECOG 1305)
    - Only 5 open industry-sponsored multi-site phase II or III trials

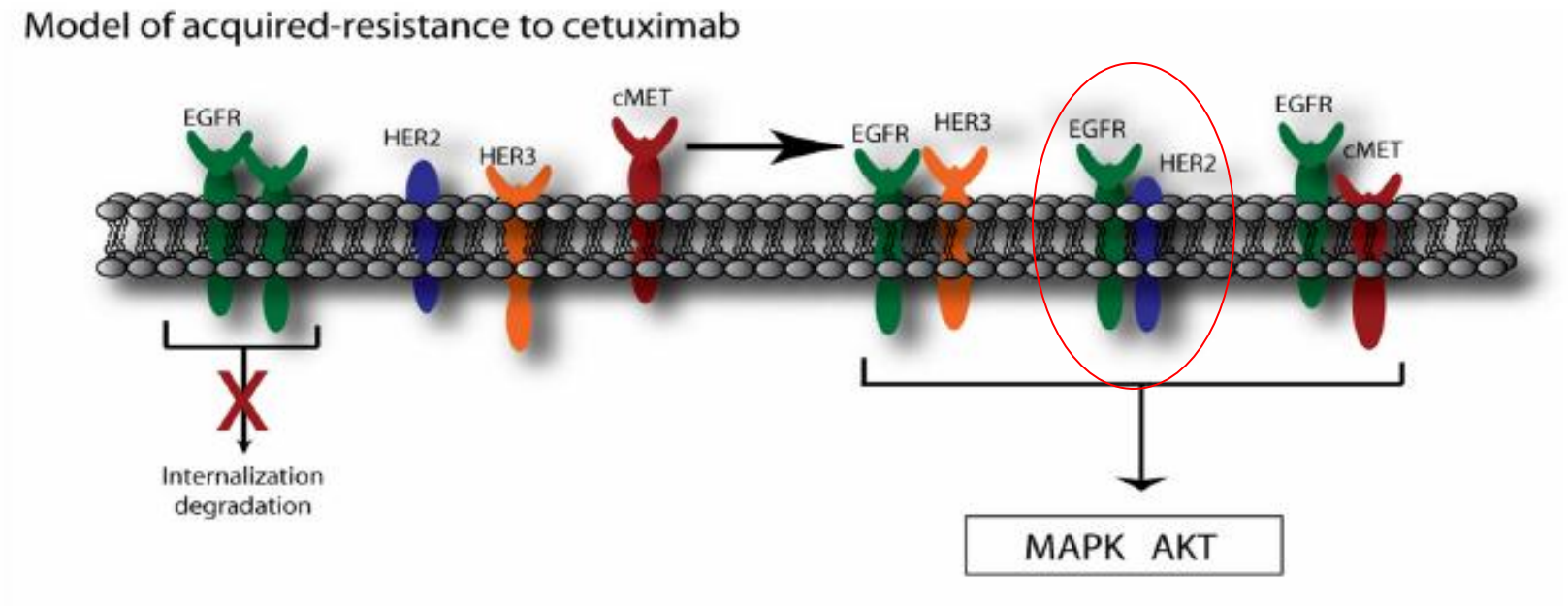
Jemal 2004, Siegel 2014; Colevas 2006, www.cancer.gov, www.clinicaltrials.gov

# EGFR therapy in H&N SCC

- Cetuximab
  - Used in newly diagnosed and recurrent disease
    - with radiation for newly diagnosed locally advanced disease
    - with platinum and 5-FU for 1st line met/recur disease
    - single agent in 2nd line met/recur
      - 10 - 13% partial response rate, up to a 33% stable disease rate, for a total of around a 45% disease control rate
  - Active in HPV-positive and HPV-negative disease
  - No clear predictive biomarker for response/resistance
    - Does not correlate with EGFR expression (similar to CRC)
    - Kras mutations are rare (<2%)
- Mixed results with other EGFR agents in met/recur disease
  - Minimal to no activity: panitumumab, gefitinib
  - Moderate activity:  afatinib, dacomitinib
    - note – dual EGFR/HER2 and pan-ErbB TKIs, respectively

Bonner 2006, Vermoreken 2007, Vermorken 2008, Bonner 2014, Licitra 2013, Vermorken 2013, Argiris 2012, Rischin 2012, Seiwert 2013, Machiels 2014, Abdul 2012

# Acquired Resistance to Cetuximab

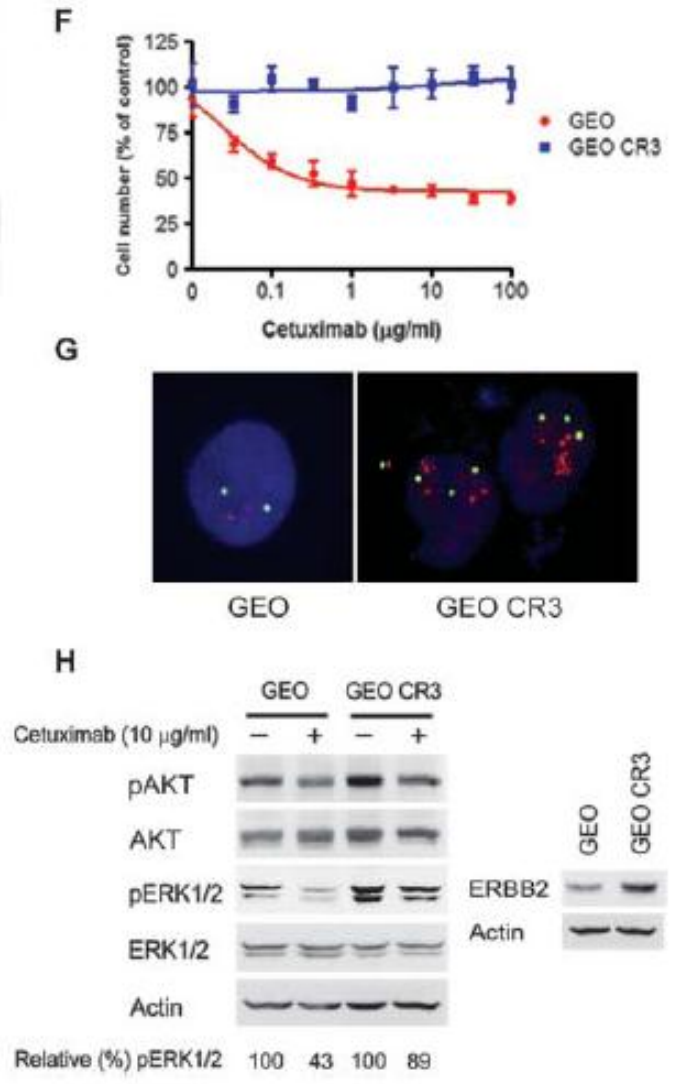



Wheeler *Oncogene* 2008.
Also, Yonesaka 2011, Wang 2014, Erjala 2006, Learn 2006, Rajput 2007, Half 2007, Wheeler 2008, Kondo 2008, Kim 2008

# Cellular Induction of HER2 Causes Cetuximab Resistance

- clone (CR3) has increased HER2 expression

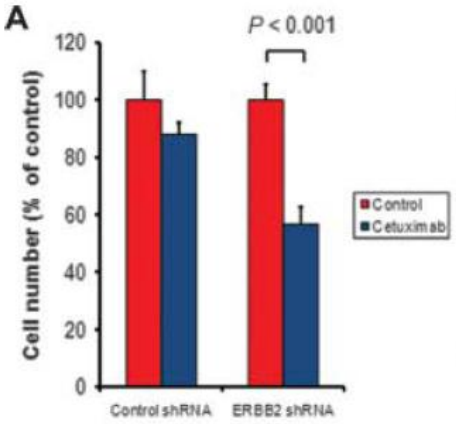
- treatment with cetuximab in resistant clone causes little reduction in pERK (↓11%) compared to parent cell line (↓57%)

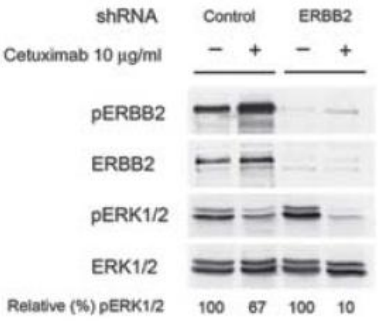


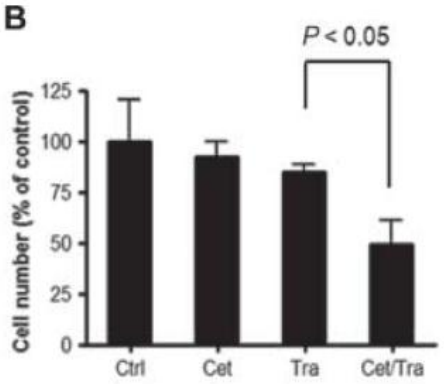

Yonesaka *Sci Tranl Med* 2011

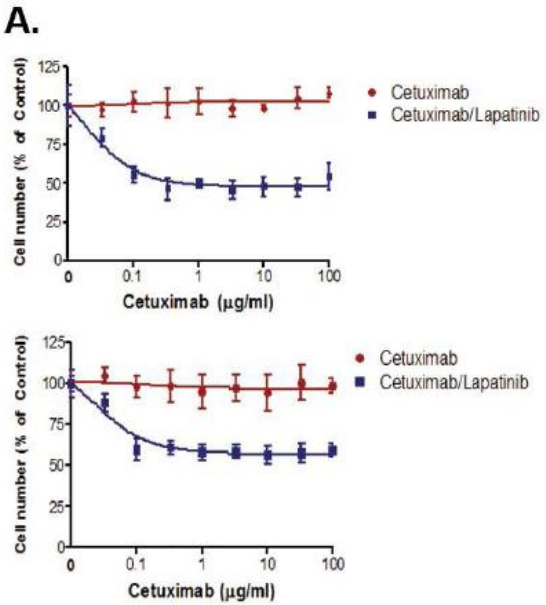
# Dual EGFR + HER2 treatment reversed Cetuximab resistance

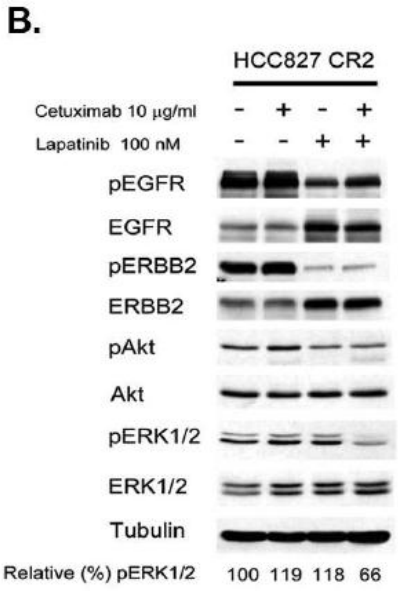
- siRNA knockdown of HER2 resensitizes resistant clone to cetuximab
- Combination of cetuximab and traztuzumab or lapatinib overcomes resistance
- Treatment with cetuximab and lapatinib down regulates pEGFR and pHER2, resulting in decreased pAKT and pERK1/2



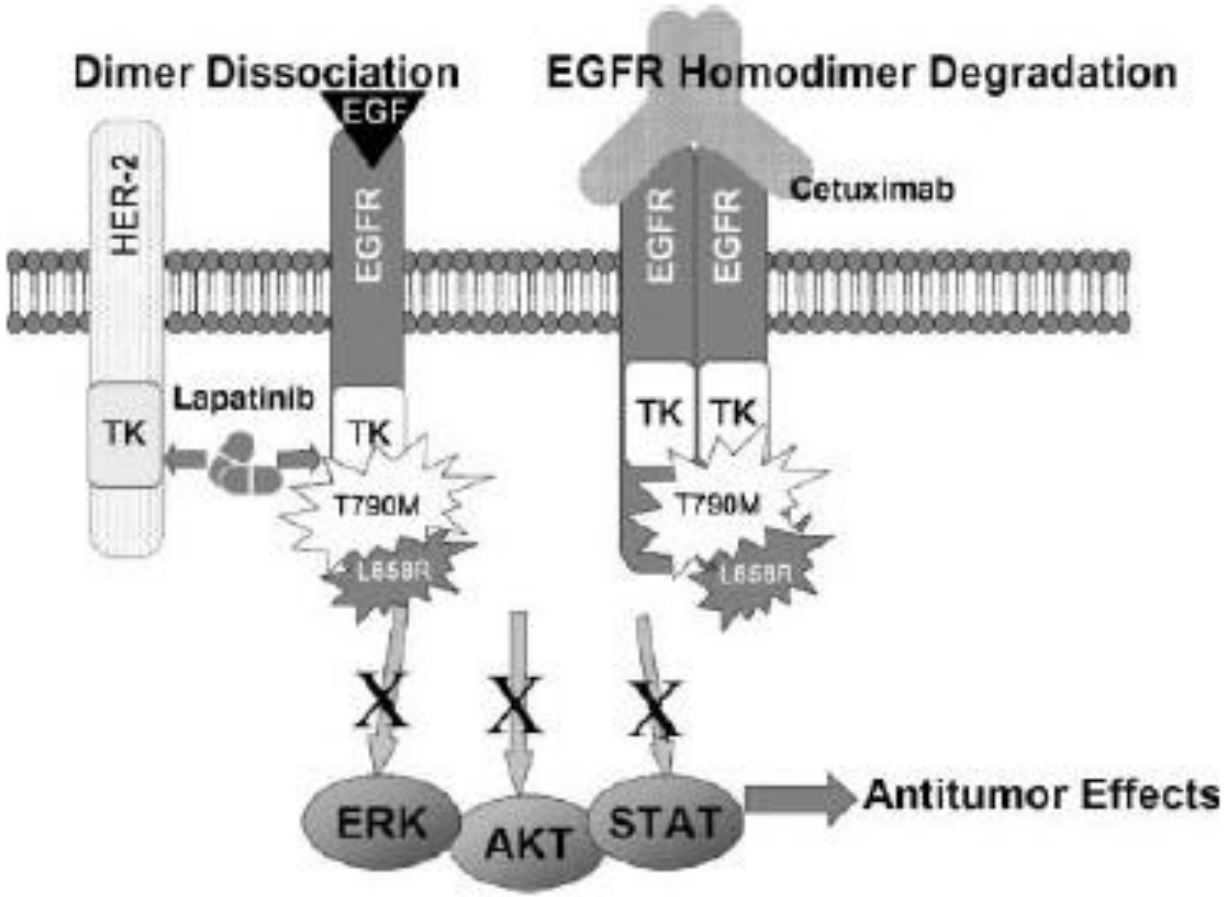




Yonesaka *Sci Tranl Med* 2011

# Proposed mechanism for synergy from combined cetuximab and lapatinib treatment




Kim *Mol Cancer Ther* 2008

# Phase I trial of Cetuximab + Lapatinib

- Single institution (Georgetown), investigator initiated
- 3+3 dose escalation design
- Patients: cetuximab sensitive cancers (circa 2010):
  - colorectal (Kras wildtype), head and neck, anal, and non-small cell lung cancers
  - Prior EGFR therapy allowed
- Skin rash care starting on Day -1 (Lacourture 2010):
  - Sunblock (SPF≥15), moisturizing cream, 1% topical cortisone cream and oral Doxycycline (100mg po bid).
- Dose levels:

| Dose Level | Cetuximab (mg/m2 per week) | Lapatinib (mg per day) |
|---|---|---|
| 1 | 400/250 | 750 |
| 2 | 400/250 | 1000 |
| 3 | 400/250 | 1250 |

# *RESULTS*

- ***Demographics***
- ***Toxicities***
  - ***18 evaluable pts***
  - ***DLTs (2):***
    - ***Rash - dose level 1 (1/6)***
    - ***Diarrhea - dose level 2 (1/6)***
    - ***No DLTs on dose level 3 (0/6)***
- ***Recommended phase II dose:***
  - ***cetuximab 400/250 mg/m2 IV weekly***
  - ***lapatinib 1250mg po daily***

| Demographic | Result |
|---|---|
| Total Enrolled | 22 |
| Age – mean (range) years | 62 (37 – 83) |
| Gender – male/female | 9 / 13 |
| Primary Disease | |
| Colorectal | 8 |
| Lung | 8 |
| Anal | 2 |
| Head and Neck | 4 |
| Lines of Therapy for Metastatic/ Recurrent Disease – mean (range) | 3.6 (1 – 11) |
| Prior anti-EGFR therapy | 13 (59%) |
| Cycles – mean (range) | 4.5 (1 – 12) |

**Treatment-Related Adverse Events During Cycle 1**

| Toxicity (experienced by >10% of pts) | Grade 1 | 2 | 3 | total |
|---|---|---|---|---|
| ***RASH (Skin, mucous membranes)*** | | | | |
| acne/acneiform | 8 | 3 | 1* | 12 |
| hand-foot skin reaction | 5 | 1 | 0 | 6 |
| Mucositis/stomatitis: oral cavity | 3 | 0 | 0 | 3 |
| ***GASTROINTESTINAL*** | | | | |
| Diarrhea | 7 | 0 | 1* | 8 |
| Nausea | 6 | 0 | 0 | 6 |
| Vomiting | 3 | 0 | 0 | 3 |
| ***CONSTITUTIONAL*** | | | | |
| Fatigue | 3 | 2 | 0 | 5 |
| Anorexia | 2 | 1 | 0 | 3 |

* Dose Limiting Toxicities

Deeken ASCO 2013

# *RESULTS*

- ***Response***

***18 evaluable pts:***

**No CRs**

**3 PRs (17%)**

**10 SD (56%)**

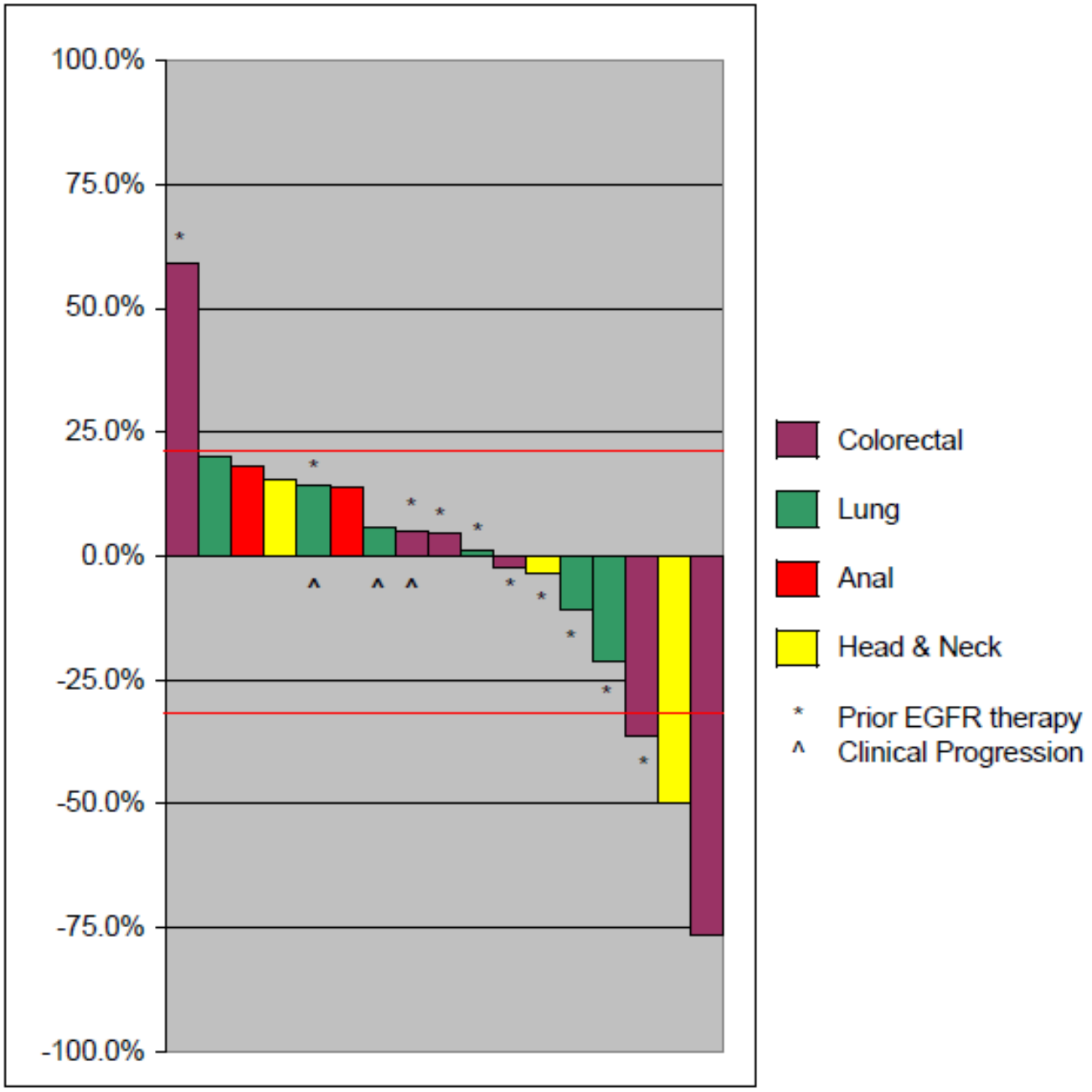
**5 DP (28%)**

In patients previously treated with anti-EGFR therapies, the clinical benefit rate was 70%.

For patients with cancers for which cetuximab has proven efficacy in the metastatic setting, the partial response rate was 33%:

2 of 6 CRC patients

1 of 3 H&N patients




Deeken ASCO 2013

# Alliance Trial Proposal: 2 options

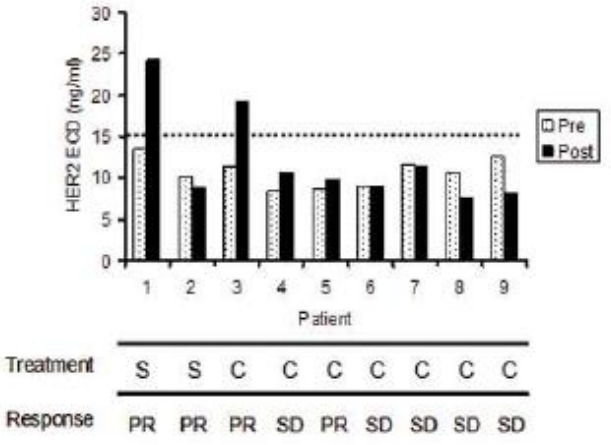
- Phase II trial in patients with metastatic/recurrent H&N SCC
- Treatment and cycle length:
  - Cetuximab 400/250 mg/m2 IV weekly, Lapatinib 1,250 mg po daily
  - Anti-skin rash regimen
  - Cycle length: 4 weeks, Restage every 2 cycles

- Option 1:
  - ***Single arm*** phase II
  - Primary endpoint: response rate
  - Possible design and size:
    - Simon's Two-stage Minimax design, p0=0.10, p1=0.25, α=0.05, β=0.20
    - First stage: n=22. If 3 or more respond, go to second stage: n=18. Positive study if 8 or more respond. Total sample size = 40.

- Option 2:
  - ***Randomized 2-arm*** phase II
  - Cetuximab vs cetuximab + lapatinib
    - Patients on single agent cetuximab arm can cross over to drug combination at time of progression
  - Primary endpoint: response rate
  - Possible design and size
    - p0=0.10, p1=0.33, α=0.05, β=0.20
    - Sample size: 46 per arm, or total of 92

# Possible Correlative Studies

- Plasma circulating levels of HER2 extracellular domain
  - (Siemens Healthcare assay?)




- Germline PGx
  - Collaborate with P&PP committee?

| Gene | SNP | Response | Diarrhea | Rash |
|---|---|---|---|---|
| *CCND1* | rs9344 | | 0.013 | |
| *ERBB2* | rs1136201 | | | |
| *EGF* | rs4444903 | | | |
| *EGFR* | rs2227983 | | | |
| *FcγRIIIA* | rs396991 | | | |
| *FcγRIIA* | rs1801274 | 0.045 | | |
| *CYP3A5* | rs41303343 | | | |
| | rs776746 | | | |
| | rs10264272 | | | |
| *ABCB1* | rs1128503 | | | |
| | rs1045642 | | | |
| | rs2032582 | | | |

- Archived tumor blocks for phosphoprotein expression analysis, including of pEGFR/PHER2
  - Note we could not optimize WB Ab for IHC to measures EGFR/HER2 heterodimers in our phase I

Yonesaka 2011, Deeken 2013

National Cancer Institute

# Molecular Analysis for Therapy Choice (NCI MATCH)

A Joint NCTN/NCI

Clinical Trial

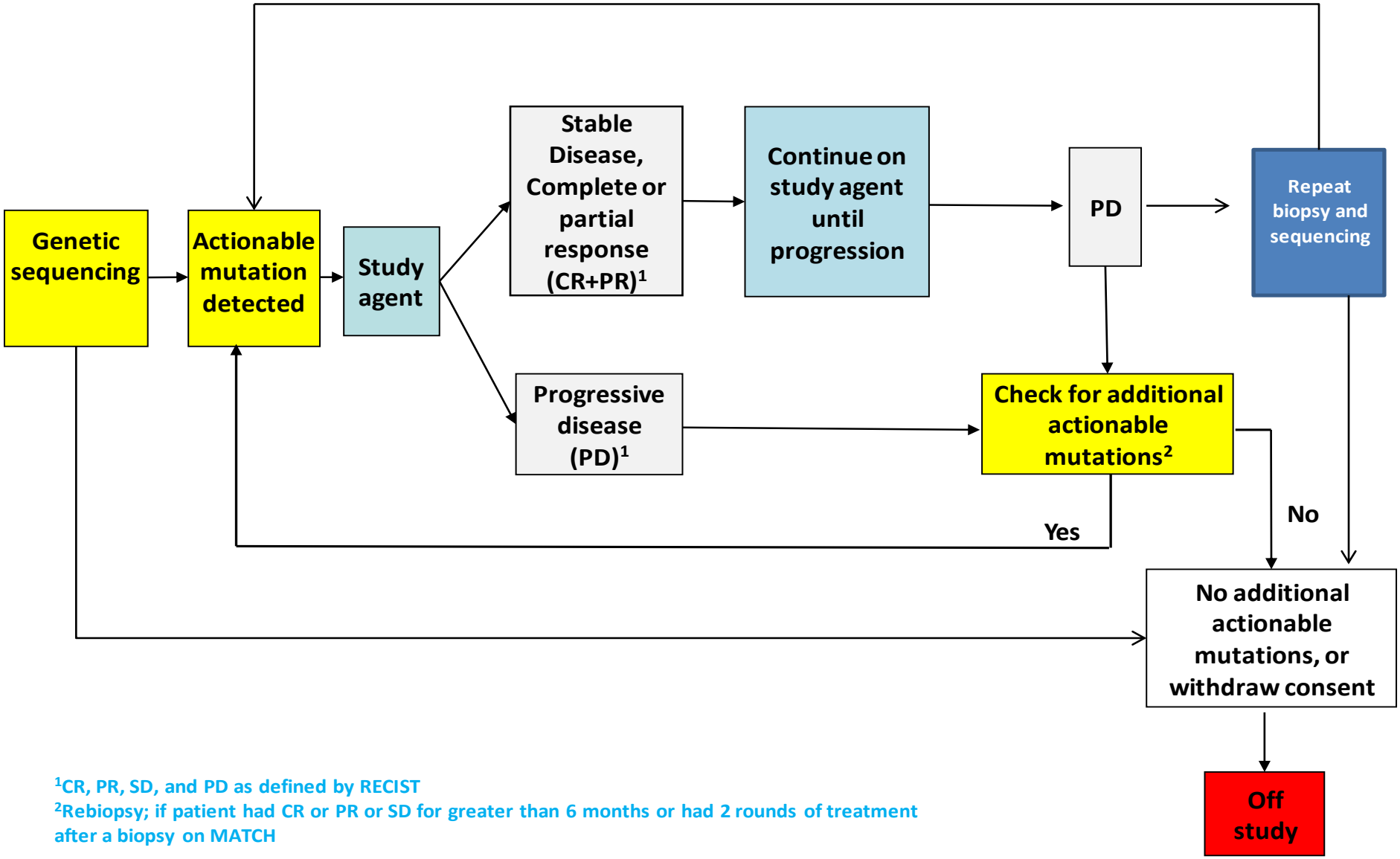
October 2014

National Cancer Institute

# NCI MATCH

- Eligibility molecularly defined; Identify mutations/amplifications/translocations in patient tumor sample - eligibility determination
- Assign patient to relevant agent/regimen
- Need to sequence large numbers of tumors and need to have large numbers of targeted treatments
- Tumor biopsies & sequencing at progression to illuminate resistance mechanisms
  - De-identified samples submitted to central labs
  - Whole-exome, mRNA sequencing (research purposes)

# SCHEMA




[1]CR, PR, SD, and PD as defined by RECIST
[2]Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH

National Cancer Institute

# Eligibility

- Patients with solid tumors or lymphomas whose disease has progressed following at least one line of standard systemic therapy (or with tumors that do not have standard therapy)
  - At the sub-protocol level will exclude histologies that had been approved by the FDA or had shown lack of efficacy with an agent
- Tumor accessible to biopsy and patient willing to undergo biopsy
- Adults
- Performance status ECOG 0-1
- Adequate organ function

National Cancer Institute

# Patient population considerations

- Target: at least 25% of total enrollment to be patients who have “rare” tumors
- “Common” defined as breast, NSCLC, colon, prostate

National Cancer Institute

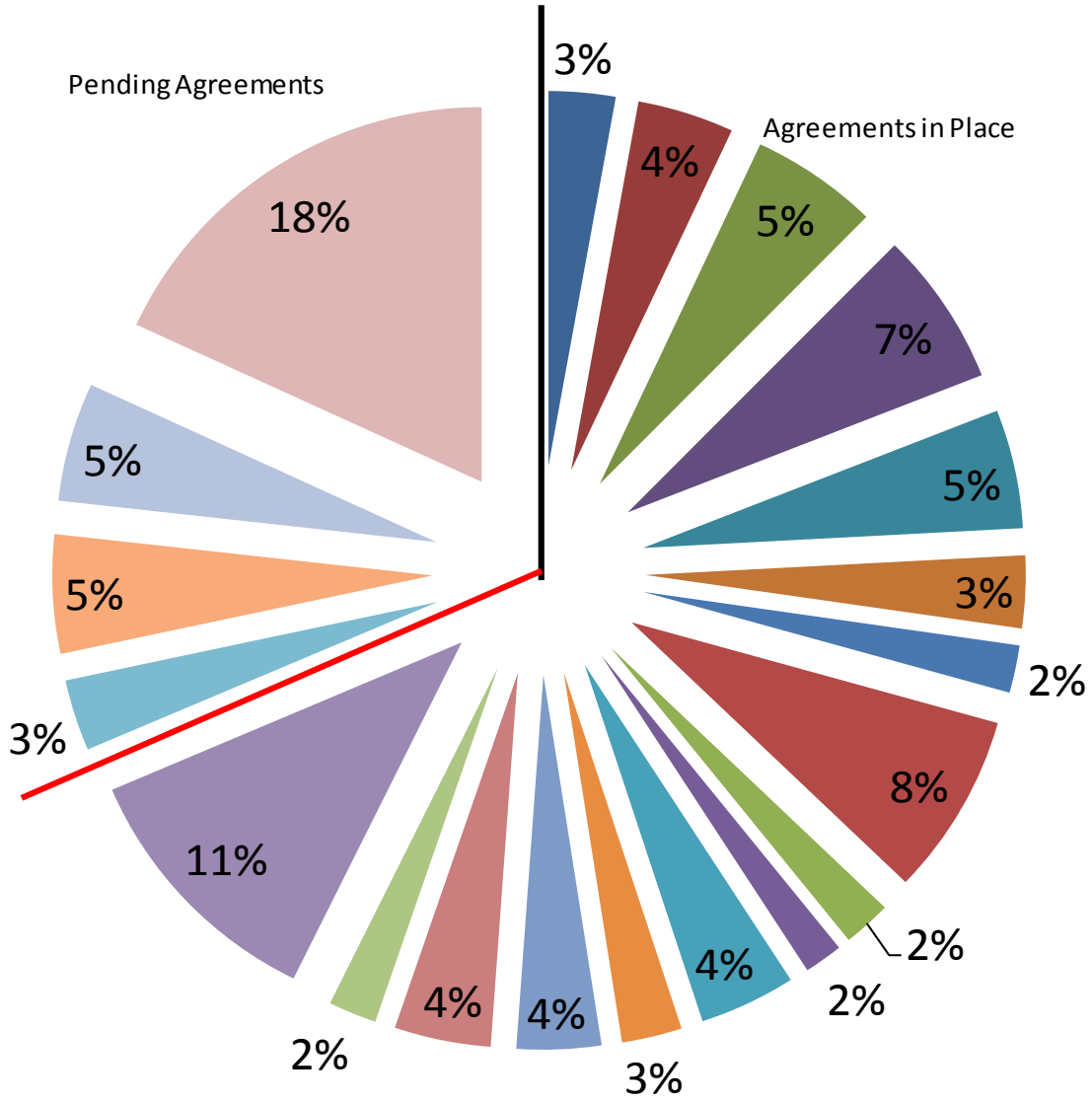
# Statistical Considerations: Each sub-protocol

- Primary Endpoint: Overall Response Rate 5% vs. 25%
- Secondary Endpoints
  - Progression Free Survival 6 months 15% (median PFS 2.2 m) vs 35% (median PFS 4 m)
  - TTP
  - Toxicity
  - Biomarker
- One stage design 31 evaluable patients per arm

National Cancer Institute

# Levels of Evidence: Drugs

- Level 1: FDA approved for any indication for that target; evidence of target inhibition, or proof of mechanism; demonstration that patient selection with CDx are more likely to respond
- Level 2: Agent met a clinical endpoint (objective response, PFS, or OS) with evidence of target inhibition; plausible evidence of a predictive or selection assay/analyte
- Level 3: Agent demonstrated evidence of clinical activity with evidence of target inhibition at some level; some evidence of a predictive or selection assay/analyte




- BRAF fustions or mutatiuons (non-V600E or V600K) (2.79%)
- ALK fusions/translocations - (4%)
- ROS1 transolcations - (5%)
- BRAF V600E or V600K - (1-12%)
- mTOR mutations - (5%)
- TSC1 or TSC2 mutations - (2.6-3.5%)
- T790M mutations - (1-2%)
- NF1 mutations -(7.7%)
- GNAQ - (2%)
- GNA11 - (1.6%)
- cKIT - (4%)
- EGFR activating mutations - (1-4%)
- HER Activating Mutations - (2-5%)
- MET amplifications - (4%)
- NF2 loss - (2%)
- PTEN (mutations and loss) - (11%)
- SMO or PTCH1 mutations -(2.63 and 3.76%)
- HER amplifications - (5%)
- FGFR amplifications or FGFR mutations - (5%)
- PIK3CA mutations - (17-18%)

National Cancer Institute

# Tumor Biopsy

- Screening:  (5 cores) FFPE, shipped to MDACC
- Adjacent section H&E: tumor content,
  % necrosis, inflammation, scan into image database
- Microdissection to 70% tumor
- RNA and DNA extracted
- Planned research assays if sufficient material:
  - whole-exome sequencing rformed for research
  - RNA for research grade mRNAseq
  - Biopsy on progression

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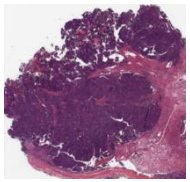
# MATCH Assay *Workflow*

**Biopsy Received**

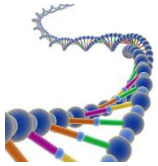
Tissue Fixation Path Review



**Tumor content >70%**

**1 DAY**

Nucleic Acid Extraction



**DNA/RNA yields > 20 ng**

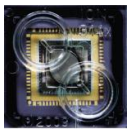
**1 DAY**

Library/Template Prep

**Library yield > 20 pM**

**1 DAY**

Sequencing , QC Checks



**Test fragments**
**Total read**
**Reads per BC**
**Coverage**
**NTC, Positive, Negative Controls**

**1 DAY**

Centralized Data Analysis

**aMOIs Identified**

**3 DAYS**

Clinical Laboratory aMOI Verification

**10-14 days**

**MATCHBOX Treatment Selection**

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# Logistics

- Master Protocol with Multi-arm phase II trials
- IND for protocol template
  - Arms can be added or deleted without affecting other arms
- Single agents or combinations where recommended phase 2 dose is known
- FDA Approved or investigational agents
- Central IRB
- 2400 NCTN sites
- CLIA lab network: validated assays, IDE

National Cancer Institute

# Status

- Concept:  approved by CTEP: Approx 20 arms to start
- Approx. 10 Agents under agreement
- Informatics structure being built
- Sub-protocol principal investigators chosen for about 15 arms
  - Orientations
  - Variant calls
  - Writing of the sub-protocols
- Master Protocol/IC draft being revised
- FDA presub/IDE: ongoing interaction
- Launch planned for Feb 2015

# Experimental Therapeutics Committee Meeting

Saturday, November 8, 2014

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY