Trials and Endpoints in GI Cancer – What is the right signal to go to phase III?

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Where do we stand?

- Only 5% of oncology drug make it from first-in human trials through registration[1]
  - 60% failure rate of randomized phase III trials
- Analysis of all phase II combination chemotherapy trials between 2001 and 2002[2]
  - 72% were reported positive, only 3.8% improved standard of care within 5 years
  - Multiple examples in GI oncology – including vatalinib and perifosine for CRC, bevacizumab and cetuximab for pancreas

1. Kola 2004, 2. Maitland 2010

Making better decisions

- How has drug development changed?
  - Not just a phase I anymore
    - Speed and cost control
    - Incorporation of extended expansion cohorts and phase Ib studies into first-in-human dose escalation studies
  - Single arm phase II vs. randomized phase II
  - Novel endpoints and companion diagnostics
- Can we learn from our successes and mistakes?

The single arm phase II

- Endpoint is based on comparison to historical controls
  - How reliable is the endpoint?
    - PFS and RR investigator vs. centrally assessed
    - Have there been changes in treatment or supportive care?
  - Random and systematic variation in historical control data can increase type I (false positive) error rates by 2-4 fold[1] (ex – pancreatic cancer, gem control 5.4-7.2)
- Limited by selection bias and confounding
  - Baseline patient factors (age, PS), baseline disease factors (tumor burden, less aggressive biology, treating center (experience, provider)[2]
  - Leads to high false positive rate
- May be appropriate for diseases where there is no active therapy or if very high response seen (ex – vemurafenib)

1. Tang 2010, 2. Korn 2008

The randomized phase II

- Have a true comparator arm
- Endpoint still makes a difference
  - Reliability of endpoint, potential bias (investigator-assessed)
  - Continuous endpoint of change in tumor size (log ratio of tumor size, Sharma, et al.)
- Can evaluate biomarkers
  - Have control arm data, know your biomarker occurence
- Error rates
  - Typical one-sided type I error rate (a) 0.10 (false positive) and type II error rate (b) of 0.85 = 85% power (true positive)
  - Small subpopulations with benefit you may not catch
- Randomized phase II's as part of randomized phase III's
  - Clean and fast design with consistent study population

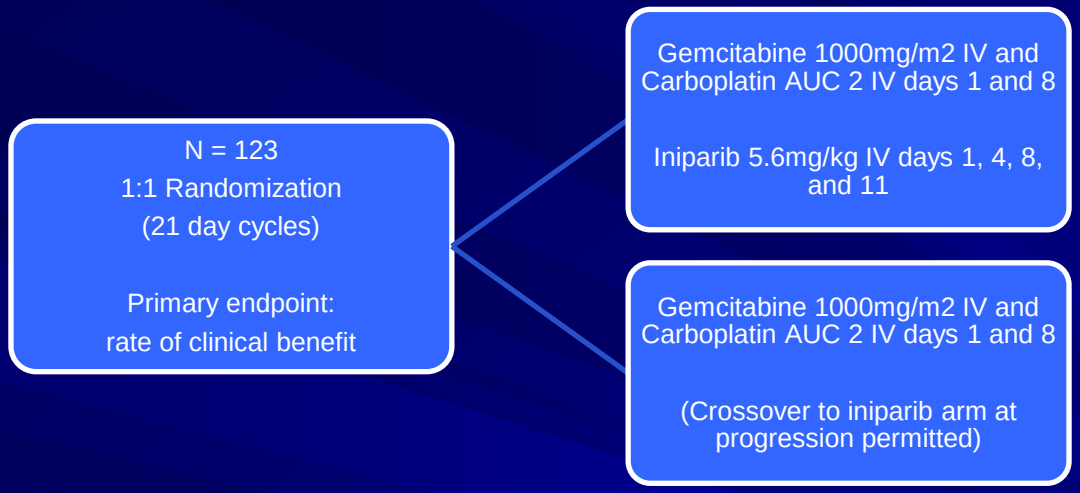
FOLFIRINOX – a success story

- First line metastatic pancreatic cancer
  - Homogenous population (no locally adv), ECOG 0-1 exc over 76 yo (tolerate treatment)
- Trial design
  - Multicenter rand phase II/III (15 to 48 centers)
  - Ph II EP = RR (11/40 responses in FOLFIRINOX pts), indep review
  - Ph III EP = OS, included Ph II pts
- Outcome – RR 34.1% in Ph II, 31.6% in Ph III, OS 11.1 vs. 6.8 months
- Same population in Ph II to III, consistency of treatment center

Perifosine – an example of inconsistency of patient population

- Randomized phase II
  - TTP 27.5 vs. 10.1 wk, HR 0.254 [0.117,0.553], OS 17.7 vs. 7.6 mo, HR 0.370 [0.180,0.763]
  - 5-FU refractory (14/13 pts each arm) TTP 17.6 vs. 9.0 wks, HR 0.170 [0.062,0.467], OS 15.1 vs. 6.5 mo, HR 0.295 [0.118,0.739]
  - Small – 38 total patients
  - Treatment regimen different (cape dose lower)
  - Patient population different
    - Only 66% had 2 lines of therapy, 50% received EGFR (pre-KRAS)
- Randomized phase III
  - Negative, though trend towards improvement in patients who were KRAS mutant and stopped oxaliplatin secondary to toxicity

Iniparib – an example of knowing your drug and patient population



Phase II enrollment from Sept 2007 through March 2009 at 20 sites within the US Oncology Network

Primary endpoint CBR and safety

Key eligibility:

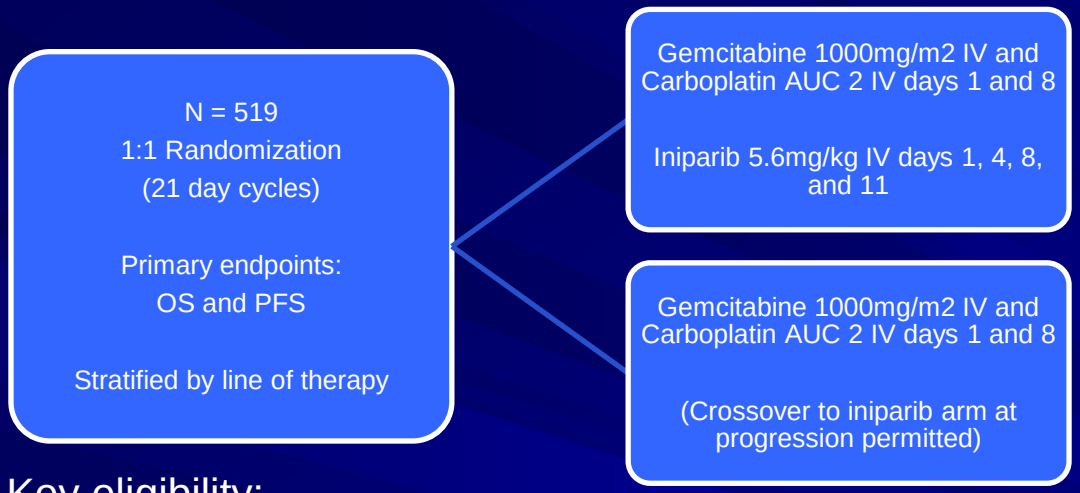
- Adult females with triple-negative metastatic breast cancer and measurable disease
- ECOG PS 0 or 1
- Up to 2 prior chemotherapy regimens for metastatic disease were allowed
  - No prior gemcitabine, carboplatin, cisplatin, or PARP inhibitor allowed

Trial met primary endpoint –

- Significantly improved CBR (34% to 56%) and ORR (32% to 52%)
- Significantly prolonged median PFS (3.6 to 5.9 mos) and OS (7.7 to 12.3 mos)

O'Shaughnessy et al. NEJM 2011

Iniparib Phase 3 Breast Trial



Enrollment from Sept 2007 through March 2009 at 102 sites in the United States

Key eligibility:

- Adult females with triple-negative metastatic breast cancer and measurable disease
- ECOG PS 0 or 1
- Up to 2 prior chemotherapy regimens for metastatic disease were allowed
  - No prior gemcitabine, carboplatin, cisplatin, or PARP inhibitor

Trial did not meet primary endpoints –

- Median OS 11.1 months compared to 11.8 months with iniparib (p=0.28)
- Median PFS 4.1 months compared to 5.1 months with iniparib (p=0.027)
- Exploratory analyses by line of therapy suggested benefit in 2nd/3rd line settings
- Crossover was allowed, more basal-type and less normal-type than phII, drug is not a PARP inhibitor (so does pt population make sense?)

O'Shaughnessy et al. ASCO 2011

Onartuzumab – the importance of the biomarker

- Many studies of targeted agents now requiring (and required to evaluate) a companion diagnostic for patient selection
- There are many complicating factors around this, including the complexity of each pathway and its interactions with other pathways, what is the optimal biomarker (IHC, FISH, mutation, other) and how consistent is the assay/cutoffs?

OAM4558g Study Design--Global, Double-Blind, Placebo-Controlled, Phase II Study

n = 128

Key Eligibility:

- Stage IIIB/IV NSCLC
- 2nd/3rd-line NSCLC
- Tissue Required
- PS 0-2

1:1 RANDOMIZATION

Stratification Factors:

- **Tobacco History**
- **Performance Status**
- **Histology**

n = 64

Arm A
Erlotinib (150 daily-oral) + MetMAb (15 mg/kg IV q3w)

n = 64

Arm B
Erlotinib (150 daily-oral) + Placebo (q3w)

PD

ADD* MetMAb

* Must be eligible

Co-Primary Objectives:

- PFS in "Met High" patients
- PFS in overall ITT population

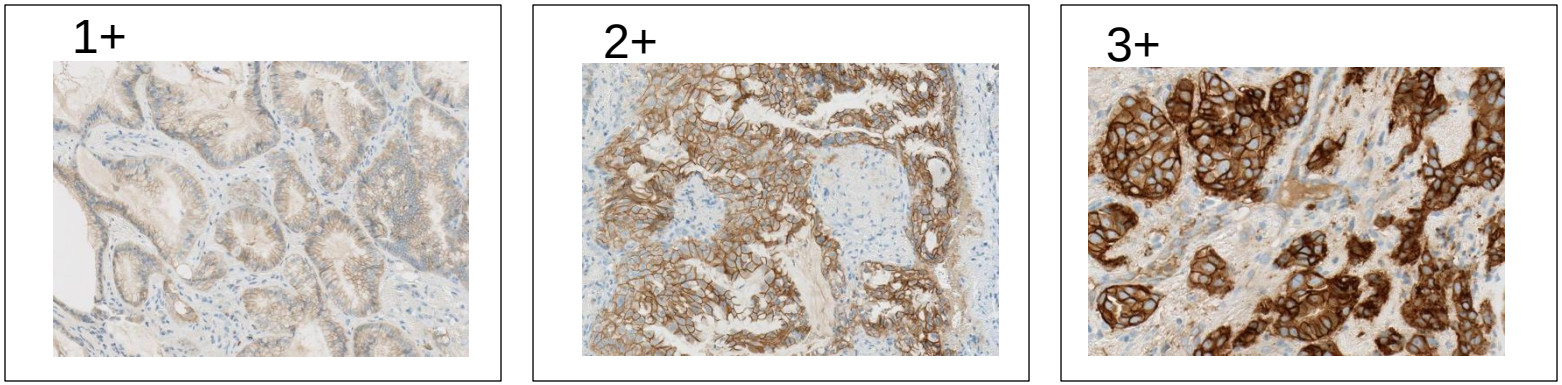
Other Key Objectives:

- OS in "Met high" patients
- OS in Overall ITT patients
- Overall Response Rate
- Safety/Tolerability

Spigel ESMO 2010

Determination of Met level

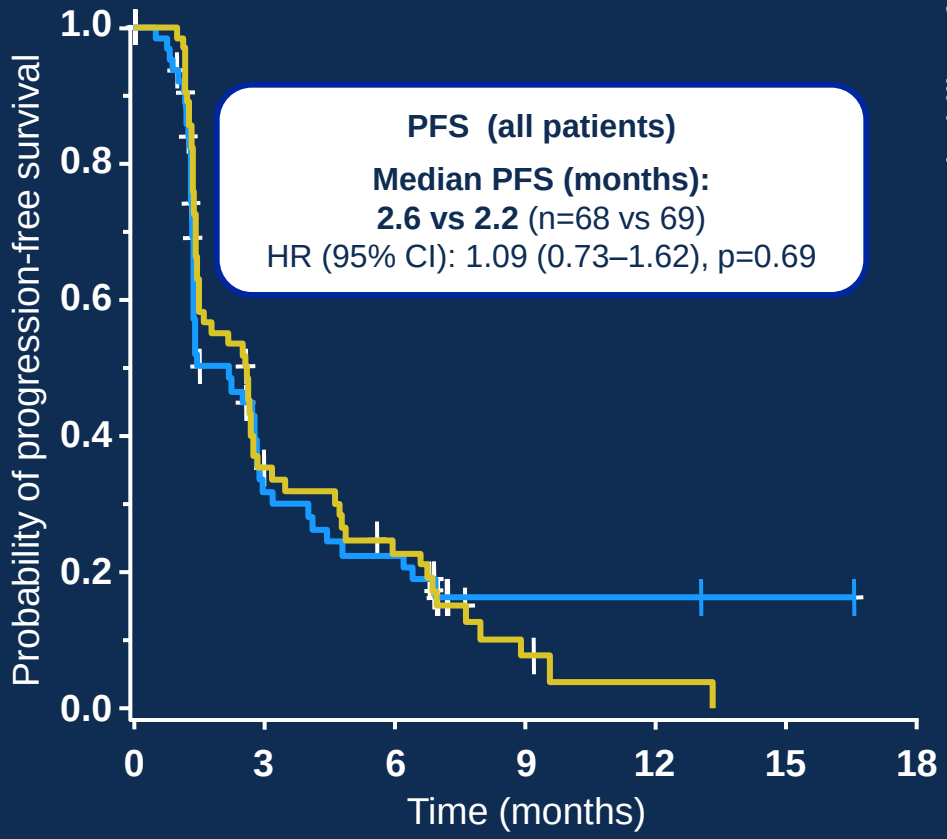
- Activity in Met High is a co-primary endpoint; Met status was determined retrospectively
- Intensity of Met staining on tumor cells scored on 0–3 scale

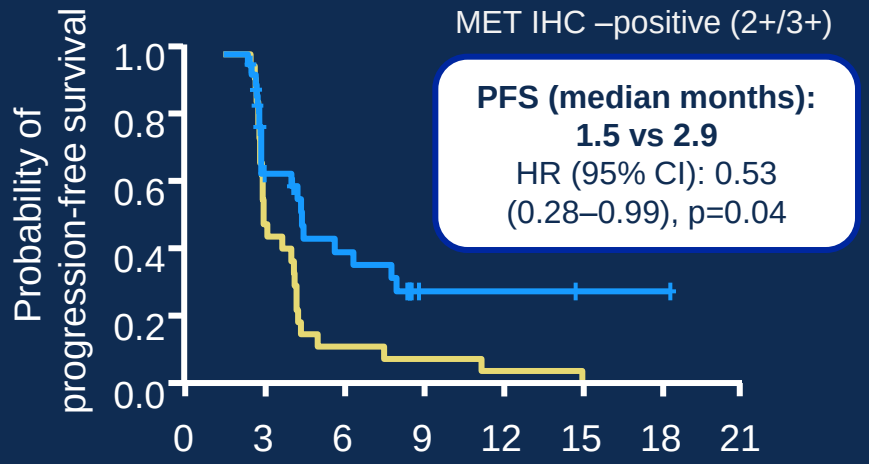


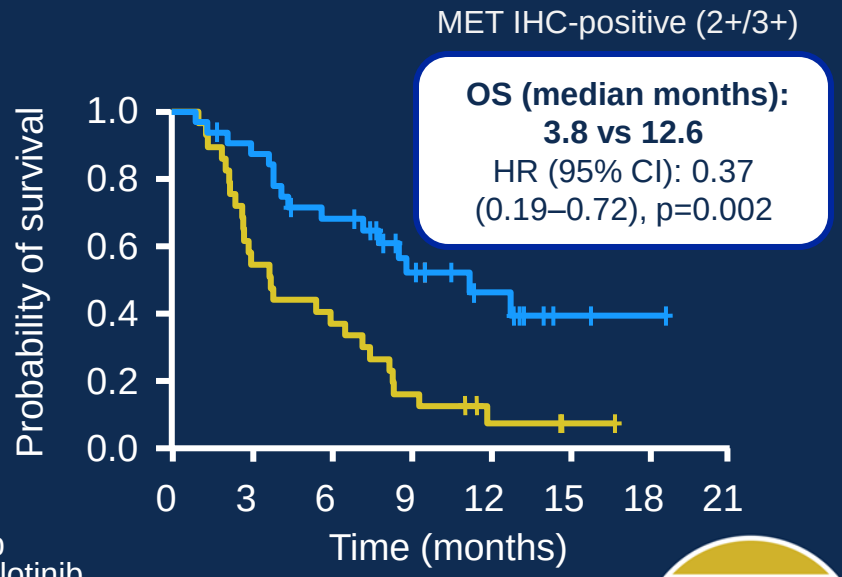
- Definition of **Met High** (prespecified, prior to efficacy analysis):
  50% or more positive cells with staining intensity of 2^+ or 3^+
- Anticipated ~50% of NSCLC samples are Met high, based on historical data

In this study:
- Tissue evaluable (for Met IHC, 1^0 endpoint) from **95%** of patients
- 54% patients had Met high NSCLC

Phase 2 Results (OAM4558g): MET IHC Status may Predict Clinical Benefit from Onartuzumab + Erlotinib



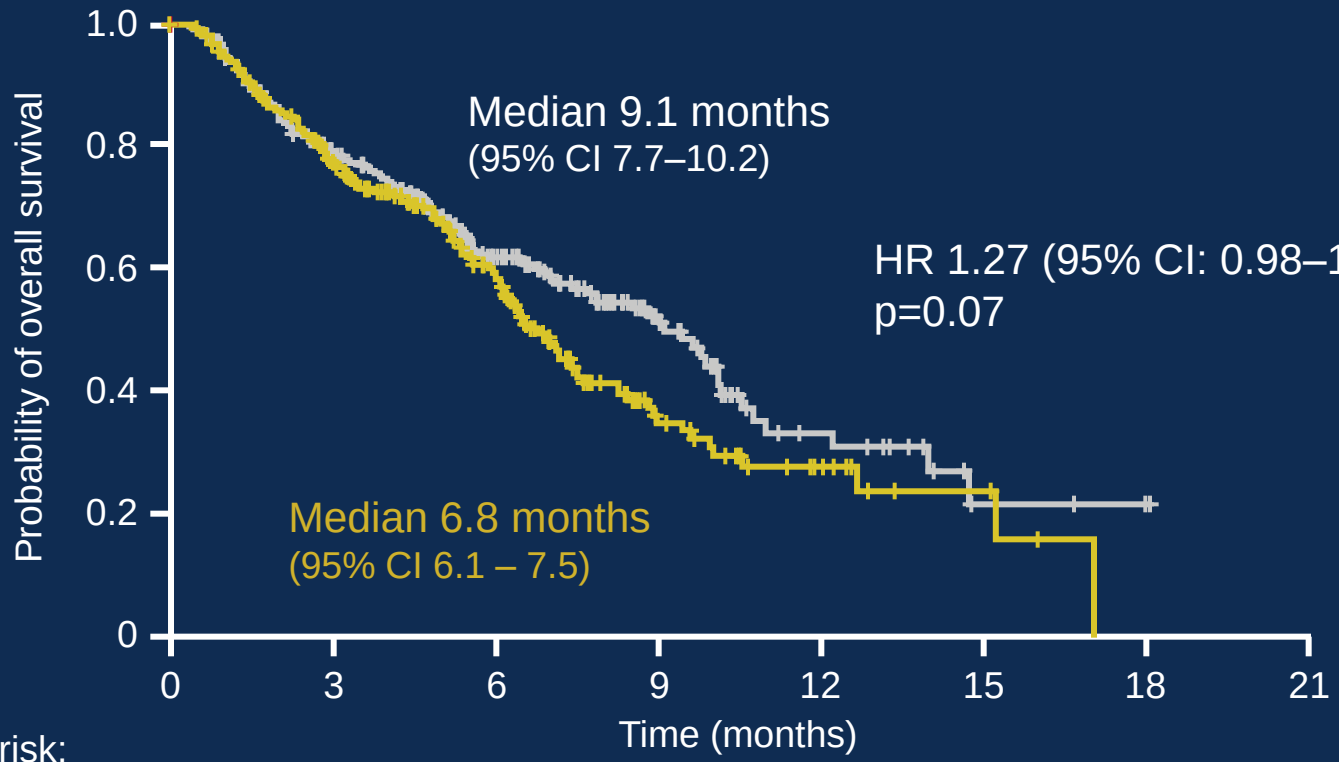




Placebo + erlotinib
Onartuzumab + erlotinib

J Clin Oncol 2013; 31:4105-4114.

OAM4971g: Randomized phase III in Met 2+/3+ IHC - Overall Survival Results



Number of patients at risk:

Placebo + erlotinib	249	183	110	43	14	3	1
Onartuzumab + erlotinib	250	177	100	29	12	4	

Placebo + erlotinib (n=249)
Onartuzumab + erlotinib (n=250)
+ Censored

Onartuzumab – what happened?

- Did we have the right biomarker?
  - IHC is subjective – were the results consistent? Did we dilute the population?
  - IHC 3+ seems to have better outcome (PFS)
  - FISH has no correlation in phase II data, but FISH + is rare group
- Is there more to this pathway and how the drug interacts with the pathway that we did not account for?
  - What about the ligand? Is the efficacy dependent on the number of receptors or high amounts of ligand?

What have we learned?

- We are going to continue to make mistakes, but we must learn from them and control as much as we can to maximize success
- Single arm phase II's should only be used for go-no-go decisions in rare situations
  - No other treatment, high response rates
- Randomized phase II's are likely the best way to decide to move forward
  - Direct comparison to control arm, way to evaluate biomarkers

The go-no-go decision

- Patient populations need to be consistent as possible between the randomized phase II and III
  - Ideally in the same trial
- Sites should be consistent as well
  - Need sites with as much experience with regimen and disease as possible (prevent early discontinuations and inadequate treatment)
- Pick the right comparator arm
  - Only one “moving part” - FLAGS

The go-no-go decision

- Pick the right endpoints
  - Better PFS/OS, watch for crossover, take into account subsequent treatment
- Have respect for cancer biology
  - Cancer cells are smarter than we are
  - Biomarkers can fool you
- Things are about to get more complicated
  - Immunotherapy