ESMO Asia 2015 Poster Discussion Session

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Overall Theme : Molecular Stratification of Patients

Clinical Prognosis and Tumor Recurrence (27 PD)

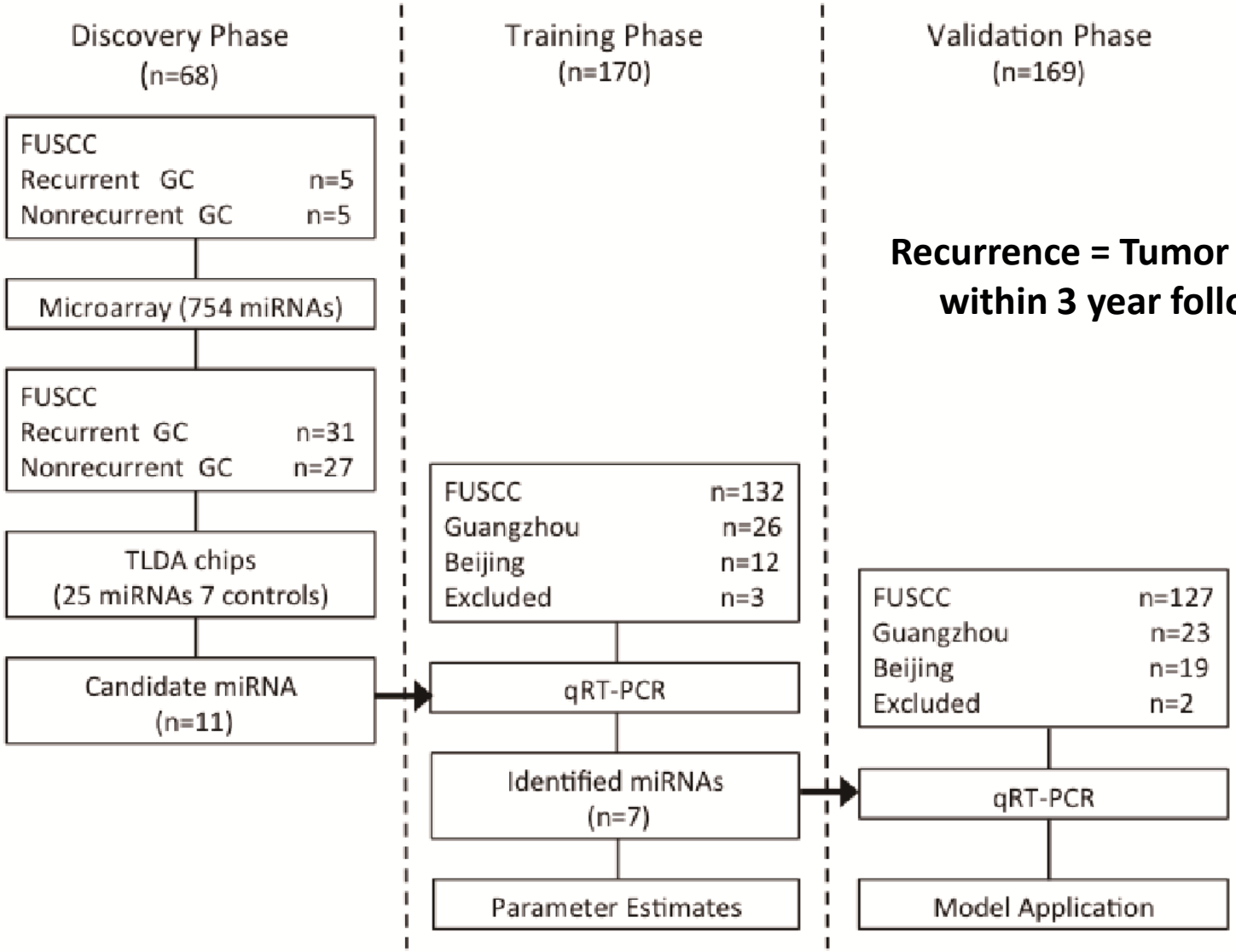
Selecting Patients For Clinical Trials (28 PD)

Drug Resistance Mechanisms And Strategies for Overcoming Resistance (2 PD, 1 PD)

Plasma miRNA-based signatures to predict 3-year postoperative recurrence risk for patients with stage II and III Gastric cancer (PD27)

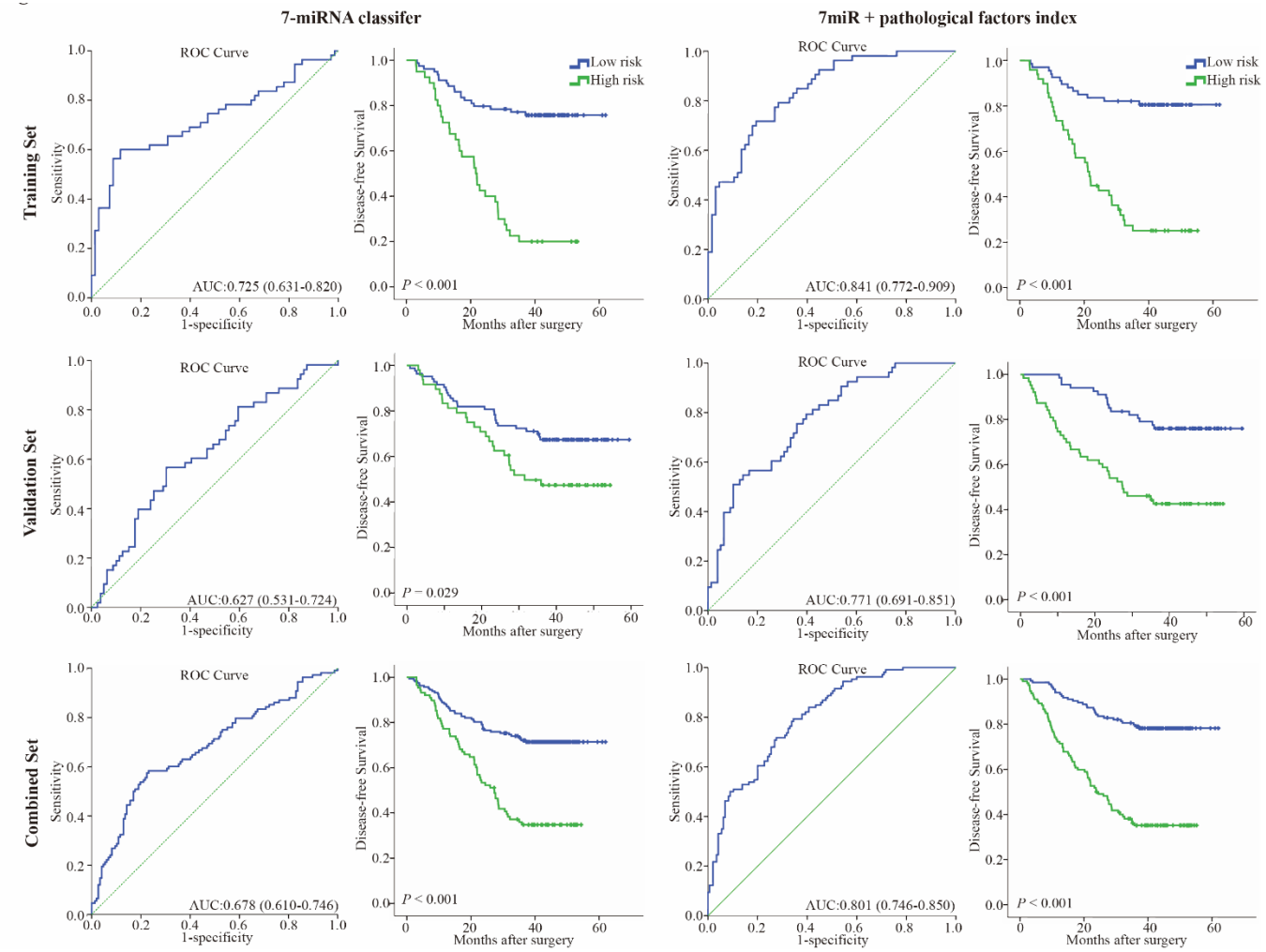
- Gastric cancer (GC) is a heterogeneous disease with large variability in disease outcome for patients with similar clinical features.
- Current TNM staging is the “gold standard” for predicting GC outcomes, but has limitations especially in stage II and III patients.
- Circulating miRNAs have been suggested as potential biomarkers for cancer diagnosis and prognosis
- Most current circulating miRNA studies in GC have focused on diagnosis, with only a few evaluating prognosis or recurrence. There is still no circulating miRNA panel for accurate prediction of GC recurrence or prognosis

Study Design (Total 407 patients with D2 Resection)



Recurrence = Tumor Relapse within 3 year followup

Results



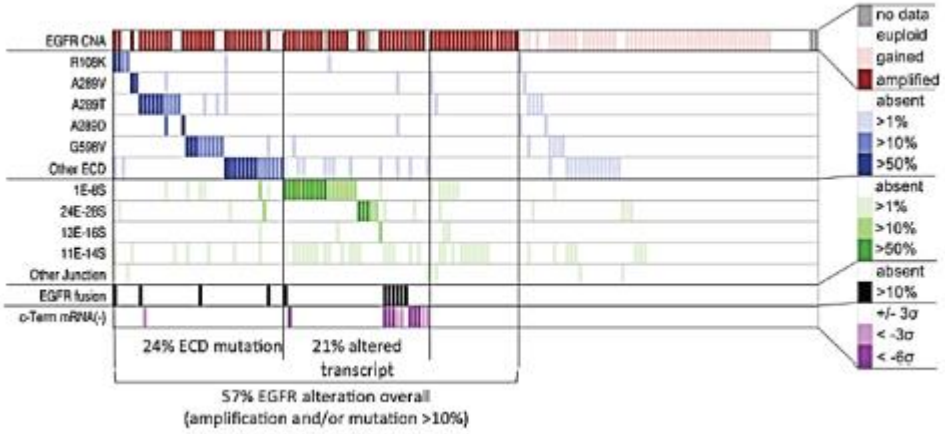
The authors identified a **7 miRNA classifier** and 7miR+pathological factors that provided high predictive accuracy on GC recurrence.

miRNA stratified “High-risk” patients showed significantly shorter disease-free survival (DFS) and overall survival (OS).

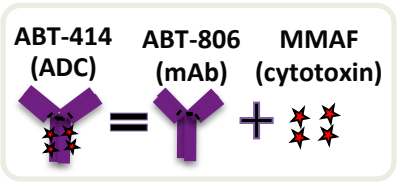
- Strengths
  - Multi-centre Study involving a fairly large cohort of GC patients
  - Circulating miRNAs represent an attractive platform, due to ease of accessibility
  - Prognostic separation appears to be hold even for Stage IIA patients, raising implications for treating patients with adjuvant chemotherapy
- Limitations
  - Little details regarding origin or identity of miRNAs
  - Exact thresholds for defining “high risk” and “low risk” are not described
  - Ability to stratify Western GC populations and impact of chemotherapy is not clear
  - These promising results should be validated in additional cohorts

Identifying the Correct Patient Population for ABT-414: Biomarker Assays for Epidermal Growth Factor Receptor in Patients with Glioblastoma (PD28)

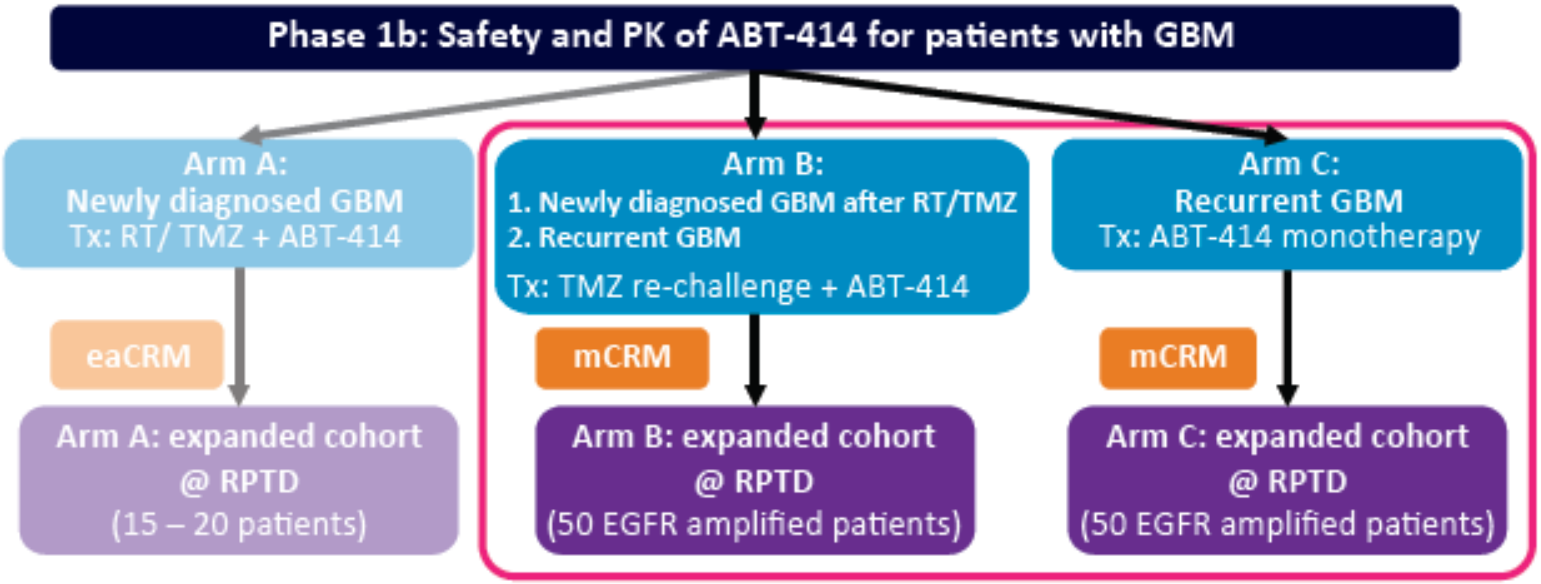
- *EGFR* alterations are common in glioblastoma (mutation, amplification, expression)



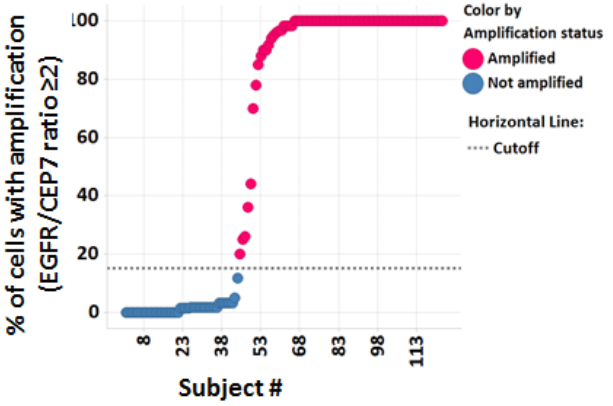
- ABT-414 is an antibody-drug conjugate that targets activated EGFR when EGFR is amplified (including EGFRvIII ECD mutation)



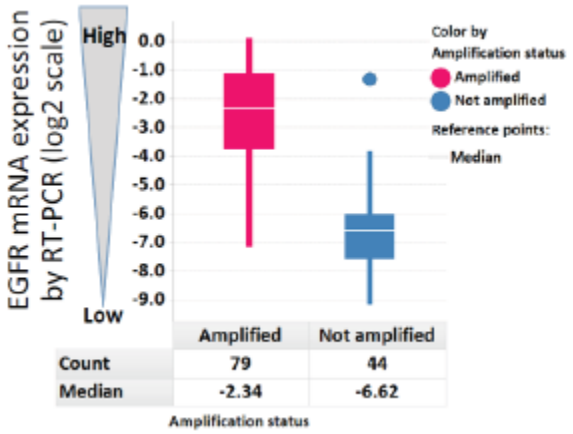
- Phase I trial M12-356 : Phase I dose escalation study, including efforts to identify patient population most likely to respond to ABT-414



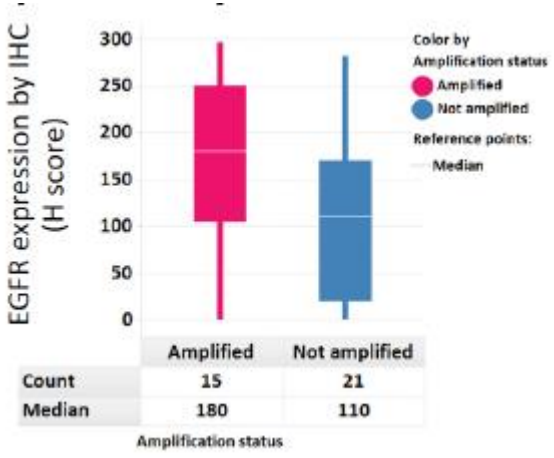
EGFR copy number (FISH)



EGFR copy number vs mRNA (RT-PCR)

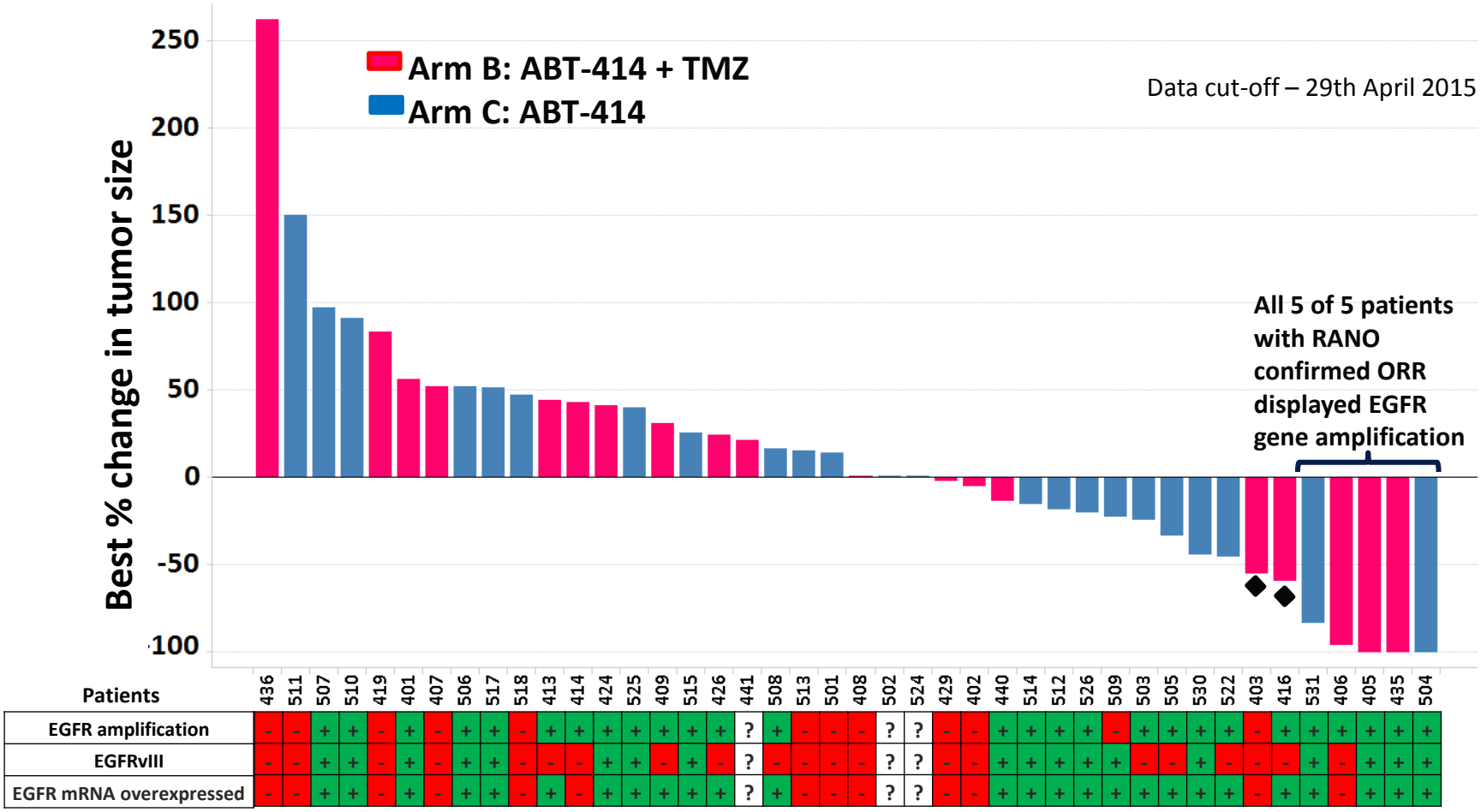


EGFR copy number vs Protein (IHC)



Response of ABT-414-treated Recurrent GBM patients

Only EGFR gene amplification identified all patients with RANO response



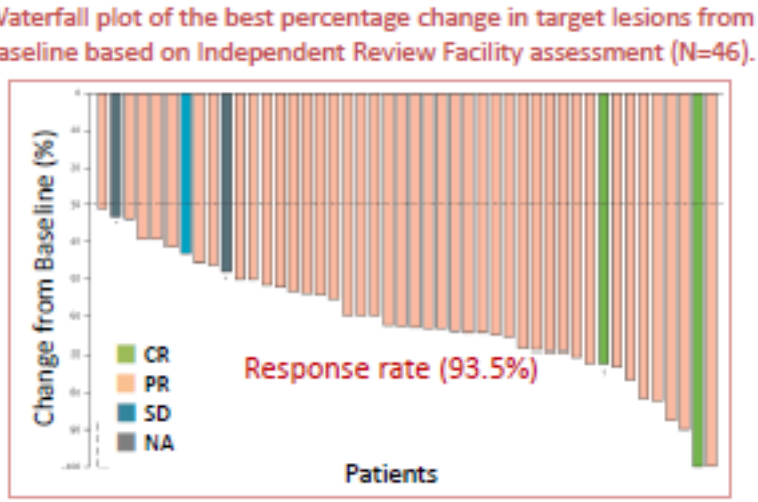
◆ Patient responses were not confirmed upon follow up scan.

EGFR, epidermal growth factor receptor; GBM, glioblastoma; ORR, objective response rate; RANO, Response Assessment in Neuro-Oncology; TMZ, temozolomide

- Strengths
  - Phase I study involving a novel anti-EGFR/drug conjugate in a malignancy where *EGFR* alterations are frequent
  - Assessment of EGFR status at multiple levels (Copy Number, mRNA, Protein)
  - Responses were observed and associated with *EGFR* amplification, which appears binary
  - *EGFR* amplification may be a selection criteria for enrolling patients into Phase II/III trials
- Limitations
  - Only *EGFR* was measured and other RTKs were not tested
  - Formal statistical assessment of correlations between *EGFR* amplification and response were not reported
  - Many *EGFR* amplified patients did not respond (22/27), suggesting the presence of additional predictive factors

Crizotinib could overcome acquired resistance to alectinib caused by HGF autocrine in ALK rearranged non-small cell lung cancer (PD2)

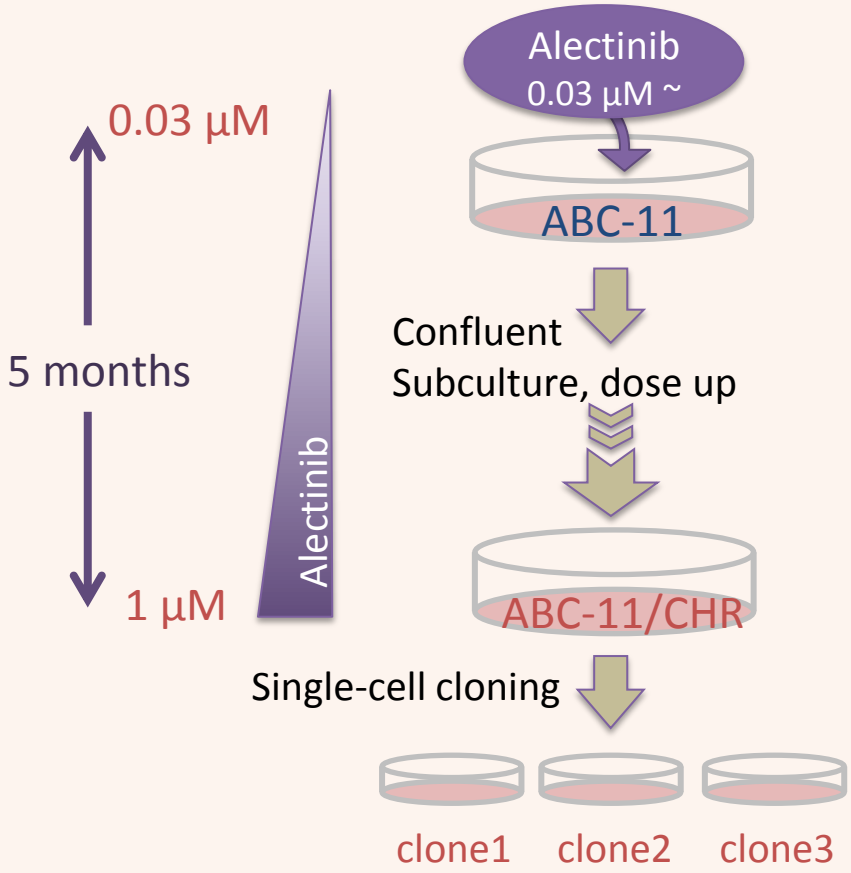
- ALK rearrangements are a major genetic driver in certain subtypes of non-small cell lung cancer (NSCLC)
- Crizotinib, which targets ALK, MET, and ROS1, is an effective therapy for ALK-positive NSCLC, but resistance can develop
- Alectinib is a new-generation selective ALK-TKI that can partially overcome acquired resistance to crizotinib (Cancer Cell 19, 2011: 679-90)
- Phase II study of alectinib demonstrated a 93.5% response rate (Lancet Oncol 14, 2013: 590-98);. However, acquired resistance is also a limitation



Preclinical Studies : Alectinib-resistance *in vitro* associated with increased MET activation

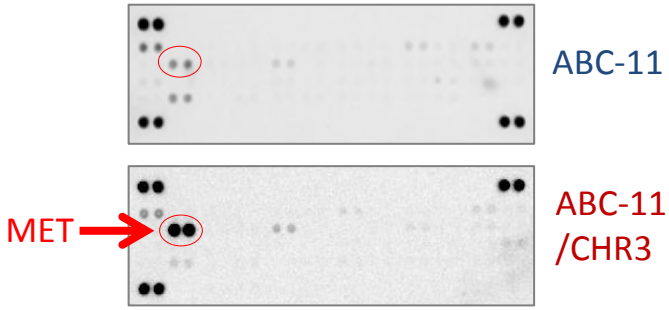
Establishment of alectinib-resistant cells

(Stepwise manner)

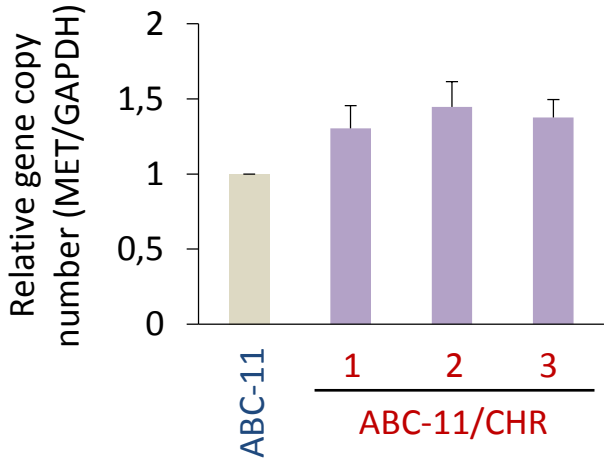


ABC-11: (EML4-ALK variant 3b E6;A20)

Survival signaling (p-RTK array)



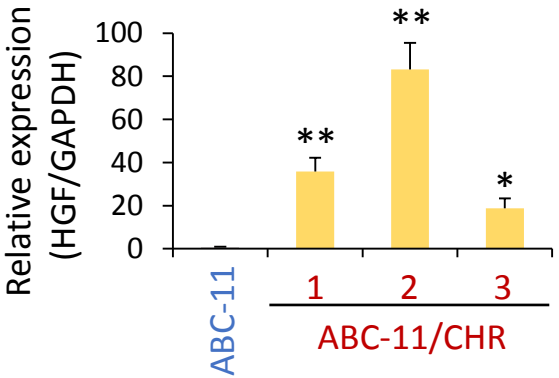
Genomic MET (qPCR)



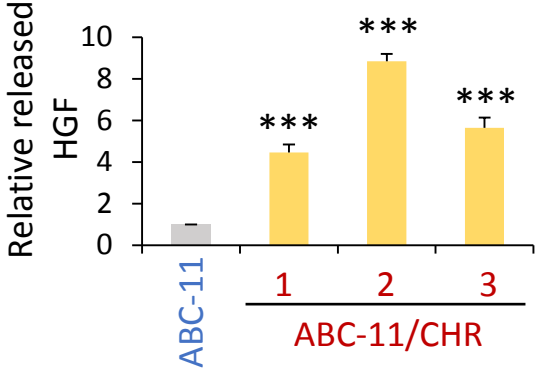
t test : not significance Bars : SE

HGF mRNA and protein are overexpressed in ABC-11/CHR

HGF mRNA (qRT-PCR)



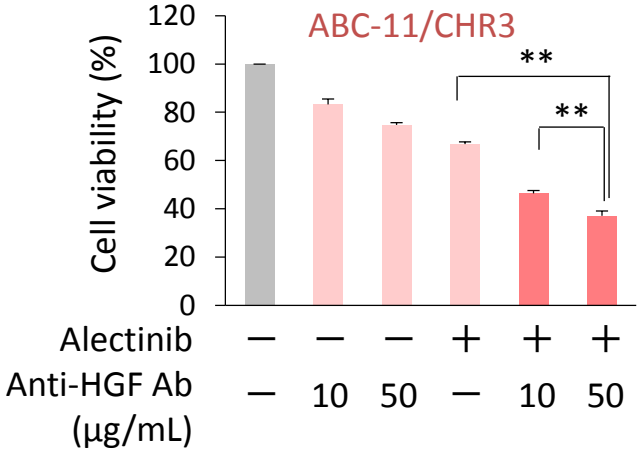
HGF protein (ELISA)

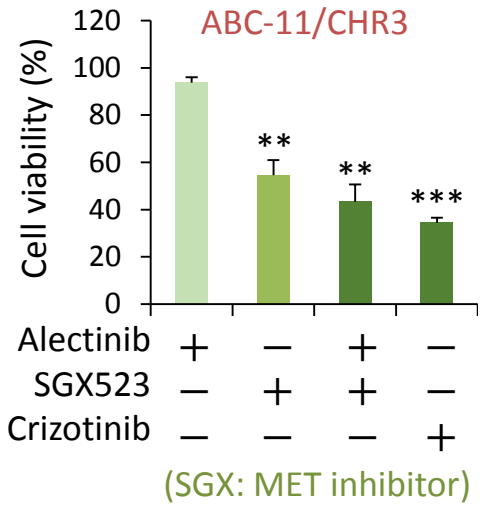


HGF protein (WB)

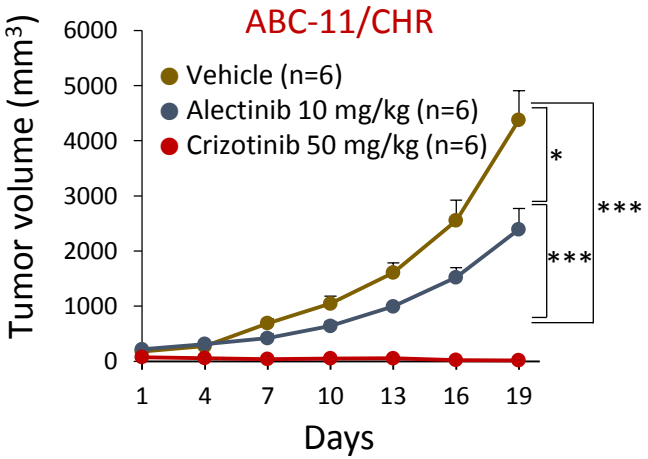
Inhibition of HGF/MET and ALK was effective on ABC-11/CHR

Sensitivity to anti-HGF Ab or MET-TKI (MTT assay)



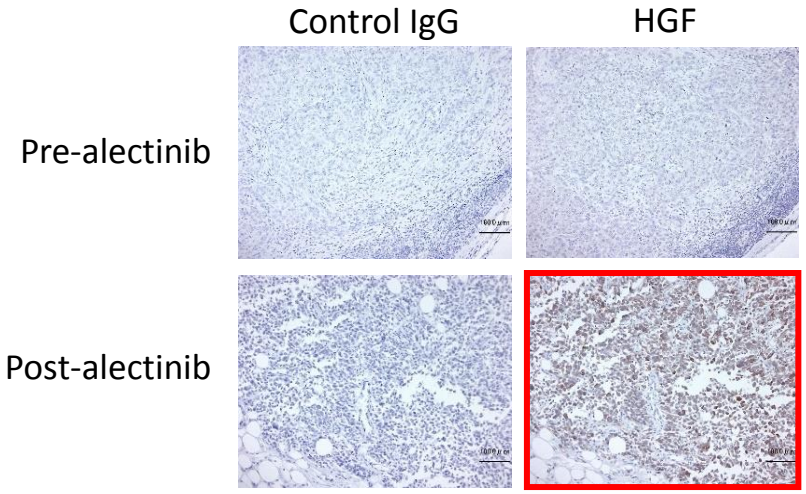


Sensitivity to Crizotinib (Xenograft model)

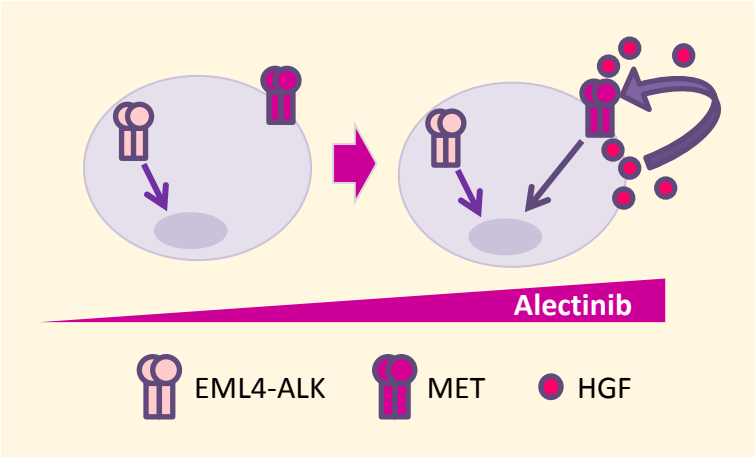


t test : *** $p<0.001$ ** $p<0.01$ * $p<0.05$ Bars: SE

Expression of HGF in an alectinib-refractory patient (IHC)



Summary
Alectinib-resistant mechanism



Efficacy of crizotinib in alectinib-refractory patients in NSCLC harboring EML4-ALK; phaseII trial (OLCSG1405)

UMIN 000015984

Alectinib-refractory patients (n=9)

EML4-ALK +
ⅢB/Ⅳ NSCLC
Age ≧20
ECOG PS 0-2

→

Crizotinib 250mg
Oral twice per day
Until PD

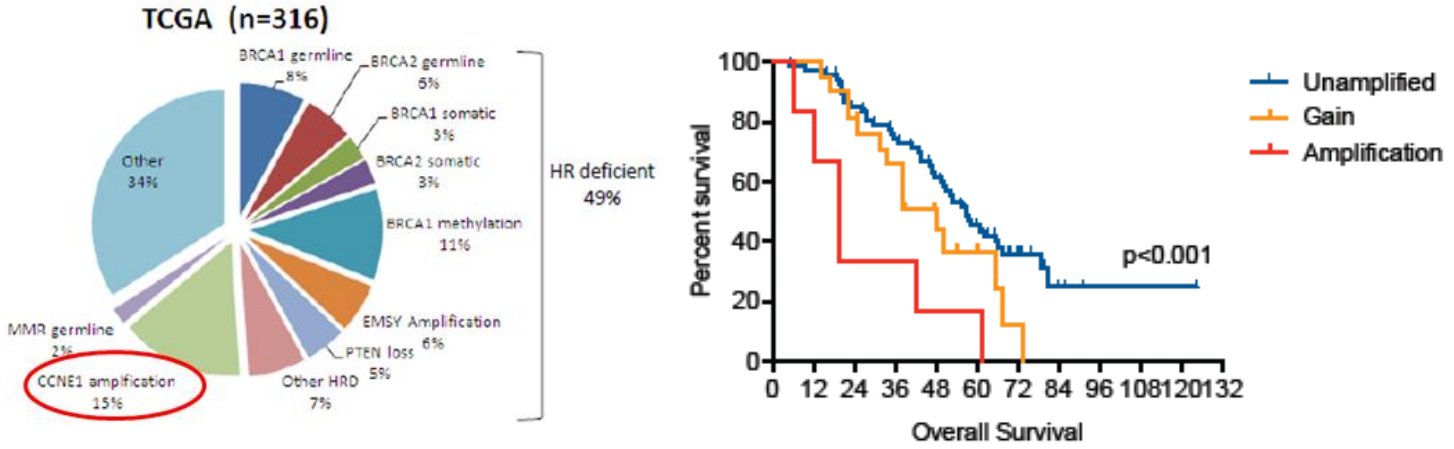
Primary endpoint: objective response rate
Secondary endpoint: PFS, OS, AE, QOL
Expression of HGF, MET, EML4-ALK … using re-biopsy samples

- Strengths
  - Studying resistance mechanisms *in vitro* can provide powerful insights into similar *in vivo* mechanisms
  - One of the few studies investigating resistance mechanisms for alectinib, with supporting data from human samples
  - Identified HGF upregulation and MET activation as a resistance mechanism
  - HGF blockade or MET inhibition via crizotinib may have potential for overcoming alectinib resistance

- Limitations
  - Contribution of HGF upregulation vs other mechanisms (eg ALK mutations) remains to be established
  - May not be applicable to crizotinib-resistant patients
  - Results are based on a single cell line

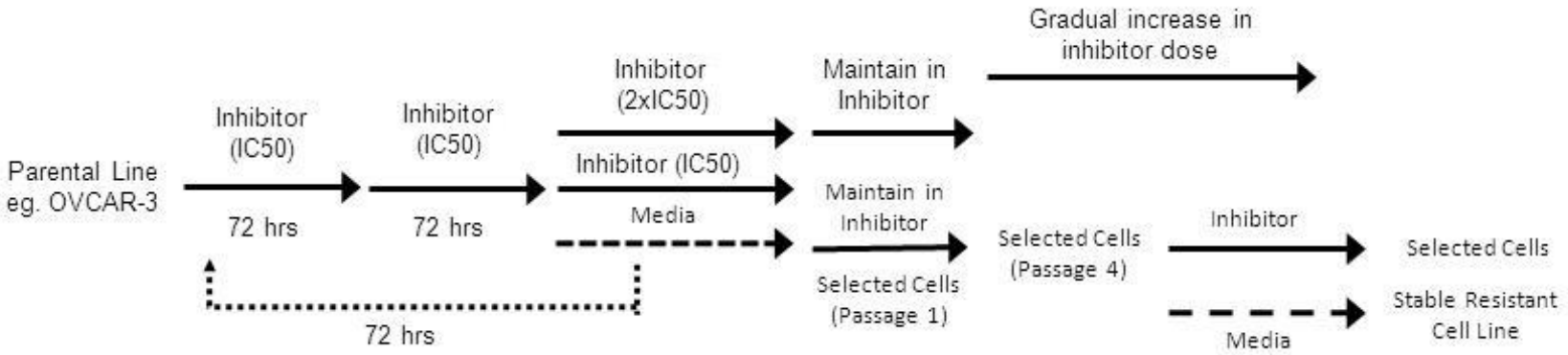
A HIGH THROUGHPUT COMPOUND SCREEN IDENTIFIES POTENTIAL COMBINATIONS TO CDK2 INHIBITOR RESISTANCE IN *CYCLIN E1* AMPLIFIED HIGH GRADE SEROUS OVARIAN CANCER (PD1)

- High grade serous ovarian cancer (HGSOC) is the most common histological subtype of epithelial ovarian cancer
- Cyclin E1 (*CCNE1*) amplification is detected in 15% of HGSOC, and associated with primary treatment resistance and poor outcome

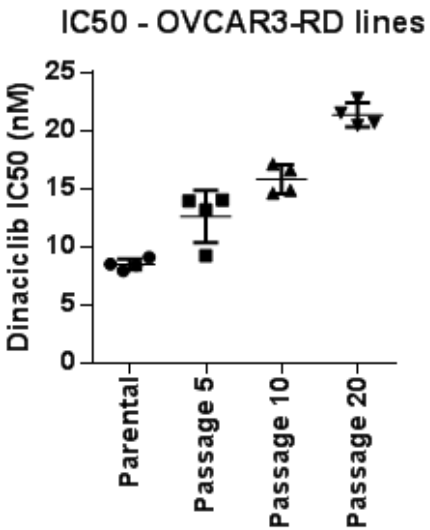


- Ovarian cancer cell lines with CCNE1 amplification are selectively sensitive to Cdk2 inhibitors (Etemadmoghadam et al, Clinical Cancer Research, 2013)

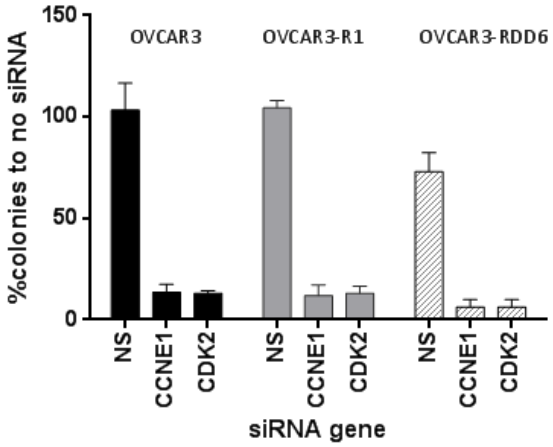
Understanding CDK inhibitor resistance *in vitro*



Resistance is Stable

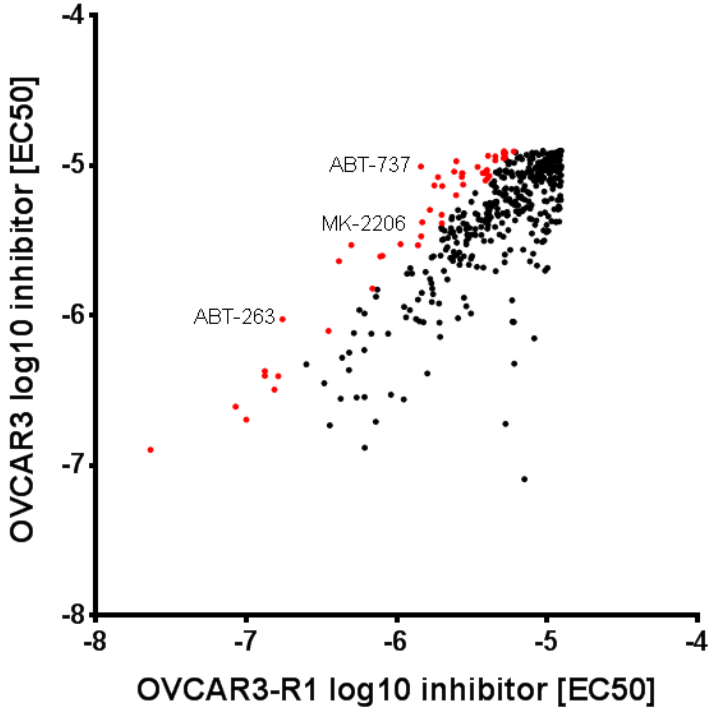


Resistant Lines still require CCNE1/CDK2

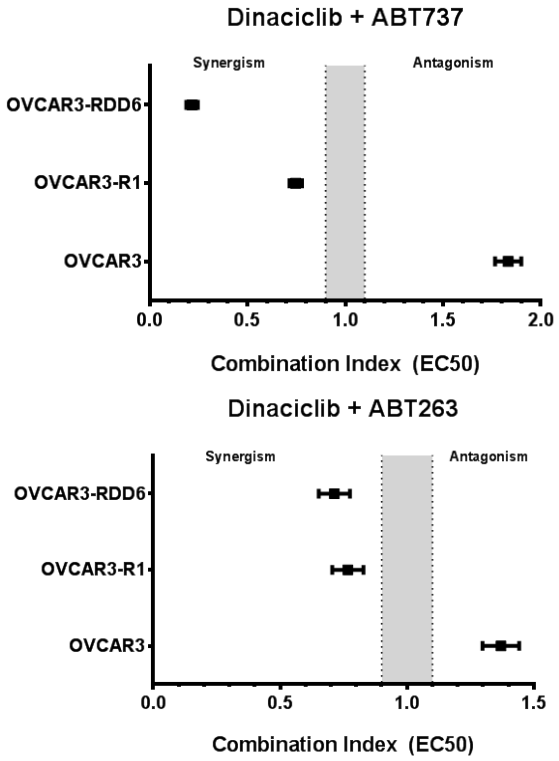


High throughput compound screening to identify drug combinations for overcoming Cdk2 inhibitor resistance

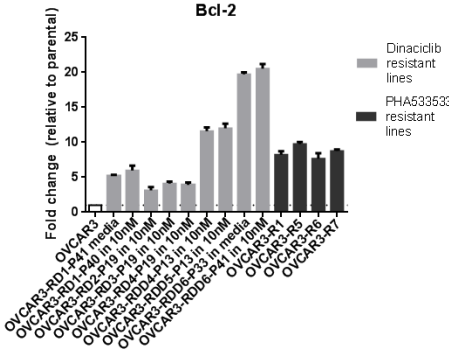
Primary screen - OVCAR3-R1 vs OVCAR3 (+Dinaciclib)

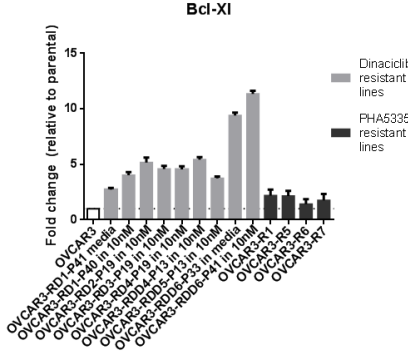


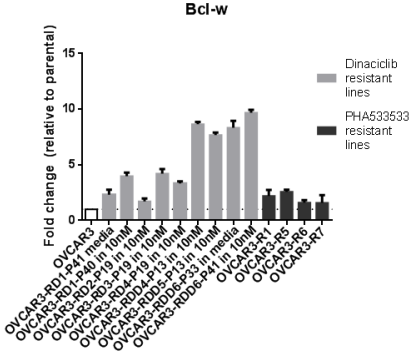
Non-selective BH3-mimetics show synergy

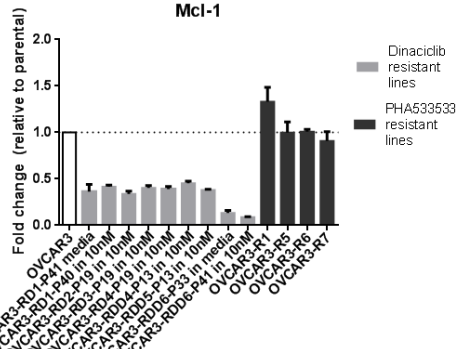


CDK2i Resistant Lines show upregulation of several anti-apoptotic genes









- Strengths
  - Stable resistance to Cdk2 inhibitors can be generated by continuous drug exposure
  - CDK2i-resistant lines are still dependent on CCNE1 and CDK
  - A high throughput compound screen identifies potential drug combinations to overcome CDKi resistance
  - Potential hits with non-selective BH3-mimetics provides evidence for upregulation of anti-apoptotic proteins

- Limitations
  - Results are based on 1 parental cell line
  - *In vivo* relevance of findings remain to be assessed
  - Do OvCAs with baseline high expression of anti-apoptotic proteins exhibit primary resistance to CDK inhibitors?

Questions