ESMO Preceptorship on Ovarian Cancer

Novel treatment pathways – Horizon scanning

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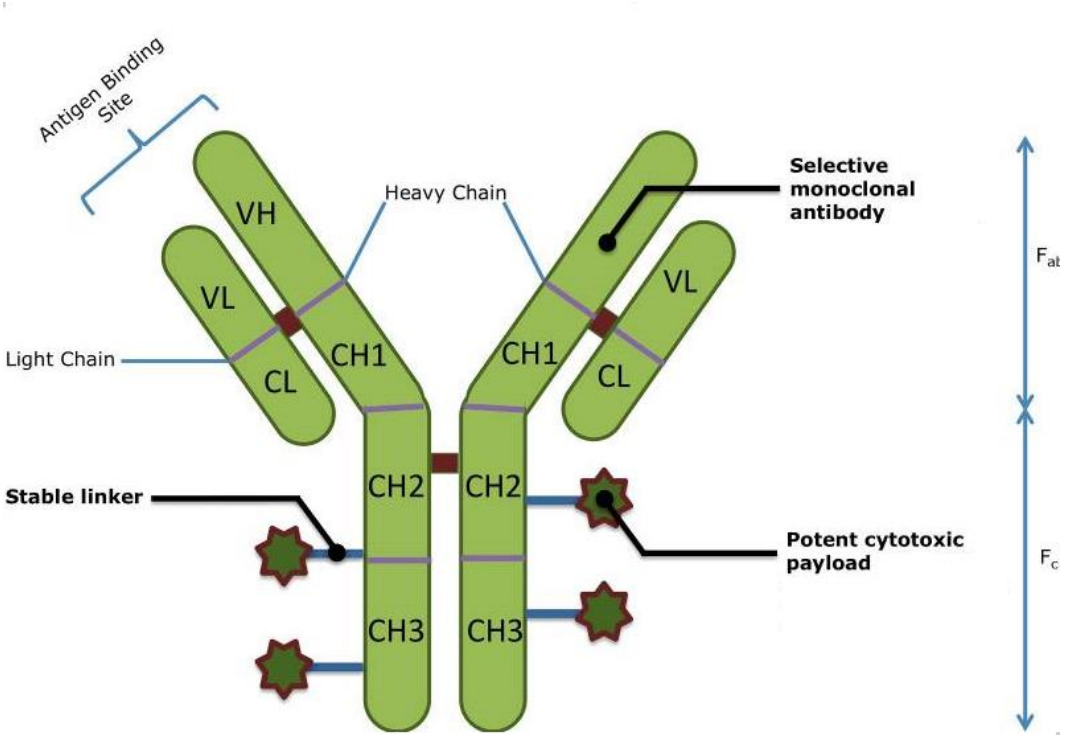
Presenter Disclosures

No disclosure

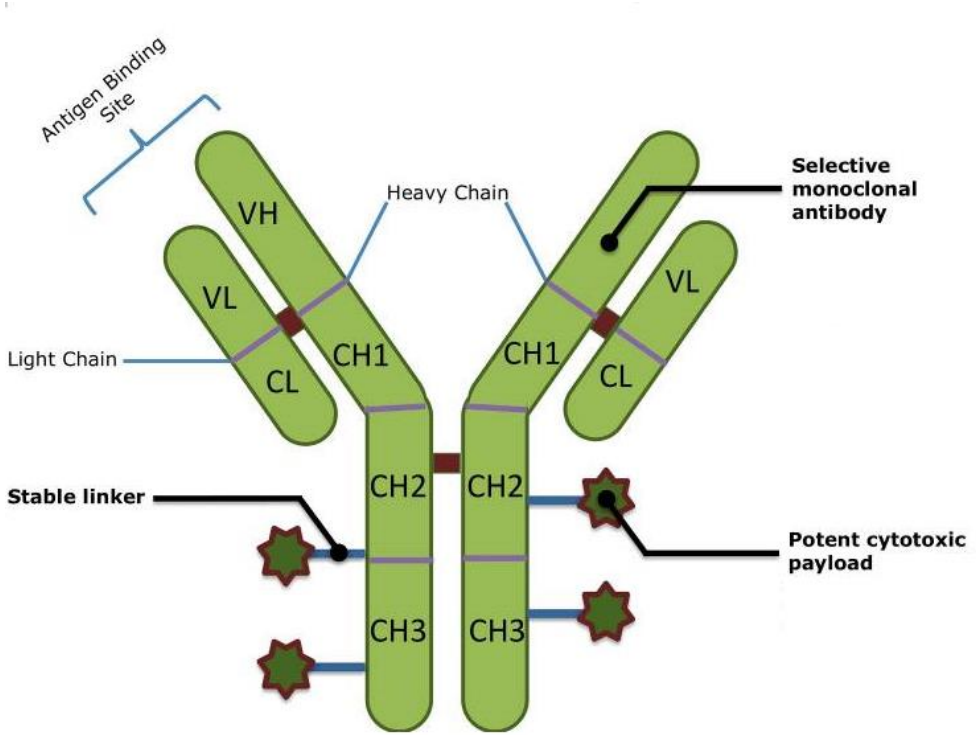
Content

- Antibody drug conjugate: new developments
- Targeting tumor-associated mesothelin
- Targeting signal pathways
  - Anti - Wnt
  - Anti - AXL

Antibody – drug conjugates (ADC)



Antibody – drug conjugates (ADC)



Linker
- Chemistry
- Stability

- Target AG
  - Site
  - Expression
  - Kinetics of internalization
  - Patient selection
  - Therapeutic Index
- Mechanism of activity

F_{at}

F_c

Payload - potency
- type

Most ADC Targets are:

Tumor Associated Antigens, Not Tumor Specific

Activity & Toxicity Dependent Upon:

The relative distribution Normal tissue / Tumor tissue: specificity

Off-target distribution of payload

Bystander effect

PK and immune effector functions

ADC: challenging clinical development

- Narrow therapeutic index
- Difficult extrapolation of preclinical data
- Low drug to antibody ratios (DAR) for microtubule destabilizing payload
- Need of payload with different MoA (DNA minor groove AA)

Mesothelin (MSLN) and OvCa

- Tumor-differentiation membrane-bound Ag with normal expression limited to mesothelial cells.
- Higher expression in mesothelioma, OvCa, pancreatic adenocarcinoma.
- Binds to CA125 possibly contributing to peritoneal spread.
- Different targeting strategies:

ADC: BAY 94-9343

DMOT4039A

BMS – 986 148

Chimeric Ab: Morab_009

BAY 94-9343 (Anetumab ravtansine)

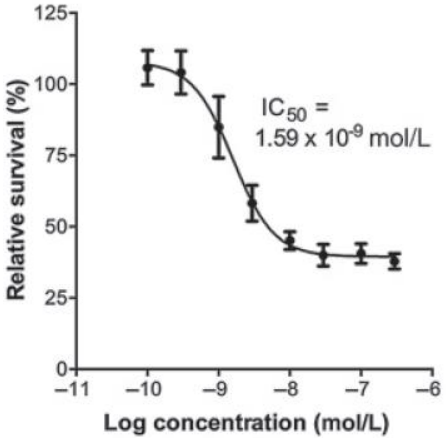
Fully human anti-MSLN mAb (MF-T) coupled by

disulfide linker to maytansinoid microtubule - targeting DM_4

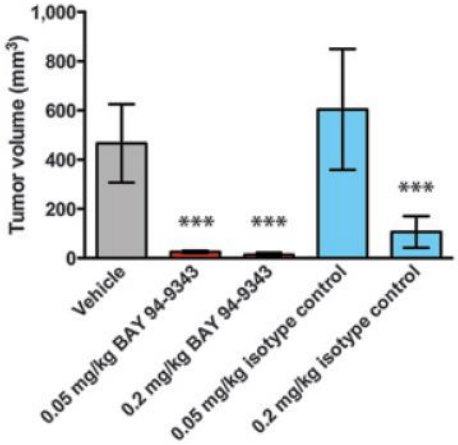
Anetumab ravtansine

Preclinical features in OVCAR-3 tumor model

In vitro cytotoxicity



In vivo antitumor activity

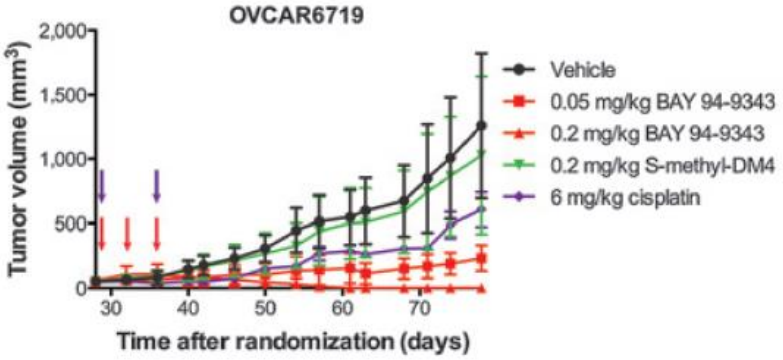


Golfier, Mol. Cancer Ther., 2014

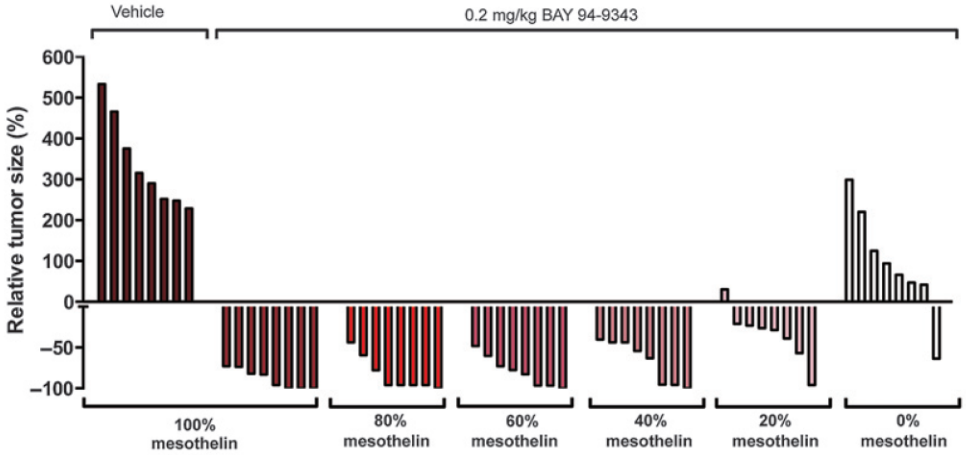
Anetumab ravtansine

Preclinical features

Antitumor activity in patient derived tumor model



Mesothelin expression dependent antitumor efficacy



Golfier, Mol. Cancer Ther., 2014

Phase I study of Anetumab Ravtansine (N=77)

- IV infusion q 3wks
  Dose escalation (mesothelioma, pancreas, ovary) followed by expansion (mesothelioma, ovary)
- DLT_S: keratitis and neuropathy
- Most common AE_S: fatigue, GI, LFT_S increase

Phase I study of DMOT 4039 A (N=71)

- Fully human anti-MSLN mAb (47D9. v3) coupled by protease sensitive cleavable linker to microtubute disrupting auristatin (MMAE)
- Phase I in unresectable pancreatic or platinum-resistant OvCa
- Dose escalation, followed by expansion with mesothelin ICH 3+
- 90 min IV q3wks
- Main toxicities: constitutional, GI, cumulative peripheral neuropathy.
- PR 3 in 10 ovary pts, additional 3 decrease of CA125 only (ICH 3+)

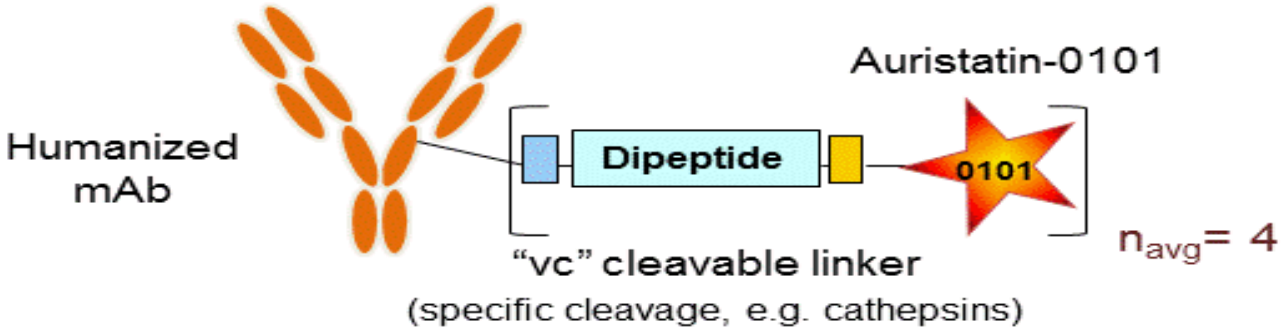
Weekes, Mol. Cancer Ther., 2016

MDX – 1204 (BMS_986148)

- Fully human anti-MSLN mAb coupled by clivable peptide linker to DNA alkylating agent related to duocarmycin.
- Antitumor activity in OvCa, lung and pancreatic xenografts.
- Phase I/IIa study ongoing with BMS_986148 alone or in combination with nivolumab in mesothelioma, NSCL, OvCa, pancreatic and gastric cancer.

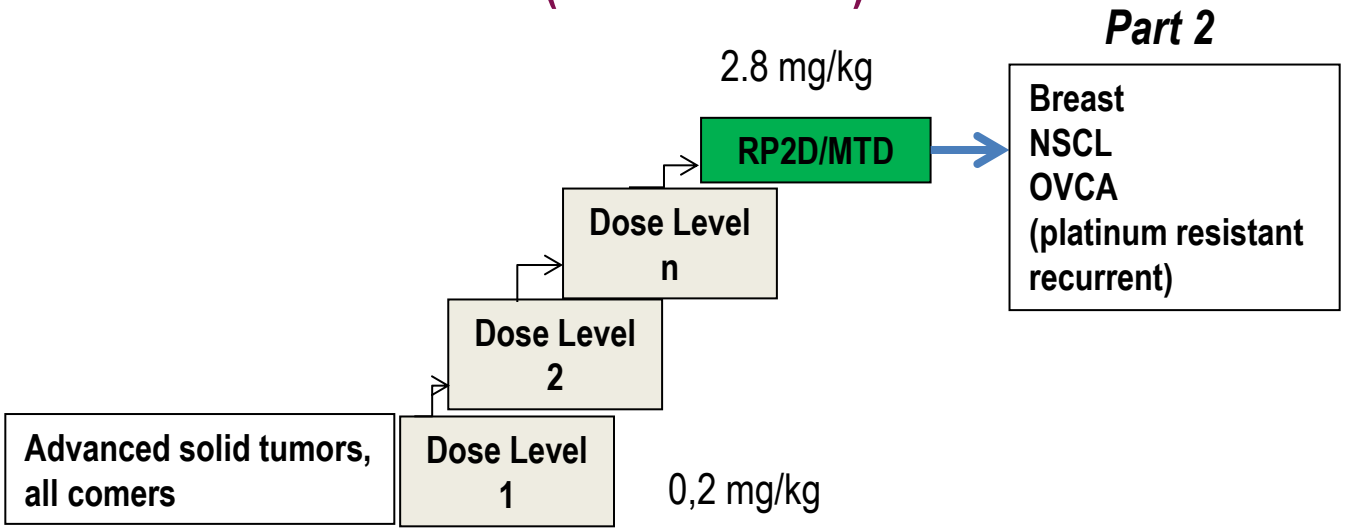
Weekes, Mol. Cancer Ther., 2016

Anti-PTK7 ADC: PF-06647020



- Protein tyrosine kinase 7, component of Wnt/planar cell polarity pathway.
  - Functions as molecular switch in Wnt, semaphorin-plexin and VEGF signaling pathway.
  - Overexpressed in different human cancers (breast, colon, lung, gastric, esophageal, AML)
  - Expression linked to poor prognosis in patients with TNBC and NSCLC

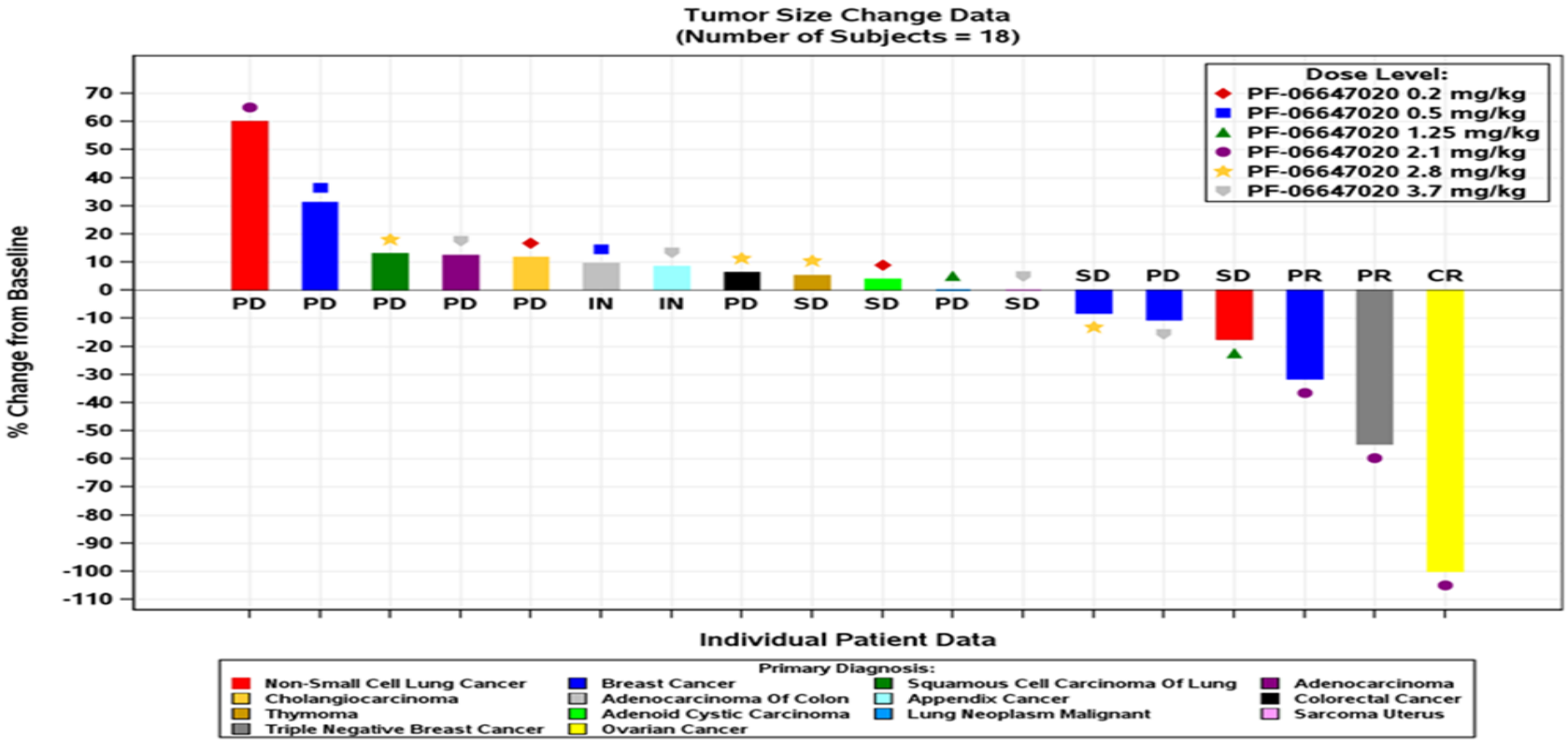
Phase I Study of PTK7 (N=76) (NCTO2222922)



- Dose escalation
  - Single agent q3wks IV in patients with advanced solid tumors
  - Unselected for PTK7 expression

ESMO, 2016

Best Response by RECIST (Dose escalation)



ESMO, 2016

Phase I Study of PTK7 (N=76)

Results

60 pts treated at RP2D, 29 with recurrent OvCa

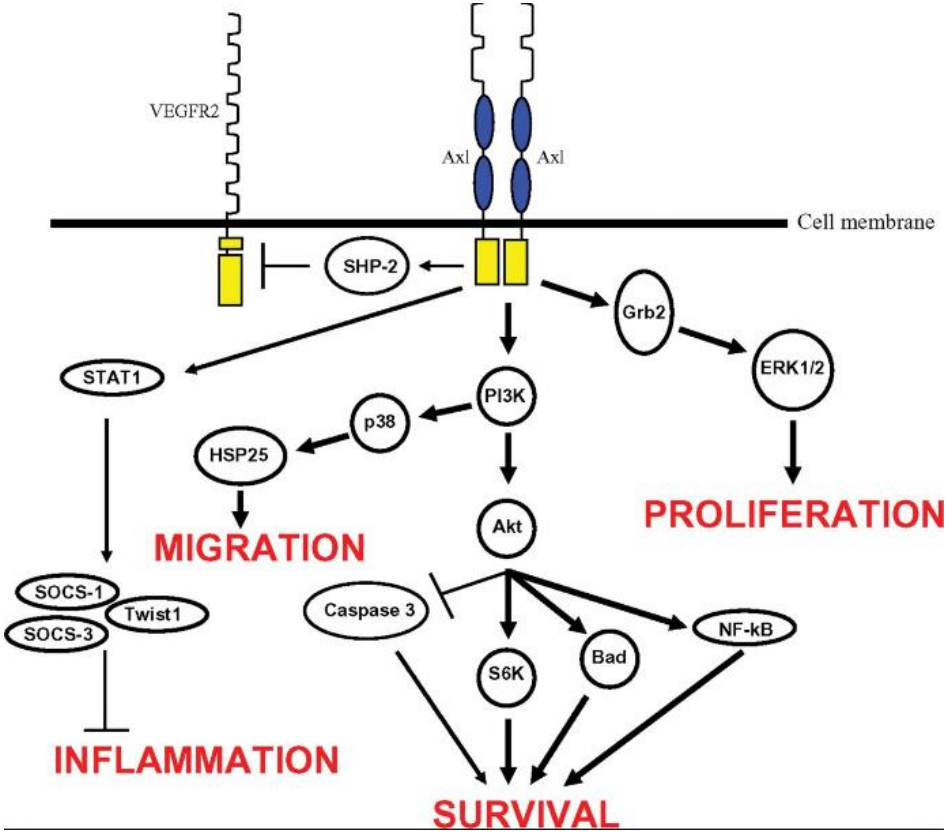
Main toxicities: nausea (46%), alopecia (34%), fatigue (30%), neutropenia (26%)

1CR, 5PR in 22 (4 platinum resistant) evaluable OvCa

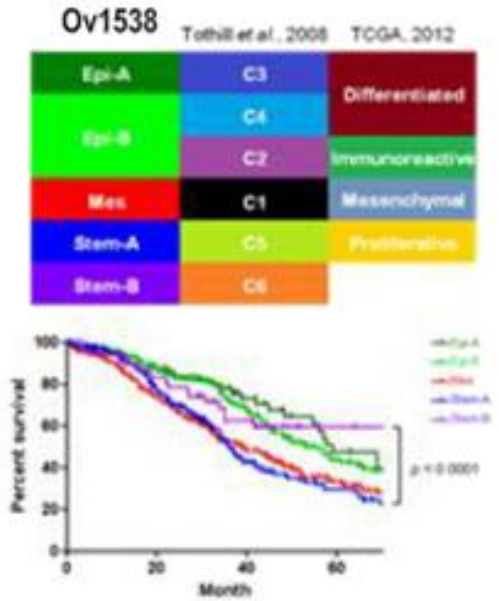
Accrual ongoing

ESMO, 2016

GAS6 - AXL signaling

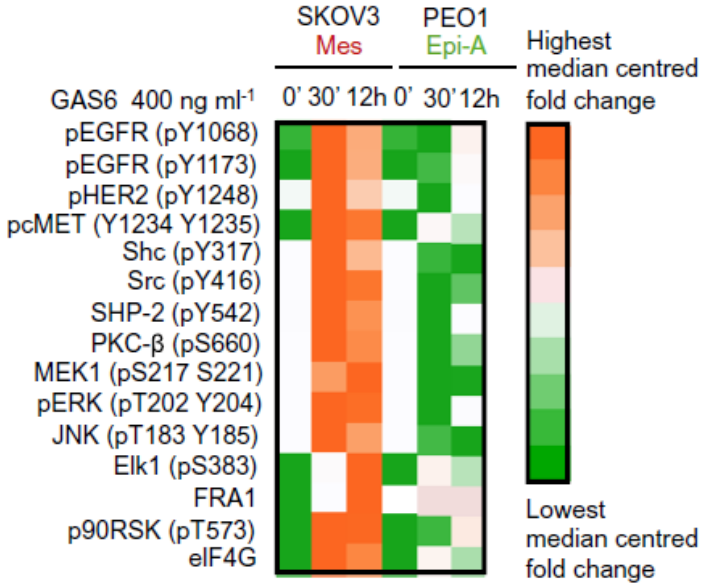


Ovarian Cancer: Heterogeneity in gene expression molecular subtypes (GEMS)



Huang, ESMO Asia, 2016

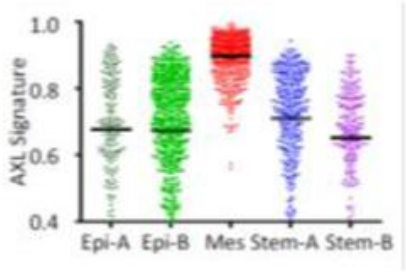
AXL and other RTKs crosstalks in MES



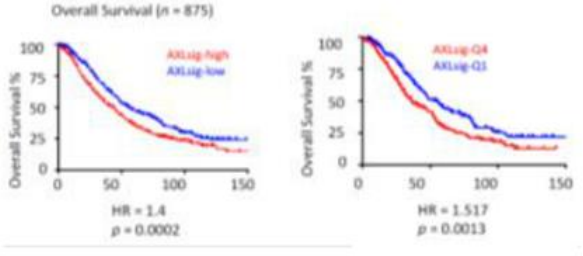
Antony et al, Sci Signal 2016

AXL signature expression

Significantly overexpressed in Mes GEMS (CSIOVDB)



Correlated to overall survival (OS) (CSIOVDB)

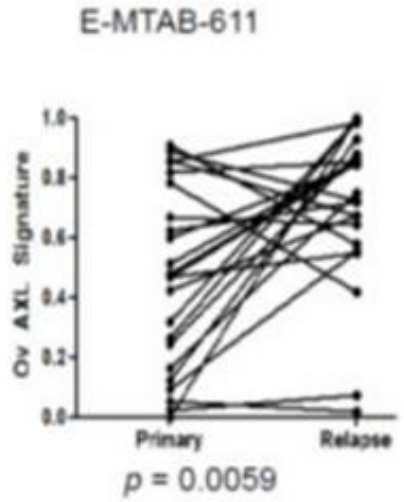


Antony et al, Sci Signal 2016

AXL signature expression

Overexpressed in metastasis and platinum resistant relapse

Resistant to platinum-based chemotherapy associated with EMT in OvCA



E-MTAB-611: Gene expression profile of primary and relapsed epithelial ovarian cancer

Marchini et al., EJC, 2012

Resistance to platinum-based chemotherapy is associated with EMT in epithelial ovarian cancer

MECHANISTIC CONSIDERATIONS

- Primary tumors and synchronous metastases express a homogenous overlapping gene expression profile.
- In 70% of cases, sensitive and resistant-relapsing tumors are associated with differential expression of genes belonging to TLR 4, ECM and TGF-β signalling pathways, all involved in the EMT.

Marchini et al., EJC, 2012

HuMax – AXL – ADC, a novel ADC

- Human AXL mAb coupled by a protease cleavable linker to MMAE
- Promising antitumor activity in lung cancer xenografts, also in a model with high expression of GAS6.

Targeting the GAS6 AXL axis in OvCa

Phase I of the HuMax-AXL-ADC (NCT 02988817)

2 escalation arms (IV q3wks, 3q 4w) with expansion at RP2D

OvCa, cervical, endometrial, NSCL, thyroid cancer

Novel treatment pathways - Horizon Scanning

Conclusions

New promising ADC targeting “new” potentially relevant signal pathways

Improved knowledge with improvement of chemical and biological properties

Possibly more efficient than small TKI

All in platinum resistant disease, mostly targeting TME