Developments in Targeted Therapy for Ovarian Cancer – 2 examples

Vergote et al.	AMG 386 and carboplatin /paclitaxel
Liu et al.	MM121 and weekly paclitaxel

Professor S Kaye
Royal Marsden Hospital
London

Vienna
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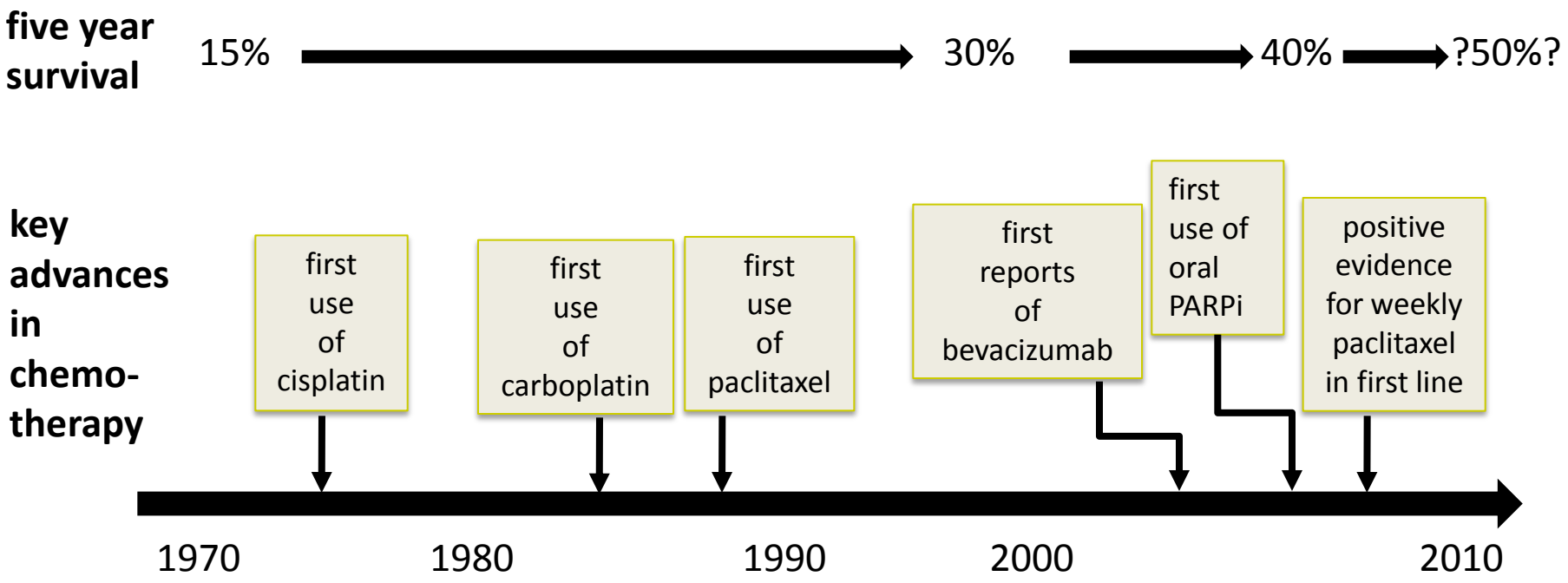
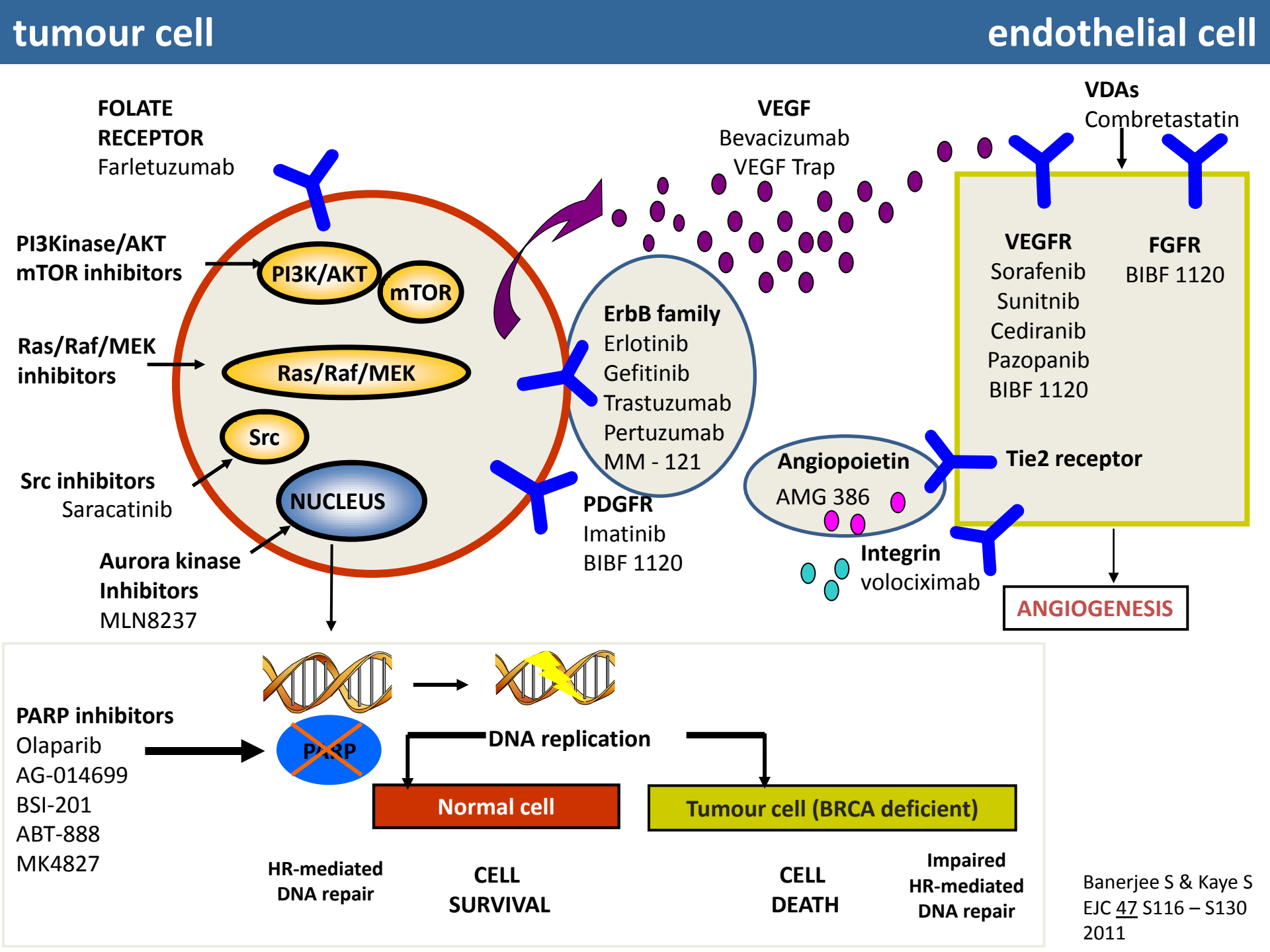
progress in the management of ovarian cancer: evolution over 40 years



in 2012, what is the potential role for molecular targeted therapy?



Banerjee S & Kaye S
EJC 47 S116 – S130
2011

bevacizumab in ovarian cancer

positive randomised trials in first/second line and in recurrent disease
(GOG 218, ICON 7, OCEANS, AURELIA)

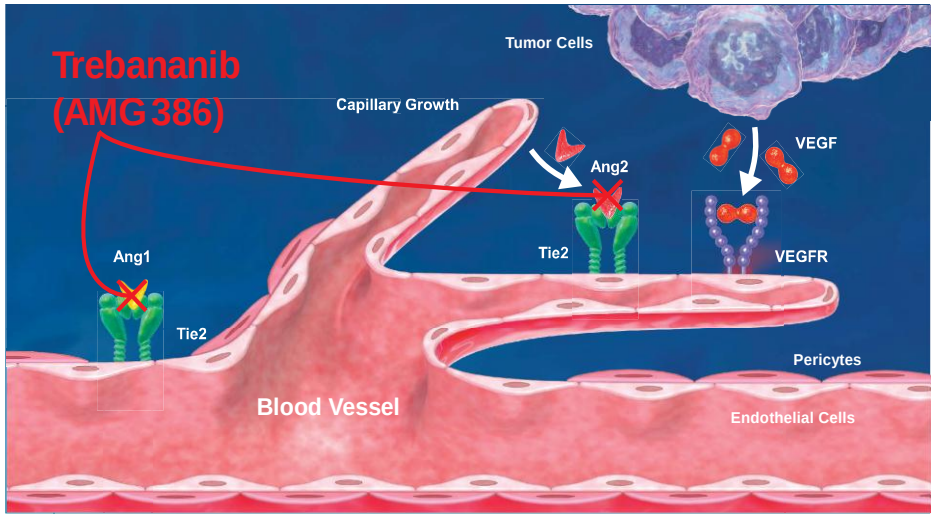
what will the limitations be (apart from cost)?

- Undue risk of bowel perforation in some patients
- other toxicities, i.e. hypertension, etc.
- resistance to VEGF-targeted therapy

how might these be addressed?

- Alternative approaches include
  - AMG 386
  - VEGFR targeted TKIs
  - Combination approaches, including vascular disrupting agents

AMG - 386 (trebananib)



AMG 386 with weekly paclitaxel in relapsed ovarian cancer			
	A	B	C
Weekly paclitaxel	+ AMG 386 10mg/kg	+ AMG 386 3mg/kg	+ placebo
	n = 53	n = 53	n = 55
Median PFS	7.2m	5.7m	4.6m
RECIST response	37%	19%	27%
CA125 response	71%	53%	28%
HR = 0.76 for A + B versus C			
Karlan et al, J. Clin. Onc. 2011			

a peptide-Fc fusion protein (peptibody), which prevents angiopoietin 1 and 2 interacting with Tie 2 receptors, thus inhibiting vascular maturation and reducing impact of VEGF stimulation.

in single agent Phase I trial, iv weekly treatment is well tolerated; hypertension, proteinuria, thrombosis not seen but peripheral oedema noted. DCE MRI confirms significant vascular effect; one response noted in ovarian cancer patients

in combination with weekly paclitaxel, randomised placebo-controlled study in relapsed disease indicated that higher dose of 10mg/kg was most effective

is there a role in first line therapy?
is higher dose (15mg/kg feasible?)

AMG 386 plus paclitaxel-carboplatin as first-line therapy....Vergote et al (975PD)

questions:

can AMG 386 15mg/kg iv weekly be given safely to patients as first-line treatment with paclitaxel/carboplatin q 3 weekly including those scheduled for interval surgery?

is AMG 386 15mg/kg iv weekly feasible as maintenance therapy for up to 18 months?

updated analysis from ASCO 2012 on 27 patients

AMG 386 plus paclitaxel-carboplatin as first-line therapy

results:

a) in combination concurrently with chemo (n = 27)

- no DLTs
- main toxicity not attributable to chemo is oedema, in 11 cases (40%) mainly peripheral. Other G1-G2 toxicities include diarrhoea, nausea, fatigue in approximately 40%
- no PK interaction between AMG 386 and paclitaxel / carboplatin
- no major difference in patients undergoing interval (n=13) or primary (n=14) surgery

b) as maintenance therapy following chemo (n=13)

- No additional toxicity to date, main side effect is localised oedema.

conclusion:

First line treatment using AMG 386 dose of 15mg/kg is safe, for use within a randomised trial

AMG 386 plus paclitaxel-carboplatin as first-line therapy

issues: **how does this compare with bevacizumab?**

advantages:
- no hypertension/proteinuria/bowel perforations/thrombo-embolic events
- no restriction on interval surgery

disadvantages:
- peripheral oedema, presumably mechanism related (Ang 1,2 blockade)
- weekly therapy

key question:
- could AMG 386 potentially replace bevacizumab on grounds of efficacy as well as toxicity profile in first-line therapy?

TRINOVA-3: first line placebo-controlled trial (n=2000)
paclitaxel/carbo ± AMG 386 q w during chemo and maintenance until PD
primary end point: PFS.

AMG – 386 (trebananib) in ovarian cancer

Other questions:

- is a combination approach, eg. AMG386/bevacizumab justified?
  - in vivo data support combined Ang 1/2 inhibition and VEGF inhibition

But note: **AMG 386 ± sorafenib in renal cancer showed no benefit in randomised trial (n= 152)**

- are dual Ang or Tie 2 / VEGF inhibitors preferable?
  - examples include CVX-241, CEP 11981 and several multi-targeted TKIs

- Is AMG-386 active in patients progressing after bevacizumab?
  - pre-clinical data indicate potential role, through Ang 1/Tie 2, but clinical data lacking.
  - What key factors underlie clinical resistance to antiangiogenic therapy?

resistance to anti-angiogenic therapy

a) acquired resistance

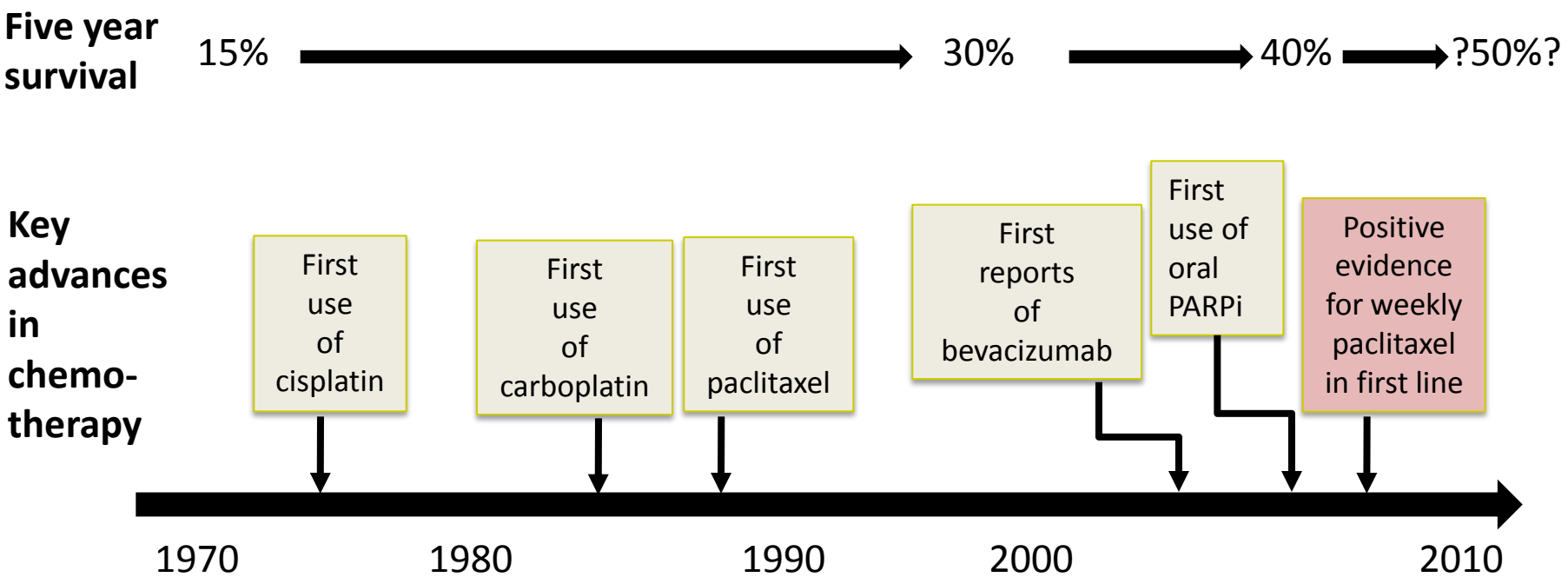
- activation/upregulation of alternative pro-angiogenic signalling, e.g. Ang 1/2
- recruitment of bone-marrow derived pro-angiogenic cells
- increased pericyte coverage of tumour vasculature, obviating need for VEGF signalling.

b) intrinsic (pre-existing) resistance

- multiple pre-existing redundant pro-angiogenic signals
- pre-existing inflammatory cell-mediated vascular protection
- invasive co-option of normal vessels.

can resistance be addressed through inhibition of signalling through Tie 2 receptors (AMG 386)?

progress in the management of ovarian cancer: evolution over 40 years



In 2012, what is the potential role for molecular targeted therapy?

weekly paclitaxel – a personal view

issues: Will this prove superior to q 3 weekly schedule at all stages of ovarian cancer?

in first line:

JGOG trial (631 patients) demonstrated superiority over q3w schedule (median PFS 28m vs 17.5m), but results from confirmatory studies needed before adoption as new standard of care.

Katasumata et al. Lancet 2009

in recurrent disease:

weekly paclitaxel should now be a standard line of treatment for most patients (response rate up to 50%)
however: response duration is short (often < 6m)

Baird, Tan, Kaye. Nat Rev. Clin. Onc. 2010

how can we do better?

- addition of other active agents, eg. Bevacizumab (AURELIA), AMG-386
- circumvention of resistance to paclitaxel

weekly paclitaxel in ovarian cancer

how do cells acquire resistance to therapy?

– through alterations in:

- transport (MDR – p glycoprotein)
- target (β tubulin mutations)
- signalling pathways (apoptosis / survival)

– modulation strategies should ideally be based on translational / clinical data indicating most likely underlying mechanism (s) of resistance.

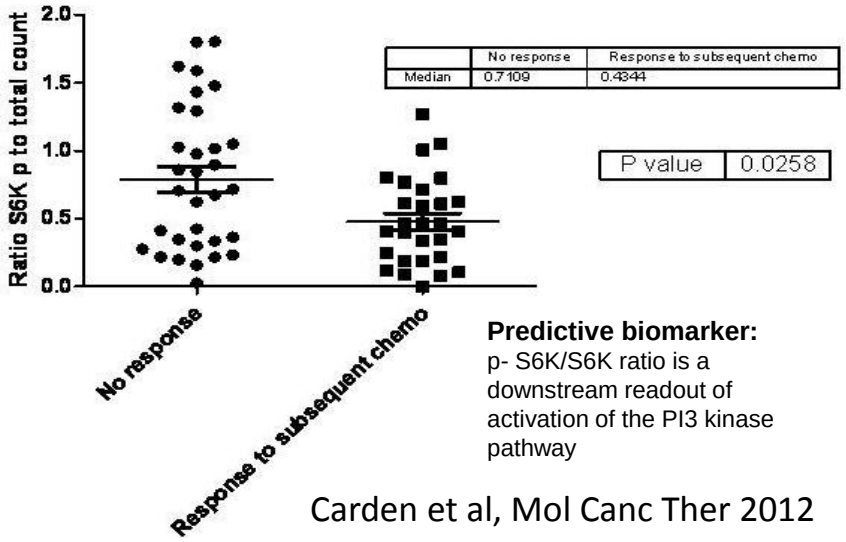
– more of these data needed.

rationale for targeting signalling pathways

negative clinical trials to date, focussing on other approaches (MDR → valspodar; tubulin mutations → epothilones)

multiple pre-clinical studies indicating potential for modulation through pathway specific inhibitors, particularly targeting P13K/AKT/MTOR pathway

Activation of PI3 kinase in tumour cells isolated from ascites, and response to subsequent chemotherapy



Predictive biomarker:
p- S6K/S6K ratio is a downstream readout of activation of the PI3 kinase pathway

Carden et al, Mol Canc Ther 2012

preliminary clinical data, correlating activity of P13K/AKT pathway in tumour cells from ascites with acquired drug resistance.

current pathway-specific clinical trials aimed at resistance reversal for weekly paclitaxel

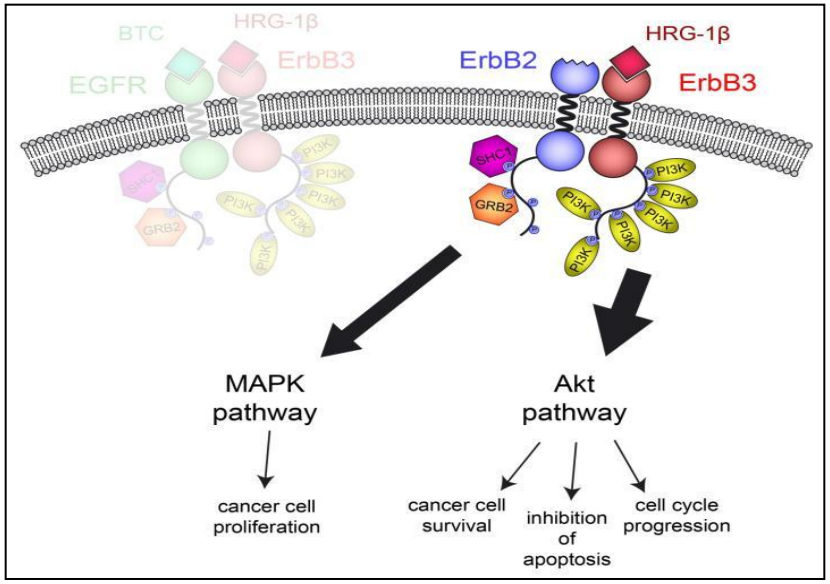
target	drug	comment
folate receptor	farletuzumab	randomised trial in platinum resistant patients discontinued following futility analysis n= >400
Src protein	saracatinib	randomised trial in platinum resistant patients complete - analysis awaited n= 102
IGF-R	OSI – 906	randomised trial in platinum resistant patients – ongoing
Erb B family – Erb B3	MM-121	feasibility study n=38

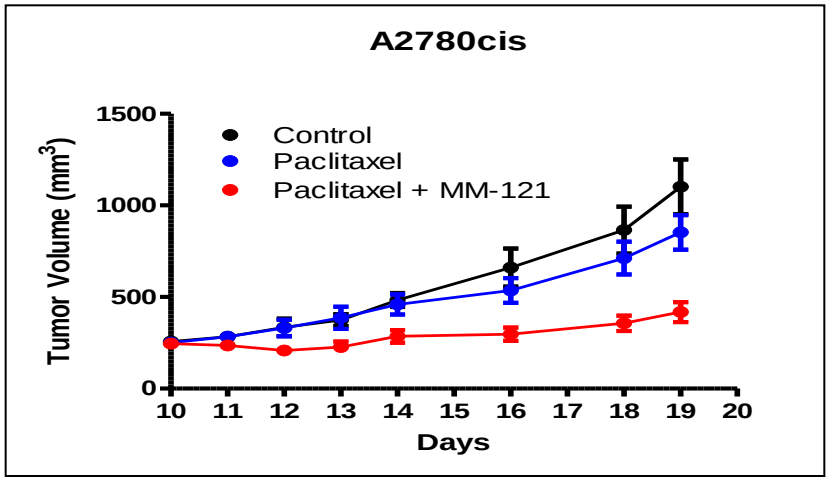
ErbB family of receptors in ovarian cancer

receptor	ligand	frequency	therapy
EGFR (Her 1)	EGF/TGFα/ amphiregulin	amplification - 4-22% activating mutations - < 4% high-expression - up to 62%	minimal efficacy for gefitinib, erlotinib (maintenance)
ErbB2 (Her 2)	none	amplification 9% (partic. mucinous)	minimal efficacy for Herceptin
ErbB3 (Her 3)	heregulin 1/2	high-expression in 53%[1] amplification also noted[2]	?
ErbB4	heregulin 1/2	expression (IHC) in >80%	_

1 . Tanner et al. JCO 24 4317-4323 2006
2 . Tsuda et al Canc. Gen Cytog. 155 97-107 2004

ErbB signalling and potential role for MM-121 in ovarian cancer





Paclitaxel: 40 mg/kg q7d
MM-121: 600 µg/kg q3d

ErbB3 as heterodimer with ErbB2, plays a key role in cancer cell survival signalling, through MAPK and Akt pathways

ErbB3 activation through autocrine loop, natural ligand is heregulin (HRG)

ErbB3 over-expression linked to decreased survival.

ErbB3 associated with resistance to chemotherapy, including taxanes

effects of ErbB3 signalling may be reversed by MM-121

MM 121 is fully human IgG2 antibody, recognises ErbB3 and blocks HRG signalling

MM-121 – clinical data

phase 1 single agent trial (Dealinger et al, AACR 2011)

- Dose escalation plus expansion in 38 patients
- G 1/2 nausea/diarrhoea/rash, and G3 fatigue seen but DLT not reached at doses up to 20mg/kg iv weekly.
- 9 patients had RECIST SD, 5 treated > 4 months

phase 2 combination studies ongoing, based on preclinical data, involve both targeted and cytotoxic agents**, including weekly paclitaxel**

MM-121 plus weekly paclitaxel... Liu et al (974 PD)

feasibility study in ovarian and breast cancer, accrual ongoing. n=28, 16 ovarian and 12 breast cancer

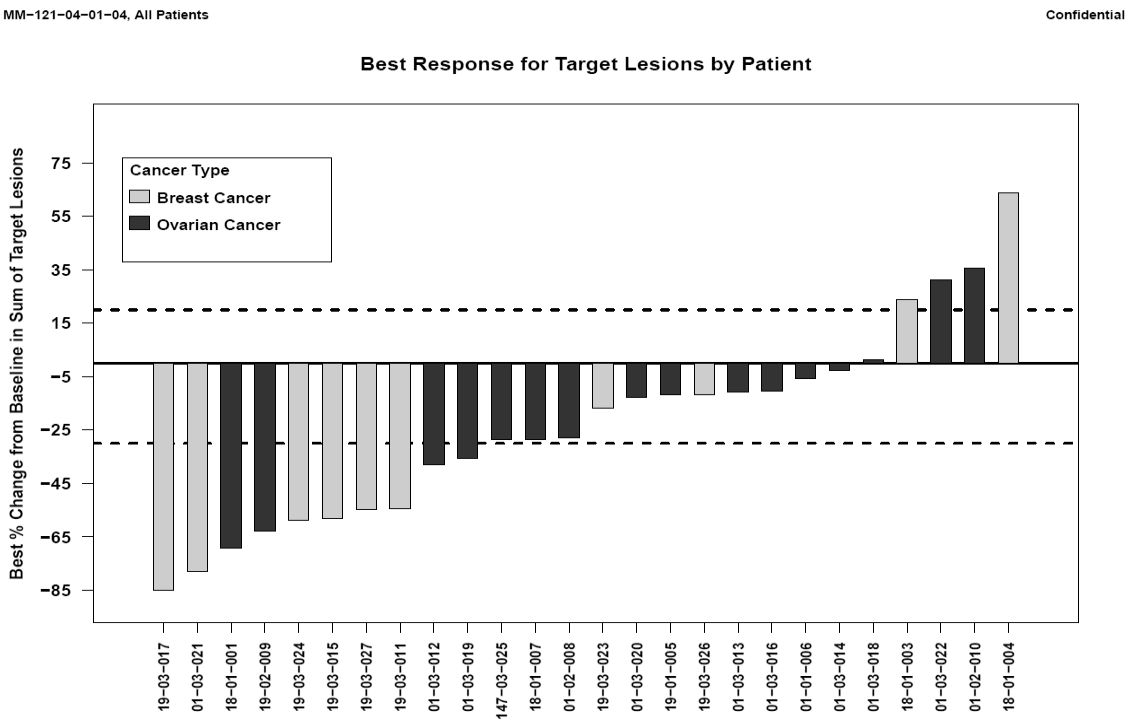
- schedule: MM-121 20-40mg/kg i.v. starting dose,
  then 12-20mg/kg i.v. weekly or 3weeks on/1 week off
  paclitaxel : 80mg/m² i.v. weekly
  DLT: not reached

main toxicity	any grade	G3 / G4
fatigue	52%	15%
neuropathy	48%	7%
diarrhoea	40%	7%
neutropenia	37%	11%
stomatitis	33%	11%

MM-121 plus weekly paclitaxel... Liu et al (974 PD)

efficacy (RECIST) in 16 ovarian cancer patients with platinum refractory/resistant disease)

- PR = 4
- SD = 10 (> 4m in 5)
- PD = 2
- med PFS = 28w



Q. how does this compare with weekly paclitaxel alone?

MM-121 plus weekly paclitaxel in ovarian cancer

summary

combination is feasible with toxicity not significantly different from weekly paclitaxel alone

efficacy in small numbers encouraging; a randomised trial in relapsed patients is clearly warranted

can a predictive biomarker be identified to aid patient selection?

development in targeted therapy for ovarian cancer

final word:

– real progress on 2 fronts:

1) established role for anti-VEGF therapeutics, particularly in context of maintenance treatment.

2) emerging identification of new molecular targets specific for (5) subtypes, leading to improved patient selection, potentially for combination approaches.