ESMO Preceptorship on Ovarian Cancer

Biology of drug resistance

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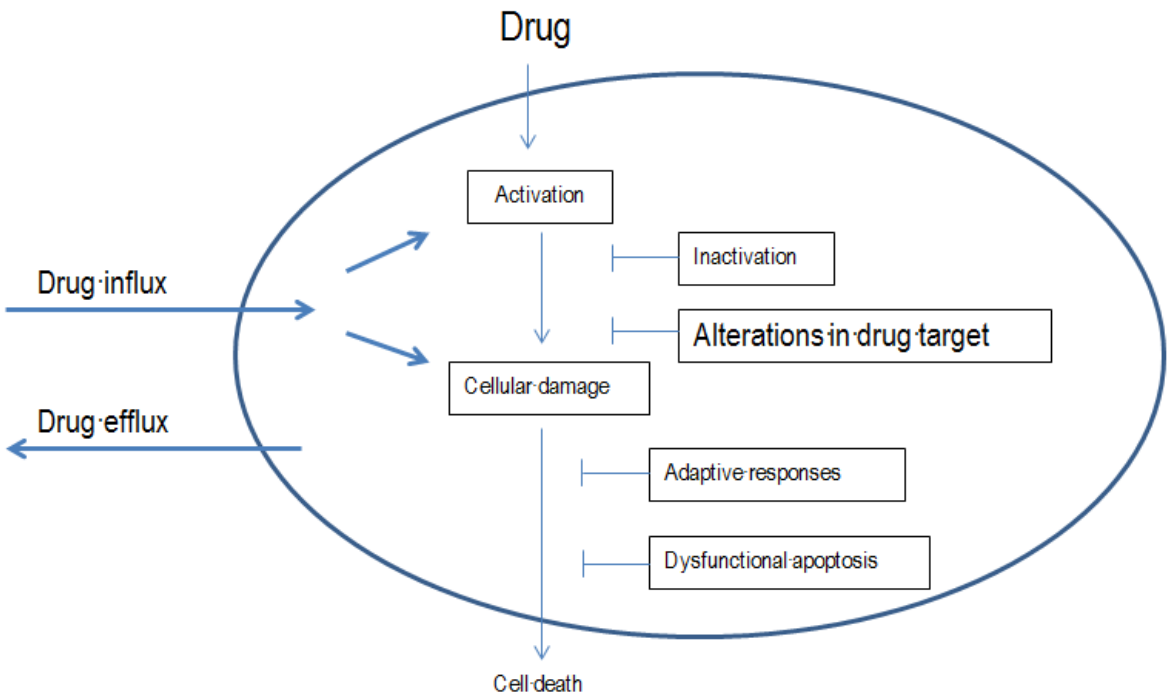
Prague, April 21st, 2017

Presenter Disclosures

No disclosure

Mechanisms of drug resistance



Tumor·cell

Holohan, Nat Rev Cancer, 2013

Promotion of drug efflux

ATP binding cassette transporters

MDR1 overexpression with intrinsic / acquired resistance

(kidney, colon and liver cancer)

High degree of functional redundancy

ABC transporters

Complex translocation system across cellular membranes

Able to export anticancer drugs, 7 distinct subfamilies

- ABCB: $ABCB_1$ (MDR_1), PgP, responsible for chemo resistance

  no correlation between $ABCB_1$SNP and outcome in OvCa

Clinical results so far disappointing, with PK alterations and ↑ toxicity

Mechanisms of alterations in drug target

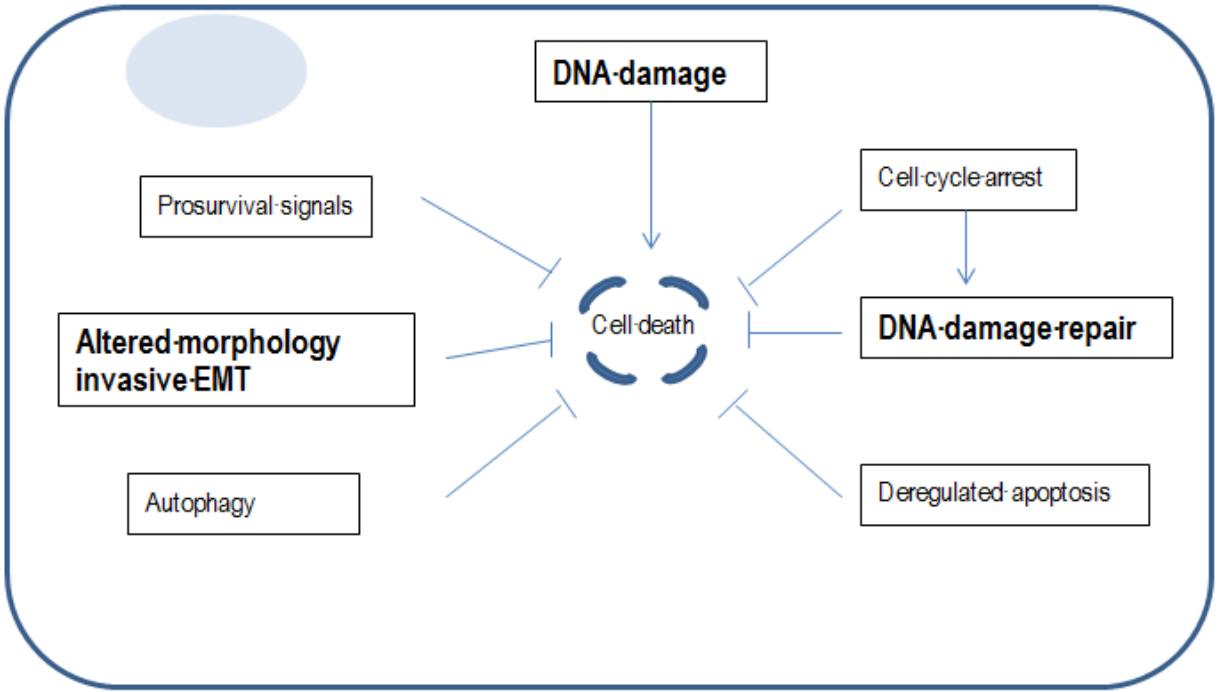
- Gene mutations or overexpression
- Gate keeper mutations: EGFR - T790M

  BCR-ABL1 - T3151

- Alterations in the signalling pathway

  that mediates drug activation: HER2 and PI3K /AKT

Downstream resistance pathways



Drug resistance

Alterations of DNA damage response (DDR)

- High degree of genomic instability in DR defective tumors
- Restoration of HR by reversion mutation

Alterations in the balance between HR and NHEJ

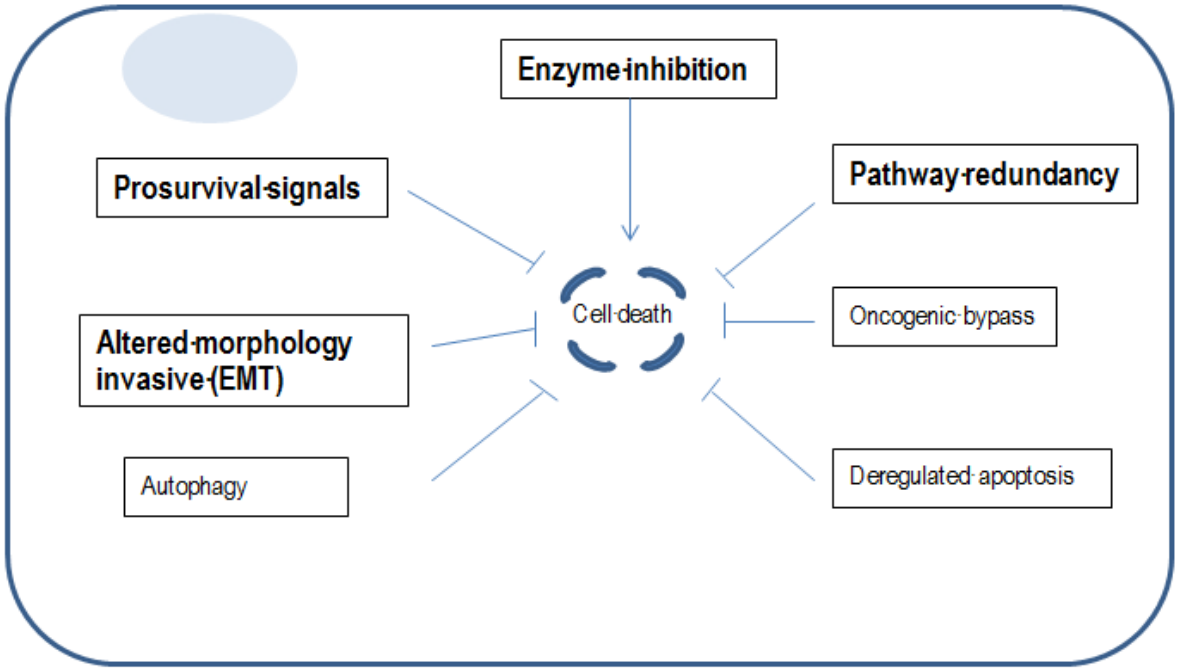
Overcoming DDR-related resistance

Identify biomarkers and select patients

	Tumor biopsy
Knowledge driven biomarkers	Mutation/ methylation of DDR genes DDR genes expression (mRNA, protein) DDR activity (phospho-protein)
Features of DDR deficiency: genomic instability	DNA copy number alterations Microsatellite instability LOH frequency
In vitro or ex vivo functional assay	RAD 51 foci formation Sensitivity to DNA damaging agents

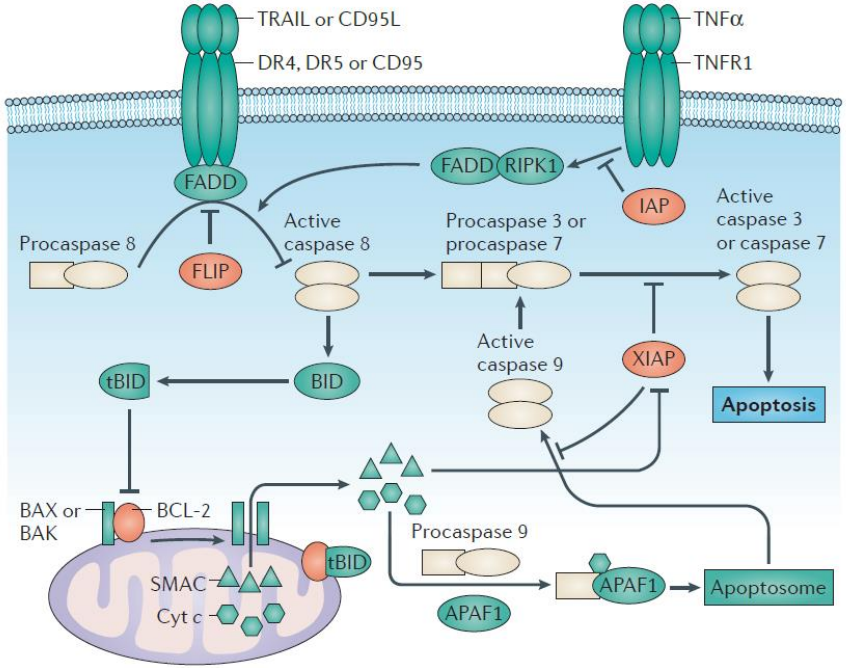
Bouwman, 2012

Downstream resistance pathways



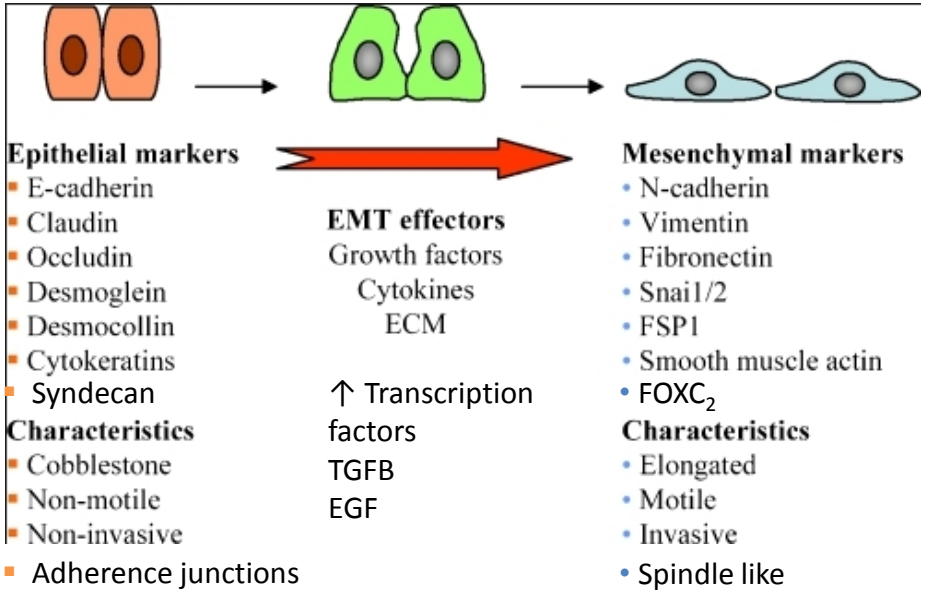
Deregulation of apotosis

Overexpression of antiapototic (BCL_2) and pro-apoptotic (BAX, BAD and BAK) family members



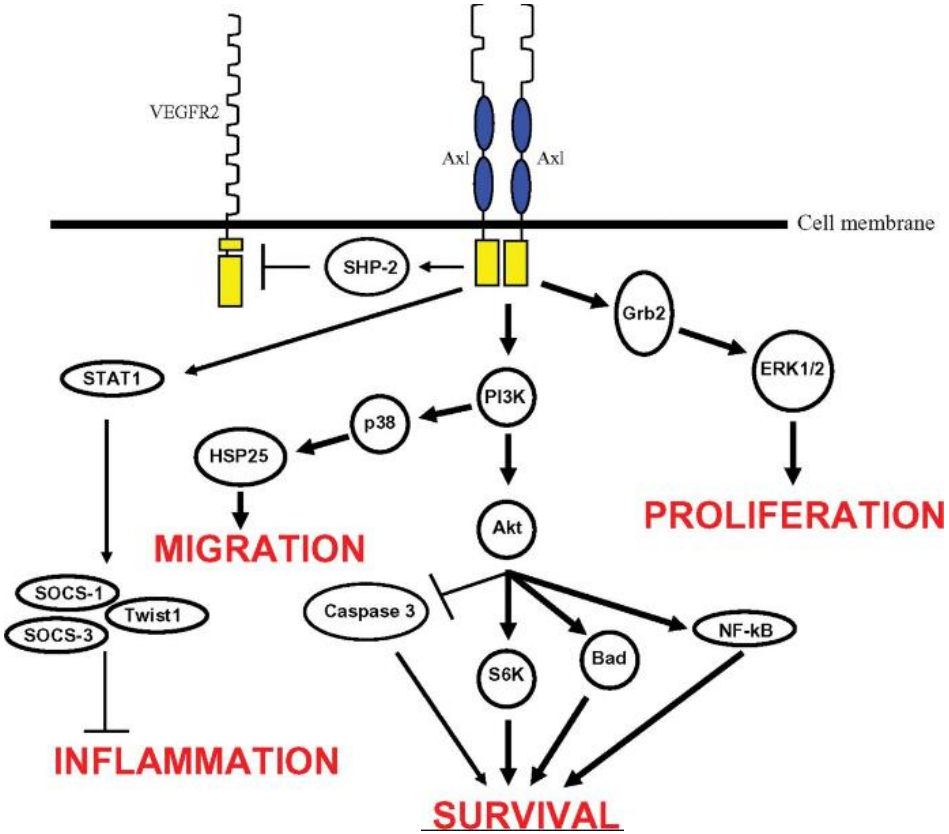
Holohan, Nat Rev Cancer, 2013

Epithelial-Mesenchymal Transition



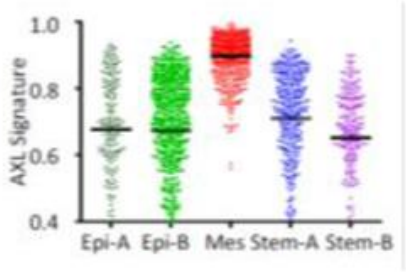
Epithelial cells lose cell-cell adhesion, gain migratory and invasive property to become mesenchymal stem cells

GAS6 - AXL signaling

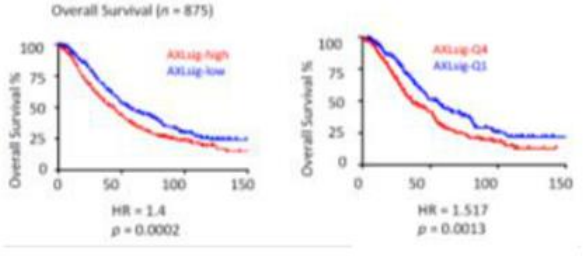


AXL signature expression

Significantly overexpressed in Mes GEMS (CSIOVDB)



Correlated to overall survival (OS) (CSIOVDB)

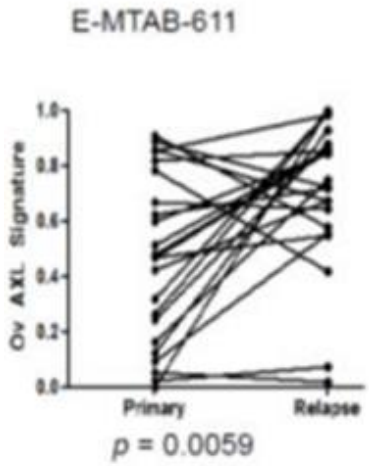


Antony et al, Sci Signal 2016

AXL signature expression

Overexpressed in metastasis and platinum resistant relapse

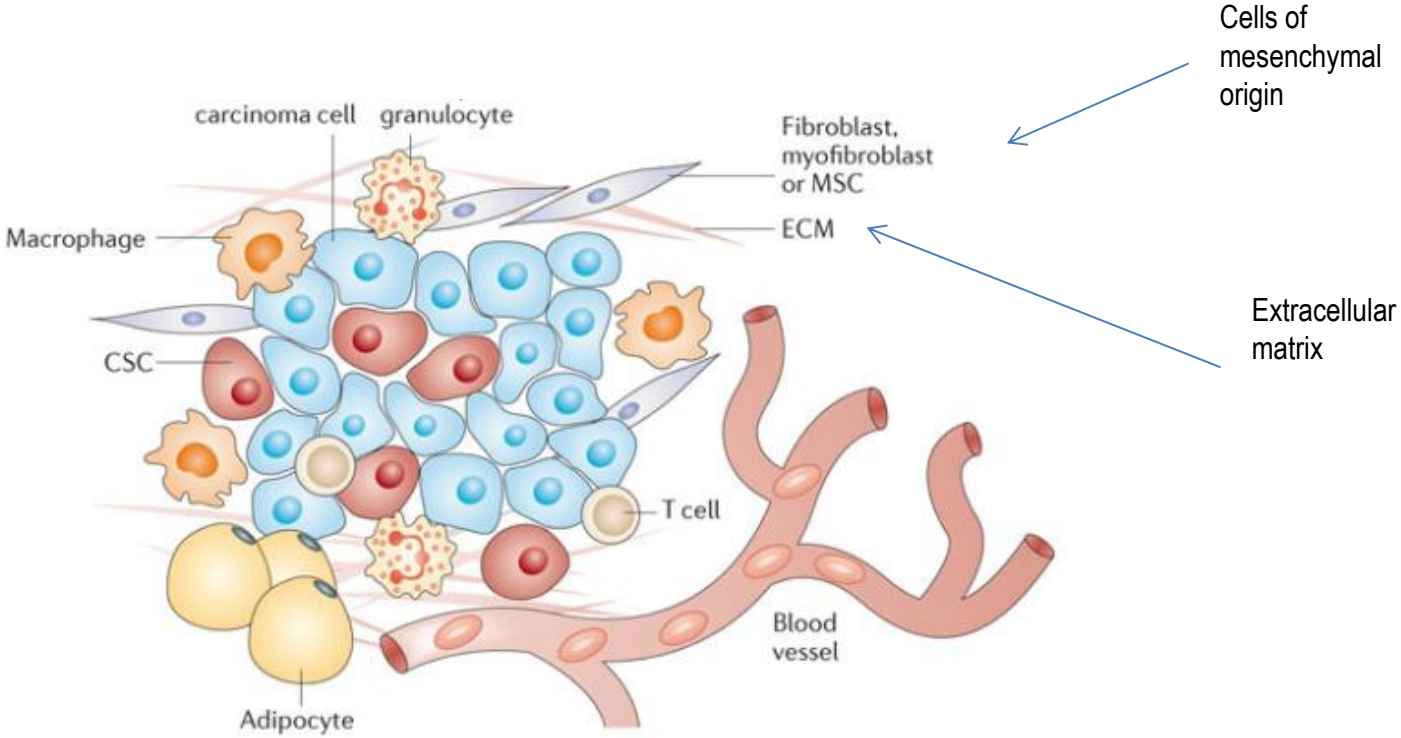
Resistant to platinum-based chemotherapy associated with EMT in OvCA



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

Marchini et al., EJC, 2012

Tumor microenvironment

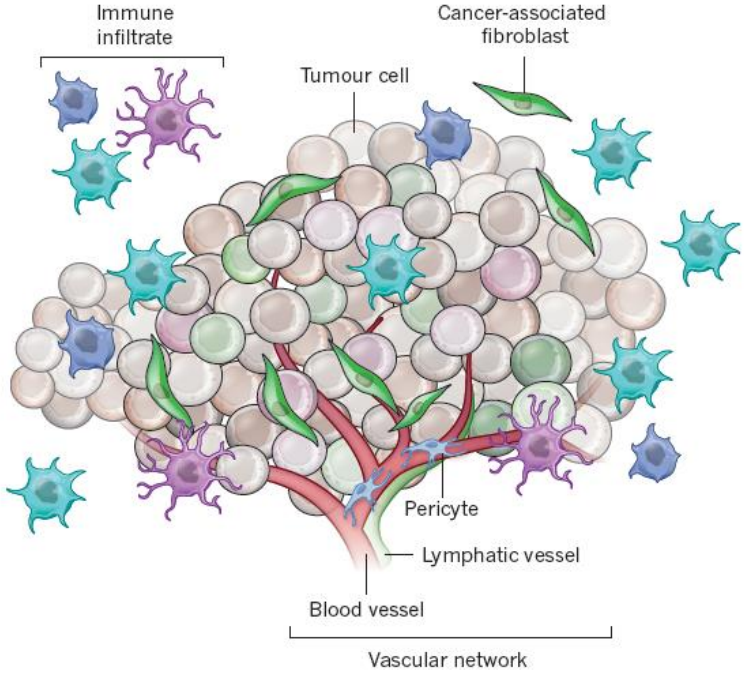


Cells of hematopoietic origin: Tcell, Bcell, NK, neutrophils, MDSC, macrophages,

Pattabiram, 2014

The tumor niche and the tumor heterogeneity

T cell activation
Expansion MDSC
TAM



Reciprocal interaction between CAF and tumor cells

Maturity, interstitial pressure functionality

Need of multitargeted approaches

Junttila, 2013

Targeting the microenvironment in ovarian cancer

Targeting stromal fibroblast (ECM)		
	MoA	
Marimastat	MMP	Phase III negative
Vismodegib	SMO	Phase II negative

Targeting vasculature		
Bevacizumab	Anti VEGFA	Phase III positive ICON 7
Pazopanib	VEGFR, PDGFR kit antagonist	Phase III negative
Nindetanib	Pan VEGFR, pan FGFR, Pan PDGFR antagonist	Phase III completed
Cediranib	Pan VEGF, PDGFRa; CKit	Phase III positive ICON 6

Targeting the microenvironment in ovarian cancer

Targeting immune cells	
Ipilimumab	Anti $CTLA_4$
Nivolumab	Anti PD_1
Atezolizumab	Anti PDL_1
Avelumab	Anti PLD_1
Pembrolizumab	Anti PD_1

Developing treatments targeting the tumor stroma

Requirements

- Need of accurate preclinical model systems
- Lack of immune effector cells in xenografts
- Develop reliable predictive biomarkers
- Study temporal and spatial heterogeneity of tumor
- Repeat serial biopsies from different sites

Development of resistance in ovarian cancer

Known mechanisms

TAM and promotion of proangiogenic pathways (resistance to anti VEGF therapy)

TAM and promotion of tumor growth, suppression of immune response

Immune recruitment in case of hypoxia with angiogenic escape VEGF and resistance to immune therapies.

Conclusions

Overcoming drug resistance

Improved basic knowlegde brought identified new pathways

Develop multitargeted approaches

Targeting the non-tumor cell compartment is challenging:

- lack of adequate preclinical animal models
- intra and inter-tumor heterogeneity