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

- Payload - potency
  - type

Linker
  - Chemistry
  - Stability

Antigen Binding Site

Select monoclonal antibody

Potent cytotoxic payload

Stable linker

Heavy Chain

Light Chain

VH

VL

CH1

CL

F_{at}

F_{c}
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 DM₄
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)
- DLTₜ: keratitis and neuropathy
- Most common AEₜ: fatigue, GI, LFTₜ 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+)

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.

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) (NCT02222922)

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

Advanced solid tumors, all comers

Dose Level 2

Dose Level 1

RP2D/MTD

Breast NSCL OVCA (platinum resistant recurrent)

Part 2

Dose Level n

2.8 mg/kg

0.2 mg/kg

ESMO, 2016
Best Response by RECIST
(Dose escalation)
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
GAS6 - AXL signaling

![Diagram of GAS6-AXL signaling pathway](image)

- **Cell membrane**
- **VEGFR2**
- **SHP-2**
- **Grb2**
- **PI3K**
- **Akt**
- **NF-kB**
- **STAT1**
- **HSP25**
- **p38**
- **SOCS-1**
- **Twist1**
- **SOCS-3**
- **Caspase 3**
- **S6K**
- **Bad**

**Categories:**
- **Migration**
- **Proliferation**
- **Inflammation**
- **Survival**
Ovarian Cancer: Heterogeneity in gene expression molecular subtypes (GEMS)
AXL and other RTKs crosstalks in MES

Significantly overexpressed in Mes GEMS (CSIOVDB)

Correlated to overall survival (OS) (CSIOVDB)
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
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