Gynecological cancers

Lurbinectedin (PM01183) activity in platinum-resistant / refractory ovarian cancer patients. Preliminary results of an ongoing two stage phase II study

Berton – Rigaud et al

Abstract 9680
Discussant: Cristiana Sessa

Disclosure information of Cristiana Sessa

Relationships Relevant to this session

Advisory Board: OSI

Corporate-sponsored research: OSI

No other relevant relationship

Lurbinectedin (PM01183)
Preclinical data

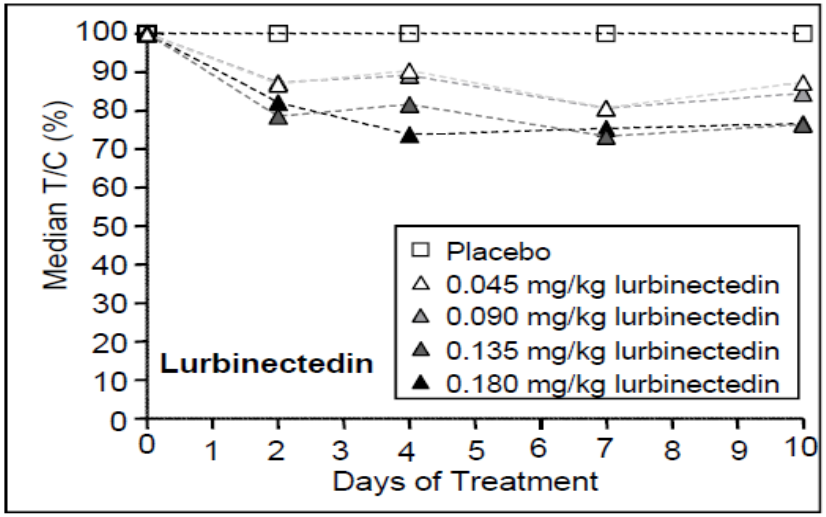
- New DNA minor groove covalent binder
- In vitro / in vivo activity against a broad tumor panel
- Antitumor activity in orthotopic primary grafts of cisplatin – resistant epithelial ovarian cancer (EOC)

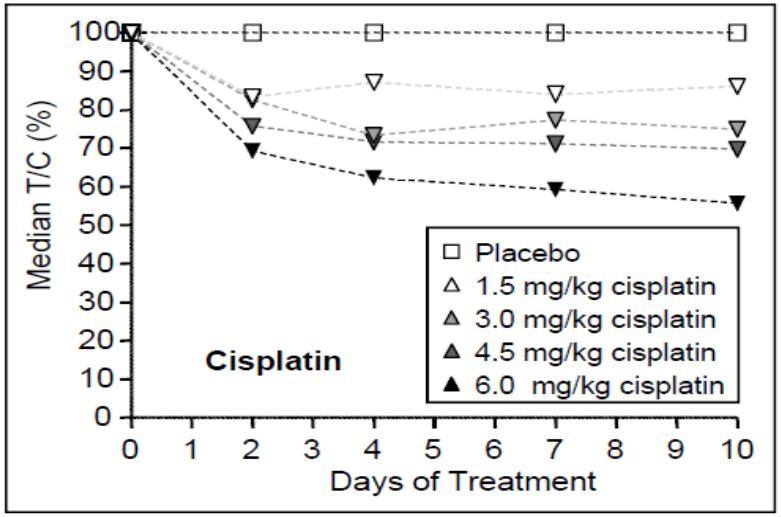
Lurbinectedin (PM01183)

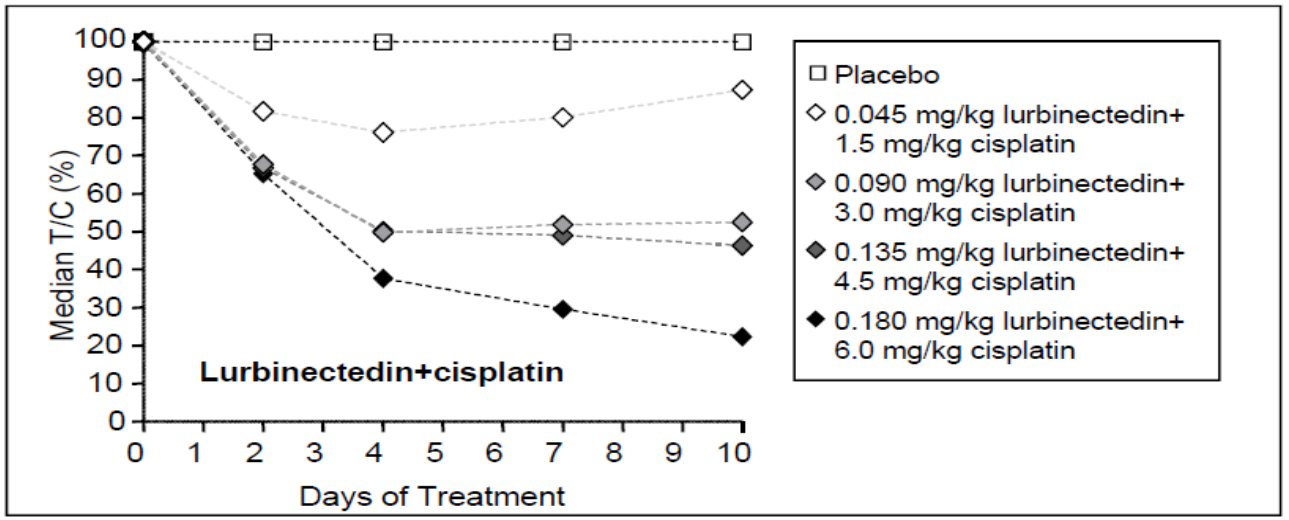
Phase I study

- IV 1hr inf q3 wks (flat dose), antiemetic prophylaxis
- RP2D 4mg/m2 (7mg FD)
- Neutropenia DLT, occuring 3 wks after treatment
- Linear PK with marked inter-intra individual variability. Low $\sqrt{}_{SS}$ and long T ½
- Stronger association of neutropenia with AUC than with dose
- Antitumor activity in ACP

Antitumor activity of Lurbinectedin and Cisplatin in A-2780 derived tumor xenografts

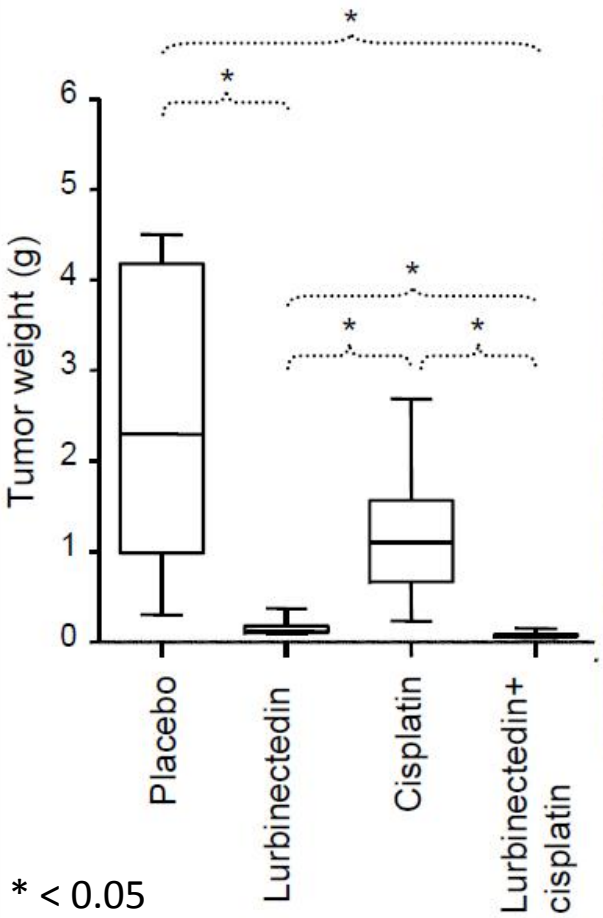


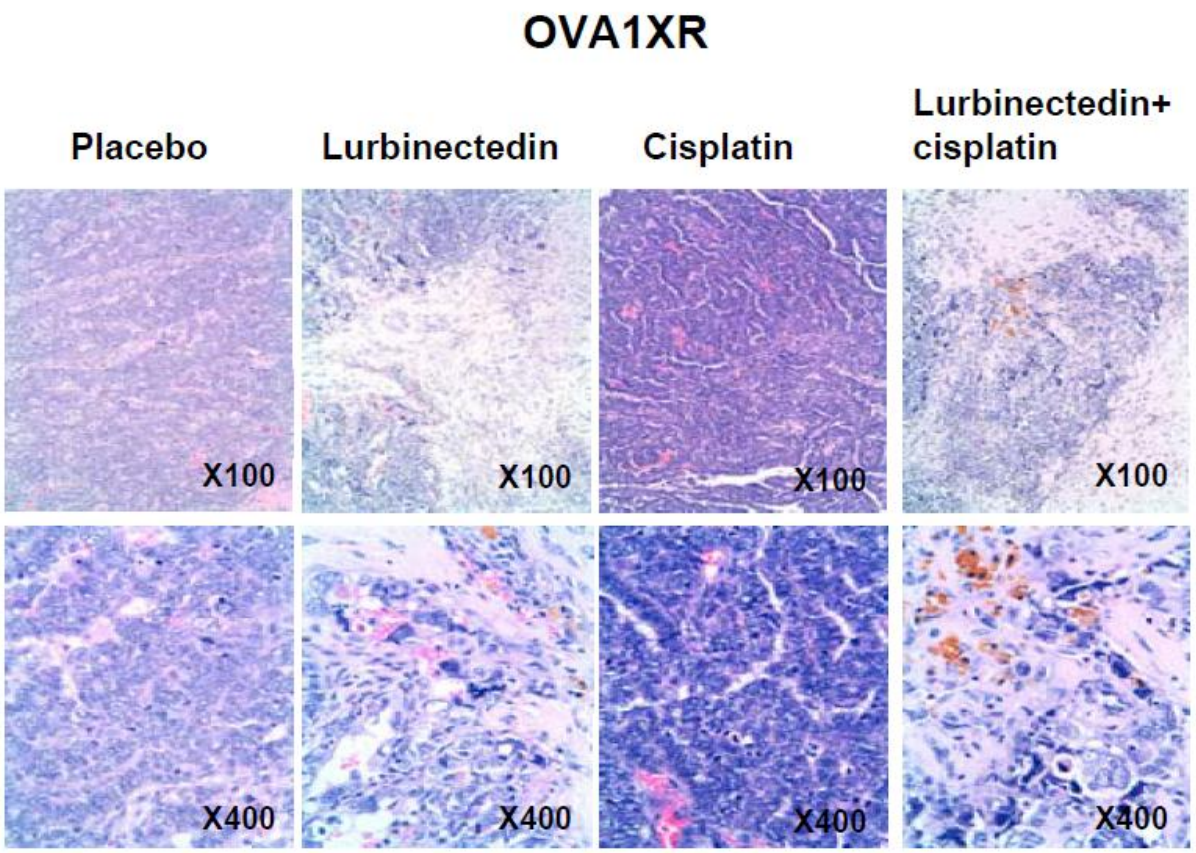




Vidal et al, CCR 2012

Response of OVA1XR to Lurbinectedin based treatments

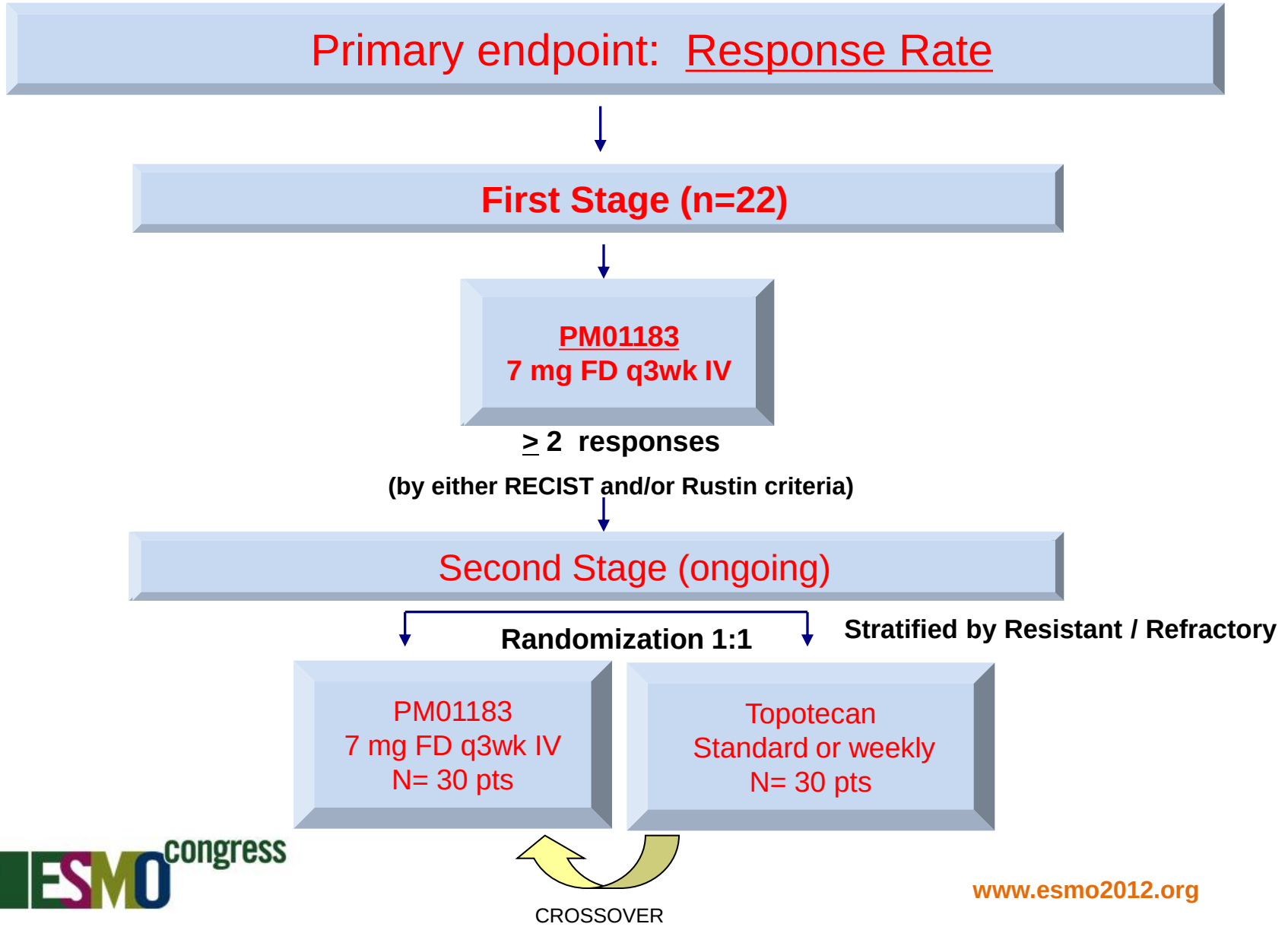




* < 0.05

Vidal et al, CCR 2012

PM1183-B-002-11 - Study Design



Lurbinectedin in platinum resistant / refractory ovarian cancer

First stage results

- 22 patients entered (6 P refractory) / 22 evaluable
- 27% RR, 4 according to RECIST 47% SD
- Nausea and vomiting, neutropenia and fatigue as main toxicities
- Second stage with randomization to topotecan ongoing

Trabectedin in relapsed advanced ovarian cancer
Pooled analysis of three Phase II trials

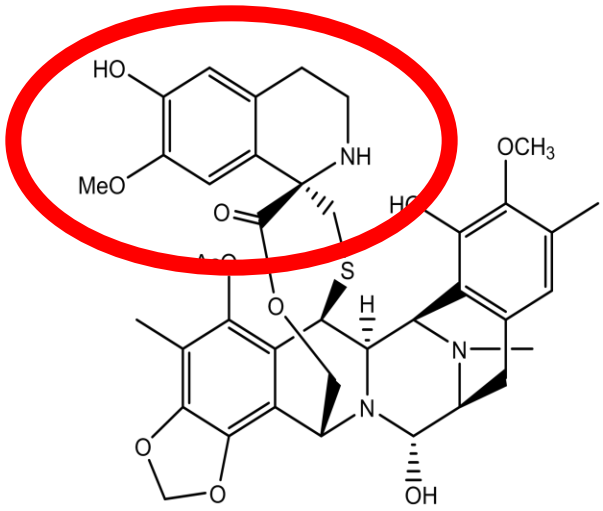
Antitumor activity

	Pt resistant (N=107)	Pt sensitive (N=187)
Median TTP (95% CI)	2.1 (1.7-2.9)	6.0 (5.3-6.6)
%CR + PR (95% CI)	7.5 (3.3-14.2)	36 (29-44)
%SD	43	39

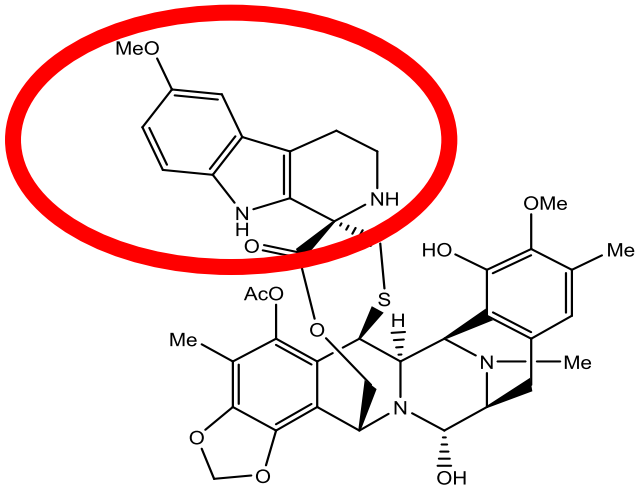
ASCO 2007

Chemical structures

Trabectedin



Lurbinectedin (PM01183)



The structural difference is in the part of the molecule that does not bind DNA but interacts with DNA binding proteins (e.g. transcription factors)

Ecteinascidins' mode of action

- **Direct effect on cancer cells**

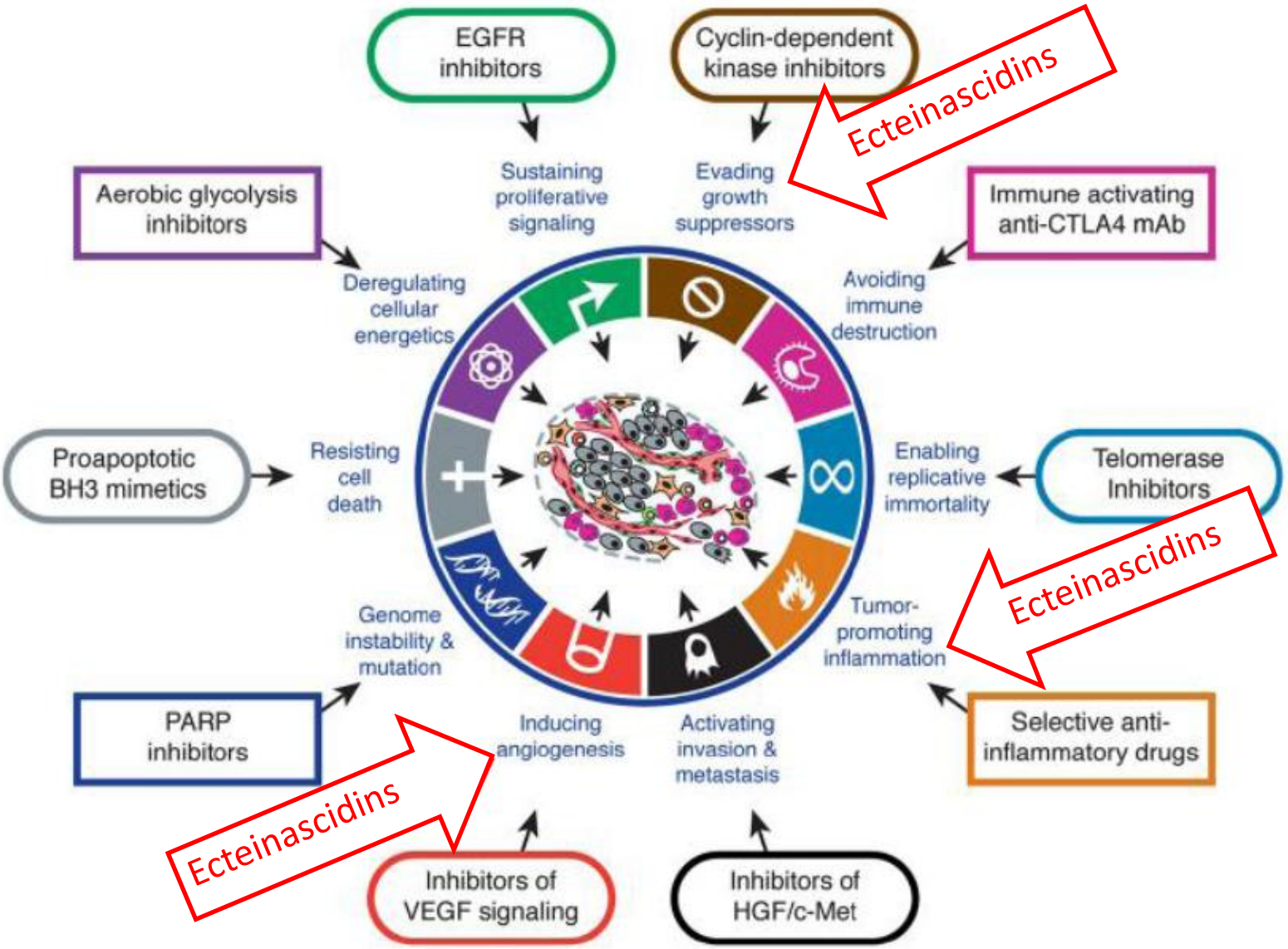
  by binding in the DNA minor groove, causing DNA damage and modulating the transcription of cancer relevant genes

- **Indirect effect on tumor microenvironment**

  by decreasing the number of tumor associated macrophages

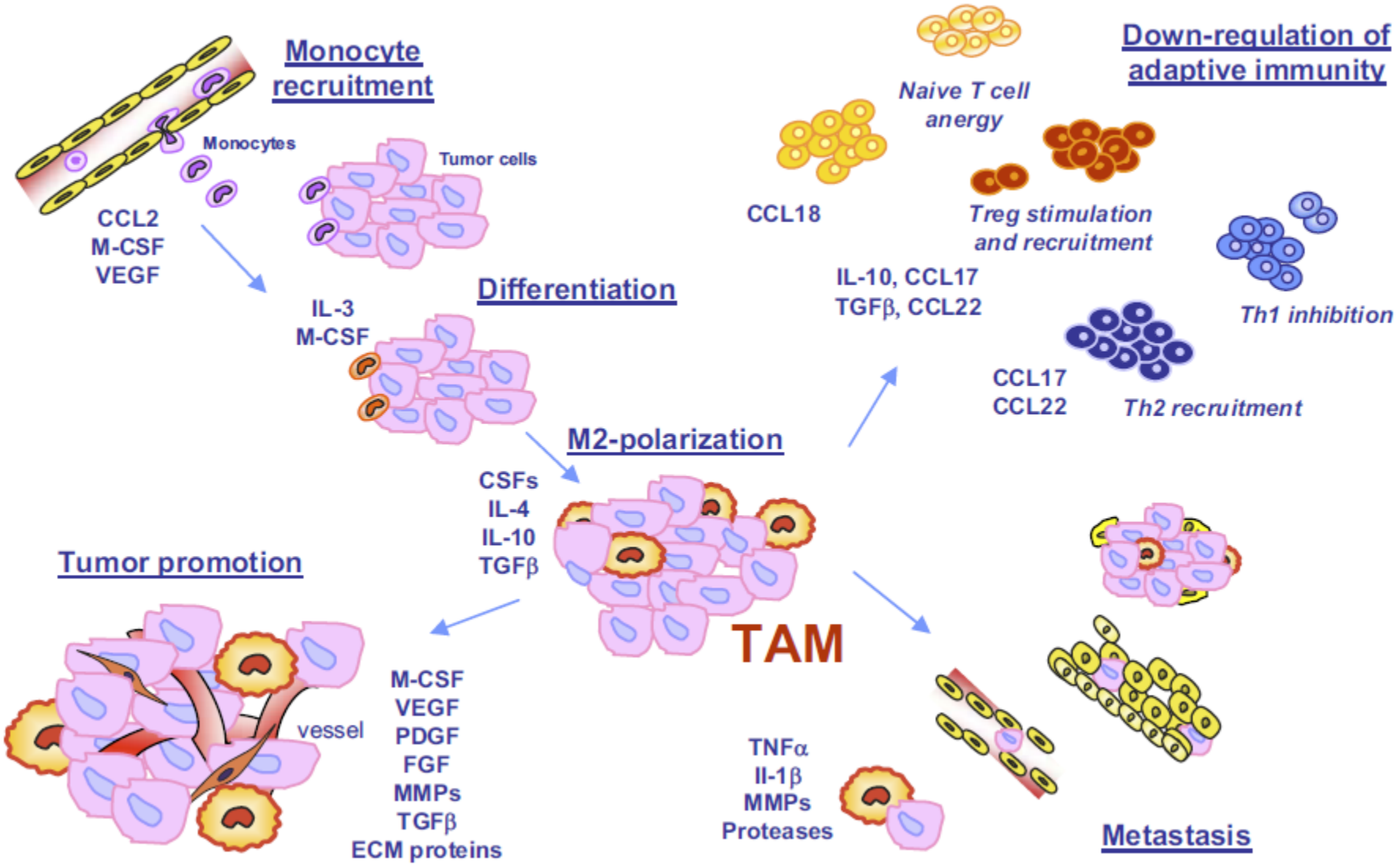
  by inhibiting the transcription and production of cytokines (e.g. IL6, IL2) chemokines (e.g. CCL2) and angiogenic factors (e.g. VEGF, Angiopoietin 2)

Ecteinascidins hit different functional aspects of tumors



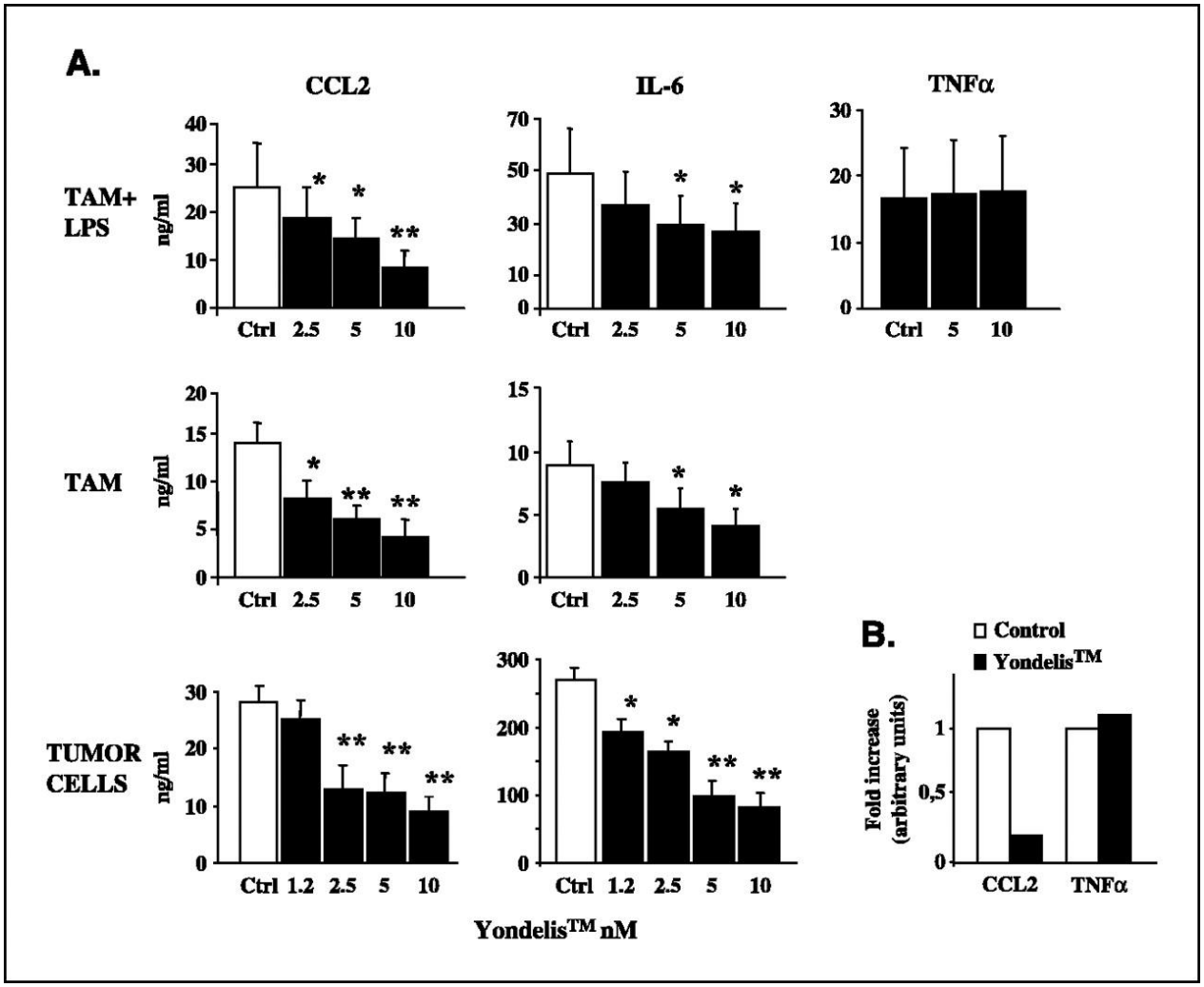
Hanahan and Weinberg. Cell 144, 2011

Pro-tumor functions of Tumor-Associated Macrophages



Solinas, Jounal of Leukocyte Biology, Vol. 86, Nov. 2009

Yondelis inhibits CCL2 and IL-6 production in TAM and tumor cells from patients with ovarian cancer.



Clinical development Lurbinectedin
Next steps

- Worthwhile pursuing the combination with chemo? Yes
- In which tumor types? So far only ovary, perhaps ACP
- Single agent or combinations? Combinations with platinum
- Additional data needed Comparison with trabectedin ± / cisplatin in ovarian xenografts

  Confirmation of the preclinical results in resistant EOC
- Evaluation of potential causes of differences from trabectedin

  different PK profile

  indirect effects on tumor microenvironment

  indirect effects on TAM