Combination Immune-Antiangiogenic Therapy: Lessons from Ovarian Cancer

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Goals

1) Explain the scientific rationale for the combinations - "Why would it work?"
2) Summarize data on use of the combinations, both preclinical and clinical
3) Summarize potential pitfalls and complications to be aware of - "Why it may not work"
4) Suggest the next steps that should be made
Why would it work?

1) Ovarian cancer is immunogenic tumor
2) Antiangiogenic therapy has produced significant results: Single agent bevacuzimab ~20% RR, higher with metronomic cyclophosphamidamide
3) VEGF suppresses the maturation of DCs
CD3+ 54.8% 38.7% 6.5%
N=174 Zhang et al., NEJM 2003
Impact of Inratumoral T cells on Outcome in Ovarian Cancer Stage III/IV patients

Zhang et al., *NEJM* 2003

Zhang et al., *NEJM* 2003

N=174
VEGF associates with poor outcome and absence of intratumoral T cells
Antiangiogenesis

Thrombosis

IFN-γ

DC

T cells

MIG

Activation

Antiangiogenesis Thrombosis

IFN-γ

DC

T cells

MIG

Suppression

VEGF

Angiogenesis

Overall Survival (%)

P<0.001

Intratumoral T cells

No intratumoral T cells

Month

0 12 24 36 48 60 72 84 96 108 120 132

100

75

50

25

0
Tumor-infiltrating dendritic cell precursors recruited by a β-defensin contribute to vasculogenesis under the influence of Vegf-A

Jose R Conejo-García¹,⁵, Fabian Benencia¹,⁵, Maria-Cecilia Courreges¹, Eugene Kang¹, Alisha Mohamed-Hadley¹, Ronald J Buckanovich¹, David O Holtz¹, Ann Jenkins¹, Hana Na¹, Lin Zhang¹,², Daniel S Wagner³, Dionyssios Katsaros⁴, Richard Caroll² & George Coukos¹,²
Discovery of Human Vascular DCs

Conejo-Garcia et al., *Blood*. 2005
Why would it NOT work?

1) Non immunogenic tumors – Immune mechanisms have little impact

2) Antiangiogenic therapy has not produced significant results as single agent – Angiogenesis more complex than anticipated, angiogenesis targets less obvious
Future Directions

1) Clinical testing in immunogenic tumors where antiangiogenic therapy has produced significant results as single agent – ovarian cancer

2) Preclinical investigation to identify angiogenesis targets in other tumors and test combination approaches