'What is the future for antiangiogenic therapies in cancer?'

Marc Pocard

Hôpital Lariboisière Paris

Service de Chirurgie digestive et carcinologique

Unité INSERM 965-Paris7 CART carcinose angiogenèse et recherche translationnelle

Target therapy /

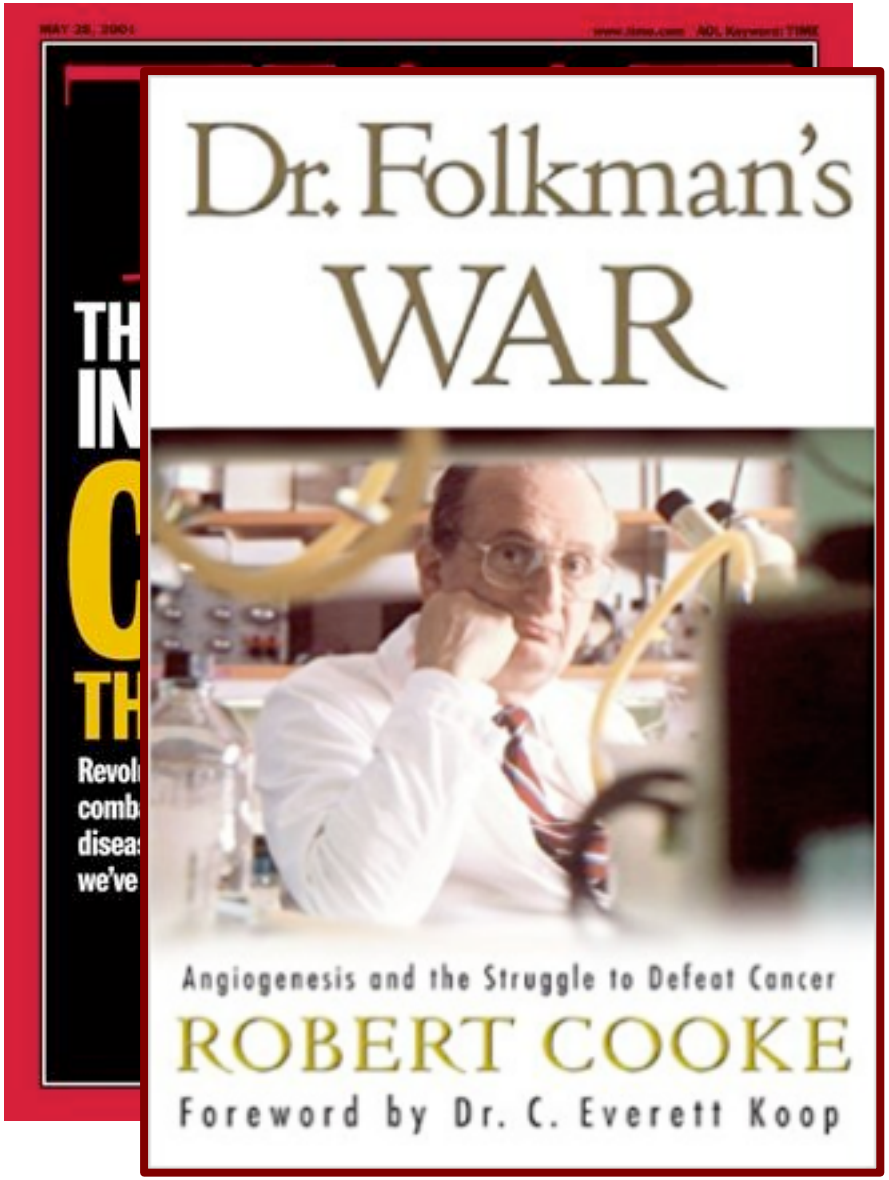
Brief Report

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

The New England Journal of Medicine

April 5, 2001 ·

Target therapy / Antiangiogenic treatment



JUNE 3, 2004

The New England Journal of Medicine

Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer

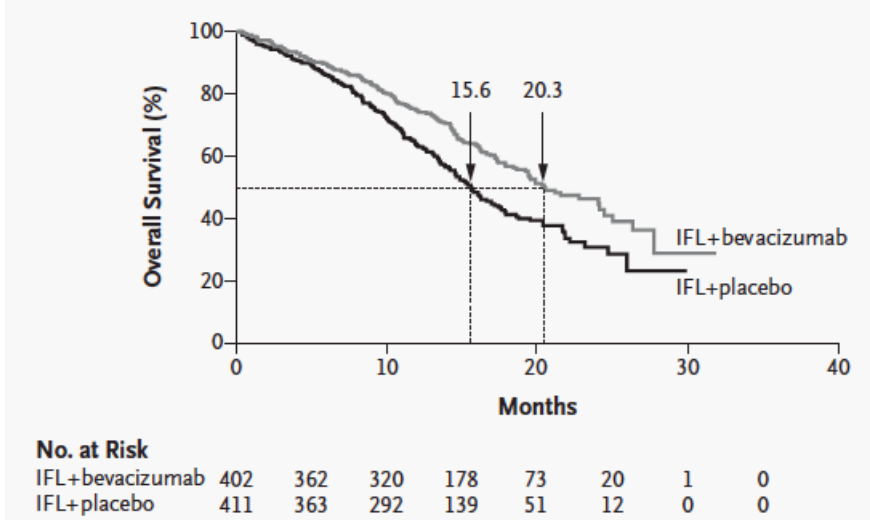
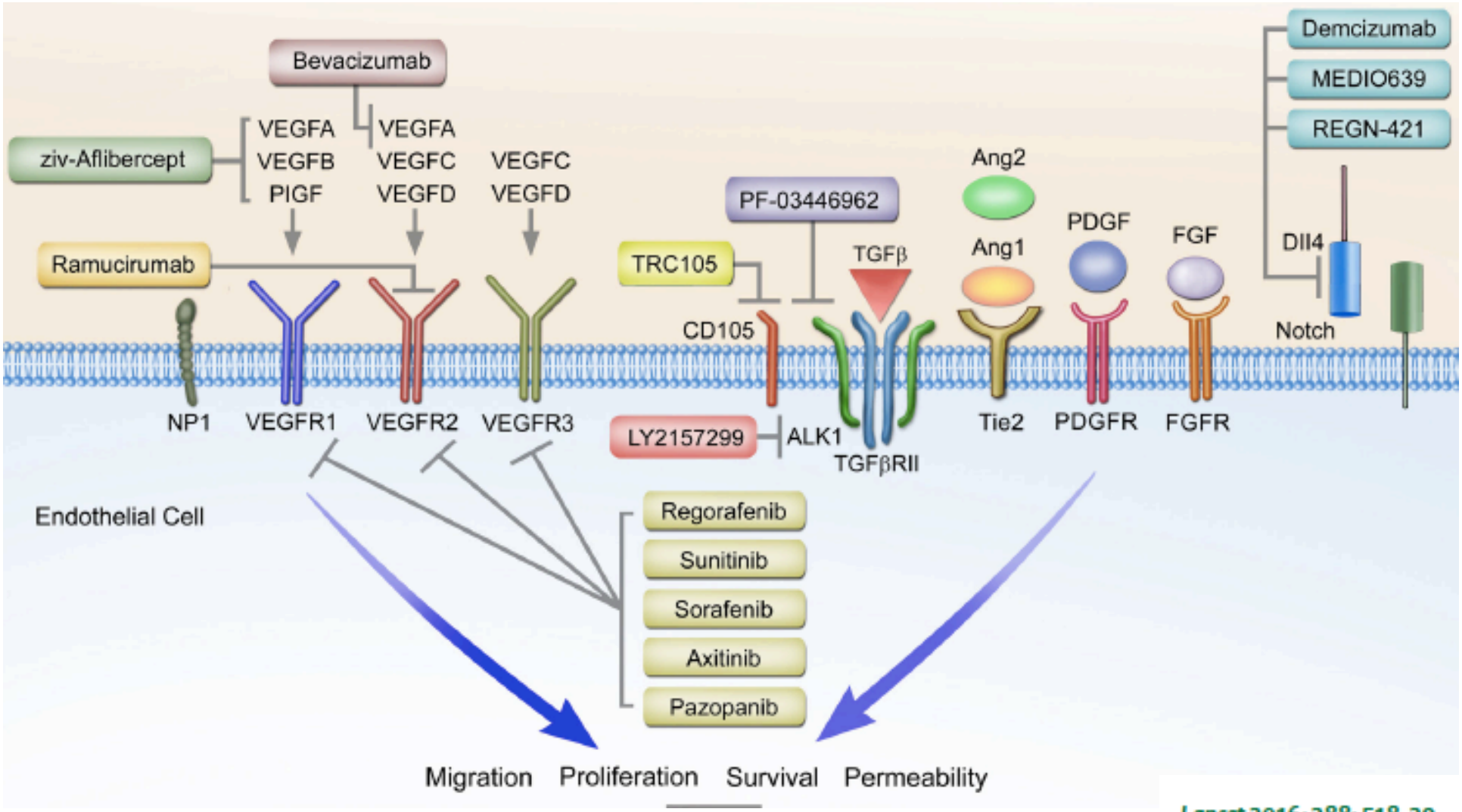


Figure 1. Kaplan–Meier Estimates of Survival.

The median duration of survival (indicated by the dotted lines) was 20.3 months in the group given irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 (P<0.001).

More than 20 different antiangiogenic drugs



Lancet 2016; 388: 518–29

Gordon C Jayson, Robert Kerbel, Lee M Ellis, Adrian L Harris

Antiangiogenic therapy in oncology: current status and future directions

The role of bevacizumab in solid tumours: A literature based meta-analysis of randomised trials

Giandomenico Roviello [a,b,*], Thomas Bachelot [c], Clifford A. Hudis [d,e], Giuseppe Curigliano [f], Andrew R. Reynolds [g], Roberto Petrioli [h], Daniele Generali [b,i]

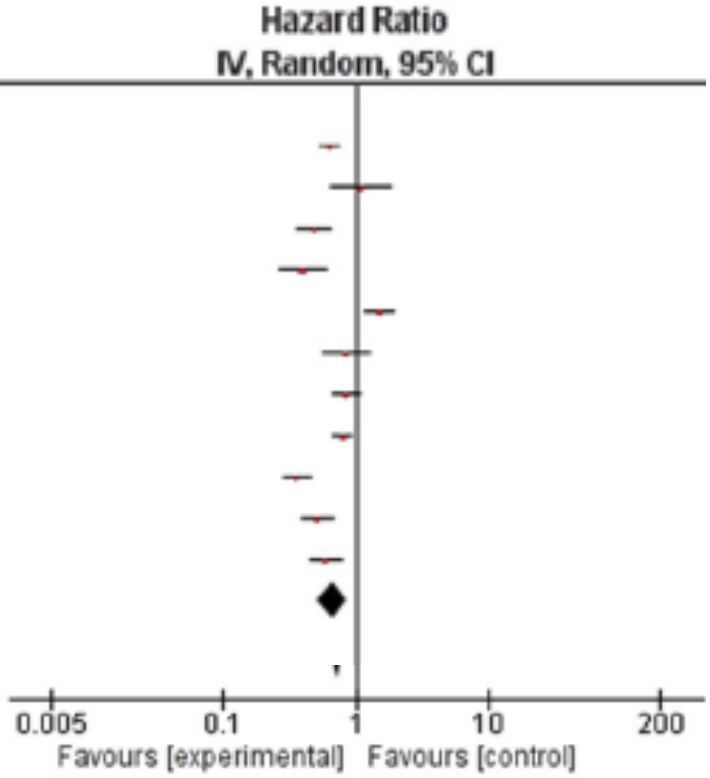
European Journal of Cancer 75 (2017) 245–258

Colon cancer

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 Colorectal				
Bennouna 2013	-0.3857	0.0724	2.5%	0.68 [0.59, 0.78]
Benson 2016	0.0871	0.2315	1.4%	1.09 [0.69, 1.72]
Cunningham 2013	-0.6349	0.131	2.1%	0.53 [0.41, 0.69]
Guan 2011	-0.821	0.1787	1.7%	0.44 [0.31, 0.62]
Hegewish Becker 2015	0.3716	0.1183	2.2%	1.45 [1.15, 1.83]
Hurwitz 2005	-0.1508	0.1837	1.7%	0.86 [0.60, 1.23]
Passardi 2015	-0.1508	0.105	2.3%	0.86 [0.70, 1.06]
Saltz 2008	-0.1863	0.0725	2.5%	0.83 [0.72, 0.96]
Simkens 2015	-0.9163	0.0982	2.4%	0.40 [0.33, 0.48]
Tebbutt 2010	-0.5852	0.1203	2.2%	0.56 [0.44, 0.71]
Tebbutt 2010 (II)	-0.4716	0.1192	2.2%	0.62 [0.49, 0.79]
Subtotal (95% CI)			**23.2%**	**0.70 [0.57, 0.87]**

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 100.63$, df = 10 ($P < 0.00001$); $I^2 = 90\%$

Test for overall effect: $Z = 3.27$ ($P = 0.001$)



for progression-free survival (PFS) comparing bevacizumab-based regimens to the control arm.

Understanding the mechanisms of action of antiangiogenic agents in metastatic colorectal cancer: A clinician's perspective

J.M. Clarke [a,*], H.I. Hurwitz [a,1], F. Rangwala [a,b,2]

Cancer Treatment Reviews 40 (2014) 1065–1072

Table 1
Mechanism of action of antiangiogenic agents for the treatment of metastatic colorectal cancer (mCRC).

	Bevacizumab [20]	Aflibercept [20]	Regorafenib [9]	Ramucirumab [21]
Type of molecule	Anti-VEGFA humanized monoclonal IgG1 antibody	Fusion protein of the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc portion of human IgG1	Small molecule kinase inhibitor; urea class	Anti-VEGFR2 fully human monoclonal IgG1 antibody
Mechanism of action	Blocks VEGFA	Blocks VEGFA, VEGFB, and PlGF	Inhibits VEGFR2, VEGFR2, TIE2, and other kinases	Blocks VEGFA binding to VEGFR2
Binding affinity	58 pM for $VEGFA_{165}$ No binding to PlGF-2	0.490 pM for $VEGFA_{165}$ 38.9 pM for PlGF-2	Not reported	50 pM for VEGFR2
IC_{50} (biochemical assays)	Not reported	Not reported	13 nM for VEGFR1 4.2 nM for VEGFR2 46 nM for VEGR3 311 nM for TIE2	0.8 nM for VEGFR2 binding to VEGFA
IC_{50} (cellular assays)	Activation of VEGFR1: 854 pM for $VEGFA_{121}$ 1476 pM for $VEGFA_{165}$ No blocking activity for PLGF2 Activation of VEGFR2: 630 pM for $VEGFA_{121}$ 1323 pM for $VEGFA_{165}$	Activation of VEGFR1: 15 pM for $VEGFA_{121}$ 16 pM for $VEGFA_{165}$ 2890 pM for PLGF2 Activation of VEGF2: 16 pM for $VEGFA_{121}$ 26 pM for $VEGFA_{165}$	3 nM for VEGFR2 31 nM for TIE2 135 nM for VEGFR3	Not reported

VEGF, vascular endothelial growth factor; IgG, immunoglobulin G; VEGFR, vascular endothelial growth factor receptor; PlGF, placental growth factor.

What we learn about AAG for Cancer

- Active treatment
- No effect or limited effect on survival
- Effect on disease free survival

First: It change part of the clinical course of cancer

Second : effect is not always related with survival

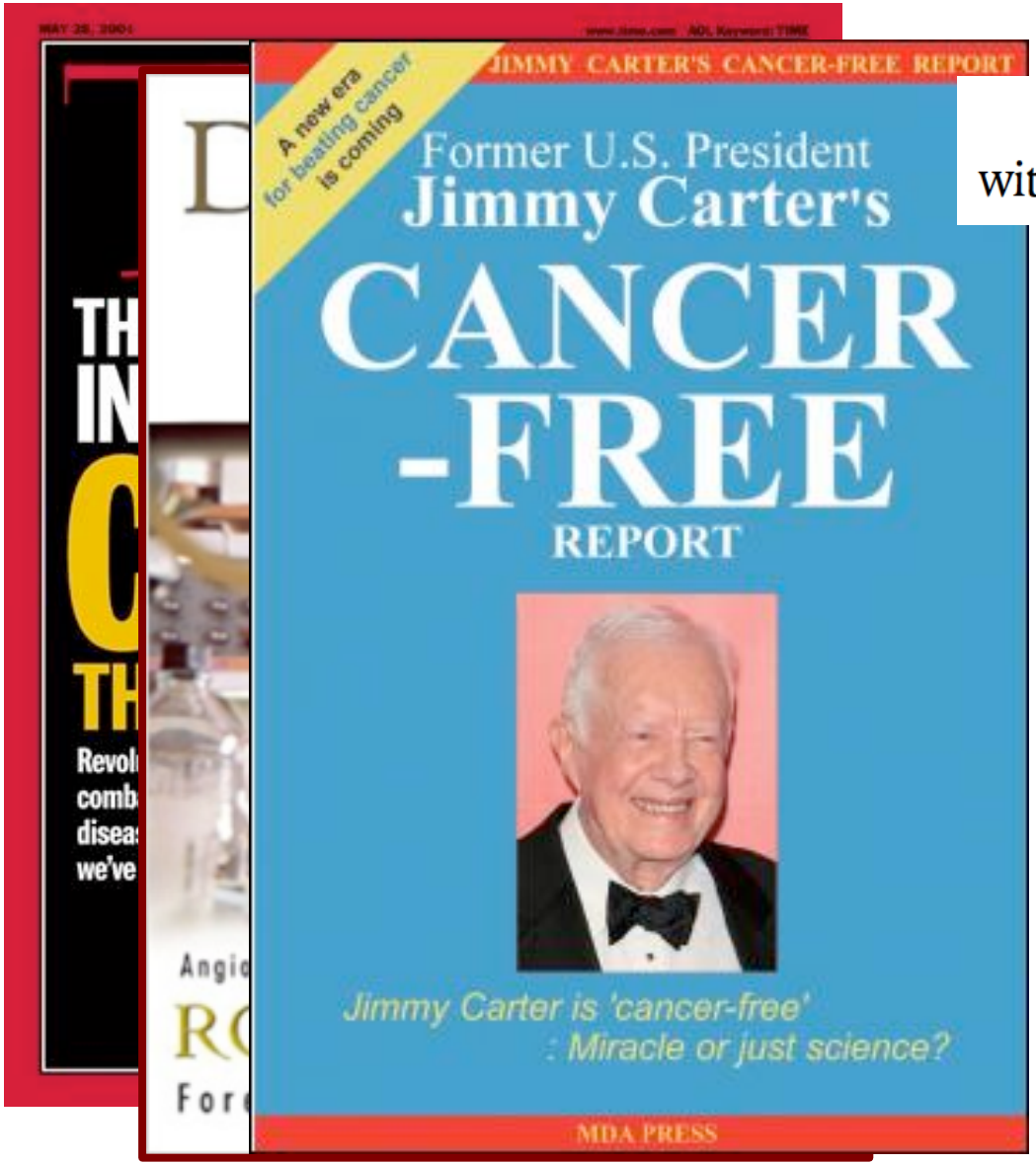
And for me / only for me

- Scare is not a definitive process
- And the angiogenic shift is a concept not a clinical reality

Colon adenocarcinoma

- Before : no treatment offer interest in metastatic situation except chemotherapy
- First demonstration : 2004 Hurwitz H
- Other antiangiogenic treatment : same effect
  - Effect of class
  - Antibody or TKI have the same effect on tumor control
  - Increase the effect of 5FU chemotherapy
- In an adjuvant situation : Major failure / 3 study
  - No clinical application of the “angiogenic switch”

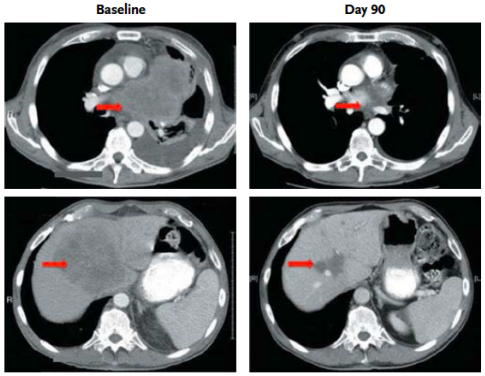
Target therapy / Antiangiogenic / Immunotherapy

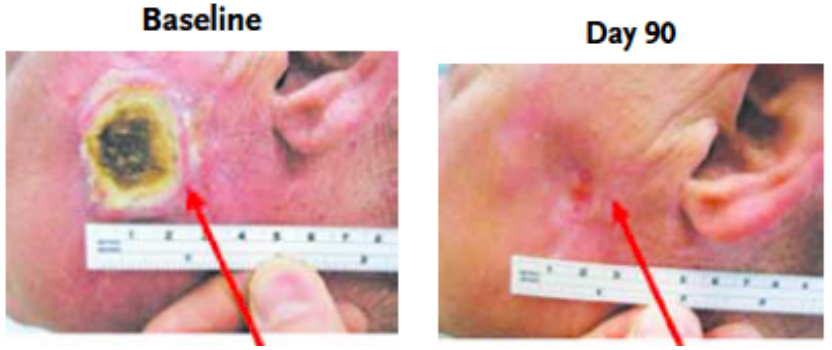


Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

The NEW ENGLAND JOURNAL of MEDICINE

JULY 11, 2013





Association of two majors process ?

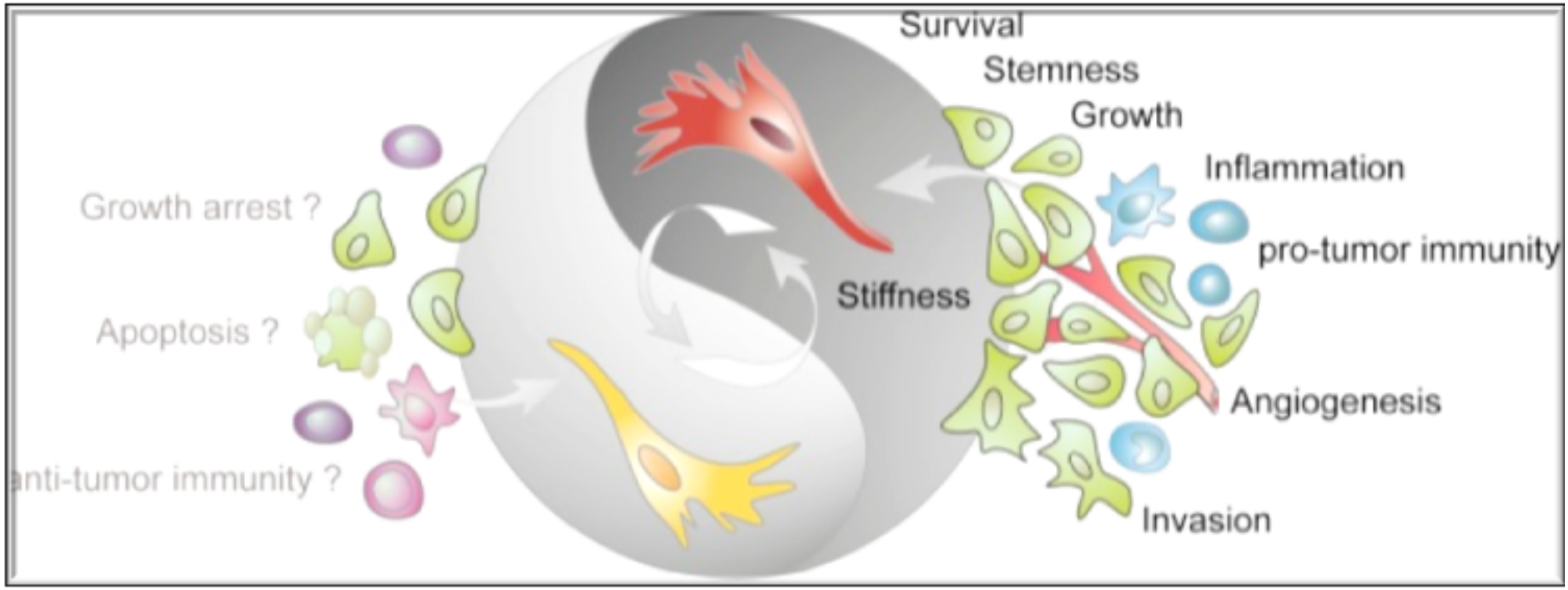
Freeman MR, Schneck FX, Gagnon ML, Corless C, Soker S, Niknejad K, Peoples GE, Klagsbrun M (1995) Peripheral blood T lymphocytes and lymphocytes infiltrating human cancers express vascular endothelial growth factor: a potential role for T cells in angiogenesis. *Cancer Res* 55: 4140–4415

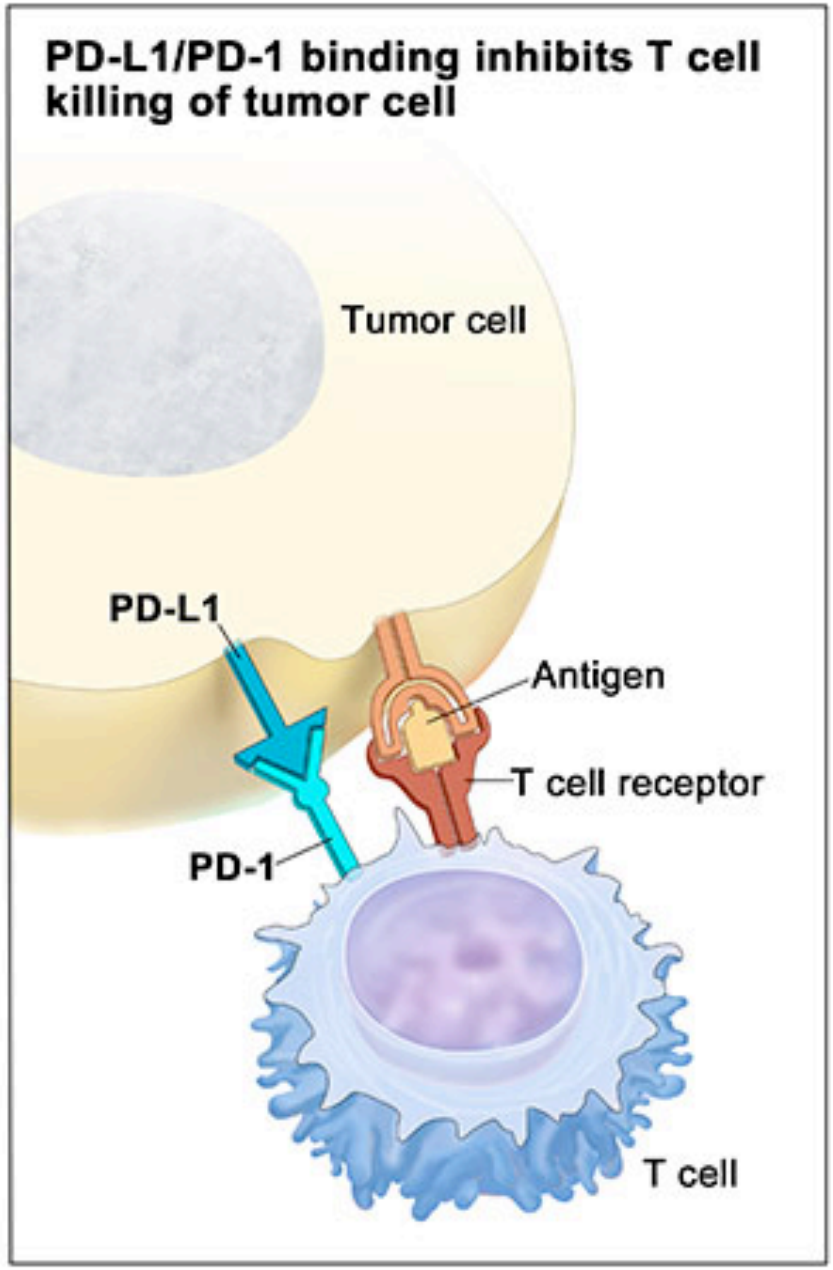
Gabrilovich DI, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, Kavanaugh D, Carbone DP (1996) Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. *Nat Med* 2: 1096–1103

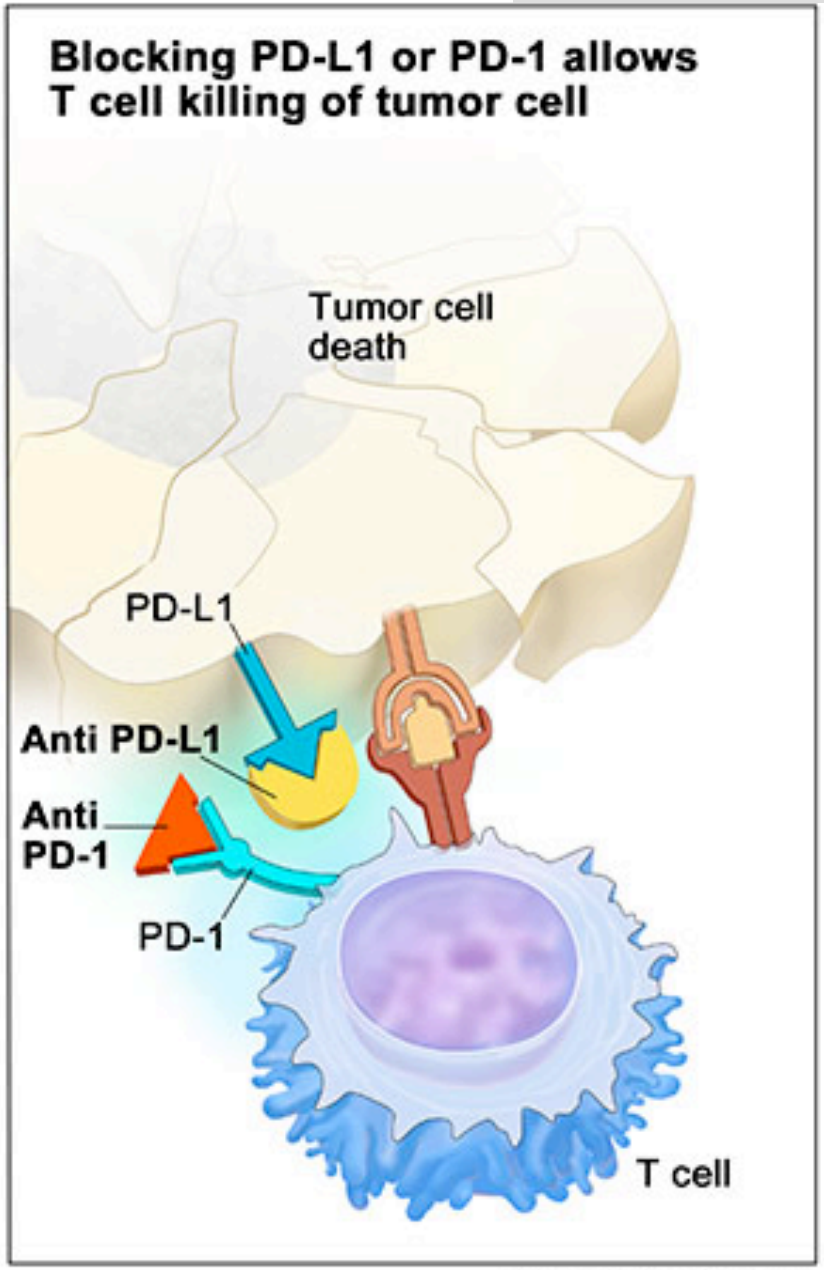
Ohm JE, Gabrilovich DI, Sempowski GD, Kisseleva E, Parman KS, Nadaf S, Carbone DP (2003) Vegf inhibits T-cell development and may contribute to tumor-induced immune suppression. *Blood* 101: 4878–4886

Association of two majors process

VEGF …. PDL1



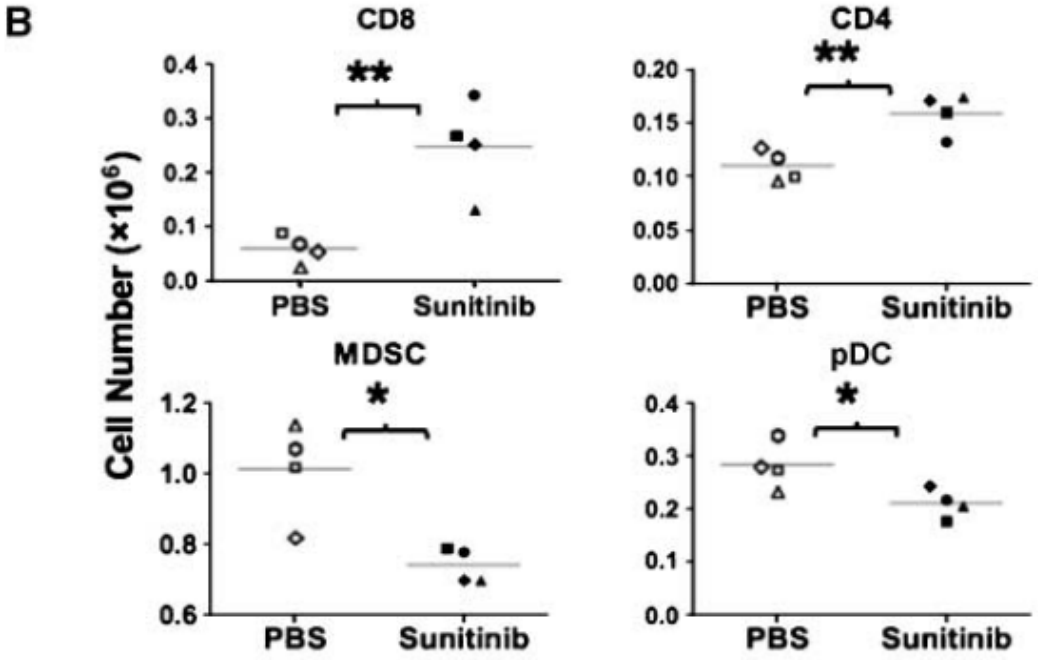




The Novel Role of Tyrosine Kinase Inhibitor in the Reversal of Immune Suppression and Modulation of Tumor Microenvironment for Immune-Based Cancer Therapies

Junko Ozao-Choy,[1,2] Ge Ma,[1] Johnny Kao,[3] George X. Wang,[1] Marcia Meseck,[1] Max Sung,[4] Myron Schwartz,[2] Celia M. Divino,[2] Ping-Ying Pan,[1] and Shu-Hsia Chen[1,2]

Cancer Res 2009; 69: (6). March 15, 2009



A significantly higher percentage and infiltration of CD8 and CD4 cells was detected in tumors of sunitinib-treated mice when compared with control-treated mice. Whereas the percentage of Treg, MDSC and pDC was decreased

MDSC: myeloid-derived suppressor cells

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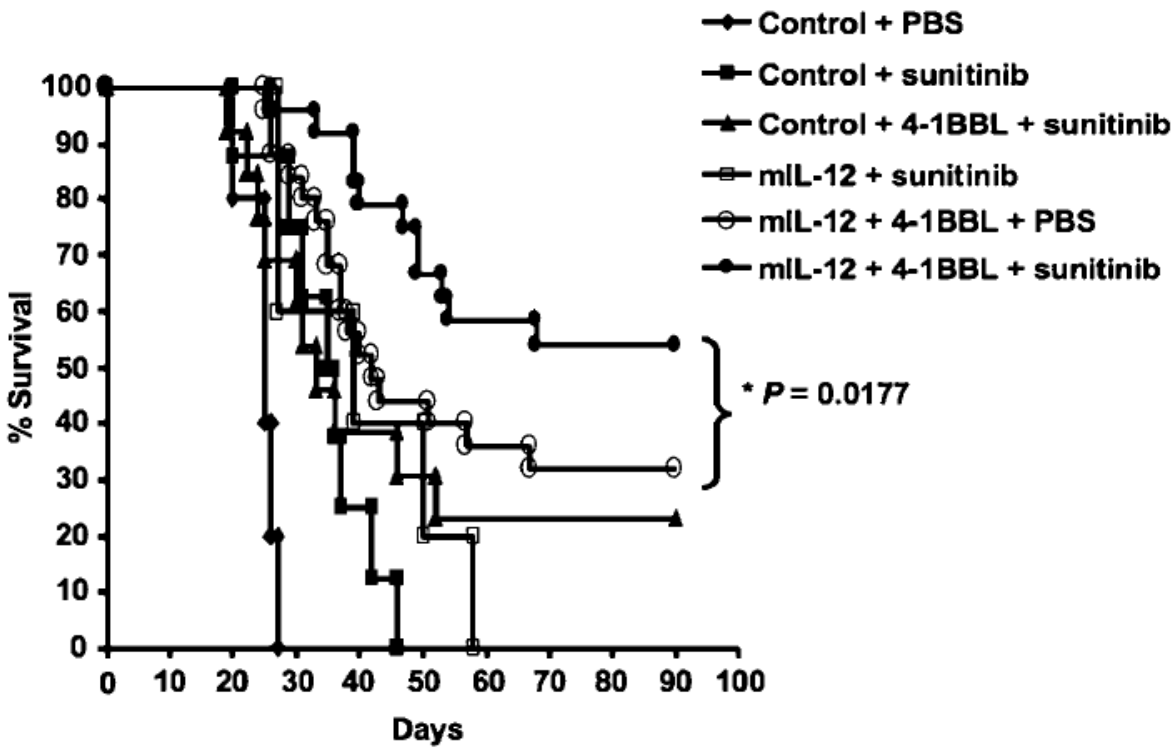

Sunitinib in combination with our immune therapy protocol (IL-12 and 4-1BB activation) significantly improves the long-term survival rate of large tumor-bearing mice. These data suggest that sunitinib can be used to reverse immune suppression and as a potentially useful adjunct for enhancing the efficacy of immune-based cancer therapy for advanced malignancies.

The Novel Role of Tyrosine Kinase Inhibitor in the Reversal of Immune Suppression and Modulation of Tumor Microenvironment for Immune-Based Cancer Therapies

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Cancer Res 2009; 69: (6). March 15, 2009

A complex model using Transgenic mice

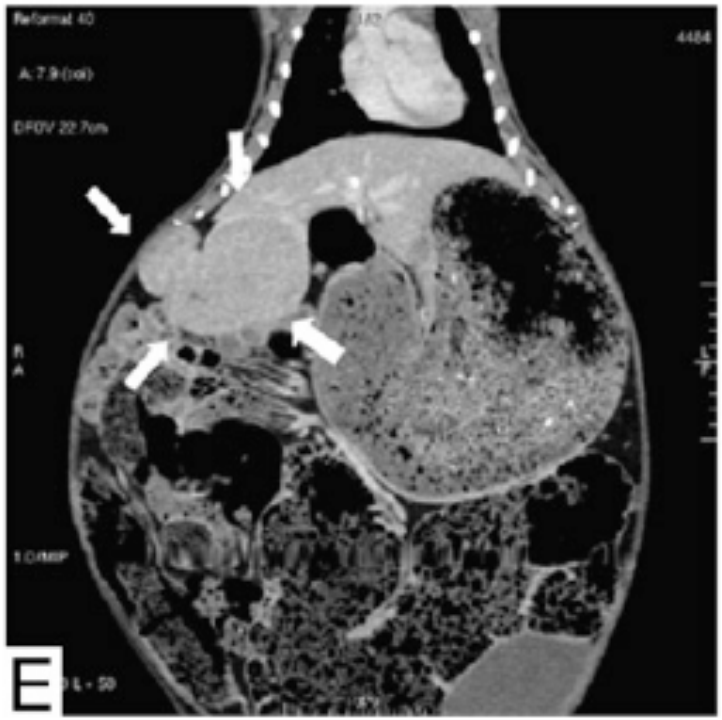
Sunitinib / non specific TKI / VEGF-R1, -R2, -R3, PDGFRa, PDGFRb, FLT3 and c-kit

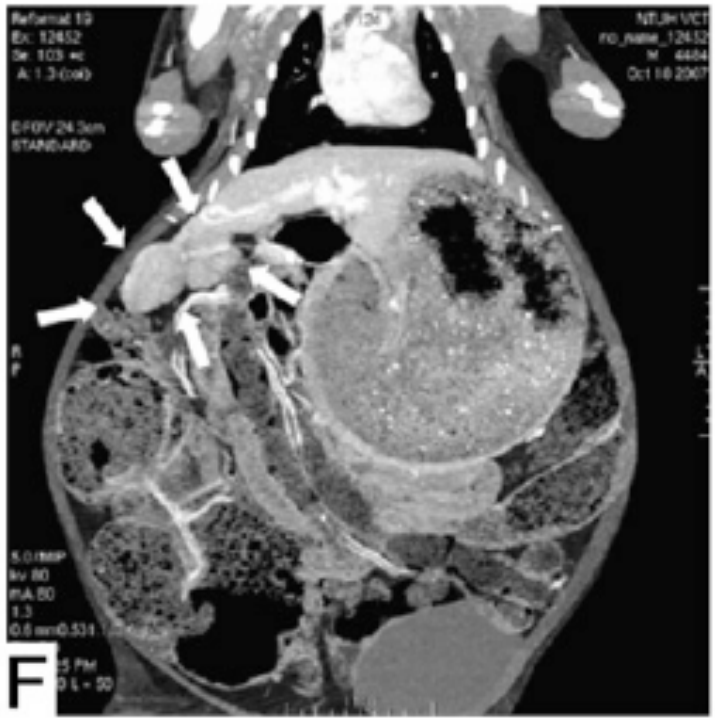
Cells lines not really relevant :
MCA26 colon carcinoma cells lines
LLCI Lewis lung carcinoma

Combining antiangiogenic therapy with immunotherapy exerts better therapeutical effects on large tumors in a woodchuck hepatoma model

Kai-Wen Huang[a,b,c,1], Hui-Lin Wu[a,b,1], Hsiu-Lin Lin[a], Po-Chin Liang[d], Pei-Jer Chen[a,b,e], Shih-Hui Chen[e], Hsin-I Lee[f], Pei-Yi Su[a], Wen-Hsuan Wu[a], Po-Huang Lee[b], Lih-Hwa Hwang[a,f,2], and Ding-Shinn Chen[a,2]

PNAS | August 17, 2010 | vol. 107 | no. 33 | 14769–14774





VEGF directly suppresses activation of T cells from ascites secondary to ovarian cancer *via* VEGF receptor type 2

British Journal of Cancer (2012) 107, 1869–1875

NG Gavalas[1], M Tsiatas[1], O Tsitsilonis[2], E Politi[3], K Ioannou[2], AC Ziogas[1], A Rodolakis[4], G Vlahos[4], N Thomakos[4], D Haidopoulos[4], E Terpos[1], A Antsaklis[4], MA Dimopoulos[1] and A Bamias*[,1]

T cells isolated from the ascites of ovarian cancer patients were cultured.
Ascites-derived T cells secrete VEGF and express VEGFR-2
VEGF directly suppresses T-cell activation via VEGFR-2

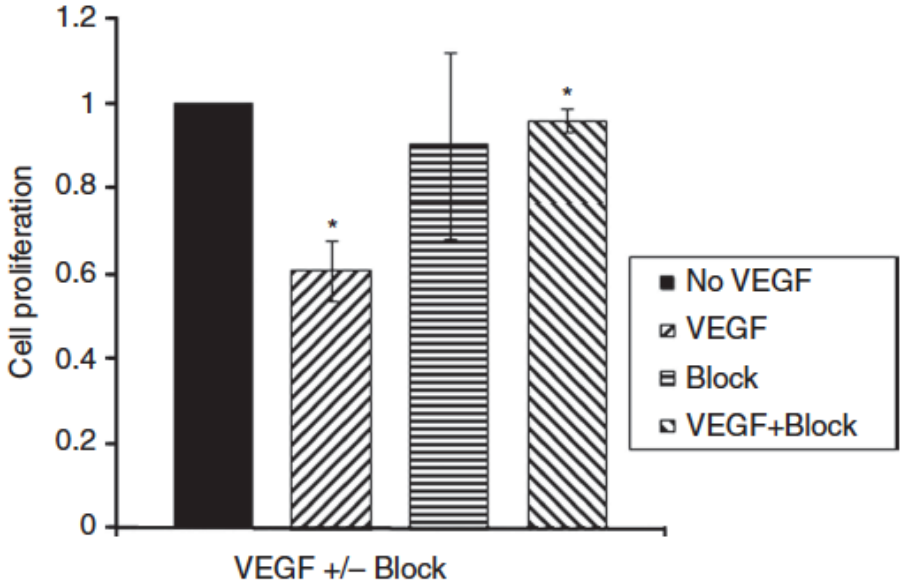
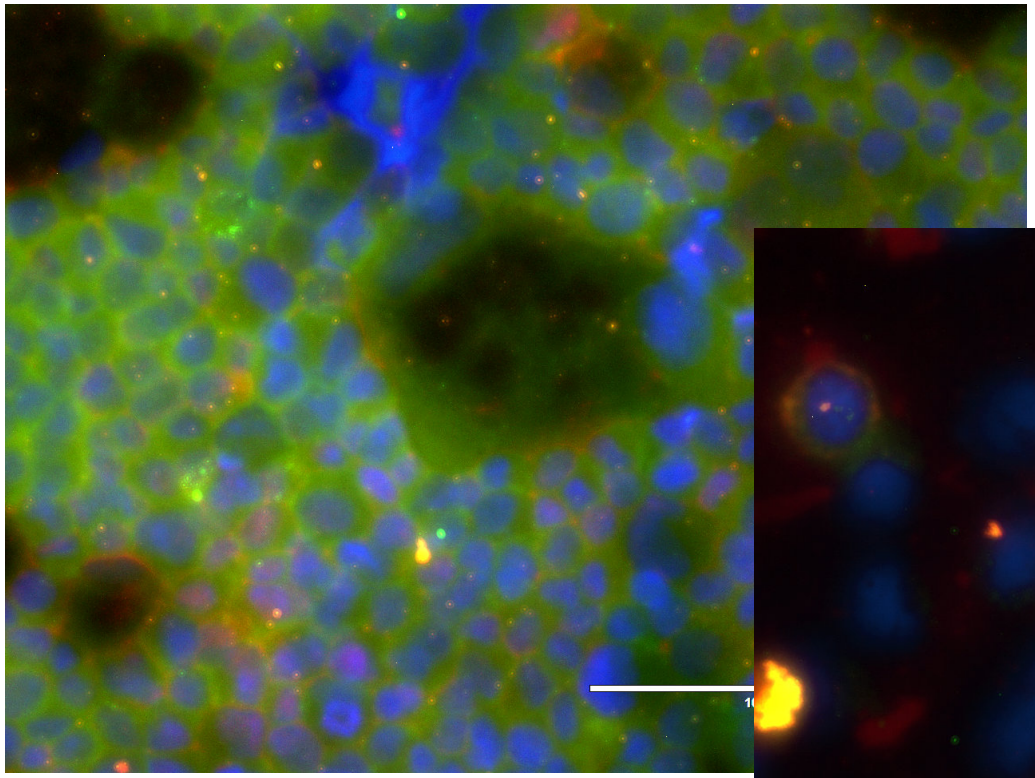


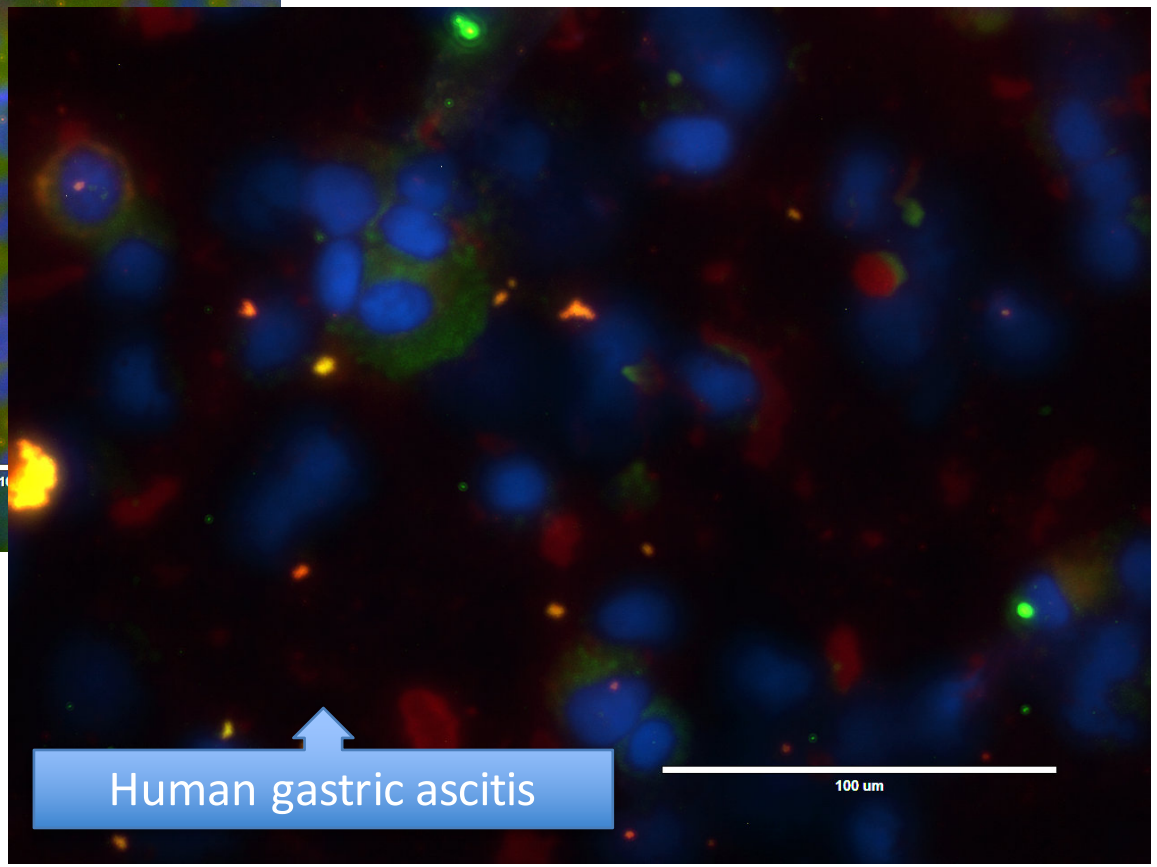
Figure 3 Anti-VEGFR-2 reverses VEGF-induced suppression of T cells. Neutralising anti-VEGFR-2 mAb (block) was added in lymphocyte cultures ($n = 5$) at a final concentration of 1 $\mu g\,ml^{-1}$ for 14 days in the presence of VEGF (100 $ng\,ml^{-1}$). *$P = 0.043$ compared with control.

Picture from Matti Ullah U965

We can detect PDL1 positive cells on ascitis of patients



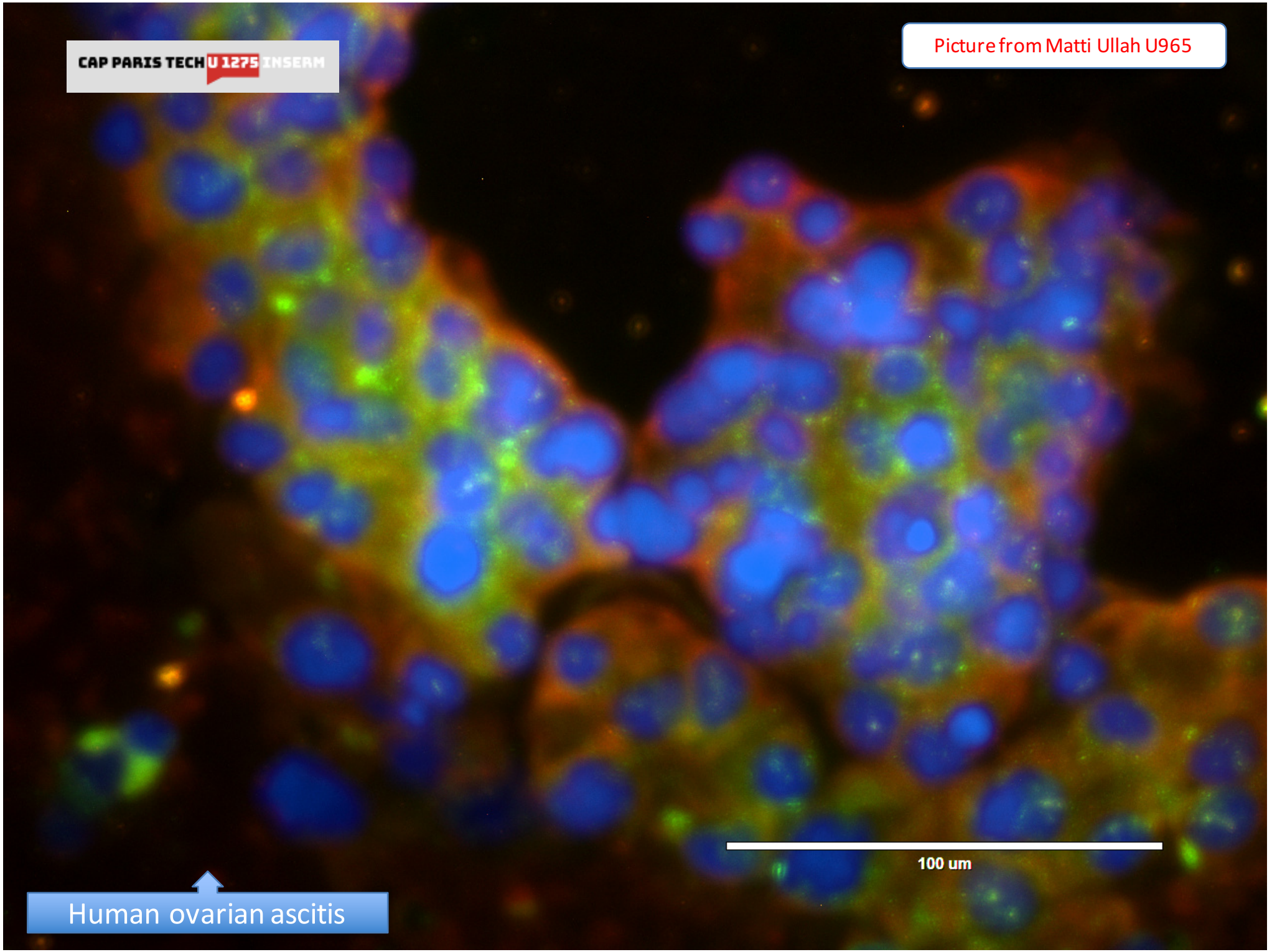
Cells lines / ovarian



DAPI

HLAG

PDL1


CAP PARIS TECH U 1275 INSERM
Picture from Matti Ullah U965
100 um
Human ovarian ascitis

VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors

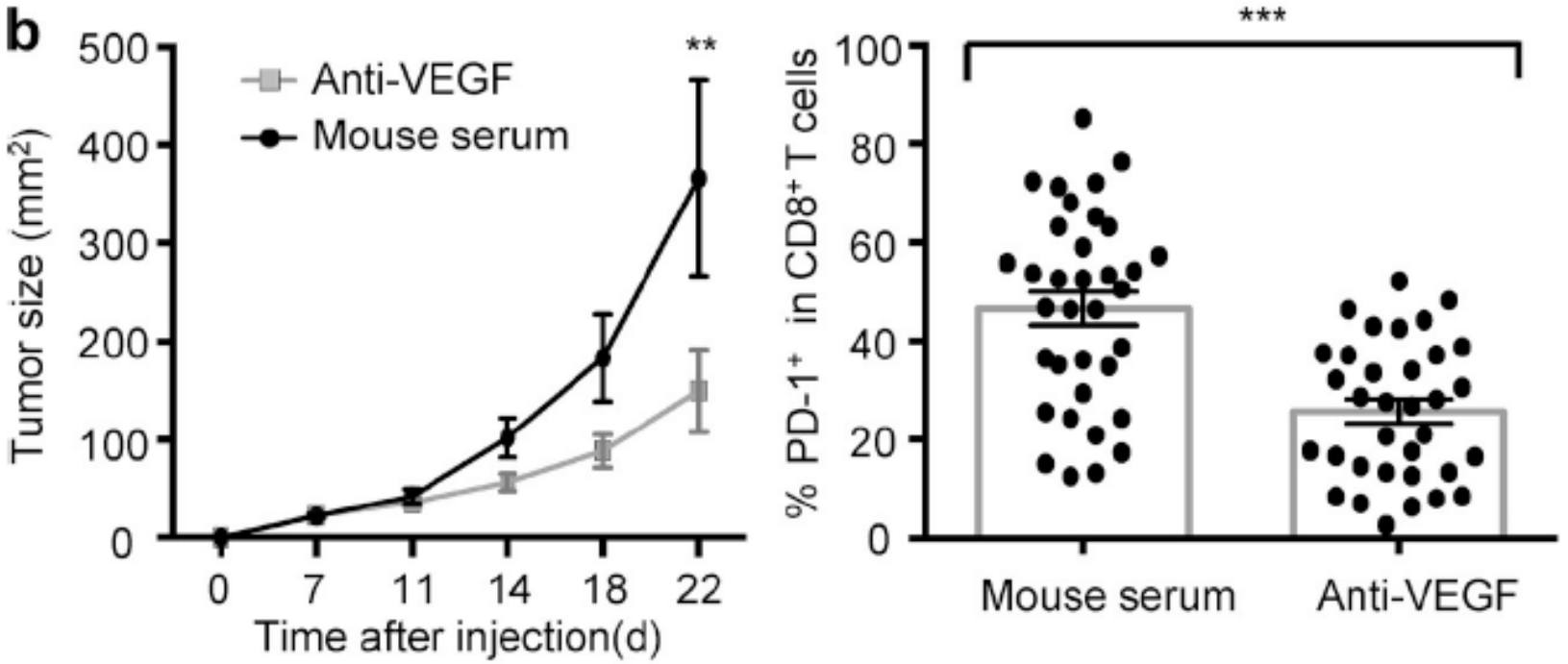
Thibault Voron,[1,4*] Orianne Colussi,[1,5*] Elie Marcheteau,[1*] Simon Pernot,[1,5] Mevyn Nizard,[1] Anne-Laure Pointet,[1,5] Sabrina Latreche,[1] Sonia Bergaya,[1] Nadine Benhamouda,[2] Corinne Tanchot,[1] Christian Stockmann,[1] Pierre Combe,[3] Anne Berger,[4] Franck Zinzindohoue,[4] Hideo Yagita,[6] Eric Tartour,[1,2] Julien Taieb,[1,5*] and Magali Terme[1*]

J. Exp. Med. 2015 Vol. 212 No. 2 139–148

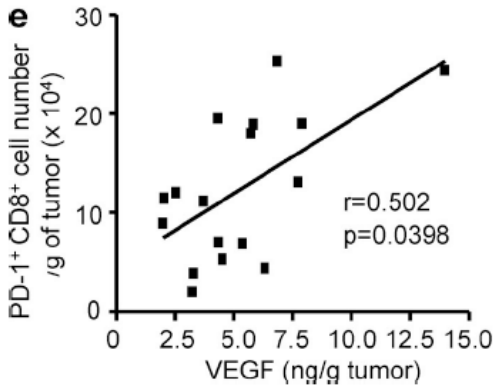
VEGF-A produced in the tumor microenvironment enhances expression of PD-1 and other inhibitory checkpoints involved in CD8(+) T cell exhaustion, which could be reverted by anti-angiogenic agents targeting VEGF-A-VEGFR. In view of these results, association of anti-angiogenic molecules with immunomodulators of inhibitory checkpoints may be of particular interest in VEGF-A-producing tumors

VEGF-A modulates expression of inhibitory checkpoints on CD8⁺ T cells in tumors

J. Exp. Med. 2015 Vol. 212



CT26 tumor-bearing mice



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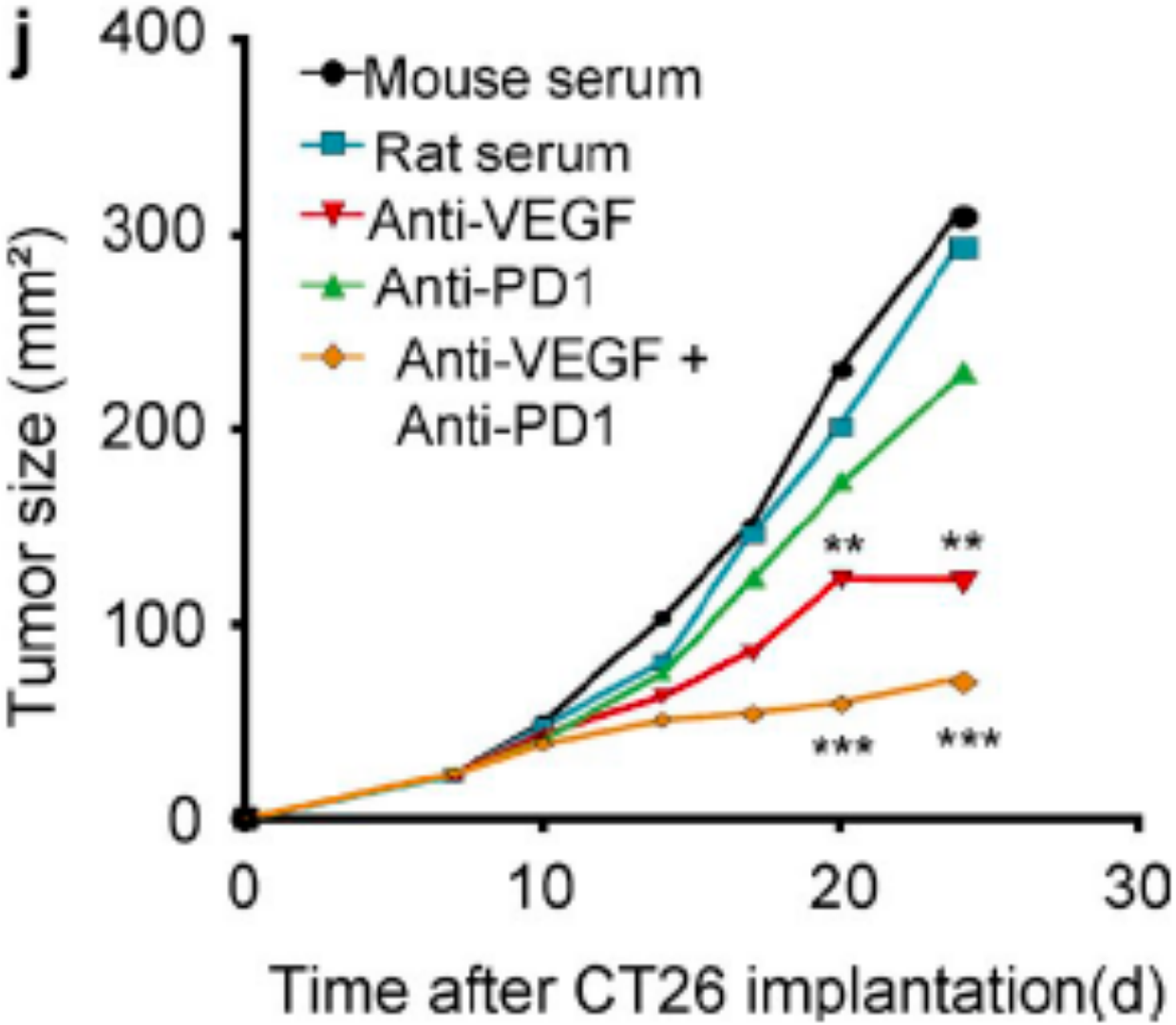
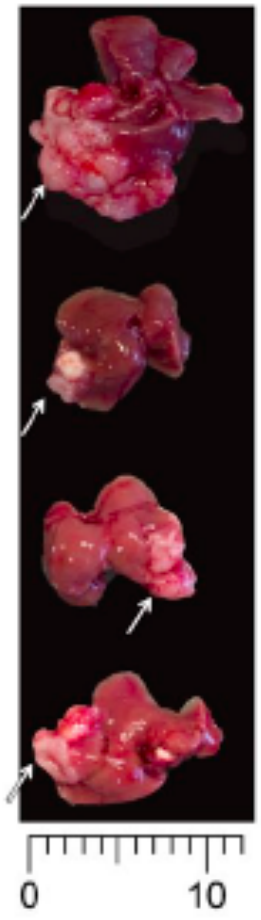
VEGF-A modulates expression of inhibitory checkpoints on CD8$^+$ T cells in tumors





The Journal of Experimental Medicine

Pro-angiogenic factors induce the development of an immunosuppressive state in tumors

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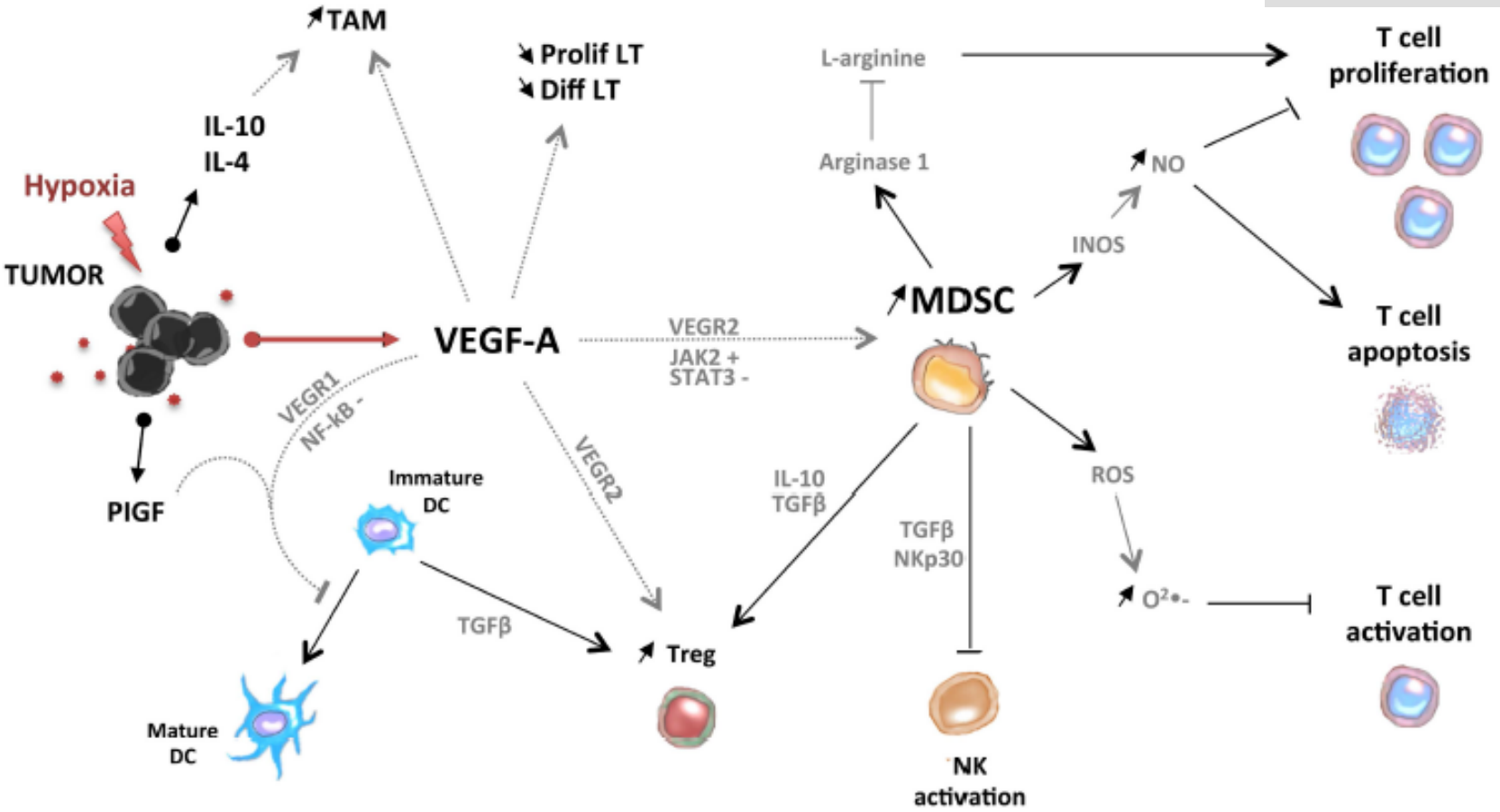


frontiers in ONCOLOGY

REVIEW ARTICLE
published: 02 April 2014
doi: 10.3389/fonc.2014.00070

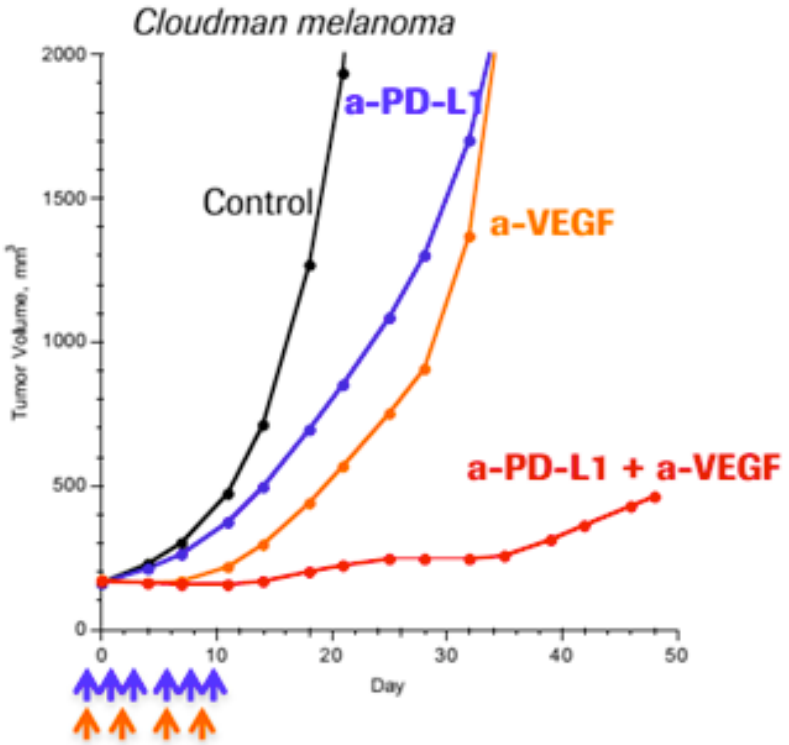
Control of the immune response by pro-angiogenic factors

*Thibault Voron[1], Elie Marcheteau[1], Simon Pernot[1,2], Orianne Colussi[1,2], Eric Tartour[1,3], Julien Taieb[1,2] and Magali Terme[1]**

Association of two majors process – on pipeline

CAP PARIS TECH U 1275 INSERM

Anti-VEGF combination: preclinical data



Source: Roche late-stage pipeline update, Oct 2013

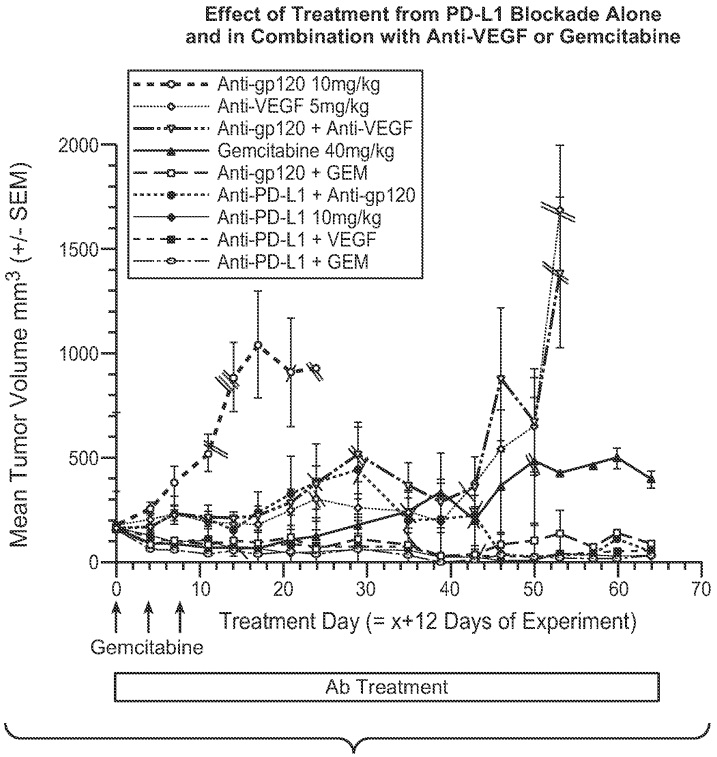


FIG. 10

Association of two majors process

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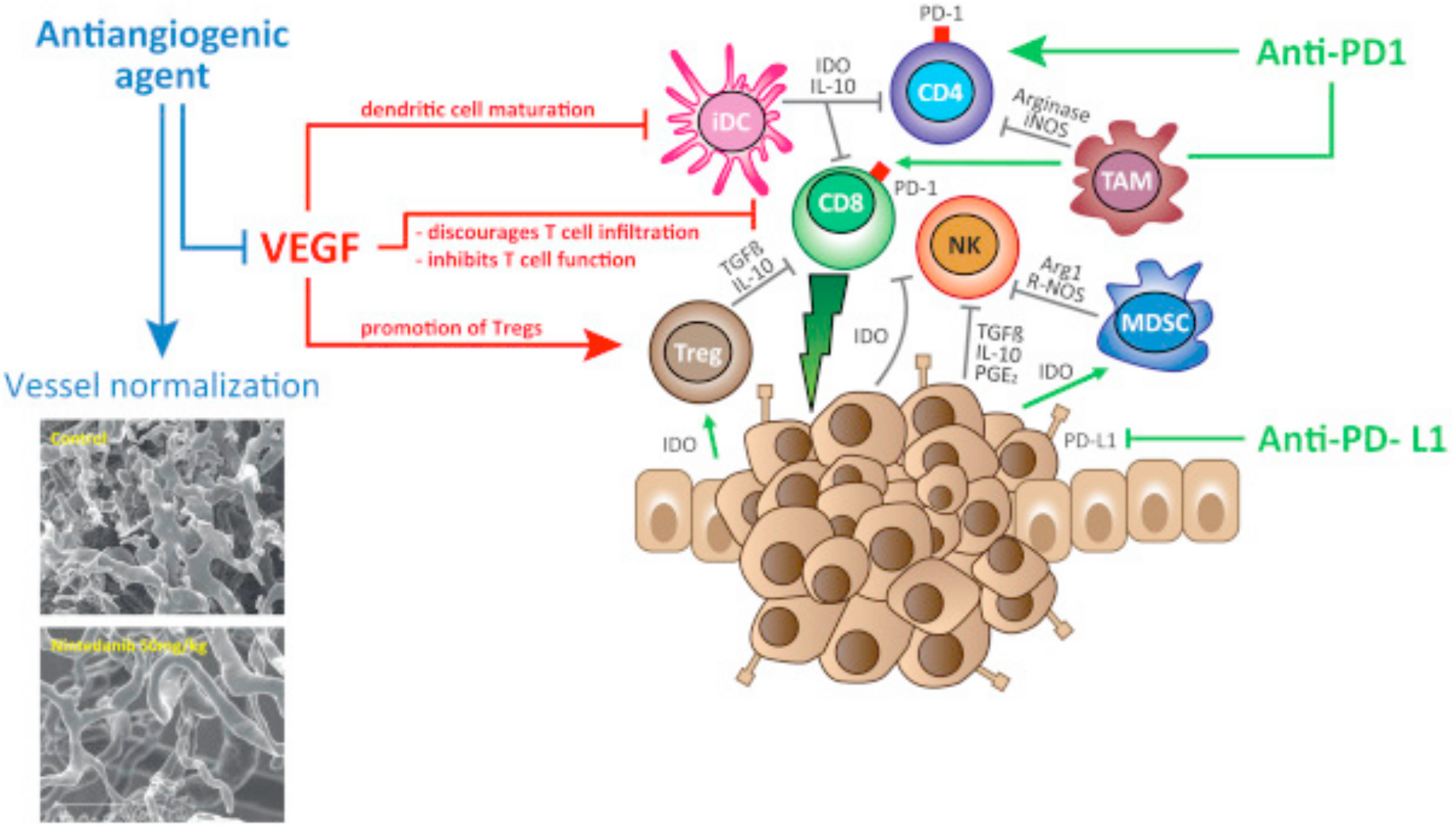

Manegold C et al Journal of thoracic oncology 2017 - The Potential of Combined Immunotherapy and Antiangiogenesis for the Synergistic Treatment of Advanced NSCLC

frontiers in ONCOLOGY

REVIEW ARTICLE
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Control of the immune response by pro-angiogenic factors

*Thibault Voron[1], Elie Marcheteau[1], Simon Pernot[1,2], Orianne Colussi[1,2], Eric Tartour[1,3], Julien Taieb[1,2] and Magali Terme[1]**

EGF-A can induce the accumulation of immature dendritic cells, myeloid-derived suppressor cells, regulatory T cells, and inhibit the migration of T lymphocytes to the tumor.

Other pro-angiogenic factors such as placental growth factor (PlGF) could also participate in tumor-induced immunosuppression,

CAP PARIS TECH U 1275 INSERM

frontiers in ONCOLOGY

REVIEW ARTICLE
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Control of the immune response by pro-angiogenic factors

*Thibault Voron[1], Elie Marcheteau[1], Simon Pernot[1,2], Orianne Colussi[1,2], Eric Tartour[1,3], Julien Taieb[1,2] and Magali Terme[1]**

Anti-angiogenic molecules, which target VEGF-A/VEGFR axis, have anti-angiogenic properties but can also counteract the tumor-induced immunosuppression.

Based on these immunomodulatory properties, anti-angiogenic molecules could be efficiently associated with immunotherapeutic strategies in preclinical models.

These combinations are currently under investigation in cancer patients.

ClinicalTrials.gov

ClinicalTrials.gov

Recurrent solid tumors

- **Combination of Bevacizumab and NK Immunotherapy for Recurrent Solid Tumors**

- Sponsor: Fuda Cancer Hospital, Guangzhou
- Primary Outcome Measures: Relief degree of tumors
  [Time Frame: 3 months]It will be evaluated by the Response Evaluation Criteria in Solid Tumors（RECIST）
- By enrolling patients with recurrent solid tumors adapted to enrolled criteria, this study will document for the first time the safety and the short and long term efficacy of the combined therapy using Bevacizumab and NK cells.

Lung Cancer

ClinicalTrials.gov

MERCK
Be well

- **A Study of Pembrolizumab (MK-3475) in Combination With Chemotherapy or Immunotherapy in Participants With Lung Cancer (MK-3475-021/KEYNOTE-021)**

- Experimental: Part I, Cohort A (Pembro + Paclitaxel [Pa] + Carboplatin [C]) pembrolizumab (2 or 10 mg/kg) + paclitaxel (200 mg/m^2) + carboplatin (6 mg/mL/minute)
- Experimental: Part I, Cohort B (Pembro + Pa + C+ Bevacizumab [B]) pembrolizumab (2 or 10 mg/kg) + paclitaxel (200 mg/m^2) + carboplatin (6 mg/mL/minute) + bevacizumab (15 mg/kg)
- Experimental: Part I, Cohort C (Pembro + Pemetrexed [Pe] + C) pembrolizumab (2 or 10 mg/kg) + pemetrexed (500 mgm^2) + carboplatin (5 mg/mL/min)

ClinicalTrials.gov

Hepatocellular carcinoma HCC

SILLAJEN

Hepatocellular Carcinoma Study Comparing Vaccinia Virus Based Immunotherapy Plus Sorafenib vs Sorafenib Alone (PHOCUS)

- A Phase 3 Randomized, Open-Label Study Comparing Pexa Vec (Vaccinia GM CSF / Thymidine Kinase-Deactivated Virus) Followed by Sorafenib Versus Sorafenib in Patients With Advanced Hepatocellular Carcinoma (HCC) Without Prior Systemic Therapy
- Primary Outcome Measures: Overall Survival
- Pexa-Vec is a vaccinia virus based oncolytic immunotherapy designed to stimulate the immune system following infection and replication within tumor cells.
- Sorafenib (Nexavar) is approved for the treatment of advanced HCC and is the Standard Of Care for this disease.

ClinicalTrials.gov

Hepatocellular carcinoma HCC

Study in Which Therapy is Either Switched to Nivolumab After 3 Months of Treatment or Therapy is Continued With a Tyrosine Kinase Inhibitor in Patients With Metastatic Renal Cell Carcinoma (RCC) and Disease Control (NIVOSWITCH)

- A Randomized Phase II Study With NIVOlumab or Continuation of Therapy as an Early SWITCH Approach in Patients With Advanced or Metastatic Renal Cell Carcinoma (RCC) and Disease Control After 3 Months of Treatment With a Tyrosine Kinase Inhibitor
- Primary Outcome Measures: Overall survival (OS)
- AIO-Studien-gGmbH

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Operable Esophageal Cancer

Genentech
A Member of the Roche Group

Chemotherapy, Radiation Therapy and Immunotherapy Prior to Surgery in Operable Esophageal Cancer

- The purpose of this study is to see if adding two targeted drugs (bevacizumab and erlotinib) further improves the response to chemotherapy (5-FU, paclitaxel, carboplatin) and radiation therapy in patients with operable esophageal cancer.
- This study has been completed in 2012 .

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Colorectal Cancer

Roche

Study of Cobimetinib in Combination With Atezolizumab and Bevacizumab in Participants With Gastrointestinal and Other Tumors

COTELLIC (cobimetinib), anti MEK TKI +

This is an open-label, multicenter, single-arm, two-stage, Phase Ib study designed to assess the safety, tolerability, and pharmacokinetics of oral cobimetinib with intravenous (IV) atezolizumab (A PD-L1) and bevacizumab in participants with metastatic colorectal cancer (mCRC) who have received and progressed on at least one prior line of therapy that contained a fluoropyrimidine and oxaliplatin or irinotecan.

There are two stages in this study: Stage 1 (safety run-in period) and Stage 2 (dose expansion with two cohorts, an expansion cohort and a biopsy cohort).

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However ? Did we have all the keys?

- If VEGF limit T-cells recruitment into tumor
- If VEGF promotes T-cell exhaustion

- Why Anti VEGF did not help after surgery complete tumor resection ?
  - Failure in colon cancer
  - Failure in oesophagus-stomach cancer
  - Failure after breast cancer resection
  - Failure after melanoma resection

'What is the future for antiangiogenic therapies in cancer?'

- Immunotherapy could be associated with antiangiogenic cancer
- Controlling two specific complex biologic system is challenging regarding :
  - Specific type of cancer
  - Increase risk of secondary effects
  - Association with a chemotherapy
- Translational research is very poor on that subject
  - Collaboration is necessary +++ before clinical trials or too late ?
  - **SFA had to be implicated**

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