

Nuovi farmaci in oncologia: tra innovazione e tradizione

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R&D Scientific Solutions

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Sanofi –aventis Oncology: combining TRADITION & INNOVATION

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Strong Heritage

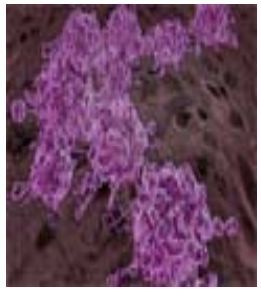
Taxotere® and Eloxatin® are the foundation of chemotherapy

Eloxatin® (OXALIPLATIN injection)

TAXOTERE® (docetaxel)

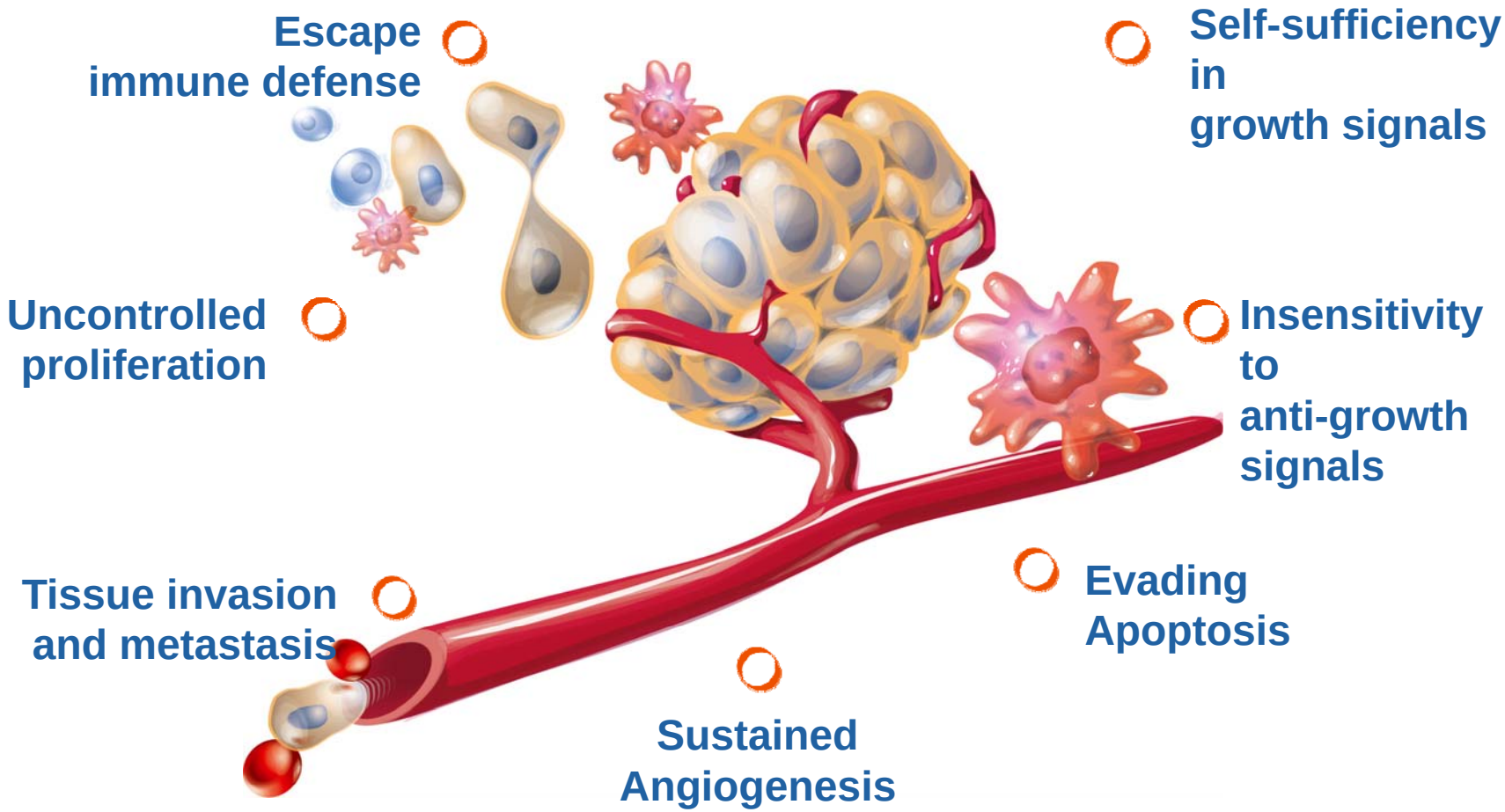
Innovative Science

Tumors now characterized at the molecular level, treatments more personalized



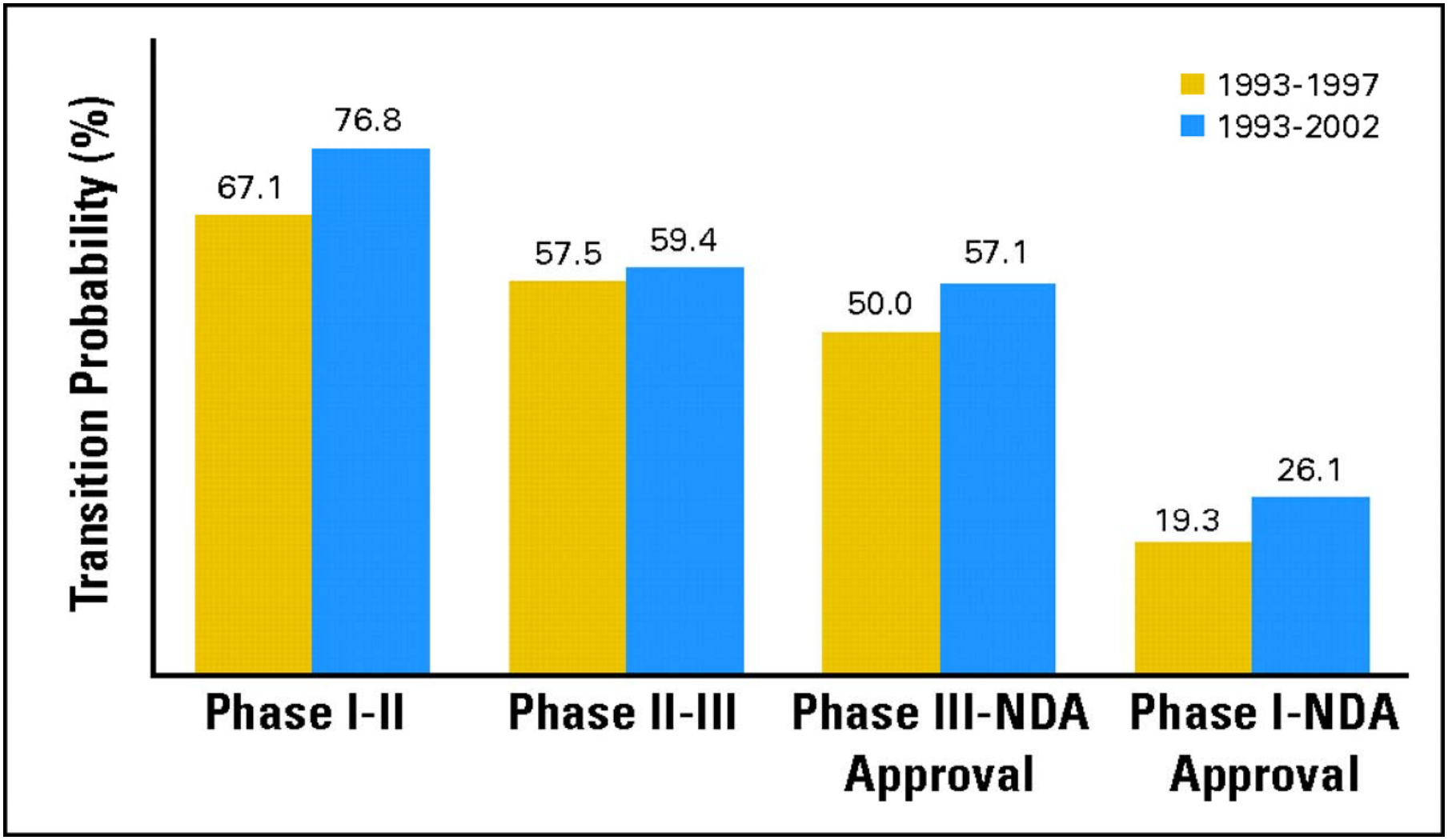
sanofi-aventis oncology

R&D focus is to attack cancer on all fronts



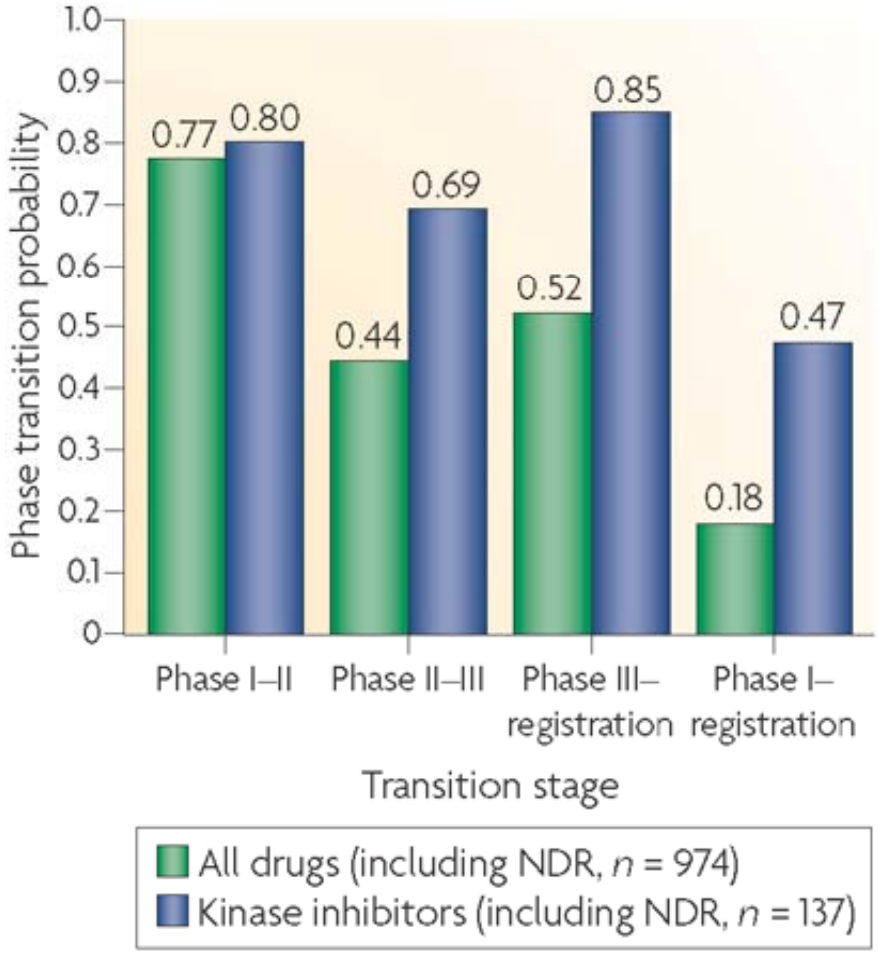
Adapted from Hannahan and Weinberg, 2000

Clinical phase transition probabilities for investigational oncology compounds for the 20 largest firms by pharmaceutical sales (2005) by period during which compound first entered clinical testing



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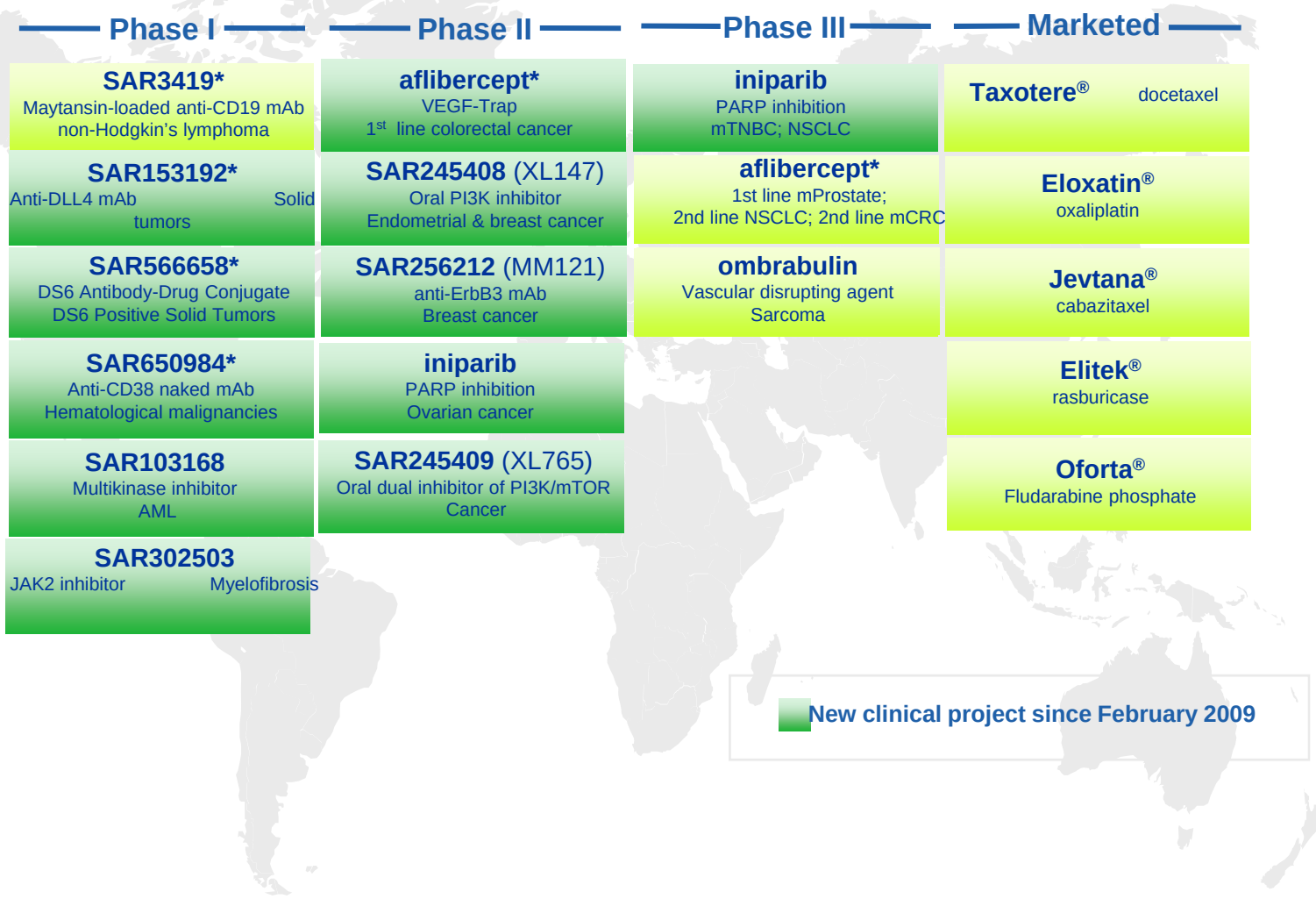
Molecularly targeted therapy have reduced attrition rates



- ✓Overall phase I to registration attrition rate of 53% (82% for all drug)
- ✓Success rate higher for TKi than for all drugs
- ✓Key: success rate at the phase II to phase III transition
- ✓Likely related to targeted nature of molecules and improvement in clinical trial design, such as biomarker-driven patient stratification
- ✓Benefits of developing molecularly targeted therapeutics for cancer

Nature Reviews | Drug Discovery /ERY 2009

Oncology Pipeline as of September 2010



* Biologic product

A New Cytotoxic Agent

The molecule

- New semi-synthetic taxane
  - Selected to overcome the emergence of taxane resistance[1]
- Mechanism of action
  - Microtubule stabilizer[2]

The unmeet medical needs in mHRPC

- Estimated new cases of prostate cancer in U.S. in 2009 =192,000; Deaths 27,360
- 575,000 new cases of Prostate Cancer diagnosed in Europe and U.S. yearly[2]
  - mHRPC accounts for 15% of patients
- Docetaxel chemotherapy is the current standard of care in mHRPC
- When progression on docetaxel occurs:
  - No currently approved standard second-line therapy [3]
  - Treatment options include supportive care or investigational drugs [3]
  - Palliation, no OS benefit demonstrated options [3]

(1) Attard G, Greystoke A, Kaye S, De Bono J. Pathol Biol (Paris). 2006;54(2):72-84.
(2) Ferley J et al. Eur J Cancer 2010 – American Cancer Society, Facts & Figures, 2009
(3)Garmey EG, Sartor O, Halabi S, Vogelzang NJ. Clin Adv Hematol Oncol. 2008; 6(2):118-1132.

TROPIC: Phase III Registration Study
146 Sites in 26 Countries

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mCRPC patients who progressed during and after treatment with a docetaxel-based regimen
(N=755)

Stratification factors

ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles
(n=378)

mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles
(n=377)

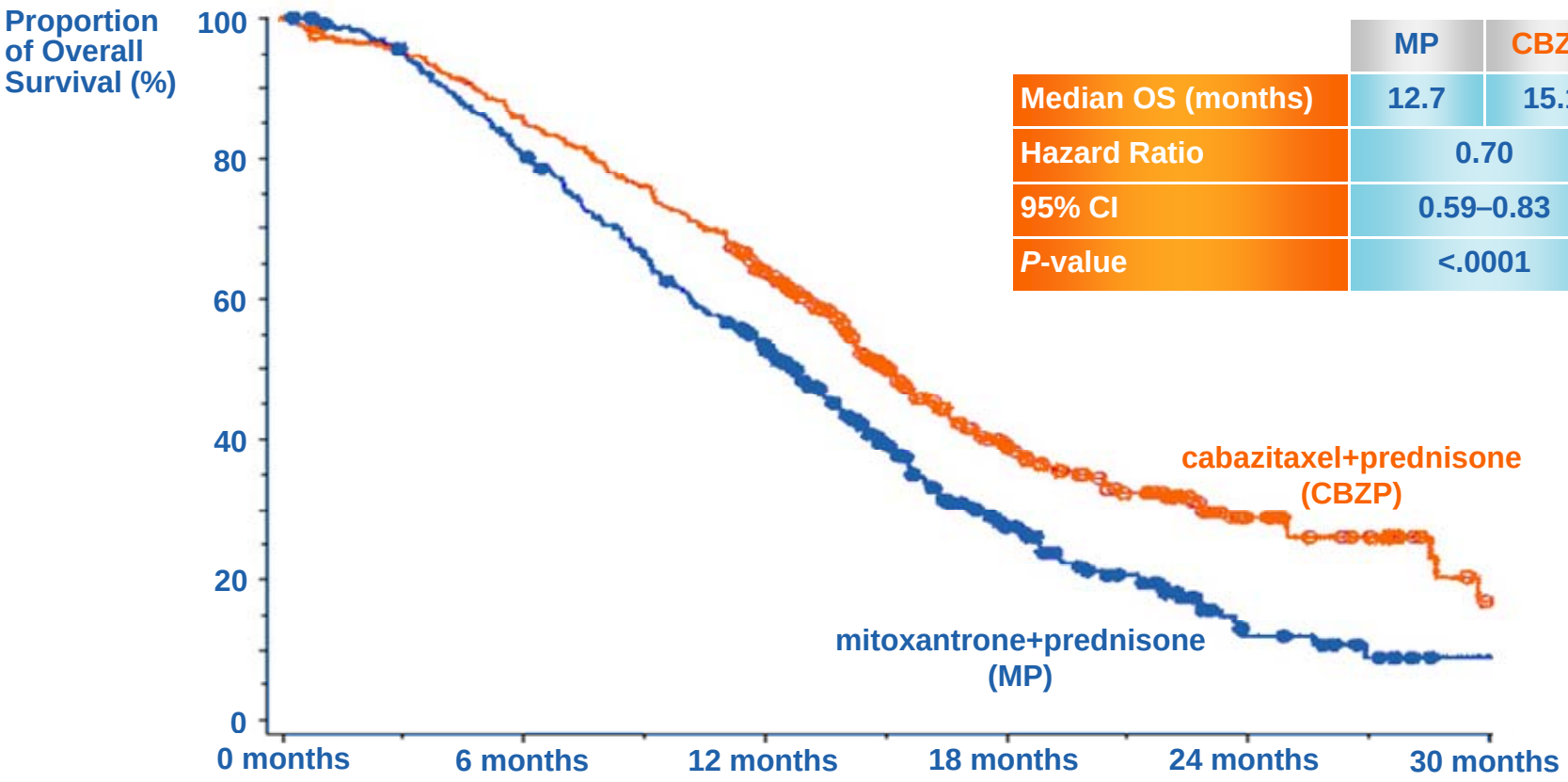
*Oral prednisone/prednisolone: 10 mg daily.

Primary endpoint: OS

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

Overall Survival (ITT Analysis) from TROPIC

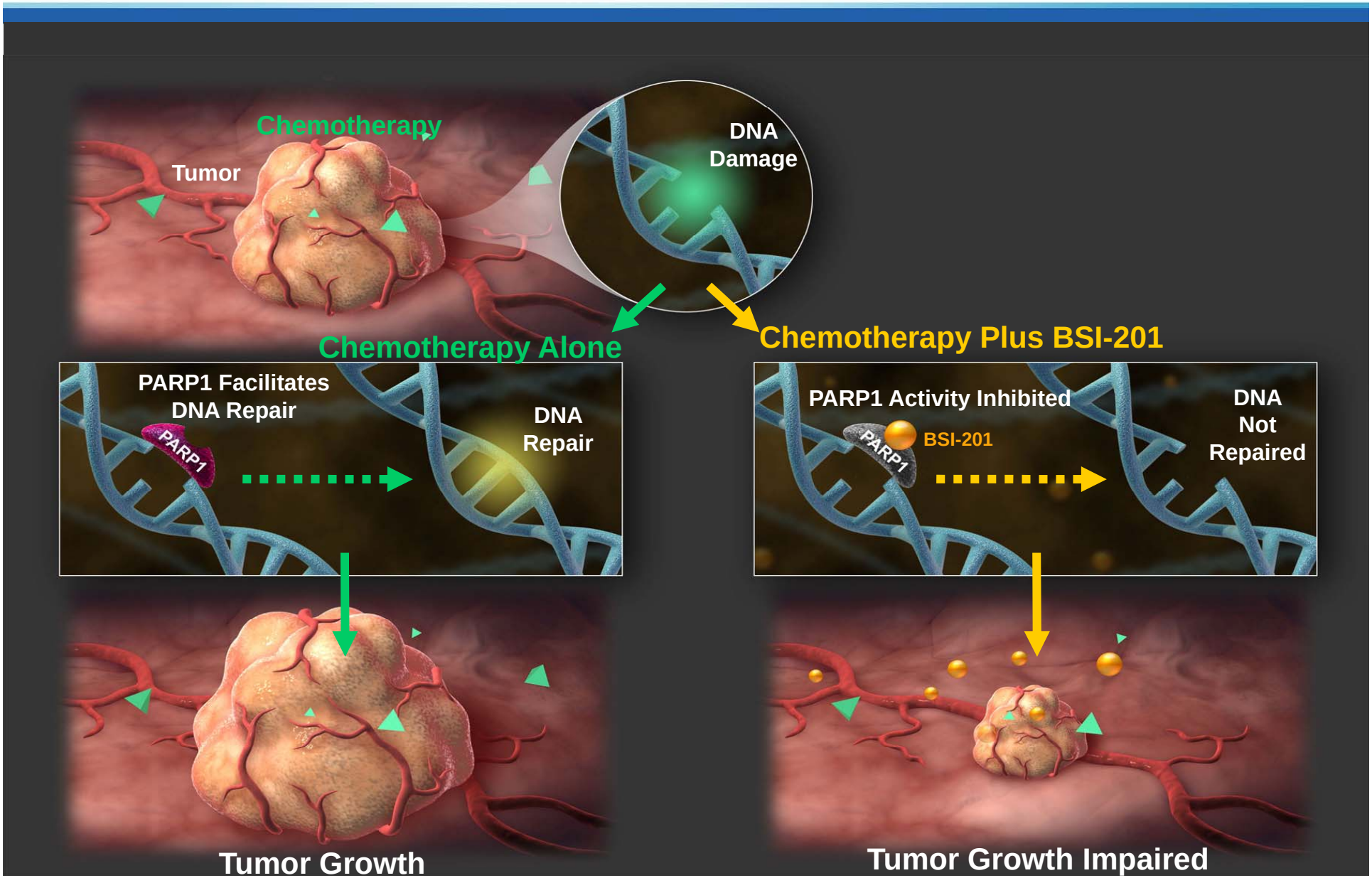


	MP	CBZP
Median OS (months)	12.7	15.1
Hazard Ratio	0.70	
95% CI	0.59–0.83	
P-value	<.0001	

Number at risk							
	mitoxantrone + prednisone	377	300	188	67	11	1
	cabazitaxel + prednisone	378	321	231	90	28	4

The Lancet Volume 376, Issue 9747, 2 October 2010-8 October 2010, Pages 1147-1154

BSI-201 – Iniparib
A novel anticancer treatment



Phase II BSI-201 in mTNBC

- Multicenter
- Open-label

Metastatic TNBC
N = 120

R 1:1

Gemcitabine (1000 mg/m^2, IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)

BSI-201 (5.6 mg/kg, IV, d 1, 4, 8, 11)
Gemcitabine (1000 mg/m^2, IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)

RESTAGING
Every 2 Cycles

*** Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression**

ASCO 2009
Focus on PARP inhibitors

- Efficacy of **BSI-201,** a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): Results of a randomized phase II trial.

J. O'Shaughnessy, ASCO 2009 abstract 3

Phase II trial of the oral PARP inhibitor **olaparib** in BRCA-deficient advanced breast cancer.
A. Tutt ASCO 2009 abstract CRA501

HOME NEWS MARKET

Bloomberg May 31,2009

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Drugs Kill Cancer by Halting Tumor's Ability to Heal Itself

By Tom Randall - May 31, 2009 08:30 EDT

"These PARP inhibitors are the biggest story in breast cancer, by far, and it's going to be a huge bombshell" at the cancer conference, said Powel Brown, director of cancer prevention at the Lester and Sue Smith Breast Center at Baylor College of Medicine in Houston, Texas, in an interview before the meeting. "This mechanism is so hugely positive that this will be FDA approved within probably a year or two."

"The biggest story in breast cancer right now is the PARP inhibitors," said Clifford Hudis, chief of breast cancer medicine at Memorial Sloan Kettering Cancer Center in New York, in a telephone interview last week. "Any time you open up a new target, that's an exciting moment. These drugs may potentially be active not just to treat metastatic disease but to prevent recurrence."

The NEW ENGLAND JOURNAL of MEDICINE

Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer

Joyce O'Shaughnessy, M.D., Cynthia Osborne, M.D., John E. Pippen, M.D., Mark Yoffe, M.D., Debra Patt, M.D., Christine Rocha, M.Sc., Ingrid Chou Koo, Ph.D., Barry M. Sherman, M.D., and Charles Bradley, Ph.D.*

January 2011

Phase II BSI-201 in mTNBC
Final results

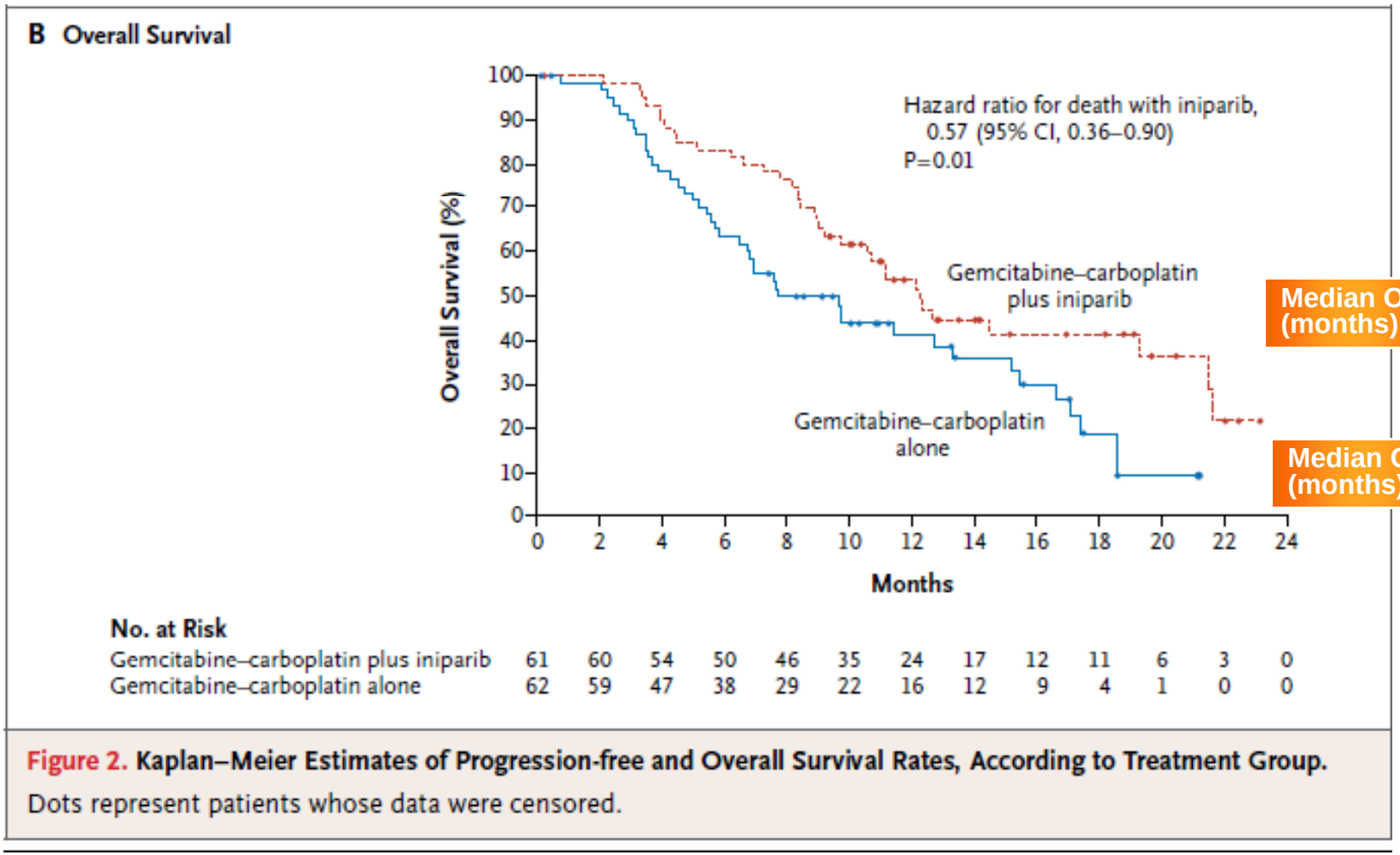


Figure 2. Kaplan–Meier Estimates of Progression-free and Overall Survival Rates, According to Treatment Group.
Dots represent patients whose data were censored.

Median OS (months) 12.3

Median OS (months) 7.7

Joyce O'Shaughnessy New England Journal Of Medicine January 11

Sanofi-aventis Press Release

Sanofi-aventis Reports Top-line Results from Phase III Study with BSI-201 in Metastatic Triple-Negative Breast Cancer

Paris, France - January 27, 2011 - Sanofi-aventis (EURONEXT: SAN and NYSE: SNY) and its subsidiary, BiPar Sciences, today announced that a randomized Phase III trial evaluating BSI-201 (iniparib*) in patients with metastatic triple-negative breast cancer (mTNBC) did not meet the pre-specified criteria for significance for co-primary endpoints of overall survival and progression-free survival.

Importantly, the results of a pre-specified analysis in patients treated in the second- and third-line setting demonstrate an improvement in overall survival and progression-free survival, consistent with what was seen in the Phase II study. The overall safety analysis indicates that the addition of BSI-201 did not significantly add to the toxicity profile of gemcitabine and carboplatin.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

PARP and Cancer — If It's Broke, Don't Fix It

Lisa A. Carey, M.D., and Norman E. Sharpless, M.D.

January 11

Learning lessons from failure ?

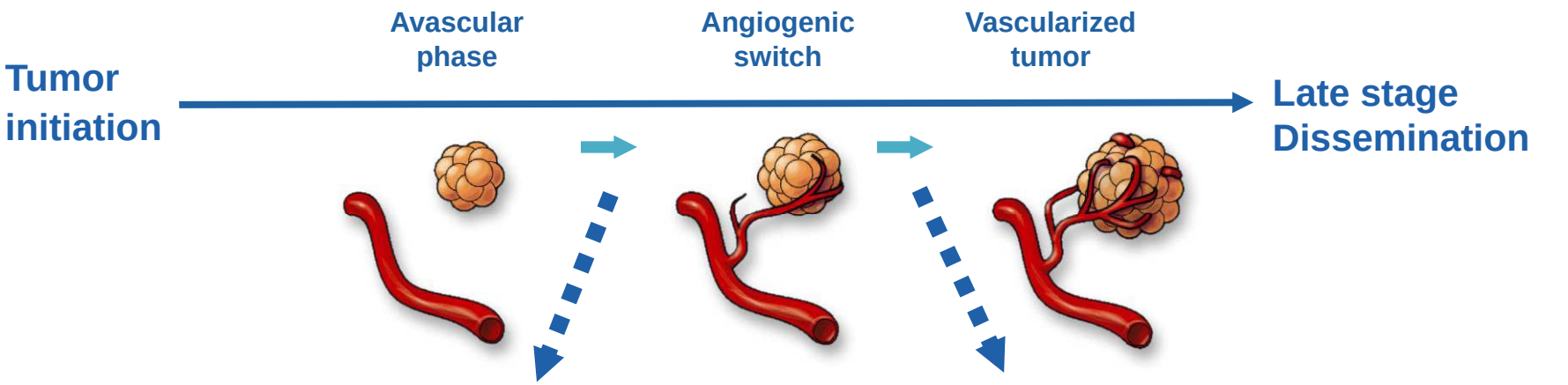
- Agents with positive phase II that eventually failed phase III

Drug	Company	n*	Phase II		Phase III	
			PFS	OS	PFS	OS
Axitinib	Pfizer	103	N/A	6.9 vs. 5.6	4.4 vs. 4.4	8.5 vs. 8.3
Elesclomol	Synta/GSK	32	3.7 vs. 1.8	12 vs. 7.8	3.4 vs. 1.9	10.6 vs.11.5
AS404	Antisoma/Novartis	70	5.4 vs. 4.4	14 vs. 8.8	N/A	N/A
Figitumumab	Pfizer	57	5 vs. 4.3	N/A	N/A	N/A
Iniparib	BiPar/Sanofi	123	5.9 vs. 3.6	12.3 vs. 7.7	N/A	N/A
Vandetanib	AstraZeneca	83	4.3 vs. 2.8	13.1 vs.13.4	4 vs. 3.2	10.6 vs. 10

*indicates the number of patients in the phase II with similar characteristics to the phase III patient population.

Aflibercept and *Ombrabulin*
A Commitment to Targeting Tumor Vasculature

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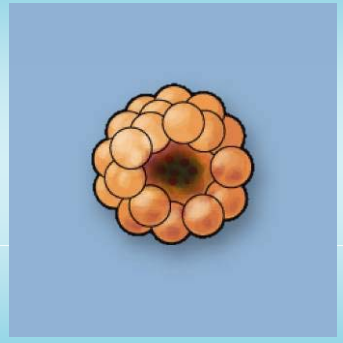
Antiangiogenic approach:

- Prevention of new vessel growth
- Chronic inhibition of neovascularization



aflibercept

Vascular-disrupting approach:



- Disruption of microvessels
- Acute blood flow shutdown, extensive tumor necrosis

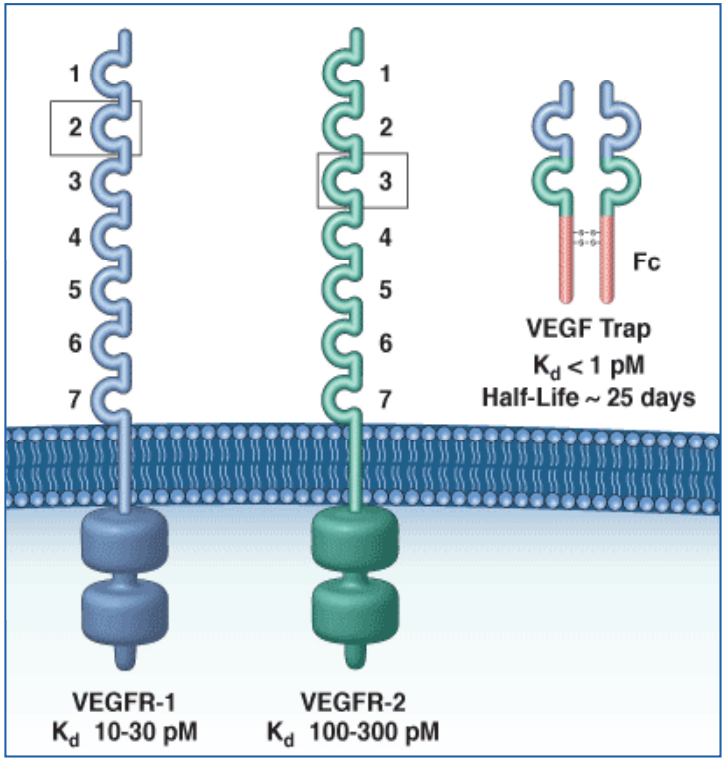
ombrabulin

Aflibercept – Novel Anti-VEGF Candidate *Differentiated from Bevacizumab*

- Partnered with REGENERON worldwide
- VEGF Trap: a fusion protein blocking VEGF, a well-validated anti-angiogenic approach

Bevacizumab	*Aflibercept*
Humanized MAb	All human amino acid sequences
~160,000 MW	~110,000 MW
Kd = 400-1000pM	Kd = 0.5pM (tighter than natural receptors)
Only blocks primate VEGF-A	Blocks all mammalian VEGF-A, as well as VEGF-B & PIGF
Forms Immune Complex with VEGF-A	Binds VEGF-A as monomer without Immune Complex formation

Structure of VEGF Trap



Aflibercept – Development Program

Phase / Study	Indication Design	# of patients	Data Expected
Phase II AFFIRM	1st line metastatic colorectal cancer	230	Final Analysis H2 2011
Phase III VELOUR	2nd line metastatic colorectal cancer + FOLFIRI (folinic acid / 5-FU / irinotecan)	1200	Final analysis H2 2011
Phase III VITAL	2nd lind metastatic non-small cell lung cancer + Taxotere®	900	Final analysis H1 2011
Phase III VENICE	1st line metastatic hormone resistant prostate cancer + Taxotere® prednisone	1240	Interim analysis H1 2011/ Final analysis H1 2012

- Three Phase III studies fully enrolled
- VELOUR study continues based on recommendation by IDMC(1)

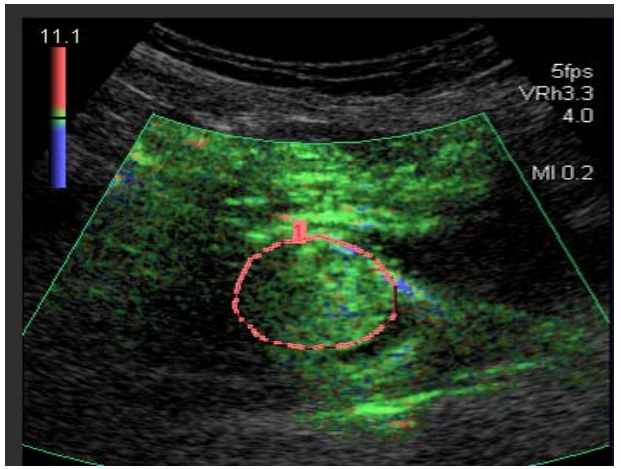
(1) IDMC: Independent Data Monitoring Committee. Recommendation of IDMC was announced in September 2010

Ombrabulin Development Program

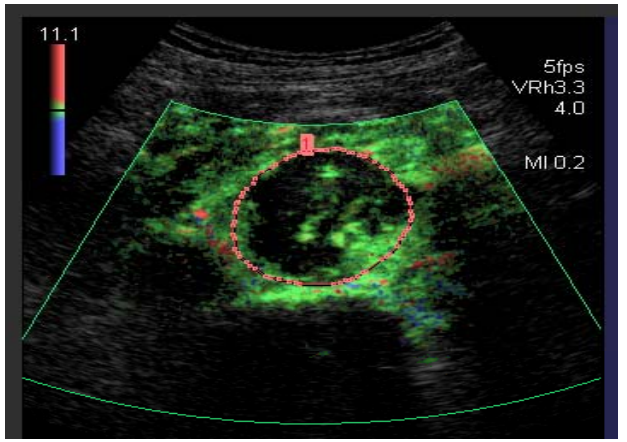
- Mechanism of action and preclinical data support development in most solid tumors
- High unmet medical need in soft-tissue sarcoma after failure of standard therapy
  - Orphan Drug status expected
  - Around 30,000 patients in the U.S. and EU with soft-tissue sarcoma
- Pivotal Phase III study is more than 85% enrolled
- On track for U.S. and EU filing in 2011
- Two Phase II proof of concept trials in preparation
  - 1st line NSCLC to start 2011
  - 2nd line ovarian cancer to start 2011

Shut Down of Tumor Blood Flow(1)

Baseline



After cisplatin/ombrabulin



(1) DCE-Ultrasound images of an ovarian cancer patient treated in a combination Phase I trial; the red contour outlines the tumor mass.

Early Clinical Stage Pipeline:
Our Oncology Discovery Approach

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1 **Discovering drugs against common cancer pathways**



2 **Focus on antibody drug conjugates**



3 **Leverage external complementary innovation**

EXELIXIS™ MERRIMACK® PHARMACEUTICALS
REGENERON IMMUNOGEN, INC.

