9. Aks Sommerschule
Frauen und Männergesundheit
Bregenz Kloster Mehrerau
30. Juli – 1. August 2015

Innovative p53-basierte Therapiestrategien am Bespiel Ovarialkarzinom

Nicole Concin, MD
Innsbruck Medical University
Austria

TP53 „Guardian of the Genome“

p53 protein =
TRANSCRIPTION FACTOR

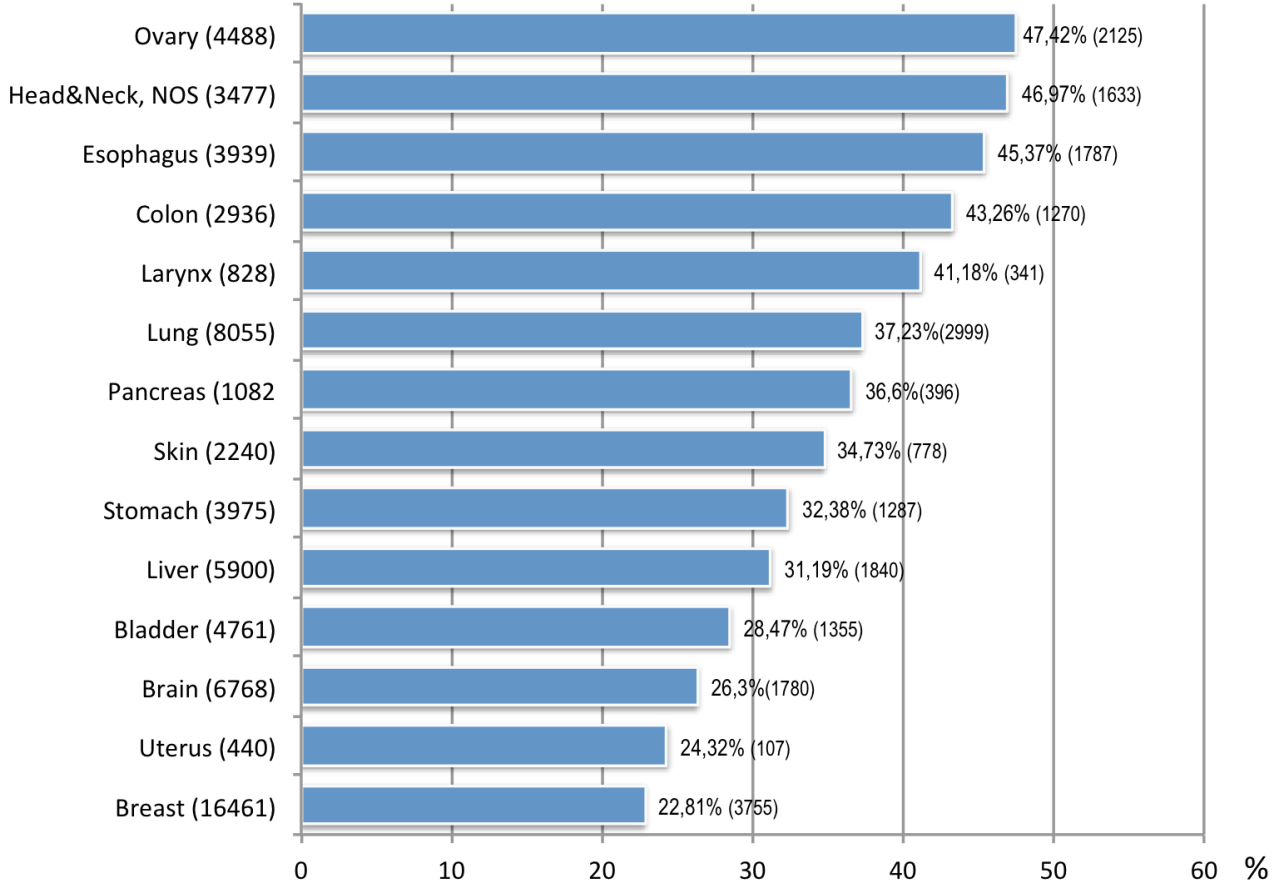
Sir David P. Lane
Nature 1992

Involved in crucial cell functions:

- **cell cycle arrest**
- **DNA repair**
- **apoptosis**
- **metabolism**
- **senescence**

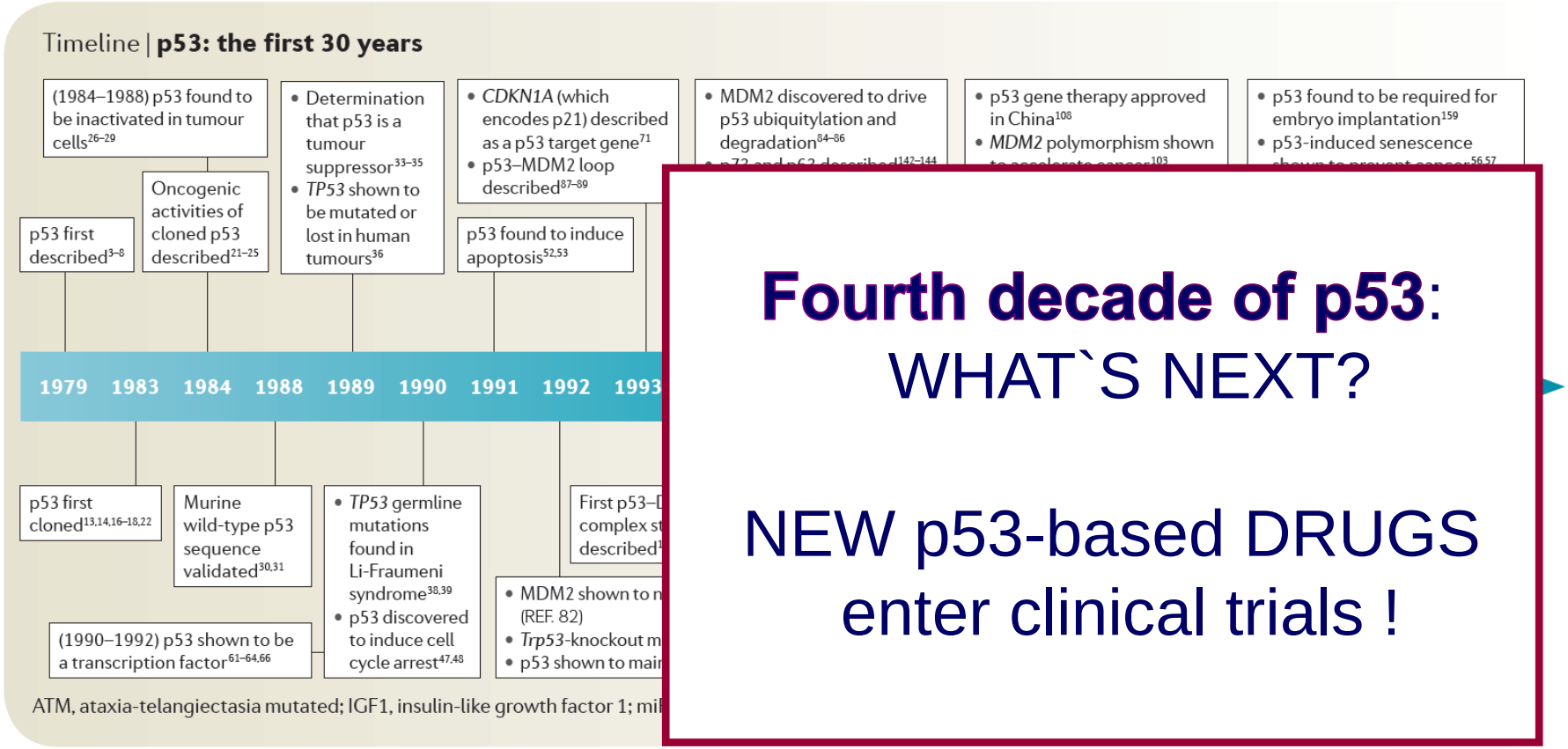
Levine AJ and Oren M, Nat Rev Cancer 2009; *Levin,* Cell 1997

Prevalence of TP53 mutations



IACR TP53 Database (http://p53.iarc.fr), November 2012
Petitjean et al, Hum Mutat. 28(6):622-9, 2007

The first 30 years of p53: growing even more complex

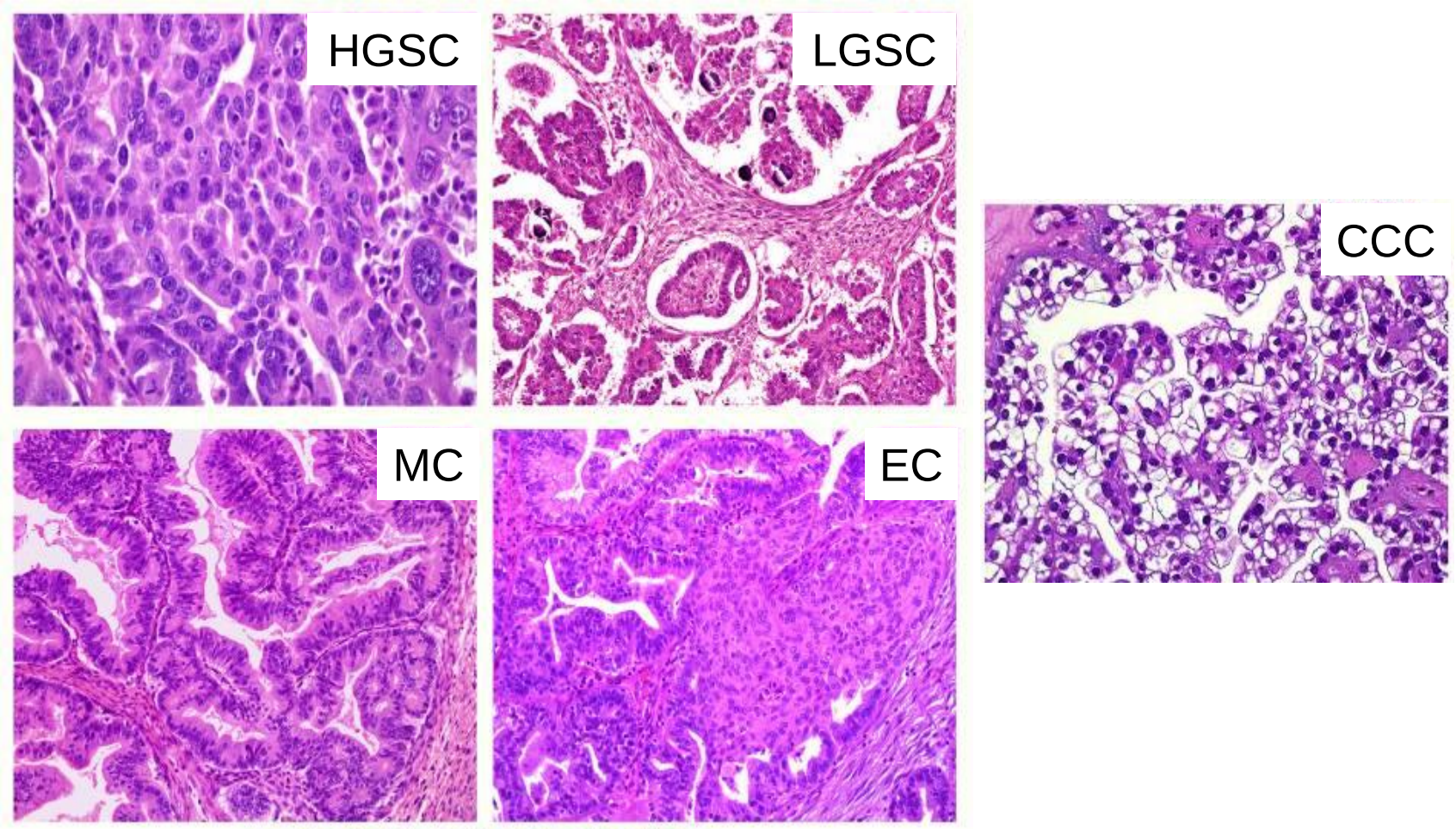


Fourth decade of p53:
WHAT`S NEXT?

NEW p53-based DRUGS enter clinical trials !

Arnold J. Levine and Moshe Oren; NATURE REVIEWS | Nat Rev Cancer 2009

Heterogeneity of ovarian cancer



Ovarian cancer: a Dualistic Model

	Type I (25%)	Type II (75%)
Clinical presentation	slow growing, early stage	highly aggressive, evolve rapidly high metastatic ability, advanced stage
Histopathology	low-grade serous low-grade endometrioid mucinous (clear cell)	**high-grade serous (HGS)** high-grade endometrioid undifferentiated (clear cell)
Precursors	borderline tumors	none
Molecular	K-RAS, B-RAF PTEN, beta-catenin	**p53** genetic instability

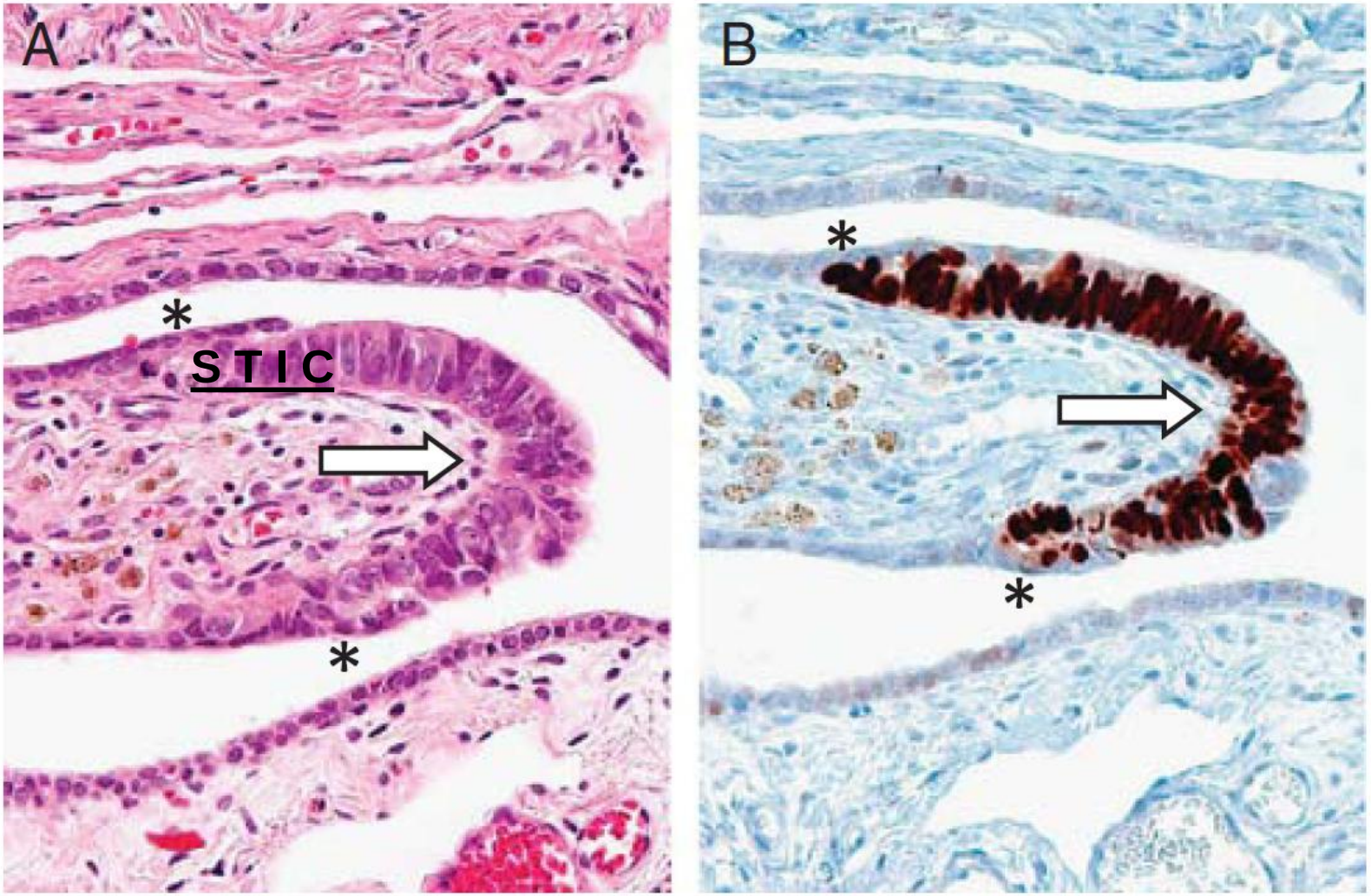
Shid and Kurman, Am J Pathol 2004; *Shid and Kurman*, Clin Canc Res 2005

Integrated genomic analyses of ovarian carcinoma

Table 2 | Significantly mutated genes in HGS-OvCa

Gene	No. of mutations	No. validated	No. unvalidated
TP53	302 **96%**	294	8
BRCA1 **3.5%**	11	10	1
CSMD3	19	19	0
NF1	13	13	0
CDK12	9	9	0
FAT3	19	18	1
GABRA6	6	6	0
BRCA2 **3.1%**	10	10	0
RB1	6	6	0

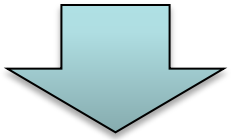
Serous tubal intraepithelial carcinoma (STIC)



Kurman RJ et al. Am J Surg Pathol 2010

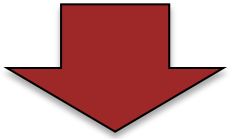
p53 is an attractive target for new therapeutic approaches

Loss of function
by mutation



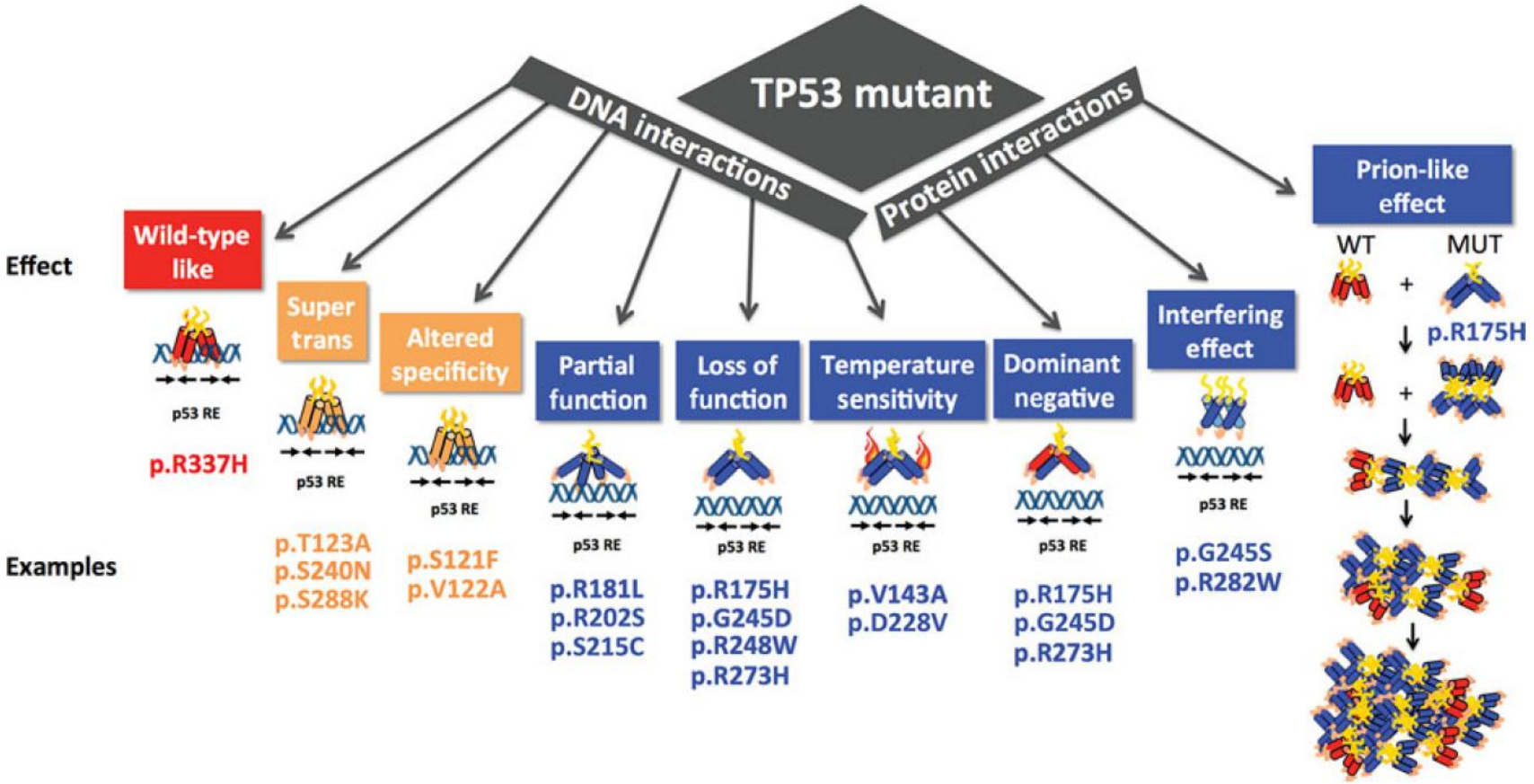
Reactivation *of the*
tumour-suppressor function

Gain-of function
by the mutant protein



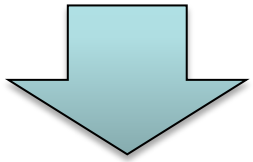
Inhibition *of the*
oncoprotein function

p53 Mutants in the Tower of Babel of Cancer Progression



Bisio et al. Human Mutations 2014

Loss of function
by mutation



Reactivation *of the*
Tumour-suppressor function

Reactivation of the tumour-suppressor-function

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

2012

Targeting p53 in Vivo: A First-in-Human Study With p53-Targeting Compound APR-246 in Refractory Hematologic Malignancies and Prostate Cancer

Sören Lehmann, Vladimir J.N. Bykov, Dina Ali, Ove Andrén, Honar Cherif, Ulf Tidefelt, Bertil Uggla, Jeffrey Yachnin, Gunnar Juliusson, Ali Moshfegh, Christer Paul, Klas G. Wiman, and Per-Ola Andersson

APR-246: induces apoptosis and activates p53 target genes

specifially in p53 mutant cancer cells

first drug of this kind to enter clincial testing!

Bykov et al, Carcinogeneses 2002; Bykov et al, Nat med 2002

PiSARRO

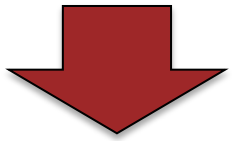
p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin Combination Chemotherapy With or Without APR-246

in patients with PLATINUM SENSITIVE RELAPS

Ib: APR-246 + Carboplatin/PLD
Dose escalation of APR-246

II: randomised trial
Arm A: APR-246 + Carboplatin/PLD
Arm B: Carboplatin/PLD

Gain-of function
by the mutant protein



Inhibition *of the*
oncoprotein function

FP7 project

Funding volume: **6 Mio Euro**
Time-frame: **5.5 years**
Coordinator: N. Concin

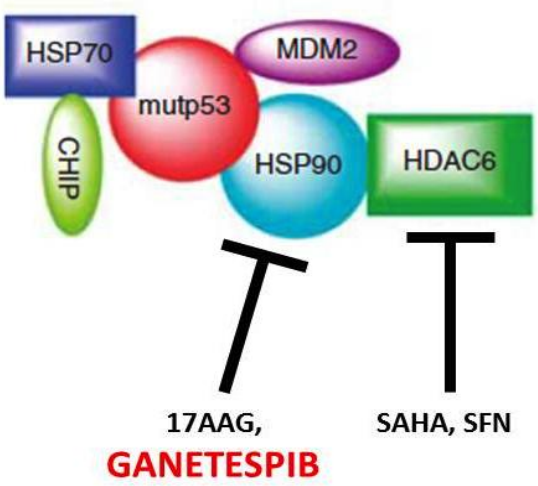
Gannet: a seabird

GANNET53
EUROPEAN PROJECT

Phase I and II trial
PLATINUM RESISTANT EOC
Ganetespib + Paclitaxel weekly

Scientific Background

Stable chaperone complex with mutant p53



Li et al, Mol Cancer Res 2011
Li et al, Cell Death & Diff 2011

Consortium: 18 partners

Participant no.	Participant organisation name	Short- name	Country
1 (Coordinator)	Medizinische Universitaet Innsbruck	IMU	Austria
2	Katholieke Universiteit Leuven	KUL	Belgium
3	Charité - Universitaetsmedizin Berlin	Charité	Germany
4	Universitaetsklinikum Hamburg-Eppendorf	UKE	Germany
5	Medizinische Universitaet Wien	MUW	Austria
6	Assistance Publique - Hôpitaux de Paris	AP-HP	France
7	Centre Anticancereux Léon Bérard	CLB	France
8	AGO Research GmbH	G-AGO	Germany
9	Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie	NOGGO	Germany
10	ARCAGY-GINECO	GINECO	France
11	Universitaetsmedizin Goettingen - Georg-August-Universitaet Goettingen	GAUG	Germany
12	OncoLab Diagnostic GmbH	OncoLab	Austria
13	xailabs GmbH	xailab	Germany
14	Klinik Essen-Mitte, Evang. Huyssens-Stiftung/ Knappschaft gemeinnutzige GmbH	KEM	Germany
15	Technische Universitaet Dresden University Hospital Carl Gustav Carus Dresden	TUD	Germany
16	Centre de lutte contre le cancer, Francois Baclesse, Caen	CFB	France
17	Ernst-Moritz-Arndt-Universität Greifswald	EMAUG	Germany
18	Otto-von-Guericke-Universität Magdeburg	OVGU	Germany

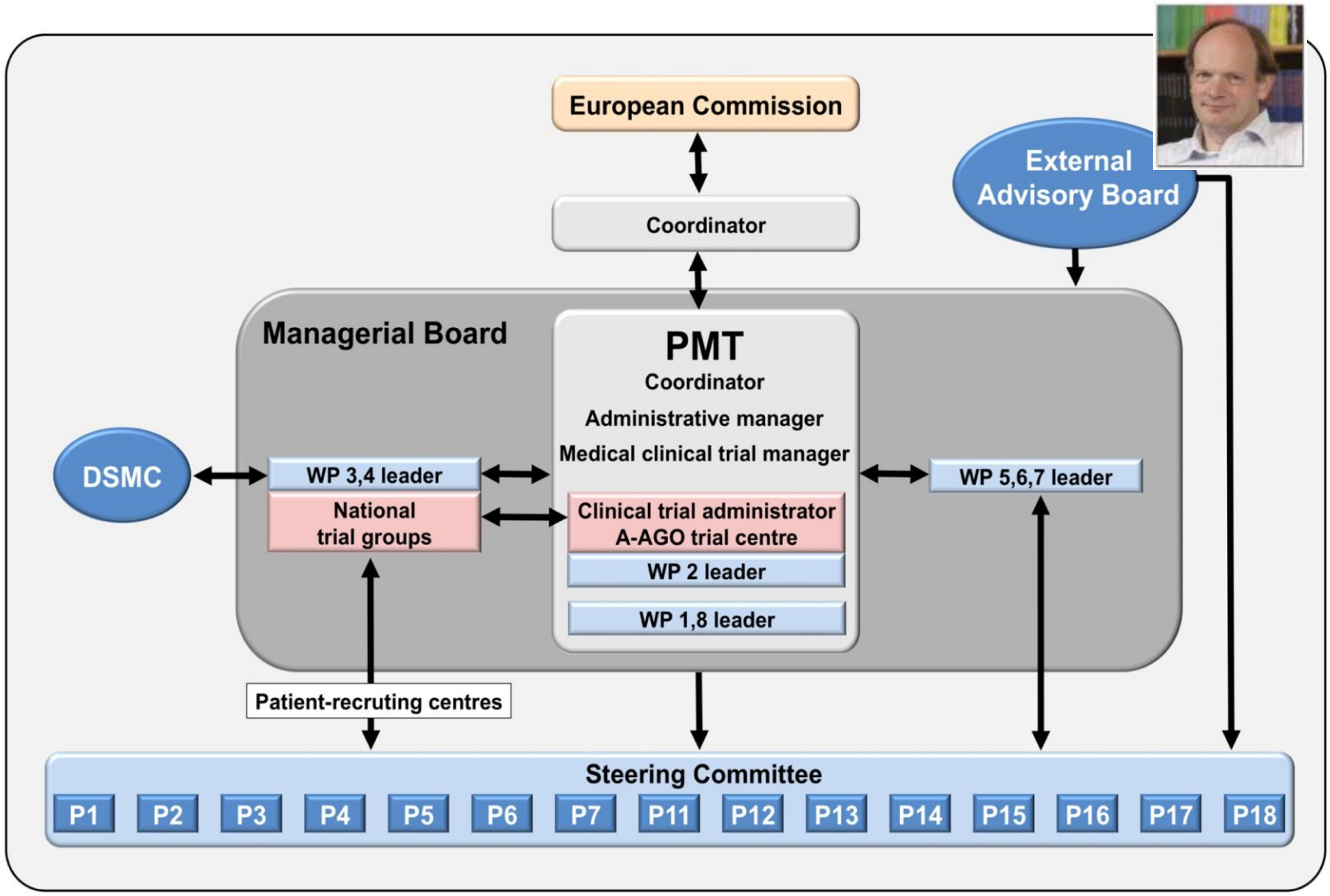
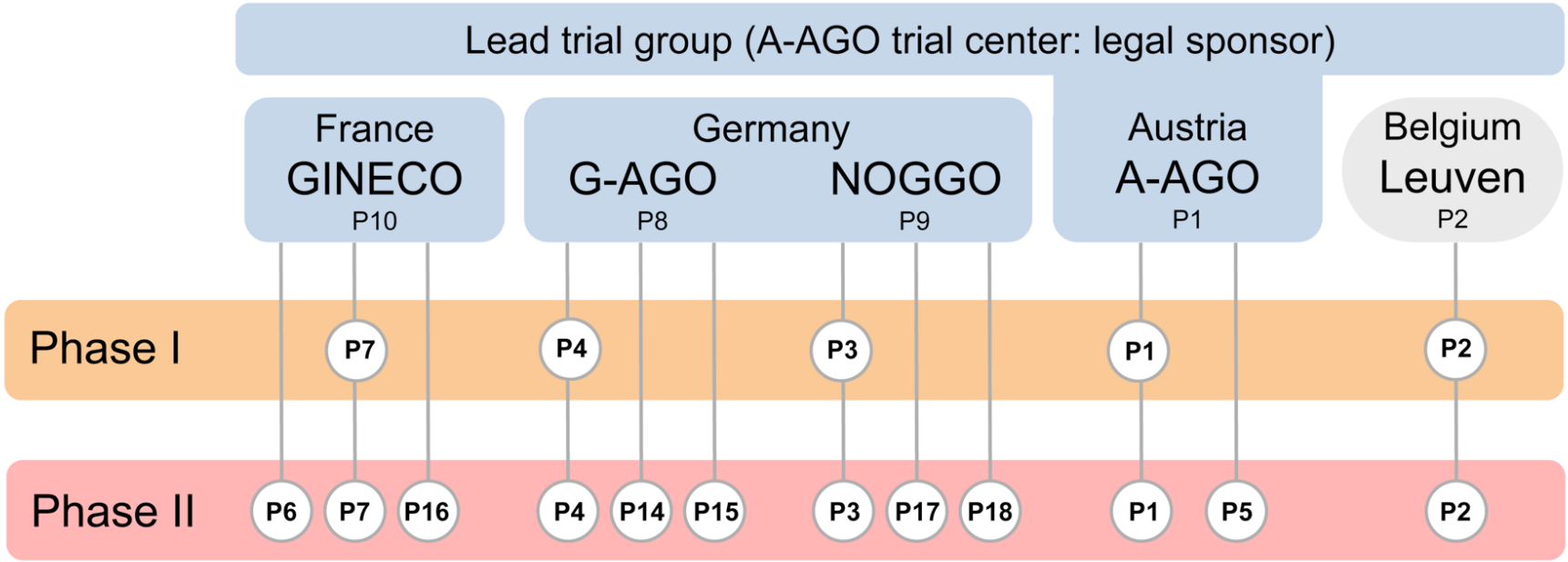
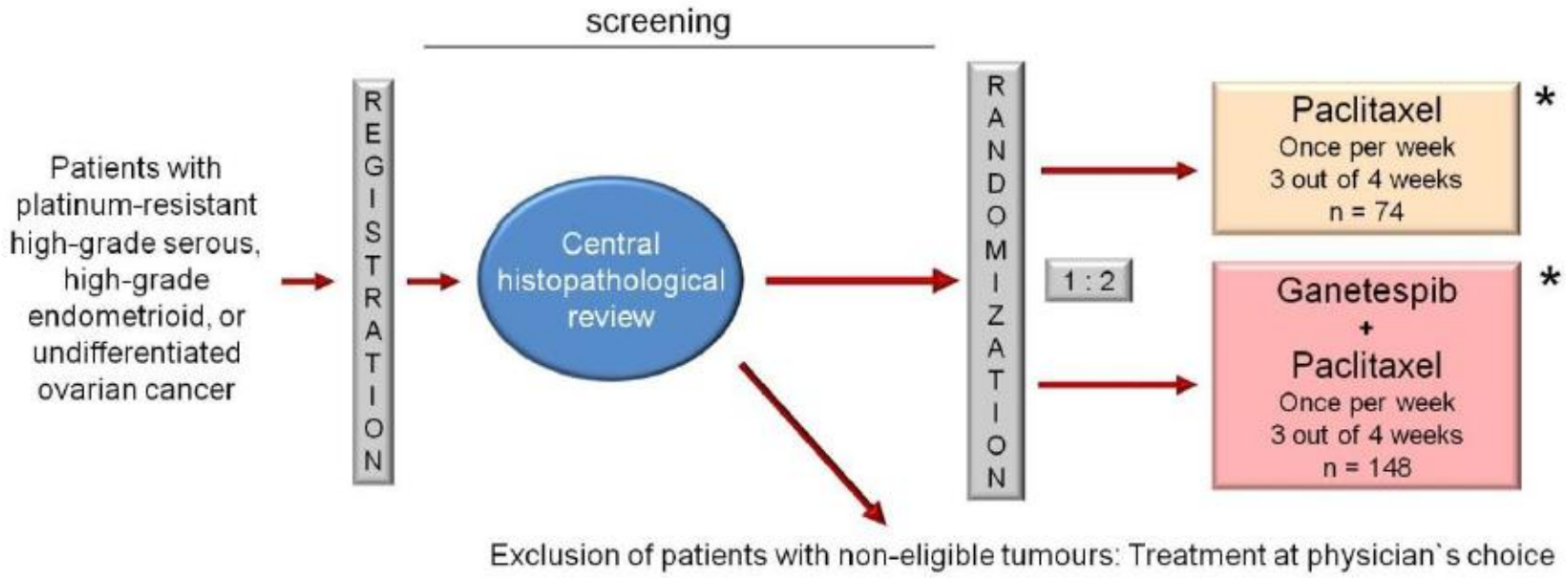


Figure: Management structure of GANNET53

Recruitment strategy

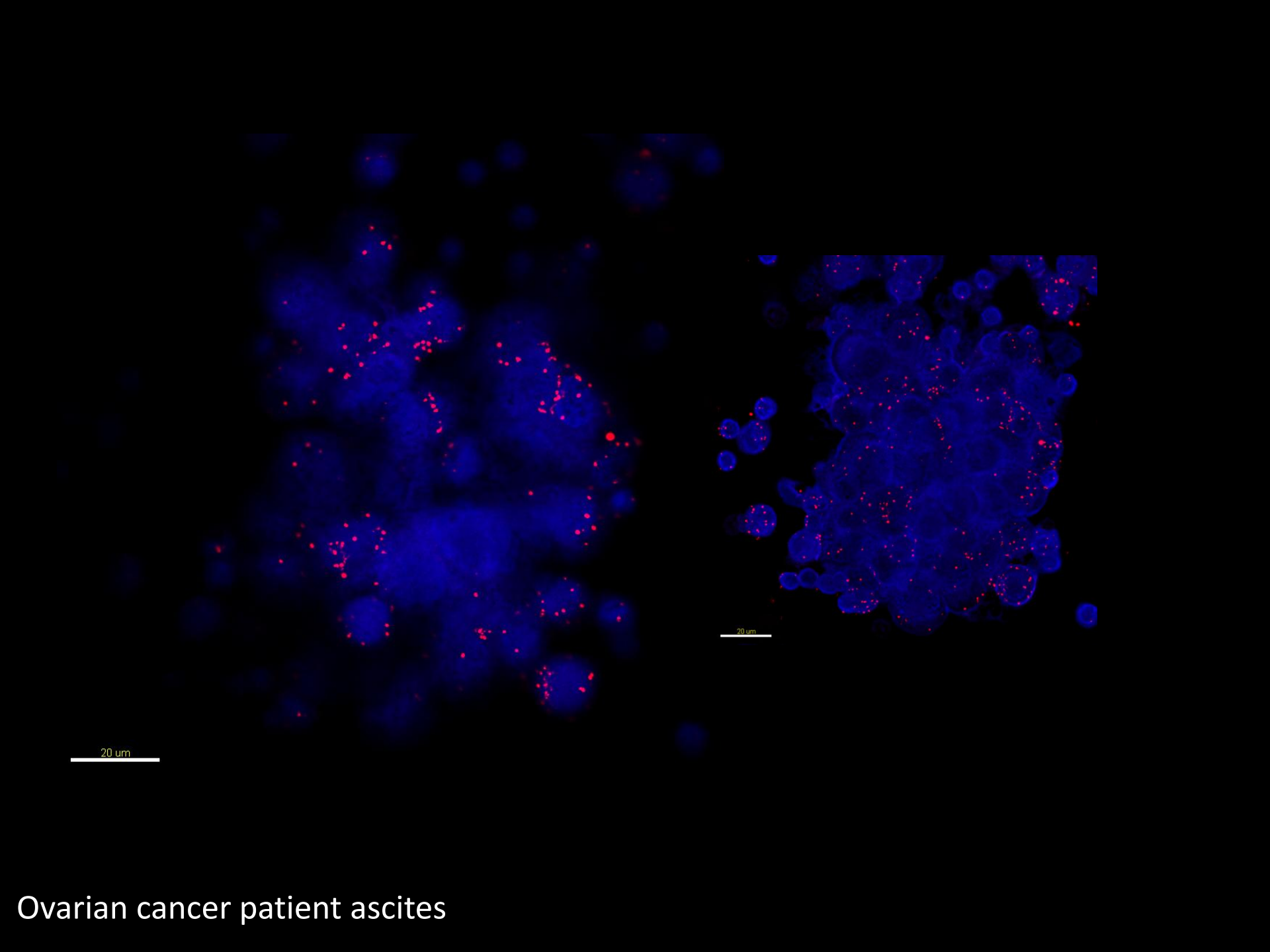


Phase II: randomised, open-label, two-arm



Companion diagnostics
is a prerequisite for new drug approval

Biological specimens
are a prerequisite for companion diagnostics



Ovarian cancer patient ascites

Impact „Proof-of-concept“ studies

Currently worldwide about
11 million people
are living with tumors expressing
highly stabilised mutp53

Danke für Ihre Aufmerksamkeit!