

Le novita' della terapia medica Il carcinoma ovarico

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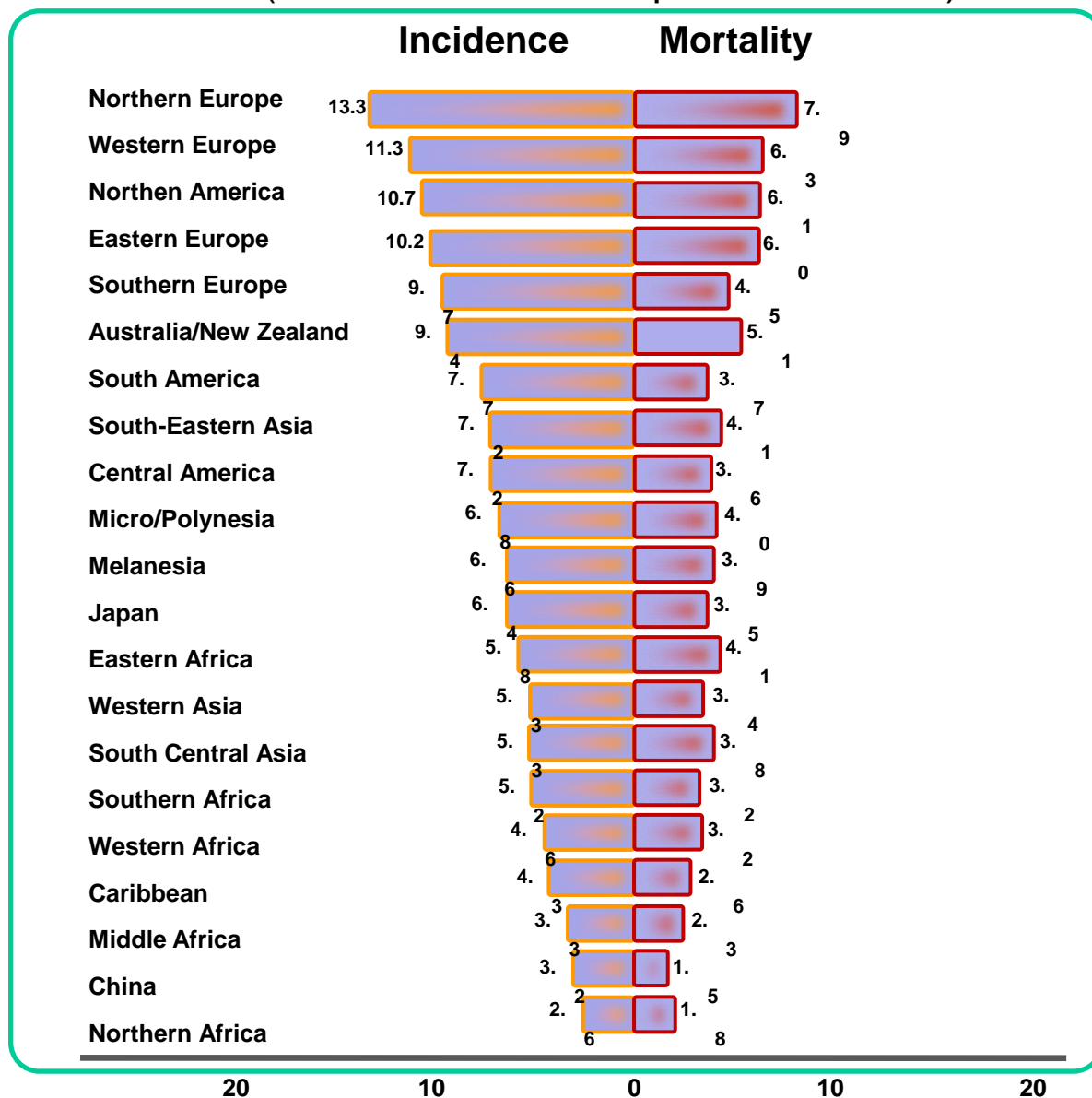
Istituto Europeo Oncologia

Milano



Incidenza e mortalità per carcinoma ovarico

(Tassi standardizzati per età/100.000)



- **204.000 casi/anno**
(4,0% dei tumori nelle donne)
- **125.000 decessi/anno**
(4,2% dei decessi per cancro nelle donne)

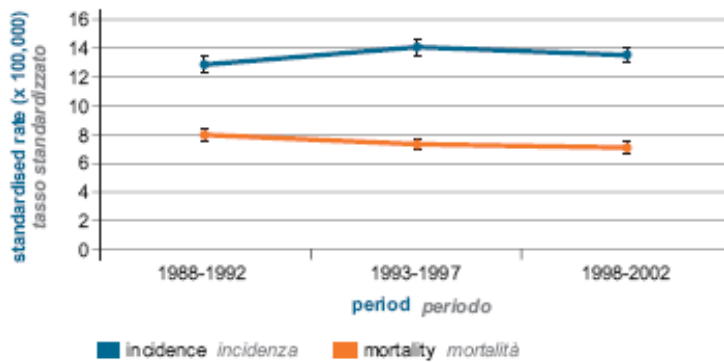
Il Carcinoma ovarico oggi

- La neoplasia ginecologica piu' letale
- Nonostante la chemioterapia sia molto efficace, la recidiva e' molto frequente.
- Nessun significativo cambiamento nella incidenza e mortalità negli ultimi 20 anni
- Ma....numerosi linee di chemioterapia consentono di vivere piu' a lungo
- La medicina personalizzata non è ancora una realtà clinica , rispetto a quanto avviene per altre neoplasie

Carcinoma ovarico

Incidenza e mortalita'

Italy



UK



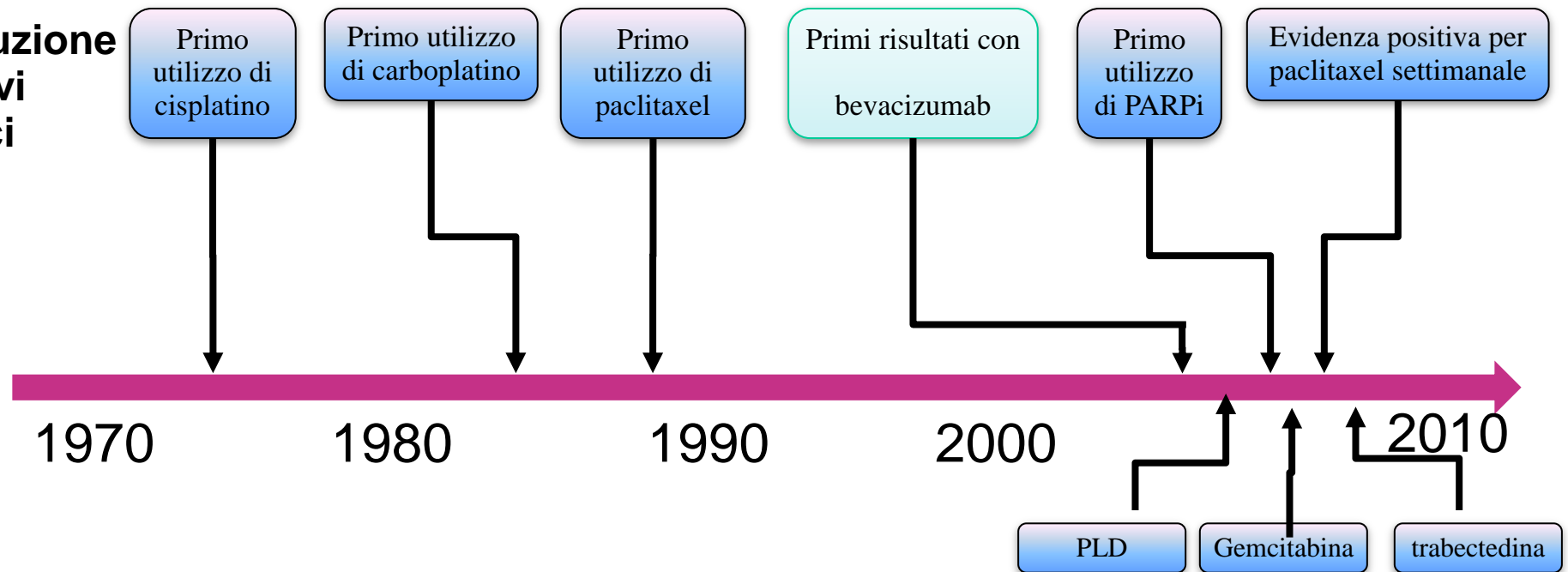
Progressi nella terapia del carcinoma ovarico

evoluzione degli ultimi 40 anni

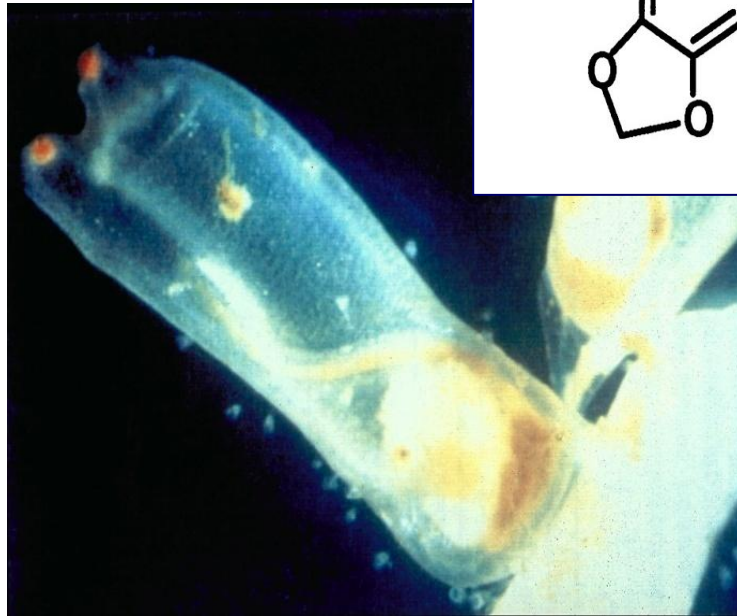
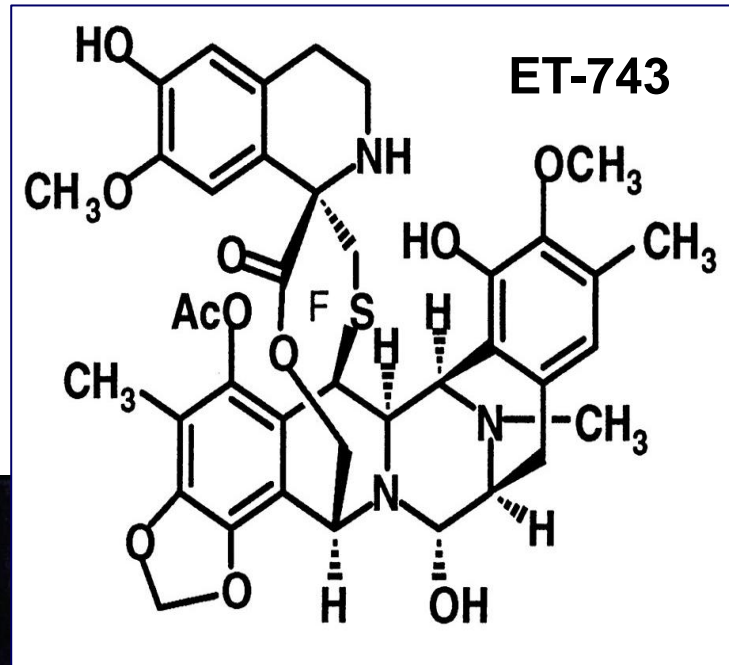
Sopravvivenza
a 5 anni

15% → 30% → 40% → 50%?

Introduzione
di nuovi
farmaci



Trabectedina (ET743)



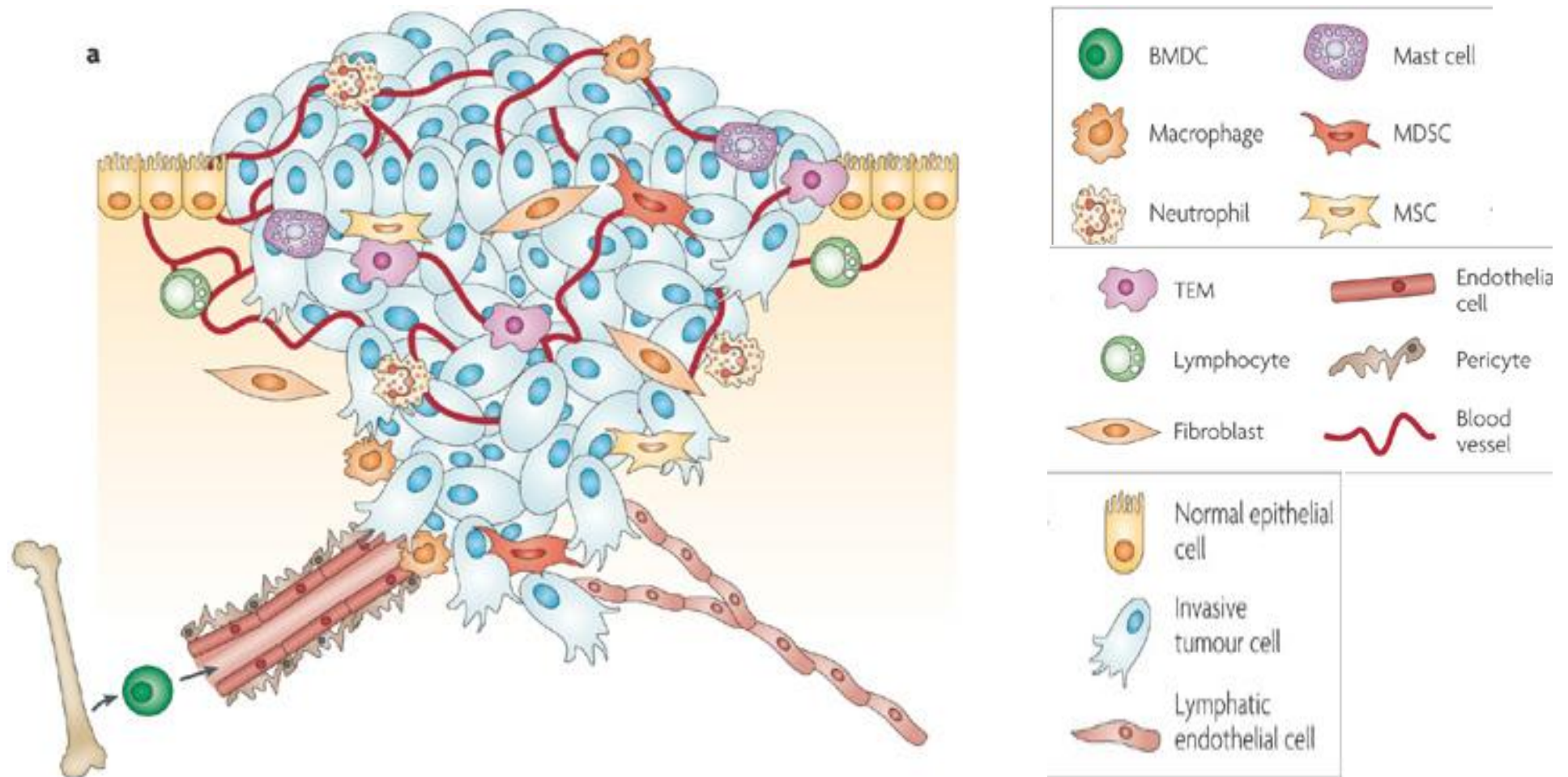
Ecteinascidia turbinata

Terapia Mirata

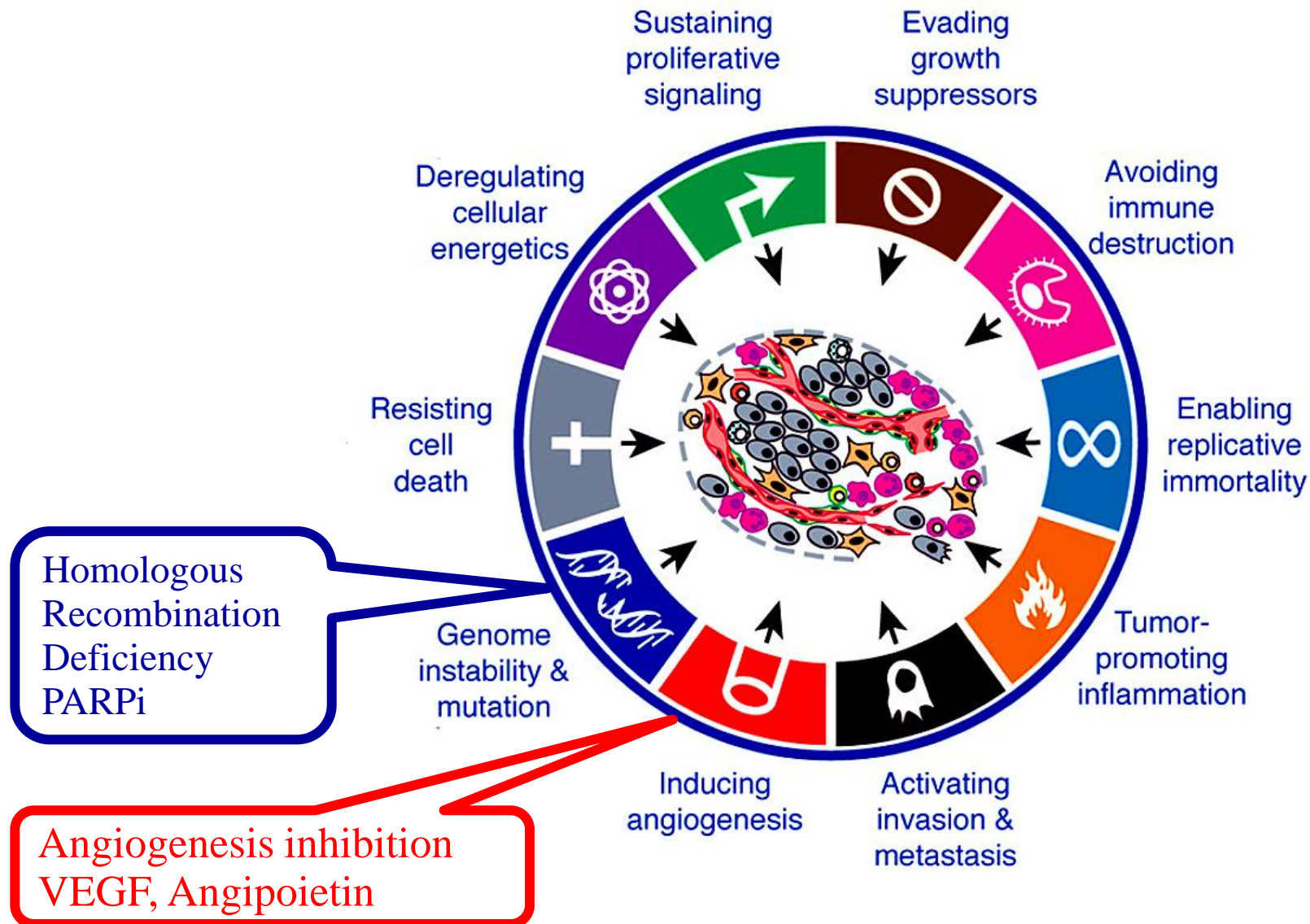


Terapia Mirata

Mirata contro uno specifico meccanismo alterato nella cellula o nel microambiente

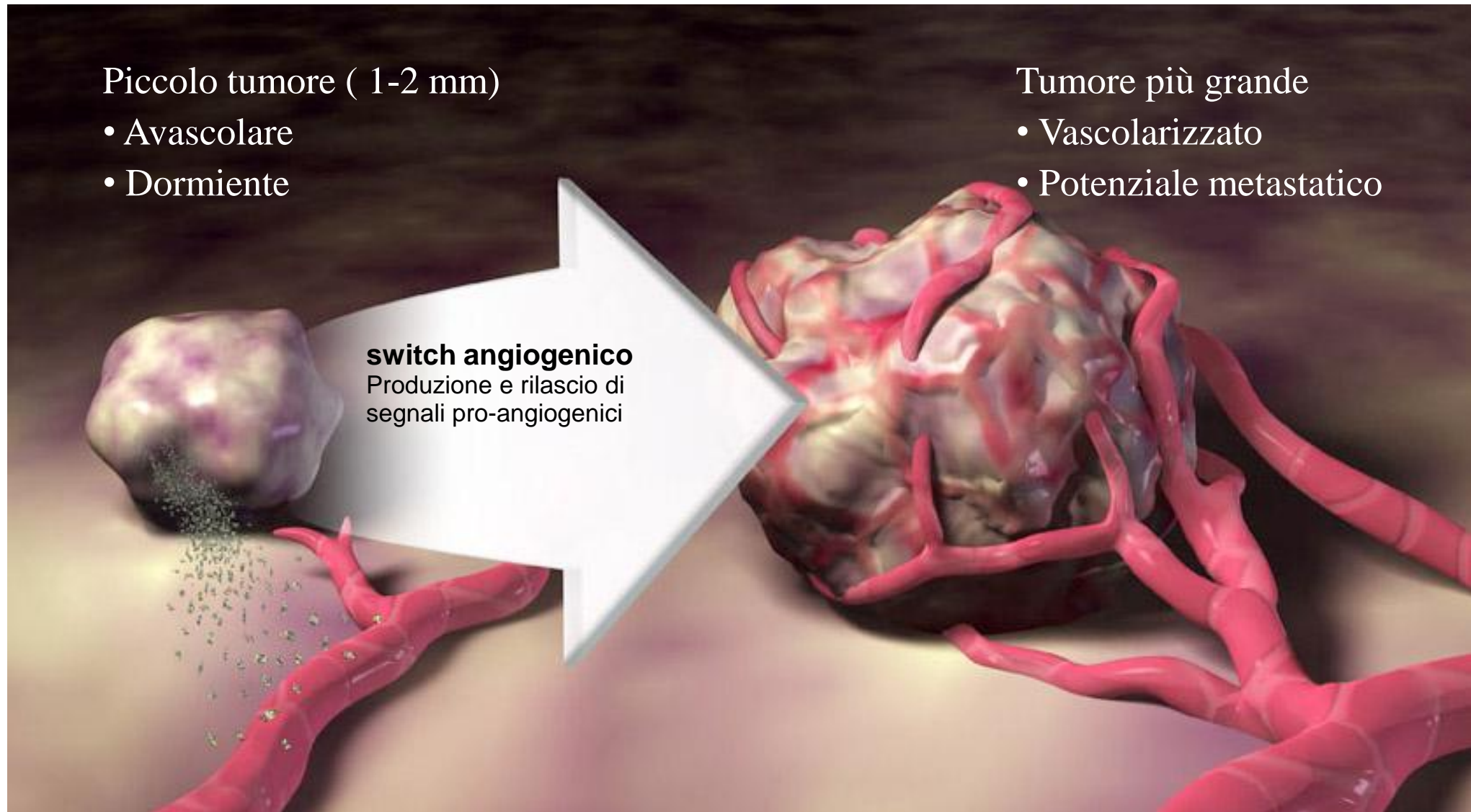


Ovarian Cancer: Therapeutic Targeting of the Hallmarks of Cancer



Modified according Hanahan and Weinberg, Cell 2011

Lo switch angiogenico nello sviluppo del tumore



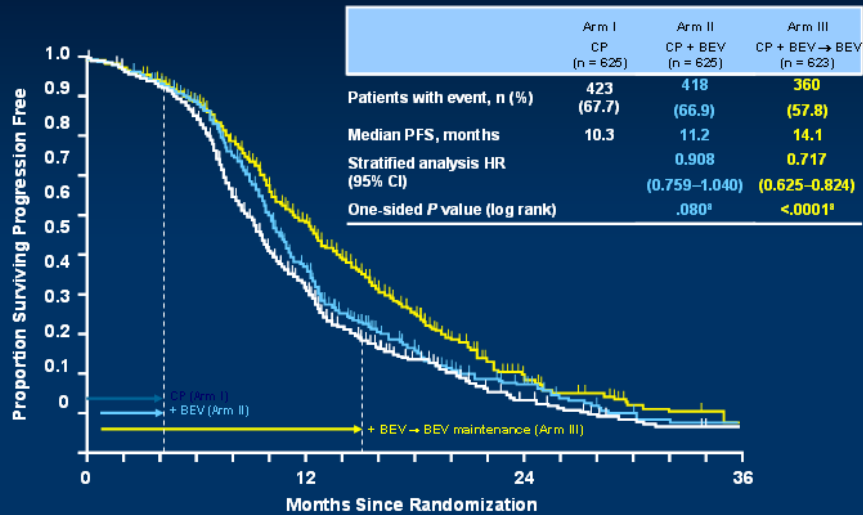
terapia Anti-VEGF

Bevacizumab



Quattro studi positivi con Bev nel carcinoma ovarico

GOG-0218: Investigator-Assessed PFS



Burger RA, et al. *J Clin Oncol*. 2010;28(18s): Abstract LBA1. Burger RA, et al. ESMO 2010.

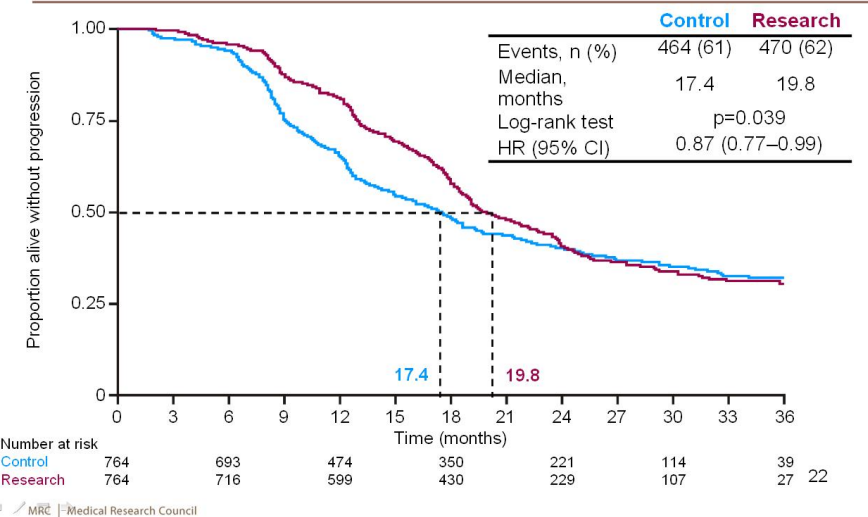
*P-value boundary = 0.0116

ICON7

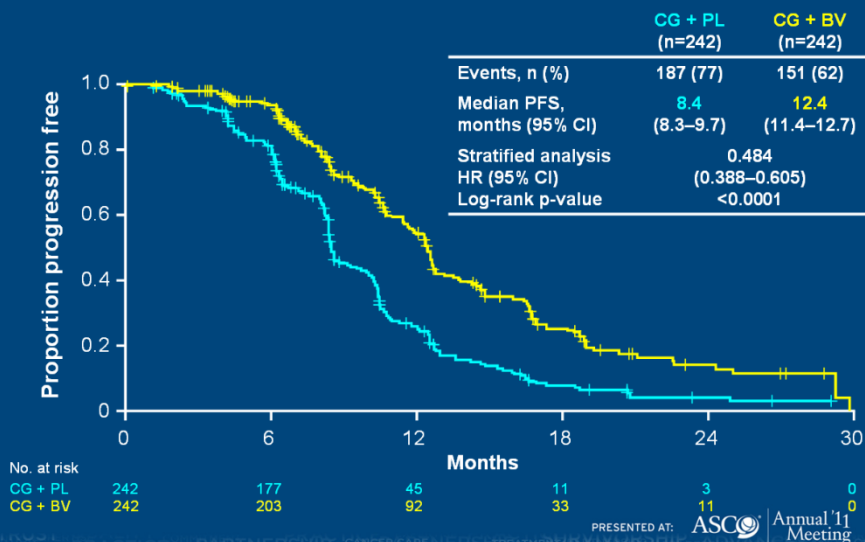
Bevacizumab in Ovarian Cancer

Updated PFS

MRC Clinical Trials Unit



OCEANS: Primary analysis of PFS



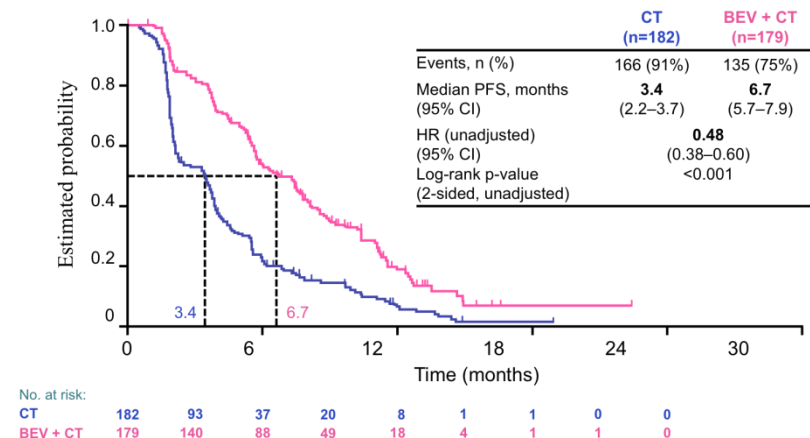
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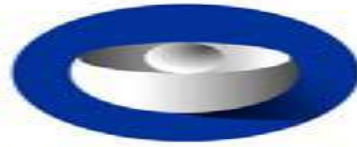
ASCO

Annual Meeting

AURELIA

Progression-free survival

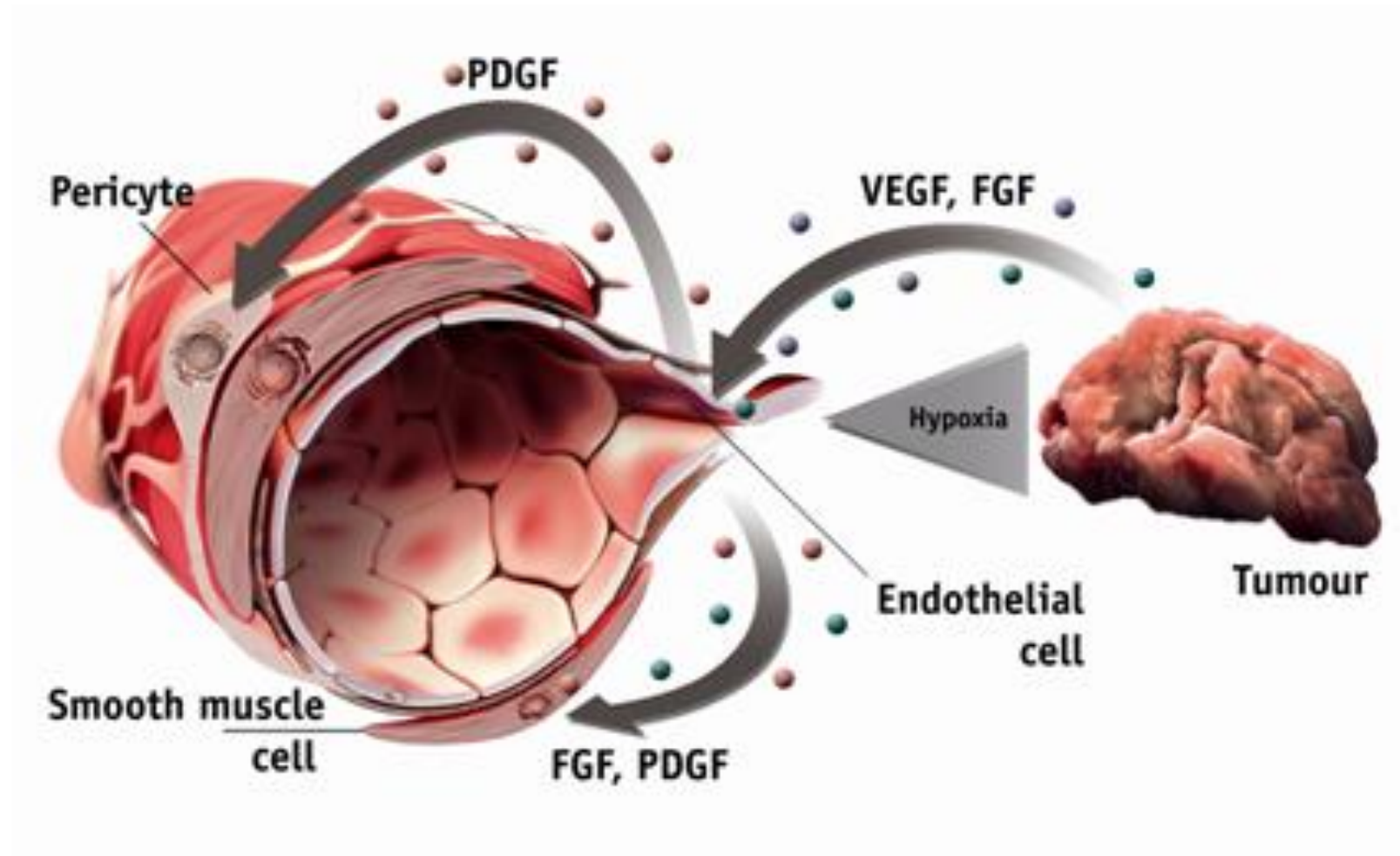




EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Avastin, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier
- The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion

Angiogenesis: Un processo complesso

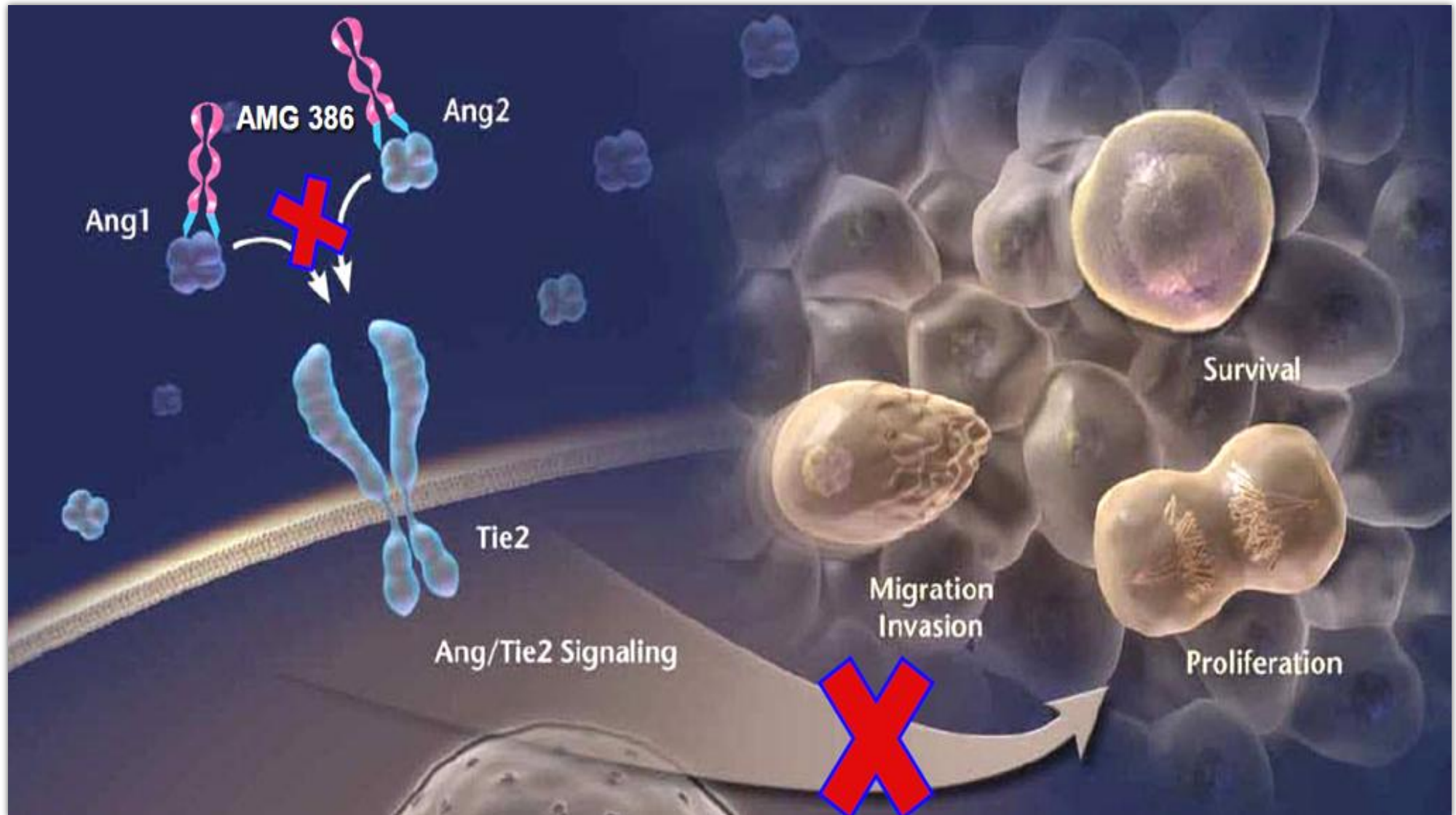


Nuovo paradigma: Terapia a bersagli multipli

| Farmaco | Classe | Target | Fase |
|---------------------------|-----------------------|---------------------------------------|------|
| Nintedanib (BIBF 1120) | Small-molecule TKI | VEGFR + PDGFR + FGFR | III |
| Cediranib | Small-molecule TKI | VEGFR + PDGFR + FGFR + c-kit | III |
| Pazopanib | Small-molecule TKI | VEGFR + PDFGR + c-kit | III |
| Sunitinib | Small-molecule TKI | VEGFR + PDGFR + c-kit | II |
| Sorafenib | Small-molecule TKI | VEGFR + PDGFR + Flt-3 + c-kit + b-Raf | II |
| Vandetanib | Small-molecule TKI | VEGFR + EGFR | II |
| Motesanib | Small-molecule TKI | VEGFR + PDFGR + c-kit | II |

Altri farmaci?

Trebananib, Angiopoietine e Angiogenesi



Terapia antiangiogenica

- GOG 218 Front-line: **Bevacizumab**
HR = 0.72; 95% CI, 0.63–0.82
- ICON 7 Front-line: **Bevacizumab**
HR = 0.81; 95% CI, 0.70–0.94
- AGO-OVAR16 Maintenance: **Pazopanib**
HR = 0.77; 95% CI, 0.64–0.91
- AGO-OVAR12 Front-line: **Nintedanib**
HR=0.84 ; 95% CI, 0.72-0.98
- AURELIA Platinum-resistant, recurrent: **Bevacizumab**
HR = 0.48; 95% CI, 0.38–0.60
- OCEANS Platinum-sensitive, recurrent: **Bevacizumab**
HR = 0.53; 95% CI, 0.41–0.70
- ICON6 Platinum-sensitive, recurrent: **Cediranib**
HR=0.57 ; 95% CI, 0.45-0.74
HR OS= 0.70; 95% CI, 0.51-0.99
- TRINOVA1 Platinum partially sensitive, recurrent: **Trebananib**
HR=0.66; 95% CI, 0.57-0.77

Farmaci antiangiogenici attivi nel carcinoma ovarico



bevacizumab



pazopanib



nintedanib



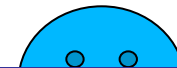
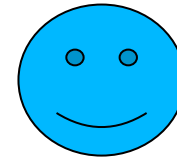
cediranib



trebananib

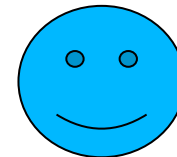
Angiogenesi e carcinoma ovarico

- Bevacizumab

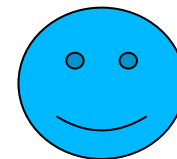


Assenza di marcatori specifici
per predire la risposta

- Trebananib

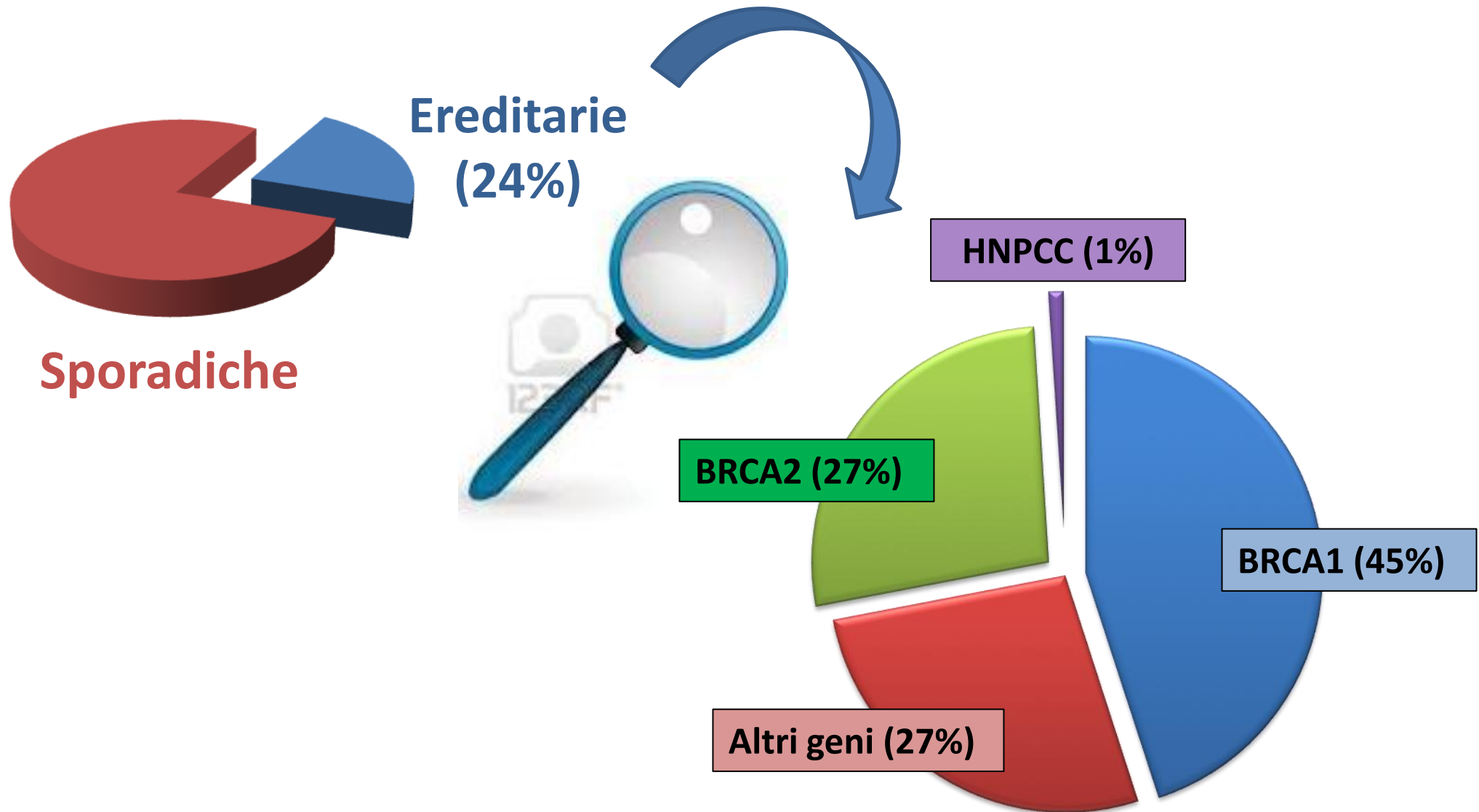


- Cediranib





CAUSE DI SUSCETTIBILITA' GENETICA nel TUMORE DELL'OVAIO

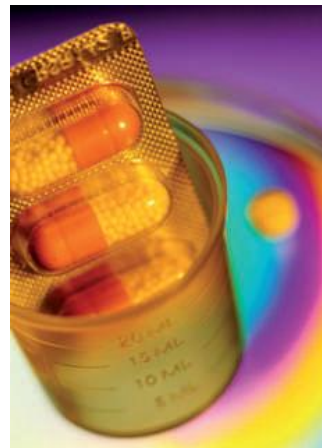


Perche' ricercare la mutazione di BRCA nelle pazienti con carcinoma ovarico ?

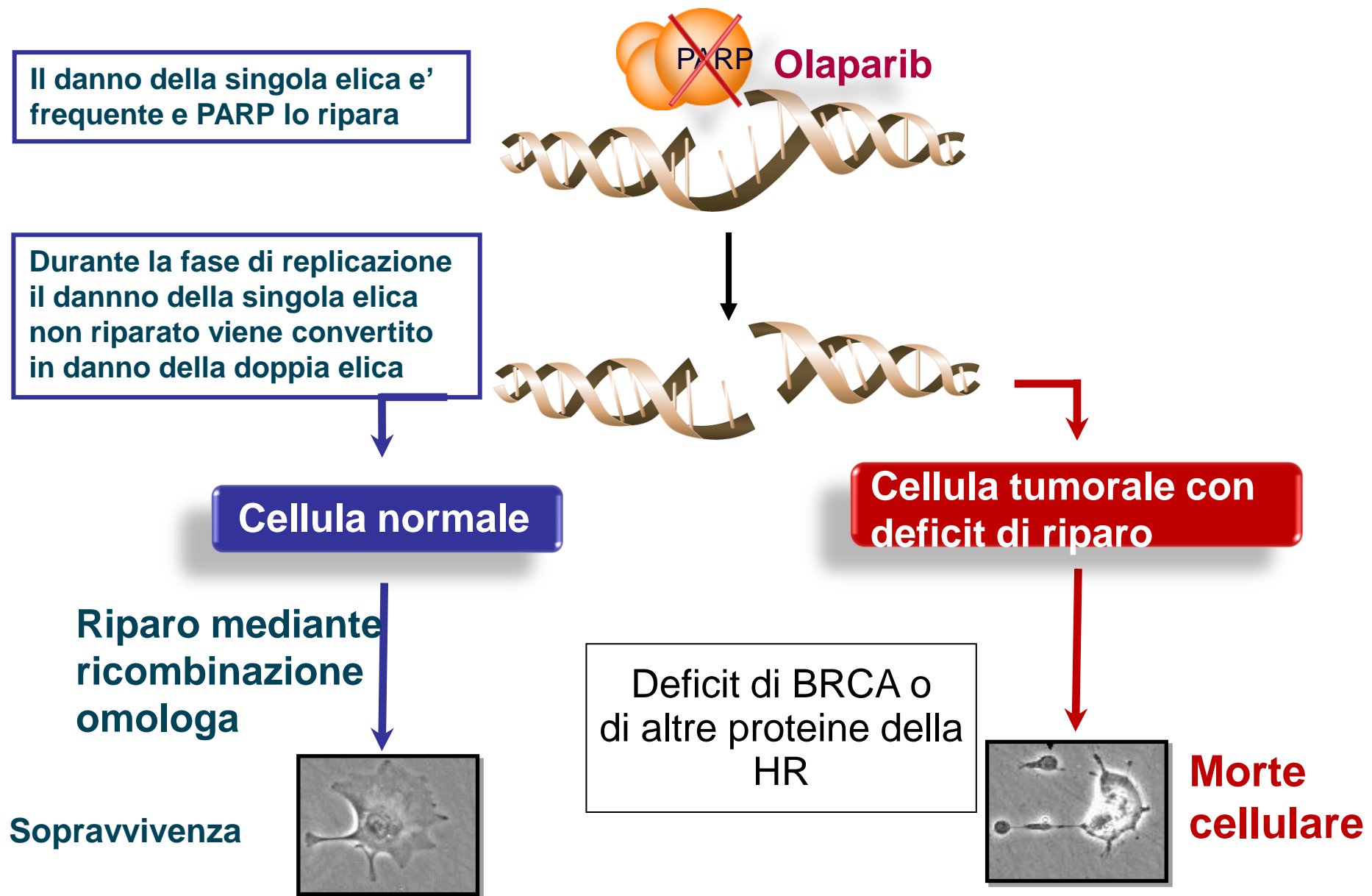
Stabilire il rischio

Stabilire la prognosi

Decisioni terapeutiche

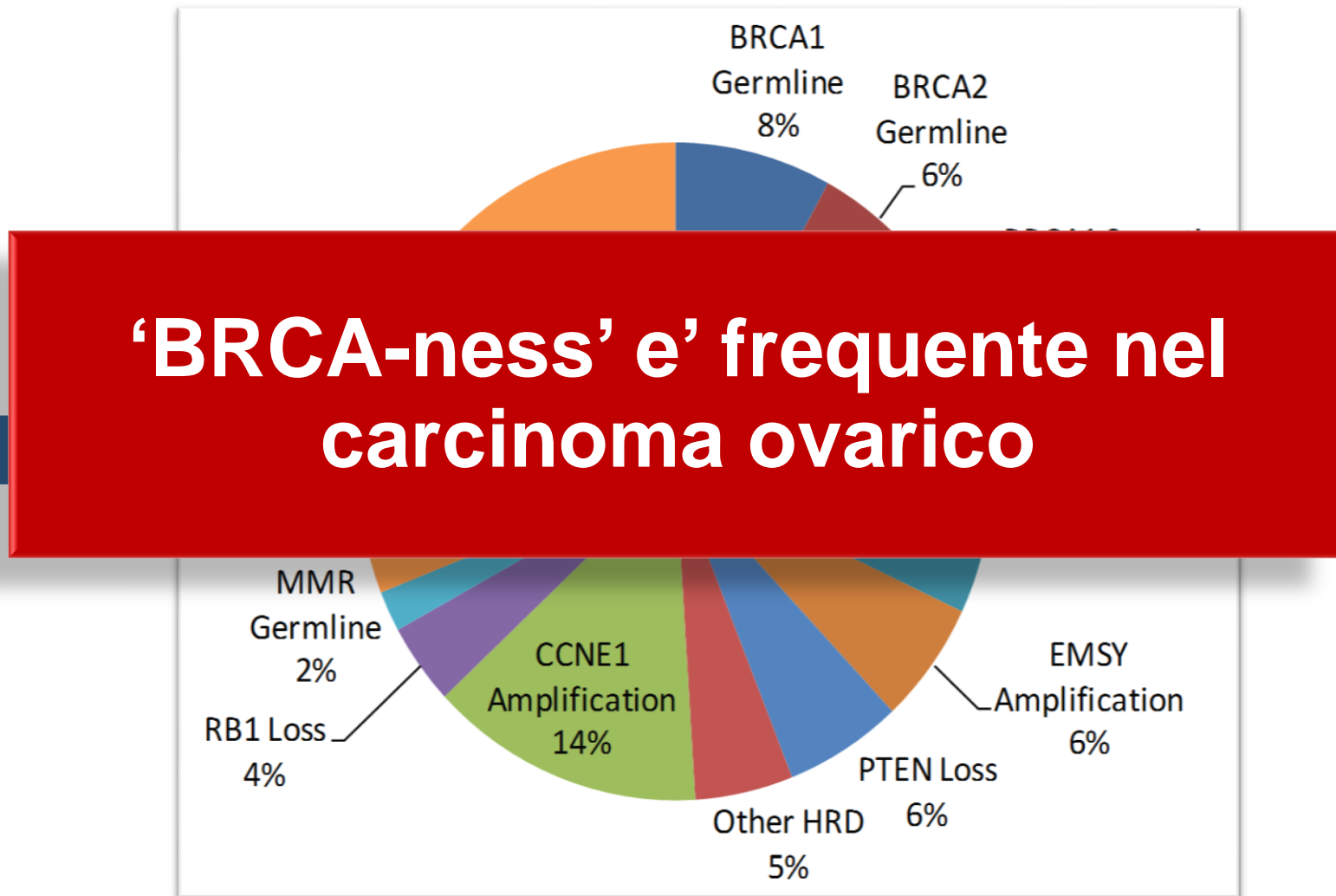


Uccisione mirata di cellule che hanno i meccanismi di riparo del DNA alterati



Quanto e' frequente il deficit di ricombinazione omologa ?

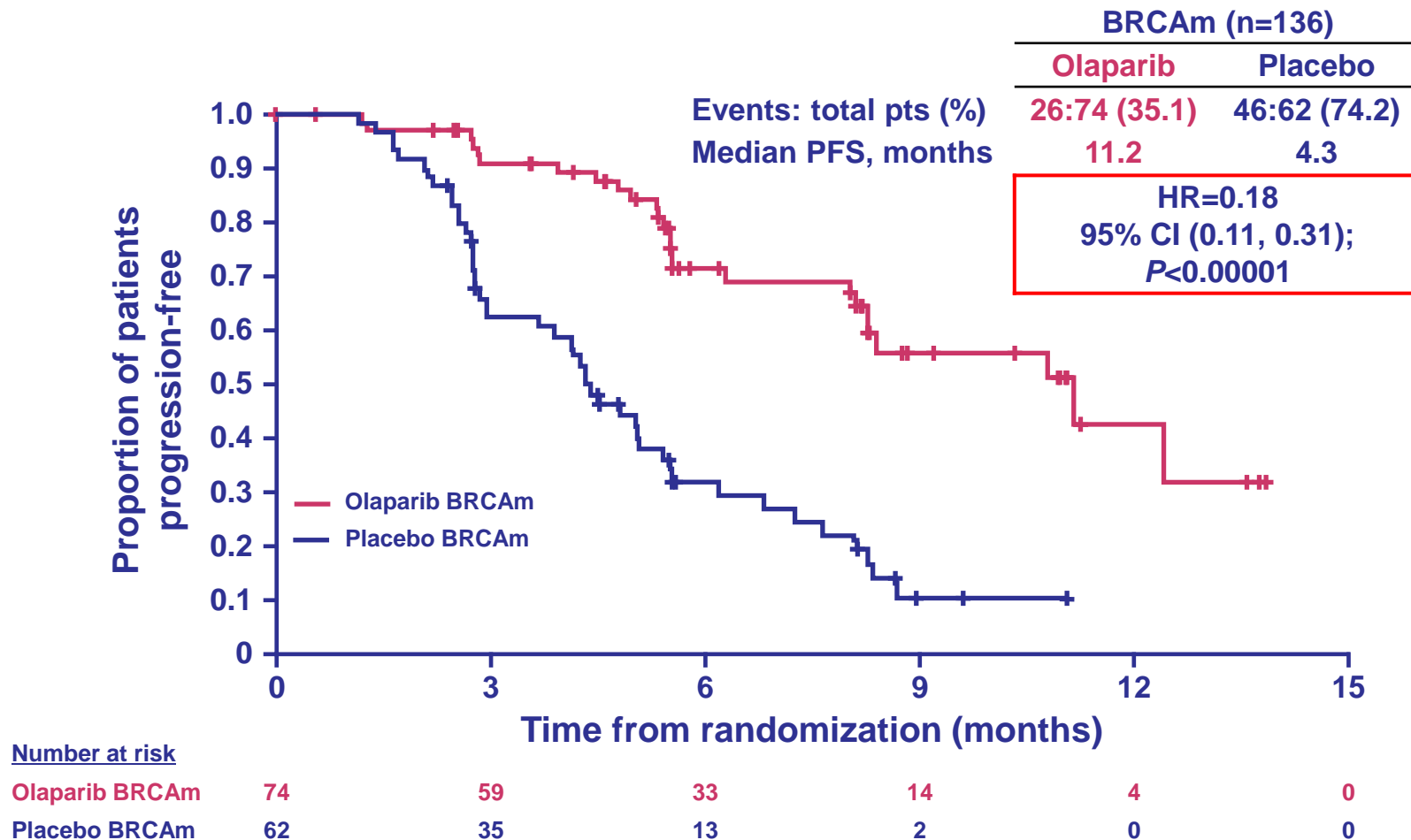
Eventi mutualmente esclusivi



No H

HR

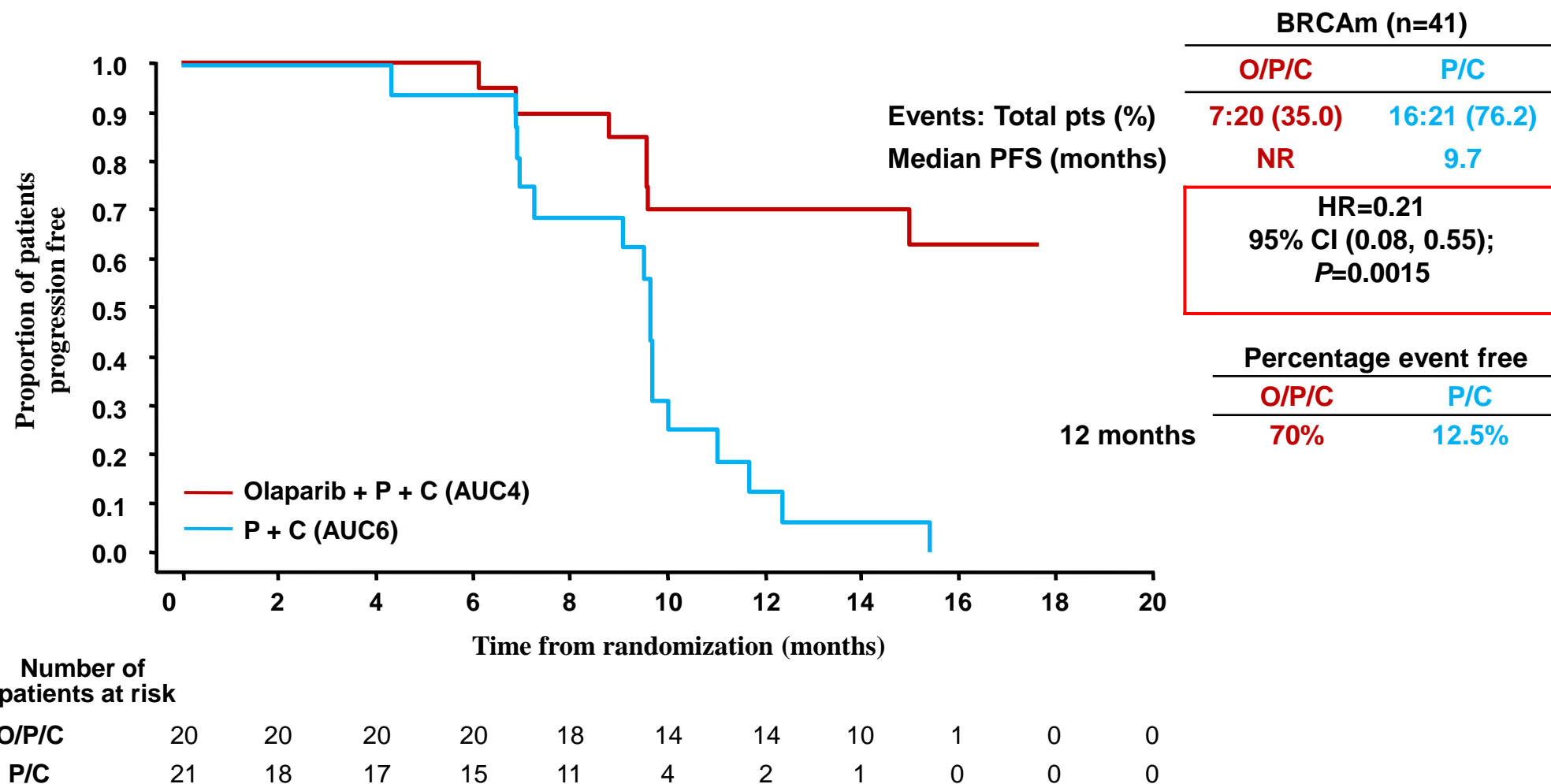
Terapia di mantenimento con Olaparib nelle recidive platino-sensibili PFS in relazione alla mutazione di BRCA



- 82% riduzione nel rischio di progressione di malattia o morte con olaparib

PFS* in BRCAm patients

Amit Oza et al. ECC 2013

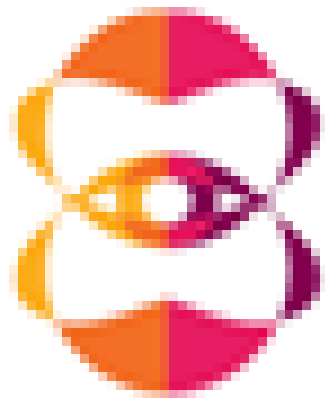


- 79% reduction in risk of disease progression with olaparib in BRCAm patients
- Clear separation between treatment arms observed at 7 months



SOLO¹

BRCAm Ovarian Cancer



SOLO²

BRCAm Ovarian Cancer

PARP Inhibitors in Clinical Trials

| | | |
|----------------------|---------------|---------|
| PF-01367 (Rucaparib) | Clovis/Pfizer | IV/oral |
| Olaparib | AZ | Oral |
| ABT 888 (Veliparib) | Abbott | Oral |
| INO-1001 | Inotek | IV |
| GP1201 | Eisai | Oral |
| CEP 9722 | Cephalon | Oral |
| MK 4827 (Niraparib) | Tesaro | Oral |
| BMN 673 | BioMarin | Oral |

Perche' il carcinoma ovarico e' rimasto indietro ?

Terapia generica
1990

Terapia stratificata
2010

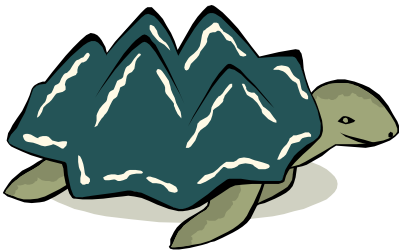
Terapia individualizzata
2020

Carcinoma della mammella

Linfoma

Carcinoma ovarico

Carcinoma pancreatico



Il tumore

1. M

2. N

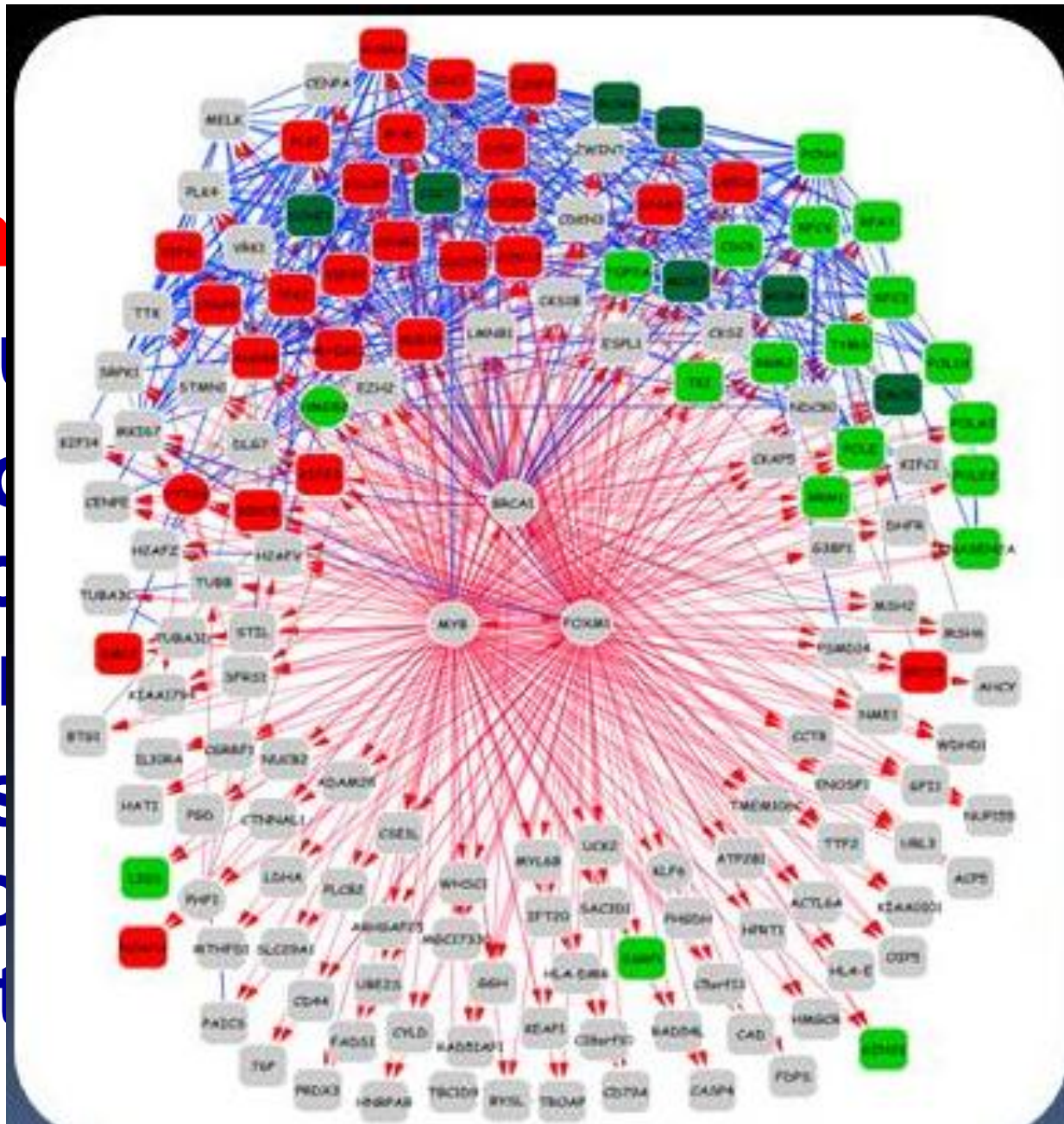
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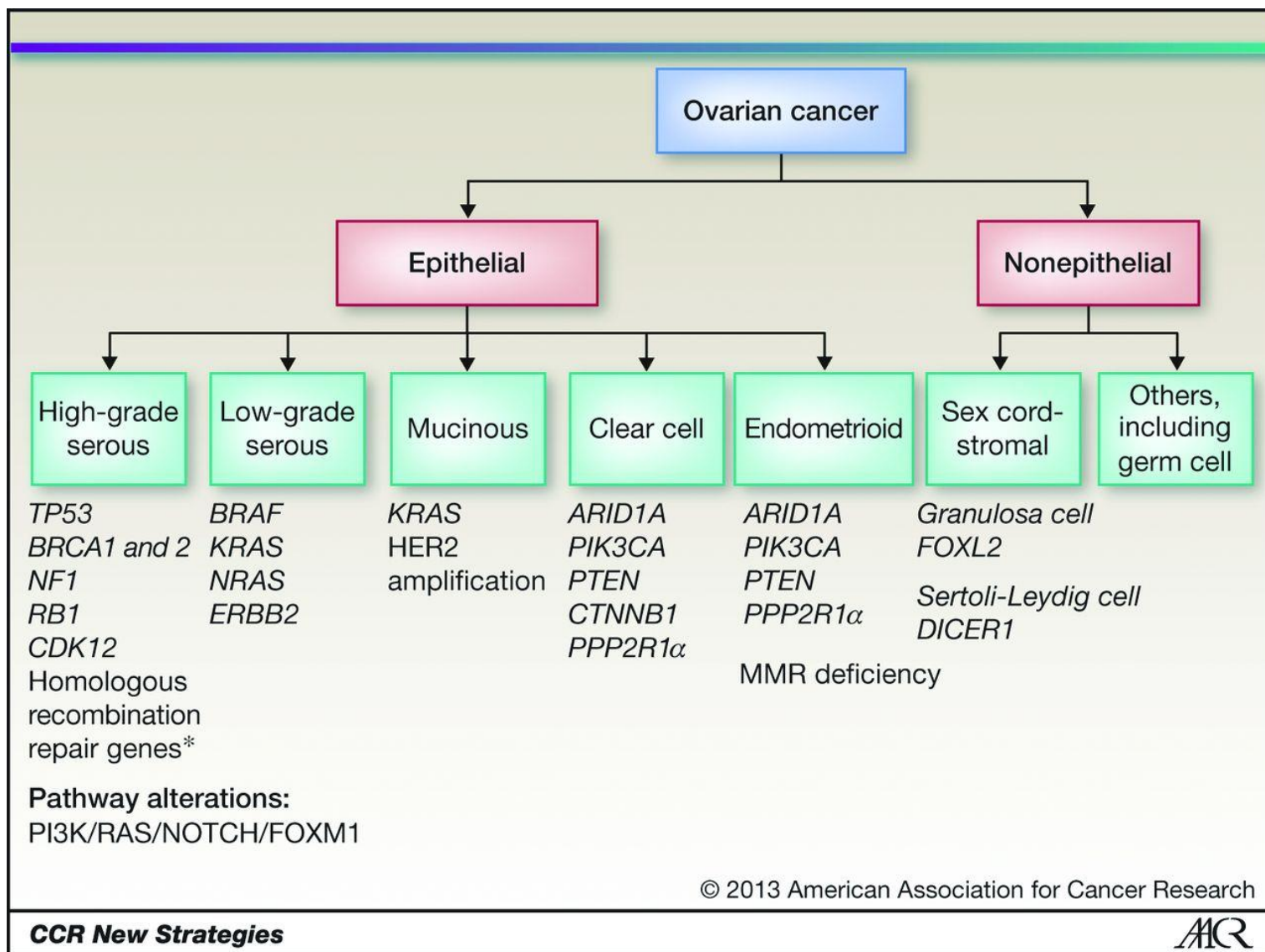


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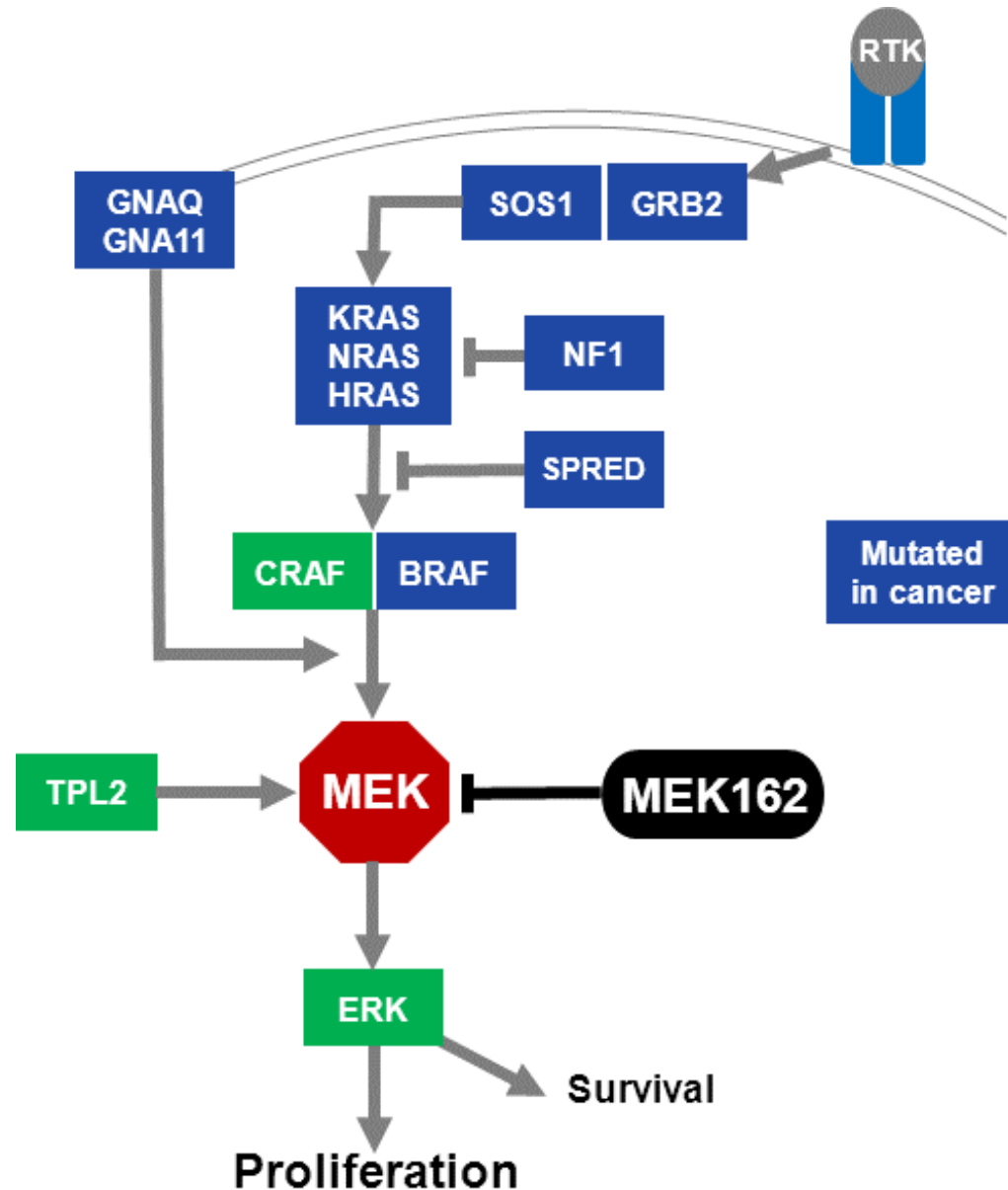
anismi
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Sottotipi istologici di carcinoma dell'ovaio e associate alterazioni molecolari.



Banerjee S , and Kaye S B Clin Cancer Res 2013;19:961-968

MEK Pathway e carcinoma sieroso ovarico di basso grado



Selumetinib nel trattamento del carcinoma ovarico sieroso di basso grado

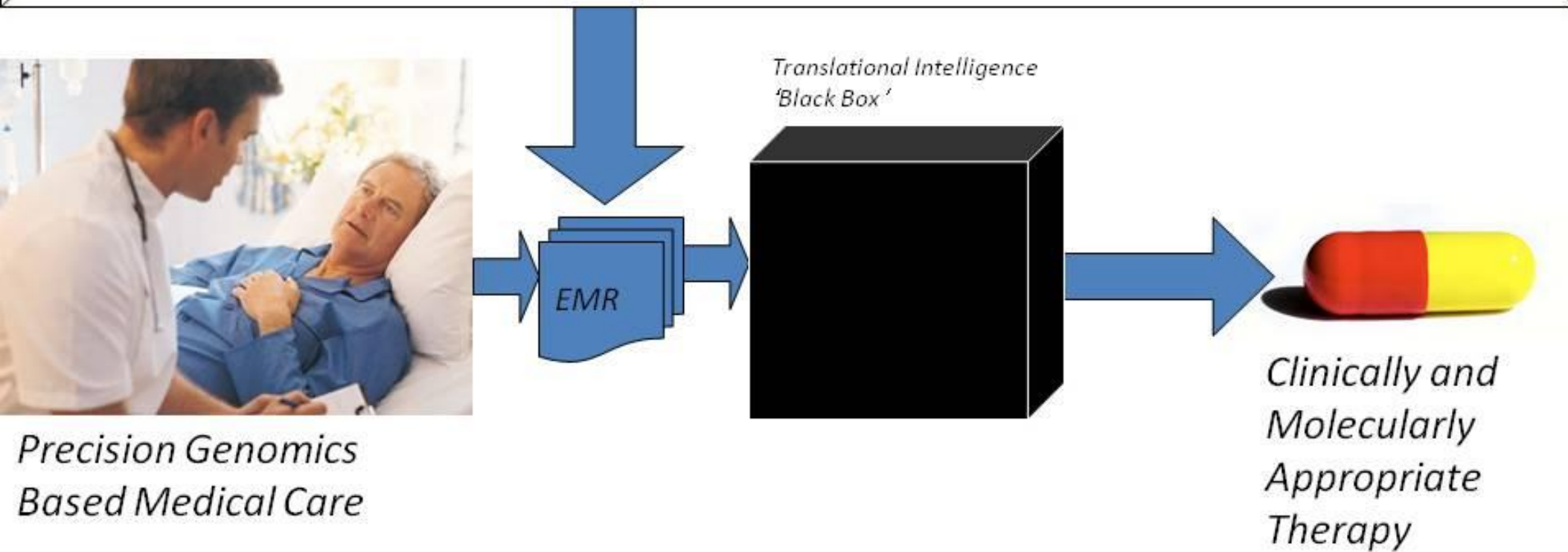
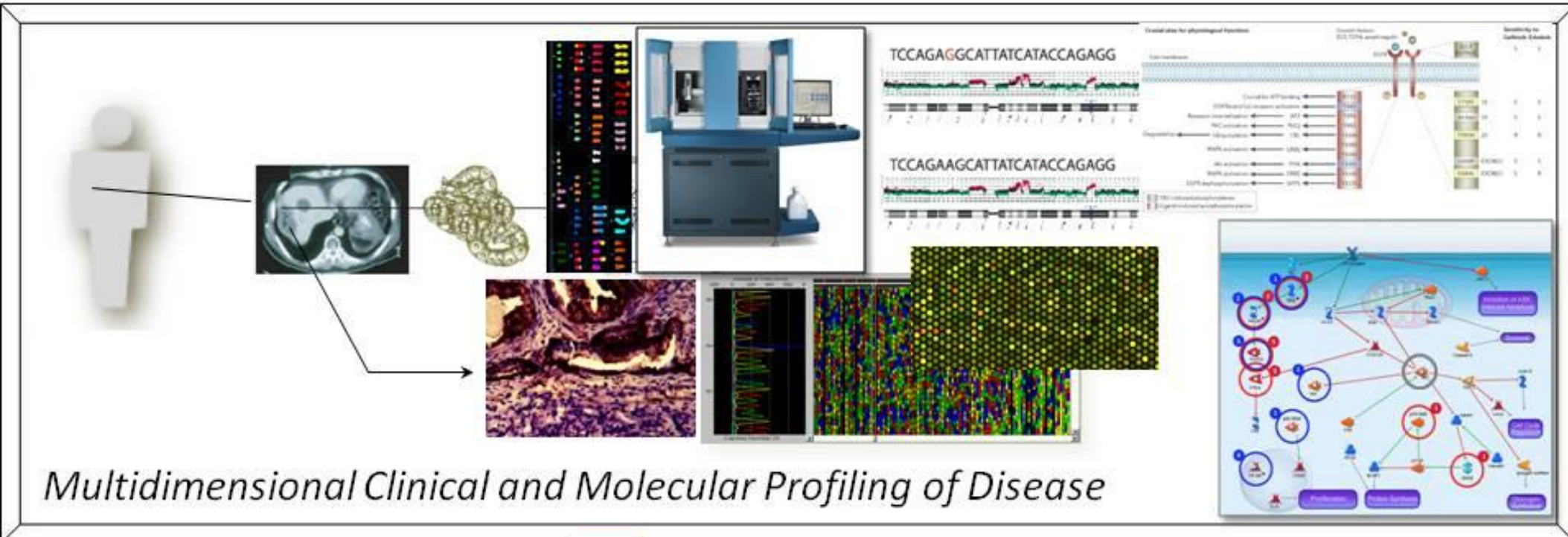
| Parameter | Chemotherapy | Hormonal therapy | Selumetinib |
|--------------------|--------------|------------------|--------------|
| N. Patients | 58 | 64 | 52 |
| N. Regimens | 108 | 89 | 52 |
| CR(%) | 1 | 7 | 2 |
| PR(%) | 2.8 | 2 | 13.5 |
| SD(%) | 60 | 62 | 65 |
| % Clinical benefit | 64 | 71 | 80.5 |
| Median PFS | 7.3 mo | 7.4 mo | 11 mo |
| % PFS>6 mos | 58 | 61 | 63 |

Gershenson et al, Gynecol Oncol 2009

Gershenson et al Gynecol Oncol 2012

Farley et al Lancet Oncol 2013

Medicina personalizzata



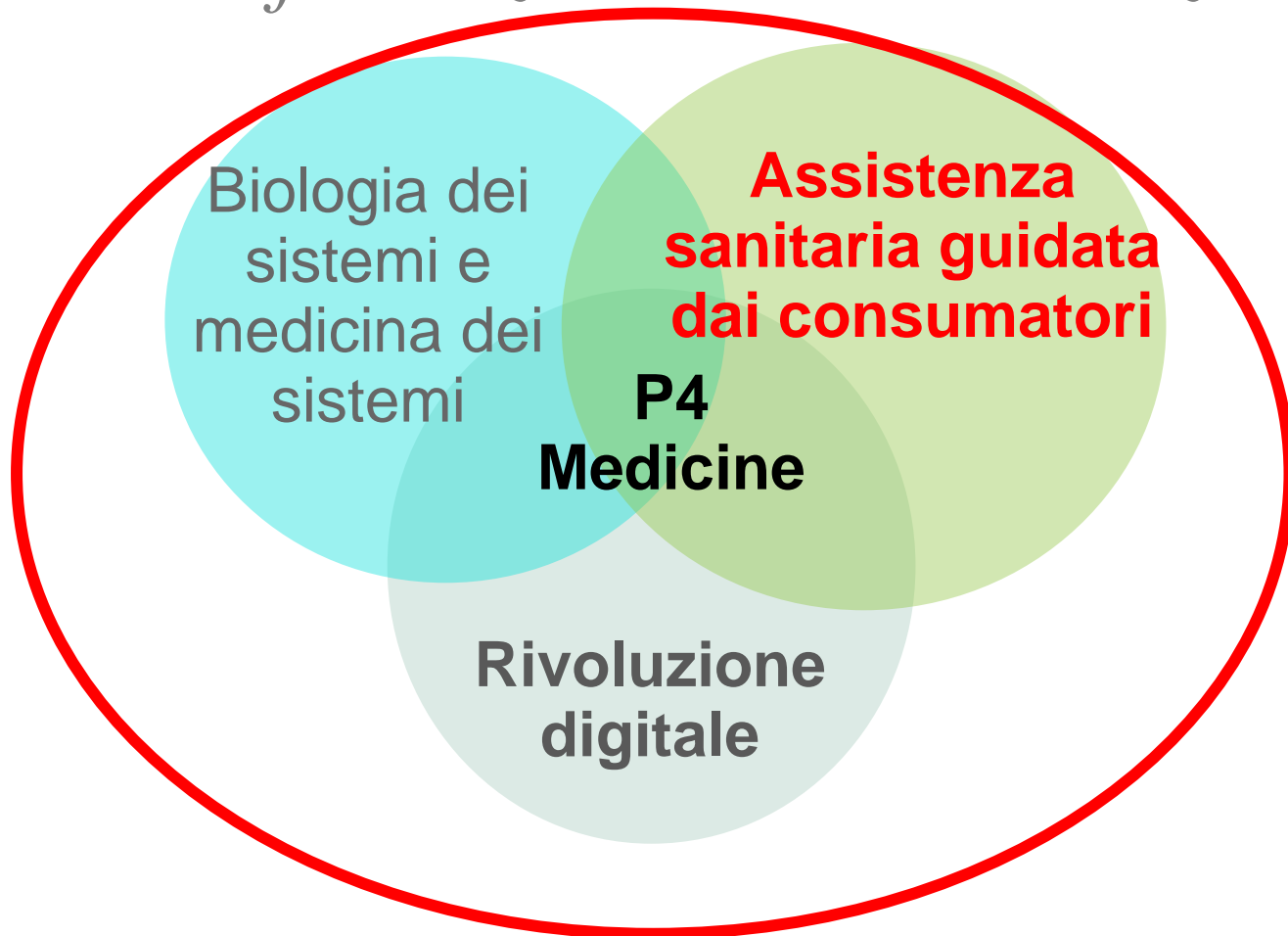
Il futuro per le pazienti



**"Here's my
sequence..."**

La emergente medicina delle 4 P : predittiva, preventiva, personalizzata e **partecipativa**

Tre “megatrends” convergenti
guidano la trasformazione dell’assistenza sanitaria





WORLD
OVARIAN
CANCER
DAY

May 8

ovariancancerday.org

Tweet with the [#WOCD](#) or
[#WorldOvarianCancerDay](#) hashtag
facebook.com/WorldOvarianCancerDay

Share this graphic and spread
awareness of ovarian cancer.



Bisogna essere informati e uniti contro il tumore ovarico





Globe athon

The Walk to End Women's Cancers
ONE STEP CAN MAKE A WORLD OF DIFFERENCE

