

**CAMBIARE
IL FUTURO
SI PUÒ**



Le novità della terapia medica Il carcinoma ovarico

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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....numeroso 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

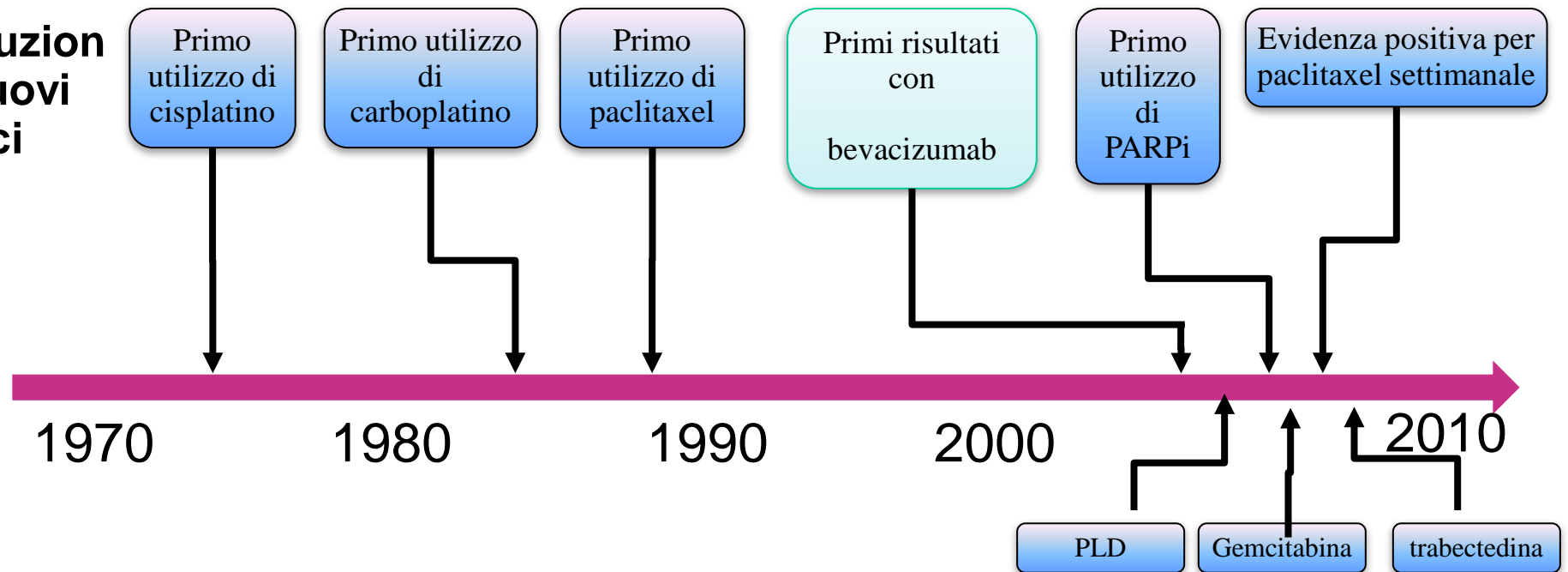
Progressi nella terapia del carcinoma ovarico

evoluzione degli ultimi 40 anni

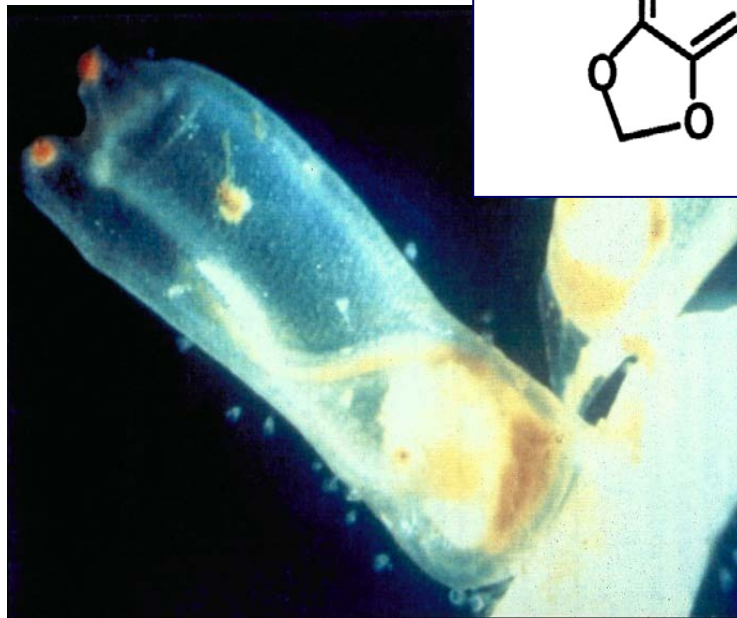
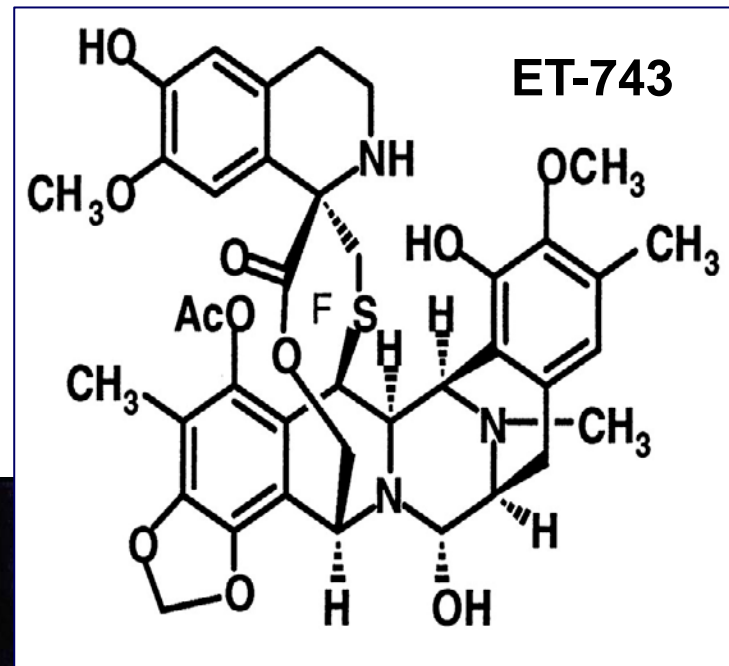
**Sopravvivenza
a 5 anni**

15% → 30% → 40% → 50%?

**Introduzione
e di nuovi
farmaci**



Trabectedina (ET743)



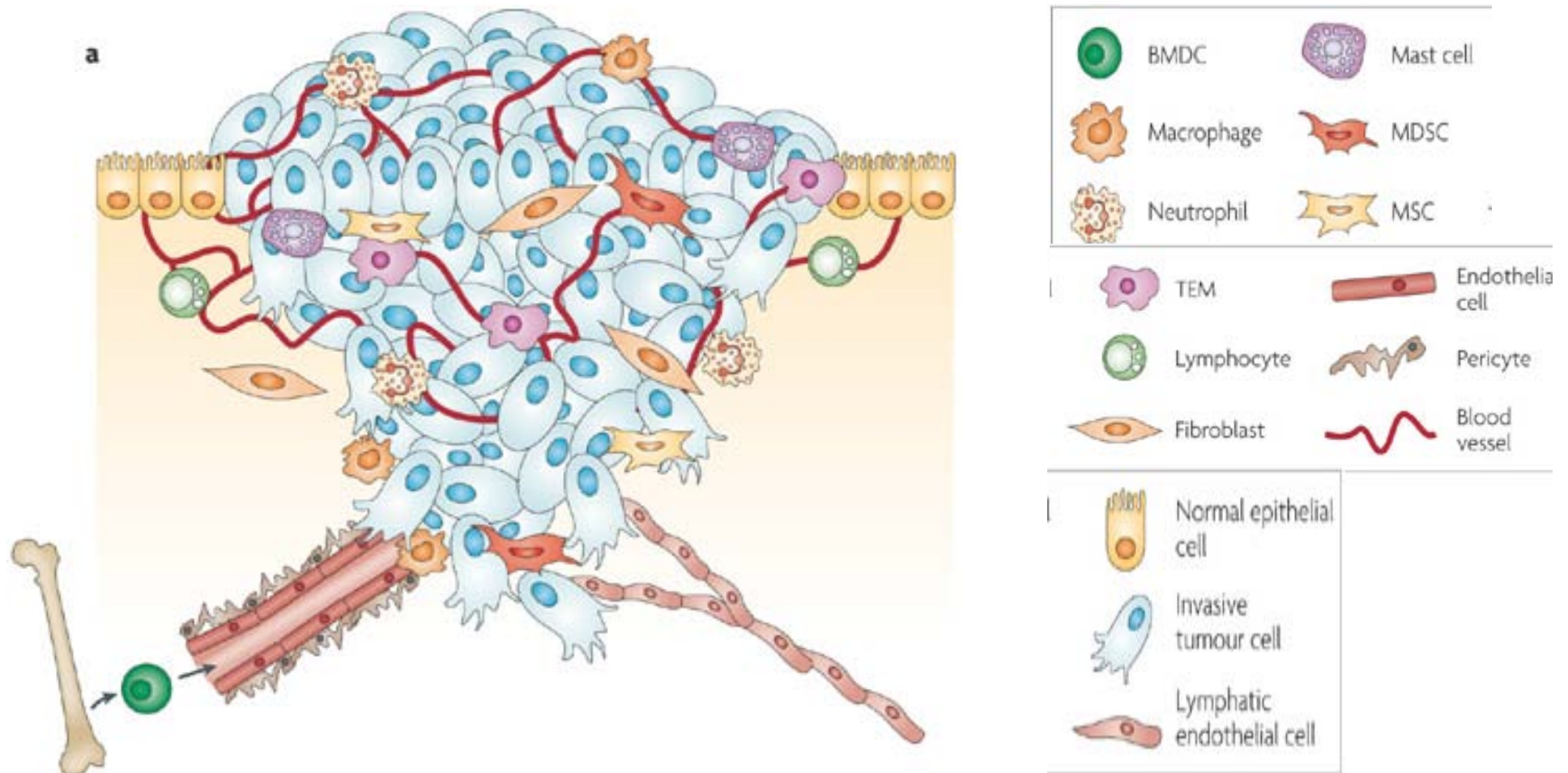
Ecteinascidia turbinata

Terapia Mirata

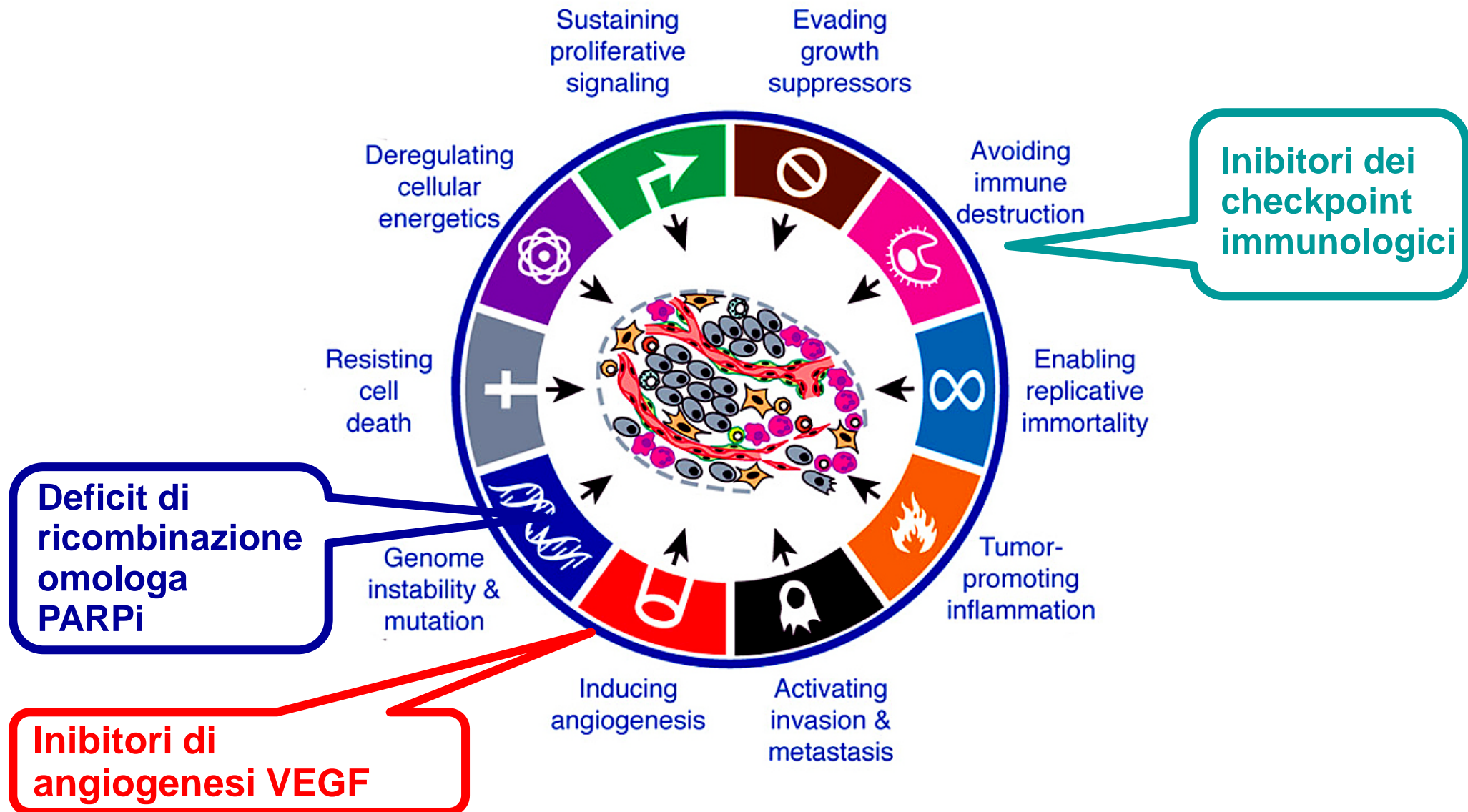


Terapia Mirata

Mirata contro uno specifico meccanismo alterato nella cellula o nel microambiente

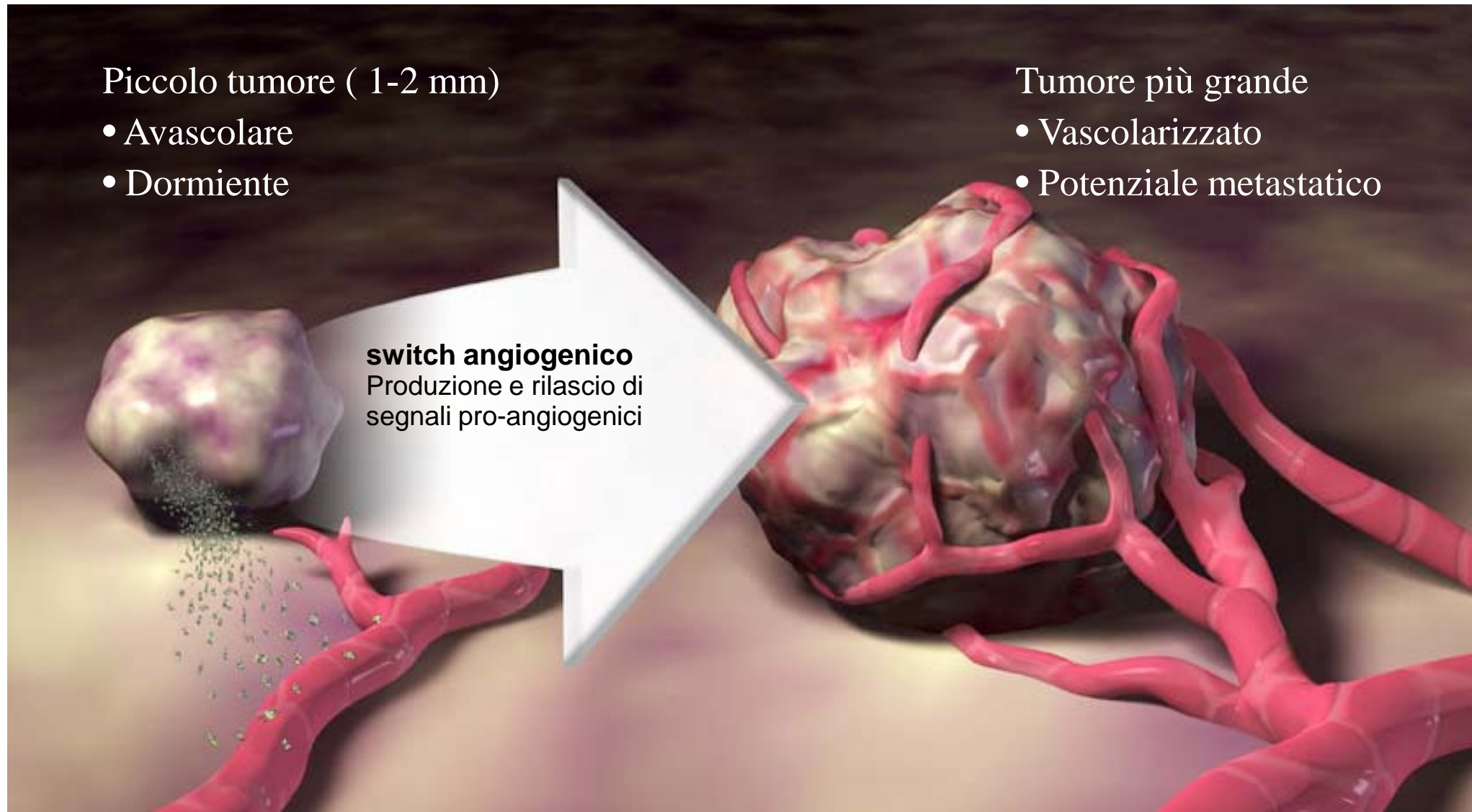


Carcinoma ovarico: target terapeutici



Modified according Hanahan and Weinberg, Cell 2011

Lo switch angiogenico nello sviluppo del tumore



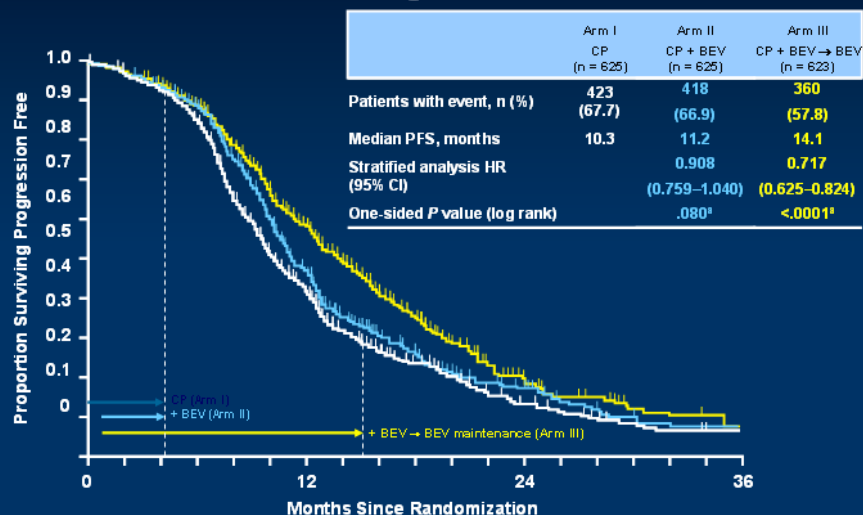
terapia Anti-VEGF

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.

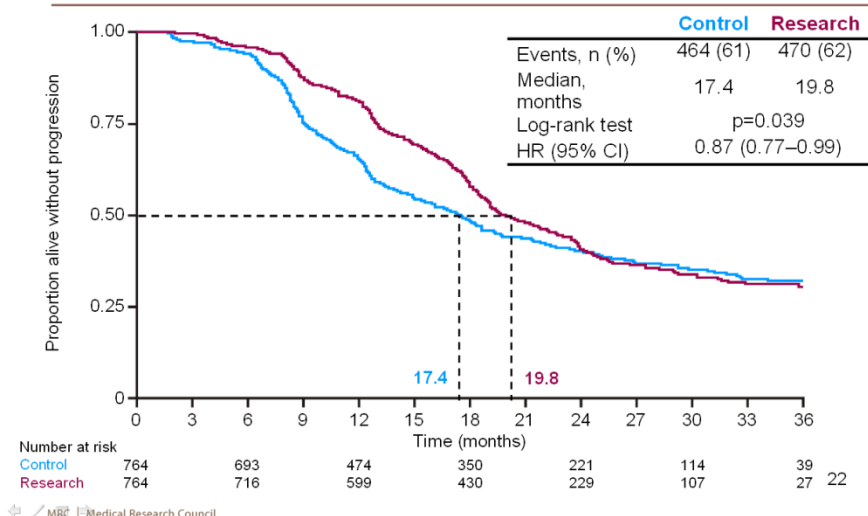
^a P-value boundary = 0.0116

ICON7

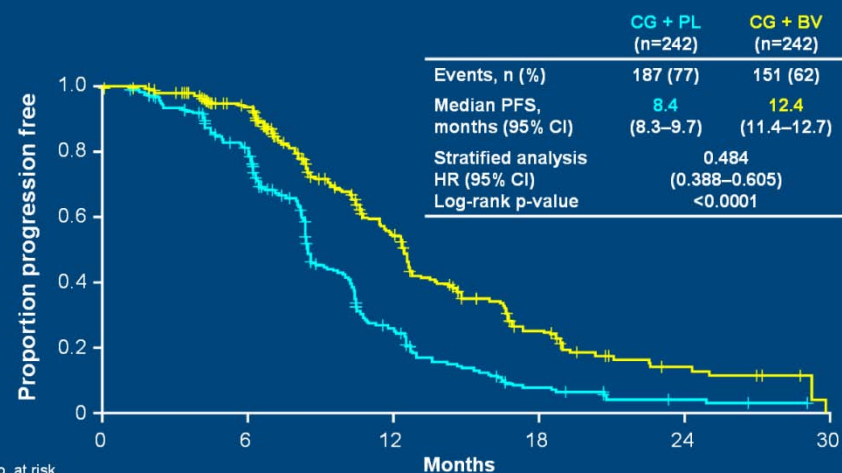
Bevacizumab in Ovarian Cancer

Updated PFS

MRC Clinical Trials Unit



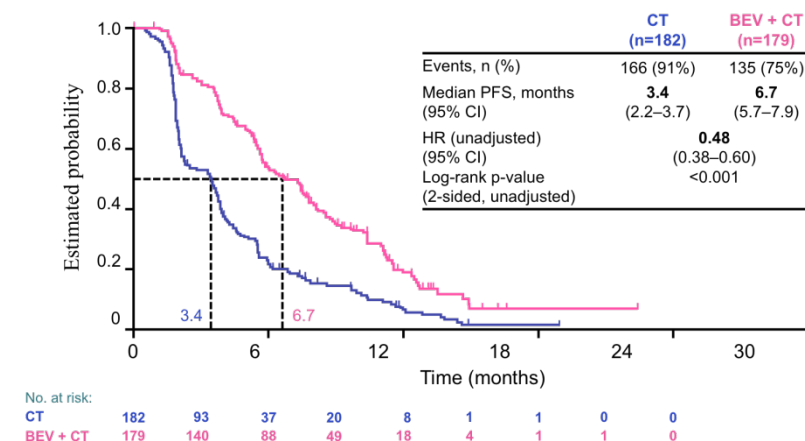
OCEANS: Primary analysis of PFS



PRESENTED AT: ASCO Annual Meeting

AURELIA

Progression-free survival



Attuali indicazioni per l'utilizzo di Avastin

- Avastin, in combinazione con carboplatino e paclitaxel e' indicato nel trattamento di prima linea del carcinoma epiteliale ovarico avanzato (stadio III B, IIIC, e IV), della tuba o primitivo del peritoneo.
- Avastin, in combinazione con carboplatino e gemcitabina e' indicato nel trattamento della prima recidiva platino-sensibile .

Study design

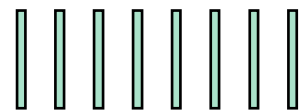
- **Epithelial ovarian, fallopian tube or primary peritoneal cancer:**

- Stage IIB–IV
- Grade 3 stage I/IIA
- Clear-cell carcinoma (any stage)
- Carcinosarcoma

- **Maximally debulked (prior neoadjuvant chemotherapy allowed)**

- **ECOG PS 0–2**

Dec 2010–May 2012:
1021 patients
enrolled



IV carboplatin AUC 5–6 q3w
(4–8 cycles)^a



IV paclitaxel 175 mg/m² d1 or
80 mg/m² d1, 8, 15 q3w (4–8 cycles)^b



BEV 15 or 7.5 mg/kg IV q3w for up to 36 cycles (2 years)
or until disease progression or unacceptable toxicity

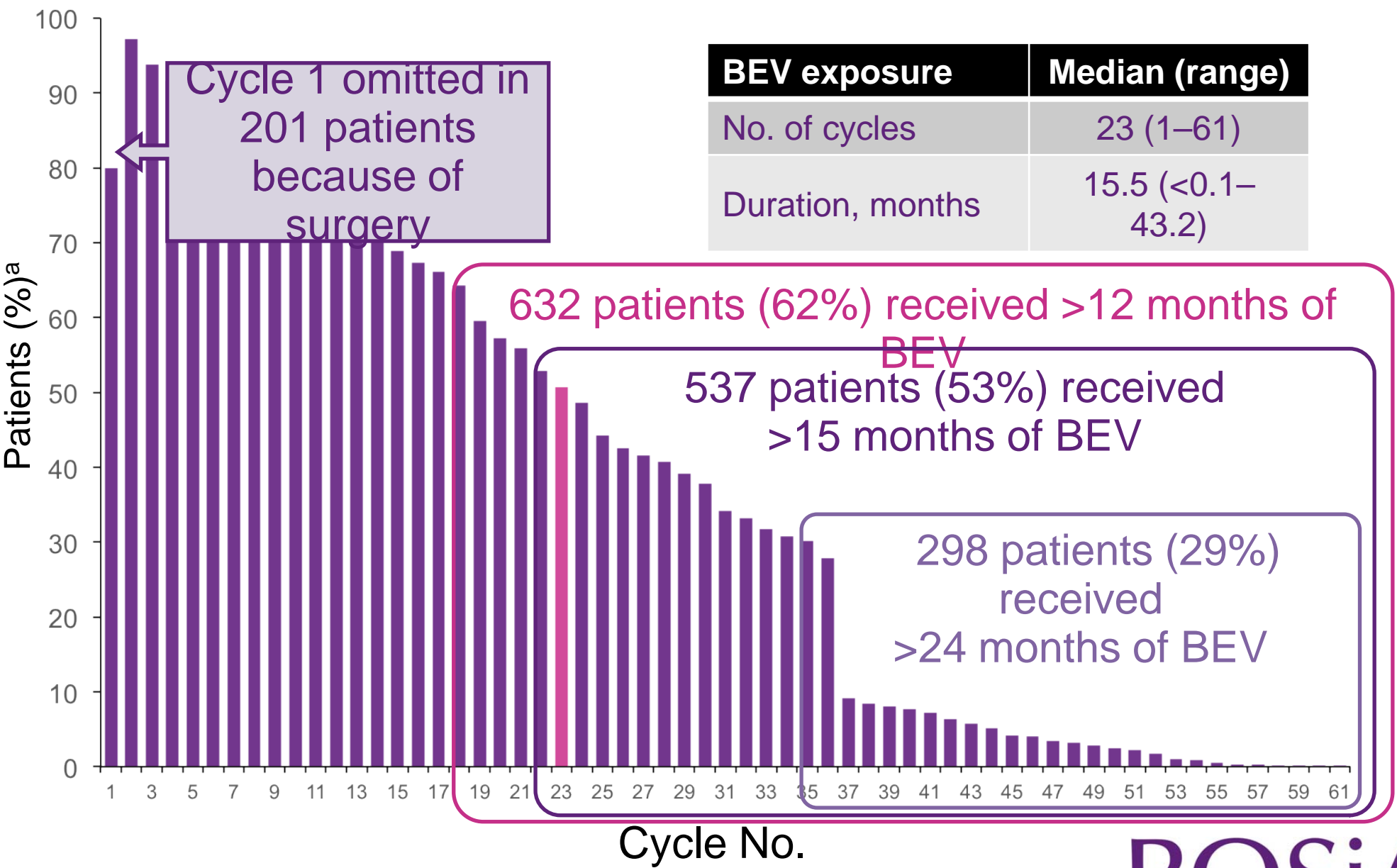
Patients without progression at cycle 36 could
continue therapy after discussion with the Steering Committee

- Primary endpoint: Safety (AEs by NCI-CTCAE version 4.03)
- Secondary endpoints: PFS, ORR, duration of response, overall survival
- Exploratory objectives: Optional translational research

^aCisplatin permitted in patients with hypersensitivity to carboplatin

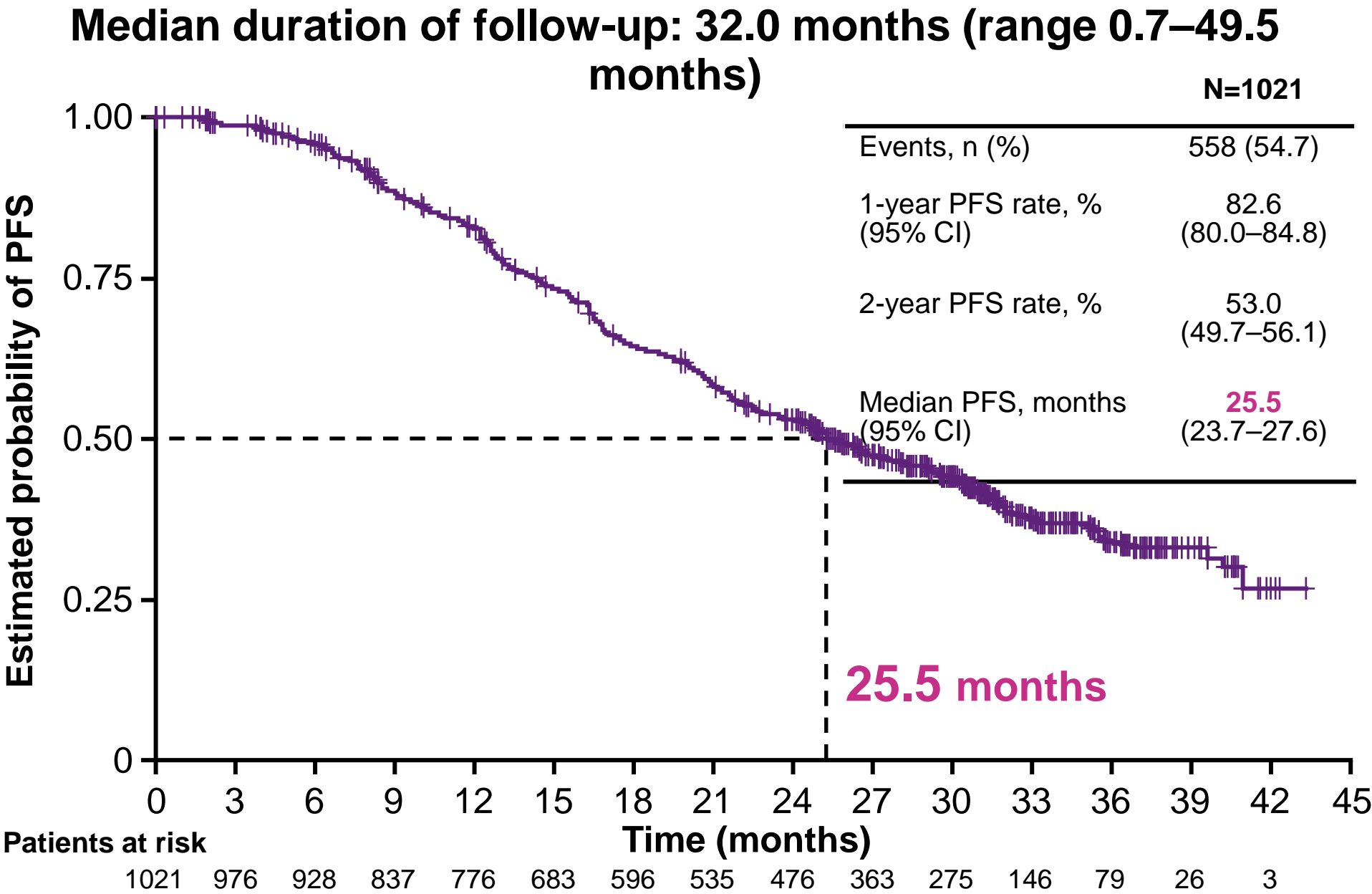
^bA change from one paclitaxel regimen to the alternative during the study was not permitted

Bevacizumab exposure by cycle



^aDenominator at each cycle is 1021

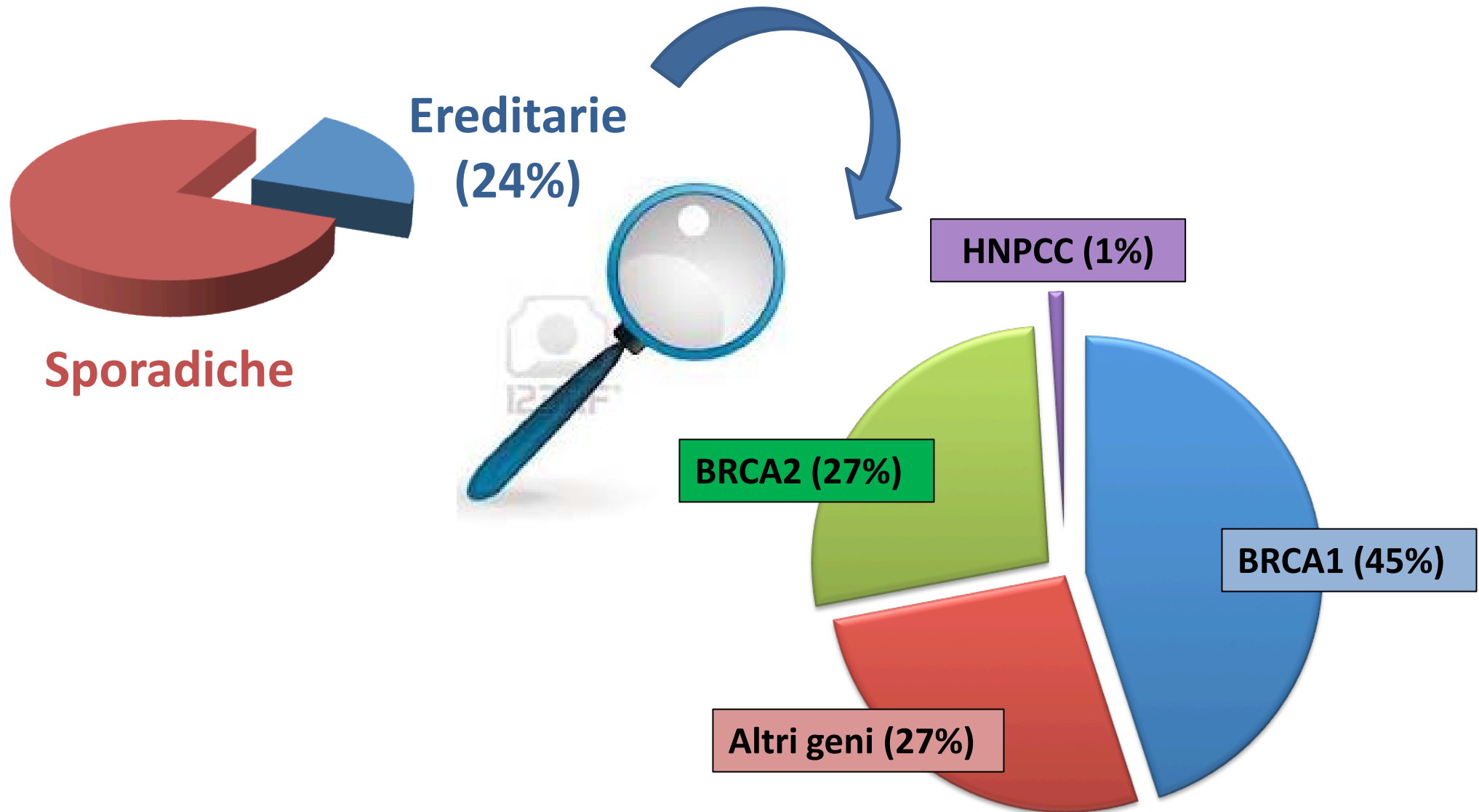
Progression-free survival (ITT population)



Data cut-off: 7 Dec 2014. ITT = intent-to-treat



CAUSE DI SUSCETTIBILITA' GENETICA nel TUMORE DELL'OVAIO



Geni BRCA

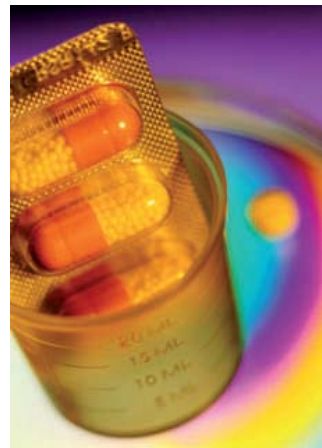
- BRCA : **B**Reast **C**Ancer geni di suscettibilità
- Due geni BRCA identificati: BRCA1 and BRCA2
- **Nonostante il nome si riferisca al tumore della mammella, sono responsabili del 15% dei carcinomi ovarici ,ma solo del 3-4 % dei carcinomi mammari.**

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

Stabilire il rischio

Stabilire la prognosi

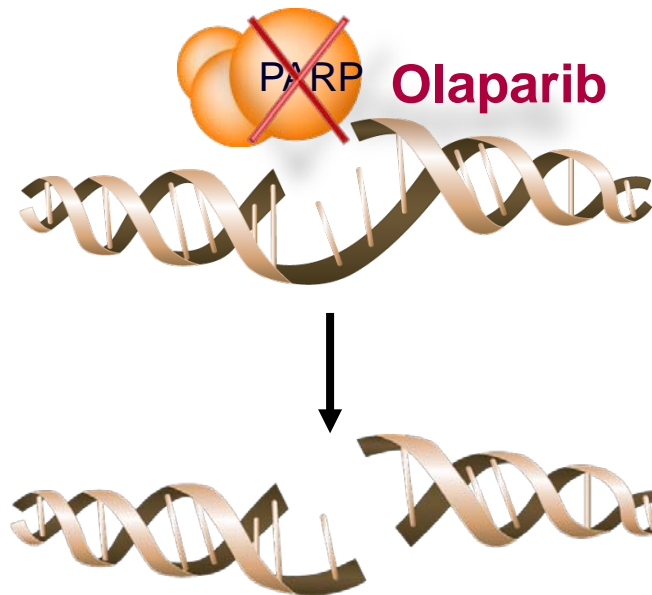
Decisioni terapeutiche



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

Il danno della singola elica e' frequente e PARP lo ripara

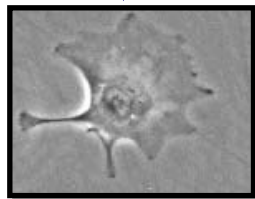
Durante la fase di replicazione il danno della singola elica non riparato viene convertito in danno della doppia elica



Cellula normale

Riparo mediante ricombinazione omologa

Sopravvivenza



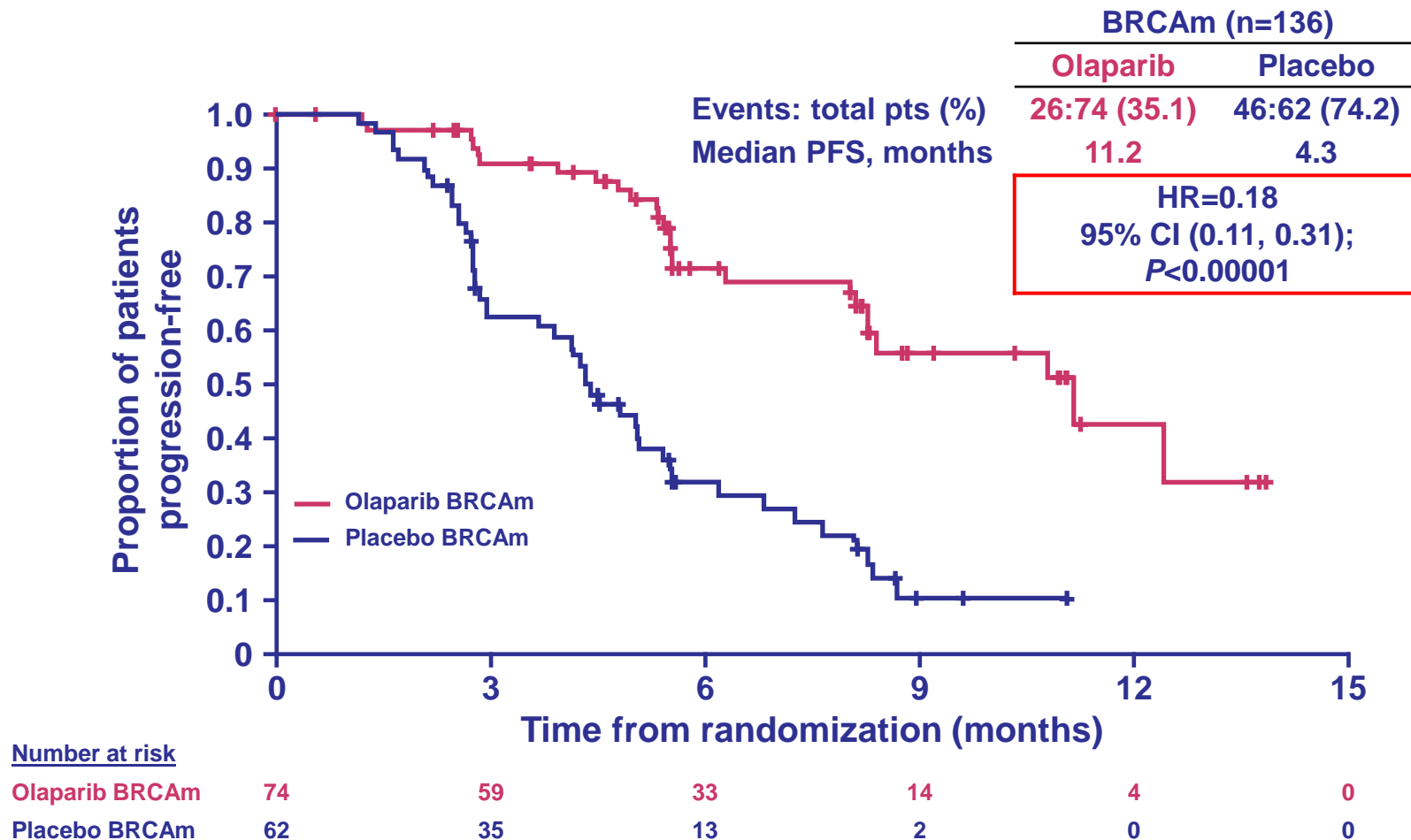
Cellula tumorale con deficit di riparo

Deficit di BRCA o di altre proteine della HR

Morte cellulare



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

Serie Generale n. 96 del 26-4-2016

LYNPARZA è indicato come monoterapia per il trattamento di mantenimento di pazienti adulte con recidiva platino-sensibile di carcinoma ovarico epiteliale sieroso di alto grado, di carcinoma alle tube di Falloppio o carcinoma peritoneale primario, BRCA-mutato (mutazione nella linea germinale e/o mutazione somatica), che rispondono (risposta completa o risposta parziale) alla chemioterapia a base di platino.

PARP Inhibitors in Clinical Trials

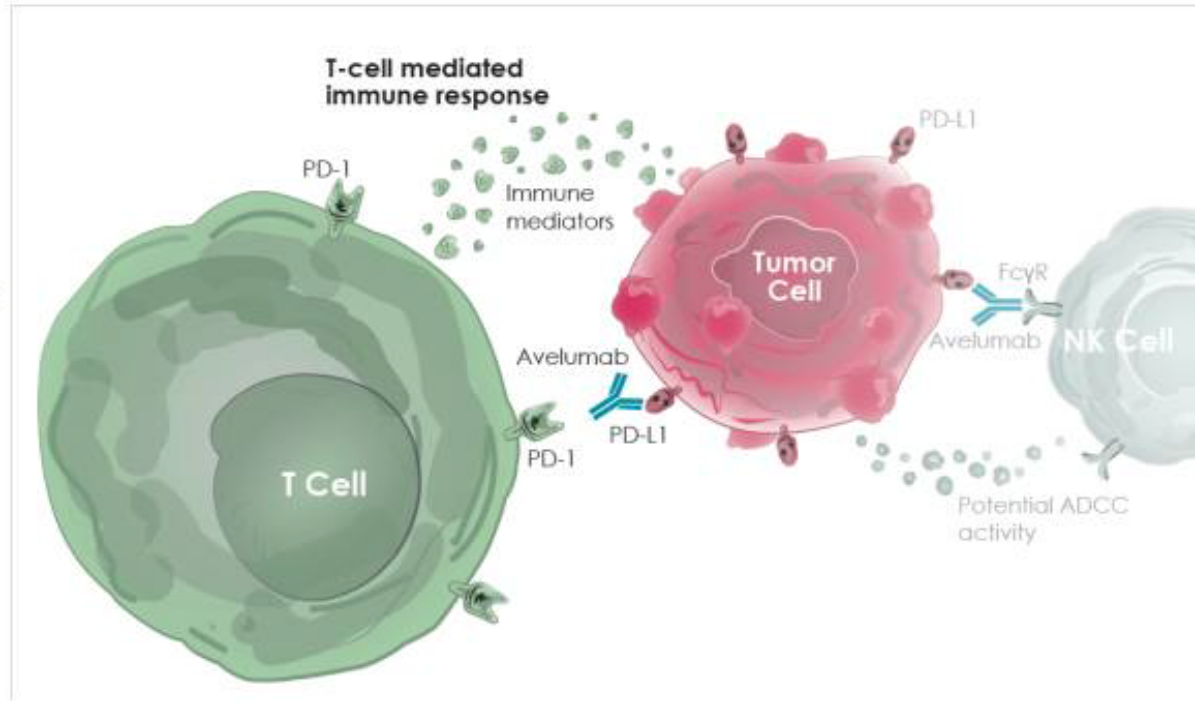
PF-01367 (Rucaparib)	Clovis/Pfizer	IV/oral
Olaparib	AZ	Oral
ABT 888 (Veliparib)	Abbott	Oral
INO-1001	Inotek	IV
GP1201	Eisai	Oral
CEP 9722	Cephalon	Oral
MK 4827 (Niraparib)	Tesaro	Oral
BMN 673	BioMarin	Oral

Any other choice for the future ?



Avelumab (MSB0010718C)

- Fully human anti-PD-L1 IgG1 antibody
- Binds PD-L1
 - Inhibits PD-1/PD-L1 interactions
 - Leaves PD-1/PD-L2 pathway intact
- Half-life of ~ 3.5 to 4.8 days; >95% TO over whole dosing period
- ADCC may contribute to activity, as shown in preclinical models^{1,2}
- Doses up to 20 mg/kg Q2W safely administered
- Antitumor activity in lung, gastric, bladder, and other malignancies



*Avelumab is the proposed international nonproprietary name (INN) for the anti-PD-L1 monoclonal antibody (MSB0010718C).
1. Heery CR, et al. J Clin Oncol 2014;32(suppl):abstract 3064; 2. Lepage LM, et al. AACR Annual Meeting. 2015:abstract 1316.

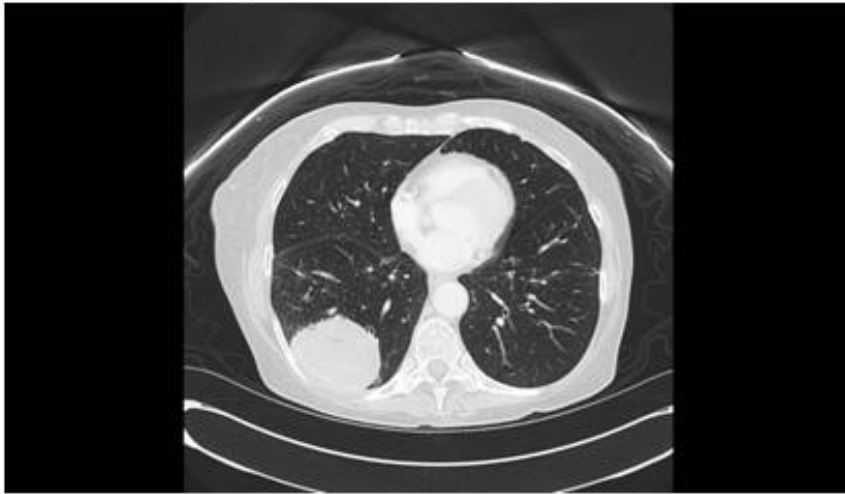
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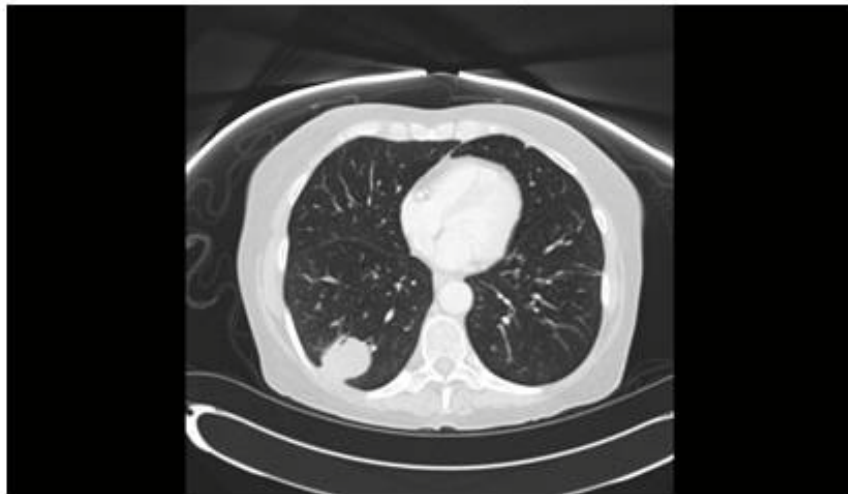
ASCO Annual '15 Meeting

PR in metastatic clear cell

Baseline: 69 mm RLL lesion



Week 25: 41 mm (-40.6%)



- 65 years old; 6 prior lines for metastatic disease
- 4th assessment cycle, still on treatment
- Safety: well tolerated (grade 1-2 rigors; grade 1 flu-like symptoms and fatigue)
- PR by RECIST ongoing at time of analysis

Courtesy of Dr. S. Ejadi, Scottsdale, AZ

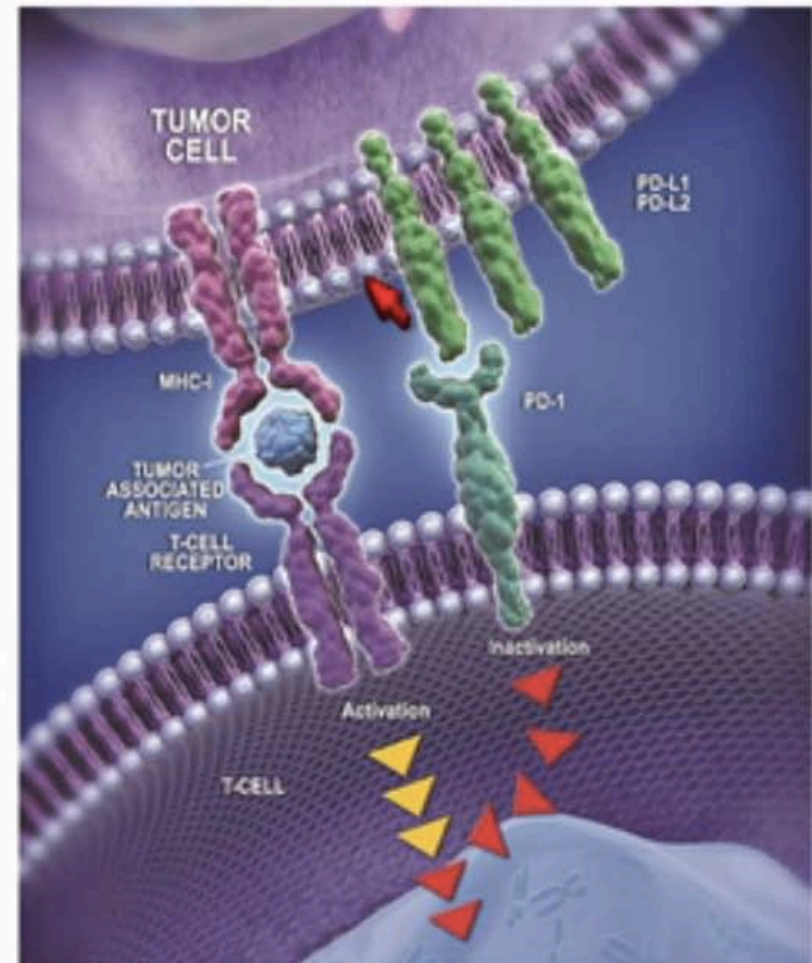
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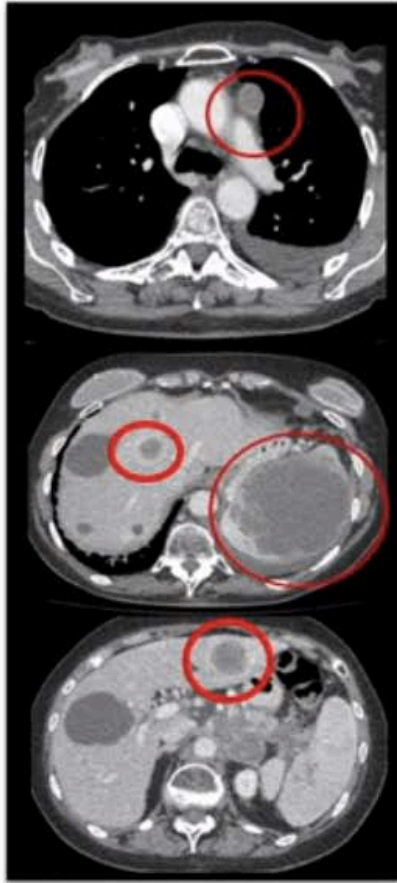
Pembrolizumab

Programmed Cell Death 1 (PD-1)

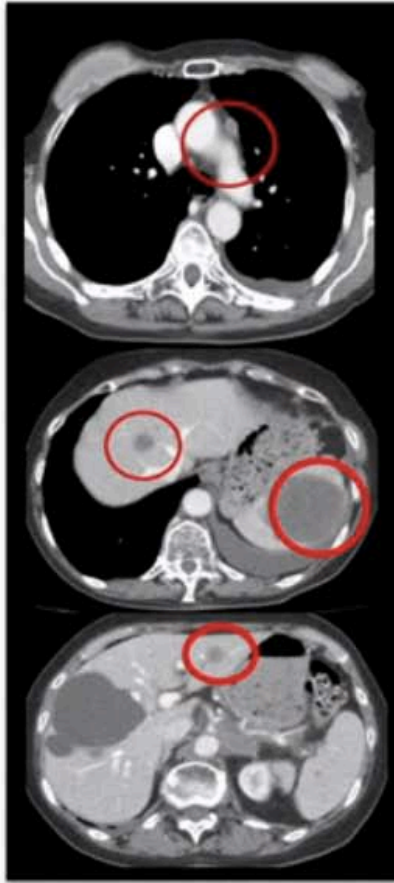
- Inhibitory receptor expressed primarily on the surface of activated T cells
- Binding of PD-1 to one of its ligands, PD-L1 or PD-L2, can inhibit tumor-specific T-cell responses
- Tumors can exploit this pathway to escape antitumor immunosurveillance



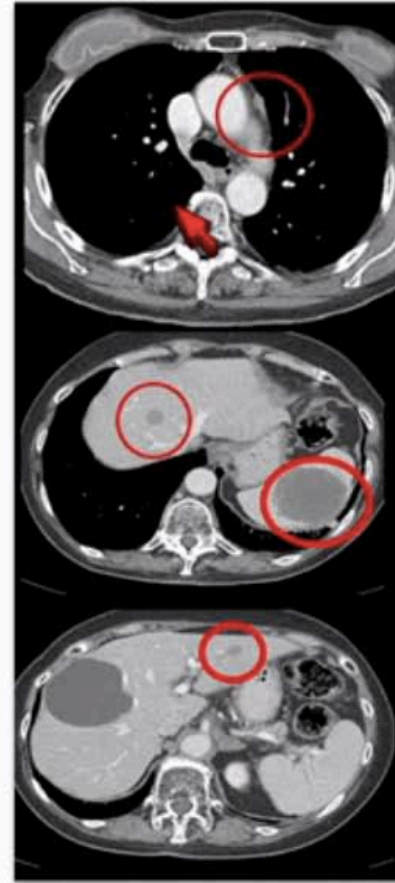
Example of Response in Ovarian Cancer



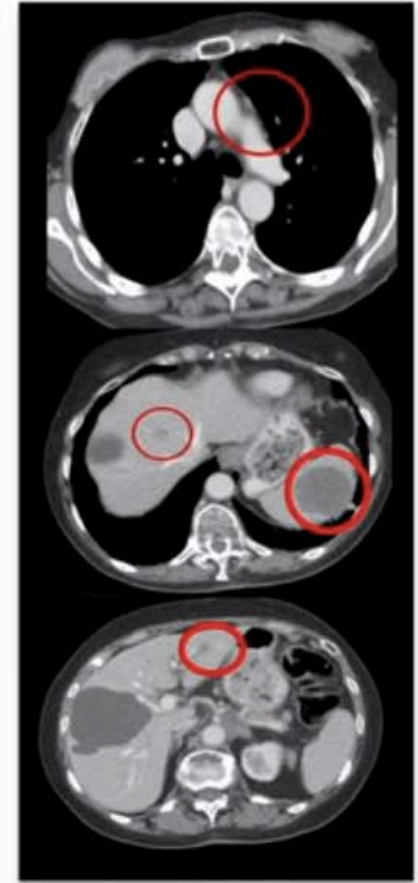
Baseline



Cycle 6 ↓42% = PR



Cycle 10 ↓56% = PR



Cycle 14 ↓56% = PR

Conclusioni

- **Angiogenesi**: l'uso prolungato di bevacizumab ha determinato la sopravvivenza libera da progressione piu' lunga mai riportata con l'uso di bevacizumab in prima linea
- **Olaparib** e' una nuova terapia standard nella recidiva platino-sensibile della paziente con mutazione BRCA
- Risultati promettenti con **immunoterapia**



THE FUTURE LOOKS BRIGHT...

