ASL 1 IMPERIESE

ONCOGERIATRIA

Qualità e quantità della vita: una problematica clinica

Lazzaro M Repetto
SC Oncologia - Ospedale Sanremo

ASL 1 IMPERIESE

PREMESSA

Incidenza e Mortalità per Tumore sono in calo

Questo è vero per il giovane adulto,
meno vero per l'anziano

Il margine di miglioramento è molto grande,
spetta ai clinici attuarlo

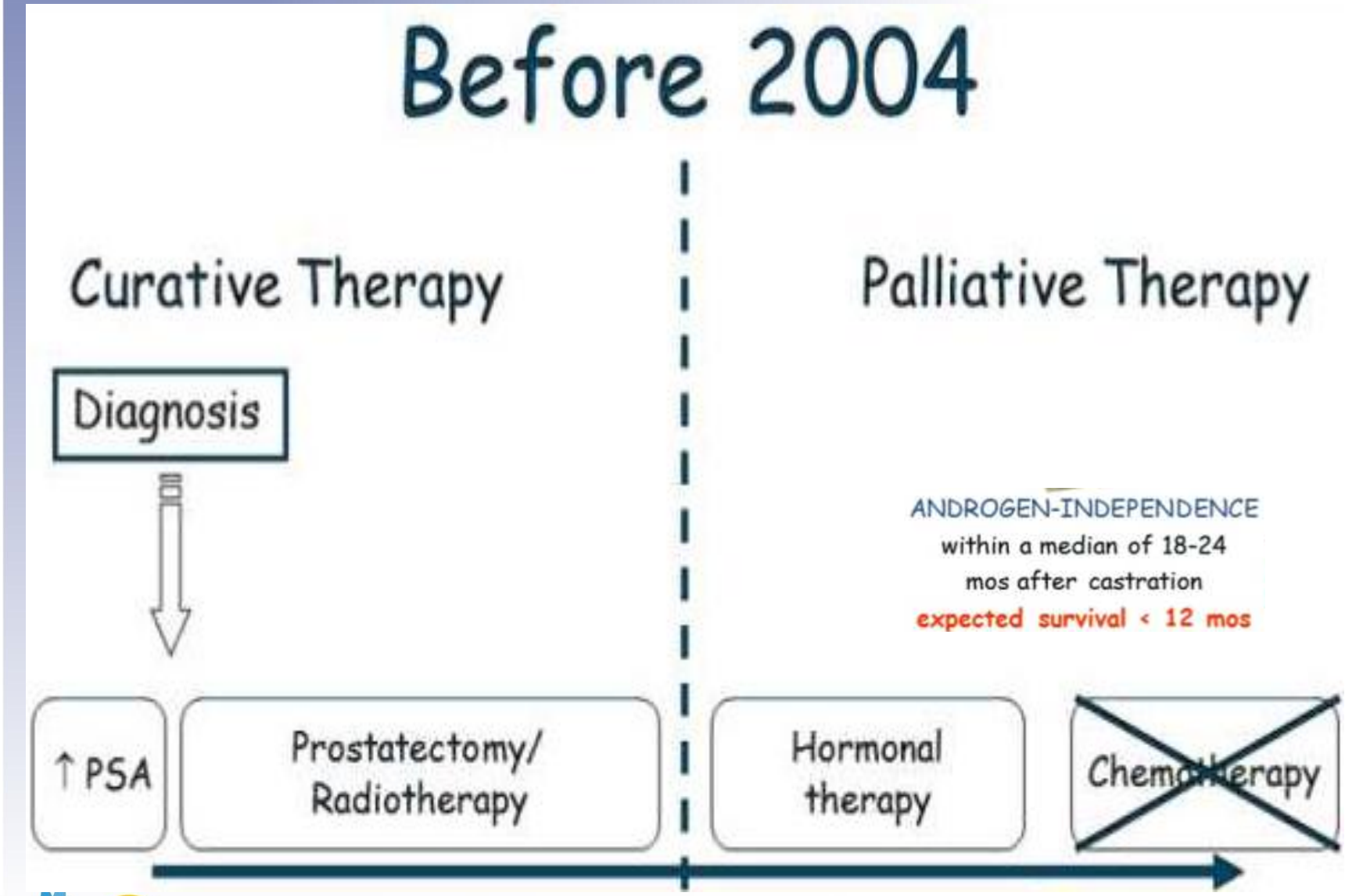
ASL 1 IMPERIESE

..alcuni esempi

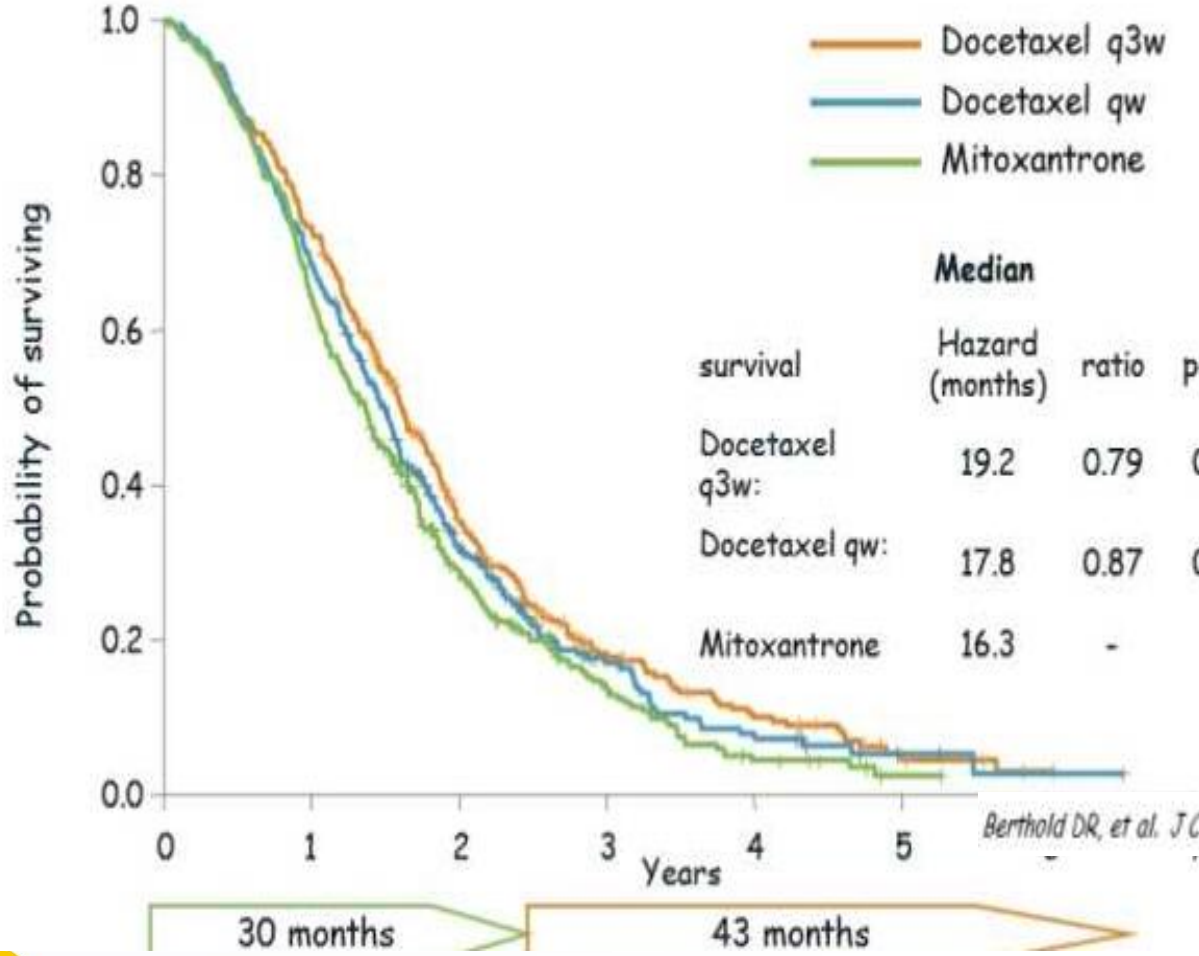
- Ca Prostata
- Ca Polmone
- Ca Colonretto
- Ca Mammella

Ca Prostata

- 1 Tumore nel maschio, superato il polmone
- Ca. 30% delle diagnosi di Tum. nel maschio
- Ca. 3/3.5% delle morti x Tum. nel maschio
- Prognosi <12m per Malattia Avanzata/Metastatica
  - **Assikis VJ ,et al.Semin Oncol 2004; 31:26-32**


Before 2004
Curative Therapy
Palliative Therapy
Diagnosis
ANDROGEN-INDEPENDENCE
within a median of 18-24
mos after castration
expected survival < 12 mos
↑ PSA
Prostatectomy/
Radiotherapy
Hormonal
therapy
Chemotherapy

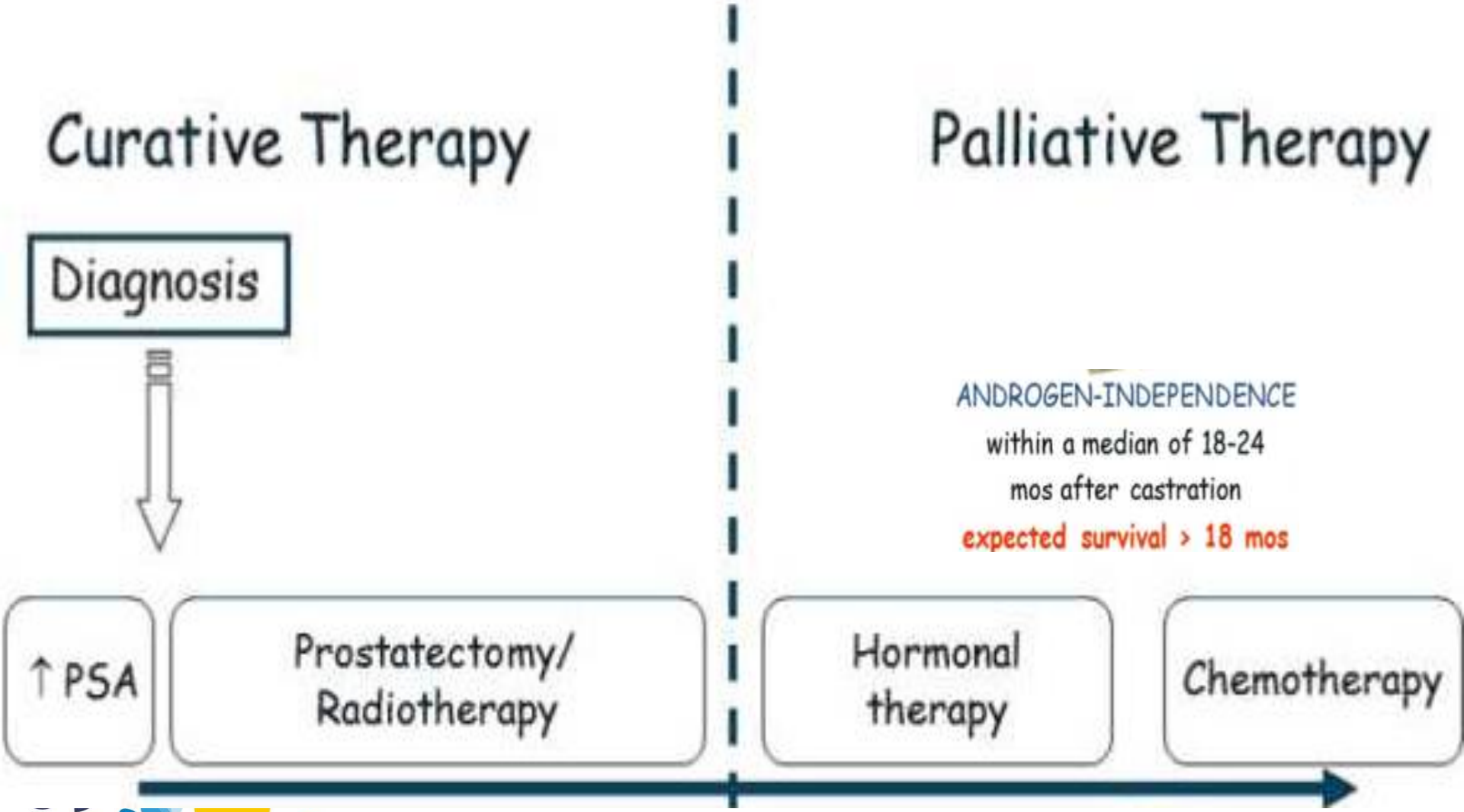
TAX 327 updated OS analysis: 4 add. yrs FU



survival	Median Hazard (months)	ratio	p-value
Docetaxel q3w:	19.2	0.79	0.004
Docetaxel qw:	17.8	0.87	0.086
Mitoxantrone	16.3	-	-

Berthold DR, et al. J Clin Oncol 2008;26:242-245

After 2004


Curative Therapy
Palliative Therapy
Diagnosis
ANDROGEN-INDEPENDENCE
within a median of 18-24
mos after castration
expected survival > 18 mos
↑ PSA
Prostatectomy/
Radiotherapy
Hormonal
therapy
Chemotherapy

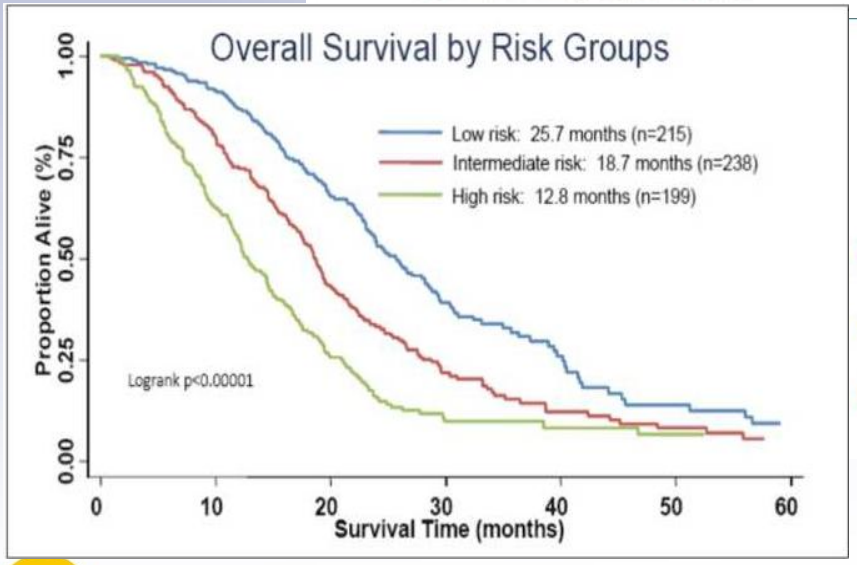
ASL 1 IMPERIESE

Simplified Model

Armstrong et al Clin Canc Res 2007;13:6396-403

Risk factors

- Anemia (hemoglobin <13.0) *laboratory data*
- Progression by bone scan criteria *clin. data*
- Visceral metastases *clin. data*
- Presence of clinically significant pain (TAX 327 definition) *clin.* data

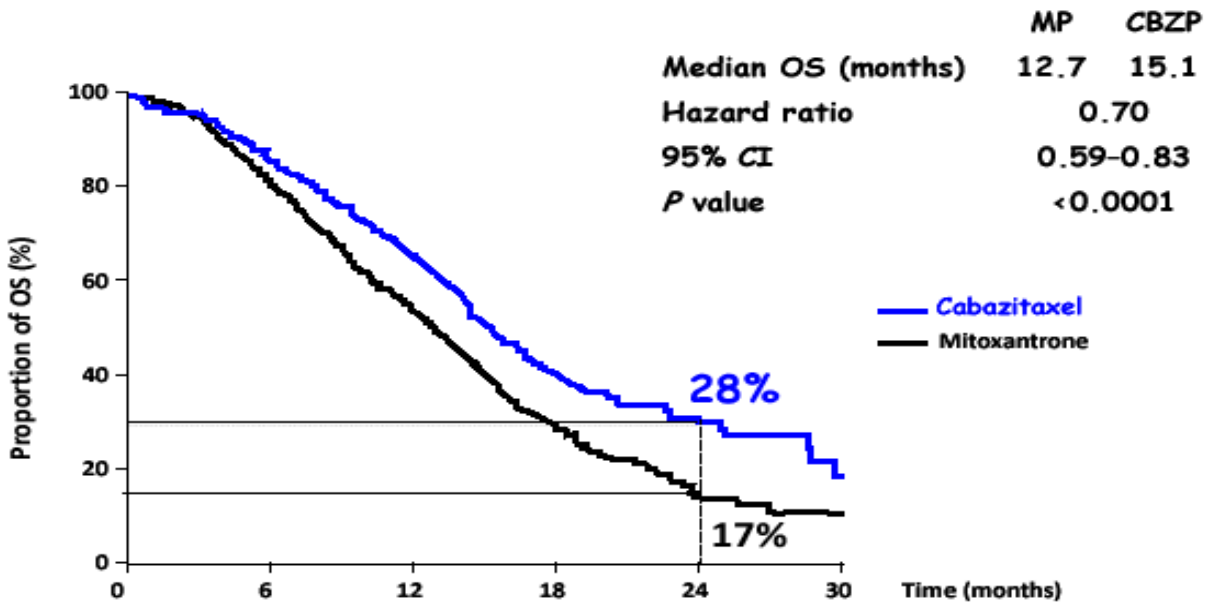


Simplified Model

- **Low Risk**: 0-1 risk factors
- **Intermediate** Risk: 2 risk factors
- **High Risk**: 3-4 risk factors

ASL 1 IMPERIESE

Phase III TROPIC study: Overall Survival



Cabazitaxel

Primo chemioterapico approvato in 2 linea
Prolunga significativamente OS (2,5 m), PFS e risposta PSA
Cambiamento della storia naturale della neoplasia

HRPC→CRPC: not only a "word problem"….

Alla luce delle nuove conoscenze è stata sostituita la definizione di Carcinoma Prostatico Ormono-Resistente

Anti-androgeni e analoghi LHRH **non sono attivi** una volta che i pazienti non rispondono alla ADT

Rimane guidato dagli androgeni anche a livelli di testosterone bassi

- **Il tumore cresce e progredisce anche se il livello di testosteronemia rimane al sotto della soglia di castrazione (20ng/dl)**
- Multipli meccanismi di resistenza

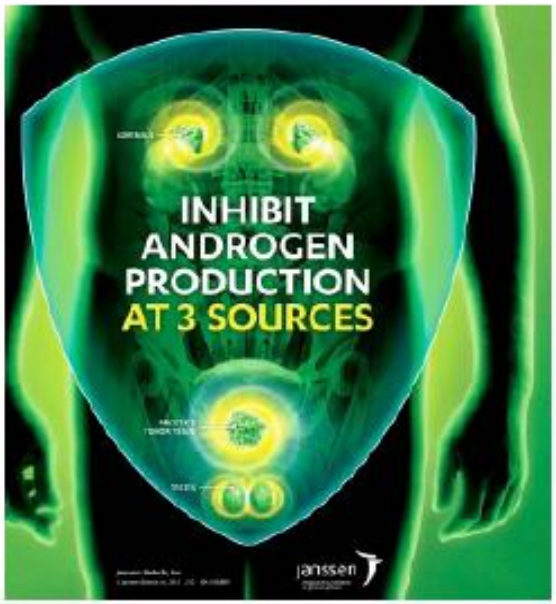
Sonpavde G. and Sternberg C.N. , Current Opinion in Urology - May 2011 - Volume 21 - Issue 3 - p 241–247

Abiraterone Acetato: la molecola

Inibitore selettivo della sintesi degli Androgeni

Gli androgeni che stimolano la proliferazione tumorale sono prodotti in tre siti critici:

- *Testicoli;*
- *Ghiandole surrenali;*
- *Cellule tumorali prostatiche.*



Abiraterone blocca la sintesi degli androgeni
in tutti i possibili siti di produzione

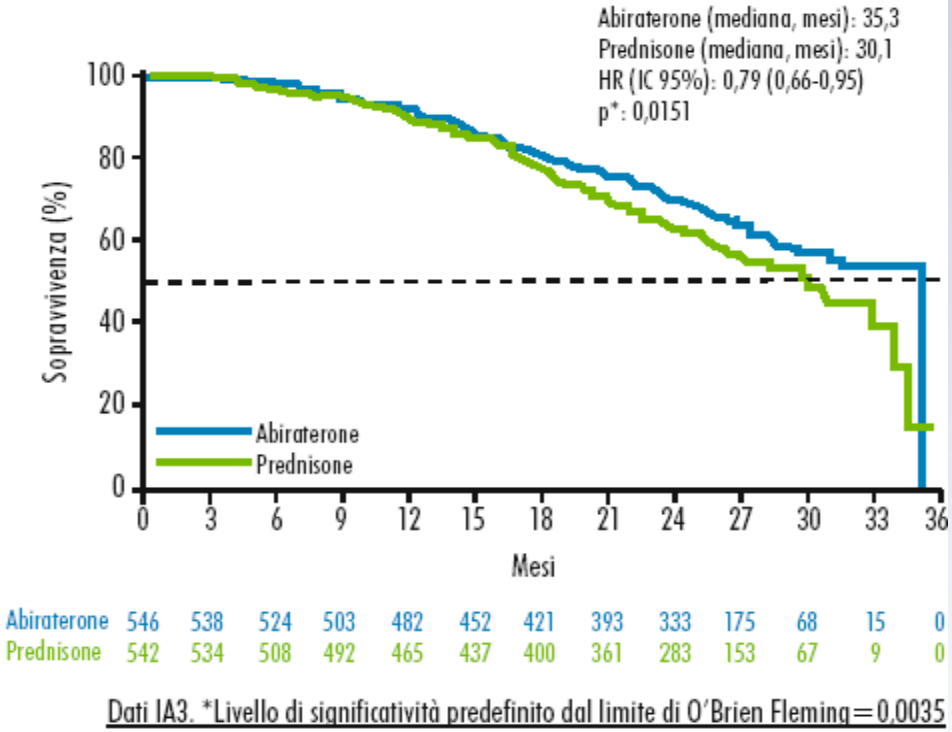
Attard G et al, J Clin Oncol, 2008; Attard G et al. J Clin Oncol. 2009; Reid AH et al. J Clin Oncol. 2010; Ryan C et al, J Clin Oncol, 2009; Danila D et al, J Clin Oncol, 2010.

2013 GENITOURINARY CANCERS SYMPOSIUM ASCO

Updated interim analysis (IA) of COU-AA-302, a randomized phase III study of abiraterone acetate (AA) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) without prior chemotherapy.

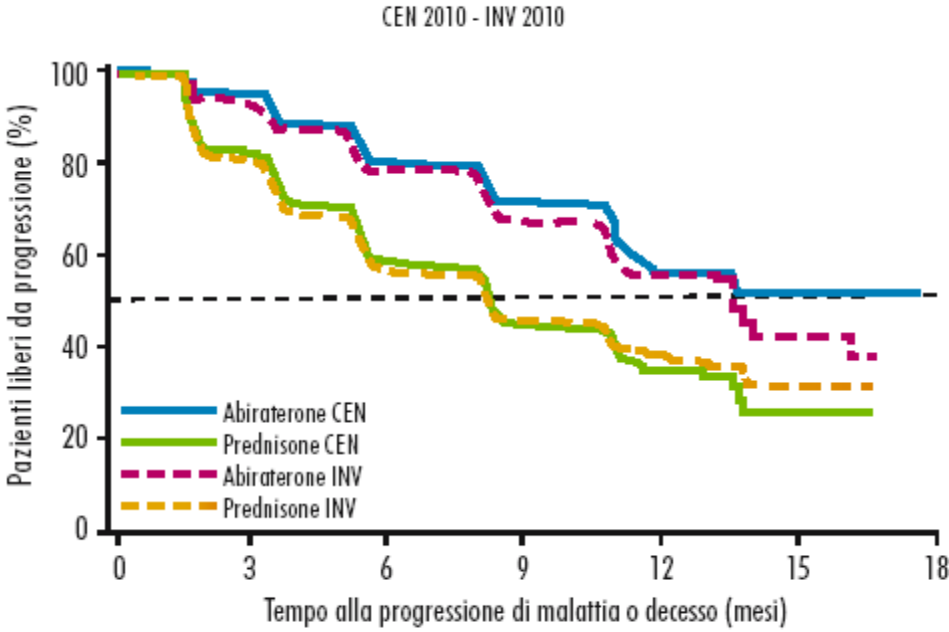
Diana E. Rathkopf et al.

Figura 1 - Overall Survival



Dati IA3. *Livello di significatività predefinito dal limite di O'Brien Fleming=0,0035

Figura 2 - PFS radiologica centralizzata vs locale[1]



CEN: revisione centralizzata; INV: revisione degli sperimentatori

Risultati presentati per la prima volta all'ASCO 2012: vantaggio per AA: interruzione dello studio e possibile cross-over; dati non erano abbastanza maturi per riportare mOS e rPFS

La 3 *interim analysis* (425 eventi) mostra vantaggio statisticamente significativo per **rPFS** (16.5 vs 8.3 m p<.0001) e trend positivo per **OS** 35,3 vs 30,1m (p=.0151).

Vantaggio rPFS : 8 m COU AA 302 e 2 m COU-AA-301. **Vantaggio OS** : 5m per entrambi trialss

Ipotesi :maggior vantaggio AA prima di docetaxel?

ASL 1 IMPERIESE

Terapia del Ca della Prostata Ormonorefrattario - 2013

Conclusioni

Gruppo di pazienti eterogeneo

Diverse possibilità di trattamento medico

Sopravvivenza Mediana di 35 Mesi

Ca.POLMONE - META-ANALISI di Sopravv.

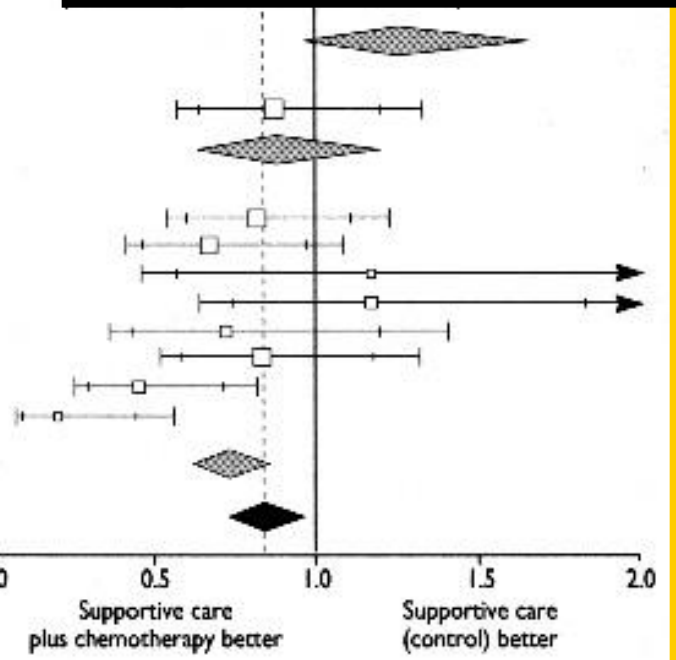
Cis-based CT vs BSC

CT ADVANTAGE

MST = + 1.5 mos

1-YS = + 10 %

Trial	No of events/ No of patients entered: Supportive care plus chemotherapy	Supportive care	Observed – expected deaths	Variance
Long term alkylating agents:				
Oxford	120/121	62/67	16.40	43.80
Quebec	20/20	18/18	-4.38	7.99
Subtotal	140/141	80/85	12.02	51.79
Vinca alkaloids/etoposide:				
Gwent 2	96/111	67/75	-5.15	38.00
Subtotal	96/111	67/75	-5.15	38.00
Cisplatin based:				
RLW 8351	84/86	80/81	-8.06	39.94
NCIC CTG	95/97	51/53	-11.28	28.24
Southampton	17/17	15/15	1.16	7.55
NRH	44/44	40/43	2.93	18.72
UCLA	31/32	30/31	-4.83	14.53
Ancona I	63/63	65/65	-5.72	30.95
AOI-Udine	52/52	50/50	-14.98	18.77
CEP-85	23/25	21/24	-10.52	6.61
Subtotal	409/416	352/362	-51.31	165.31
Total	645/668	499/522	-44.44	255.09



NSCLC Collaborative Group, BMJ 1995

ASL 1 IMPERIESE

Gefitinib/erlotinib: l'istotipo come sede più frequente delle mutazioni di EGFR

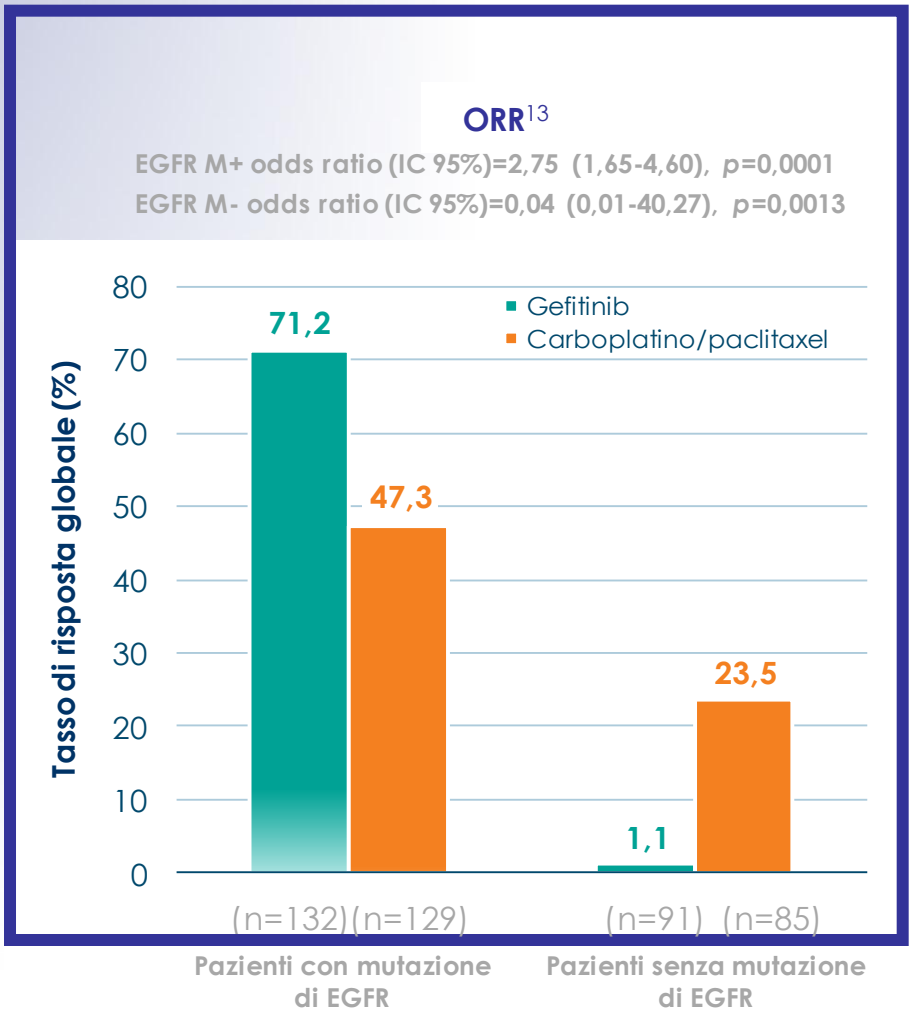
Gli inibitori di EGFR sono + attivi negli ADK rispetto agli squamosi, nelle femmine, nei non fumatori e negli asiatici.

In queste sottopopolazioni la mutazione attivante il gene di EGFR che conferisce maggior sensibilità a questa classe di farmaci è + frequente.

E' dimostrato una maggior attività rispetto alla chemioterapia nei pazienti positivi per la mutazione di EGFR col il trattamento in prima linea con gefitinib o erlotinib[13-16].

tasso di risposte nei pazienti mutati >70%, superiore alla chemioterapia,

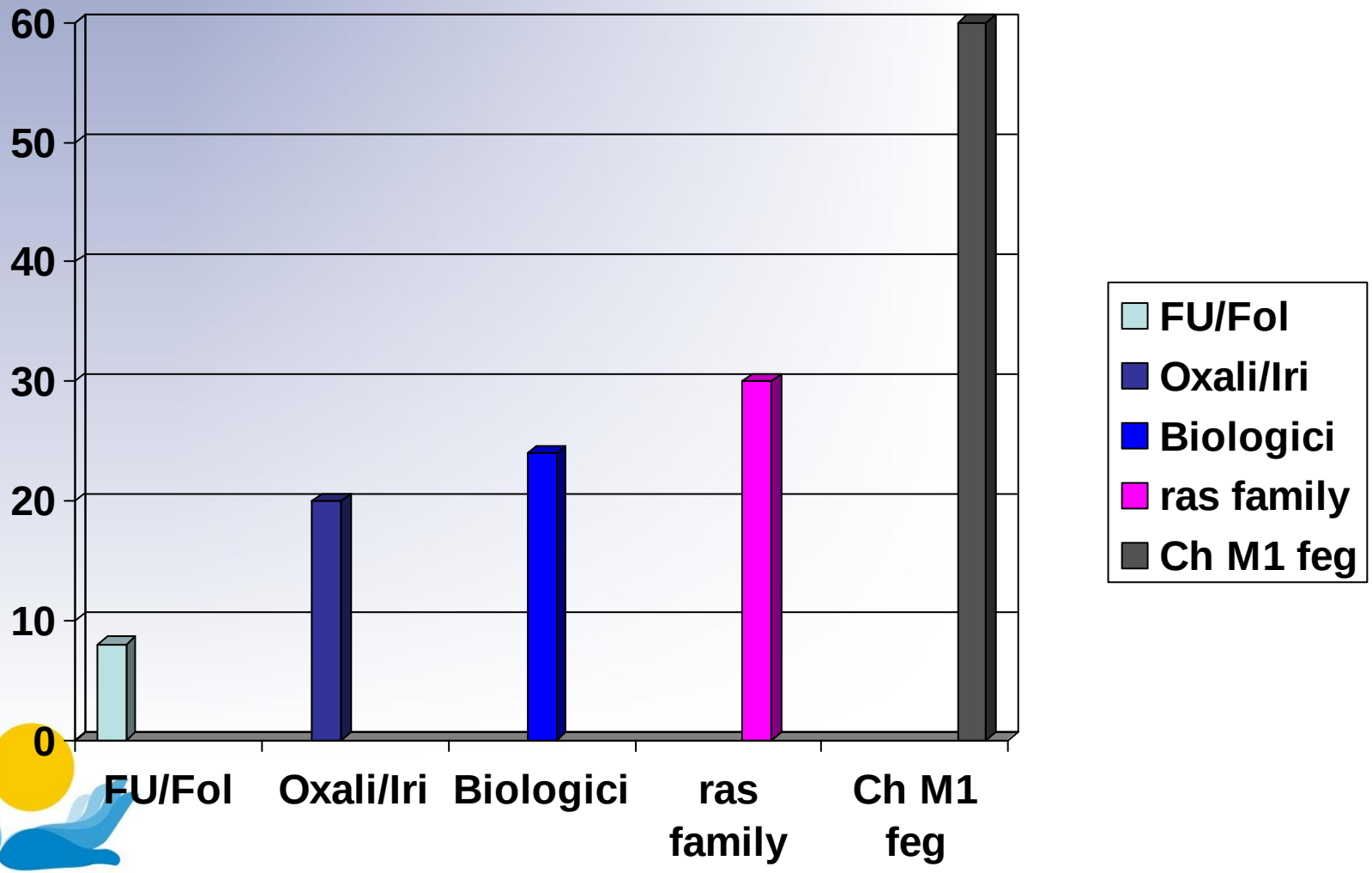
Studio Mok



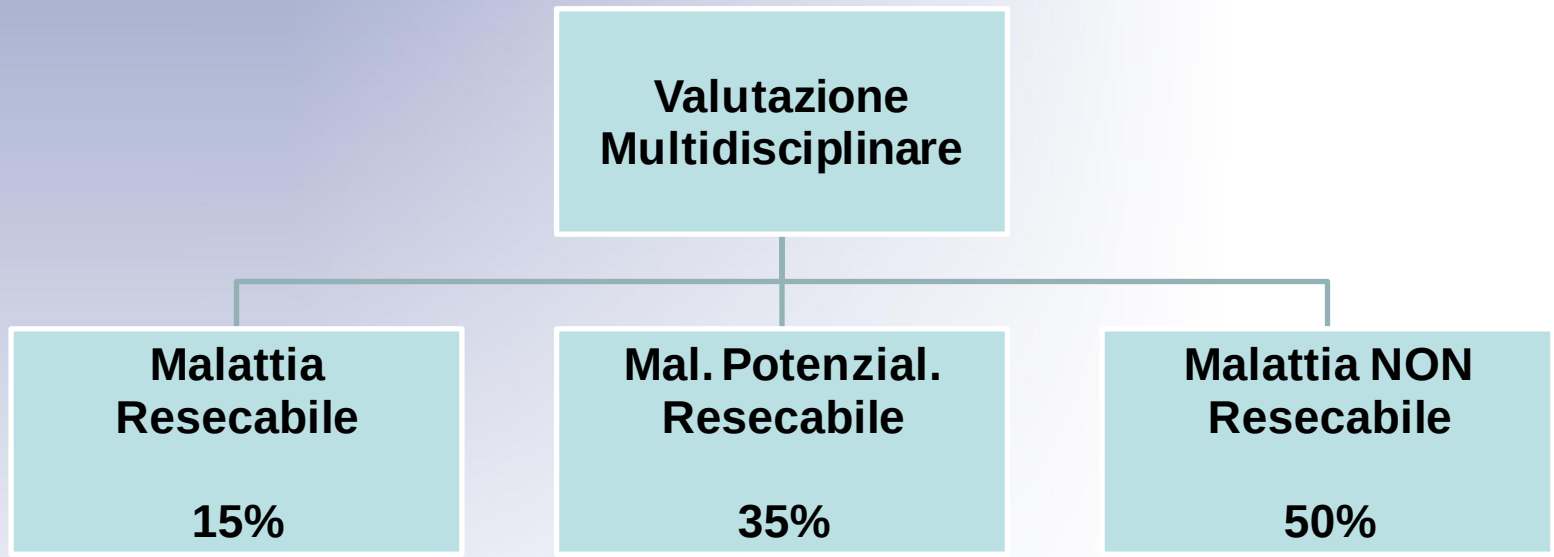
13. Mok T et al. NEJM 2009; **14.** Rosell R et al. NEJM 2009;
15. Kobayashi K et al. J Clin Oncol 2009 (ASCO 2009); **16.** Tsurutani J et al. Ann Oncol 2009 (ECCO/ESMO 2009)

ASL 1 IMPERIESE

Ca Colonretto Avanzato – Risultati Clinici



Ca. Colon Metastatico



Margini radiol. Adeguati
>4 lesioni ?
Fattori Prognostici

Margini radiol. Inadeguati
Fattori Progn. Neg. x PFS
Chir solo dopo Tum.

Categoria Eterogenea di Pazienti

CH per mts epatiche

Sopravvivenza a 5 aa	25-30%
Sopravvivenza a 10 aa	10-20%

(Fernandez FG et al. Ann Surg 2004, Abdalla EK et al. Ann Surg 2004, Tomlinson JS et al. J Clin Oncol 2007)

ASL 1 IMPERIESE

I TUMORI DEL COLON RETTO

prevenzione, diagnosi e trattamento

Guarire si può

Ca. Colon Stadio	Sopravvivenza	% Guarigioni
II	/	85
III	/	70
IV	30m?	5/10

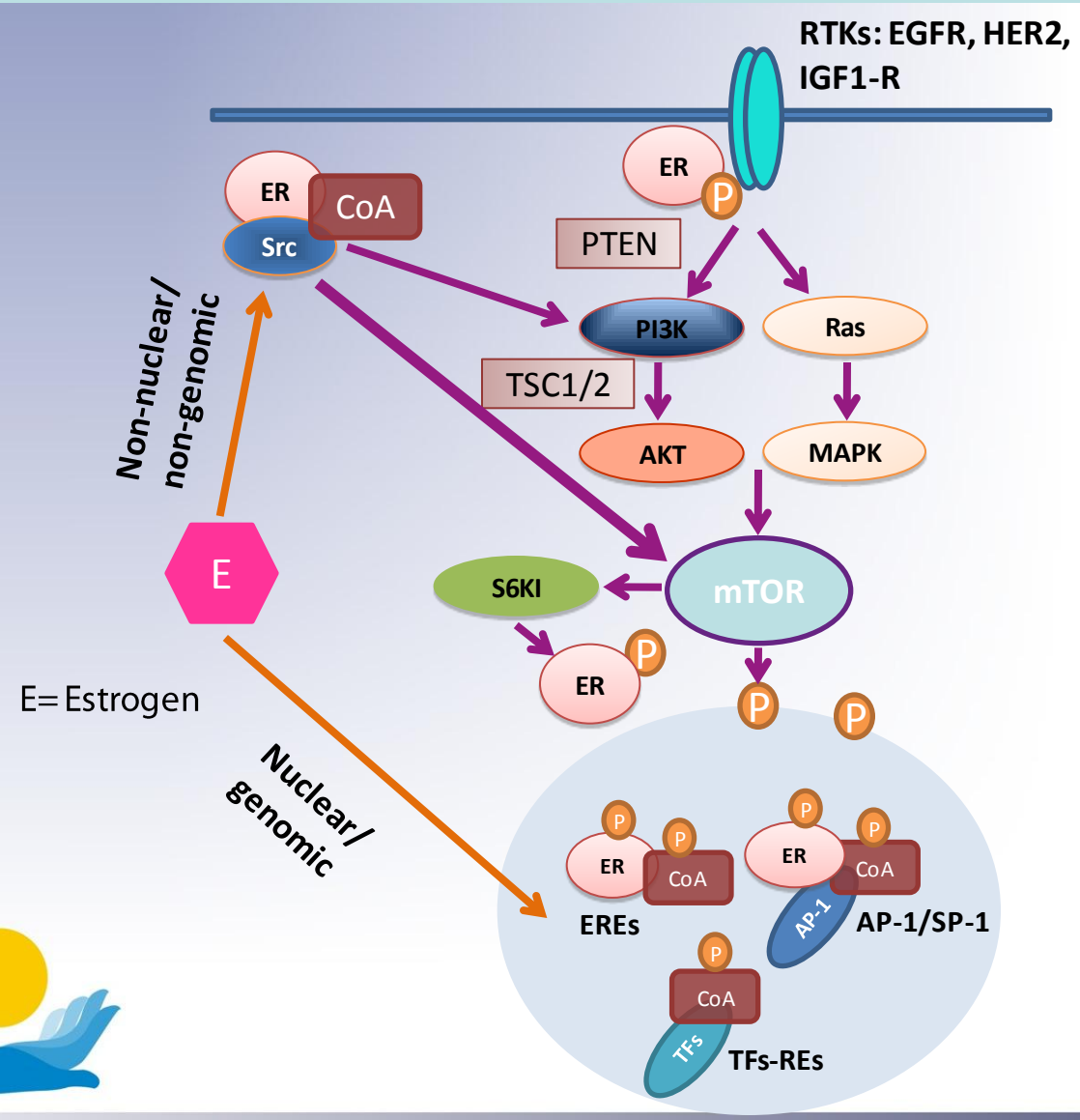
ASL 1 IMPERIESE

Ca. Mammella

CLASSIFICAZIONE	CARATTERISTICHE BIOLOGICHE	CT	OT
LUMINAL A	ER/PgR+++(95-100%) G1 Mitosi 1-5x10HPF Ki67 <12% HER2-	**CHEMIORESISTENZA**	**ELEVATA ORMONOSENSIBILTA'**
LUMINAL B	ER+/PgR++(10%-60%) G1-2-3 Mitosi >10x10HPF Ki67 > 12% HER2-	**PARZIALE CHEMIOSENSIBILITA'**	**DISCRETA ORMONOSENSIBILITA'**
TRIPLE NEGATIVE / BASAL LIKE	ER-/PgR- (0%) G3 Mitosi=60x10HPF Ki67=80% HER2-	**ELEVATA CHEMIOSENSIBILITA'**	**ORMONORESISTENZA**
HER2+	ER e PgR+/- (0%-100%) G3 Mitosi=40-60x10HPF Ki67=60-80% HER2+	**ELEVATA CHEMIOSENSIBILITA'**	**ORMONORESISTENZA VARIABILE**

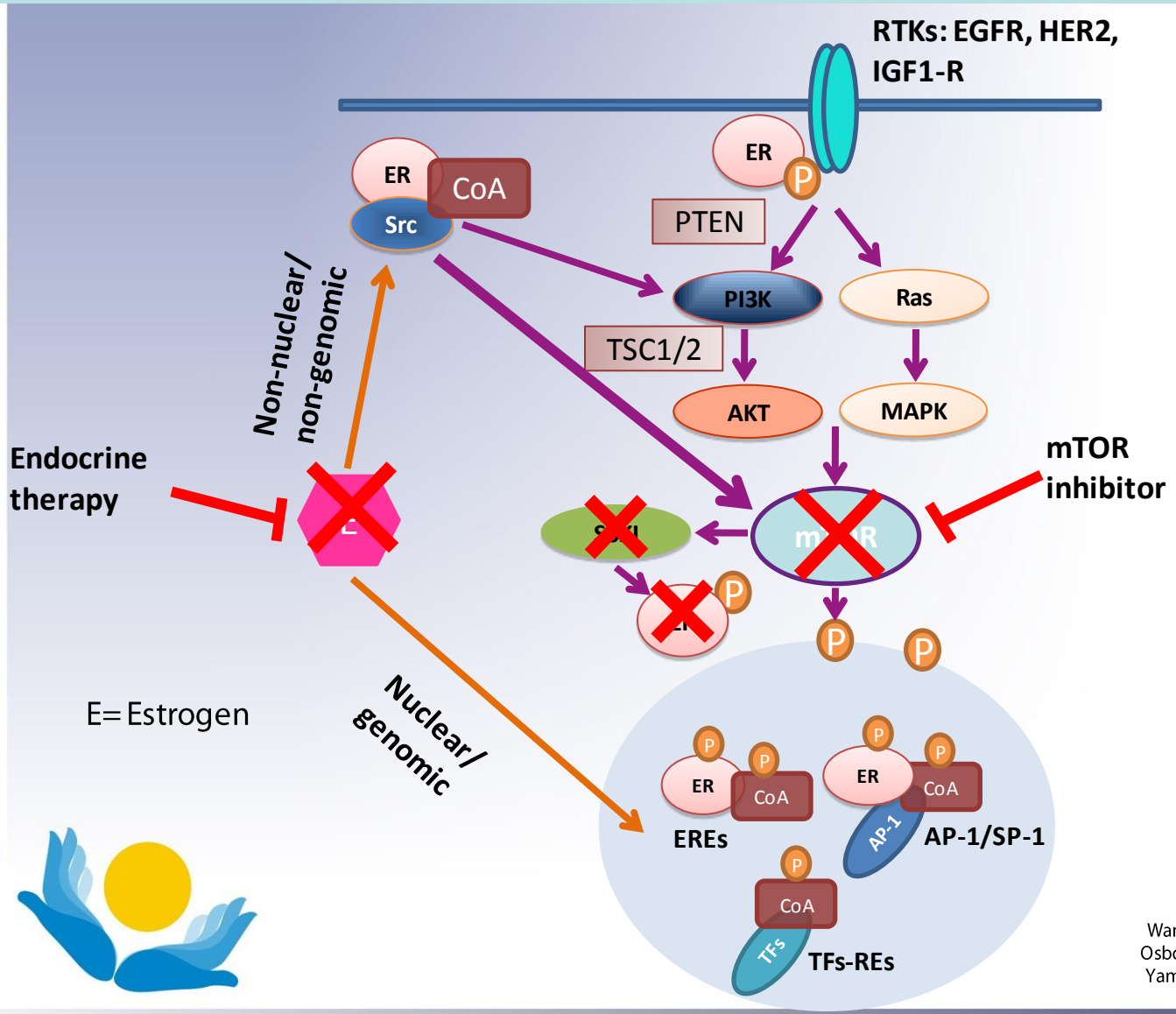
Fattori Predittivi di Ricaduta e Risposta

Biology of breast cancer – important pathways



Wander SA, et al. J Clin Invest. 2011;121:1231–124
Osborne CK, et al. Annu Rev Med. 2011;62:233–247
Yamnik RL, et al. J Biol Chem. 2009;284:6361–6369

Biology of breast cancer – important pathways



We have entered a new era where endocrine therapy can be combined with targeted therapy

Wander SA, et al. J Clin Invest. 2011;121:1231–124
Osborne CK, et al. Annu Rev Med. 2011;62:233–247
Yamnik RL, et al. J Biol Chem. 2009;284:6361–6369

BOLERO-2 (Ph III): Everolimus in Advanced BC

24 Countries, 196 sites

N = 724

- Postmenopausal ER+
- Unresectable locally advanced or metastatic BC
- Recurrence or progression after letrozole or anastrozole

R

2:1

EVE 10 mg daily + EXE 25 mg daily (n = 485)

Placebo + EXE 25 mg daily (n = 239)

Stratification: Sensitivity to prior hormone therapy and presence of visceral metastases

Endpoints

- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, QOL, safety, bone markers, PK

Abbreviations: BC, breast cancer; ER+, estrogen receptor-positive; EVE, everolimus; EXE, exemestane; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ph, phase; PK, pharmacokinetics; QOL, quality of life.

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO-2: Baseline Characteristics Were Generally Balanced Between Arms

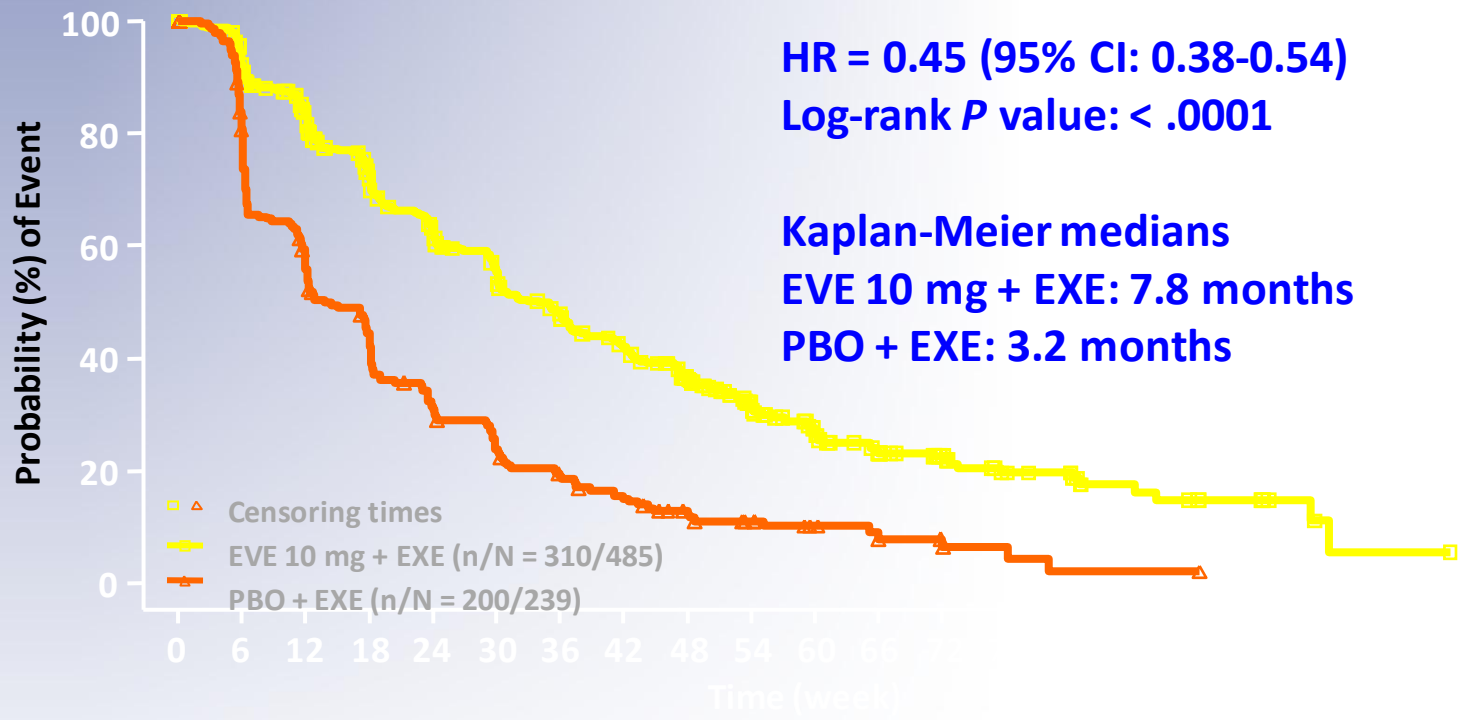
Characteristic	Everolimus + Exemestane (N=485), %	Placebo + Exemestane (N=239), %
Median age (range), years	62 (34, 93)	61 (28, 90)
Race		
Caucasian	74	78
Asian	20	19
Performance status 0	60	59
Liver involvement	33	30
Lung involvement	29	33
Measurable disease[a]	70	68

[a] All other patients had ≥ 1 bone lesion.

Adapted from: Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

ASL 1 IMPERIESE

PFS Based on Local Assessment at 18-mo Follow-up in BOLERO-2 Confirms Earlier Reports



HR = 0.45 (95% CI: 0.38-0.54)
Log-rank *P* value: < .0001

Kaplan-Meier medians
EVE 10 mg + EXE: 7.8 months
PBO + EXE: 3.2 months

Number of patients still at risk

EVE 10 mg + EXE	485	436	366	304	257	221	185	158	124	91	66	5	
PBO + EXE	239	190	132	96	67	50	39	30	21	15	10	1	

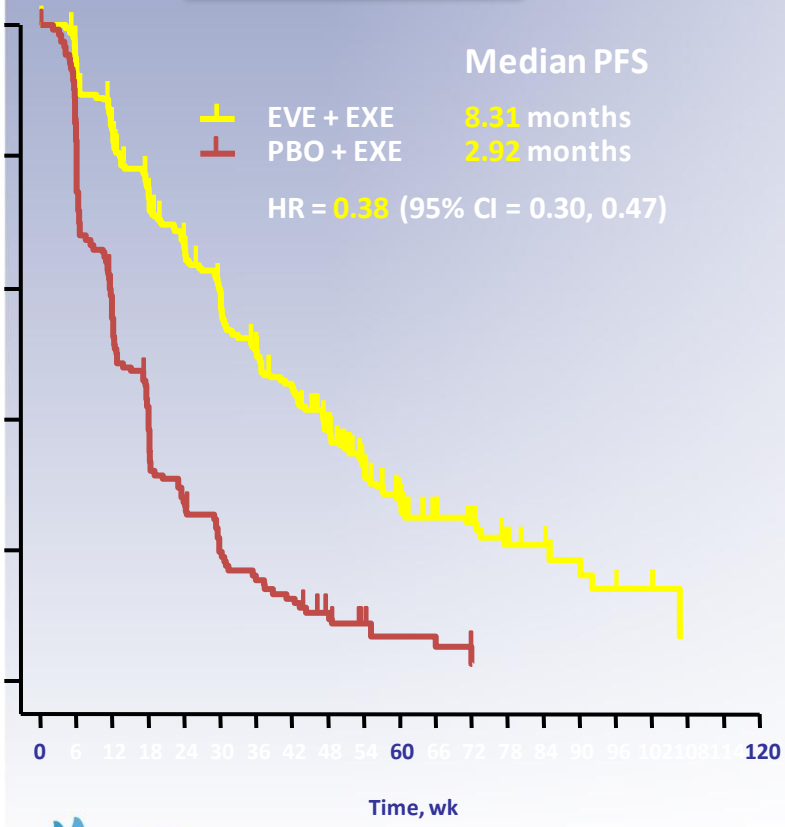
Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.

Piccart M, et al. ASCO 2012; abstract 559 (poster).

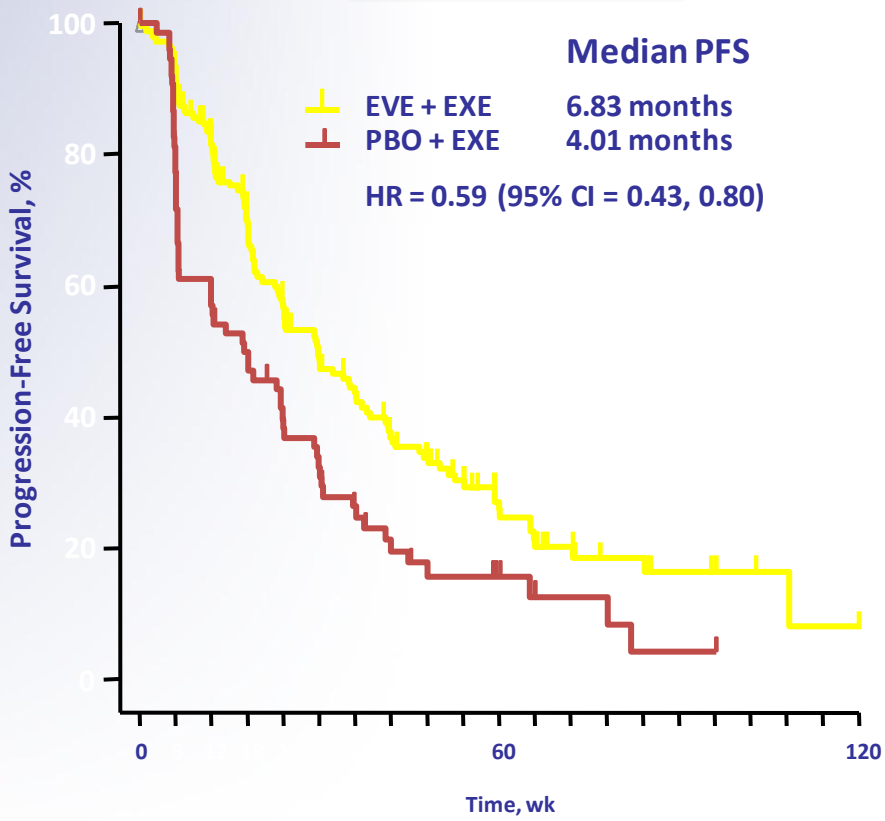
BOLERO-2 (18-mo follow-up):

PFS Benefits Were Comparable in Elderly vs Younger Patients

< 65 years old



≥ 65 years old

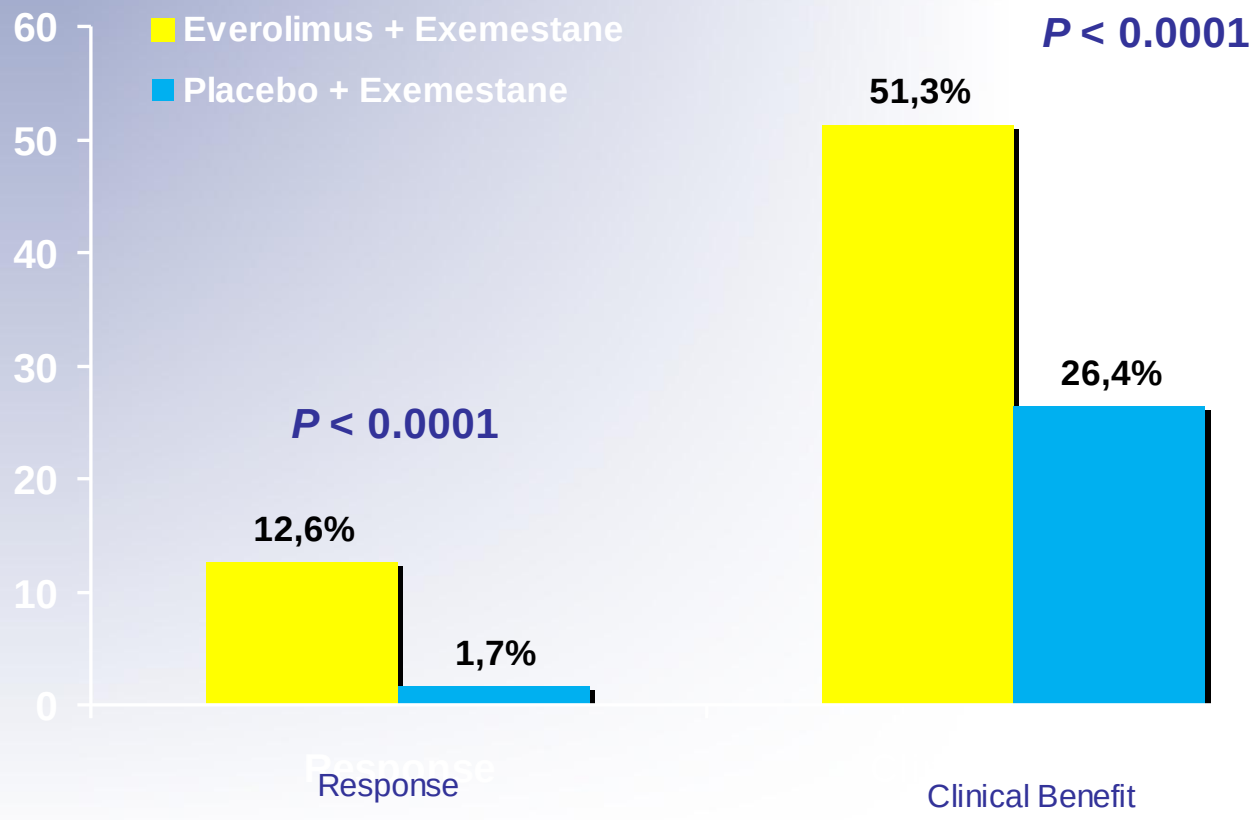


Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

Pritchard KI, et al. ASCO 2012; abstract 551 (poster).

ASL 1 IMPERIESE

BOLERO-2 (18 mo f/up): Response Rates & Clinical Benefit Were Significantly Higher in the Everolimus Arm



Piccart M, et al. ASCO 2012; abstract 559 (poster).

BOLERO-2 (18 mo f/up): Conclusion

- Everolimus is the first agent to enhance the clinical benefit of endocrine therapy in patients with HR^+, $HER2^-$ advanced BC progressing after NSAI therapy

- The addition of everolimus in advanced BC could represent a paradigm shift in the management of this patient population

Abbreviations: BC, breast cancer; $HER2^-$, human epidermal growth factor receptor 2-negative; HR^+, hormone receptor-positive; NSAI, nonsteroidal aromatase inhibitor.

Piccart M, et al. ASCO 2012; abstract 559 (poster).

ASL 1 IMPERIESE

Conclusioni

- Sono disponibili nuove terapie, somministrabili a pazienti oncologici anziani
- Tali terapie sono efficaci in specifici gruppi di pazienti e neoplasie
- E' necessaria una accurata valutazione geriatrica ed oncologica per migliorare l'efficacia dei trattamenti prescritti