Cancers du Sein Triple Négatifs
Problèmes cliniques et
Voies de développement

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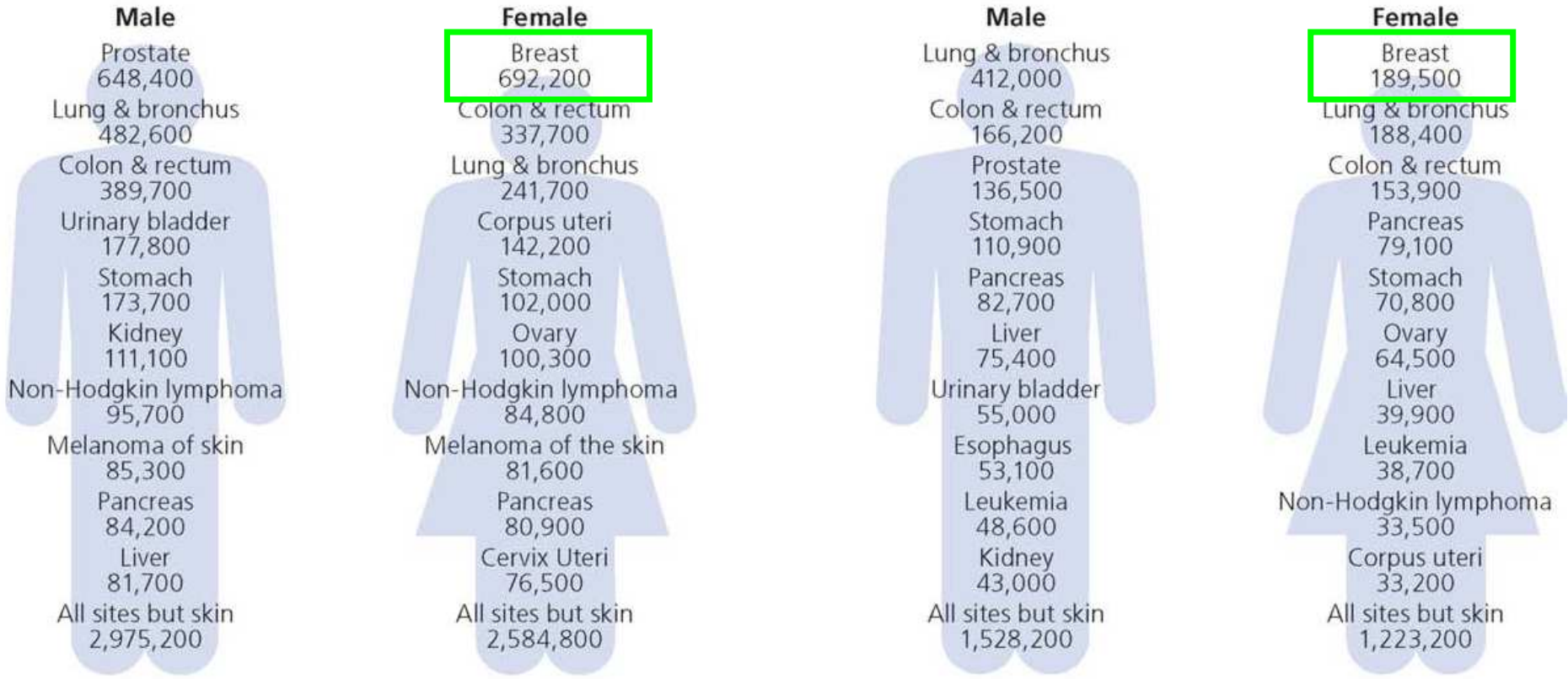
Cancer du sein : les données du problème



Jemal, Global Cancer Statistics 2011

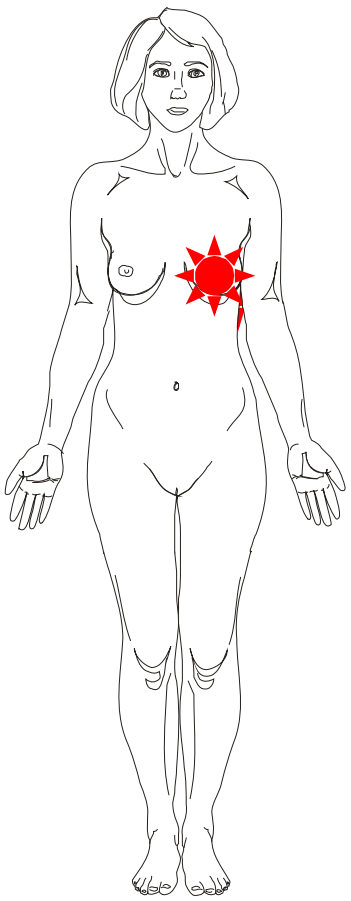
Le cancer du sein en France

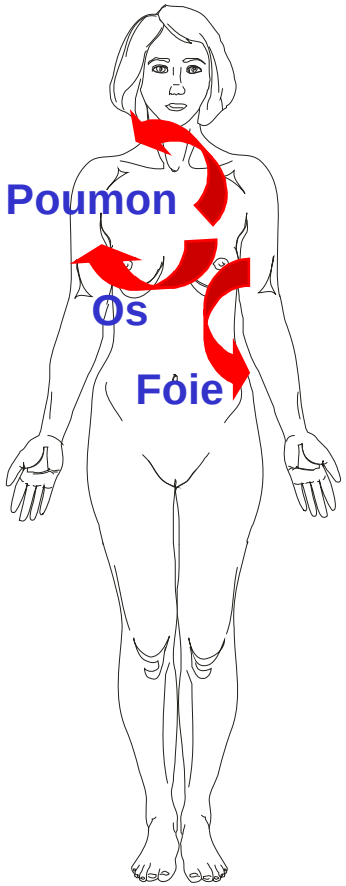
- 49.814 nouveaux cas en 2005
- 11.441 décès en 2006
- 40% des décès prématurés avant 65 ans
- Probabilité pour une femme française d'avoir un cancer du sein au cours de sa vie : 10,1 %

Guérin et al., Bull Cancer vol. 96 • N°1 • janvier 2009, 51-7

Les données du problème

Approximativement 30% des patientes atteintes d'un cancer du sein localisé vont développer une maladie métastatique





Pronostic en fonction du stade

- Étude EUROCARE4, survie à 5 ans

- T1N0M0 : 28,9% des stades, survie 98%
- T2-T3N0M0 :18,6% des stades, survie 87%
- T1-3N+M0 :31% des stades, survie 77%
- T4NxM0 : 6,8% des stades, survie 55%
- **M1 : 6,2% des stades, survie 18%**

Sant et al., Int. J. Cancer: **106, 416–422 (2003)**

Sous Types et Prise en charge

- La prise en charge systémique du cancer du sein peut-elle et/ou doit-elle être guidée par la biologie ?
  - Récepteurs Hormonaux
  - HER-2
  - Profil Triple Négatif

"Poor man's" IHC definitions of microarray-based intrinsic subtypes of breast cancer [5,33,34]

Breast cancer subtype	ER	PgR	HER2
Luminal A	ER and/or PgR pos		neg
Luminal B*	ER and/or PgR pos		pos
HER2+/ER–	neg	neg	pos
Basal-like	neg	neg	neg

Linn S and Van't Veer, EJC Suppl 2009

Les Cancers Triple Négatifs

- RE-
- RP-
- HER-2-

- Environ 15% des cancers du sein
- Forte agressivité clinique
- Carence en cibles thérapeutiques
- TN / Basal-like / BRCA-mutés

Le phénotype « Triple Négatif »

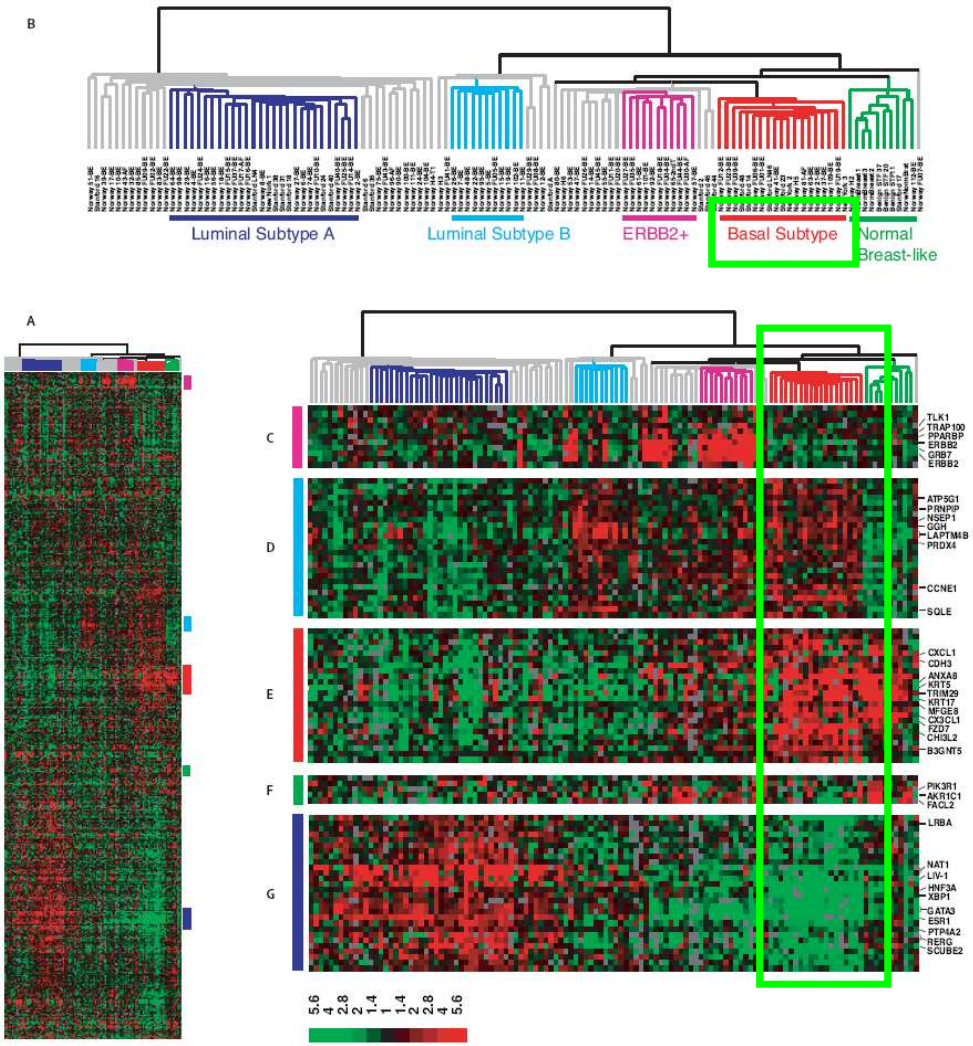
Prototypical features of triple negative breast cancer

Morphological features	High histological grade
	Lack of tubule formation
	Prominent nuclear abnormalities
	High mitotic count
	Broad pushing borders
	Necrotic and fibrotic areas
	Prominent lymphocytic infiltrate
Biological features	Lack of ER and PgR immunoreactivity
	Negative HER2 status
	High Ki-67 labelling index
	p53 mutations
	Immunoreactivity for basal cytokeratins, vimentin, P-cadherin, EGFR, PDGFR, IGF-IR and c-kit
Molecular classification	Basal-like (most commonly)

Viale and Bottiglieri, EJC Suppl Sept 2009

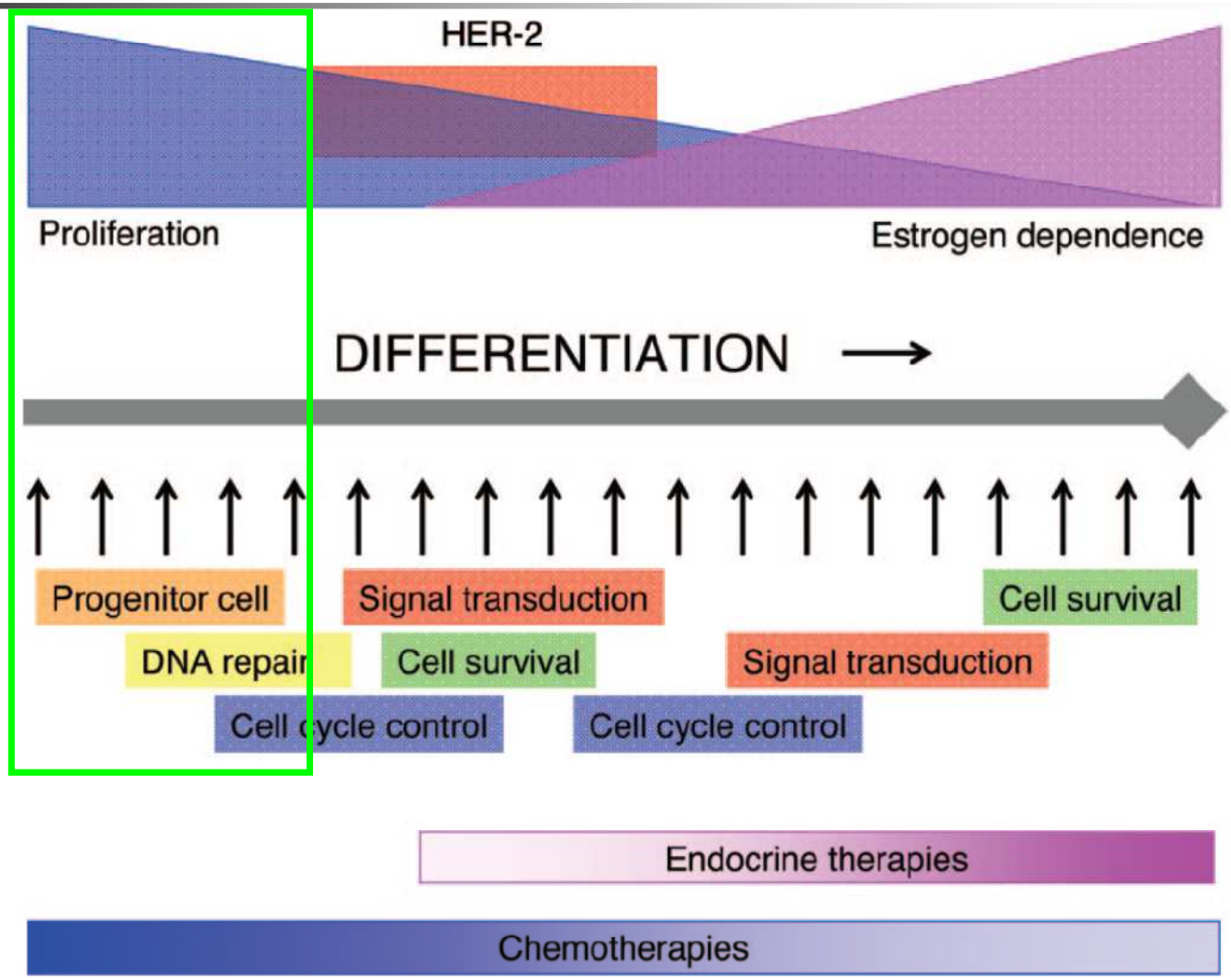
Profil Génomique et Cancer « Basal-Like »

- Une classification moléculaire permettant de distinguer différents groupes
  - Biologiques
  - Pronostiques

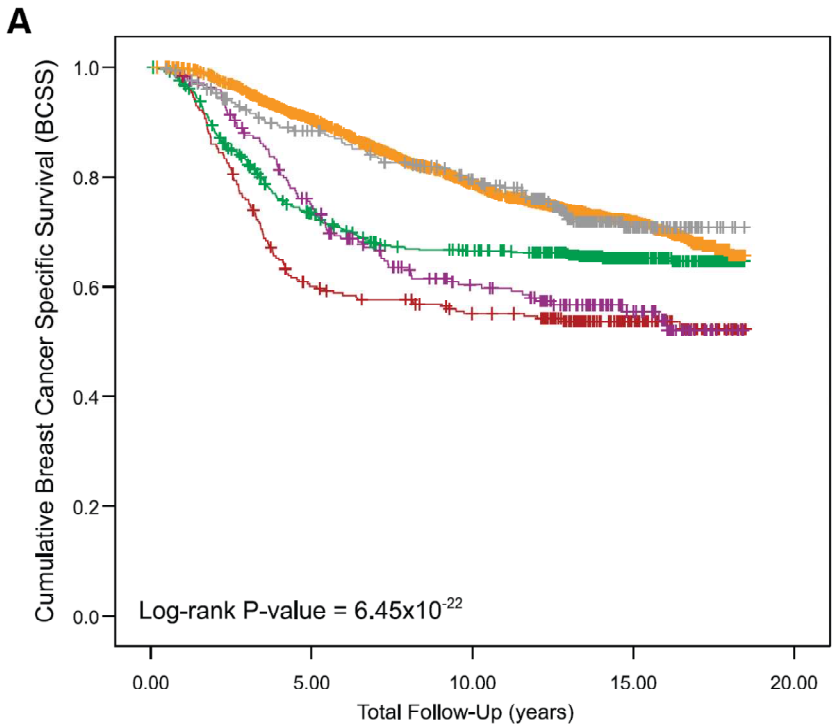


Sorlie et al., *Proc Natl Acad Sci USA* 2003; 100: 8418–23.

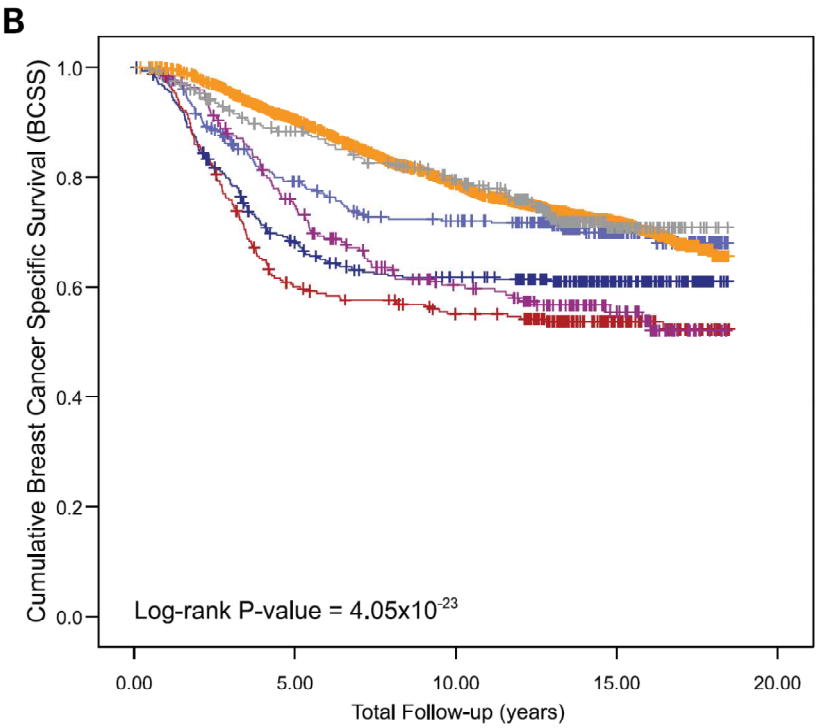
Théorie de la différenciation tumorale



TN : TN vs 5N vs Basal-Like



Breast Cancer Subtypes	5-yr BCSS (95% C.I.)	10-yr BCSS (95% C.I.)	Patients (n)	Events (n)
Luminal'	91 (89-92)	79 (77-80)	2620	669
Luminal/HER2+	75 (68-80)	60 (53-67)	221	91
HER2+/ER–PR–	60 (54-66)	55 (49-61)	258	118
TNP	73 (70-77)	67 (63-70)	639	213
unassigned	89 (85-92)	80 (74-84)	302	76



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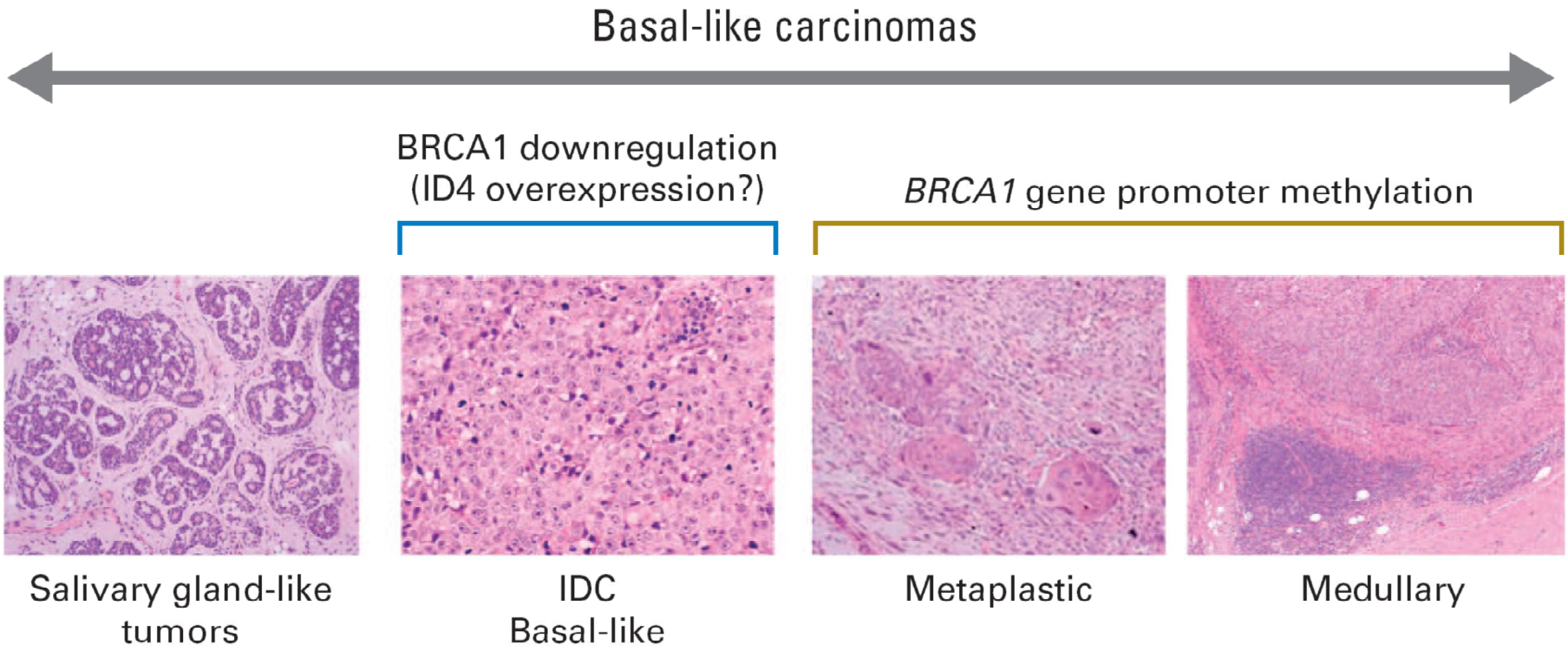
Luminal/HER2+	75 (68-80)	60 (53-67)	221	91
HER2+/ER–PR–	60 (54-66)	55 (49-61)	258	118
Core Basal	68 (63-73)	62 (56-67)	336	127
5NP	79 (74-83)	72 (66-77)	303	86
unassigned	89 (85-92)	80 (74-84)	302	76

Cheang et al., Clin Cancer Res 2008;14(5)March 1, 2008

Carcinomes Basal-Like



Rakhah et al., J Clin Oncol 26:2568-2581.

Cancers du Sein BRCA1 mutés

	BRCA1-associated breast cancer	Controls (sporadic cancers)	p	Ref
High grade	66%*	36%	0·001	35
Express EGFR	67%*	21%	0·0001	36
ER negative	90.4%*	33%	--	36
ERBB2 negative	97%*	85%	0·018	37
p53 mutation	66%*	35%	0·05	38
Express CK 5/6	58%*	7%	<0·0001	36
c-MYC amplification	53%	23%	0·003	39
Cytogenetic abnormalities	Relatively high	Relatively low	--	40

*Feature of triple-negative/basal-like cancer.

Table 2: **Pathological and molecular features of BRCA1-associated breast cancer**

***Cleator et al., Lancet Oncol* 2007; 8: 235–44**

Overlaps...

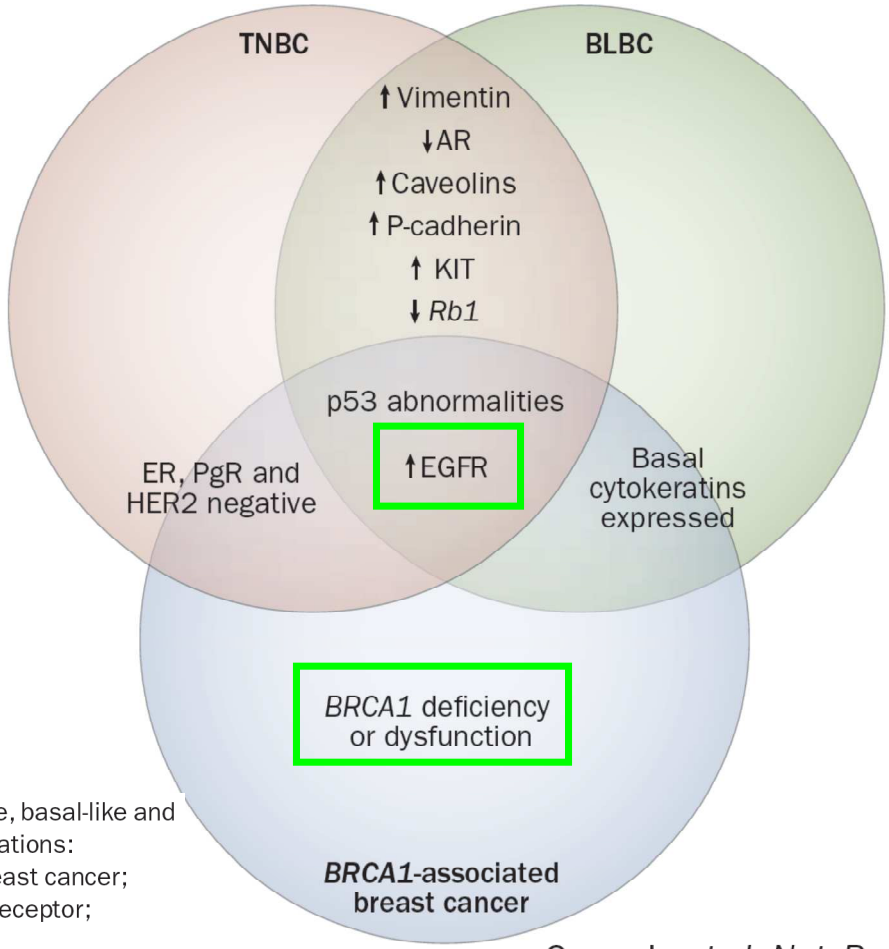
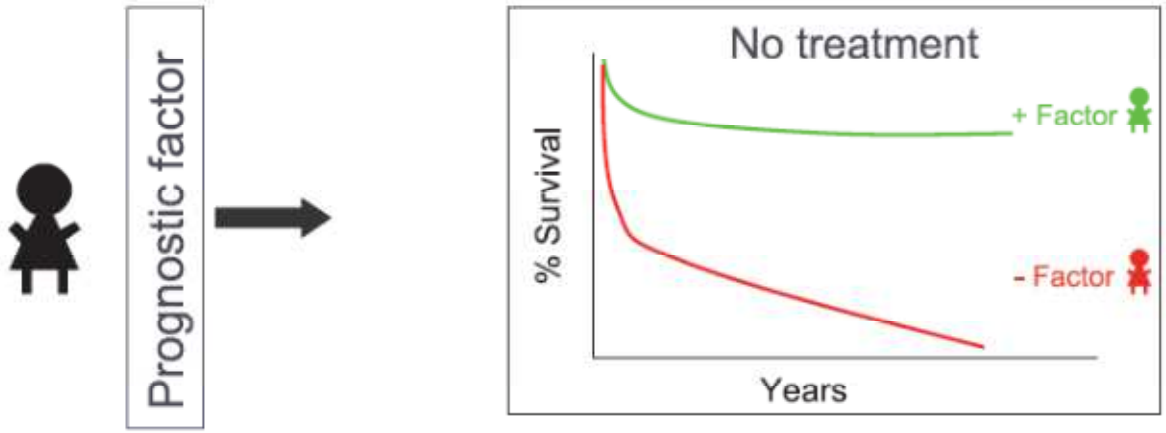
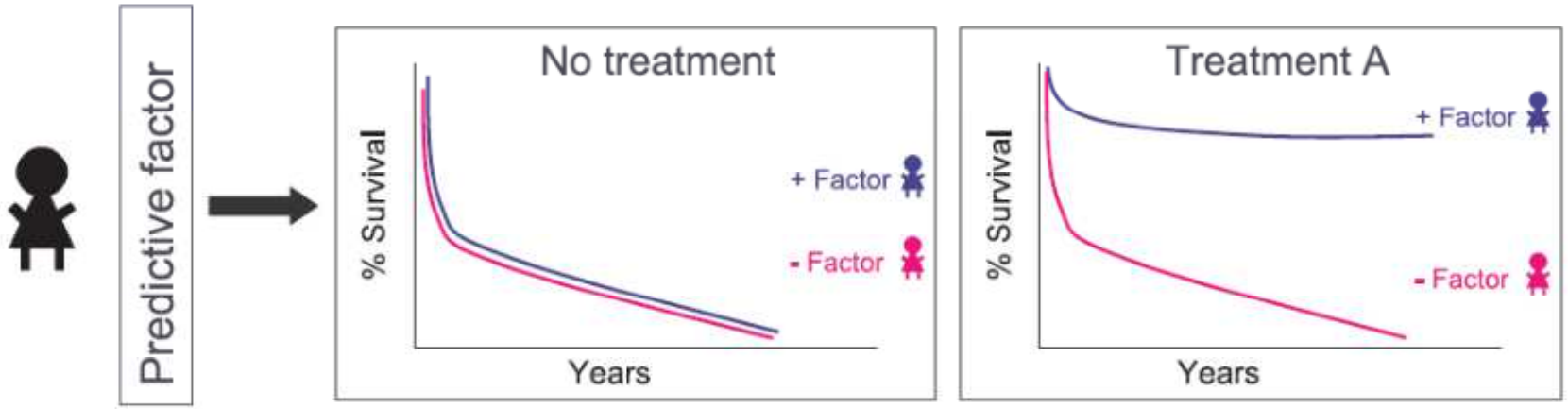


Figure 1 | Shared features of triple-negative, basal-like and *BRCA1*-associated breast cancers. Abbreviations: AR, androgen receptor, BLBC, basal-like breast cancer; ER, estrogen receptor; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

Carey, L. *et al*. *Nat. Rev. Clin. Oncol*. **7**, 683–692 (2010)

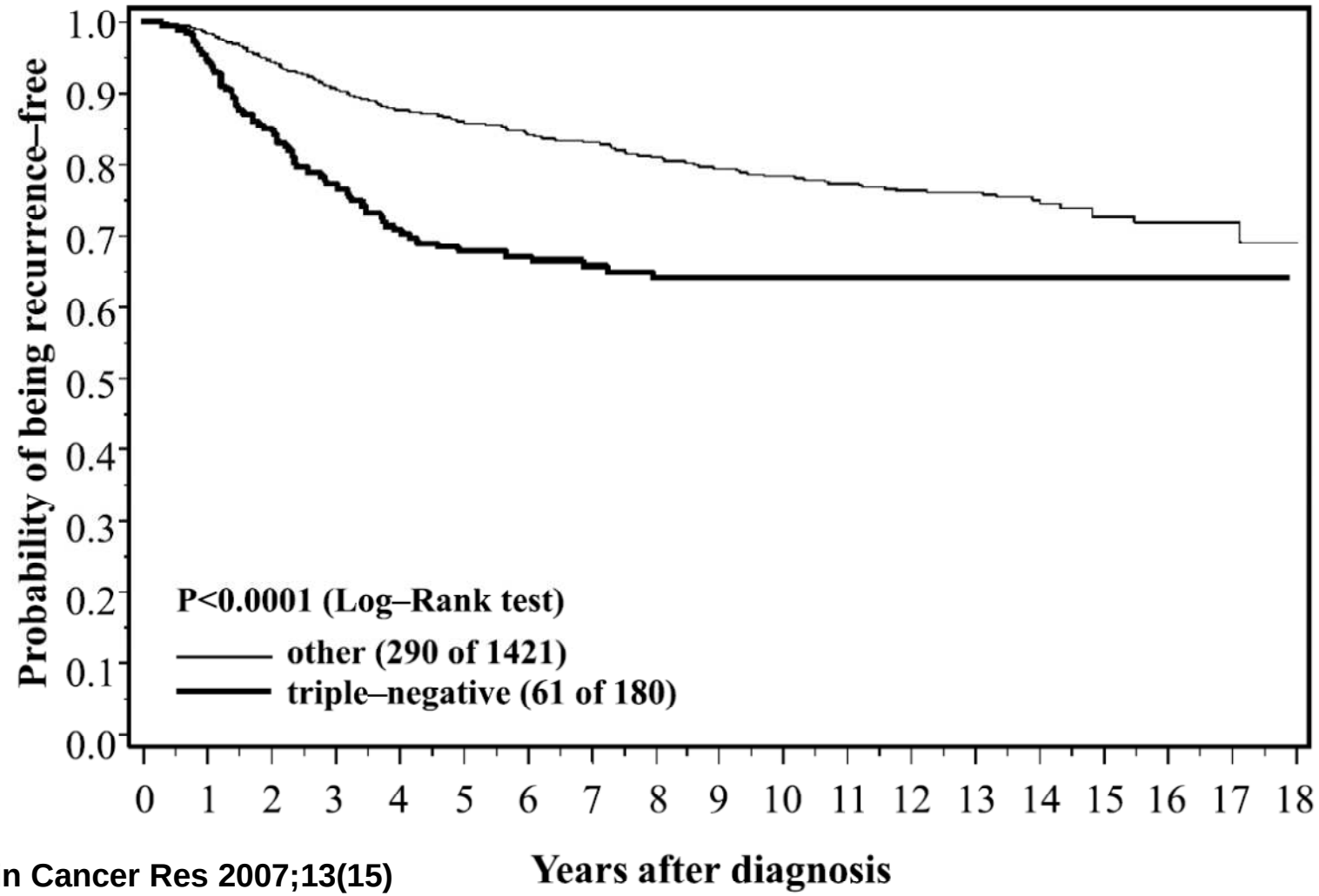
Facteur Pronostique, Facteur Prédictif et Cible Thérapeutique





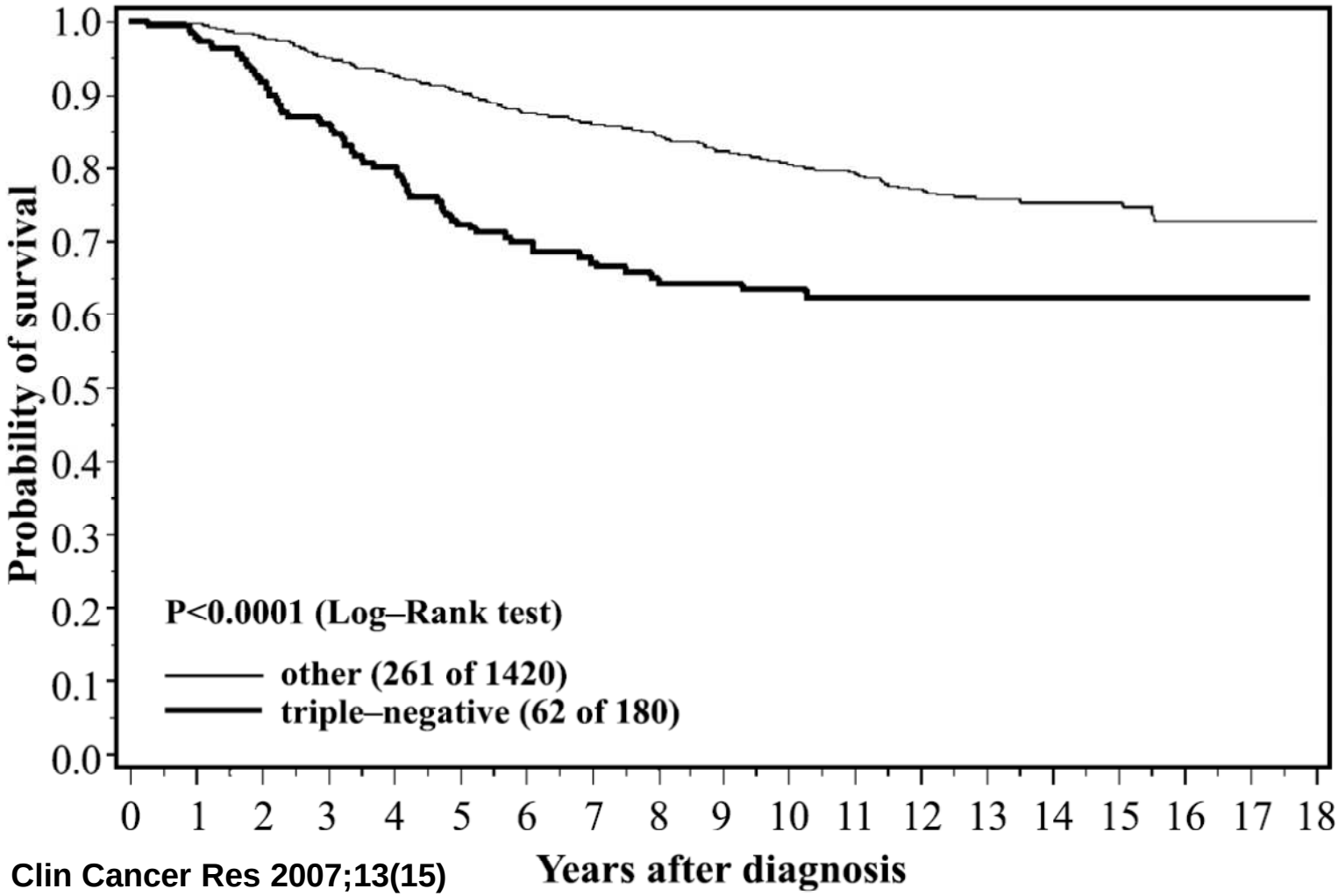
Linn S and Van't Veer, EJC Suppl 2009

Pronostic



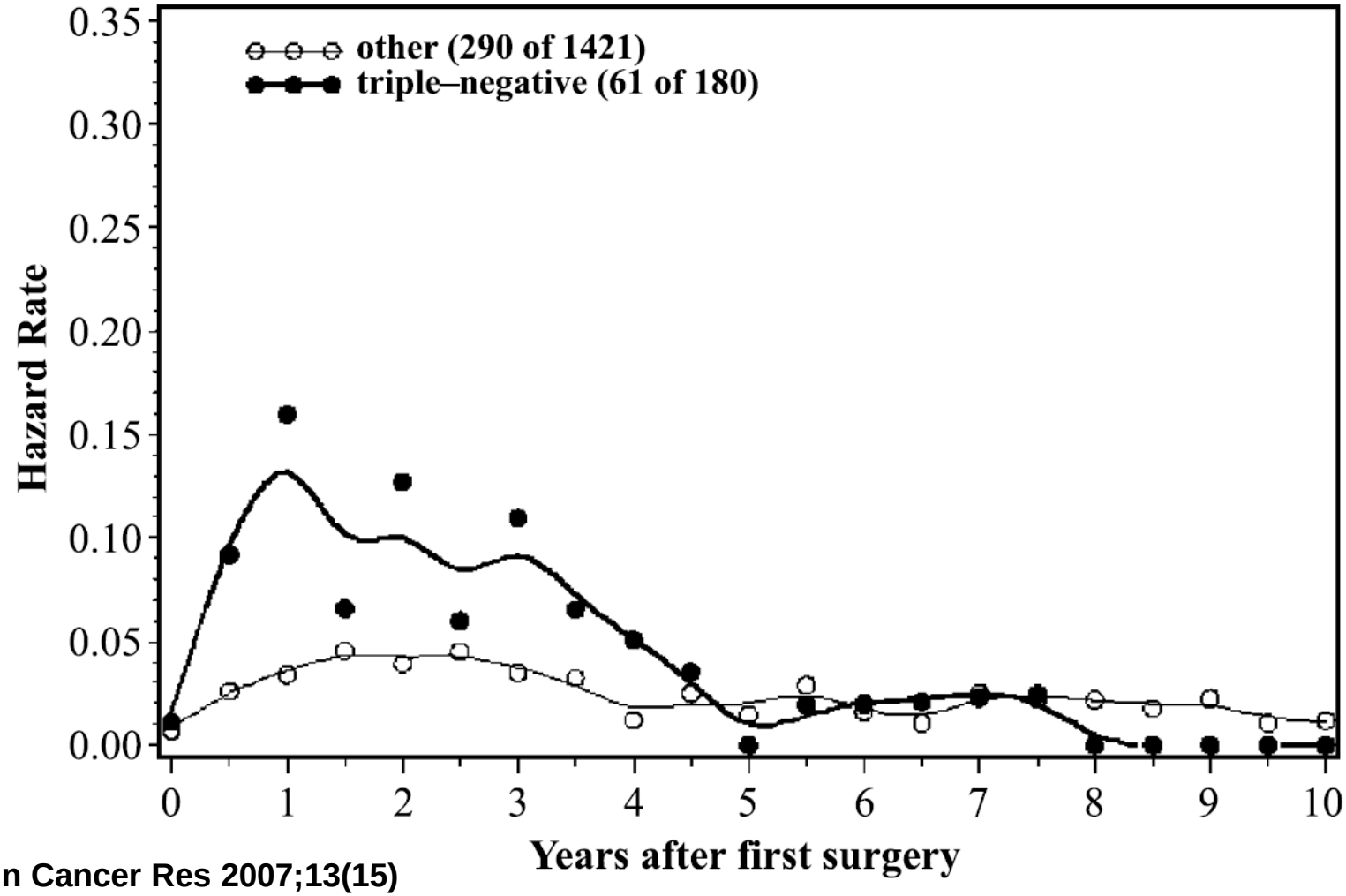
Dent et al., Clin Cancer Res 2007;13(15)

Pronostic



Dent et al., Clin Cancer Res 2007;13(15)

Pronostic



Dent et al., Clin Cancer Res 2007;13(15)

Prédictivité

- Facteur prédictif de réponse et de pRC à la CT
- Plus forts taux de réponse
- Cependant durée de réponse souvent brève

Table 3 Markers and their value in prediction in breast cancer

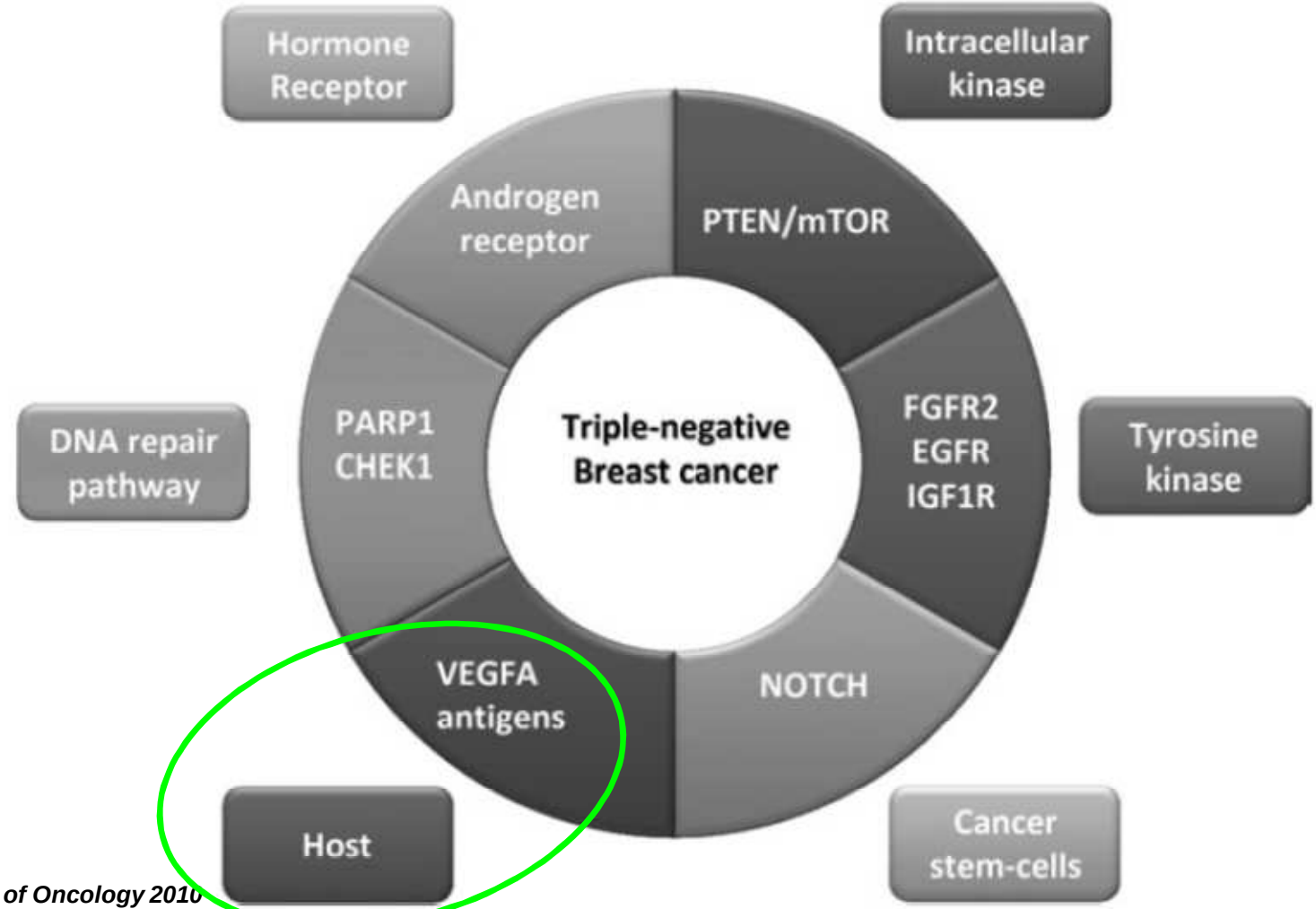
Established and in routine clinical use	Potential for clinical use; need refinement of scoring systems or antibodies	Research interest, less likely to be used clinically
Oestrogen receptor	Epidermal growth factor receptor	P53
Progesterone receptor	Ki-67 (MIB-1)	Cyclin E, cyclin D1, p21, p27
HER2	Topoisomerase II alpha	Bcl2, bax, bcl-x, survivin

Walker et al., J Clin Pathol 2008;61:689–696.

En synthèse

- Environ 15% des cancers du sein
- RE-
- RP-
- HER-2-
- Forte agressivité
- Recouvrement avec une partie des cancers basal-like
- Enrichi en tumeurs BRCA mutées
- Anomalies de la réparation de l'ADN (?)

Cibles putatives dans les tumeurs TN



Berrada et al., Annals of Oncology 2010

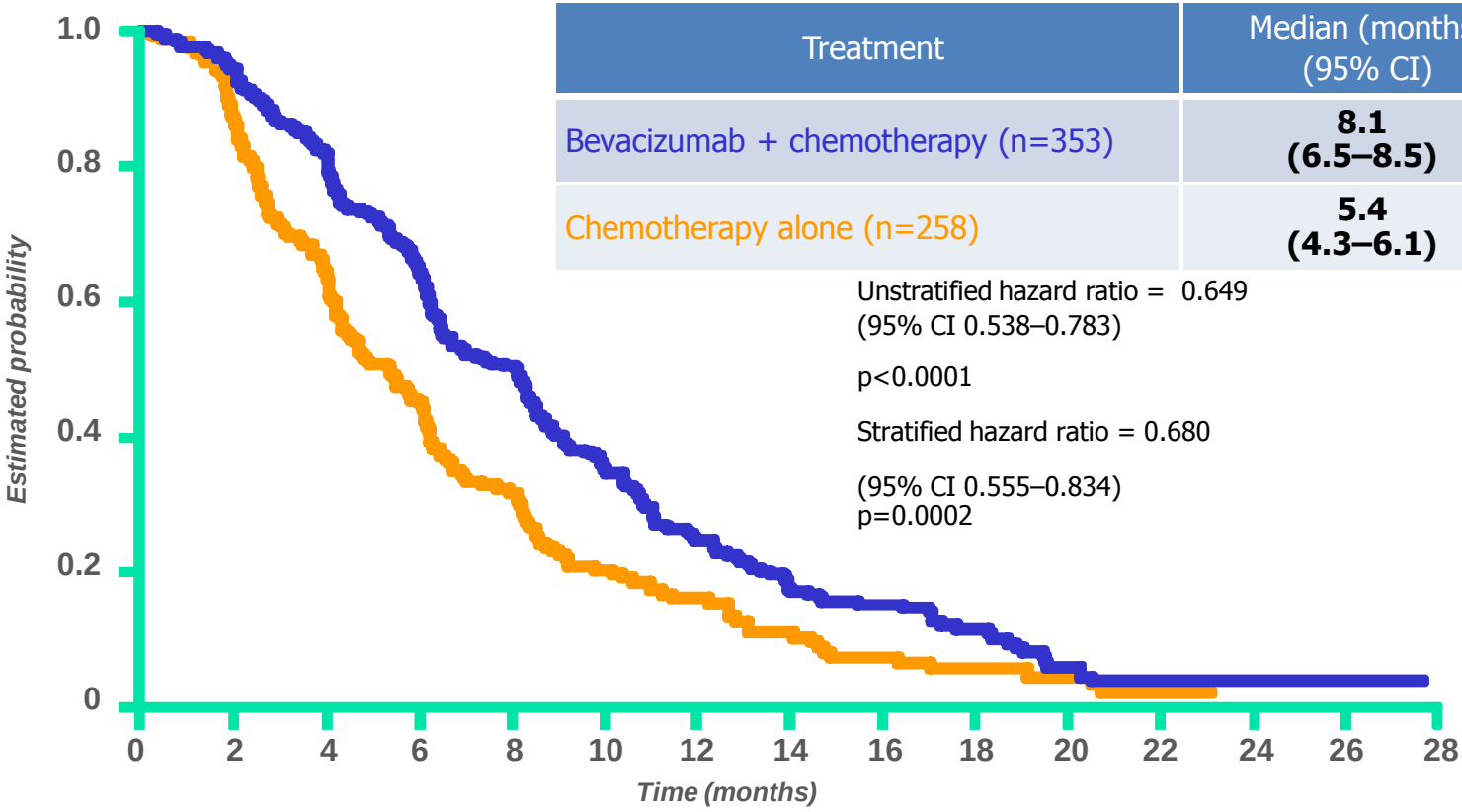
Meta-Analysis of Patients with Triple-Negative Disease from Three Randomized Trials of Bevacizumab (BV) and First-Line Chemotherapy as Treatment for MBC

Trial	Chemotherapy partner	No. of patients with TNBC (%)		Hazard ratio for PFS	Median PFS, months	
		Bev + chemotherapy	Chemotherapy alone		Bev + chemotherapy	Chemotherapy alone
E2100	Weekly paclitaxel	**122 (33)**	**110 (31)**	**0.49**	**10.6**	**5.3**
AVADO	3-weekly docetaxel	**58 (23)b**	**52 (22)**	**0.68**	**8.1**	**6.1**
RIBBON-1 (taxane/ anthracycline)a	Docetaxel/ nab-paclitaxel monotherapy or anthracycline-based combination therapy	**96 (23)**	**46 (22)**	**0.78**	**6.5**	**6.2**
RIBBON-1 (capecitabine)a	Capecitabine	**87 (21)**	**50 (24)**	**0.72**	**6.1**	**4.2**

[a]Randomized 2:1. [b]59 patients (24%) in earlier analyses of AVADO; one patient excluded after further review.

1. O'Shaughnessy J, *et al.* Cancer Res 2009;69(Suppl. 8)512s (Abstr. 207); 2. Glaspy J, *et al.* Eur J Cancer Suppl 2010;8:202(Abstr, 489)

Kaplan–Meier estimate of PFS (TNBC subgroup)



Treatment	Median (months) (95% CI)
Bevacizumab + chemotherapy (n=353)	**8.1 (6.5–8.5)**
Chemotherapy alone (n=258)	**5.4 (4.3–6.1)**

Unstratified hazard ratio = 0.649
(95% CI 0.538–0.783)

p<0.0001

Stratified hazard ratio = 0.680

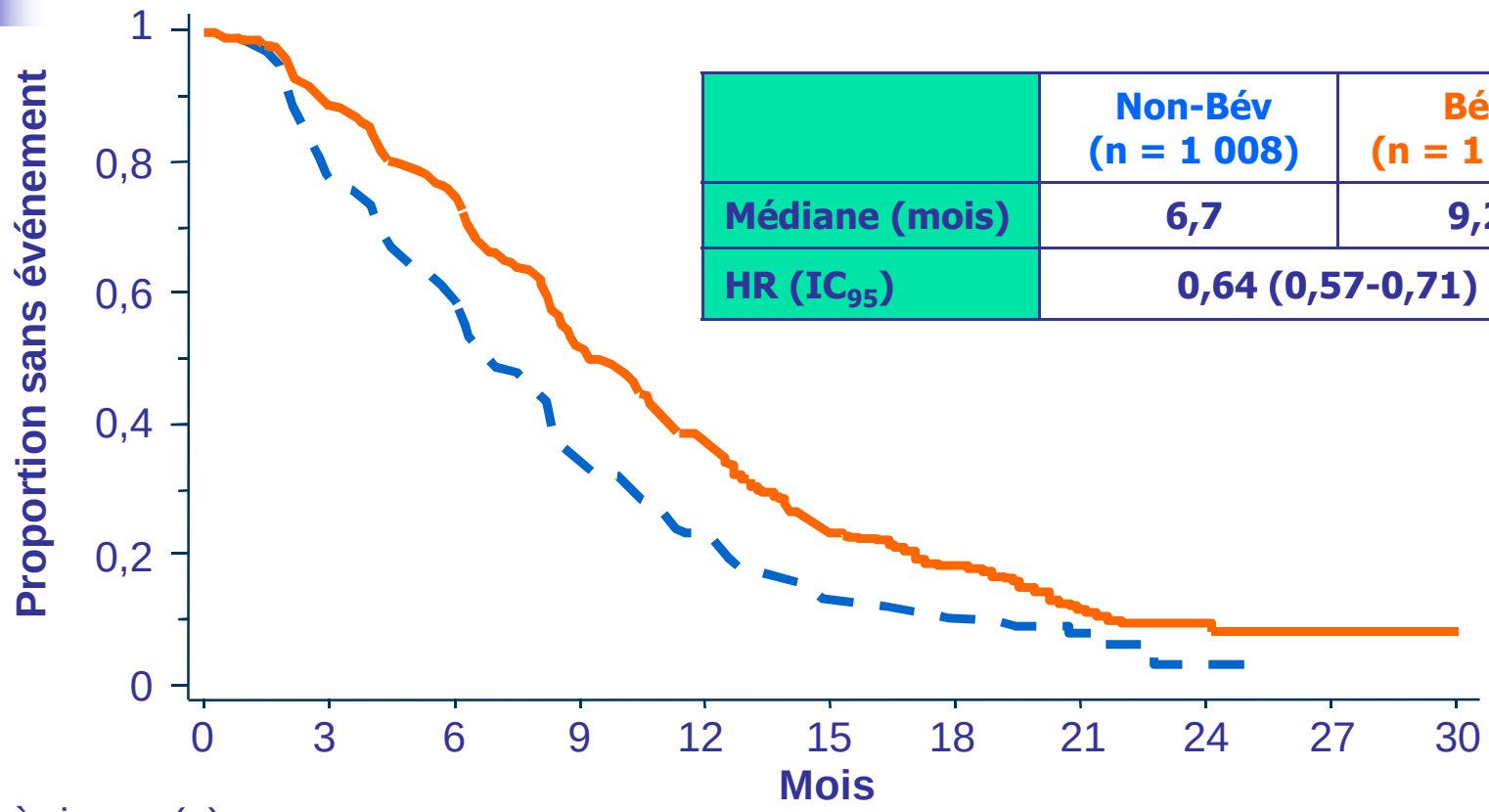
(95% CI 0.555–0.834)
p=0.0002

No. at risk:

Bevacizumab + chemo	353	317	263	191	141	93	59	37	27	18	9	4	1	0
Chemo alone	258	206	142	88	60	36	24	15	9	6	4	2	0	0

SABCS 2010. O'Shaughnessy J. *et al*, P6-12-03

Ensemble de la population (ASCO 2010)



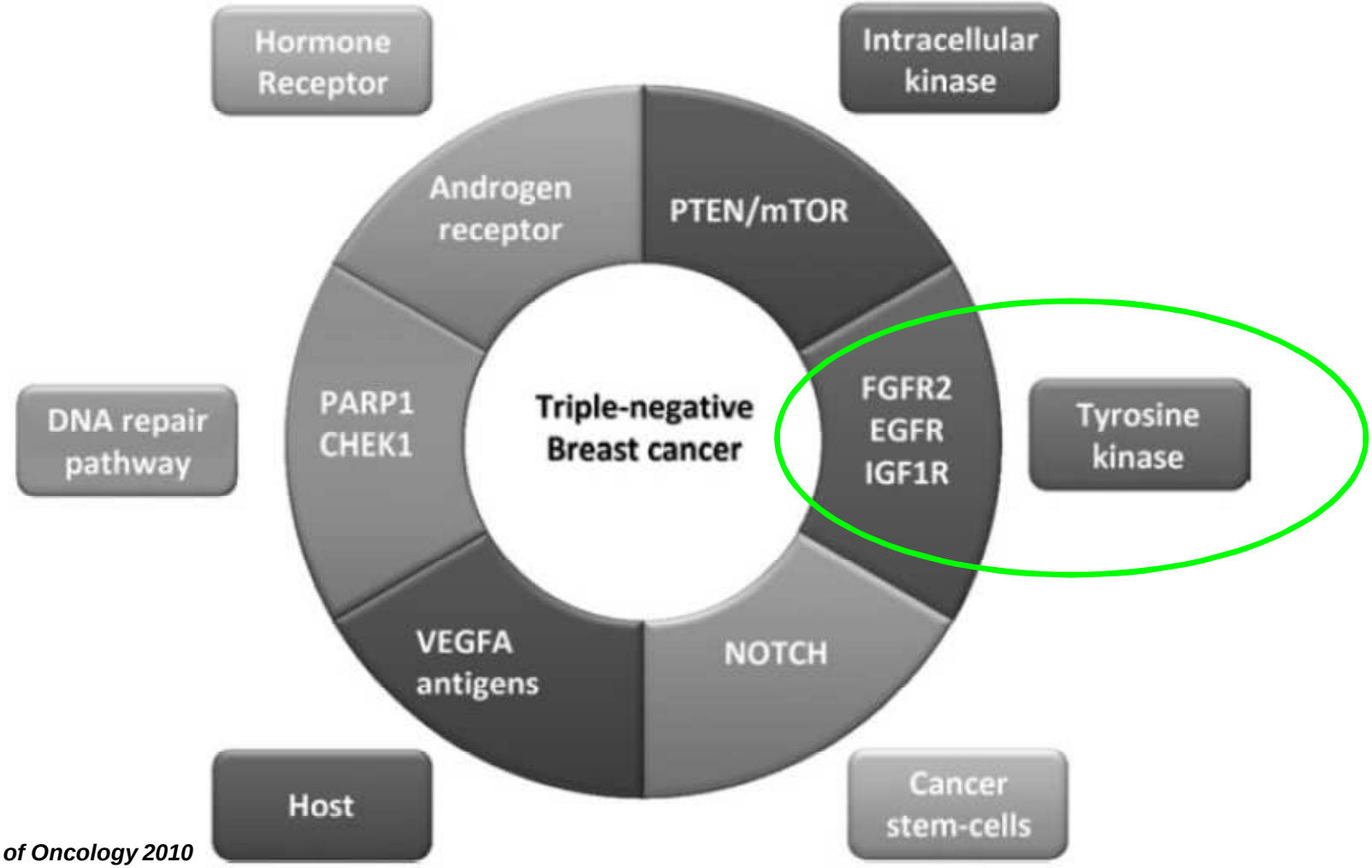
	Non-Bév (n = 1 008)	Bév (n = 1 439)
Médiane (mois)	6,7	9,2
HR (IC_{95})	0,64 (0,57-0,71)	

Patientes à risque (n)

Non-Bév	1 008	680	464	210	111	38	18	9	1	0	0
Bév	1 439	1 157	885	491	292	134	67	22	8	2	1

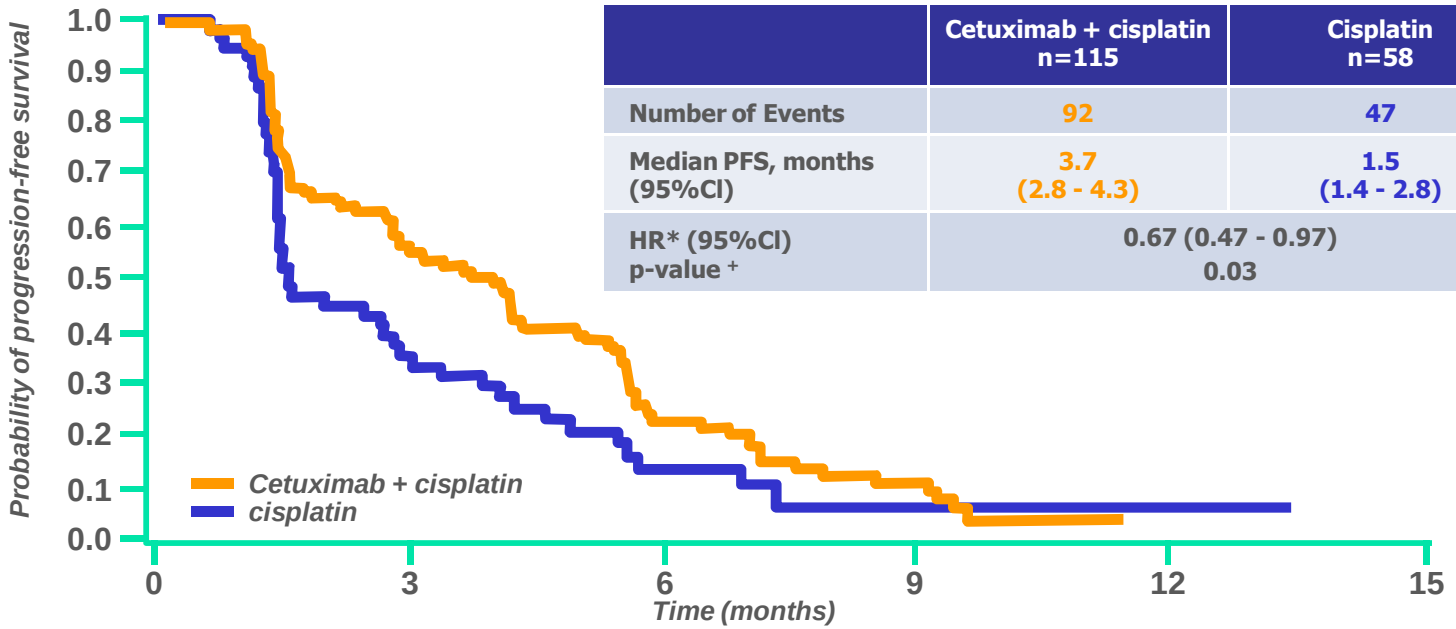
ASCO 2010 - D'après O'Shaughnessy J et al., abstr. 1005 actualisé

Cibles putatives dans les tumeurs TN



Berrada et al., Annals of Oncology 2010

Tumeurs TN, Phase II
Cisplatine vs Cisplatine + cetuximab



	Cetuximab + cisplatin n=115	Cisplatin n=58
Number of Events	92	47
Median PFS, months (95%CI)	3.7 (2.8 - 4.3)	1.5 (1.4 - 2.8)
HR* (95%CI) p-value +	0.67 (0.47 - 0.97) 0.03	

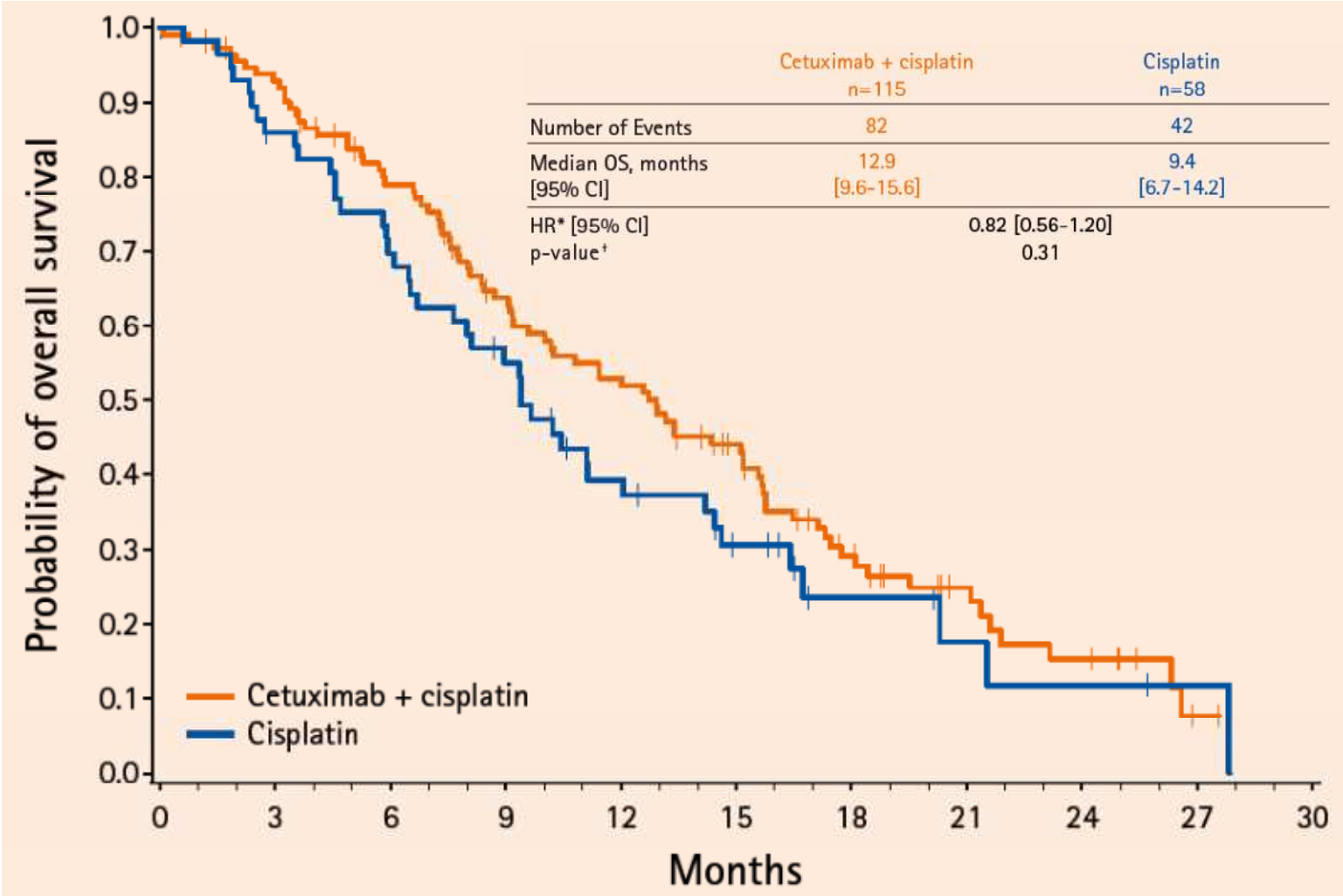
No. of patients still at risk

Cetuximab + cisplatin	115	53	18	6	0	0
Cisplatin	58	16	5	1	1	0

**Stratified Cox's proportional hazards model, +Two-side log-rank test stratified by line of treatment. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival*

Baselga et *al.* SABCS 2010. Abs PD01 01

Tumeurs TN, Phase II
Cisplatine vs Cisplatine + cetuximab



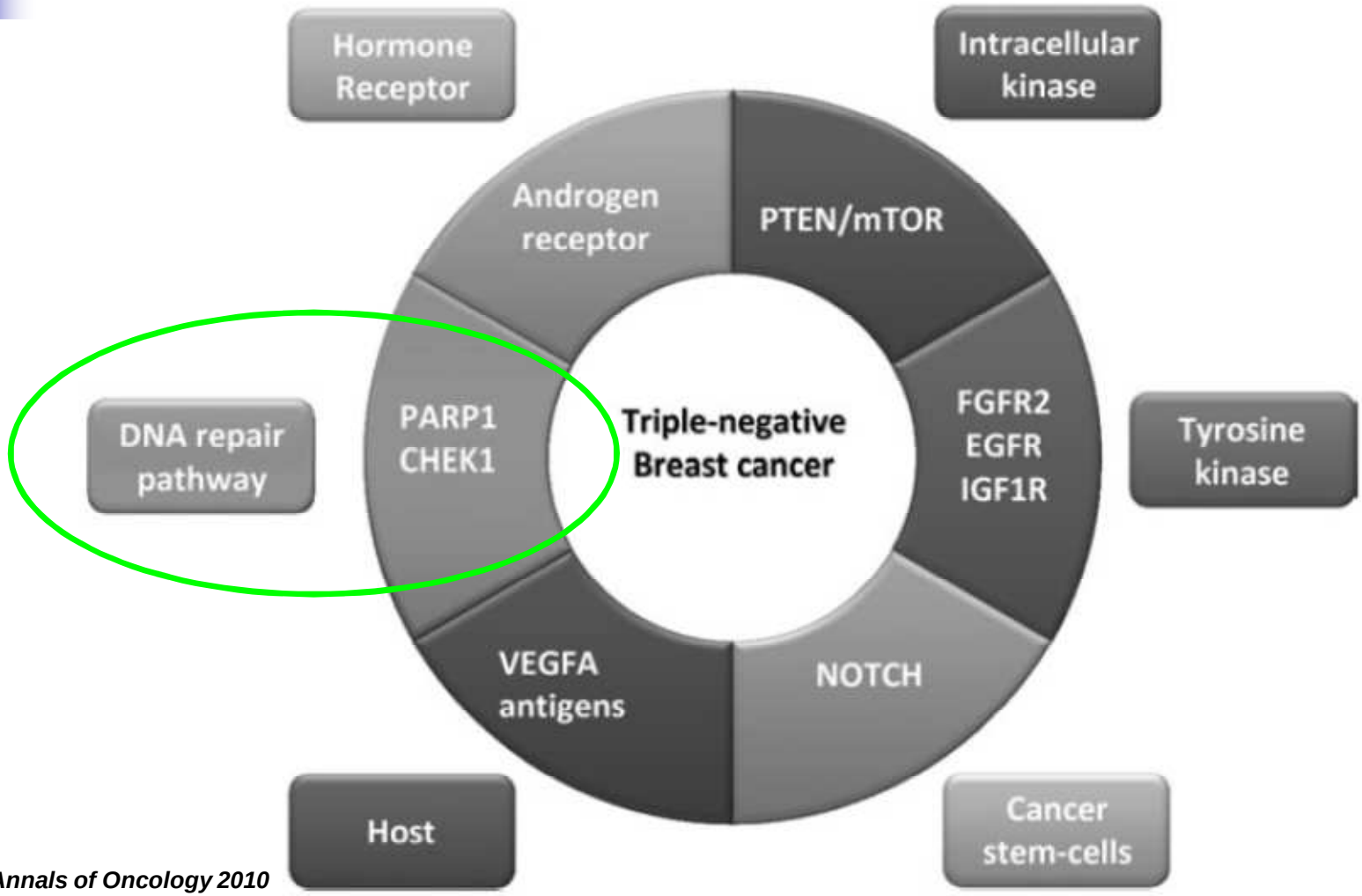
Mutations in the epidermal growth factor receptor (EGFR) gene in triple negative breast cancer: possible implications for targeted therapy

Yvonne Hui-Fang Teng[1], Wai-Jin Tan[1], Aye-Aye Thike[1], Poh-Yian Cheok[1], Gary Man-Kit Tse[2], Nan-Soon Wong[3], George Wai-Cheong Yip[4], Boon-Huat Bay[4] and Puay-Hoon Tan[1*]

Table 4 Summary of EGFR mutations detected in primary tumours of triple negative breast cancers (*n* = 8)

Mutations	Number of samples (%)
Exon 19	
del E746 to A750 (15 bp deletion)	2/70 (2.9%)
del S752 to I759 (24 bp deletion)	2/70 (2.9%)
inversion of complementary strand	1/70 (1.5%)
Exon 21	
L858R	1/70 (1.5%)
T847I	2/70 (2.9%)
Total	**8/70 (11.4%)**
Single nucleotide polymorphisms	
Exon 18	
T725T	3/70 (4.3%)
Exon 20	
Q787Q	6/70 (8.6%)

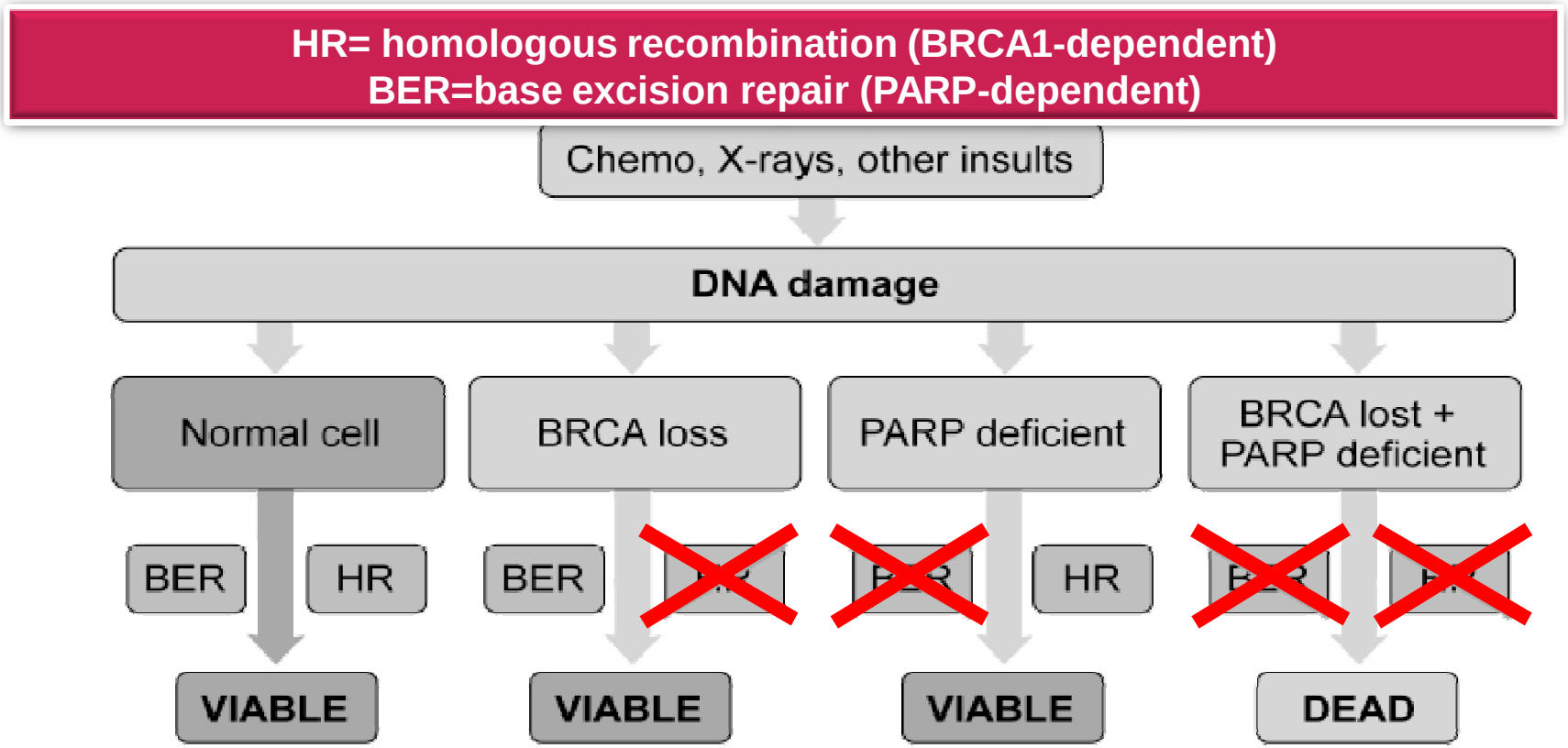
Cibles putatives dans les tumeurs TN



Berrada et al., Annals of Oncology 2010

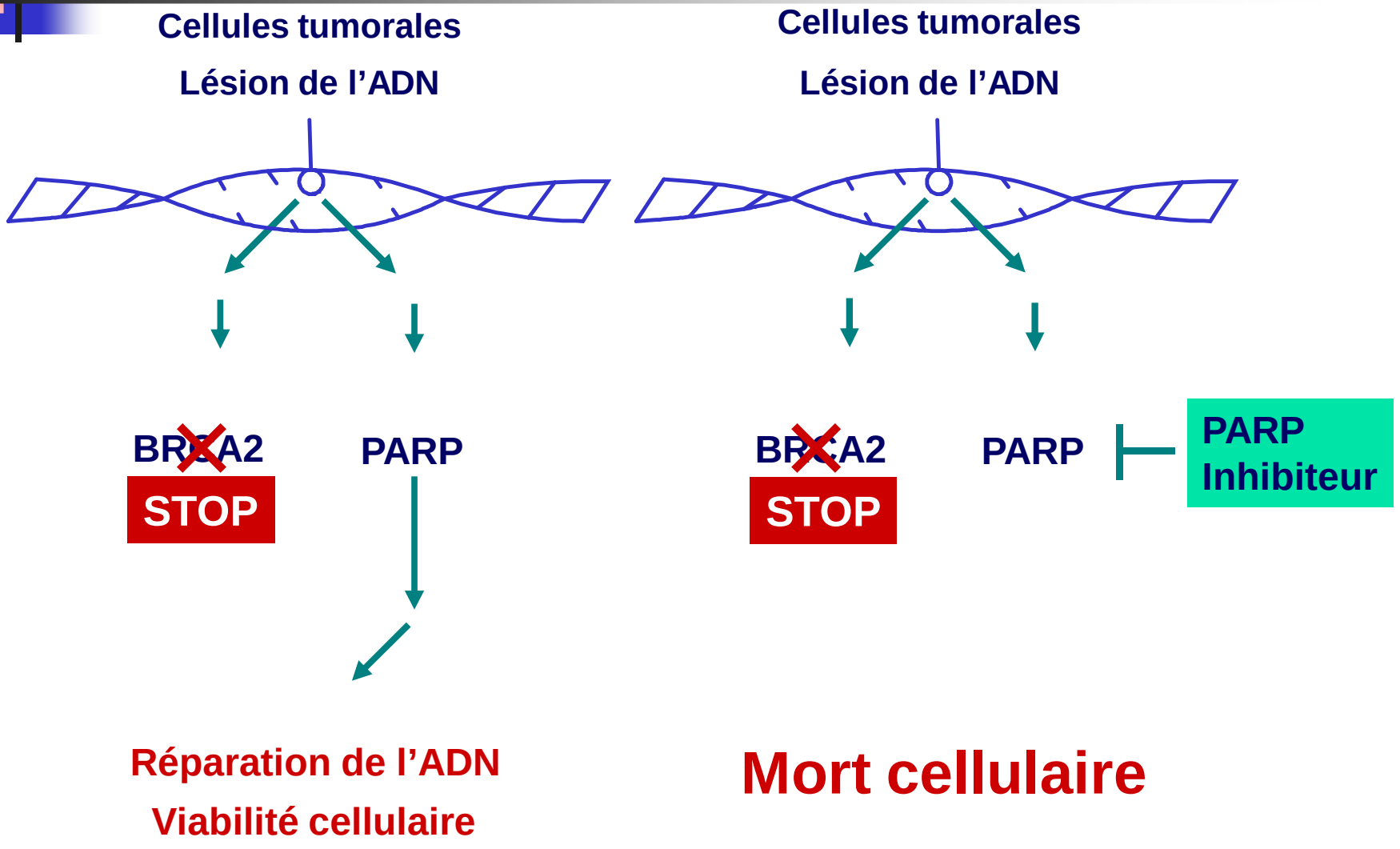
Synergie des dysfonctions des voies BRCA1 et PARP et létalité cellulaire

"SYNTHETIC LETHALITY"



Adapted from Comen and Robson, Oncologist 2010

Cancer du sein TN, BRCA, PARP et PARPi



Rôle exact des agents induisant des cassures de l'ADN

- Sels de platine, alkylants
  - Très hauts taux de pCR en néoadjuvant
  - BRCA- >> autres TN
- Place non clairement définie
- Essais cliniques en cours

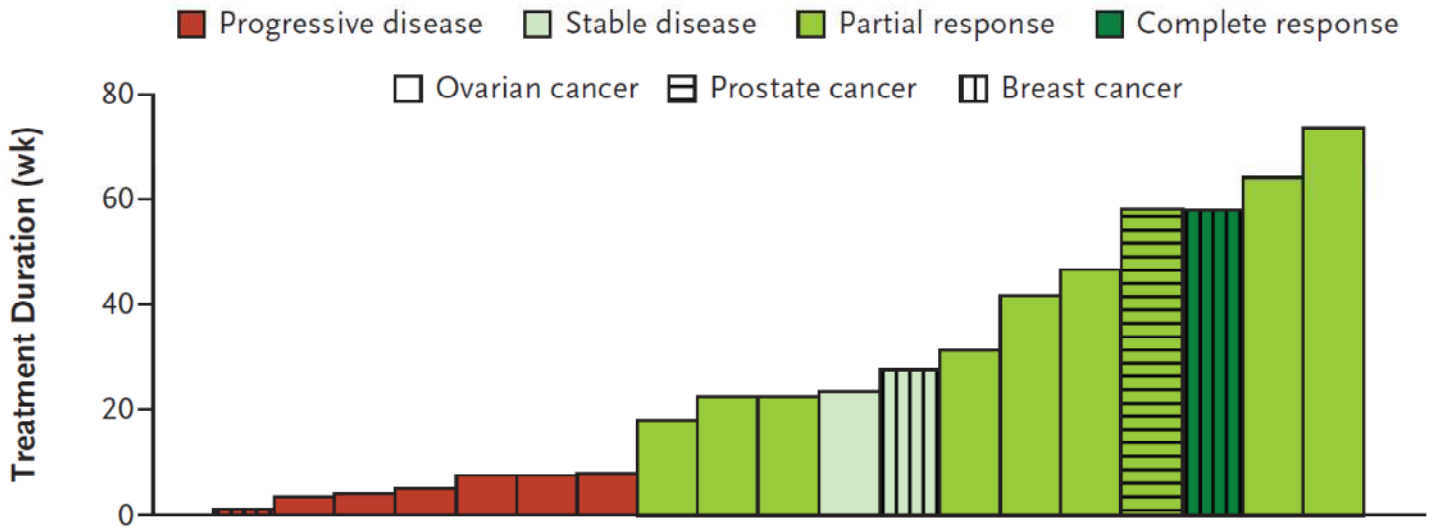
Olaparib
Tumeurs BRCA mutées, phase I

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2009 VOL. 361 NO. 2

Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

Peter C. Fong, M.D., David S. Boss, M.Sc., Timothy A. Yap, M.D., Andrew Tutt, M.D., Ph.D., Peijun Wu, Ph.D., Marja Mergui-Roelvink, M.D., Peter Mortimer, Ph.D., Helen Swaisland, B.Sc., Alan Lau, Ph.D., Mark J. O'Connor, Ph.D., Alan Ashworth, Ph.D., James Carmichael, M.D., Stan B. Kaye, M.D., Jan H.M. Schellens, M.D., Ph.D., and Johann S. de Bono, M.D., Ph.D.



Phase II Study Olaparib in BRCA1/2-Associated Breast Cancer (Tutt et al.)

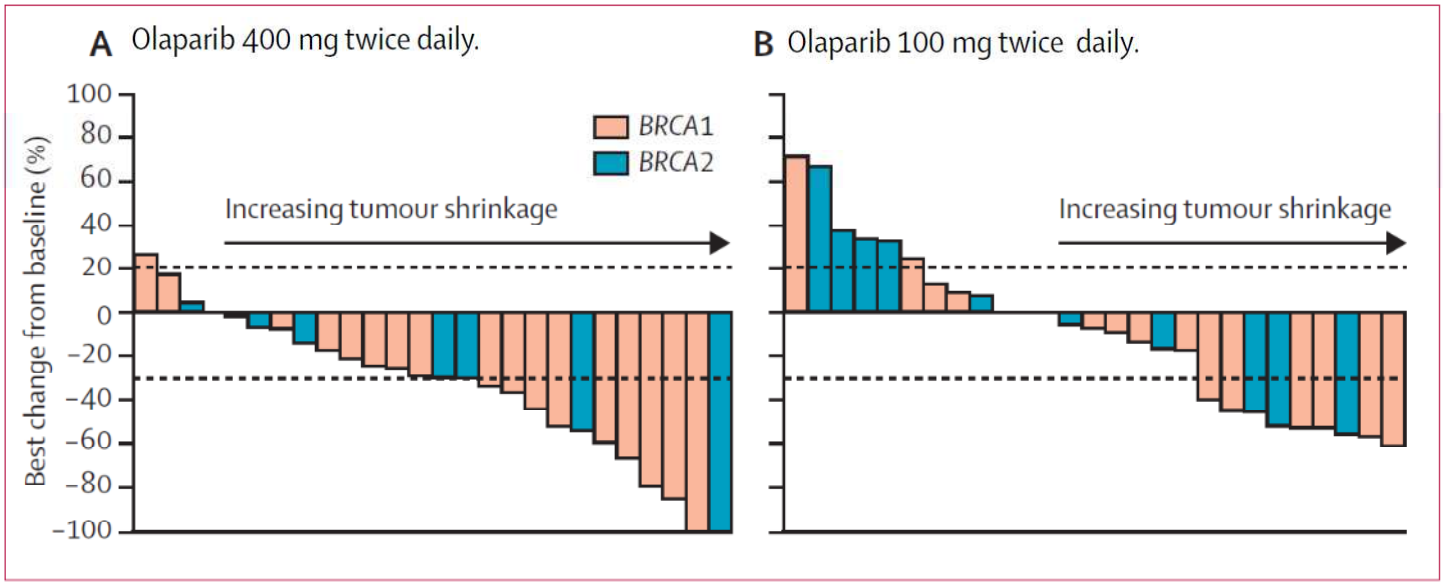
54 patientes stade IV
• BRCA1/2 mutées

Olaparib 100 mg po X2/J

↓

Olaparib 400 mg po X2/J

- **Objectif primaire = Réponse objective**
- **Objectifs secondaires :**
  - **% modifications de volume**
  - **Survie sans progression**

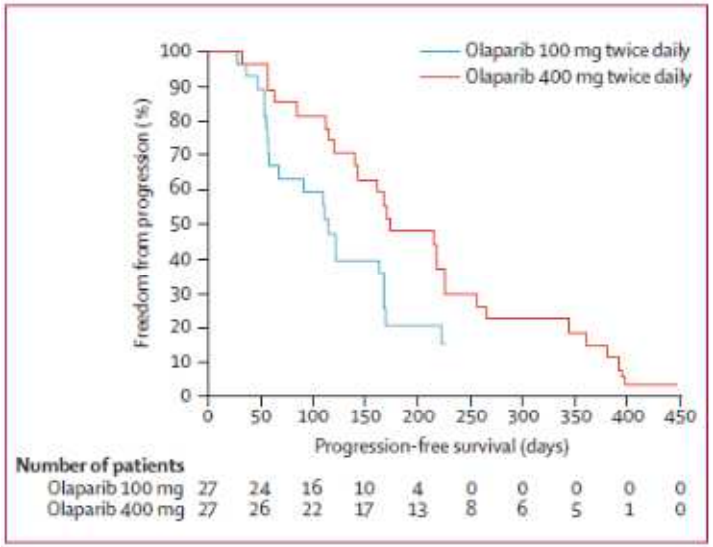


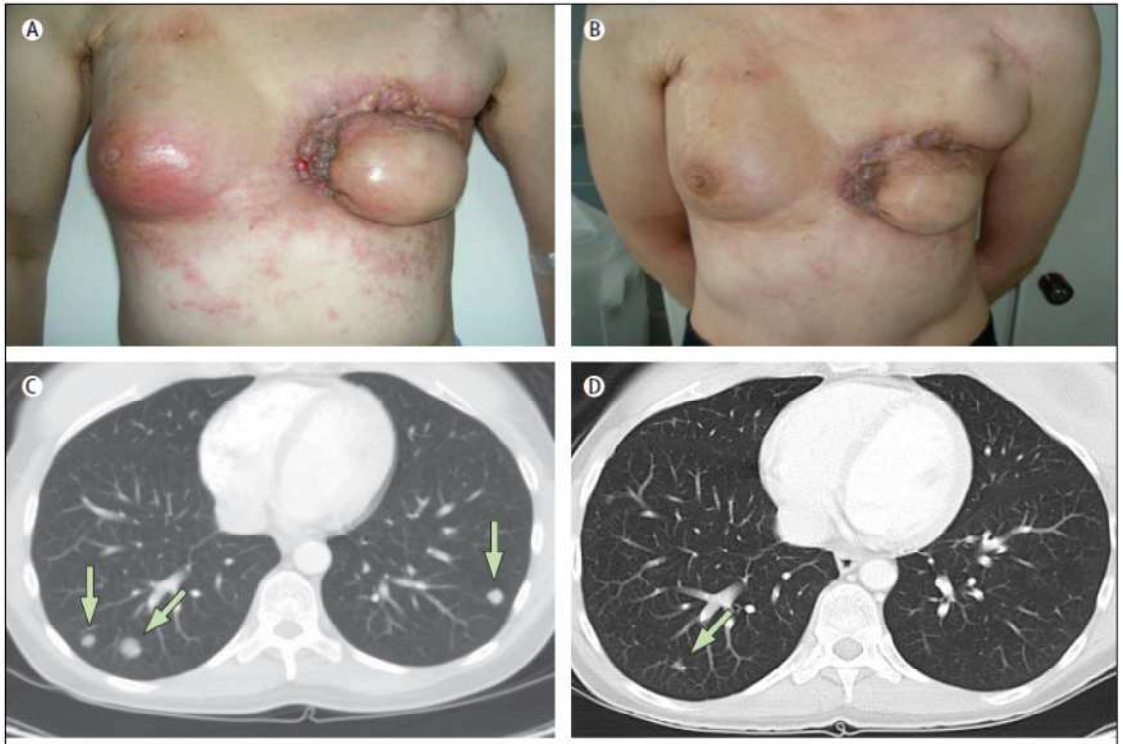
Lancet 2010; 376: 235-44

	Olaparib 400 mg twice daily (n=27)				Olaparib 100 mg twice daily (n=27)			
	BRCA1 (n=18)	*BRCA2* (n=9)	Triple negative (n=13)	Non-triple negative (n=14)	*BRCA1* (n=16)	*BRCA2* (n=11)	Triple negative (n=16)	Non-triple negative (n=11)
Objective response	9 (50%)	2 (22%)	7 (54%)	4 (29%)	3 (19%)	3 (27%)	4 (25%)	2 (18%)
Complete response	1 (6%)	0	0	0	0	0	0	0
Partial response	8 (44%)	2 (22%)	7 (54%)	4 (29%)	3 (19%)	3 (27%)	4 (25%)	2 (18%)
Stable disease	7 (39%)	5 (56%)	4 (31%)	8 (57%)	9 (56%)	3 (27%)	7 (44%)	4 (36%)
Progressive disease	2 (11%)	2 (22%)	2 (15%)	2 (14%)	4 (25%)	5 (45%)	5 (31%)	5 (45%)

Data are number (%).

***Table 3*: Best overall confirmed tumour response status (intention-to-treat population) by *BRCA* mutation status and hormonal status**





Tolérance

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Nausea		
1 or 2	11 (41%)	11 (41%)
3 or 4	4 (15%)	0
Fatigue		
1 or 2	11 (41%)	7 (26%)
3 or 4	4 (15%)	1 (4%)
Vomiting		
1 or 2	3 (11%)	4 (15%)
3 or 4	3 (11%)	0
Anaemia*		
1 or 2	1 (4%)	2 (7%)
3 or 4	3 (11%)	2 (7%)
Anorexia		
1 or 2	3 (11%)	3 (11%)
3 or 4	0	1 (4%)
Diarrhoea		
1 or 2	3 (11%)	2 (7%)
3 or 4	0	0

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Discontinuations	0	1 (4%)
Dose interruption	8 (30%)	2 (7%)
Dose reduction	9 (33%)	1 (4%)

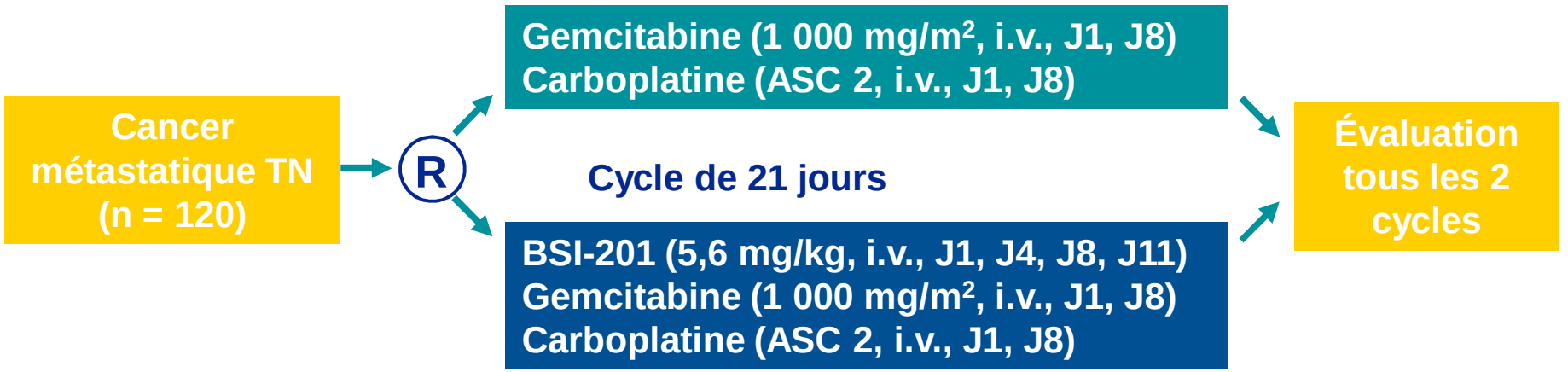
Data are number (%).

Table 5: **Dose interruptions and reductions due to adverse events**

Lancet 2010; 376: 235–44

Inhibiteur de PARP BSI-201
Phase II randomisée dans les tumeurs TN

Schéma du traitement



2009 ASCO Meeting - O'Shaughnessy J et al., abstract 3 actualisé

Inhibiteur de PARP BSI-201
Phase II randomisée dans les tumeurs TN

Résultats préliminaires d'efficacité

	Gemcitabine/ carboplatine (n = 44)	BSI-201 + gemcitabine/ carboplatine (n = 42)	*p*
Réponse objective n (%)	7 (16 %)	20 (48 %)	0,002
Bénéfice clinique n (%)	9 (21 %)	26 (62 %)	0,0002

2009 ASCO Meeting - O'Shaughnessy J et al., abstract 3 actualisé

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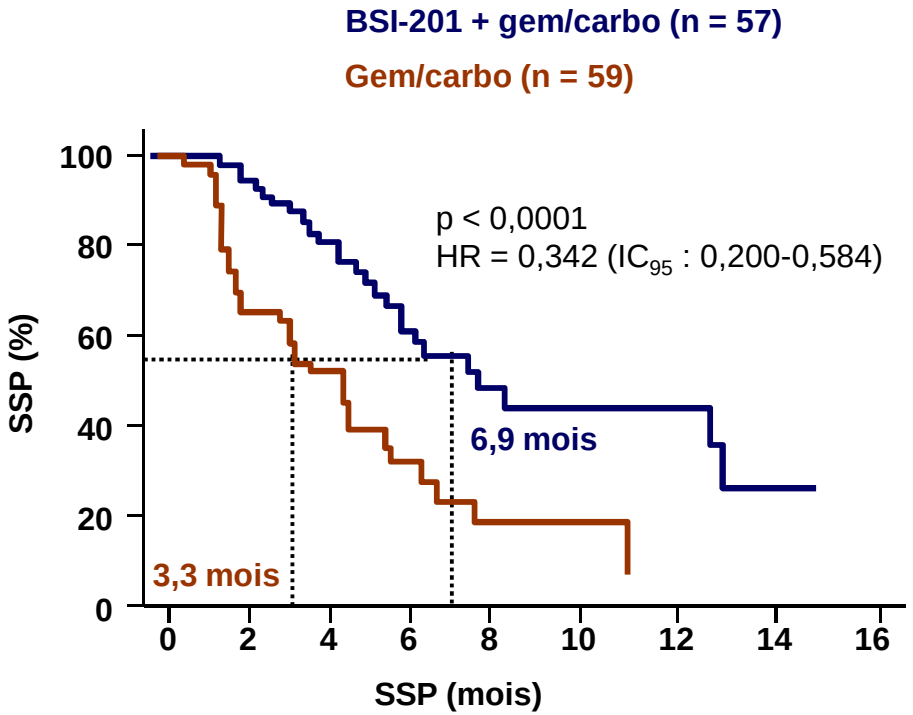
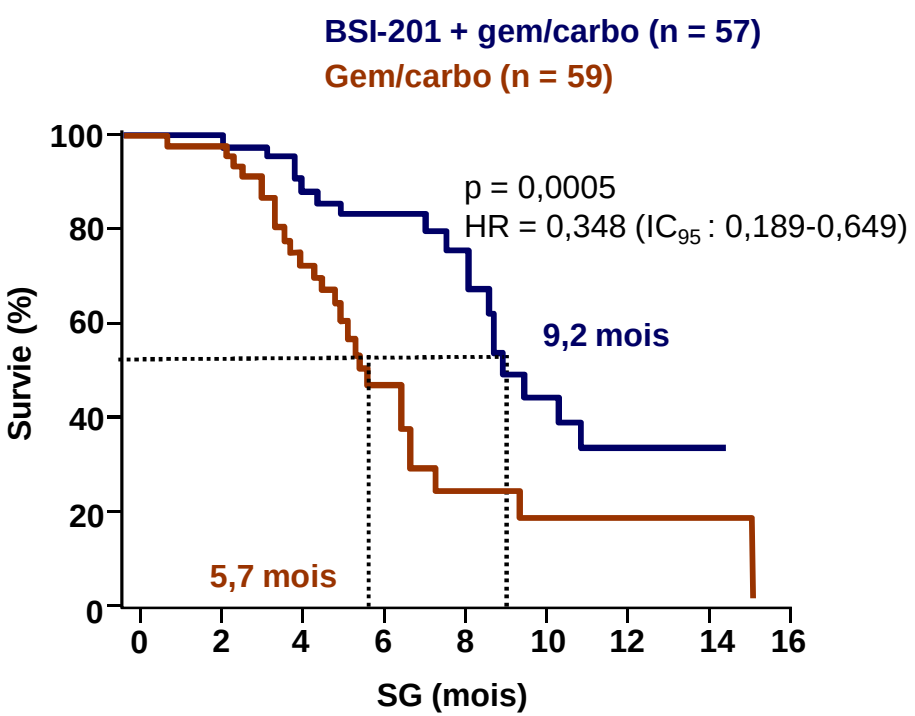
Phase II randomisée dans les tumeurs TN

Survie sans progression (SSP)

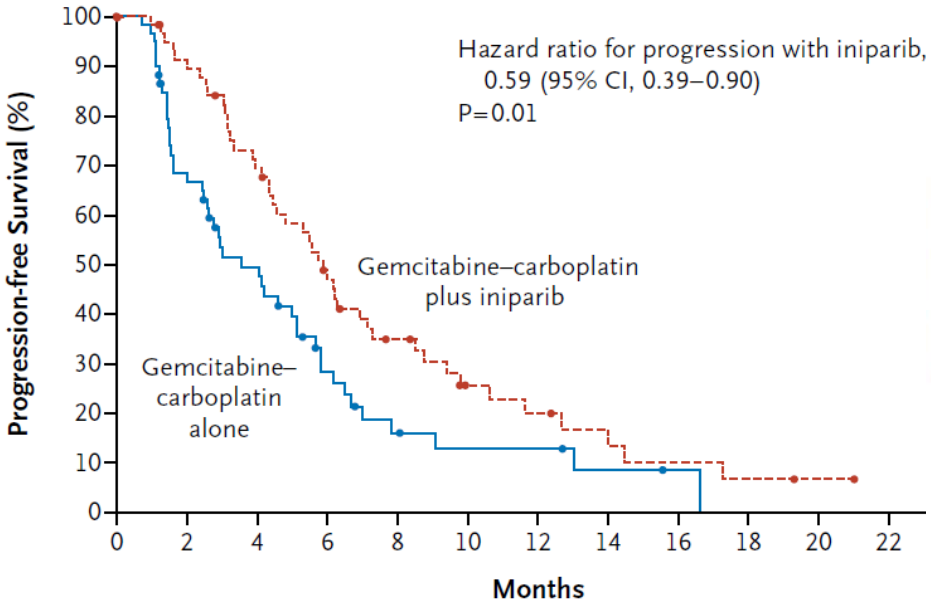


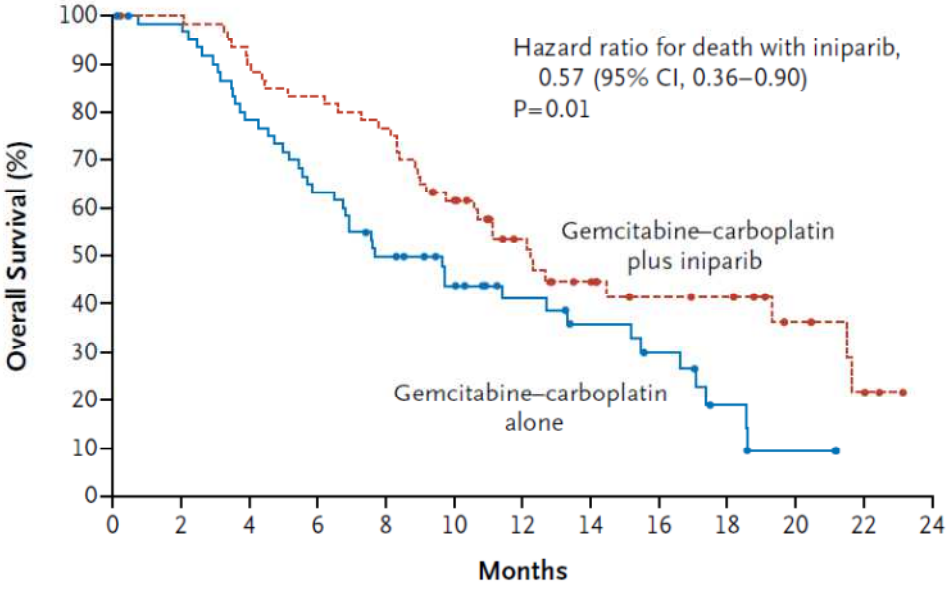
Survie globale (SG)



2009 ASCO Meeting - O'Shaughnessy J et al., abstract 3 actualisé

Inhibiteur de PARP BSI-201
Phase II randomisée dans les tumeurs TN



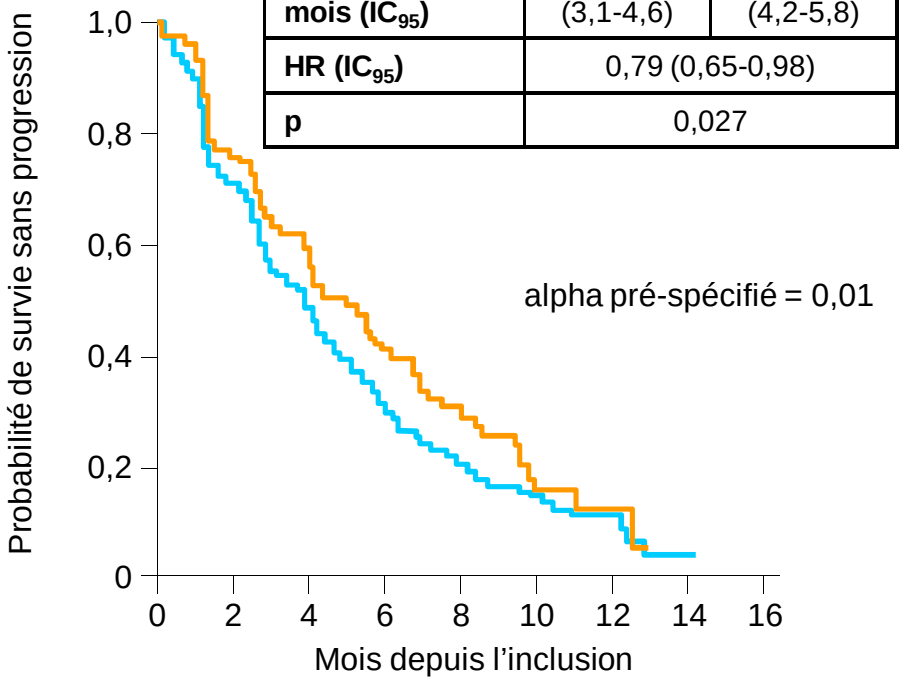


O'Shaughnessy J et al., NEJM 2011

Etude de phase III : iniparib dans les tumeurs triple négatives

Critères d'efficacité – population en ITT

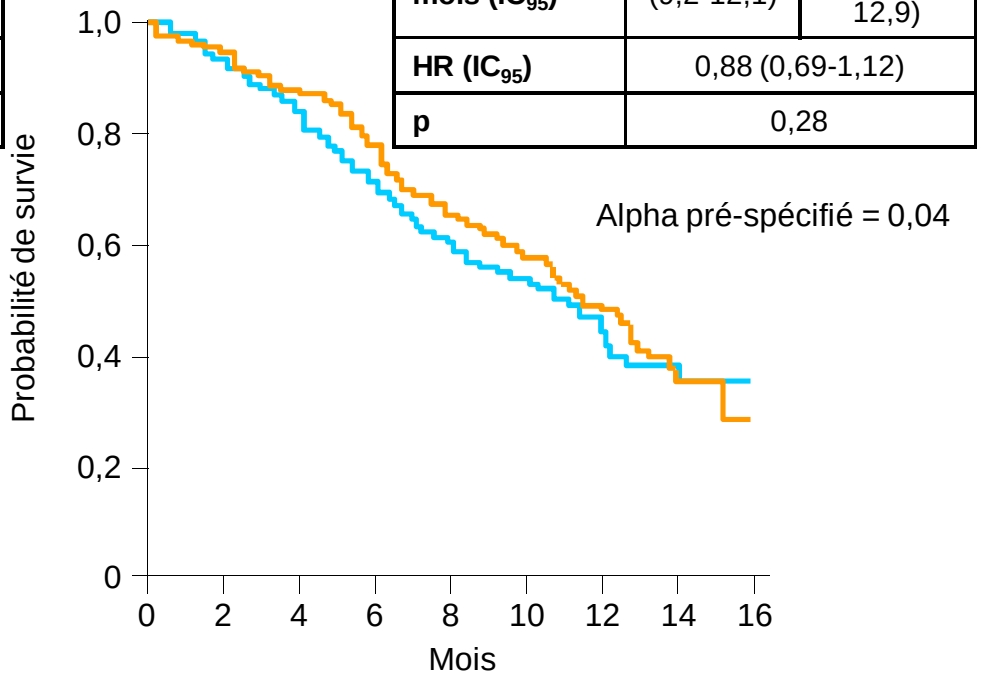
SSP	GC (n = 258)	GCI (n = 261)
Médiane SSP, mois (IC_{95})	4,1 (3,1-4,6)	5,1 (4,2-5,8)
HR (IC_{95})	0,79 (0,65-0,98)	
p	0,027	



Patients à risque

GC	258	171	116	63	38	18	6	1	0
GCI	261	187	138	83	53	11	2	0	0

SG	GC (n = 258)	GCI (n = 261)
Médiane SSP, mois (IC_{95})	11,1 (9,2-12,1)	11,8 (10,6-12,9)
HR (IC_{95})	0,88 (0,69-1,12)	
p	0,28	



Patients à risque

GC	258	239	214	181	151	99	38	11	0
GCI	261	248	230	204	169	111	52	15	0

D'après O'Shaughnessy J et al., abstr. 1007 actualisé

Etude de phase III : iniparib dans les tumeurs triple négatives

Analyse multiparamétrique - Survie globale

	ITT population		1re ligne		2e/3e ligne	
	HR	p	HR	p	HR	p
Non ajustée	0,88	0,28	1,1	0,56	0,65	0,012
Avec facteurs spécifiés initialement	0,81	0,08*	0,91	0,62*	0,72	0,07*
Avec facteurs spécifiés initialement **+ intervalle libre**	0,78	0,05*	0,83	0,32	0,71	0,05*

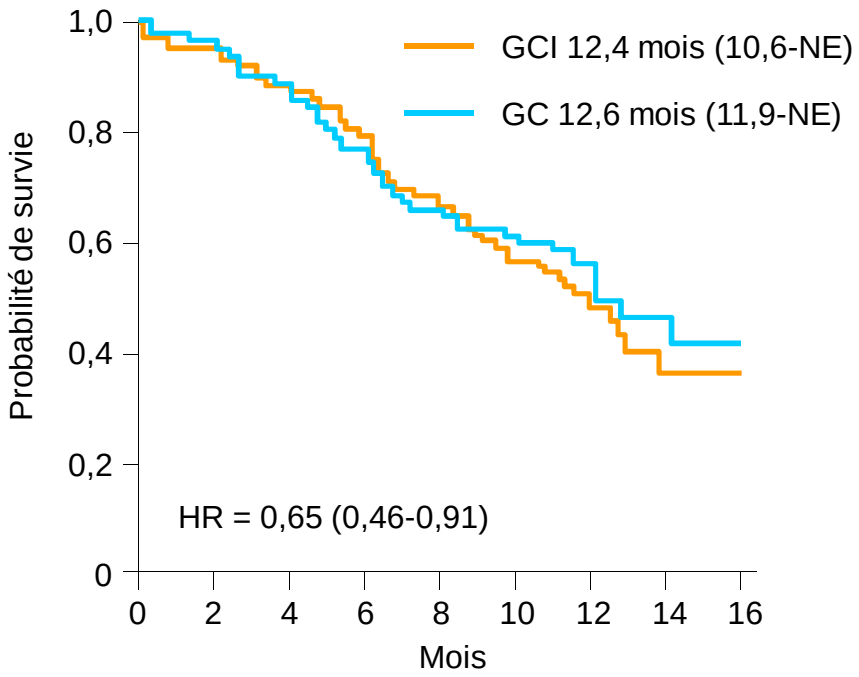
* p-value os Wald Chi-Square test

D'après O'Shaughnessy J et al., abstr. 1007 actualisé

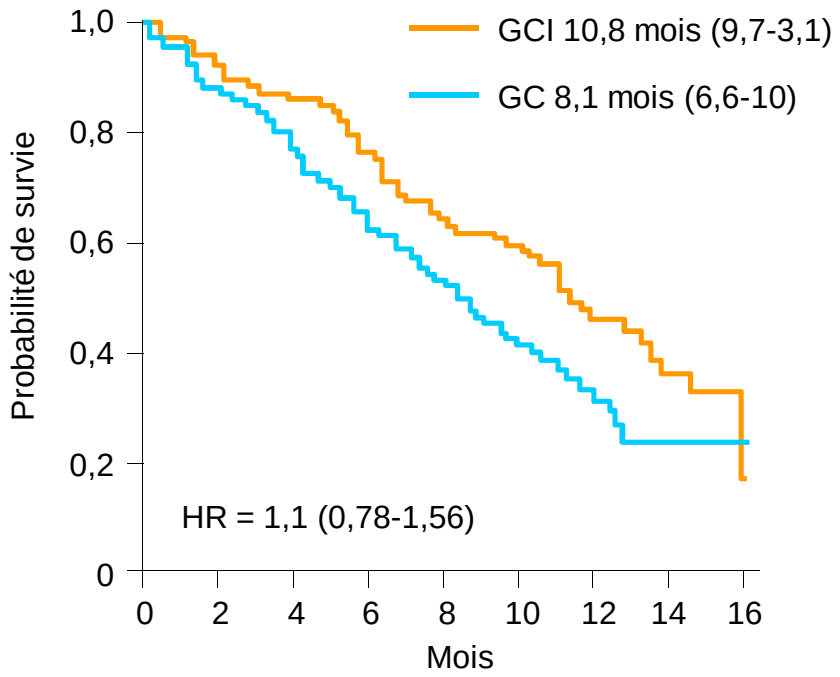
Etude de phase III : Iniparib dans les tumeurs triple négatives

Analyse exploratoire

1ère ligne (n = 297) [57 %]



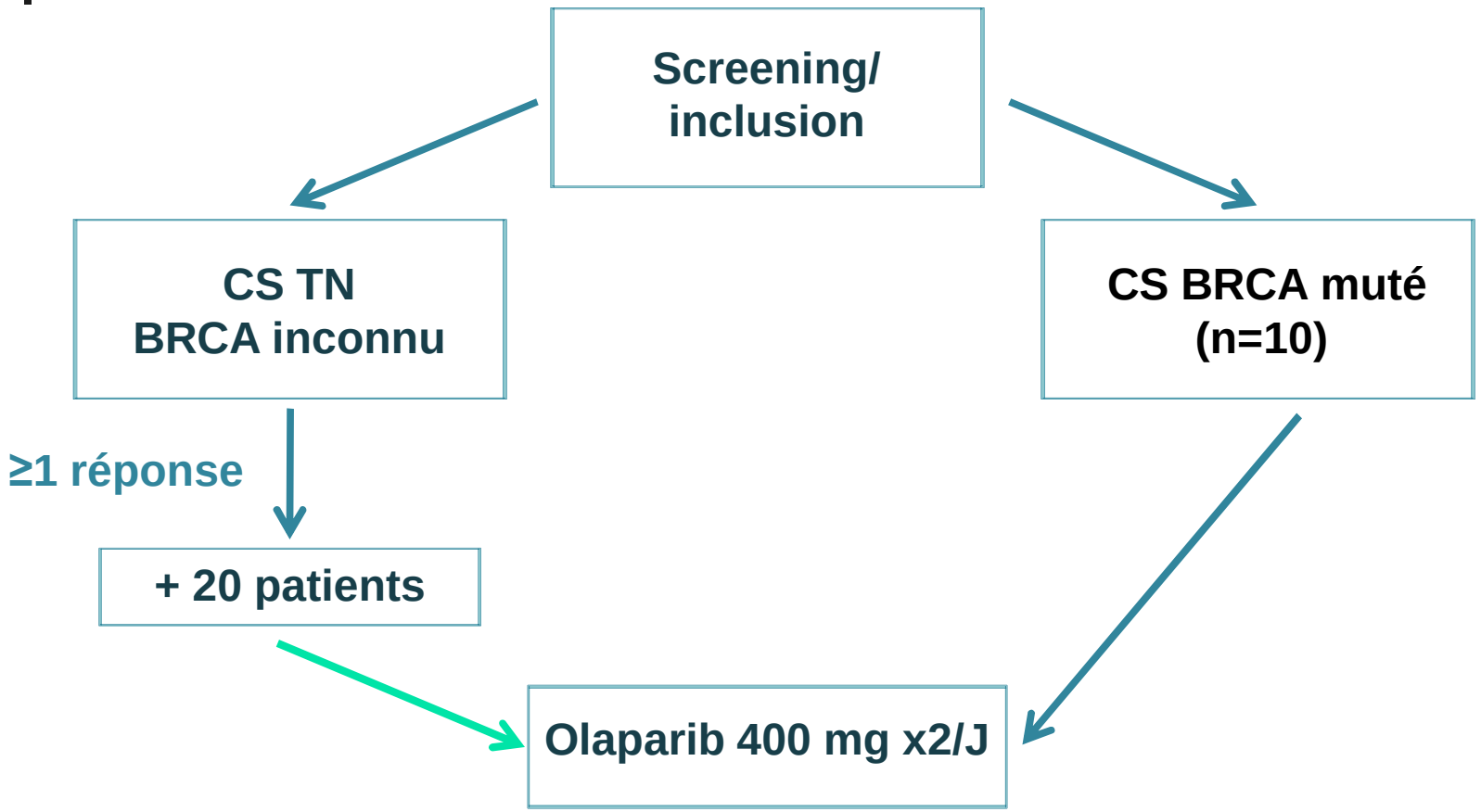
2ème /3ème ligne (n = 222) [43 %]



- Ajustement sur la différence en intervalle libre à la baseline

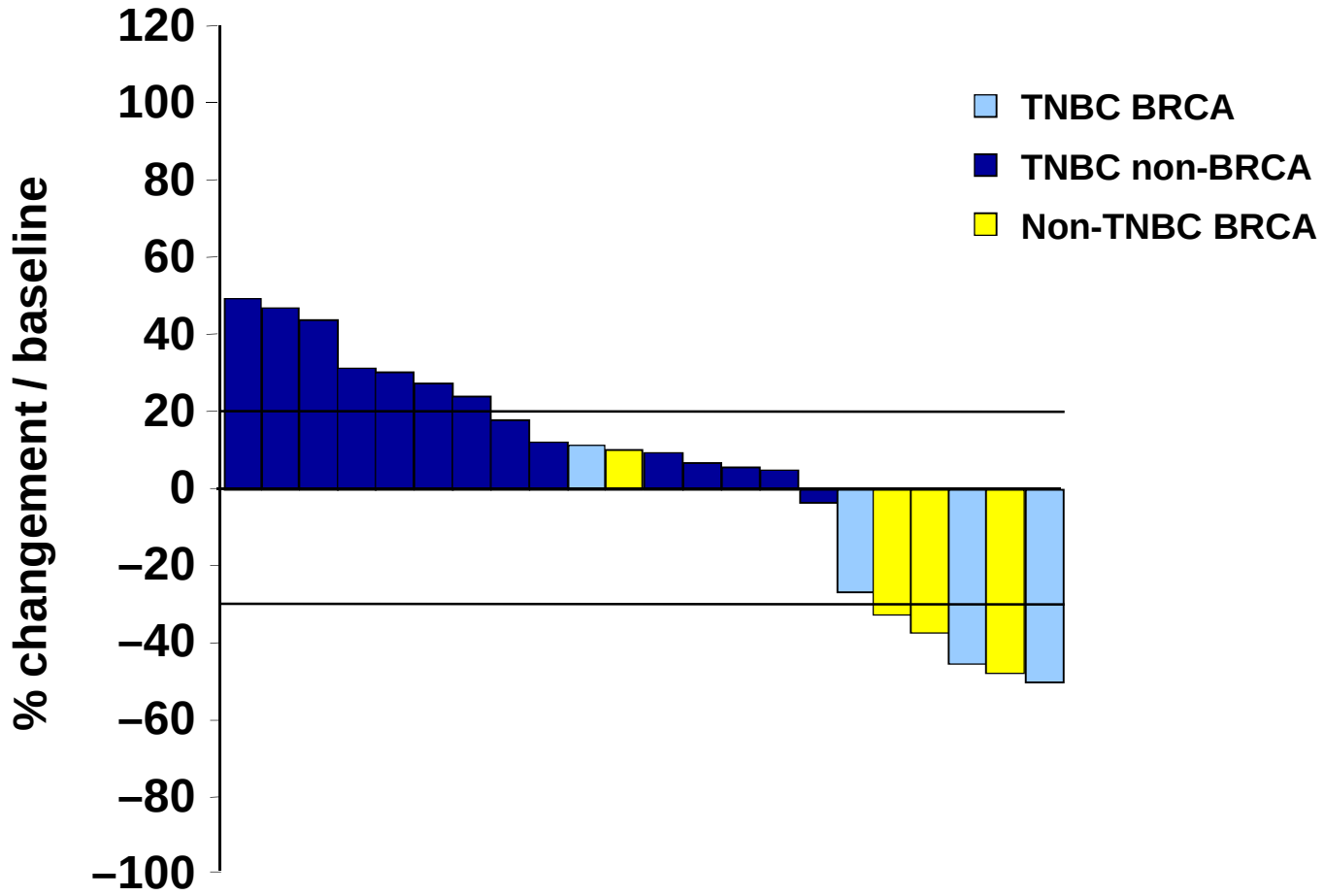
D'après O'Shaughnessy J et al., abstr. 1007 actualisé

Olaparib et le phénotype "BRCAness"



Gelmon, ASCO 2010

Olaparib et le phénotype "BRCAness"



Gelmon K, ASCO 2010

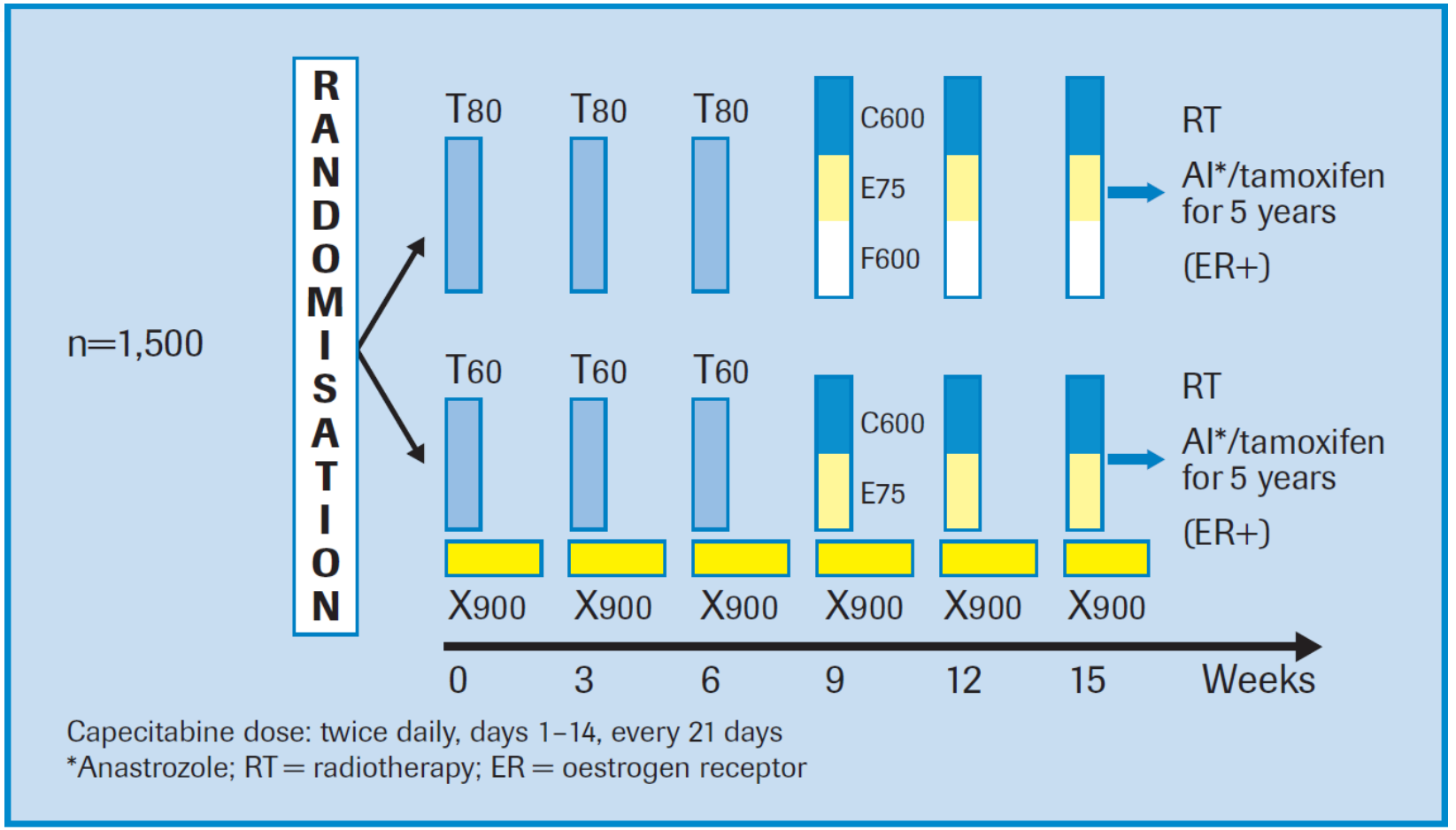
Méthylation du promoteur

Breast Cancer Subtypes	LumA	LumB	HER2	Basal/TN
BRCA1 methylated (n = 18) [Sporadic]	5 (28%)	2 (11%)	1 (5%)	10 (56%)
Not BRCA1 methylated (n = 59) [Sporadic][a, b]	25 (42%)	21 (36%)	3 (5%)	10 (17%)

Stefansson et al., Epigenetics 2011

Et simplement en changeant notre chimiothérapie ???

FinXX final 5-year analysis: Results of the randomised, open label, phase III trial in medium-to-high risk early breast cancer Schéma de l'étude



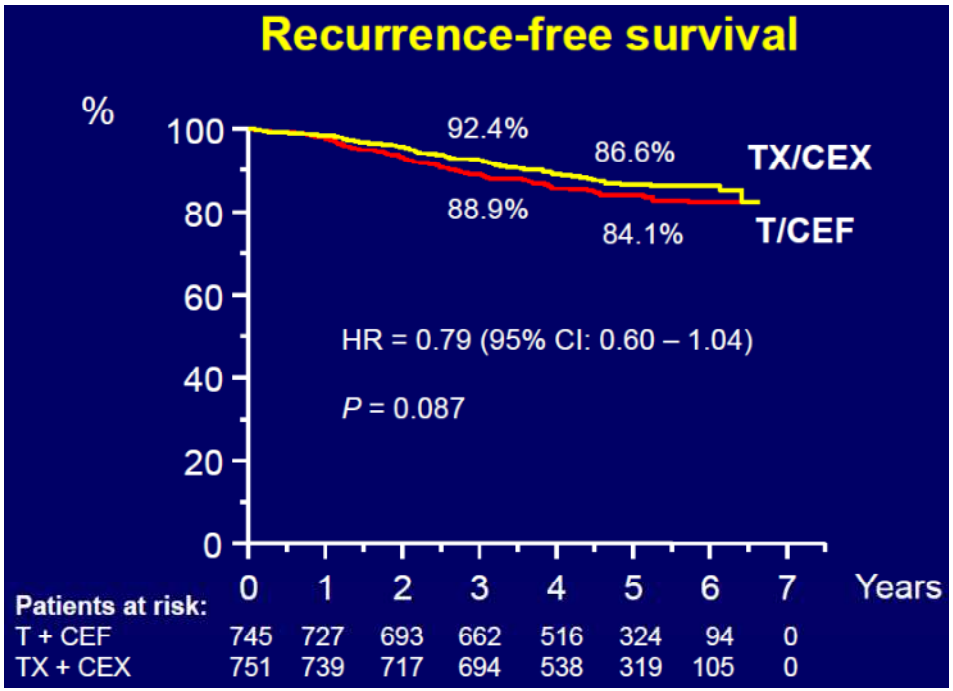
- Primary endpoint: RFS; secondary endpoints: OS, safety
- Interim analysis based on 3-year follow-up

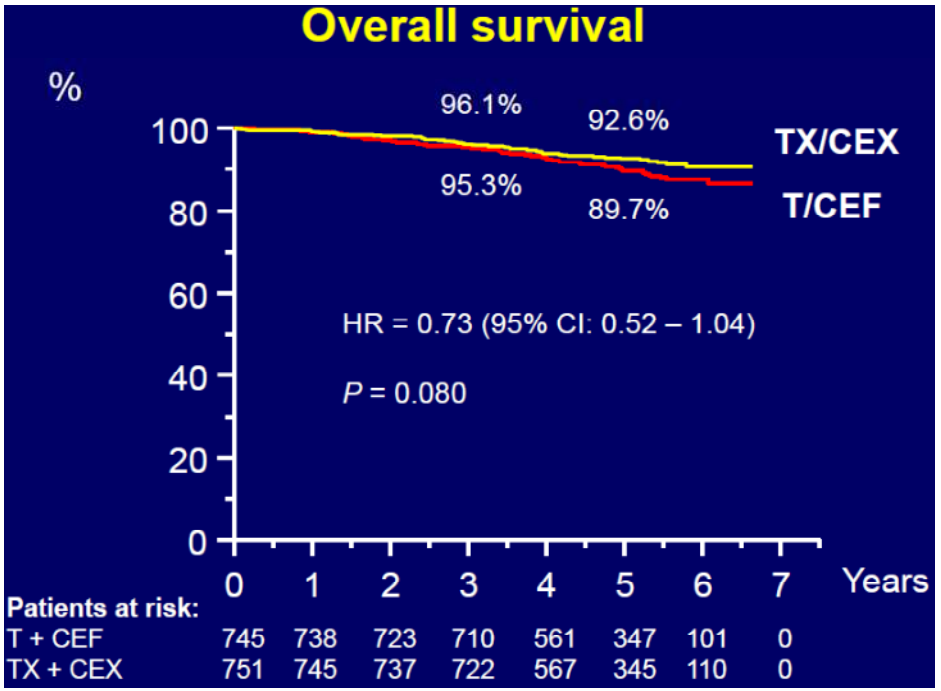
Joensuu H *et al.* SABCS 2010. Abs S4.1

INTEGRATION OF CAPECITABINE INTO ANTHRACYCLINE- AND TAXANE-BASED ADJUVANT THERAPY FOR TRIPLE-NEGATIVE EARLY BREAST CANCER: FINAL SUBGROUP ANALYSIS OF THE FINXX STUDY

	T→CEF (n=747)	XT→CEX (n=753)
Median age, years (range)	53 (27–65)	52 (26–65)
Premenopausal, %	44	43
Z score, %		
0	89	88
1	11	12
Tumour size (pT), %		
1 or 2	93	94
3 or 4	7	6
Nodal status (pN), %		
pN0	10	11
pN+	90	89
Histological grade, %		
1/2/3	11/47/42	12/48/40
Receptor status, %		
ER positive	76	77
PgR positive	61	63
HER2 positive	19	19
Triple negative	15	12

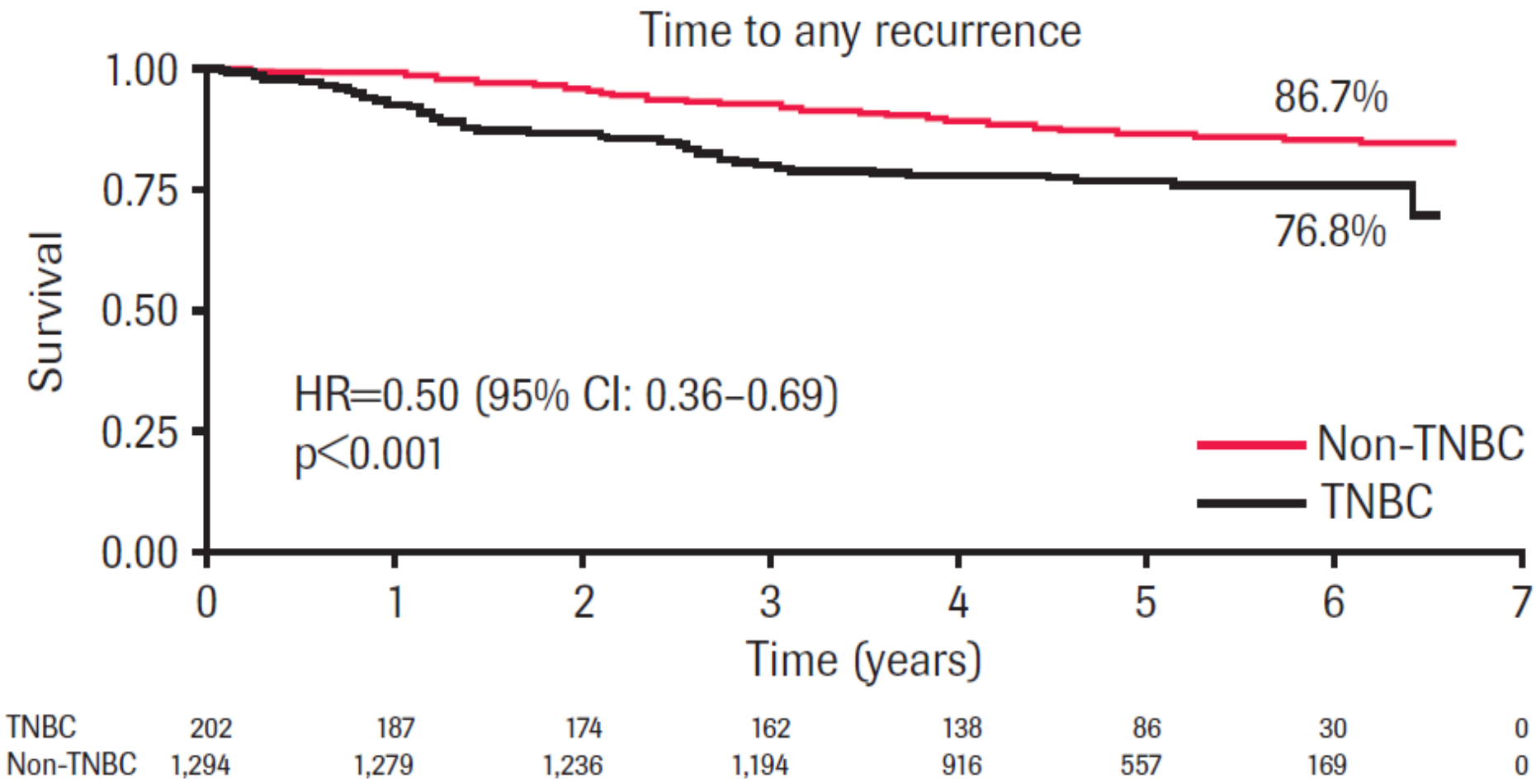
FINXX



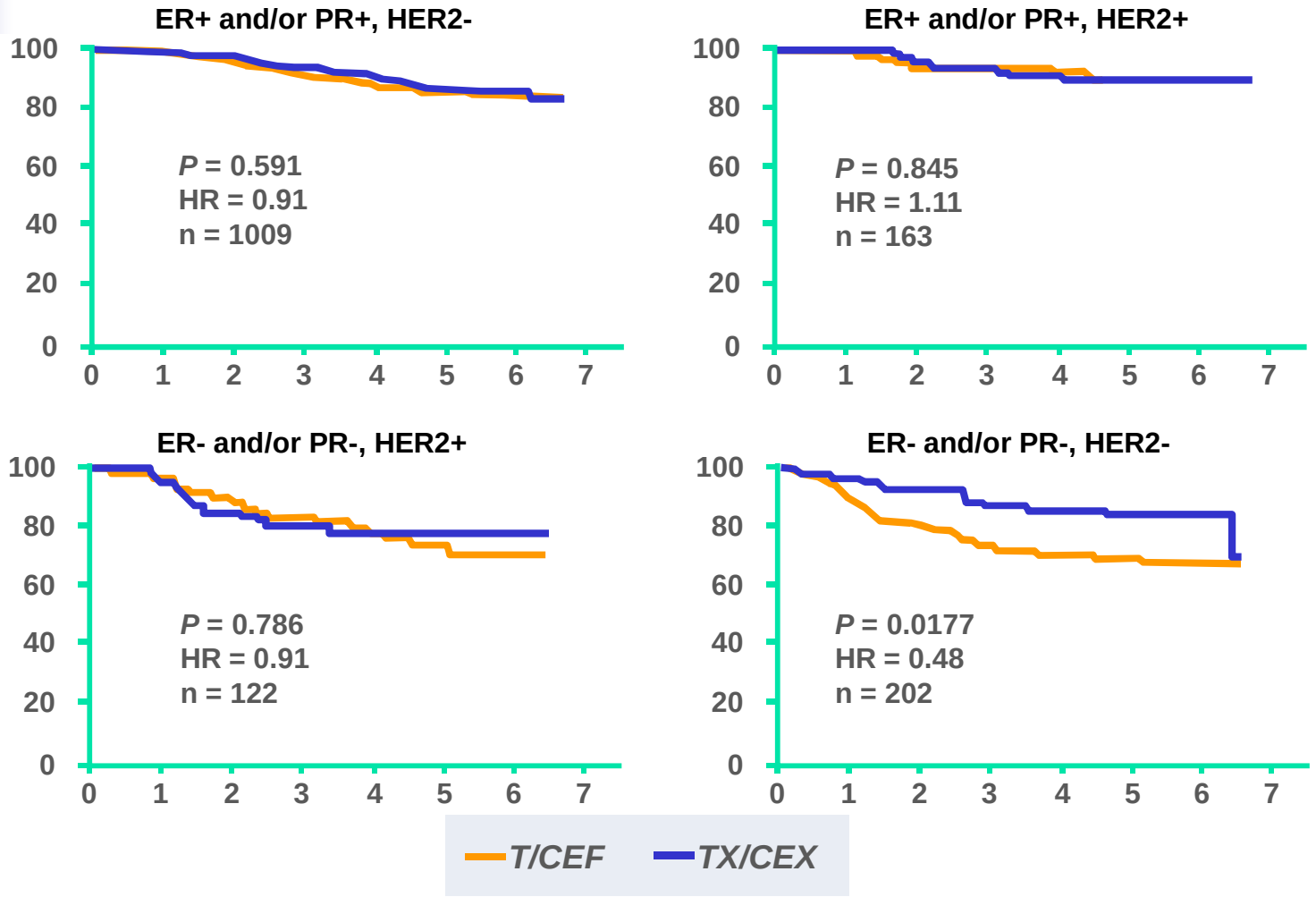


- Absence d'amélioration de la survie sans rechute, objectif principal (HR=0,79), et de la survie globale (HR=0,73) par l'addition de capécitabine dans la chimiothérapie adjuvante

Mauvais pronostic des TN



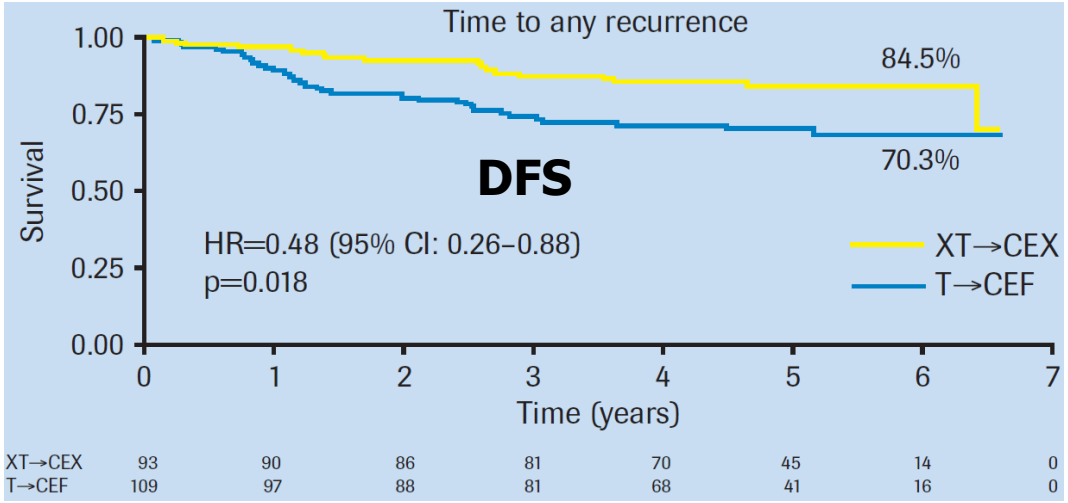
Analyses exploratoires : Sous type tumoral et RFS

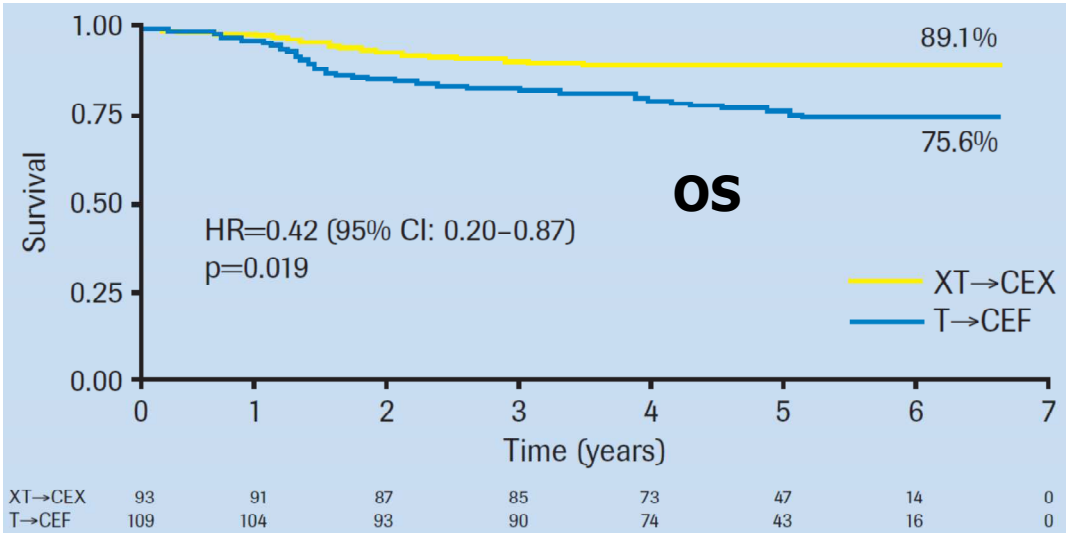


Joensuu H *et al*. SABCS 2010. Abs S4.1

FINXX : analyse exploratoire Sous-groupe TN

Des analyses exploratoires révèlent une amélioration de la survie sans rechute et de la survie pour les tumeurs TN dans le bras capécitabine





... mais analyse exploratoire...

Conclusion - Perspectives

- Environ 15% des cancers du sein
- Agressivité clinique
- Peu de cibles thérapeutiques validées

- Ciblage des mécanismes de réparation de l'ADN
  - Intérêt de la détermination de leur fonctionnalité ?
- Recherche de nouvelles cibles thérapeutiques
- Modèles précliniques plus « réalistes » ?