

Diagnostic moléculaire et inhibiteurs de kinase

Pr. Alexandre Harlé

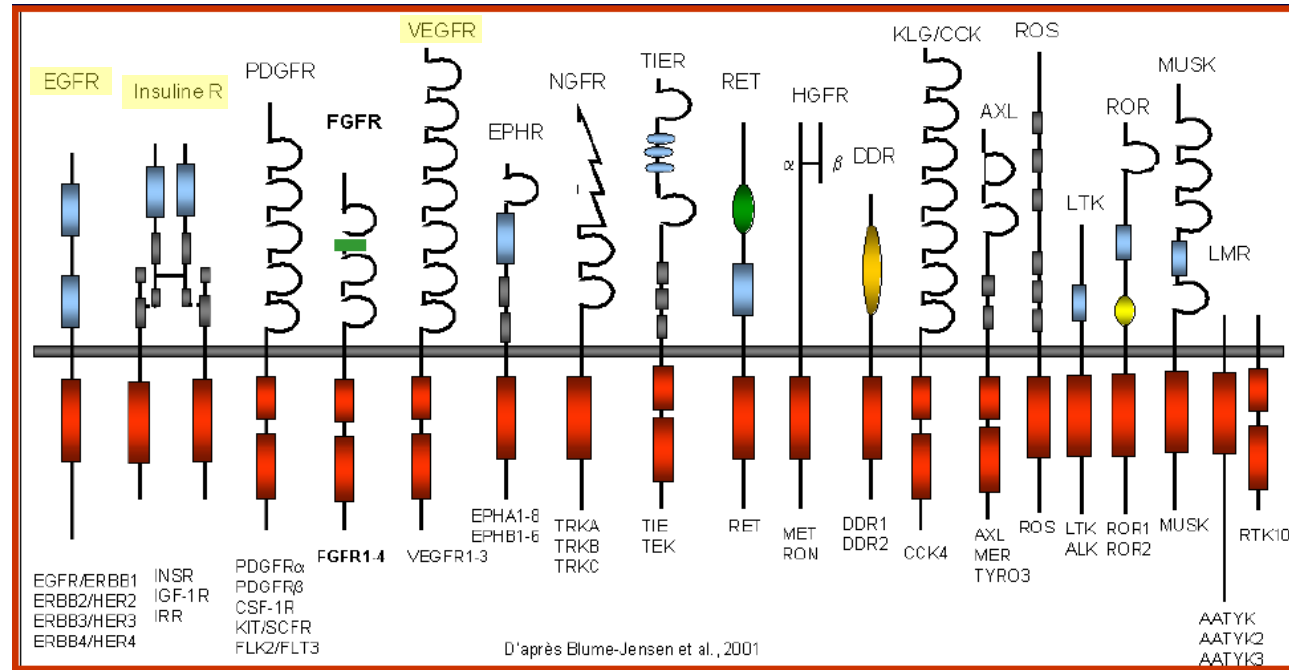
a.harle@nancy.unicancer.fr / alexandre.harle@univ-lorraine.fr

Institut de Cancérologie de Lorraine
Service de Biopathologie
CNRS, UMR 7039 CRAN, Université de Lorraine

Récepteurs à activité Tyrosine Kinase

Importante famille de récepteurs membranaires impliqués dans de nombreux processus cellulaires

18 familles chez les vertébrés

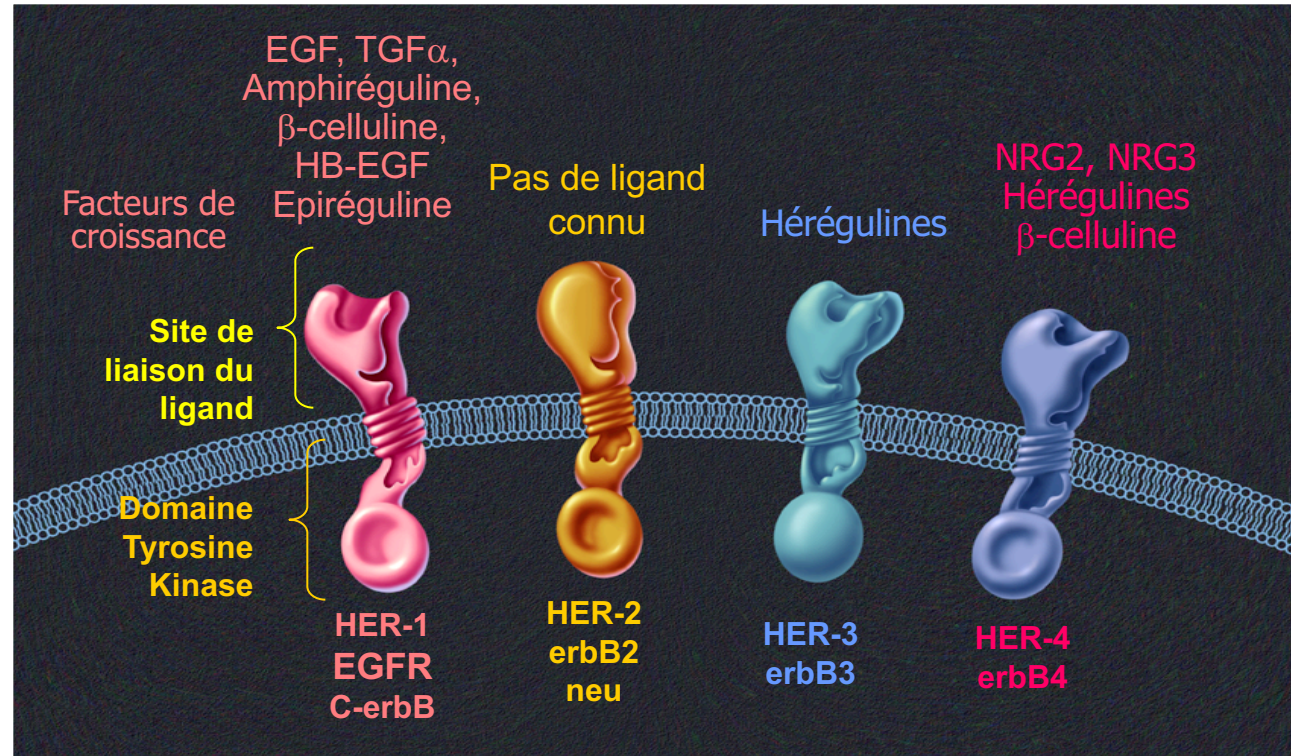


A. Harlé – Thérapies Ciblées

Récepteurs à activité Tyrosine Kinase

Les récepteurs HER

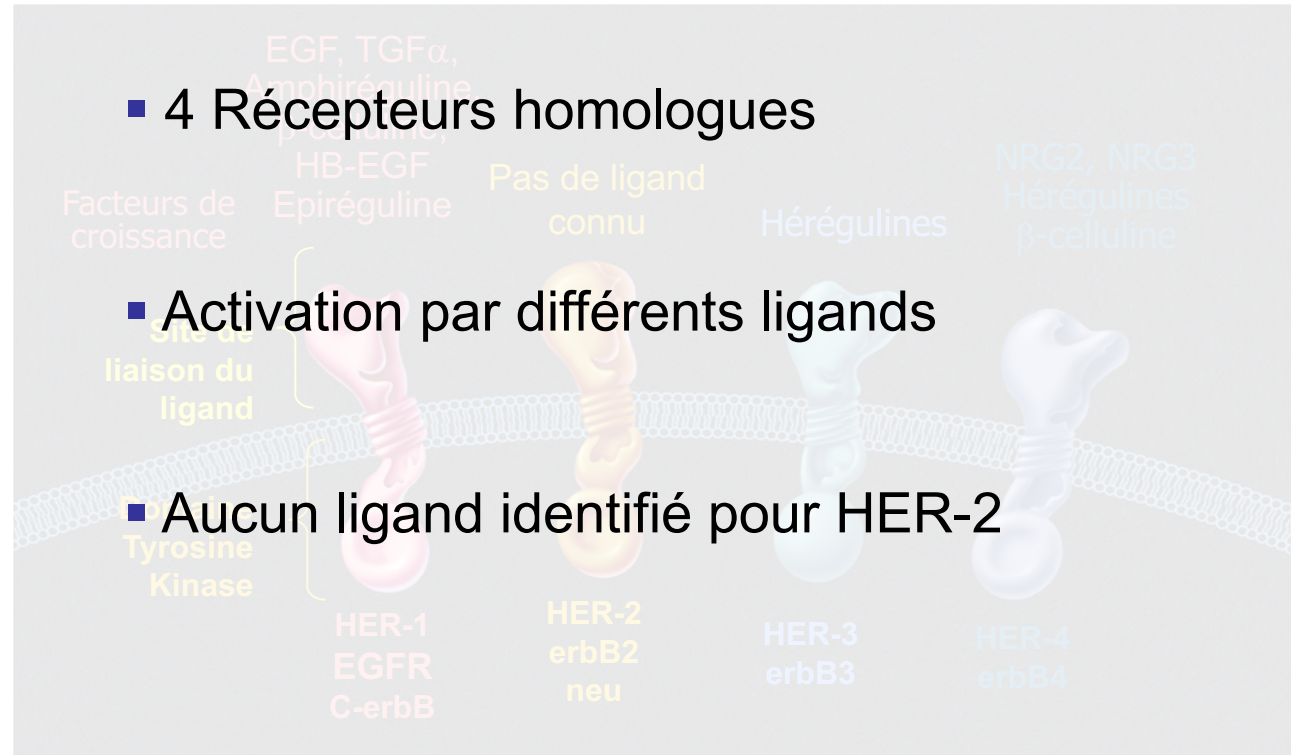
(Human Epidermal Growth Factor Receptors)



Récepteurs à activité Tyrosine Kinase

Les récepteurs HER

(Human Epidermal Growth Factor Receptors)

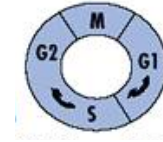
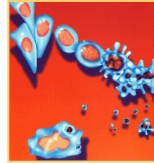


Rôle de HER-1

(Human Epidermal Growth Factor Receptors)

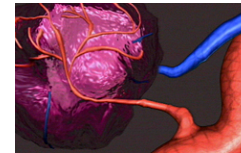
- Essentiel pour promouvoir la division et la survie cellulaire

- Stimule la progression du cycle cellulaire
- Inhibe l'apoptose

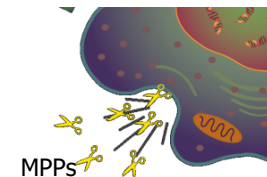


- Impliqué dans l'angiogenèse

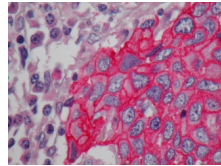
- Le signal médié par HER-1 stimule la production de VEGF (*Vascular Endothelial Growth Factor*)



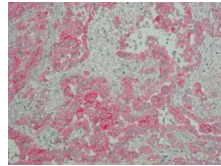
- Rôle dans l'invasion



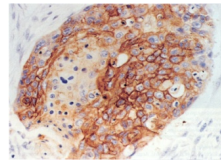
Expression de HER-1 dans les tumeurs humaines



Cancer tête et cou



Cancer colorectal



Cancer poumon non
à petites cellules

<u>Type tumoral</u>	<u>HER-1</u>
Tumeurs tête et cou	80-100%
Bronchique	45-90%
Adénocarcinome pancréas	30-50%
Côlon-rectum	28-77%
Oesophage	43-89%
Estomac	33-74%
Col utérin	90%
Sein	14-91%
Ovaire	35-70%
Prostate	65%
Vessie	31-48%
Rein	50-90%
Gliomes	40-63%

HER-1 : facteur pronostique de nombreuses tumeurs solides

- Son expression :
 - indicateur de l'agressivité tumorale
- ↑ niveaux d'expression :
 - survie + courte
 - et/ou potentiel métastatique ↑ dans de nombreux cancers

Expression de HER-2 dans les tumeurs humaines

Type tumoral	HER-2
Tumeurs tête et cou	33-76%
Bronchique	20-30%
ADK pancréas	17-82%
Côlon-rectum	51%
Oesophage	10%
Estomac	25%
Sein	15 à
Ovaire	4-30%
Prostate	35-56%
Vessie	17-71%

- L'amplification du gène HER2 ou la surexpression de la protéine transcrite produit une activation des récepteurs qui stimulent la croissance cellulaire
- La surexpression de HER2 est un facteur pronostique défavorable pour différents types de tumeurs

HER et les tissus tumoraux

(Human Epidermal Growth Factor Receptors)

- Famille HER fortement impliquée dans le développement tumoral
 - Découverte de mutations sur les gènes codant les récepteurs HER
 - Ces mutations s'expriment généralement par une surexpression de HER
 - Surexpression globalement un facteur défavorable
- Inhibition de HER-1 et HER-2 : cible de choix pour le traitement de certains cancers

Récepteurs à activité Tyrosine Kinase

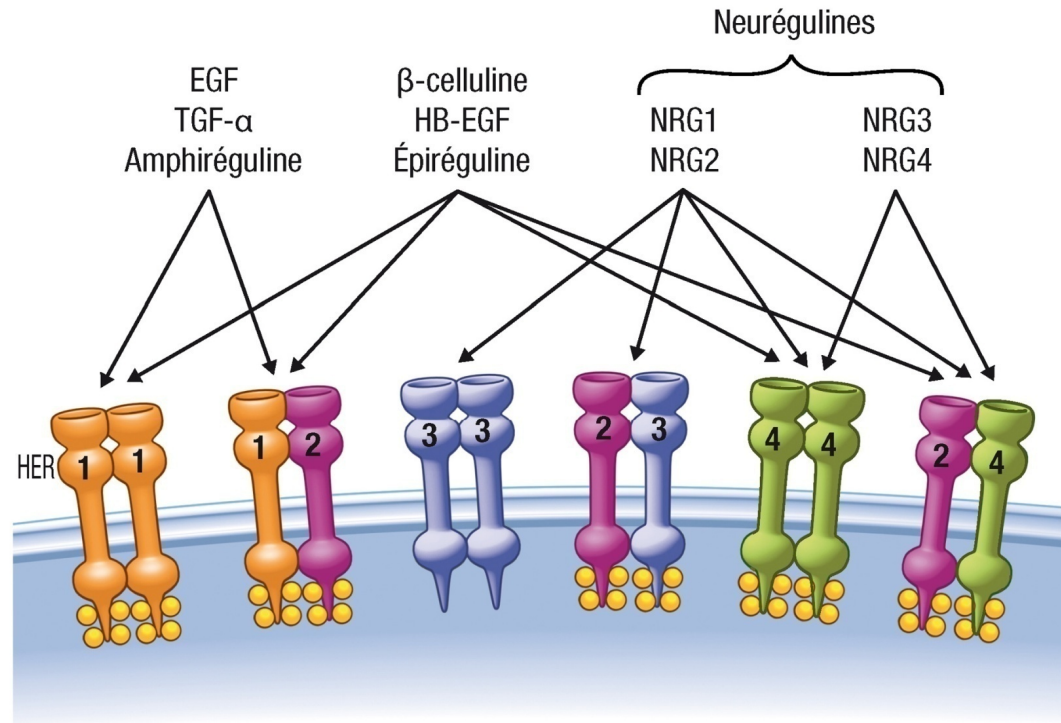
Les récepteurs HER

(Human Epidermal Growth Factor Receptors)

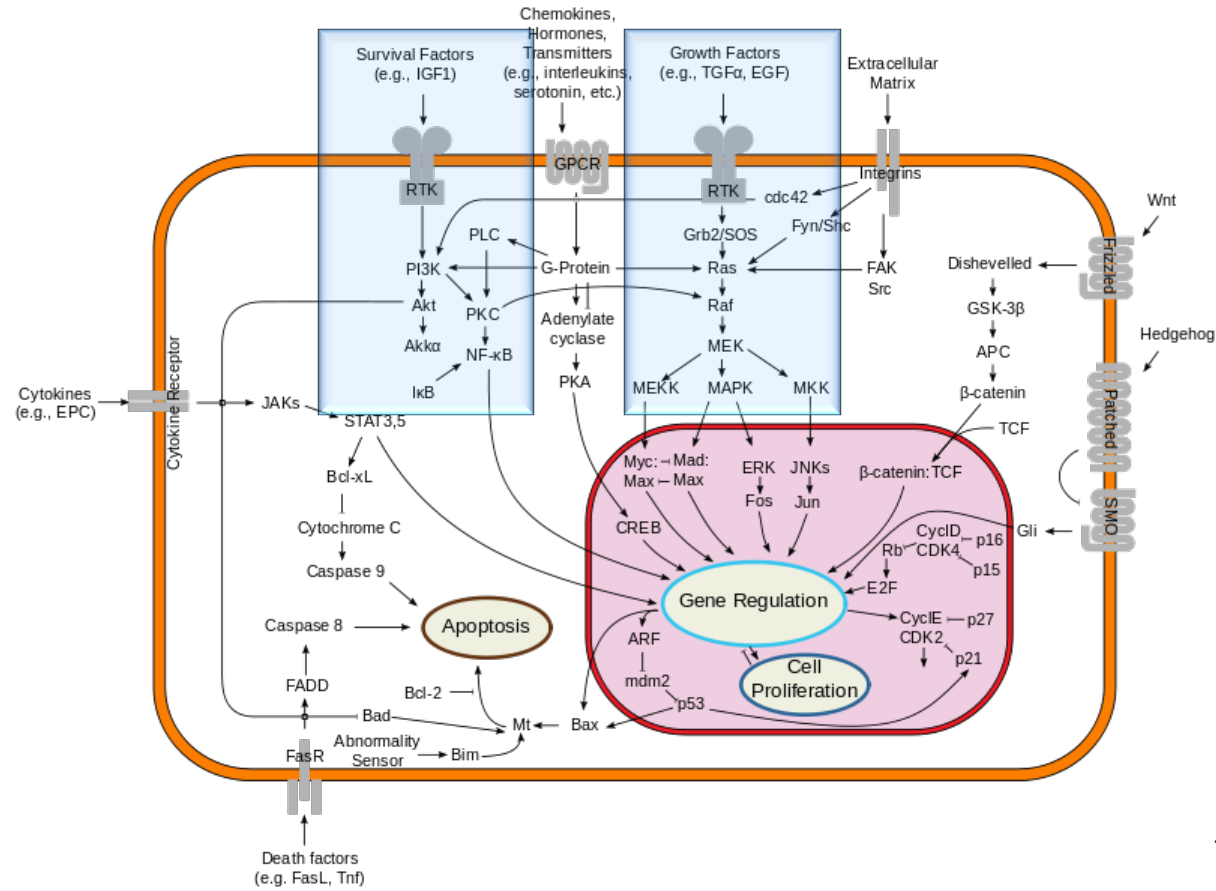
Récepteurs à activité Tyrosine Kinase

Les récepteurs HER

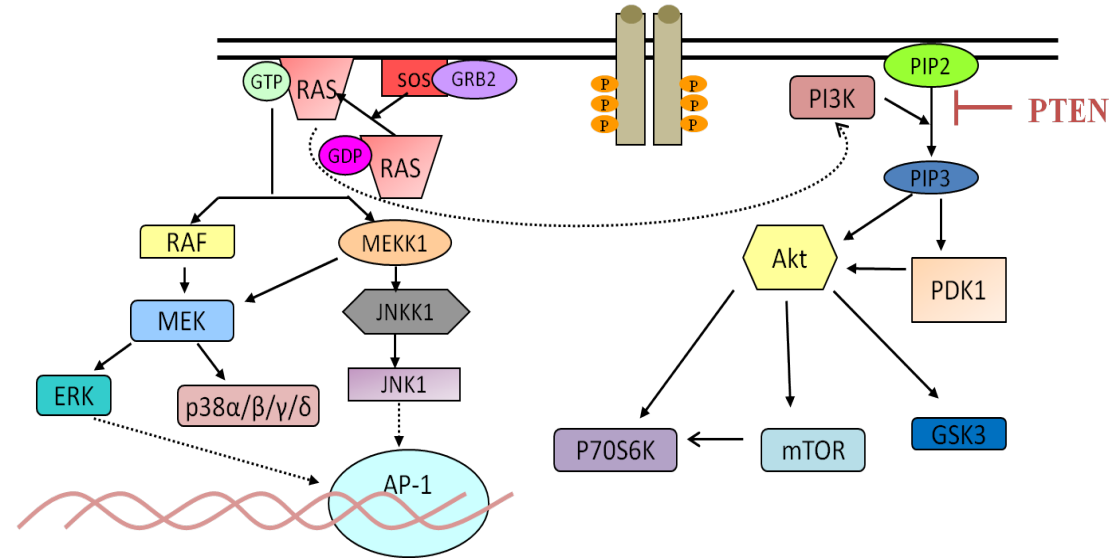
(Human Epidermal Growth Factor Receptors)



Voies de signalisation



Voies de signalisation



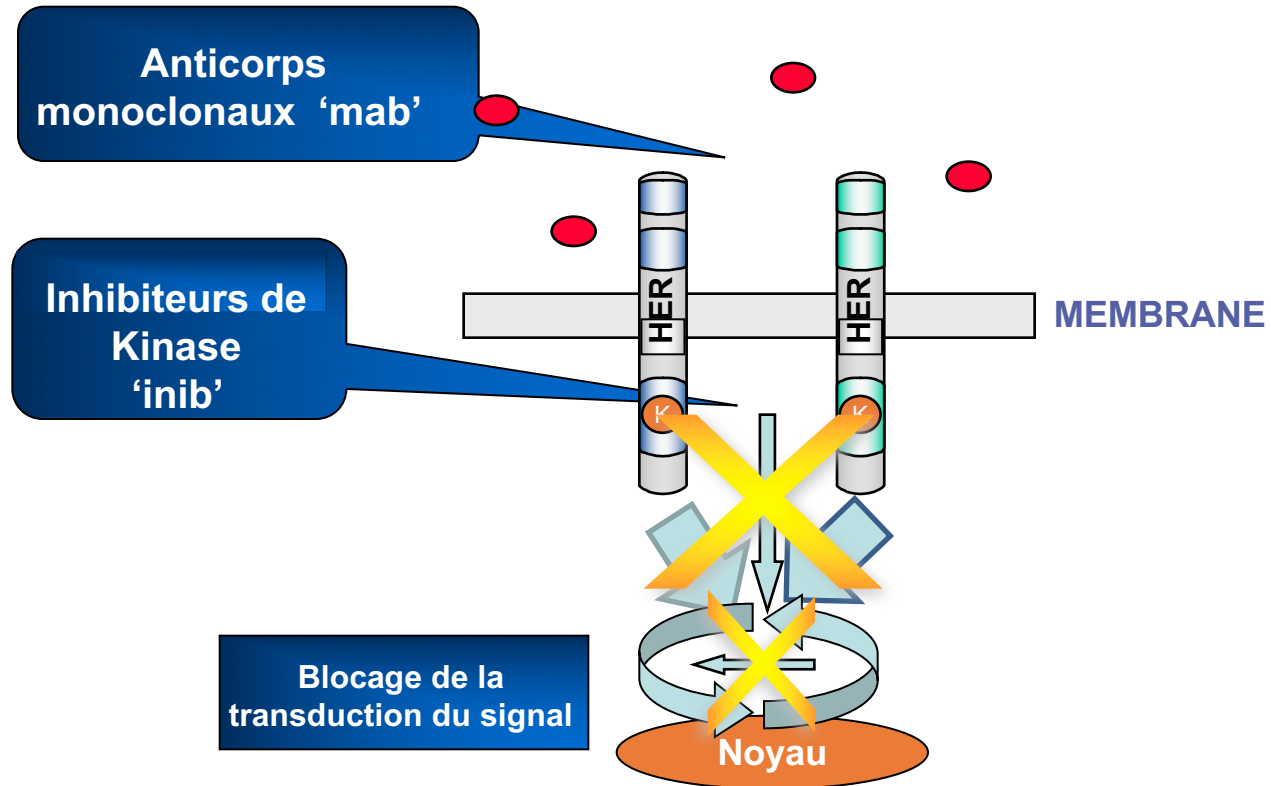
- La suractivation de ces voies de signalisation dans la maladie cancéreuse est responsable de l'**hyperprolifération**, de la **croissance**, de la **résistance à l'apoptose**, ...

- Le cancer apparaît aujourd'hui comme une **maladie de la signalisation cellulaire**

→ Mission
Bloquer la signalisation cellulaire

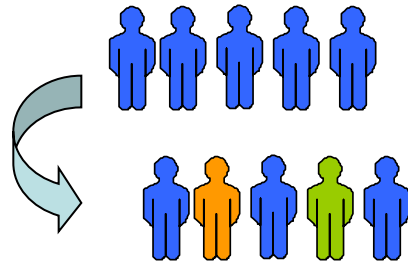


Thérapies ciblées anti HER



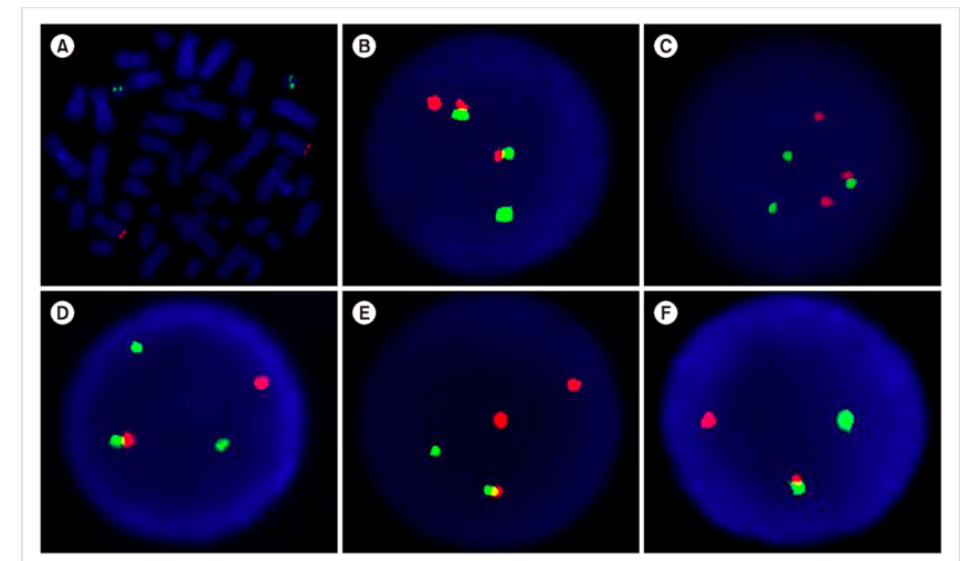
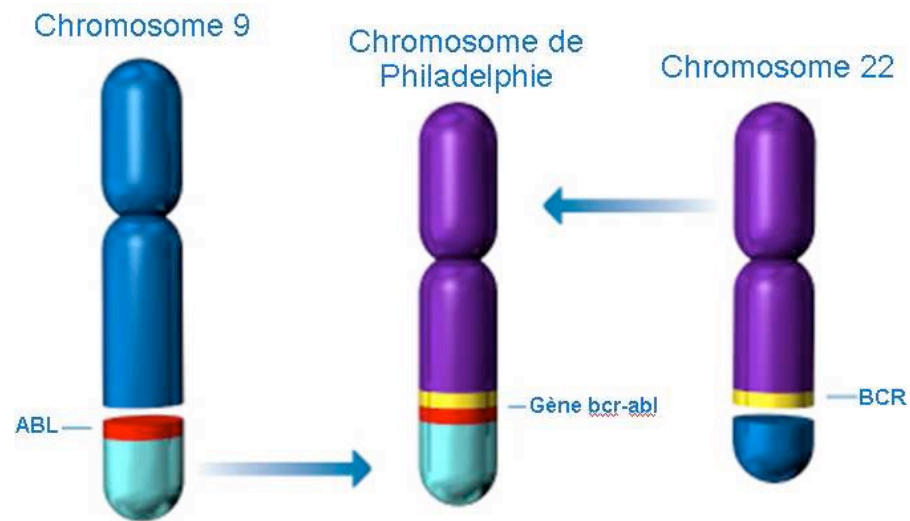


- La tumeur possède son propre génome.
- A un patient donné correspond une thérapie donnée
→ Médecine personnalisée
- Utilisation de molécules plus sélectives, en théorie moins toxiques et dont on attend plus d'efficacité
- Prédire la résistance à un traitement



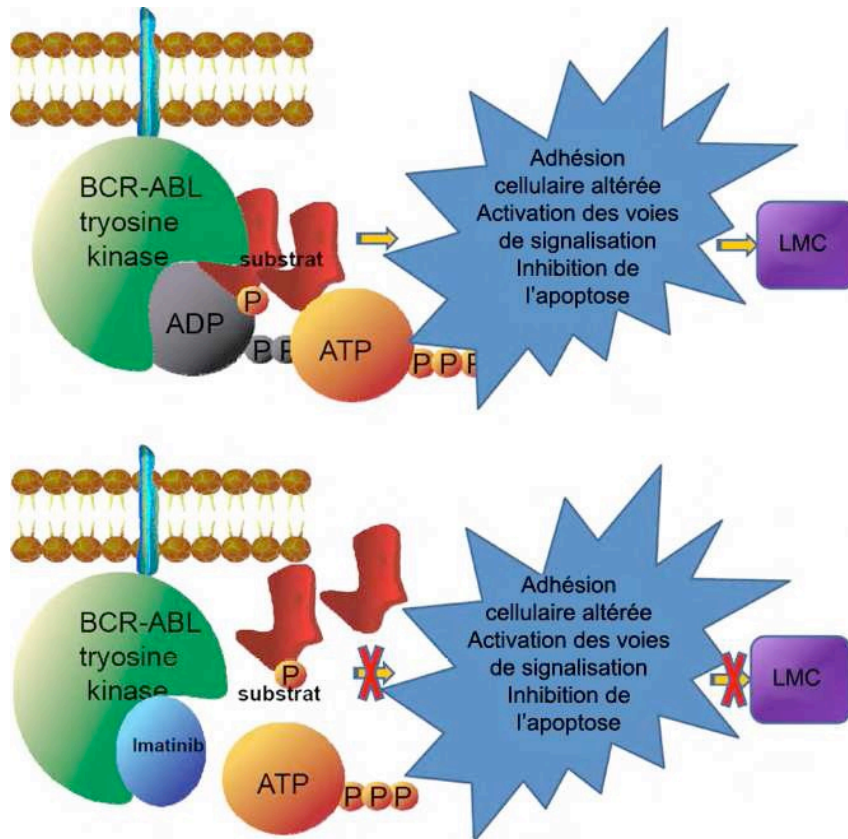
Epidémiologie

- Décrite pour la première fois en 1885 par John Hughes Bennett (Royal Infirmary Edimburgh)
- Fait partie de la famille des **syndromes myéloprolifératifs**
- Touche environ 2 personnes sur 100 000
- Pas d'étiologie connue
- Maladie en 3 phases : Chronique, accélérée et blastique.
- Anomalie chromosomique identifiée : **Chromosome de Philadelphie**



- Translocation **bcr-abl**

→ Protéine de fusion à **activité Tyrosine Kinase**



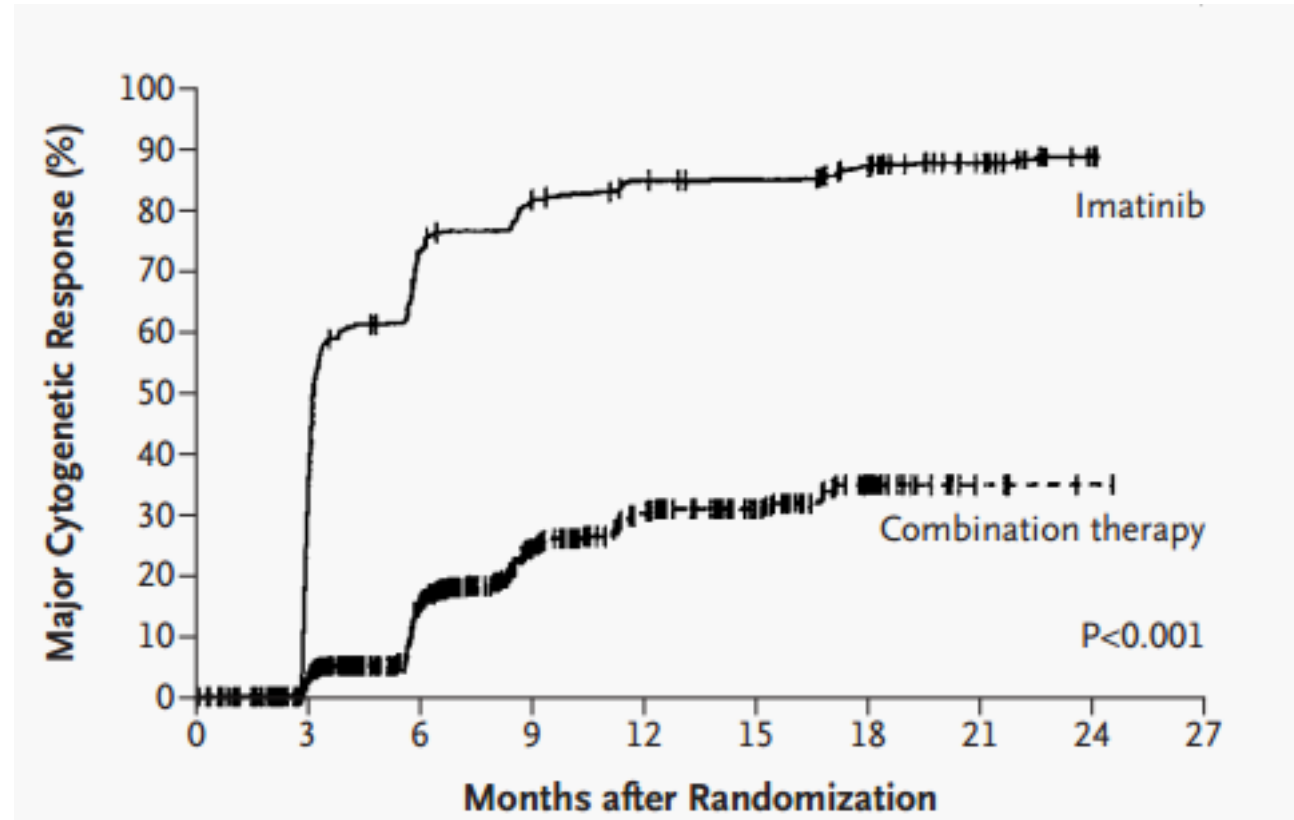
- L'Imatinib se lie sélectivement à la conformation inactive de la protéine ABL et bloque de manière compétitive la liaison de l'ATP et par conséquent empêche le passage de la protéine à sa forme active

→ inhibition de la prolifération cellulaire et de la formation de tumeurs

- ITK disponible depuis 2002 :
 - Imatinib (Glivec®) - 96% de réponse hématologique complète
- En cas d'échec du traitement par Imatinib, ITK de 2nde génération :
 - Nilotinib (Tasigna®) et Dasatinib (Sprycel®), Bosutinib (Bosulif®)
- Si présence d'une mutation **T315I** (c.944C>T p.(Thr315Ile) de *bcr-abl* → **Résistance**
 - Ponatinib (Iclusig®)



- Réponse cytogénétique majeure avec l'imatinib par rapport à la combinaison Aracytine + Interferon¹

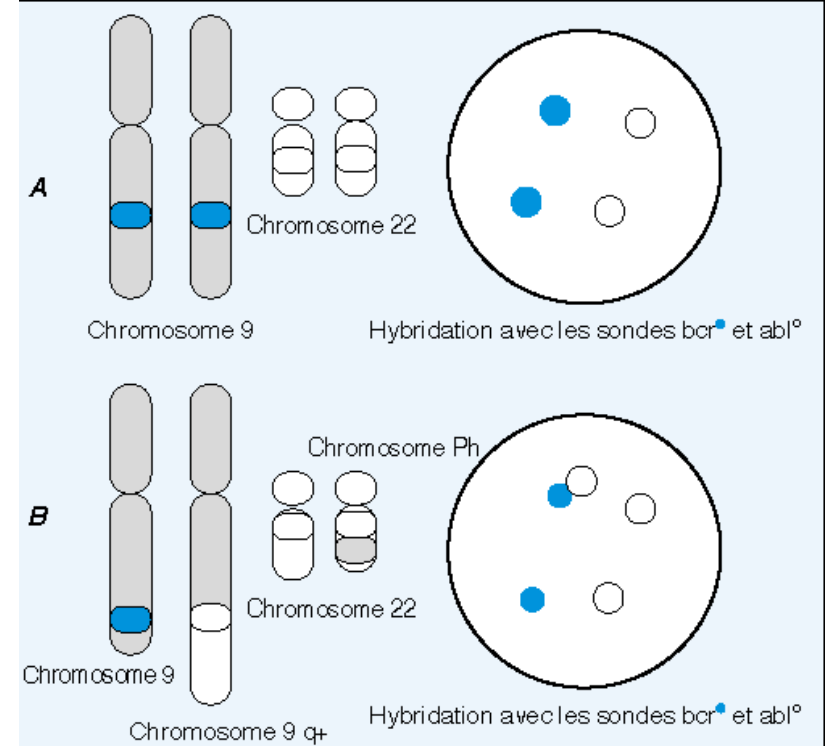


- Survie globale à 5 ans de l'ordre de 90%²

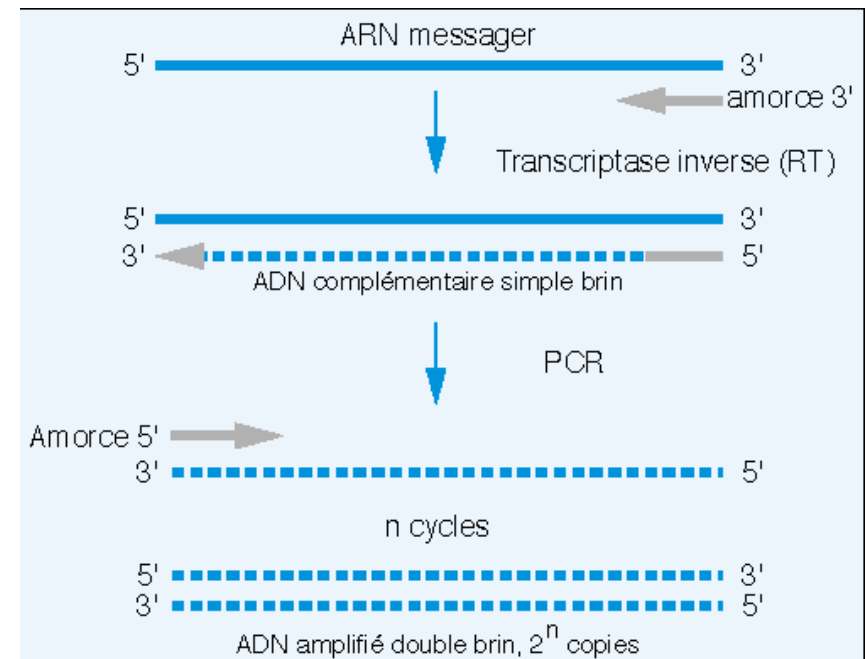
¹ O'Brien *et al.*, NEJM 2003

² Druker *et al.*, NEJM 2006

- Utilisation de la **FISH** pour le diagnostic
- Suivi de la maladie grâce à la **RT-PCR** (transcrits **bcr-abl**)
- Adaptations posologiques en fonction du nombre de copies de **transcrits bcr-abl** détectées dans le sang

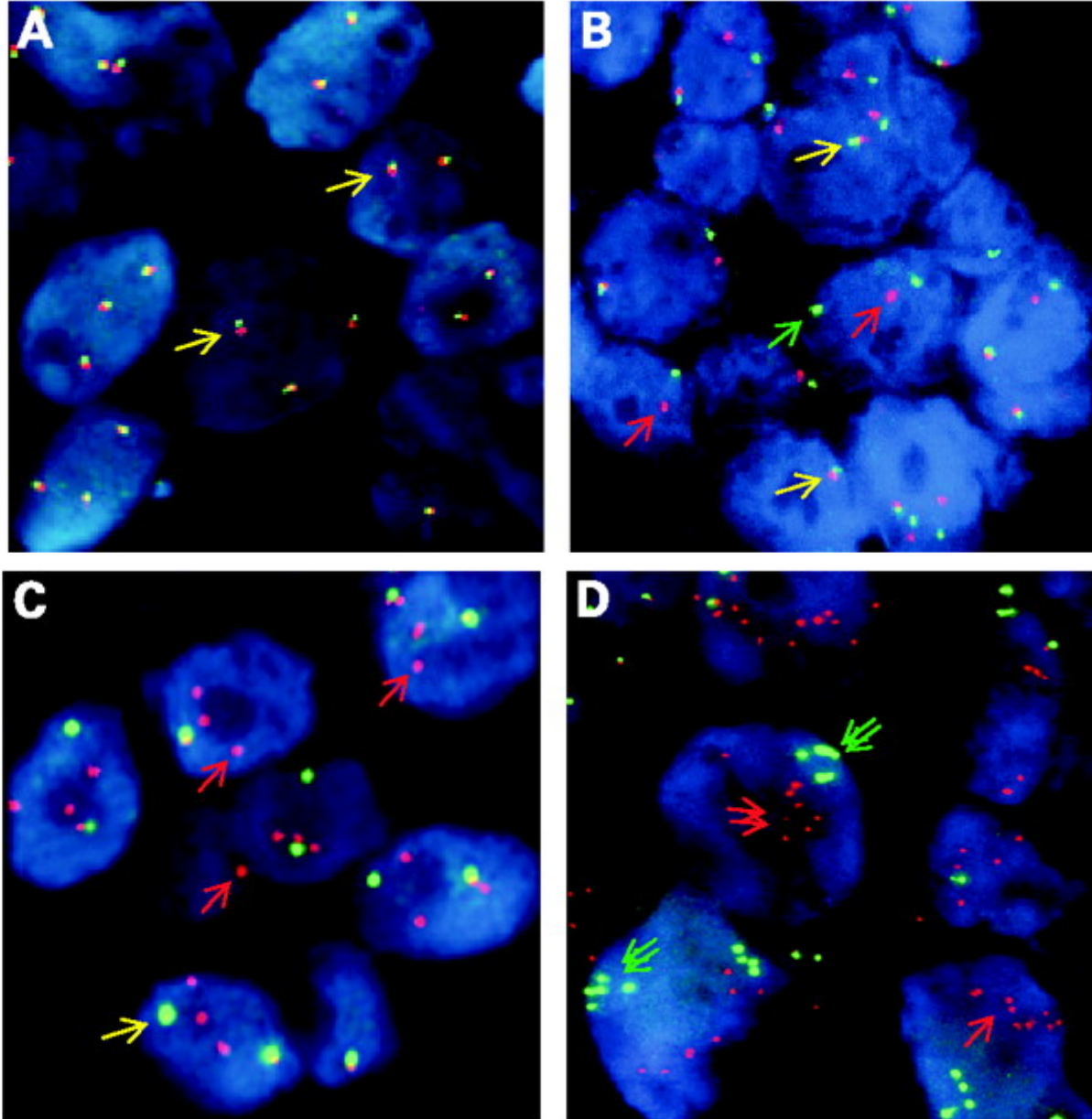


Nombre de transcrits bcr-abl/ μ g d'ARN	Statut hématologique
5×10^5 à 10^6	LMC non traité (diagnostic initial)
1 600 à 70 000	rechute cytogénétique pure
< 10 à 10^4	rémission cytogénétique (après interféron)



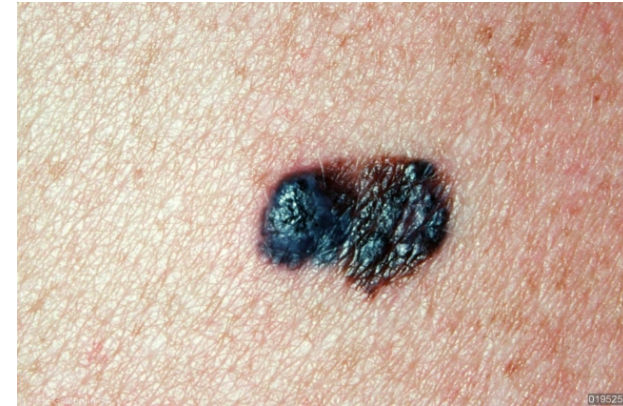
■ FISH : Hybridation *in situ* en Fluorescence

(*Fluorescence in situ hybridization*)



Epidémiologie

- Incidence de 9 pour 100 000
- 8 000 nouveaux cas par an en France
- Gravité de la forme métastatique
- Traitement historique disponible : Dacarbazine (Deticene®)



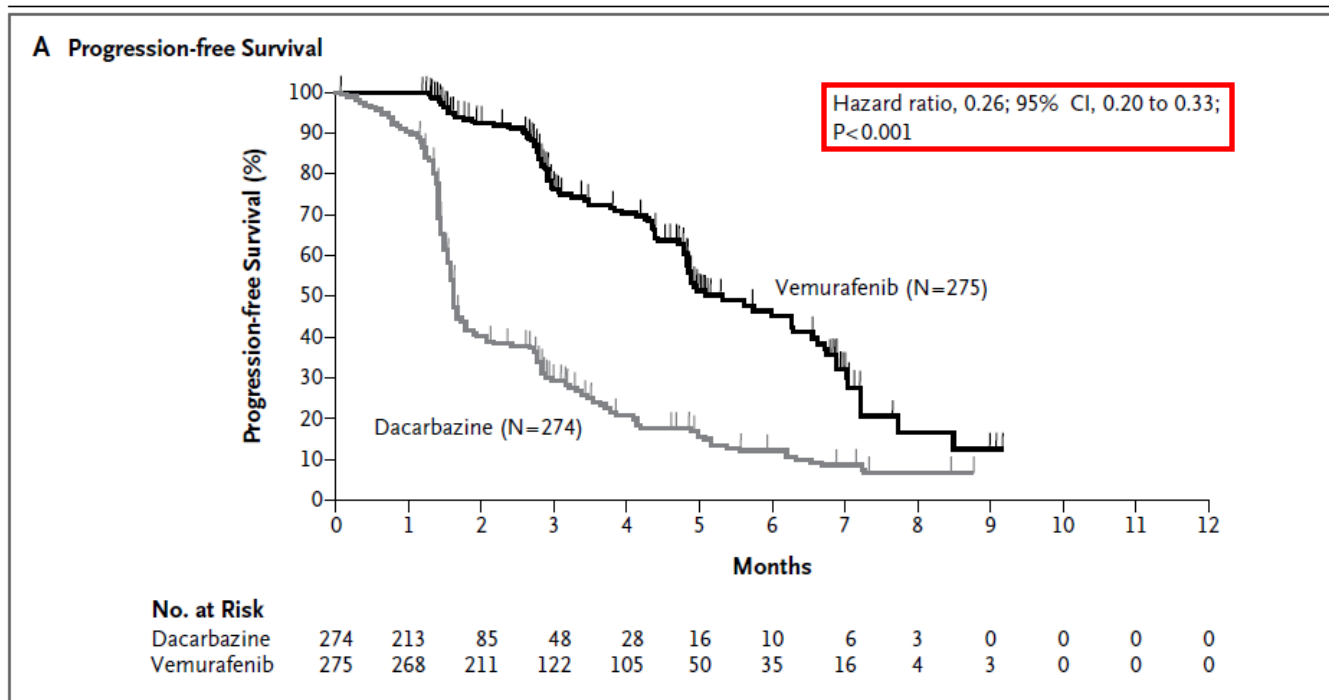
Inhibiteurs de BRAF

- **Vémurafenib - Zelboraf®**
- **Dabrafénib – Tafinlar®**
- **Efficaces chez les patients dont la tumeur possède une mutation **V600** du gène **BRAF****
- **PFS et OS considérablement améliorées**



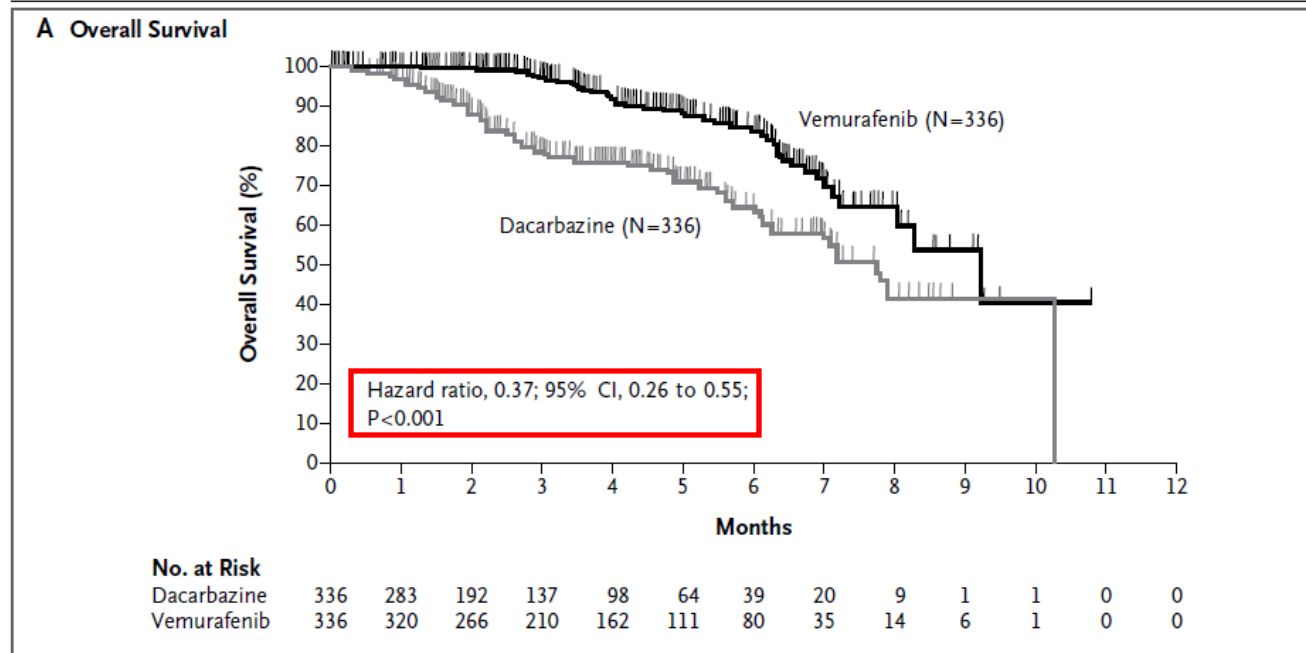
A. Harlé – Thérapies Ciblées

MEMURAFENIB IN MELANOMA WITH BRAF V600E MUTATION

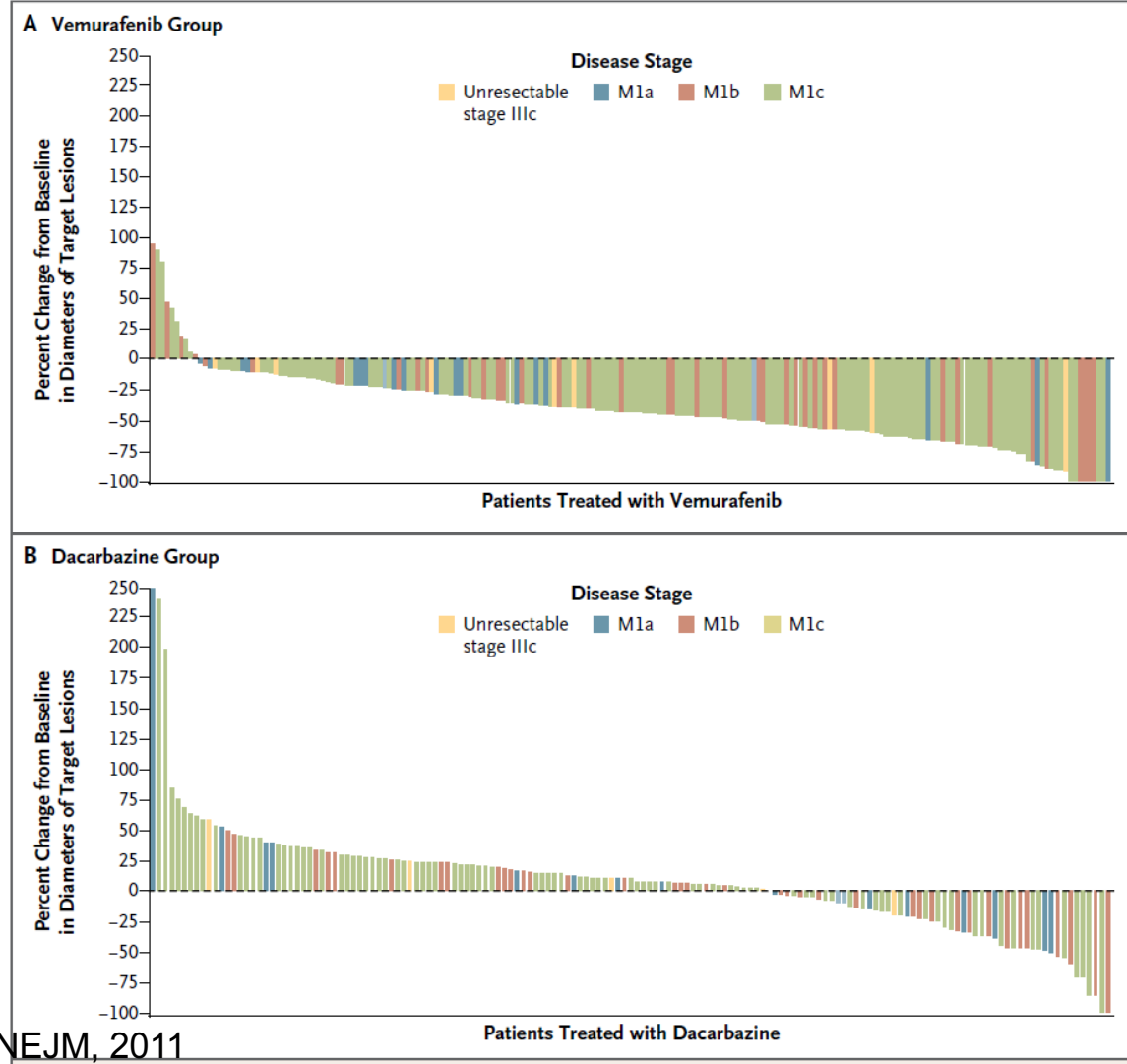


Chapman *et al.*, NEJM, 2011

VEMURAFENIB IN MELANOMA WITH BRAF V600E MUTATION



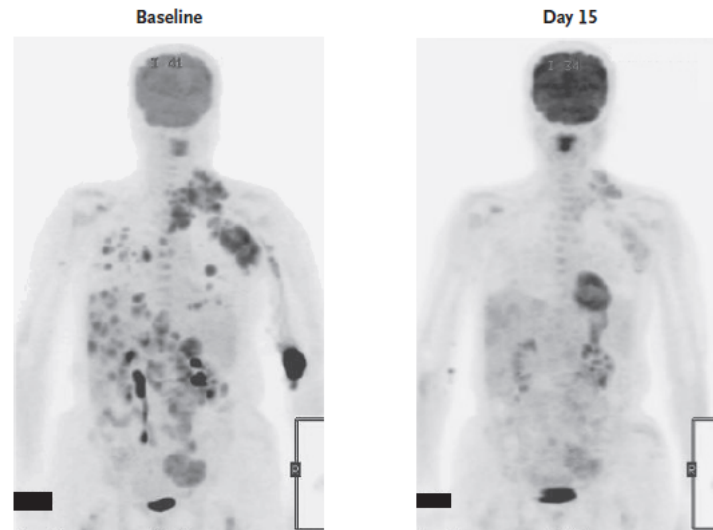
Chapman *et al.*, NEJM, 2011



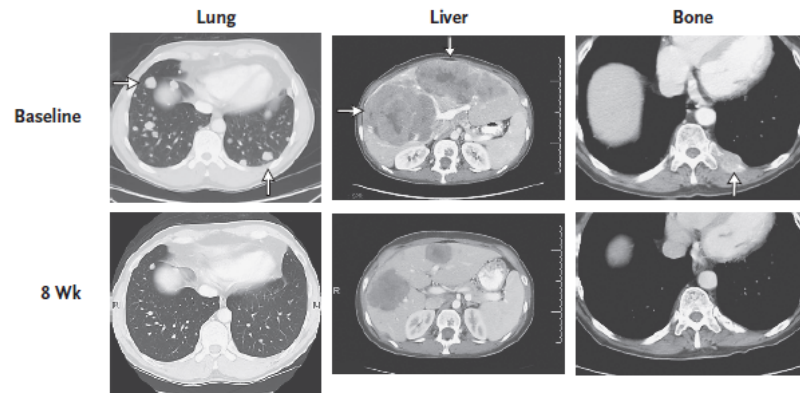
Chapman *et al.*, NEJM, 2011

A. Harlé – Thérapies Ciblées

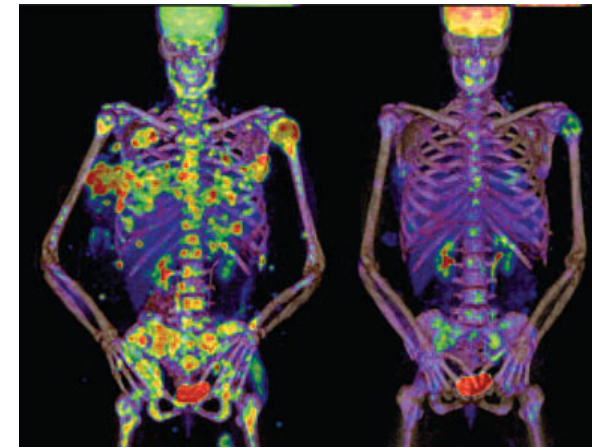
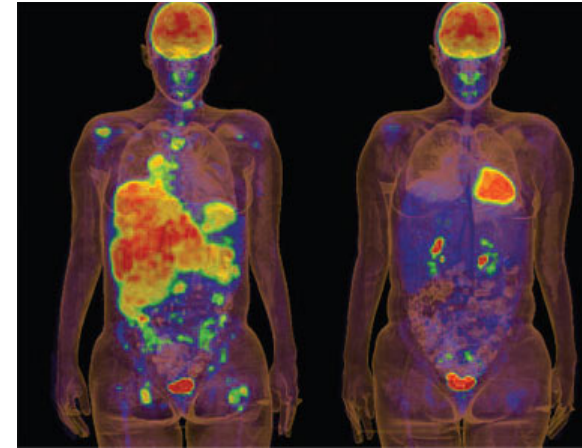
B FDG-PET



C Computed Tomography



Flaherty *et al.*, NEJM, 2010



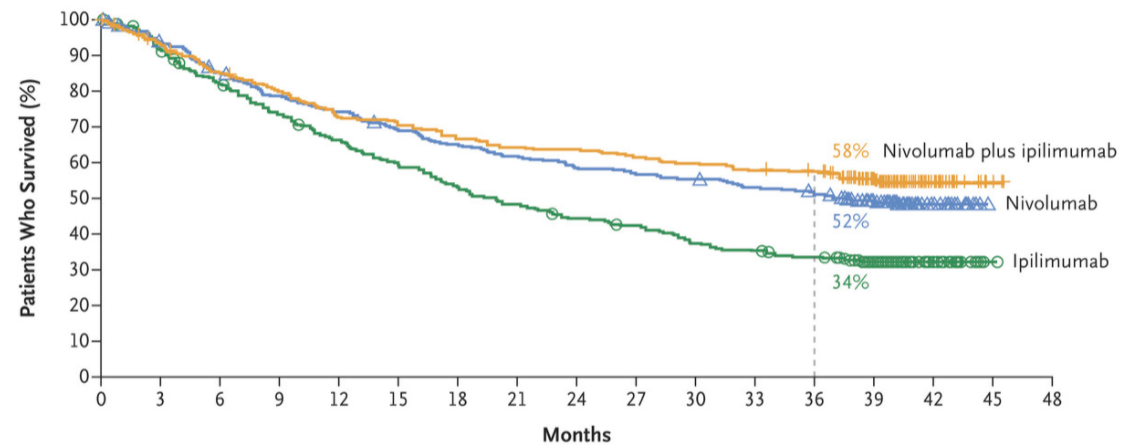
A. Harlé – Thérapies Ciblées

Inhibiteurs de BRAF

- Possibilité d'associer les **anti-BRAF** avec un **anti-MEK**
 - **Vémurafenib** + **Cobimetinib**
 - **Dabrafénib** + **Trametinib**
 - **Encorafenib** + **Binimetinib**
- Très bonnes réponses avec l'immunothérapie
 - Anti CTLA-4
 - ipilimumab - **Yervoy**[®]
 - Anti PD-1 ou PD-L1
 - nivolumab – **Opdivo**[®]
 - pembrolizumab – **Keytruda**[®]

Anti-PDL1

B Overall Survival



No. at Risk

Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

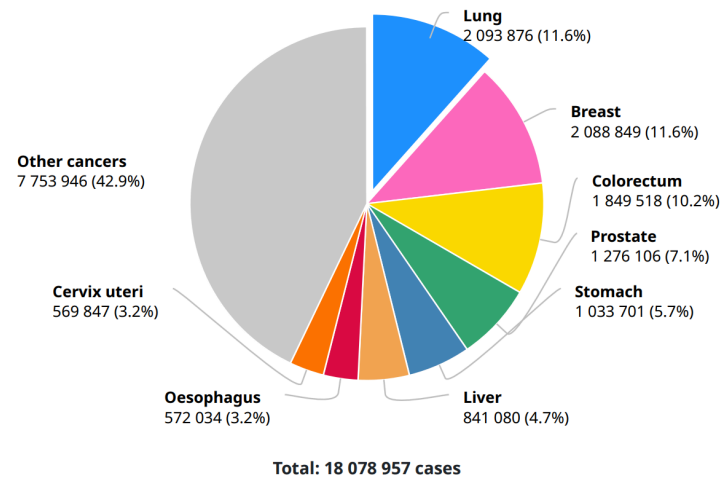
- **Rappel en 2011 : OS 7 mois avec la Dacarbazine seule et 9 mois avec le Dabrafenib seul**

Wolchok J. *et al.*, NEJM, 2017

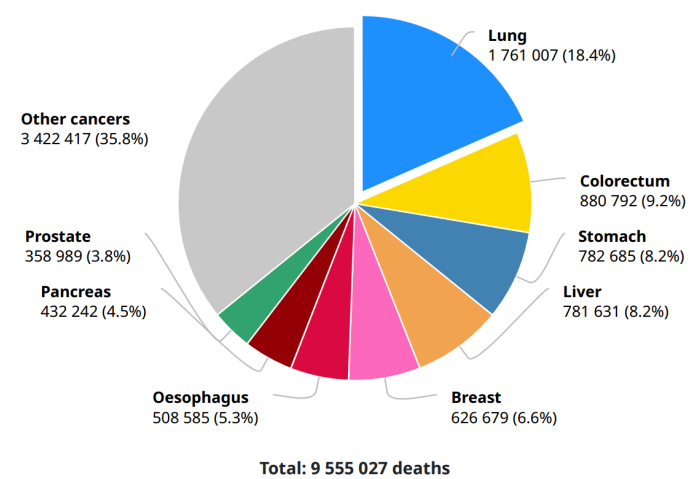
A. Harlé – Thérapies Ciblées

■ **Le cancer bronchique est le cancer le plus fréquent et le plus meurtrier au monde**

Number of new cases in 2018, both sexes, all ages



Number of deaths in 2018, both sexes, all ages



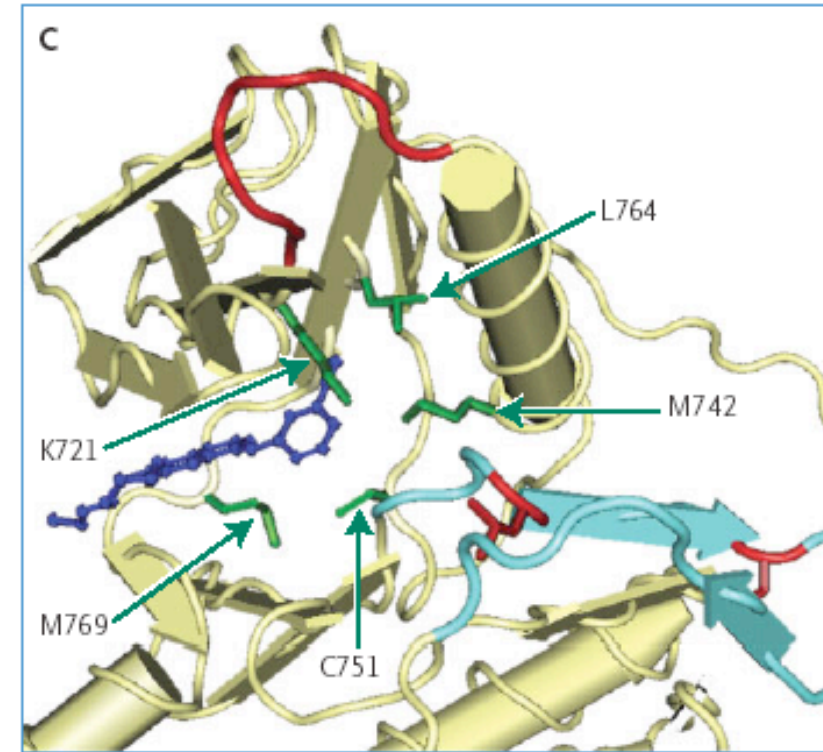
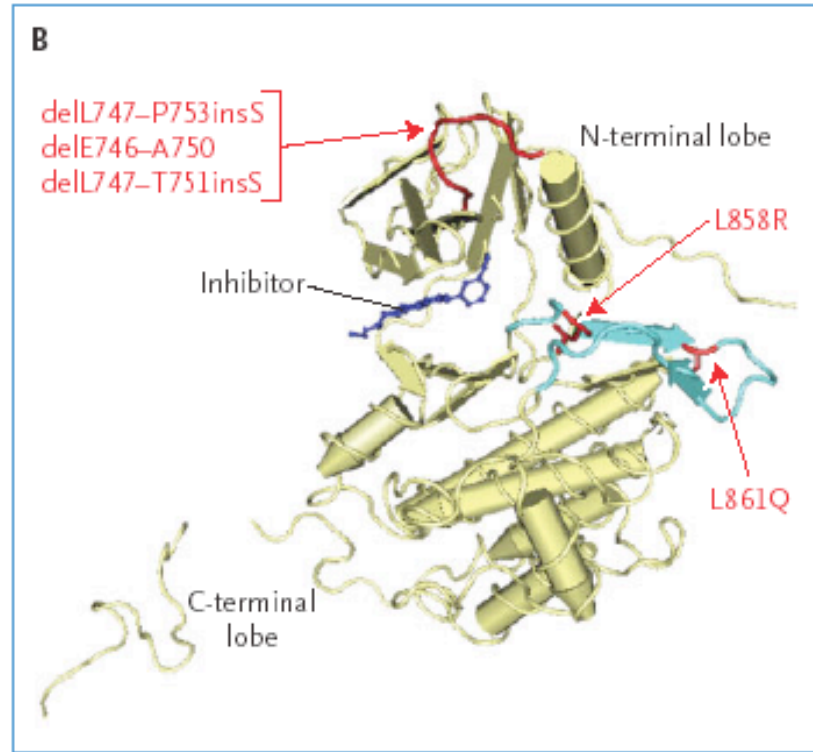
Epidémiologie

- Cancer du poumon lié au tabac : Première cause de décès par cancer dans le monde
- Non lié au tabac : 7ème cause de décès par cancer
- 75% de carcinomes non à petites cellules
- 25% de carcinome à petites cellules
- Amélioration de la détection précoce
- Amélioration du sevrage



Cancer du Poumon - Gefitinib

- La mutation du site catalytique d'**EGFR** augmente l'activité du **gefitinib** (Iressa[®]), de l'**erlotinib** (Tarceva[®]) (ITK), de l'**afatinib** (Giotrif[®]) et de l'**osimertinib** (Tagrisso[®])



D'après Lynch et al, NEJM, 2004

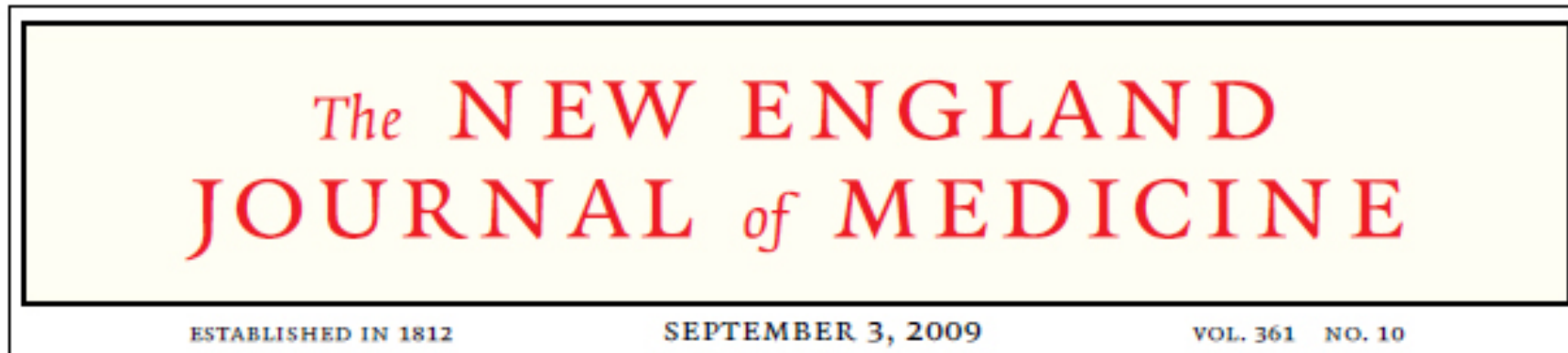
EGFR et Poumon

- Mutations somatiques du récepteurs EGFR
→ 8 % à 13 % des patients.
- Fréquence supérieure dans les adénocarcinomes
→ 21% contre 2%.
- Fréquence
→ Femme > homme (20% contre 9%)
→ Asiatiques > Caucasiens



Gefitinib (Iressa[®])

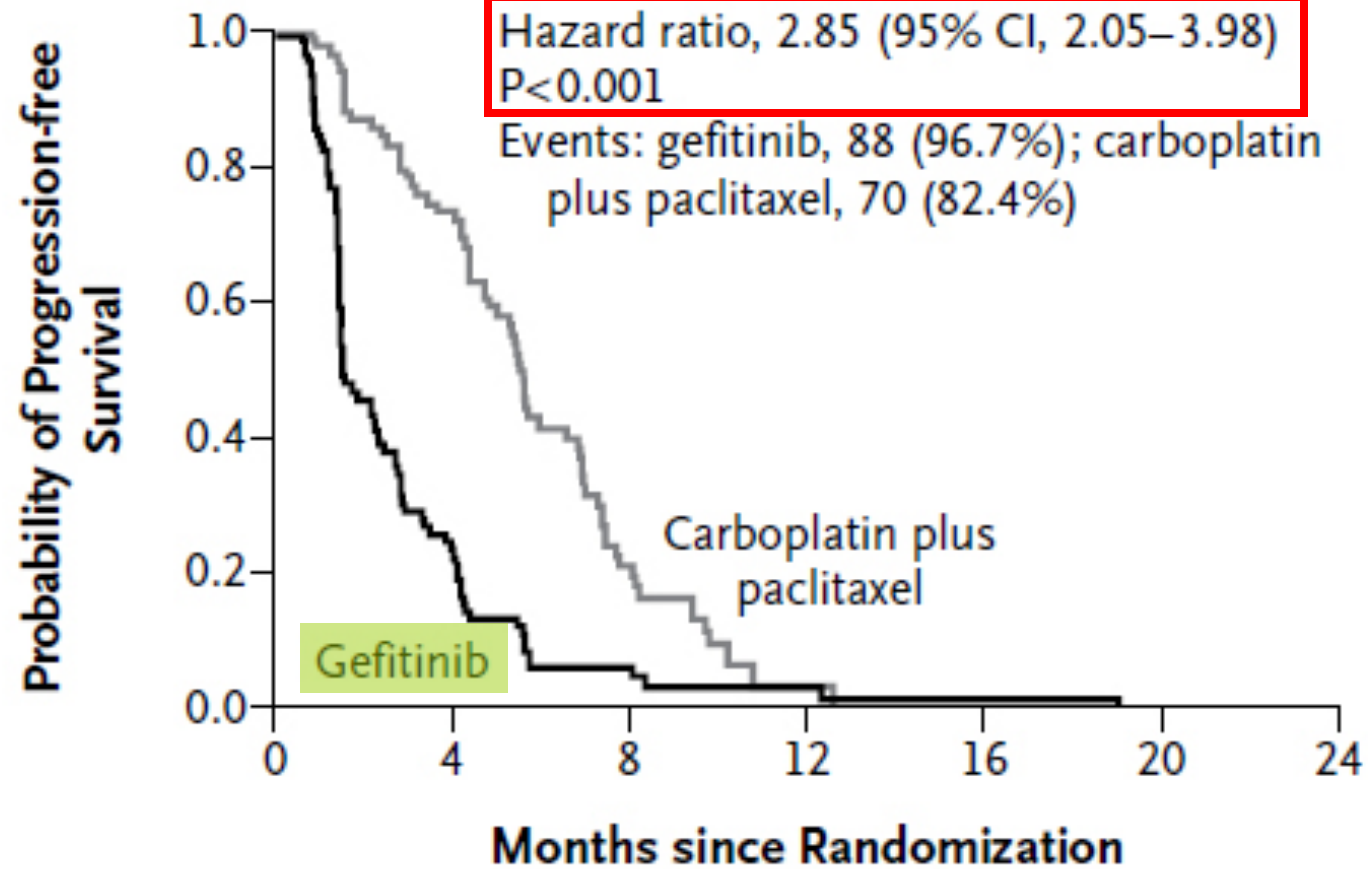
Mok et al, NEJM, 2009



Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.

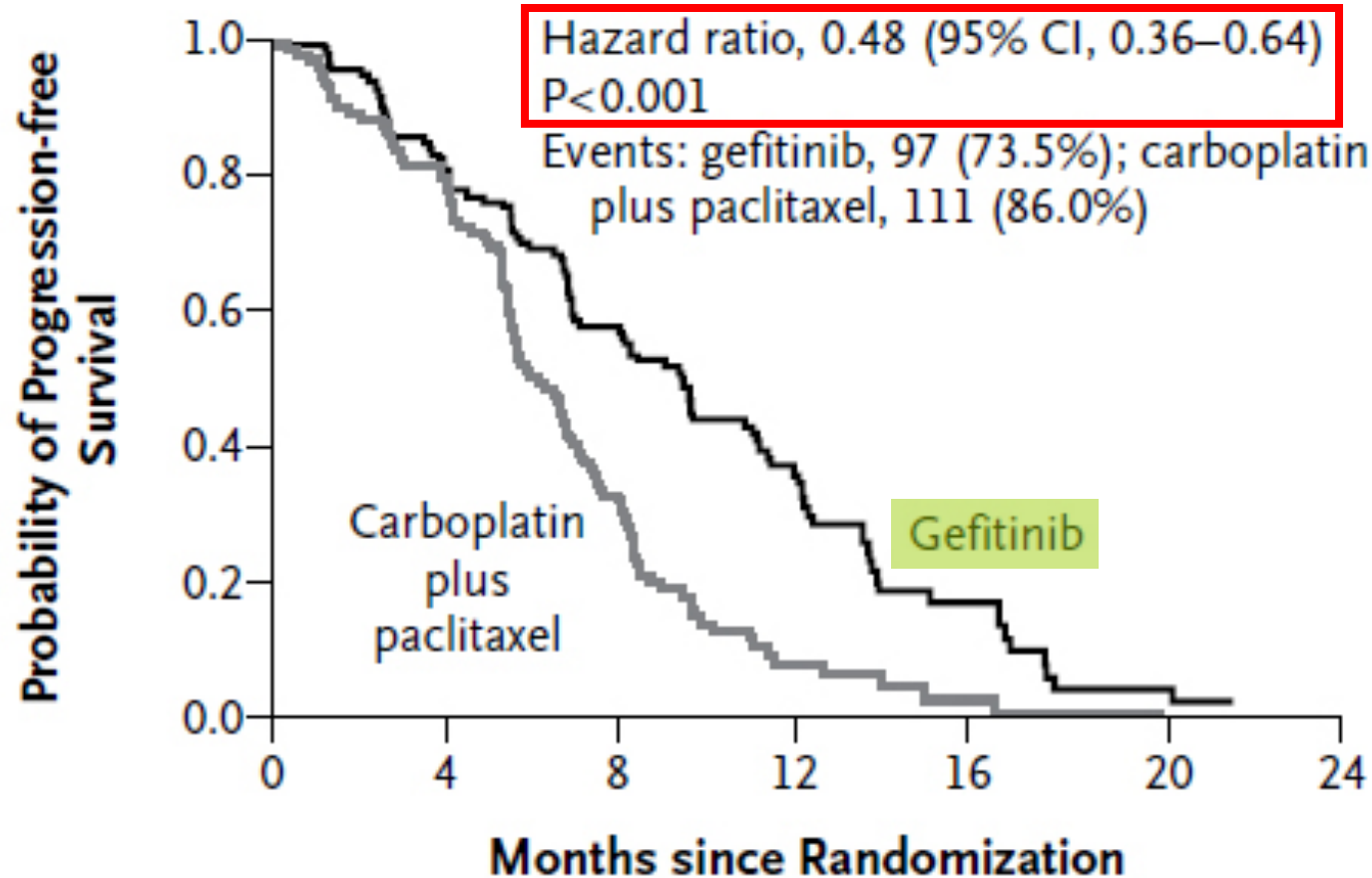
C EGFR-Mutation–Negative



No. at Risk

Gefitinib	91	21	4	2	1	0	0
Carboplatin plus paclitaxel	85	58	14	1	0	0	0

B EGFR-Mutation-Positive



No. at Risk

Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

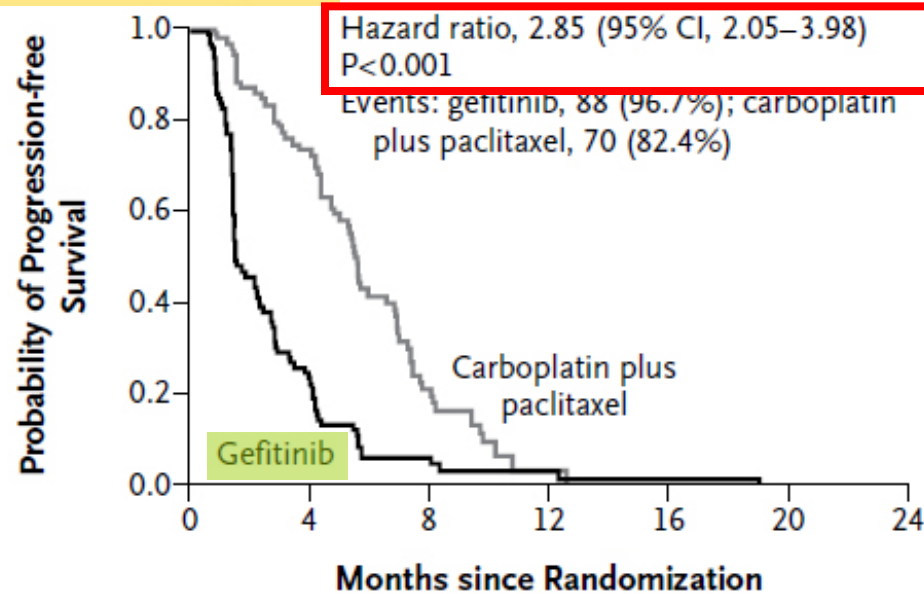
EGFR et Poumon

Auteur	Etude	N EGFR muté	% RO (TKI vs CT)	SSP (HR, IC 95%)
Mok et al	IPASS	261	71,2% vs 47,3%	0,48 (0,36-0,64)
Lee et al	First SIGNAL	42	84,6% vs 37,5%	0,61 (0,31-1,22)
Mitsudomi et al	WJTOG 3405	198	62,1% vs 32,2%	0,49 (0,34-0,71)
Maemondo et al	NEJGSG 002	177	74,5% vs 29%	0,32 (0,22-0,42)
Zhou C et al	OPTIMAL	165	68% vs 26%	0,16 (0,10-0,26)

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

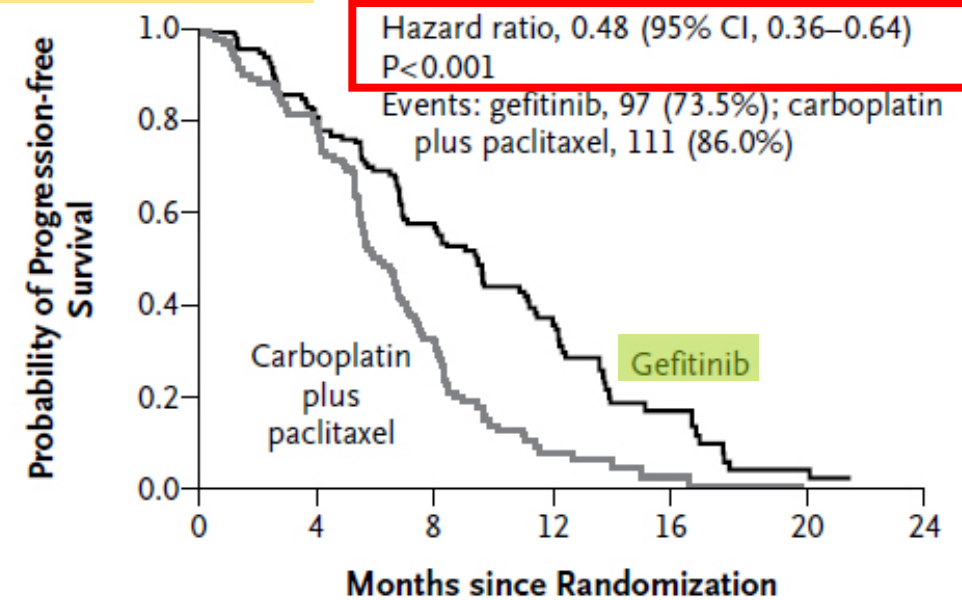
Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.

C EGFR-Mutation–Negative



No. at Risk	0	4	8	12	16	20	24
Gefitinib	91	21	4	2	1	0	0
Carboplatin plus paclitaxel	85	58	14	1	0	0	0

B EGFR-Mutation–Positive



No. at Risk	0	4	8	12	16	20	24
Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

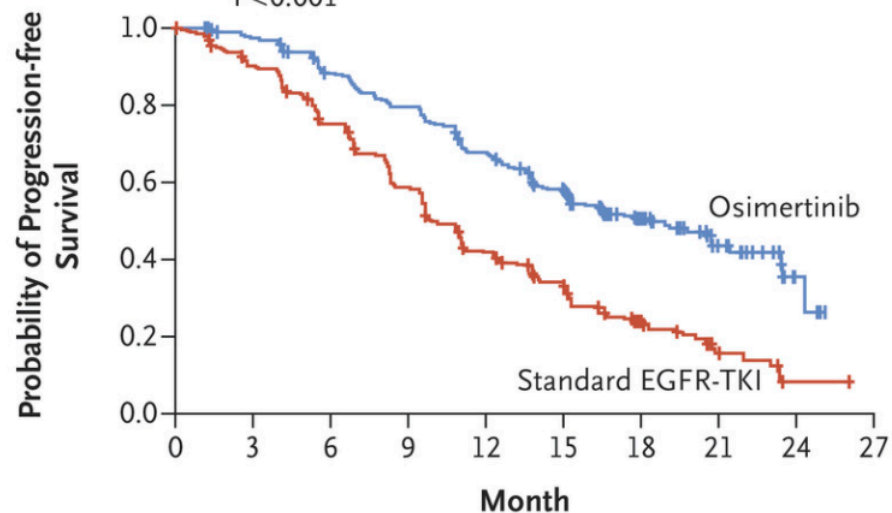
Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer

Jean-Charles Soria, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Thanyanan Reungwetwattana, M.D., Busyamas Chewaskulyong, M.D., Ki Hyeon Lee, M.D., Ph.D., Arunee Dechaphunkul, M.D., Fumio Imamura, M.D., Ph.D., Naoyuki Nogami, M.D., Takayasu Kurata, M.D., Ph.D., Isamu Okamoto, M.D., Ph.D., Caicun Zhou, M.D., Ph.D., *et al.*, for the FLAURA Investigators*

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI) <i>mo</i>
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



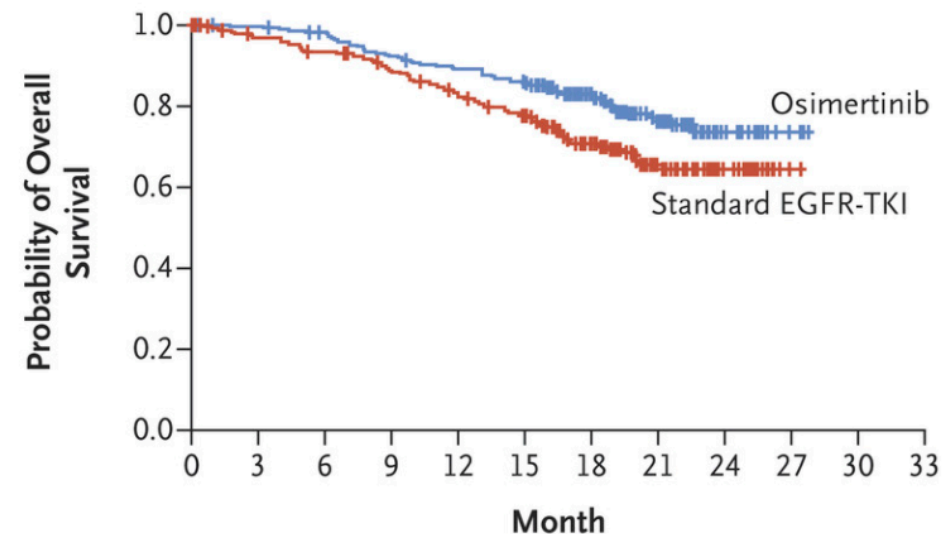
No. at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

D Overall Survival

	No. of Patients	Median Overall Survival (95% CI) <i>mo</i>
Osimertinib	279	NC (NC–NC)
Standard EGFR-TKI	277	NC (NC–NC)

Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007

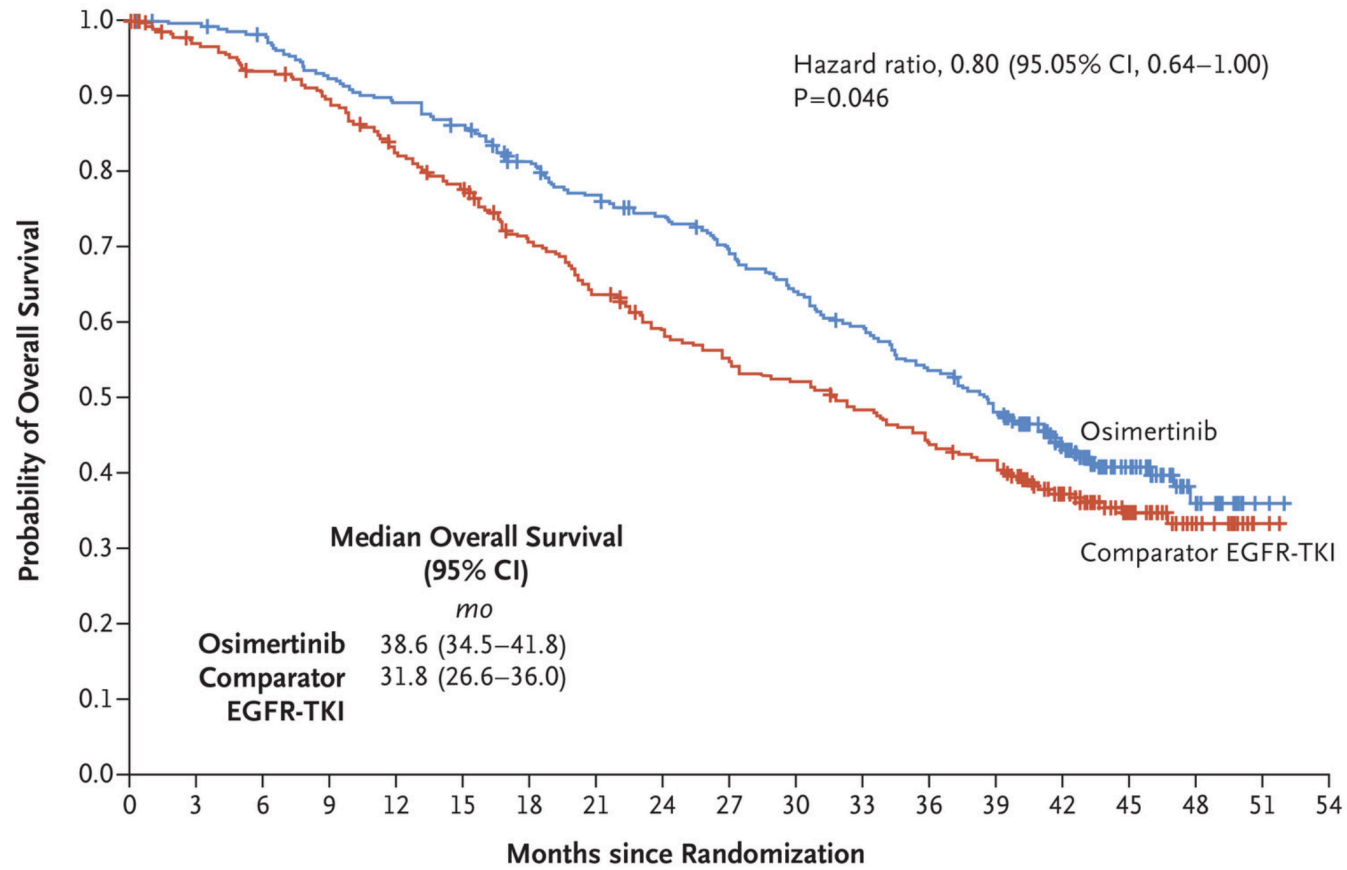


No. at Risk

Osimertinib	279	276	269	253	243	232	154	87	29	4	0	0
Standard EGFR-TKI	277	263	252	237	218	200	126	64	24	1	0	0

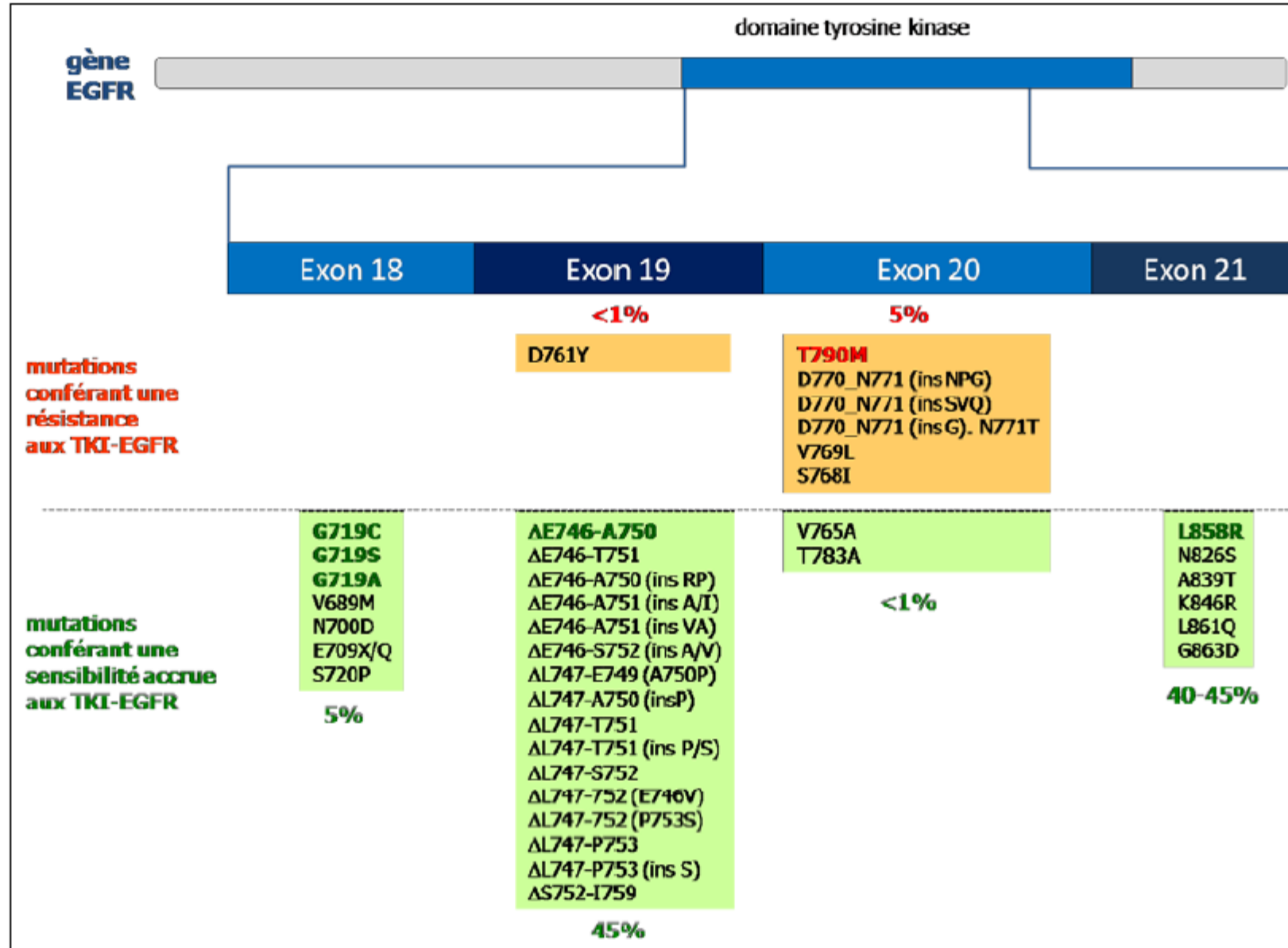
Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC

Suresh S. Ramalingam, M.D., Johan Vansteenkiste, M.D., Ph.D., David Planchard, M.D., Ph.D., Byoung Chul Cho, M.D., Ph.D., Jhanelle E. Gray, M.D., Yuichiro Ohe, M.D., Ph.D., Caicun Zhou, M.D., Ph.D., Thanyanan Reungwetwattana, M.D., Ying Cheng, M.D., Busyamas Chewaskulyong, M.D., Riyaz Shah, M.D., Manuel Cobo, M.D., *et al.*, for the FLAURA Investigators*

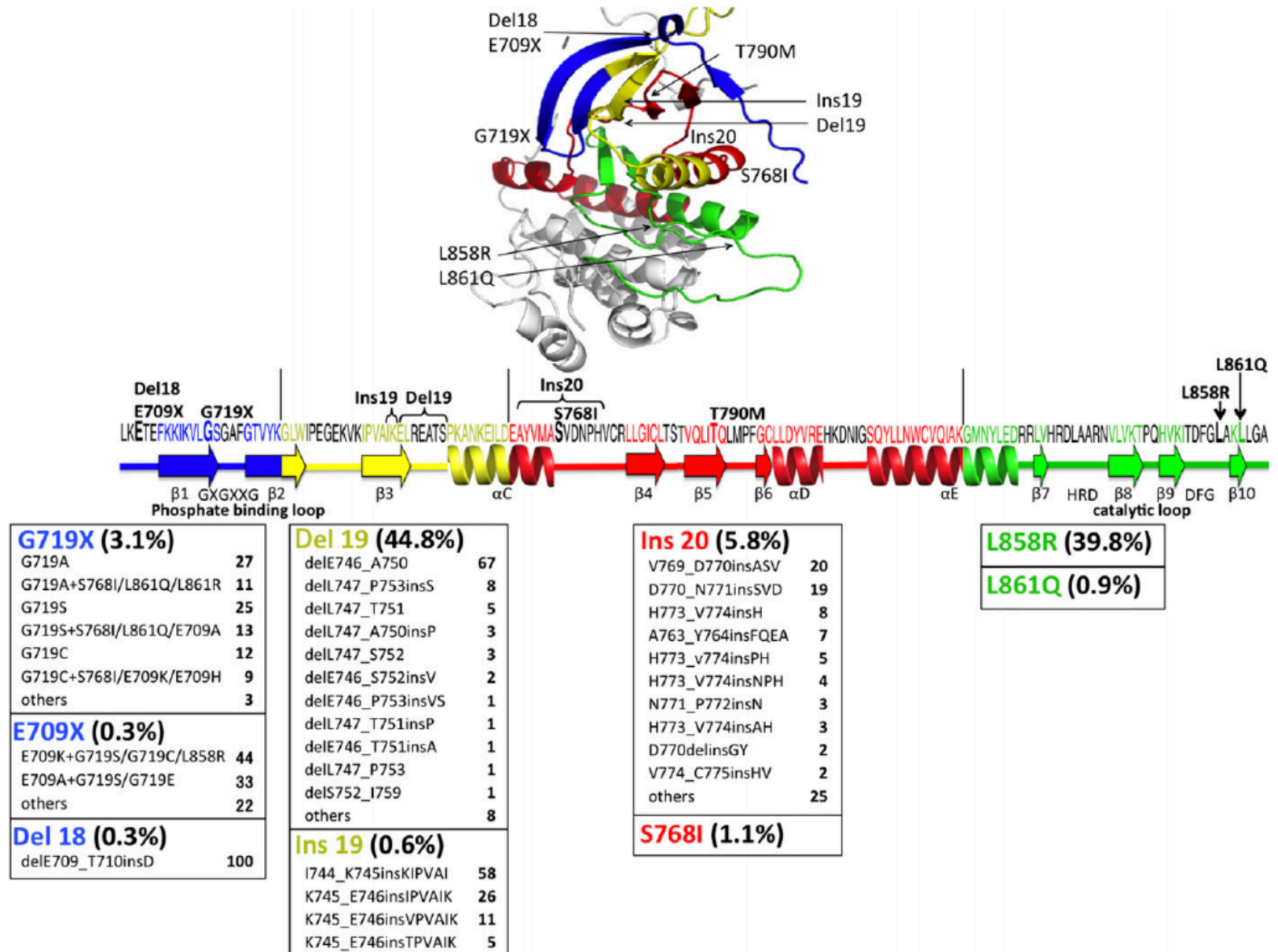


No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

EGFR et Poumon



EGFR et Poumon



EGFR et Poumon

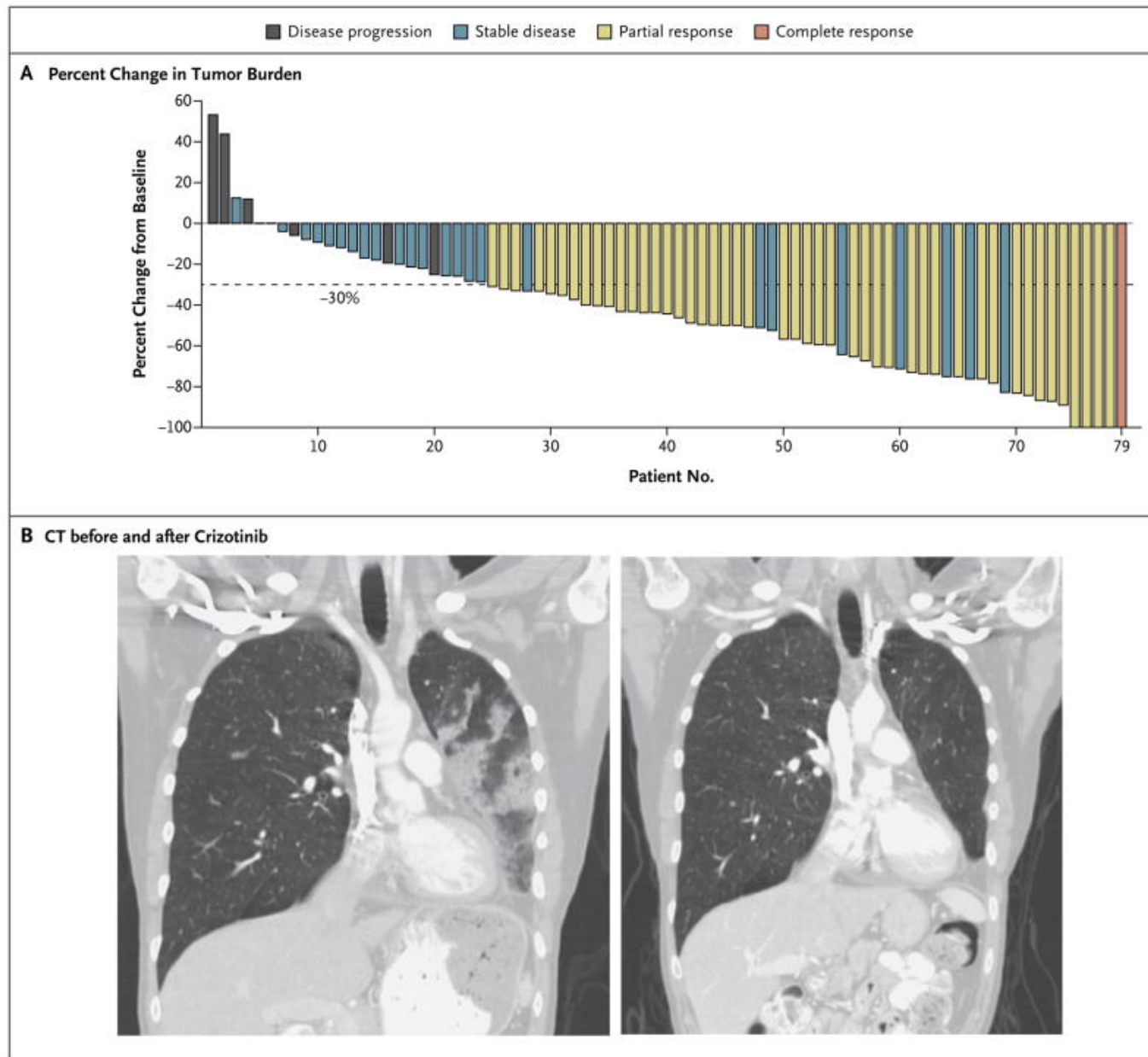
Exon	Category	Mutations	First generation		Second generation			Third generation	
			Gefitinib	Erlotinib	Afatinib	Dacomitinib	Neratinib	Osimertinib	Rociletinib
18	Del18	delE709_T710insD	882	884	1.7	29	27	93	999
	E709X	E709K	187	215	0.7	16	6	62	706
	G719X	G719A	213	167	0.9	6	1.1	53	214
19	Del19	delE746_A750	4.8	4.9	0.9	<1	60	1.1	19
	Del19	delE746_S752insV	306	14	0.2	1.4	86		
	Del19	delL747_A750insP	7.4	13	1	1.6	30		
	Del19	delL747_P753insS	4.1	5.4	2	1.9	38		
	Del19	delS752_I759	35	7.9	0.2	2	6.7		
	Ins19	I744_K745insKIPVAI	400		7				
	Ins19	K745_E746insTPVAIK	100		0.9				
20	Ins20	A763_Y764insFQEA	174	48	3.7			44	673
	Ins20	Y764_V765insHH	>1000	3845	79			237	1730
	Ins20	M766_A767insAI		3403	79				
	Ins20	V769_D770insASV	3100	4400	72	230	48	333	5290
	Ins20	D770_N771insNPG	3356	3700	72		230	42	262
	Ins20	D770_N771insSVD		3187	86				
	Ins20	H773_V774insH		>10 000	268		550		
	S768I	S768I	315	250	0.7			49	
	T790M	T790M+delE746_A750	8300	>10 000	64	140		3	28
	T790M	T790M+L858R	>10 000	>10 000	119	300		21	13
21	L858R	L858R	26	16	4	2.6	1.4	9	140
	L861Q	L861Q	170	103	0.5		3.3	9	
EGFR wild type with interleukin-3			9350	>10 000	>100	>1000	>1000	3078	1549
Plasma drug concentration			(448–2717)	(2717–4040)	(69–130)	(166–238)	(N/A–132)	(400–600)	N/A–N/A

IC50 values (nM) of <10, 10–99, 100–999 and ≥1000 are shown in blue, light blue, yellow and red, respectively. When the exact value was not described in the literature, the approximate number was estimated from each figure. IC90 values are described in delE709_T710insD, E709K, G719A and wild type. EGFR, epidermal growth factor receptor; N/A, not available TKI, tyrosine kinase inhibitors.

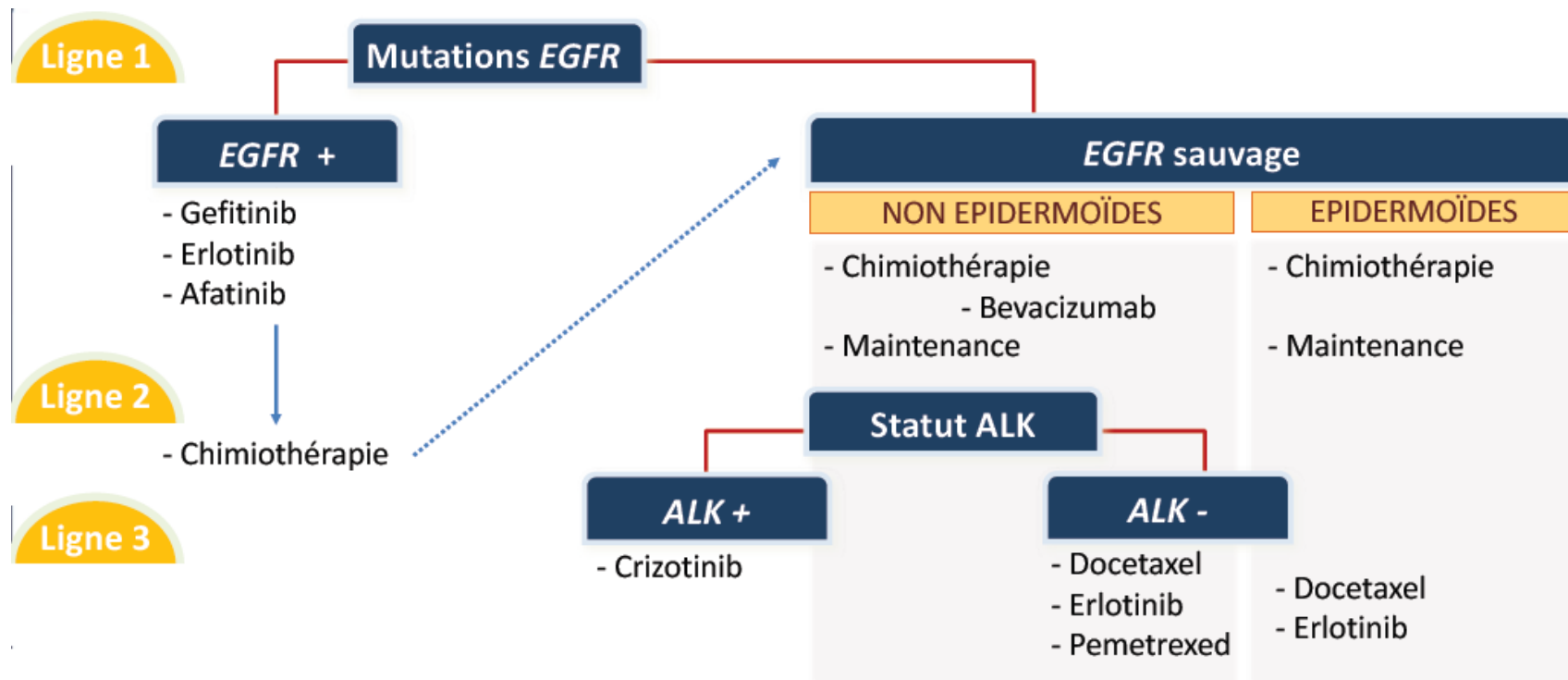
Réarrangements du gène ALK

- Translocation observée dans 5% des cas dans les CBNPC
- Gène de fusion *EML4-ALK*
- Surtout chez les non fumeurs avec un adénocarcinome
- Inhibiteurs de kinase anti-ALK : *crizotinib* (Xalkori[®]), *alectinib* (Alecensa[®]), *ceritinib* (Zykadia[®]), *lorlatinib* (Lorviqua[®]), *brigatinib* (Alunbrig[®])

→ PFS 72% à 6 mois



D'après Kwak et al, NEJM, 2010



D'après N.Girard et référentiel RCP

■ Translocations ALK

VOLUME 34 • NUMBER 7 • MARCH 1, 2016

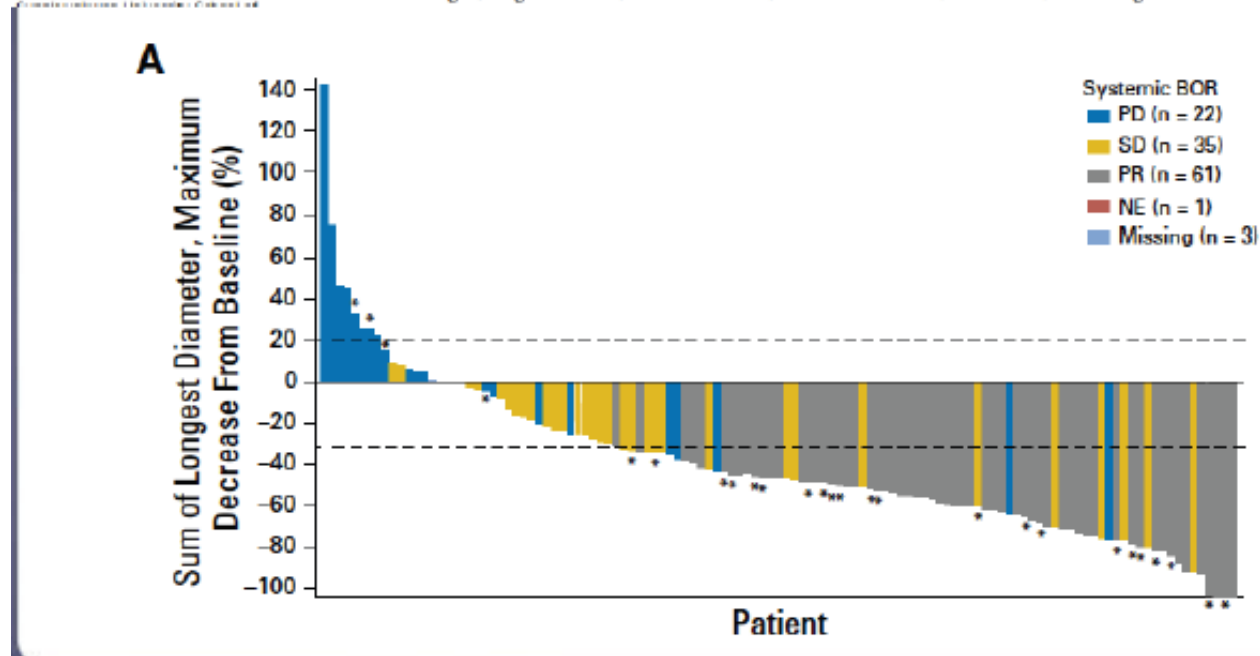
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study

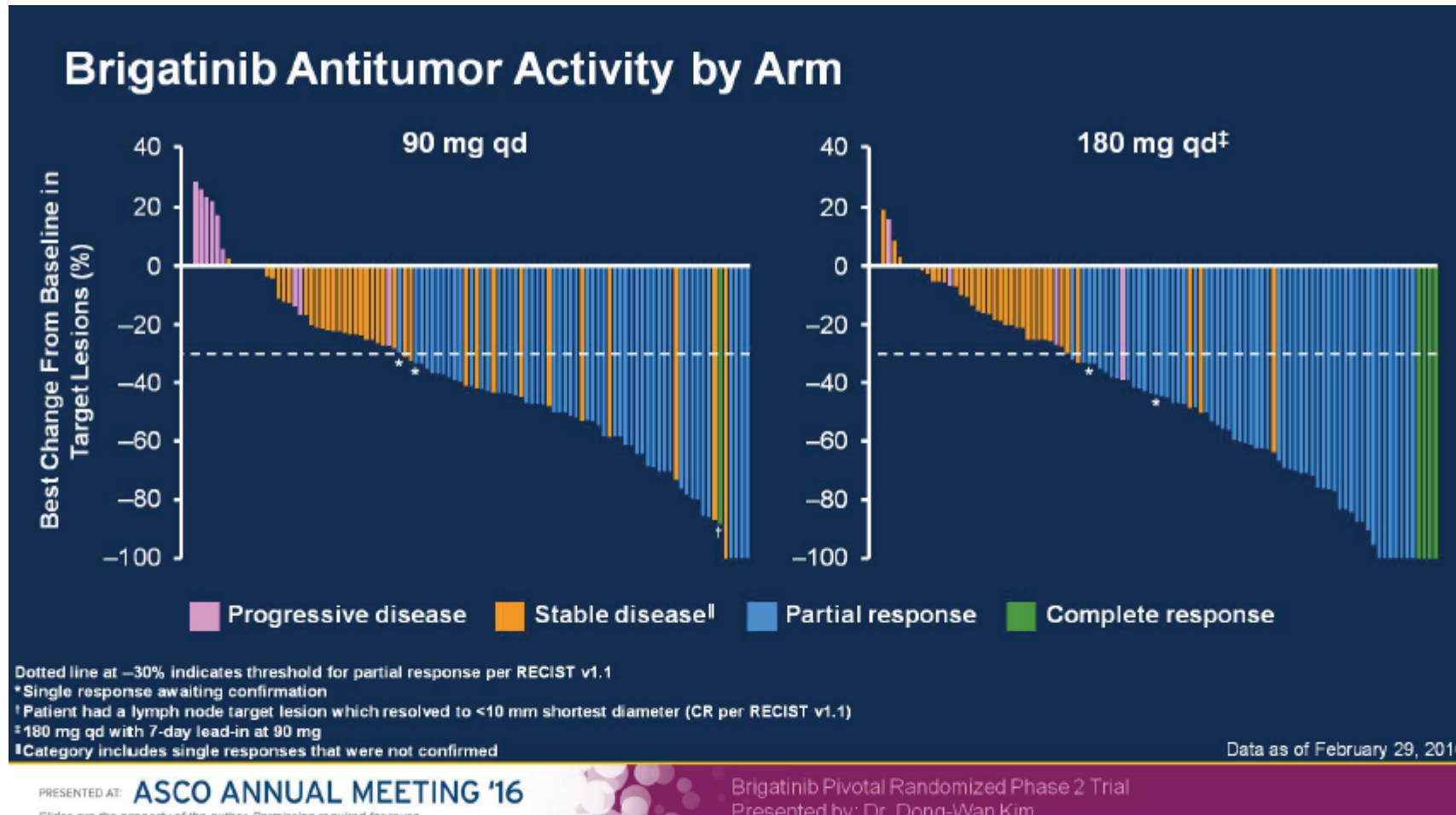
Sai-Hong Ignatius Ou, University of California Irvine School of Medicine, Orange, CA; Jin Seok Ahn, *et al.*

Sai-Hong Ignatius Ou, Jin Seok Ahn, Luigi De Petris, Ramaswamy Govindan, James Chih-Hsin Yang, Brett Hughes, Hervé Lena, Denis Moro-Sibilot, Alessandra Bearz, Santiago Viteri Ramirez, Tarek Mekhail, Alexander Spira, Walter Bordogna, Bogdana Balas, Peter N. Morcos, Annabelle Monnet, Ali Zeaiter, and Dong-Wan Kim



■ Translocations ALK

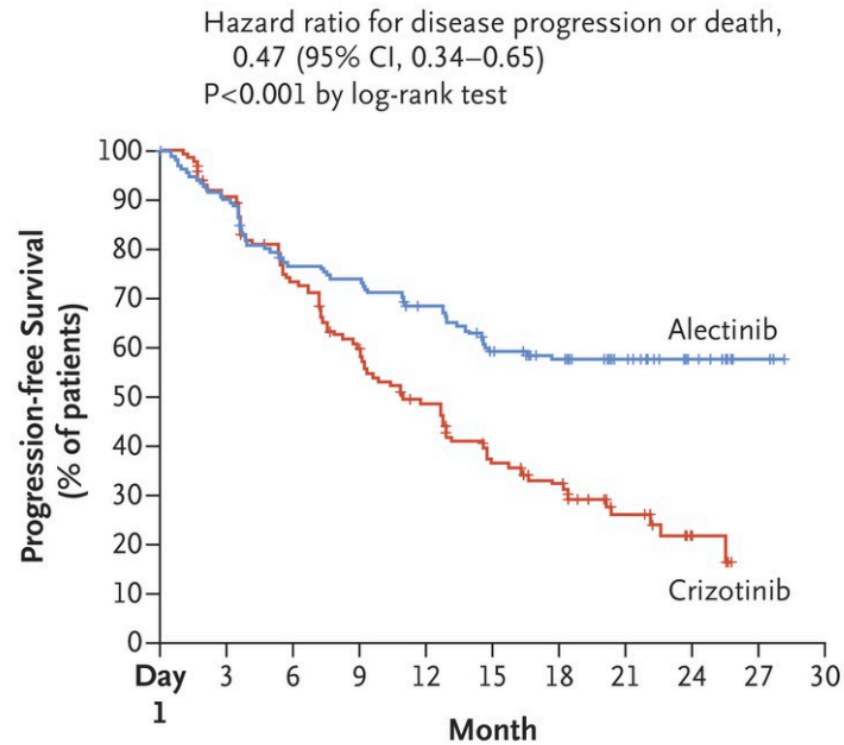
Phase II



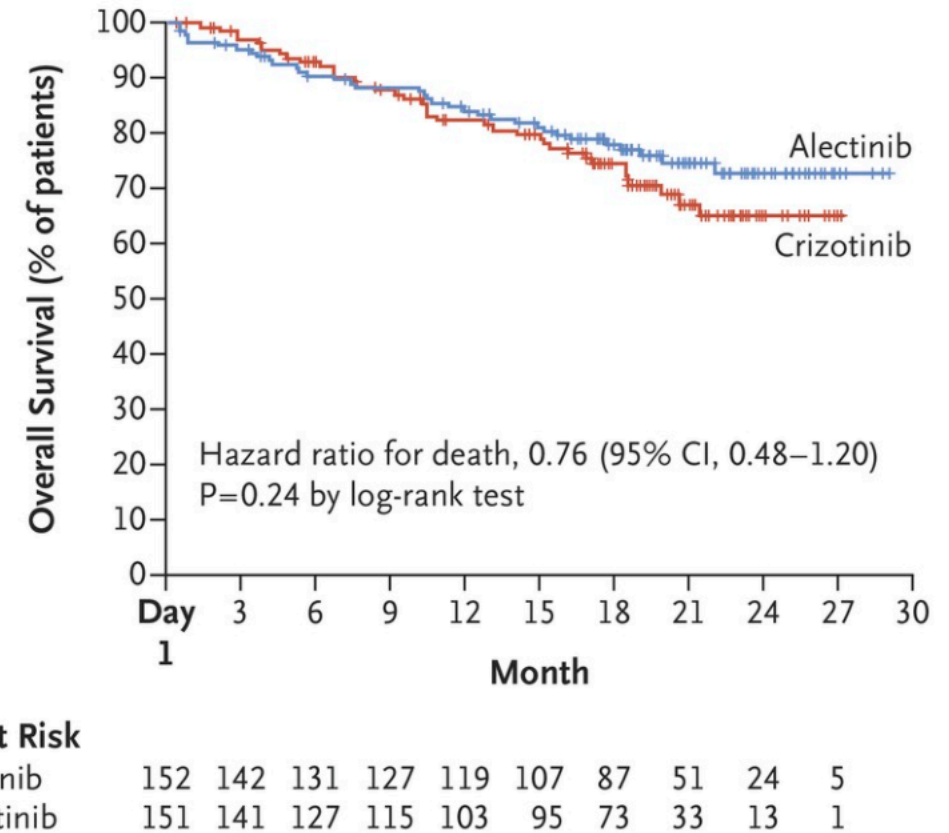
Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, M.D., Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Pérol, M.D., Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zeaiter, M.D., Emmanuel Mitry, M.D., Ph.D., *et al.*, for the ALEX Trial Investigators*

A Progression-free Survival

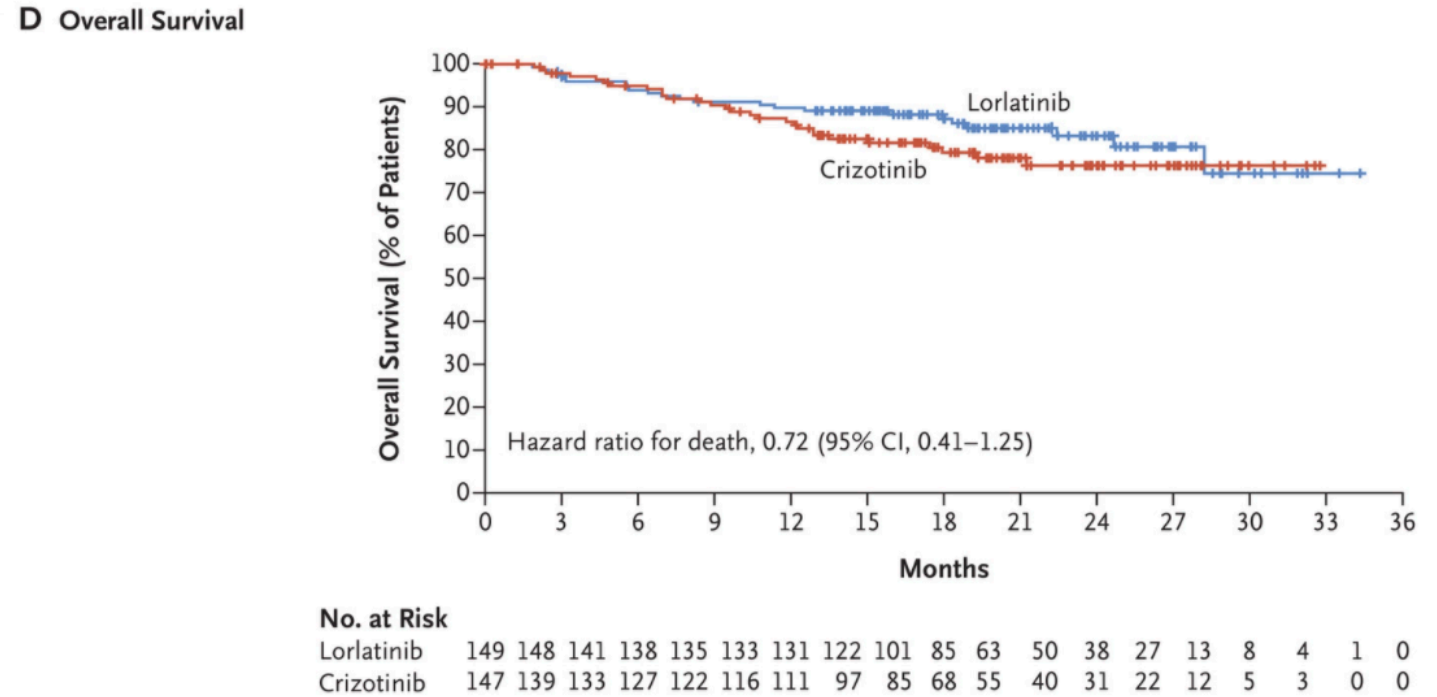
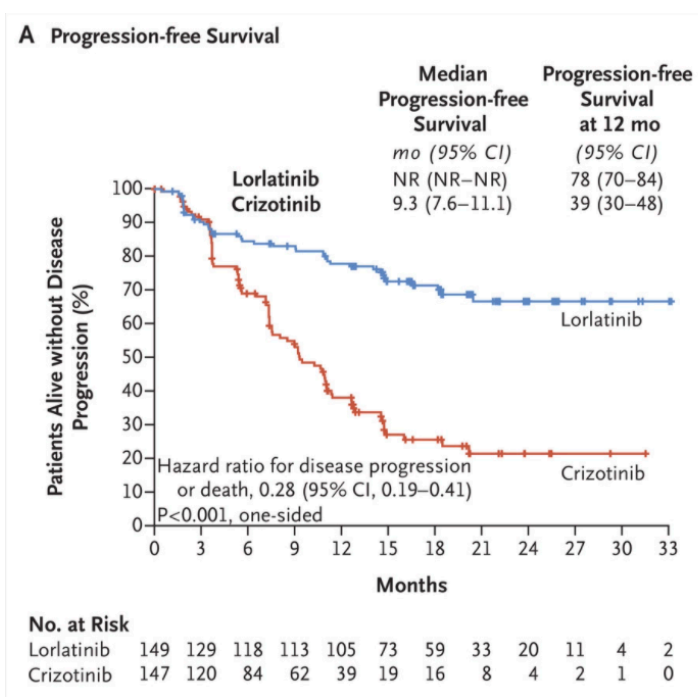


D Overall Survival



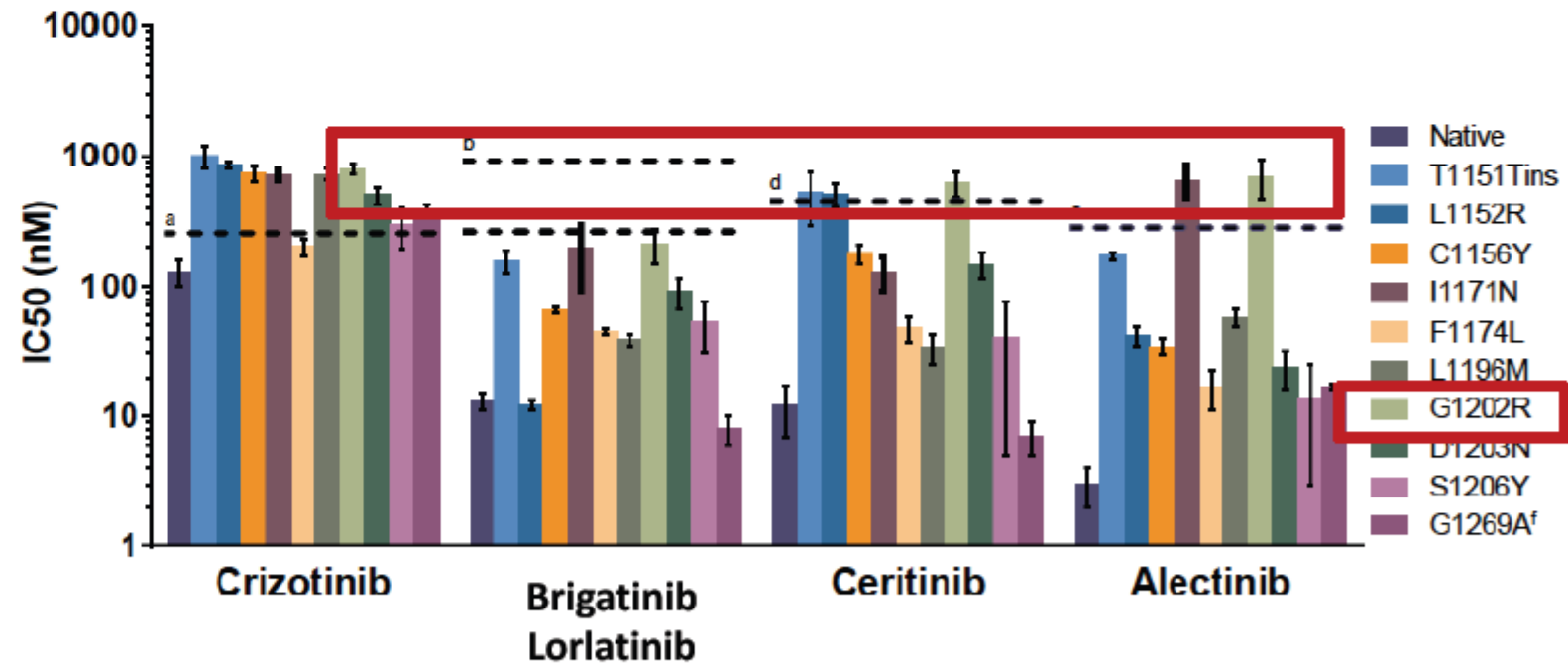
First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D., Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D., Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D., *et al.*, for the CROWN Trial Investigators*



■ Translocations ALK

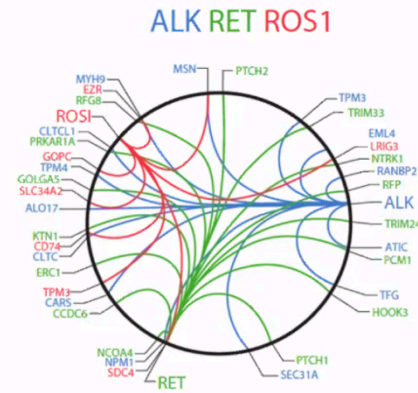
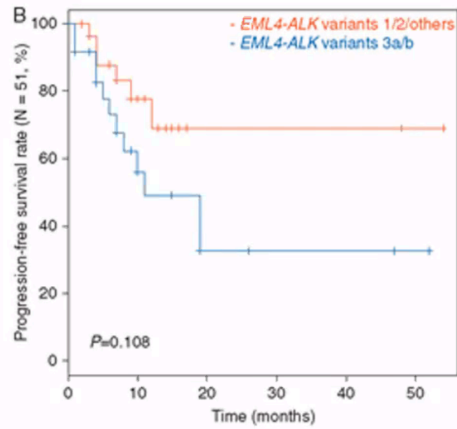
Sensibilité des mutations de résistance à divers inhibiteurs de ALK



Gettinger et al. ASCO 2014

■ Translocations ALK

- Est-il important de connaître le partenaire de fusion de ALK ?

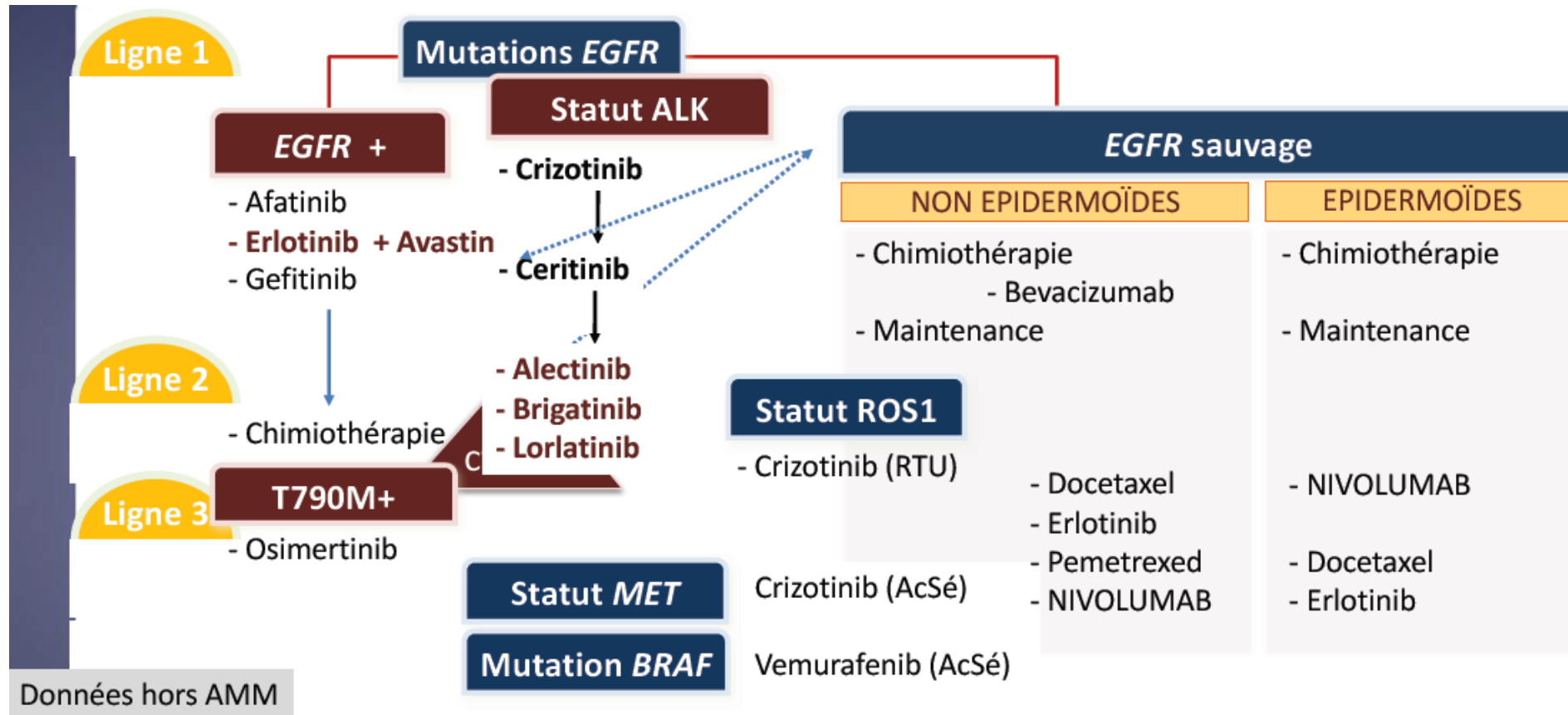


	Crizotinib	Alectinib	Ensartinib	Lorlatinib
ALK F1174L	79.5 67.3 to 94.0	83.9 70.3 to 100.1	43.1 36.9 to 50.2	23.8 19.7 to 28.8
TFG-ALK	87.4 68.9 to 110.9	35.96 32.3 to 40.0	11.7 9.4 to 14.6	7.8 6.3 to 9.6
EML4-ALK V3	122.5 96.0 to 156.6	136.7 112.7 to 166	39.9 27.3 to 58.1	6.1 5.4 to 6.9
FN1-ALK	153.3 127.0 to 185.2	273.1 219.7 to 341.1	48.8 37.6 to 62.9	35.2 28.4 to 43.6
EML4-ALK V1	165.8 134.9 to 204.0	48.21 39.03 to 59.68	11.2 9.0 to 14.0	7.7 6.1 to 9.7
RANBP2-ALK	220.7 180.1 to 270.5	163.9 138.1 to 194.6	91.4 71.6 to 117.0	171.6 226.5 to 377.5
Empty Vector	357.1 294.8 to 432.2	5170 3661 to 8218	1277.0 832.8 to 2005	1097 638 to 1526
KIF5B-ALK	405.1 283.9 to 580.0	84.11 65.84 to 107.9	24.3 15.8 to 36.9	89.1 56.4 to 145
PRKAR1A-ALK	461.8 291.4 to 743.2	406.7 327.7 to 507	123.2 91.3 to 167.1	328.5 262.7 to 418.8

200 nmol/L
400 nmol/L
600 nmol/L
800 nmol/L
1,000 nmol/L

- Place de la recherche de fusion dans le suivi ?
 - Recherche diagnostic ou de mécanisme de résistance

■ Algorithmme 2017 CBNPC



D'après Girard N.

■ Mutations BRAF V600

Dabrafenib plus trametinib in patients with previously untreated $BRAF^{V600E}$ -mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial



David Planchard, Egbert F Smit, Harry J M Groen, Julien Mazieres, Benjamin Besse, Åslaug Helland, Vanessa Giannone, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

■ Mutations BRAF V600

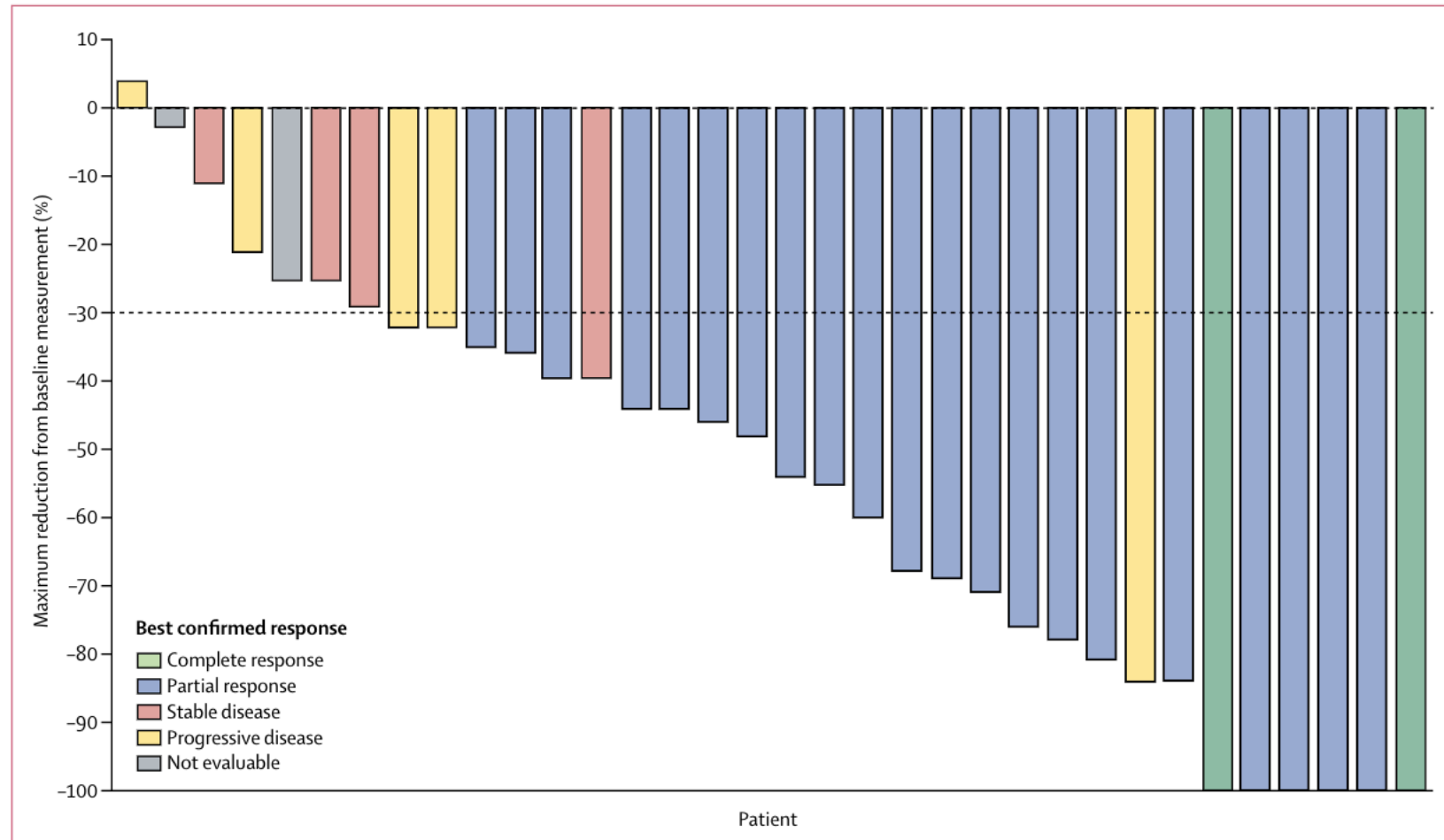


Figure 2: Confirmed maximum reduction in target lesions according to investigator assessment

Dashed line at -30% represents the threshold for partial response, according to Response Evaluation Criteria In Solid Tumors version 1.1. Bars show maximum reduction from baseline sum of diameters by best confirmed response. Two patients were not included because they did not have a post-baseline assessment of target lesions.

Mutations BRAF V600

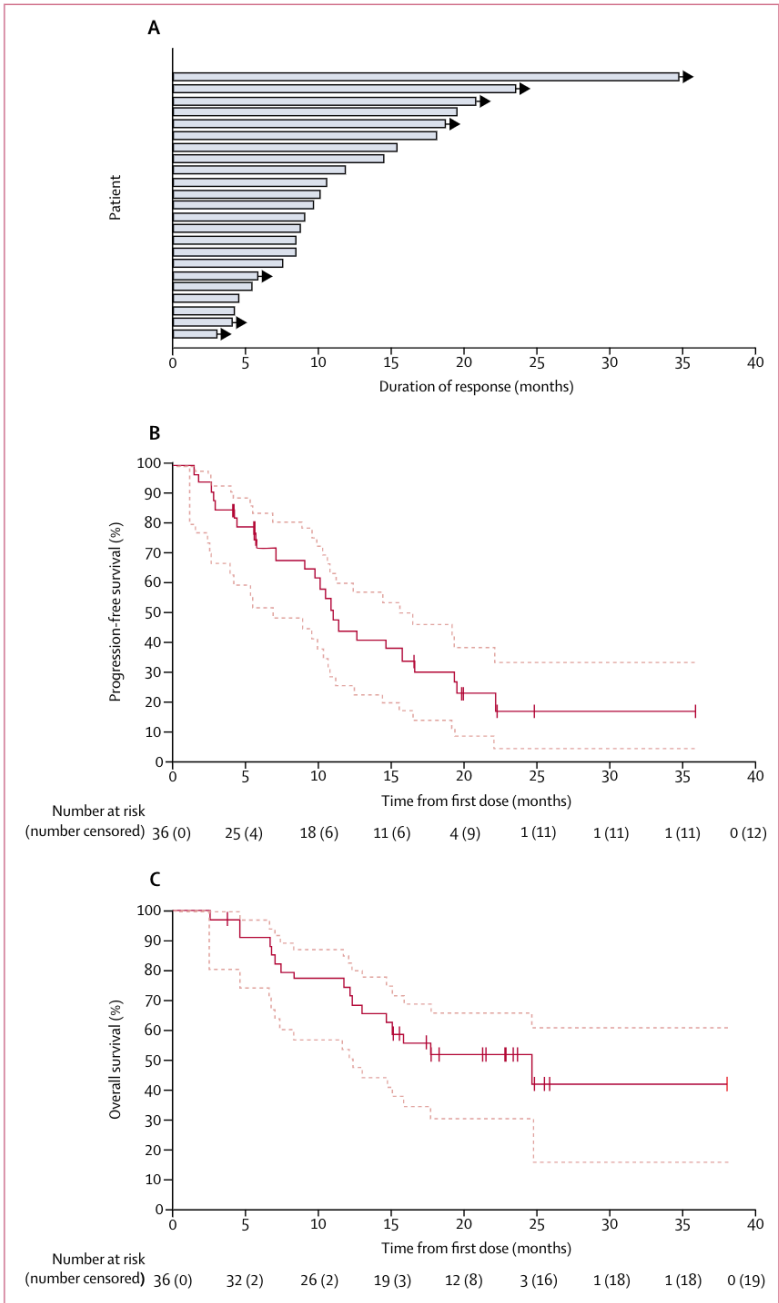


Figure 3: Investigator-assessed duration of response (A), investigator-assessed estimated progression-free survival (B), and estimated overall survival (C). Arrows indicate censored patients with follow-up ongoing. Tick marks represent censored patients. Dotted lines in Kaplan-Meier estimated curves represent 95% CIs.

- Mutations KRAS G12C

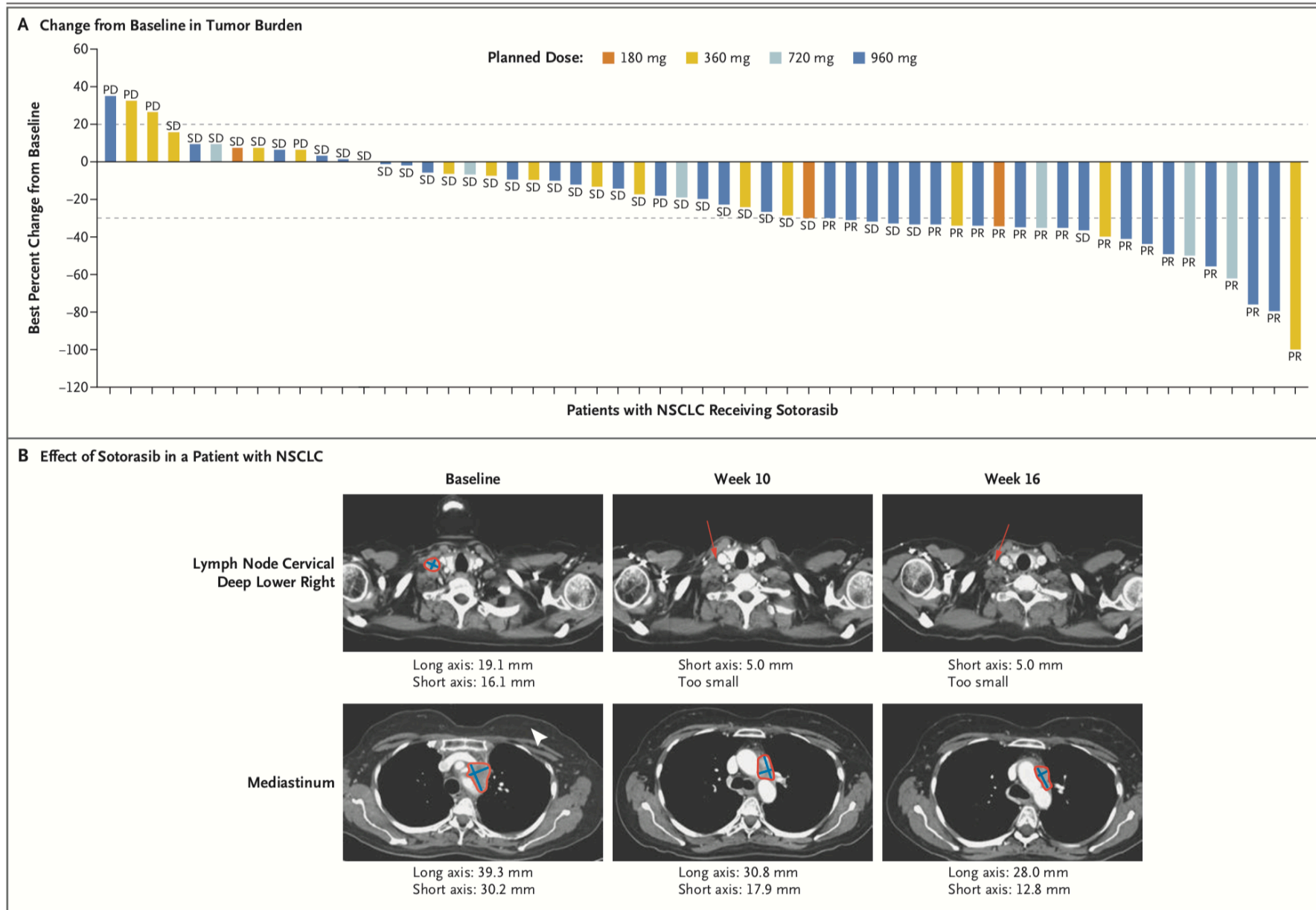
The NEW ENGLAND JOURNAL of MEDICINE

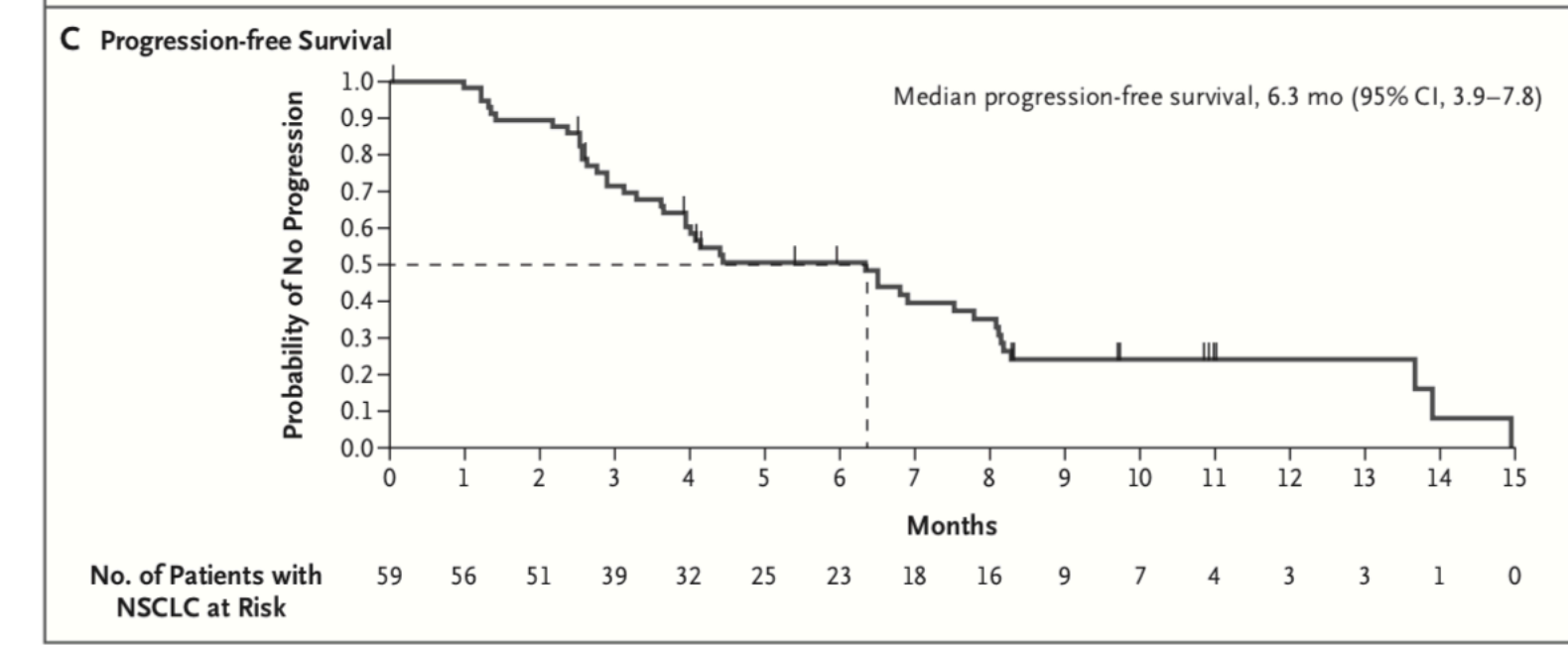
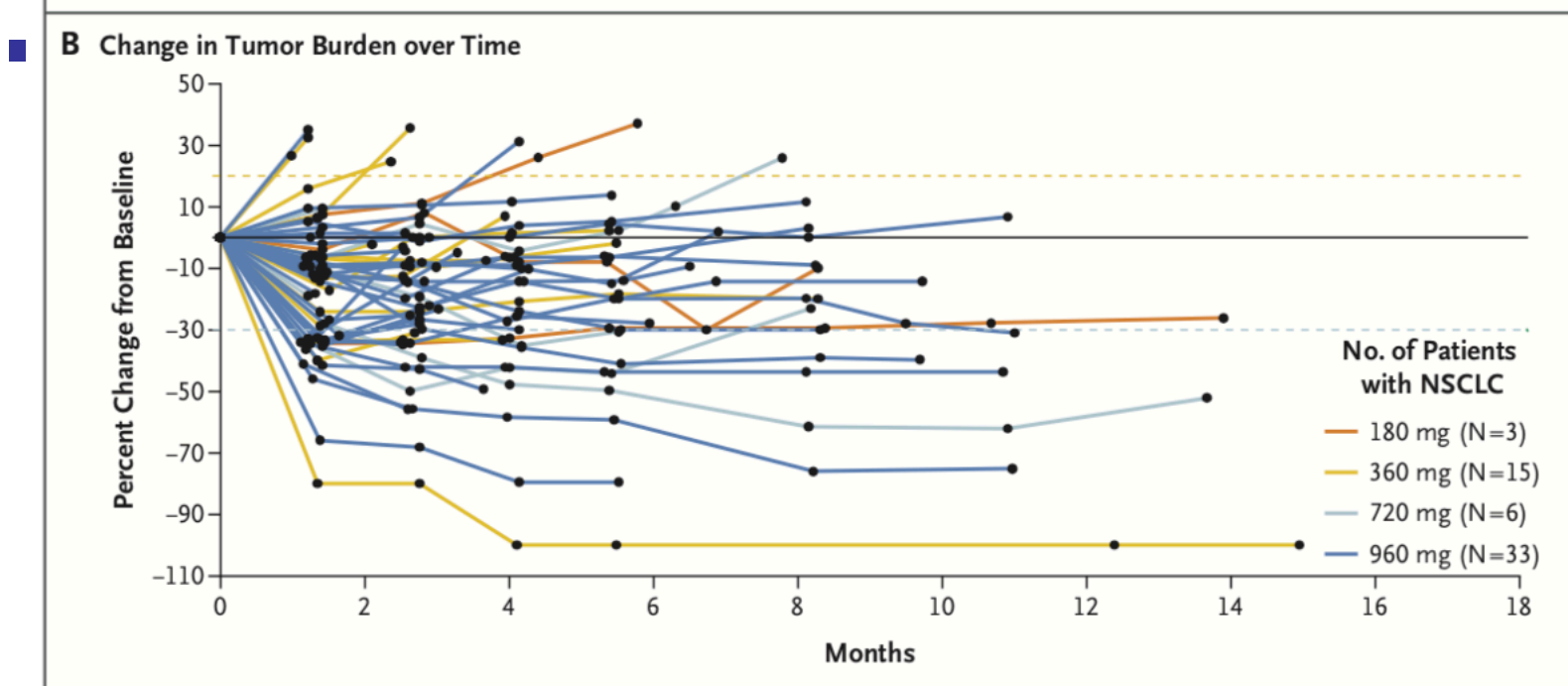
ORIGINAL ARTICLE

KRAS^{G12C} Inhibition with Sotorasib in Advanced Solid Tumors

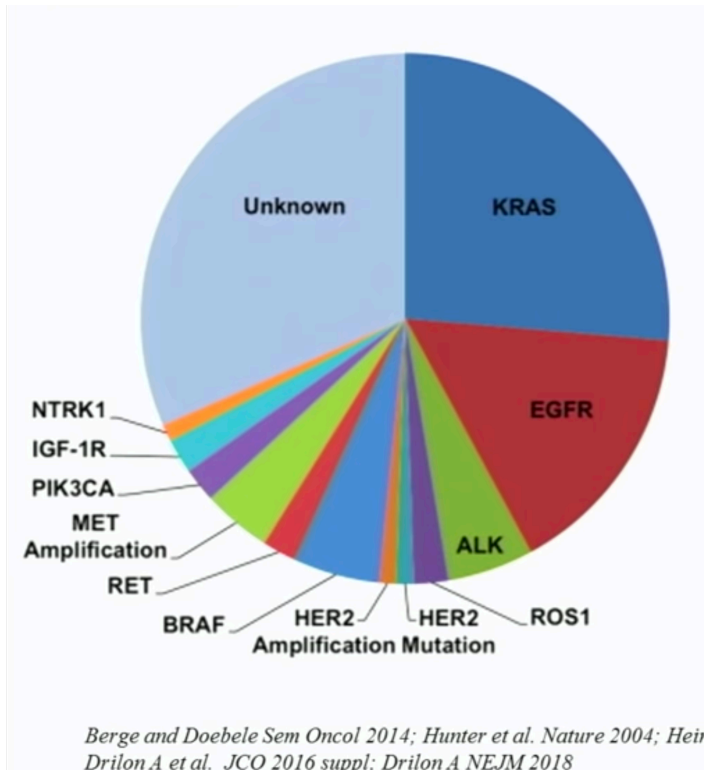
D.S. Hong, M.G. Fakih, J.H. Strickler, J. Desai, G.A. Durm, G.I. Shapiro,
G.S. Falchook, T.J. Price, A. Sacher, C.S. Denlinger, Y.-J. Bang, G.K. Dy,
J.C. Krauss, Y. Kuboki, J.C. Kuo, A.L. Coveler, K. Park, T.W. Kim, F. Barlesi,
P.N. Munster, S.S. Ramalingam, T.F. Burns, F. Meric-Bernstam, H. Hearn,
J. Ngang, G. Ngarmchamnanrith, J. Kim, B.E. Houk, J. Canon, J.R. Lipford,
G. Friberg, P. Lito, R. Govindan, and B.T. Li

■ Mutations KRAS G12C





- Il existe aujourd'hui de nombreuses thérapeutiques ciblées et des immunothérapies, plus efficaces que la chimiothérapie traditionnelle



Targetable mutations/gene fusions

- EGFR
 - multiple drugs
- ALK
 - multiple drugs
- ROS1
 - crizotinib
- BRAF-V600E only
 - dabrafenib/trametinib
- RET
 - Experimental drugs (BLU-667)
- NTRK
 - larotrectinib
- MET exon 14 skipping
 - crizotinib
- HER2/Neu – exon 20 mutations
 - HER2 antibodies + chemo
- KRAS G12C only
 - AMG510

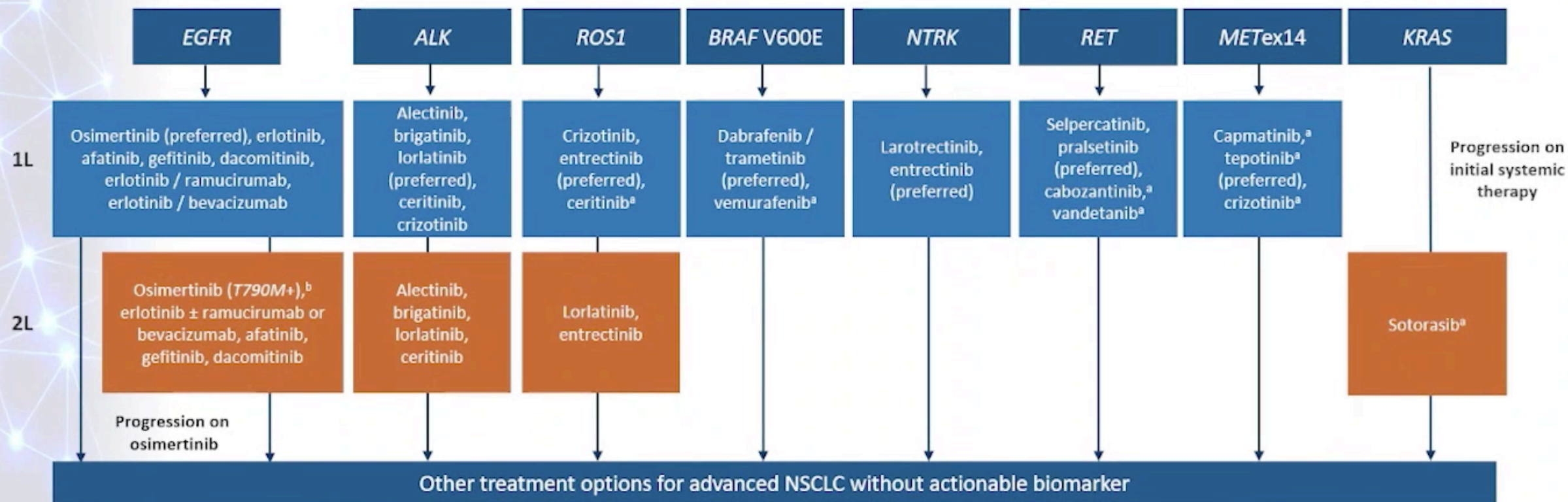
***Response rates 50-80%**

Berge and Doebele Sem Oncol 2014; Hunter et al. Nature 2004; Heinmoller P et al. Clin Cancer Res 2003; Drilon A et al. JCO 2016 suppl; Drilon A NEJM 2018

- Au final en 2022 pour le traitement des CBNPC
 - EGFR
 - ALK (Fusions et mutations)
 - BRAF V600
 - KRAS G12C
 - PD1/PDL1
 - ROS1
 - RET
 - MET
 - PIK3CA

There is a growing number of biomarkers for which targeted therapies are available

- As more mutations become clinically actionable, pathology labs are tasked with testing for an increasing number of biomarkers



^a These compounds are not approved by the European Medicines Agency for the treatment of NSCLC with the indicated mutation.

^b Osimertinib is recommended as 2L and beyond for patients with *EGFR T790M+* metastatic NSCLC who have progressed on erlotinib, afatinib, gefitinib, or dacomitinib. 1L/2L, first line/second line.

Detecting HRD in ovarian cancers using a deep learning solution based on low pass whole-genome sequencing





HRD testing: Why, for who, how?

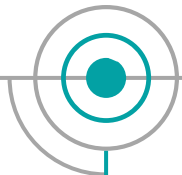
Development of PARP inhibitors

Discovery of benzamide as competitive PARP inhibitor

Role for nuclear PARPs in DNA damage repair

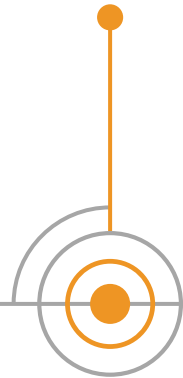
Pre-clinical data BRCA 1/2 deficient cells sensitive to PARP inhibitors

1963



Detection of poly(ADP-ribose) in nuclei

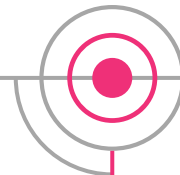
1980



Discovery of benzamide as competitive PARP inhibitor

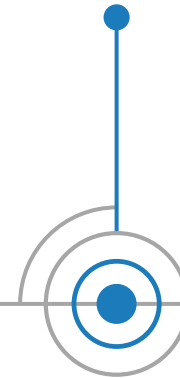
Role for nuclear PARPs in DNA damage repair

1994-1995



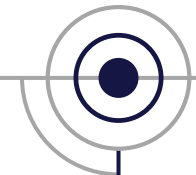
BRCA1 and BRCA2 isolated

2011



Pre-clinical data BRCA 1/2 deficient cells sensitive to PARP inhibitors

2014



1st Approval - Treatment Advanced Ovarian ≥ 3 chemotherapy
Germline BRCA
Olaparib

Development of PARP inhibitors

Treatment for **advanced ovarian cancer** ≥ 3 chemotherapy
Germline and/or somatic BRCA mutated
Olaparib and Rucaparib

Maintenance for **recurrent ovarian cancer***, in CR or PR to Platinum
Regardless of BRCA
Olaparib and Niraparib

Treatment for **advanced ovarian cancer*** ≥ 3 chemotherapy
HRD positive
Niraparib

Maintenance of **metastatic pancreatic cancer**
Germline and/or somatic BRCA mutated
Olaparib

2016 - 2017

2018

2019

2020

Treatment for **breast cancer**
Germline BRCA - HER2 neg
Olaparib (metastatic who underwent chemotherapy)
Talazoparib (advanced or metastatic)

Maintenance for **advanced ovarian cancer*** in CR/PR to 1st line Platinum
Germline or somatic BRCA
Olaparib

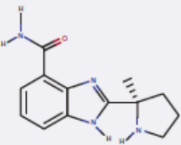
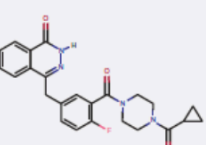
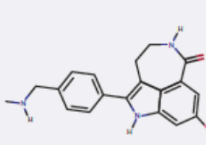
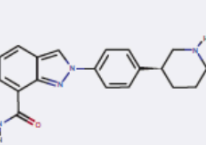
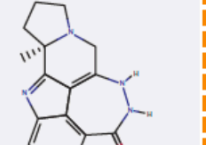
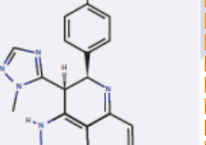
Maintenance of **ovarian cancer***
Regardless of BRCA
Rucaparib

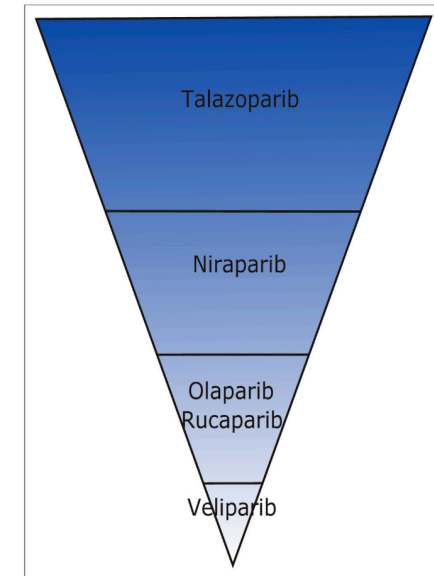
Treatment for **advanced ovarian cancer** who responded to Platinum
regardless of BRCA mutation
Niraparib

Treatment in mcr **prostate cancer** resistant to hormonal treatment
Germline or somatic HRR mutated
Olaparib

CR : Complete response; PR : Partial respons, mcr : metastatic castration resistant
* including Epithelial ovarian, fallopian tube and primary peritoneal cancer

PARPi

						
	Veliparib ^E	Olaparib	Rucaparib	Niraparib	Pamiparib ^F	Talazoparib
Relative PARP-trapping capacity (nM)	-	Proof of concept for a synthetic lethal approach in oncology				
Single agent dose	400 mg PO BID	300 mg PO BID	600 mg PO BID	300 mg PO QD	60 mg PO BID	1 mg PO QD
Toxicities Most frequent	Nausea (30%)/fatigue (25%)/lymphopenia (16%)	Nausea (58–76%)/fatigue (29–66%)/vomiting (30–37%)/diarrhea (21–33%)/dysgeusia (27%)/headache (20–25%)	Nausea (75%)/fatigue (69%)/vomiting (37%)/diarrhea (32%)/dysgeusia (39%)/LFT elevation (34%)	Nausea (74%)/fatigue (59%)/LFT elevation (36%)/vomiting (34%)/headache (26%)/insomnia (24%)/HTN (19%)	Limited early-phase trial data from abstracts only: nausea (56%)/fatigue (40%) ^F	Nausea (49%)/fatigue (50%)/headache (33%)/vomiting (25%)/alopecia (25%)/diarrhea (22%)
Grade ≥3 hematological toxicities in ≥5% of study population	NTD	Anemia (16–19%), neutropenia (5–9%)	Anemia (19%), neutropenia (7%)	Thrombocytopenia (34%), anemia (25%), neutropenia (20%)	Limited early-phase trial data from abstracts only: anemia (10.3%), neutropenia (8.8%) ^F	Anemia (39%), neutropenia (21%), thrombocytopenia (15%)
Clinical benefit	NTD	OlympiAD (HER2-breast), HR 0.50, PFS benefit SOLO2 (relapsed ovarian maintenance), HR 0.30, PFS benefit SOLO1 (ovarian maintenance), HR 0.30, PFS benefit POLO (deleterious HRR mutations in relapsed pancreas) HR 0.53, PFS benefit	ARIEL2 (relapsed ovarian maintenance), HR 0.27, PFS benefit ARIEL 3 (relapsed ovarian maintenance), HR 0.27, PFS benefit TRITON2 (BRAC1/2 relapsed pancreas), ORR 43.9% TRITON3 (ongoing)	NOVA (relapsed ovarian maintenance), HR 0.27, PFS benefit	Ongoing, data not mature (NCT03427814)	EMBRACA (HER2-breast), HR 0.54, PFS benefit
Approvals	NTD	Ovarian Breast Prostate (mCRPC)	Ovarian Prostate (mCRPC)	Ovarian	NTD	Breast



Capacité de “trapping” des PARP-i

Benefits of PARPi – BRCA1/2 +

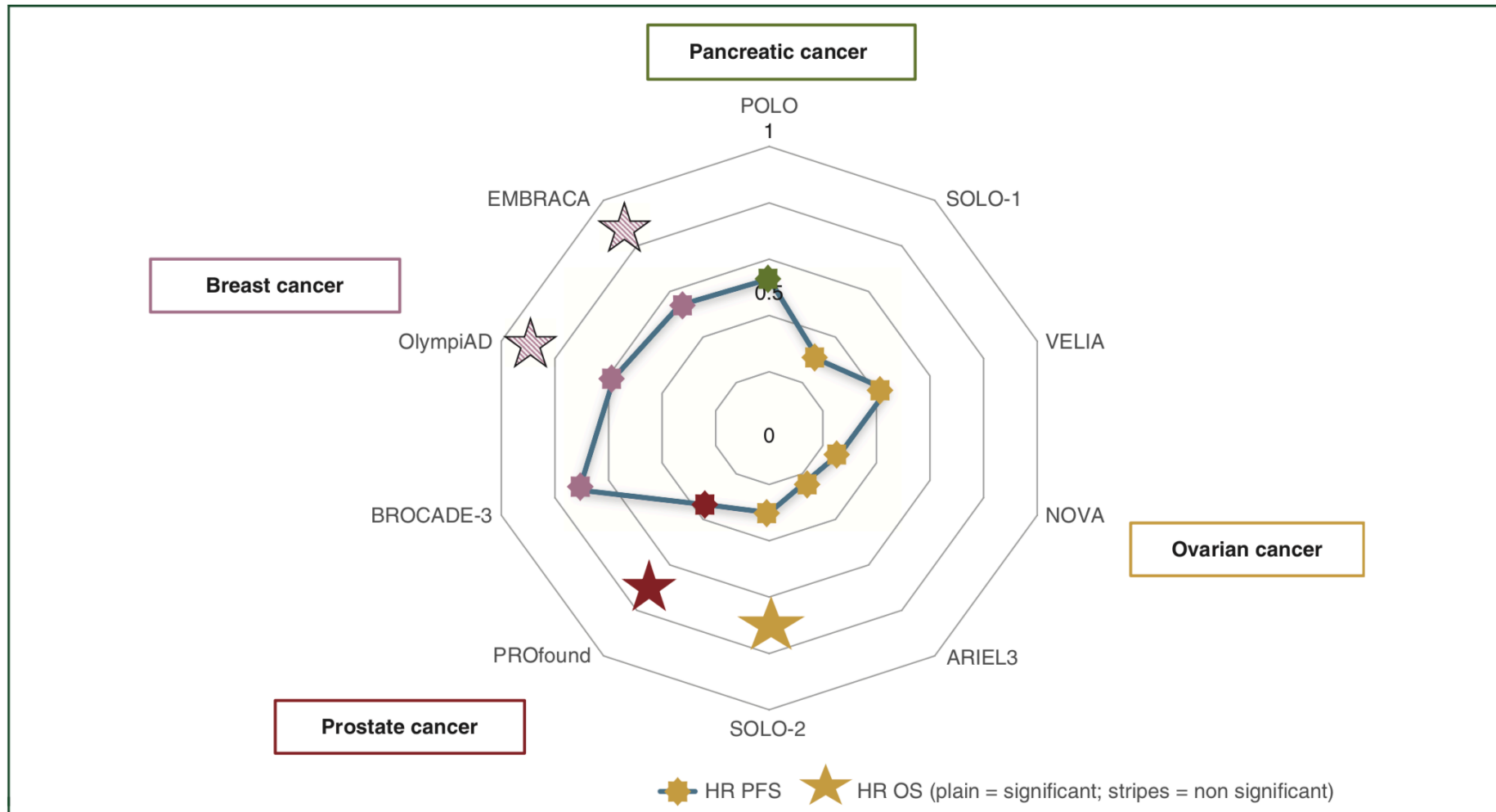


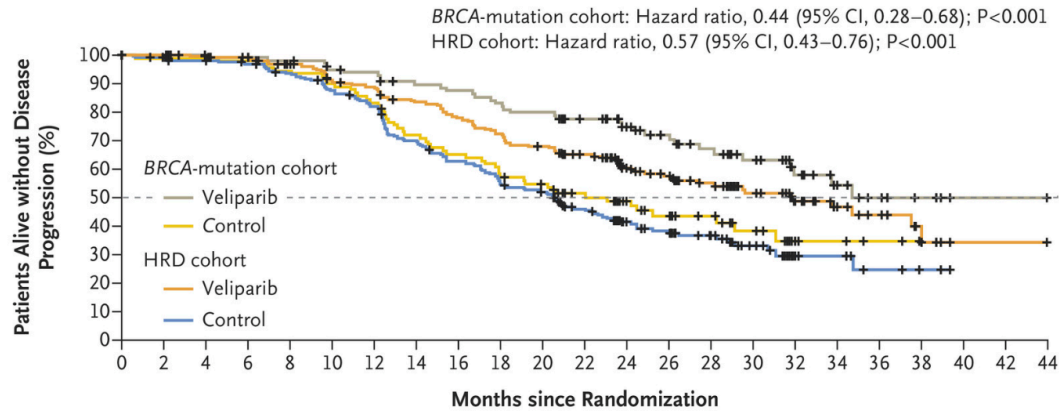
Figure 1. Progression-free and overall survival results of phase III trials evaluating PARP inhibitors in patients with BRCA1/2-mutated tumors and across cancer locations.

Ovarian cancer, first line trials: olaparib in SOLO-1¹² and veliparib in VELIA.¹³ Ovarian cancer, platinum sensitive relapse: niraparib in NOVA,¹⁴ rucaparib in ARIEL3,¹⁵ olaparib in SOLO-2.⁵ Prostate cancer, castration-resistant: olaparib in PROfound.⁶ Metastatic breast cancer: olaparib in OlympiAD,⁷ talazoparib in EMBRACA,¹¹ veliparib in BROCADE-3.⁹ Pancreatic cancer: olaparib in POLO.¹⁶

Benefits of PARPi – Ovarian cancer HRD

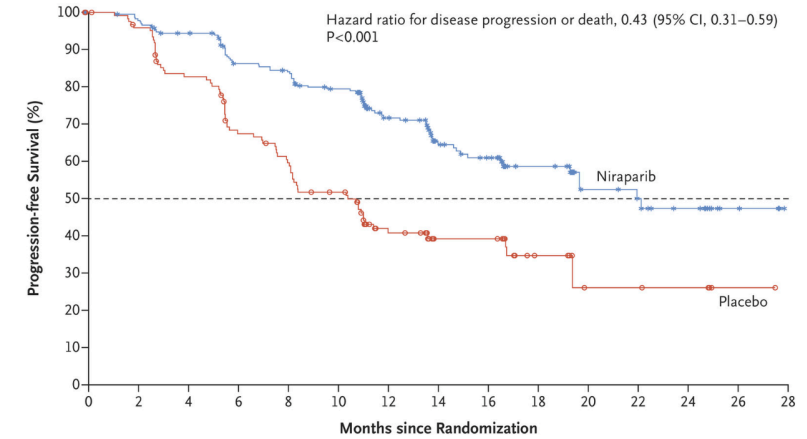
VELIA¹

B Progression-free Survival in Trial Cohorts

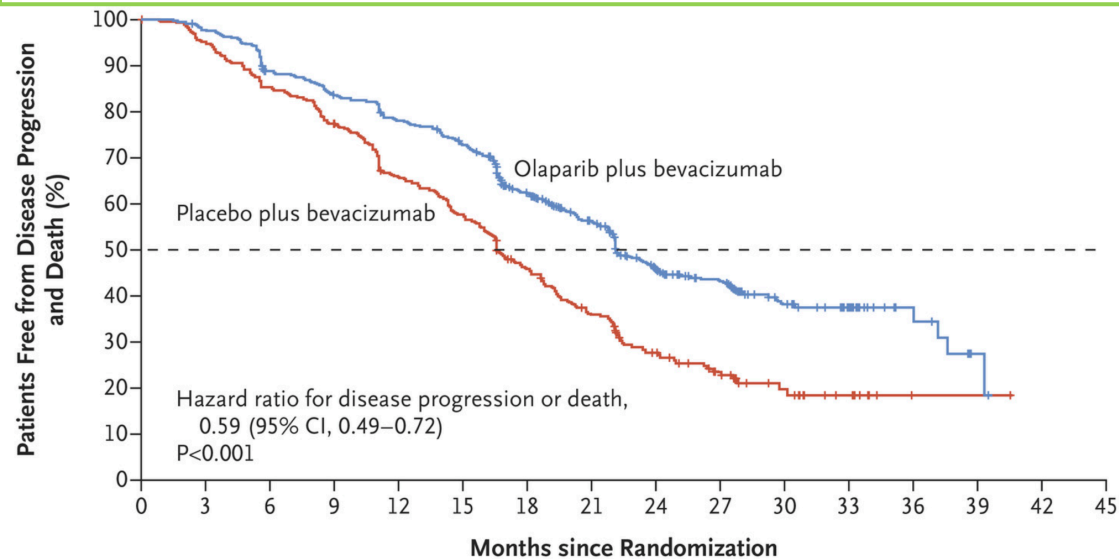


PRIMA²

A Progression-free Survival in Population with Homologous-Recombination Deficiency



PAOLA³

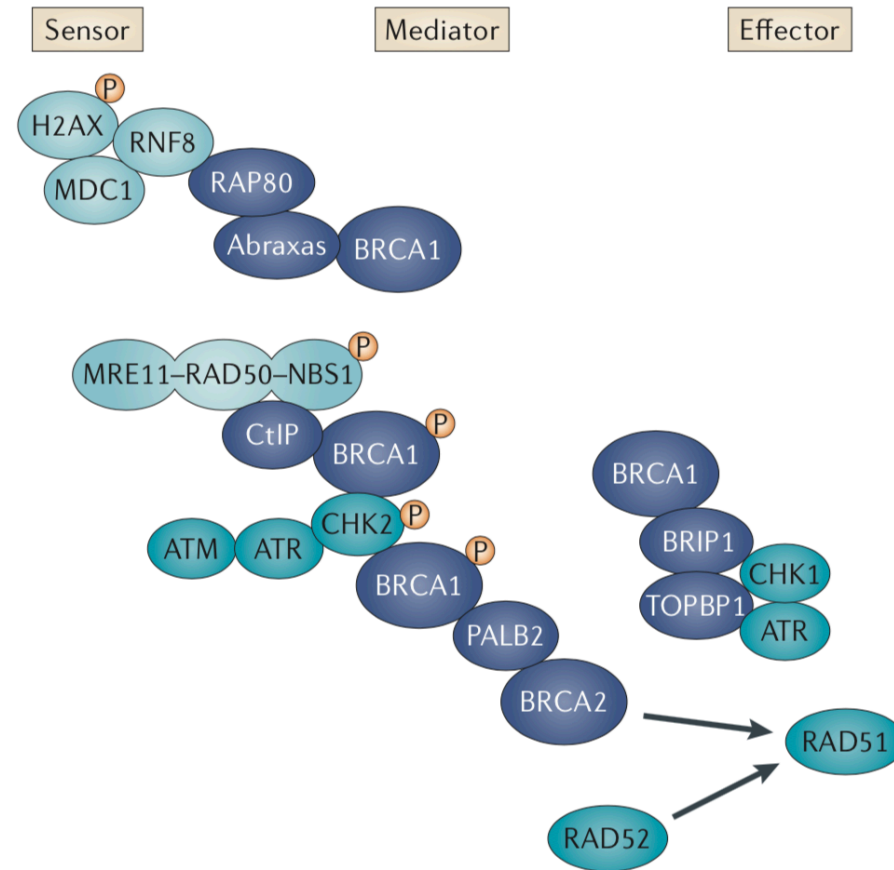
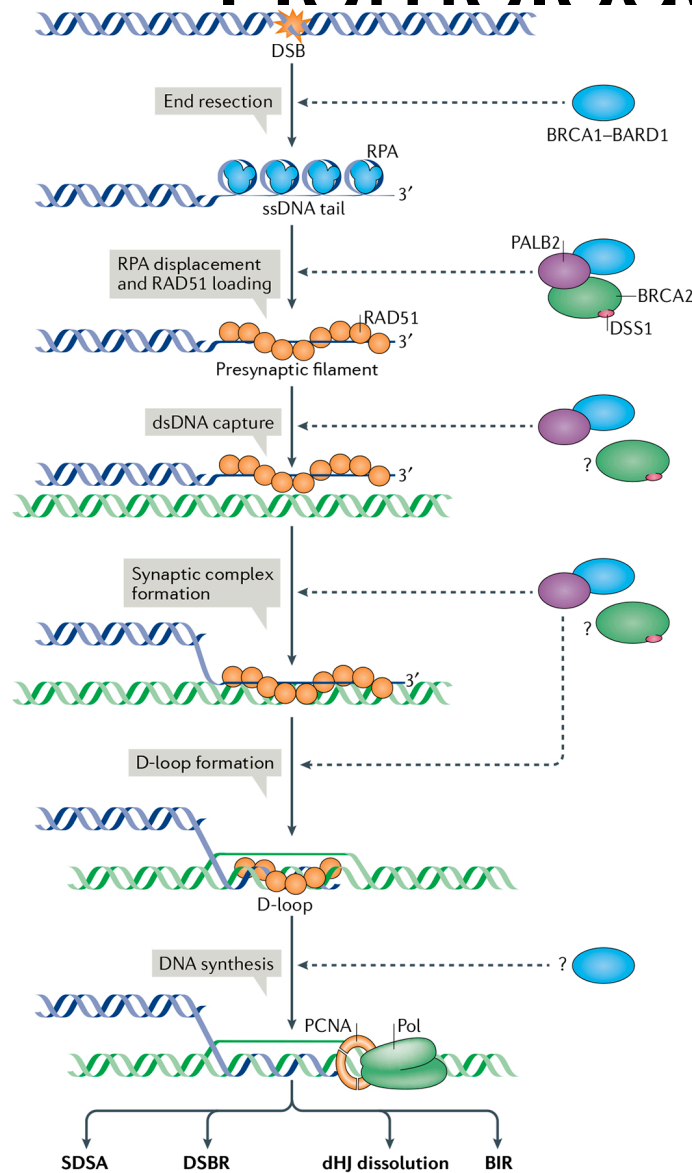


1 Coleman *et al.*, N Engl J Med. 2019

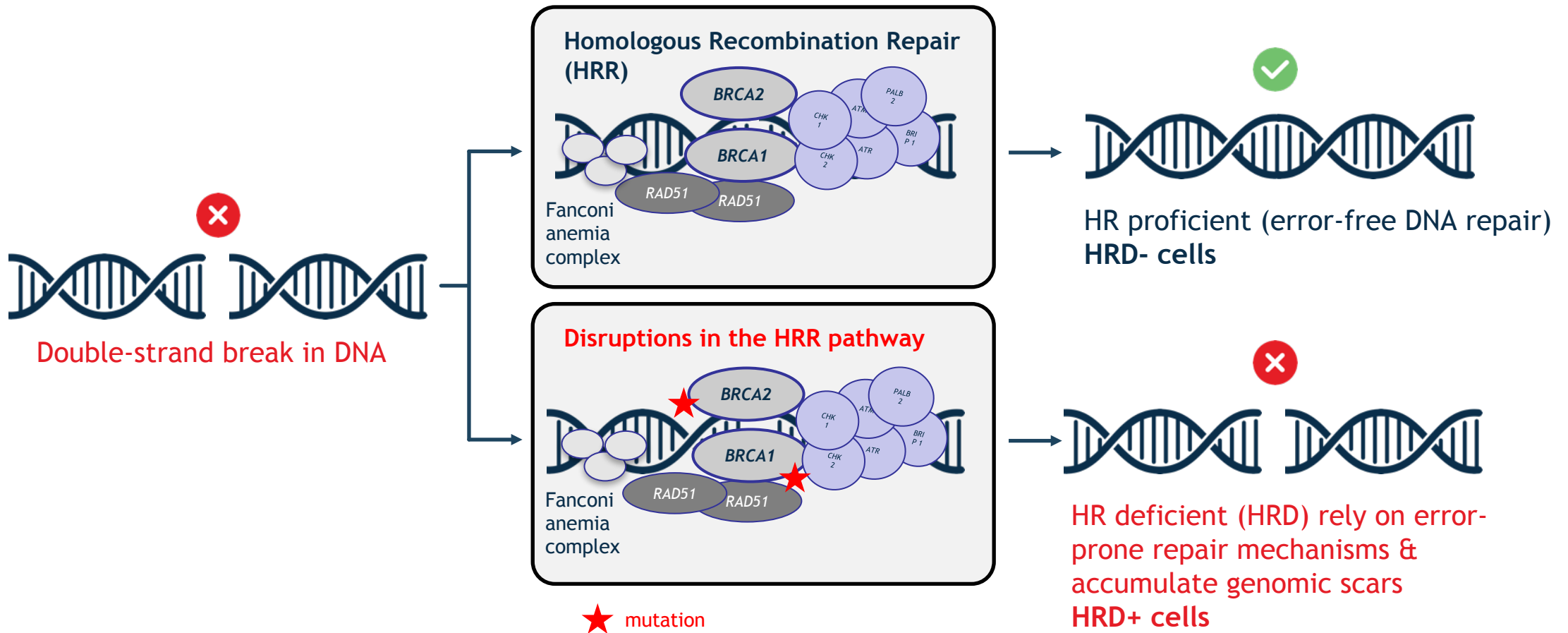
2 González-Martín *et al.*, N Engl J Med. 2019

3 Ray-Cocquard *et al.*, N Engl J Med. 2019

Homologous Recombination

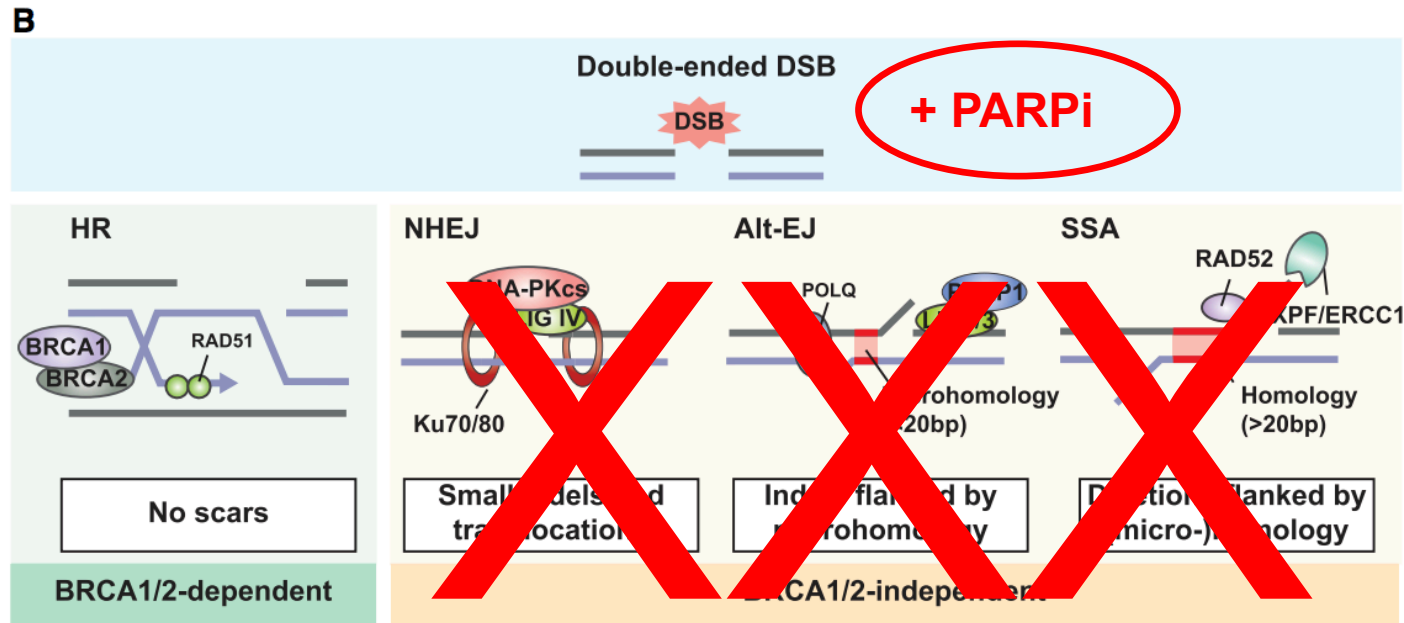


Homologous Recombination



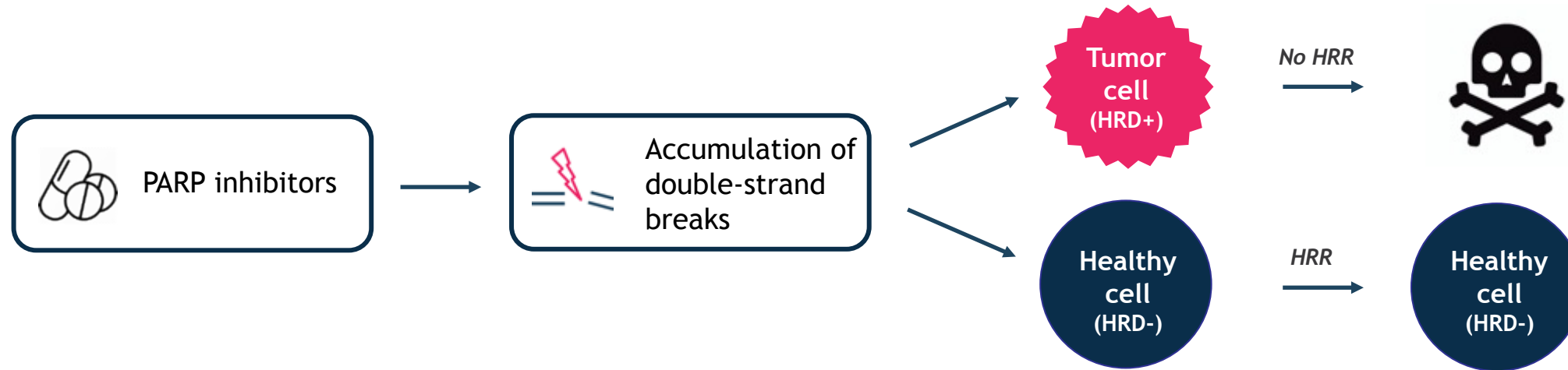
DNA repair + PARPi

PARP inhibitors will prevent DNA repair by non-HR repair mechanisms



Homologous Recombination

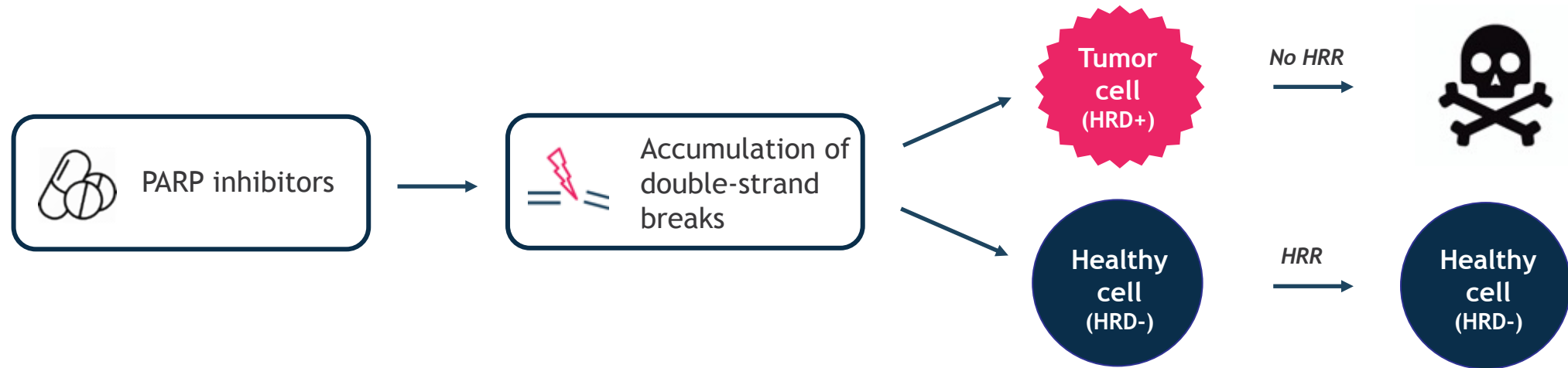
PARP inhibitors selectively induce synthetic lethality in HRD tumor cells



HRD, homologous recombination deficiency; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase.

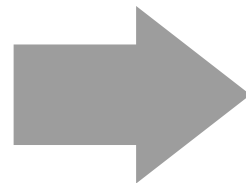
Homologous Recombination

PARP inhibitors selectively induce synthetic lethality in HRD tumor cells



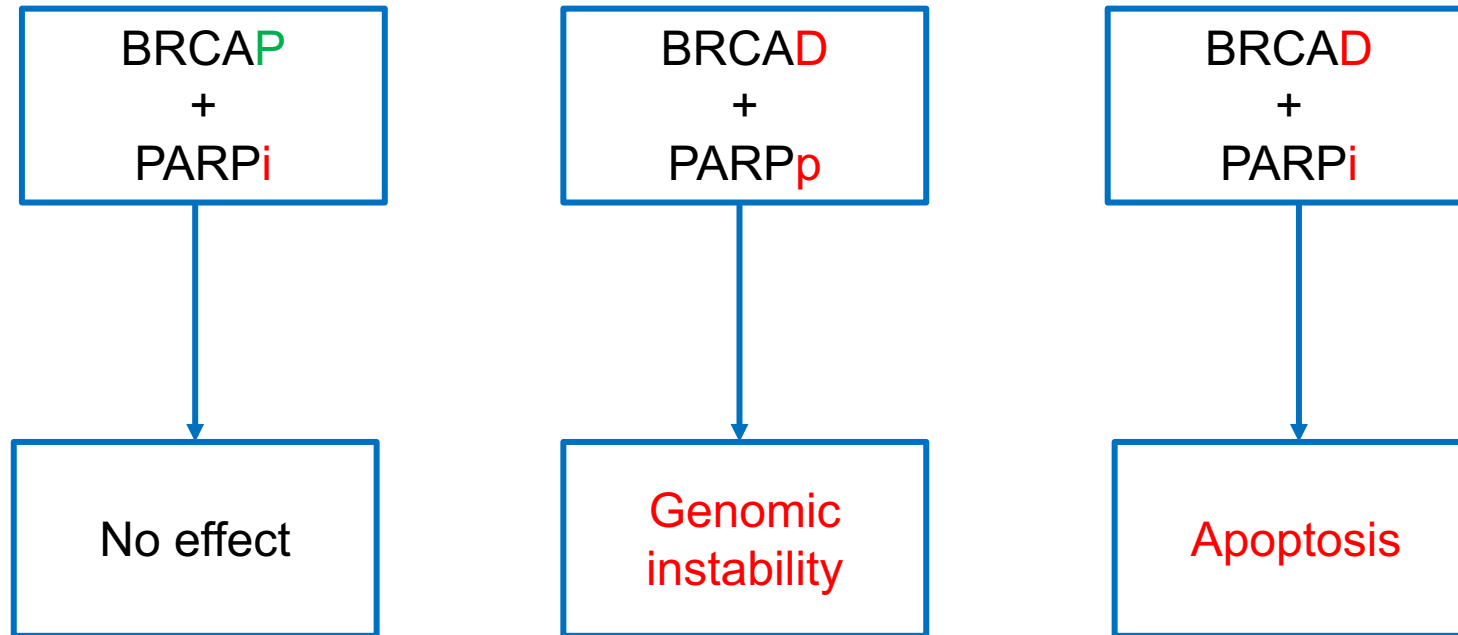
HRD is frequent in many tumors:

- Ovary: ~30%
- Breast: ~12%
- Pancreas: ~13%
- Prostate: ~13%

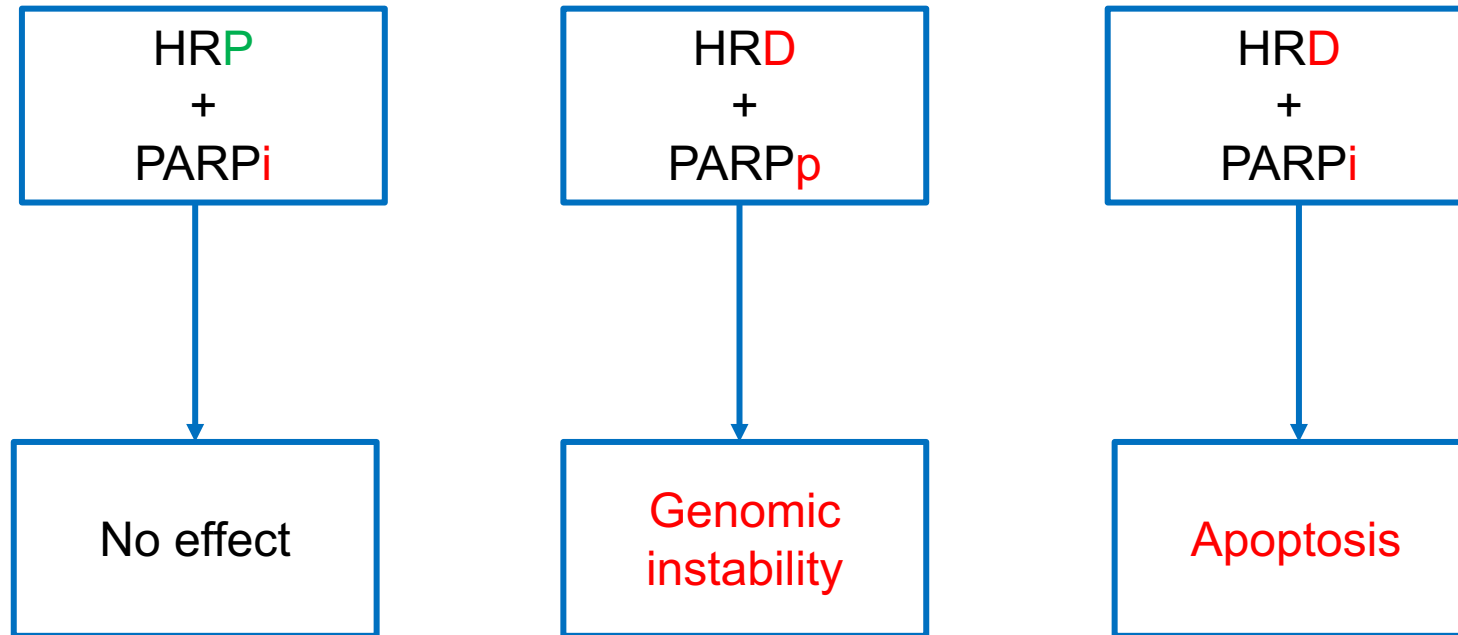


HRD testing may expand opportunity for PARP inhibitor benefit

Synthetic Lethality Concept



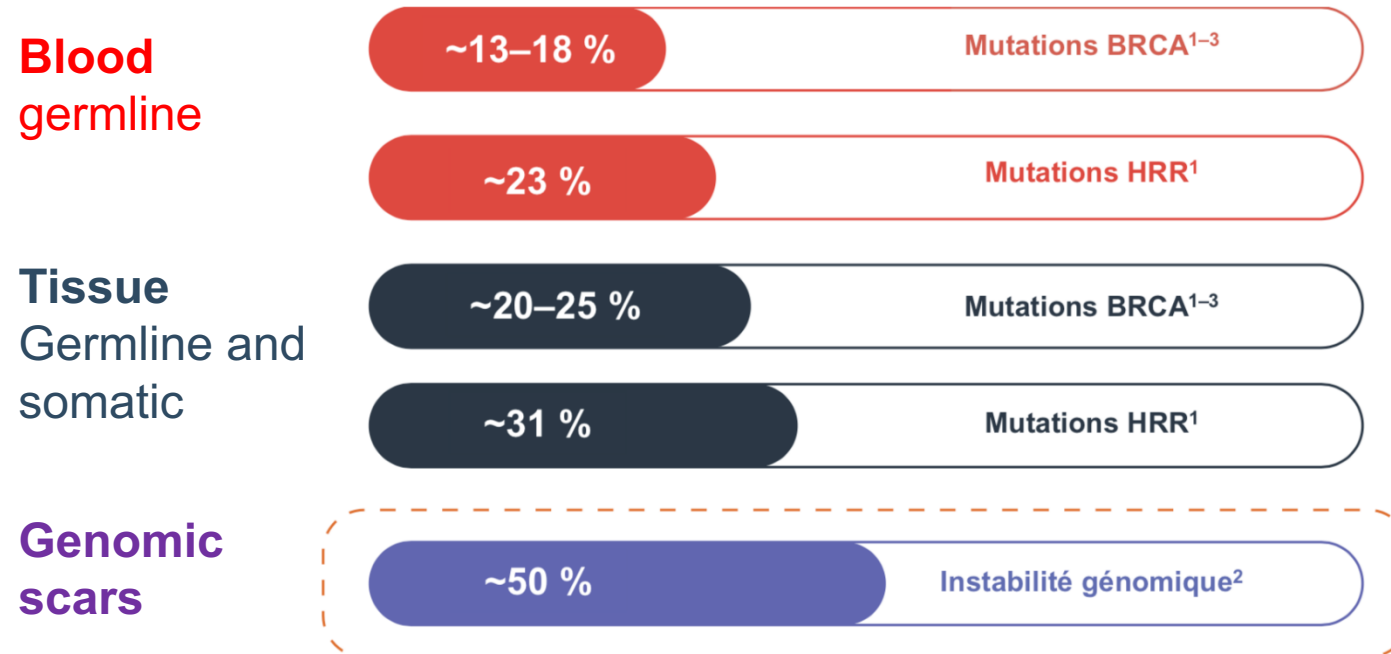
Synthetic Lethality Concept



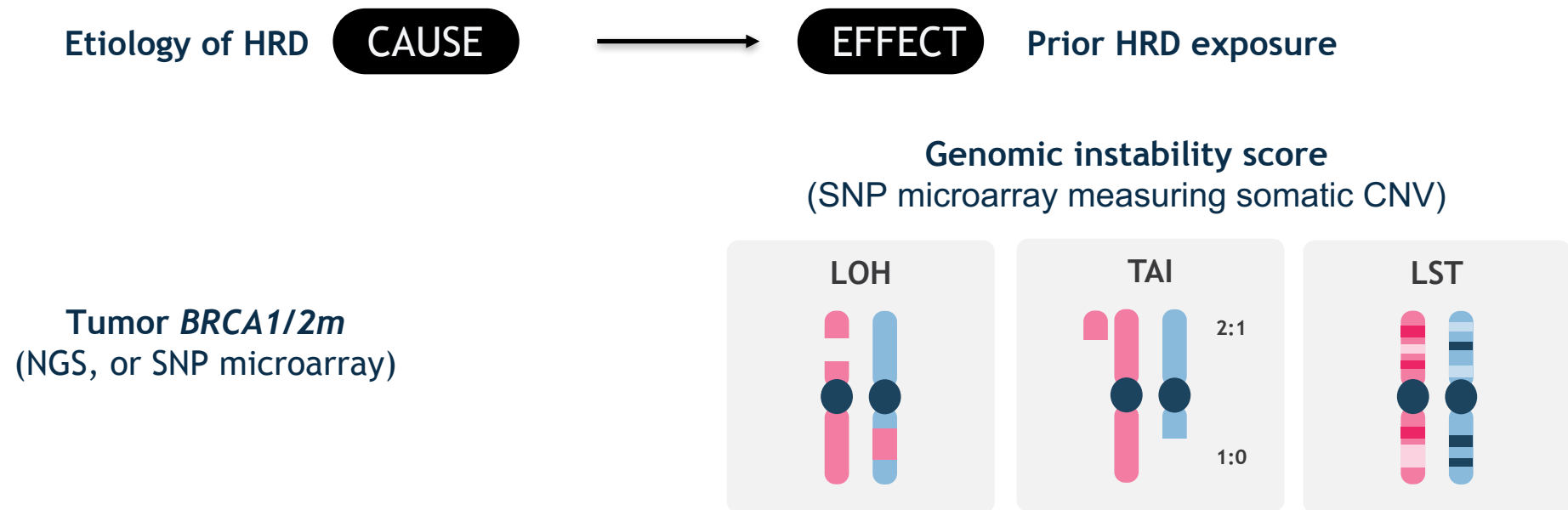
BRCAness, HRR, HRD...

- **BRCAness = HRD** : Homologous recombination deficient
- **HRR** : Homologous Recombination Repair
→ **HRR panel** = genes involved in the HRR pathway
- **“HRD determination”** = Investigating a proof or an explanation to HR deficiency

From gBRCA to genomic instability



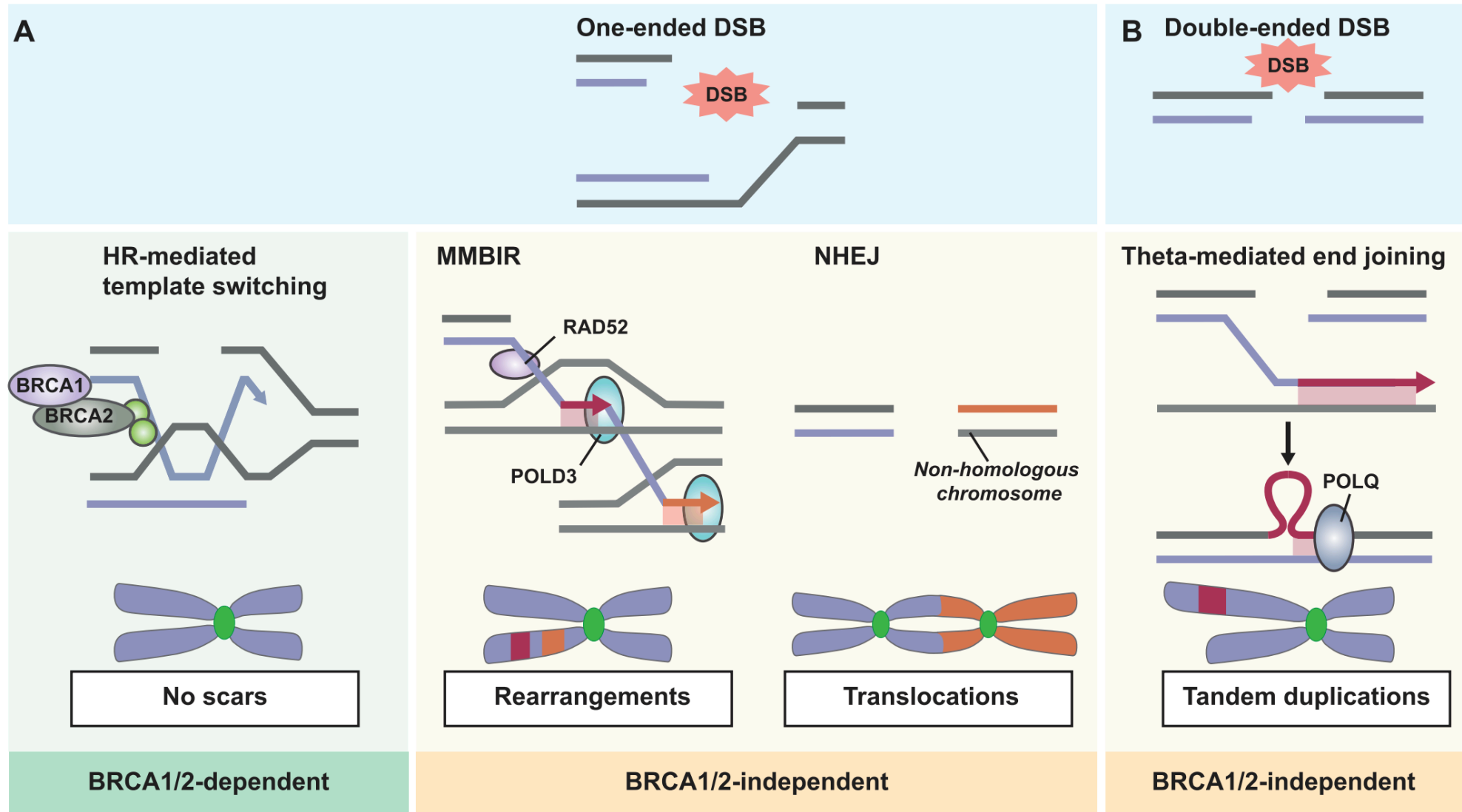
Permanent footprint of genomic changes that causes 'genomic scars' is used as a proxy to identify HRD



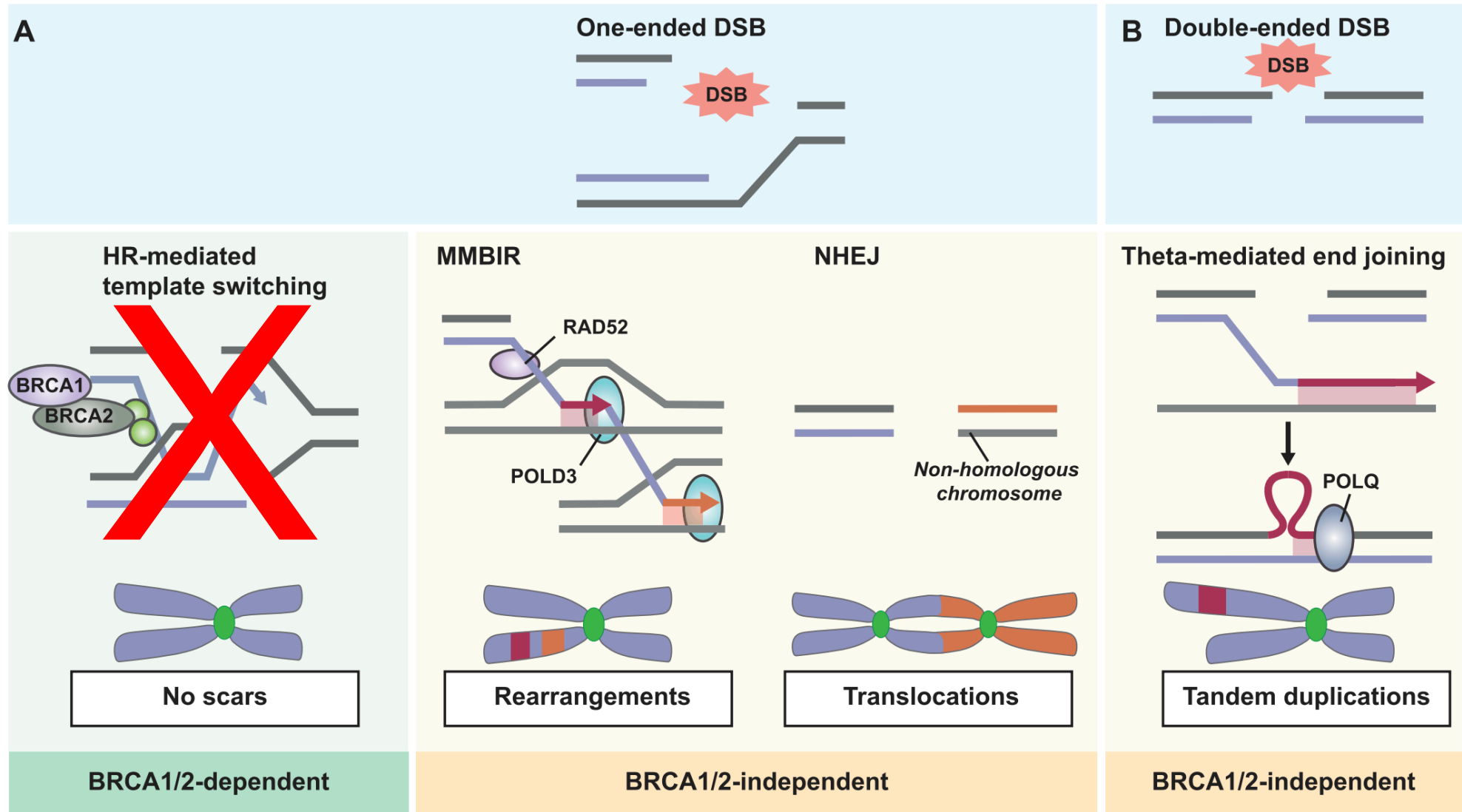
CNV, copy number variation; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; LST, large scale transitions; m, mutation; NGS, next generation sequencing; SNP, single nucleotide polymorphism; TAI, telomeric allelic imbalance; WGS, whole genome sequencing.

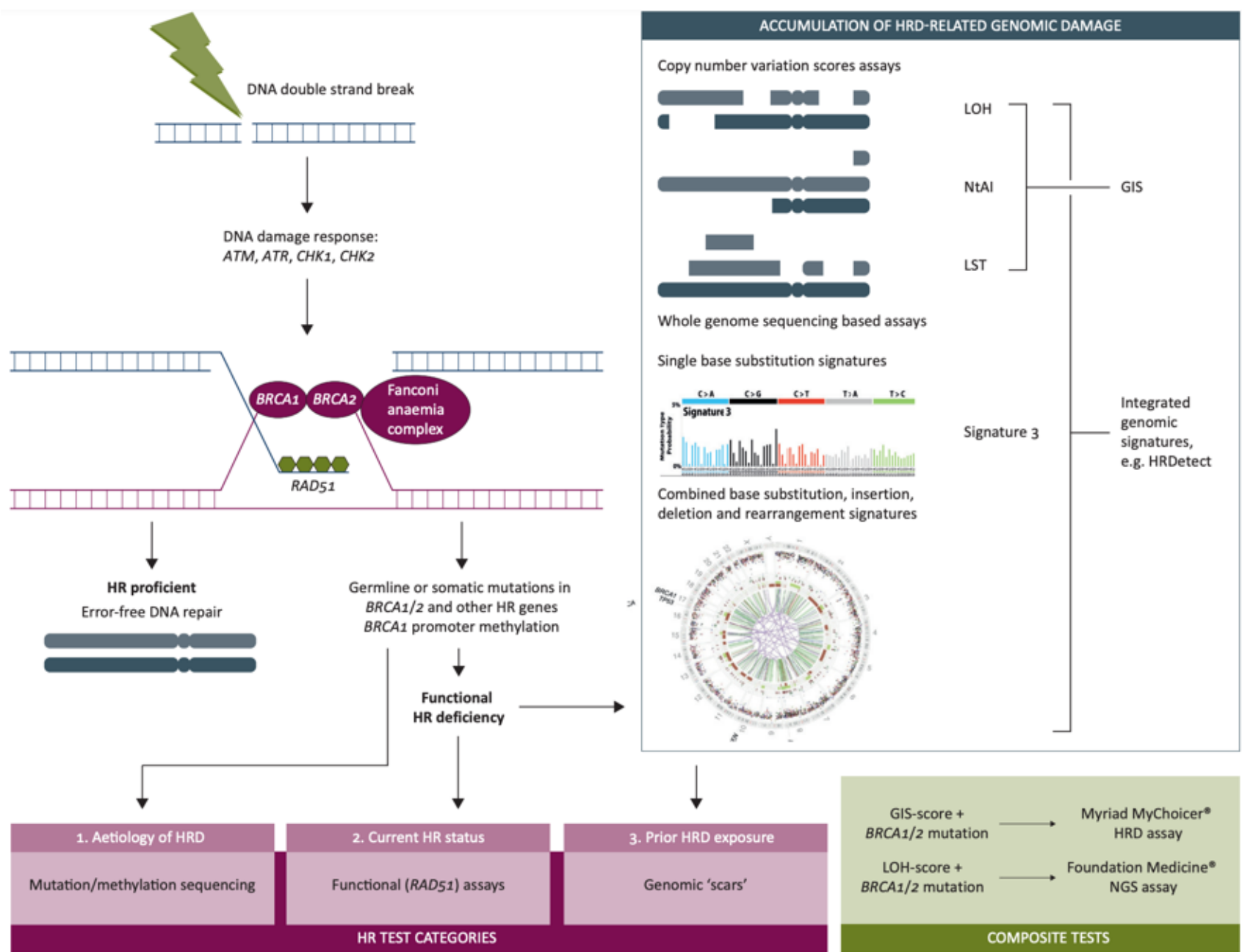
Timms et al. Breast Cancer Res. 2014;16(6):475; Miller et al. Ann Oncol. 2020;31(12):1606–22.

Where do these scars come from?



Where do these scars come from?





Investigating the cause

Investigating the consequences