

XVII journées de sénologie interactive

Point actuel sur les cellules tumorales circulantes et ADN libre circulant dans le cancer du sein

L. Teixeira

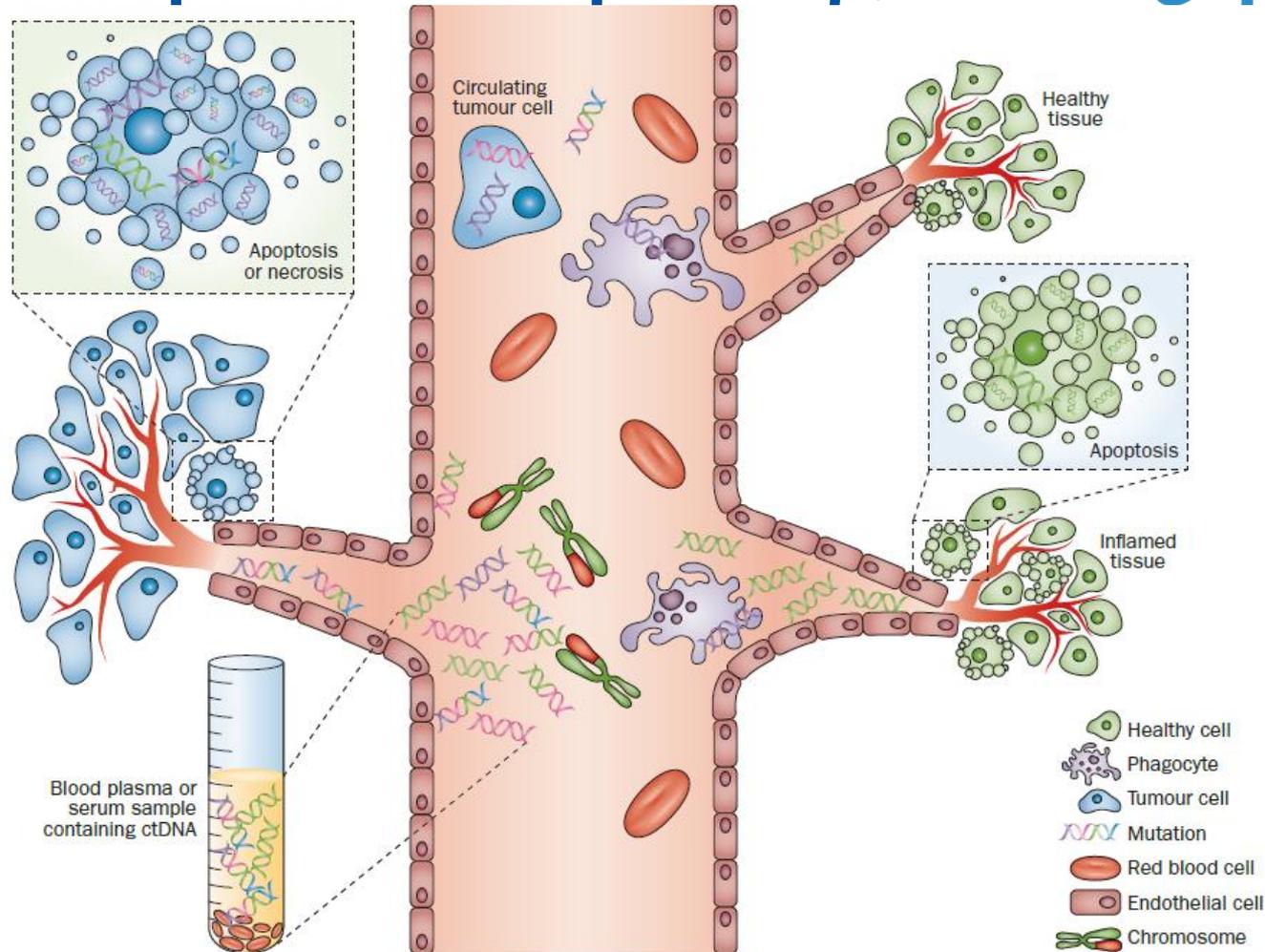
M.D., Ph.D.

Centre des Maladies du Sein

Plan

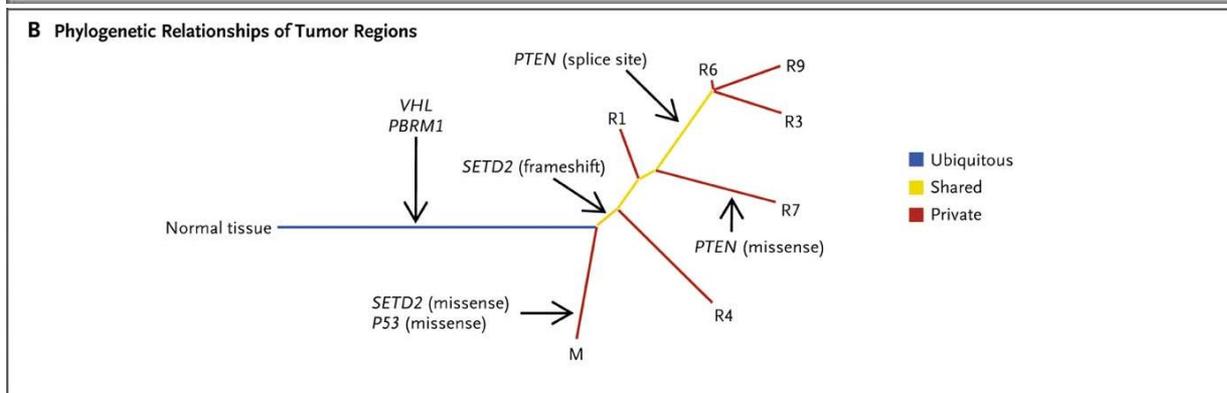
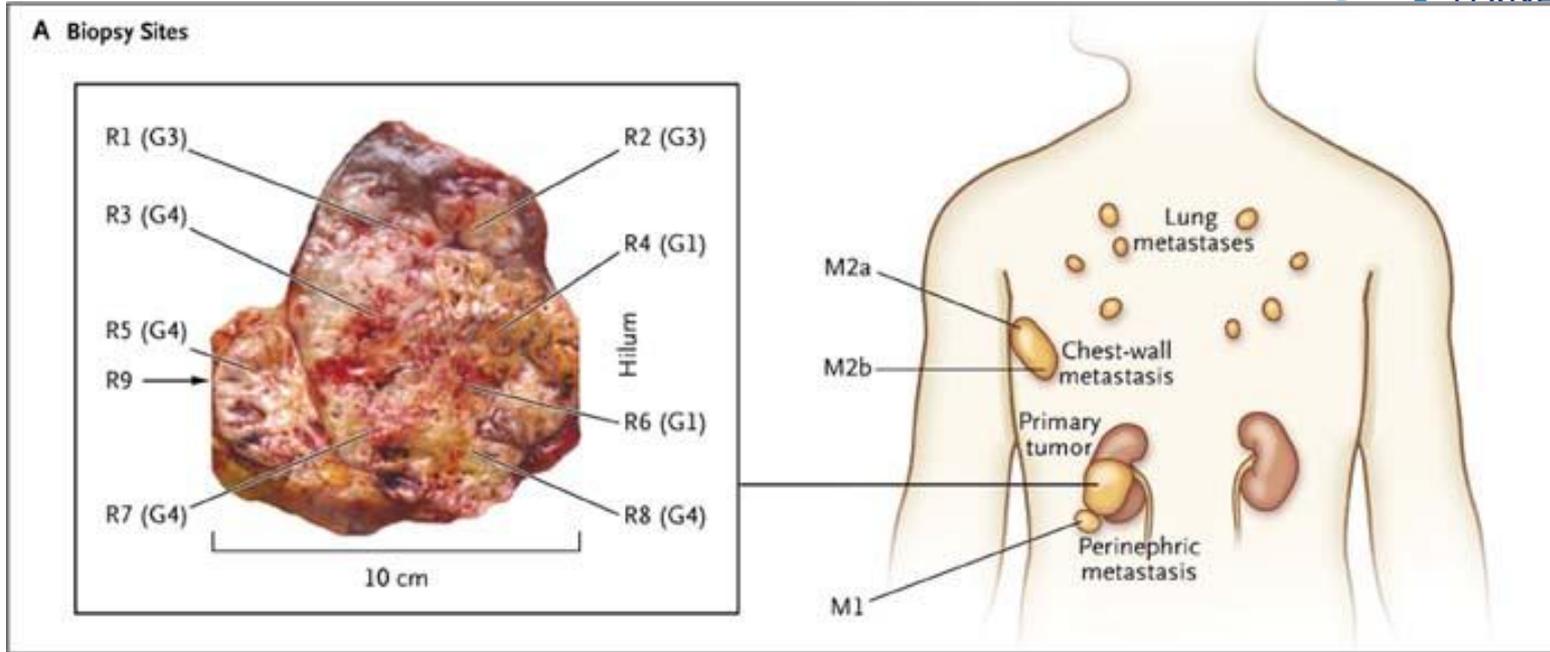
- **Concept de biopsie liquide**
- **Les Cellules tumorales circulantes (CTC)**
- **L'ADN tumoral libre circulant**
- **Conclusion**

Concept de « biopsie liquide »



Crowley et al, Nat Rev Clin Oncol 2013

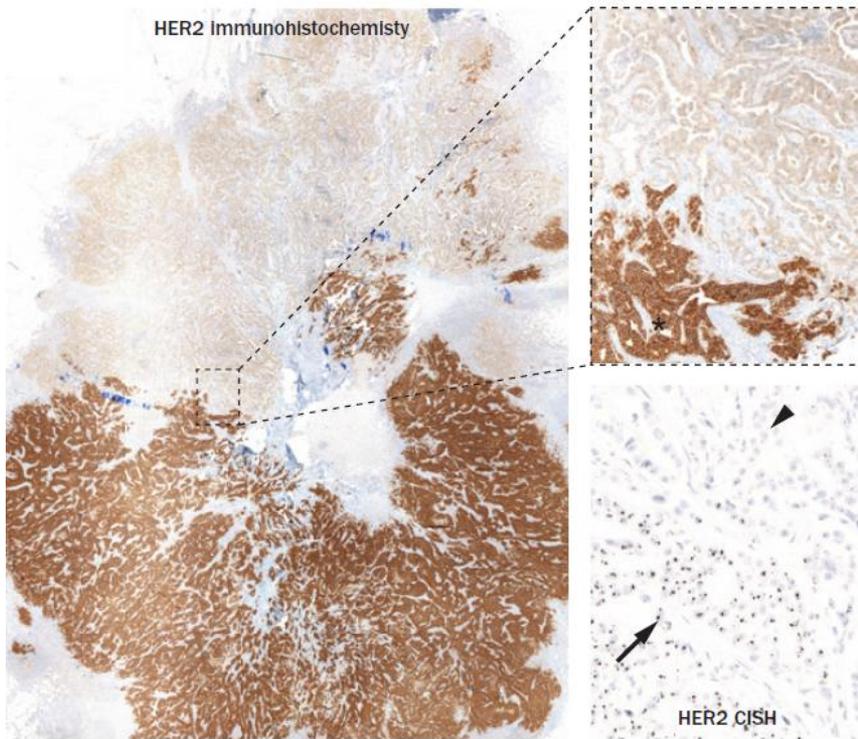
Hétérogénéité tumorale



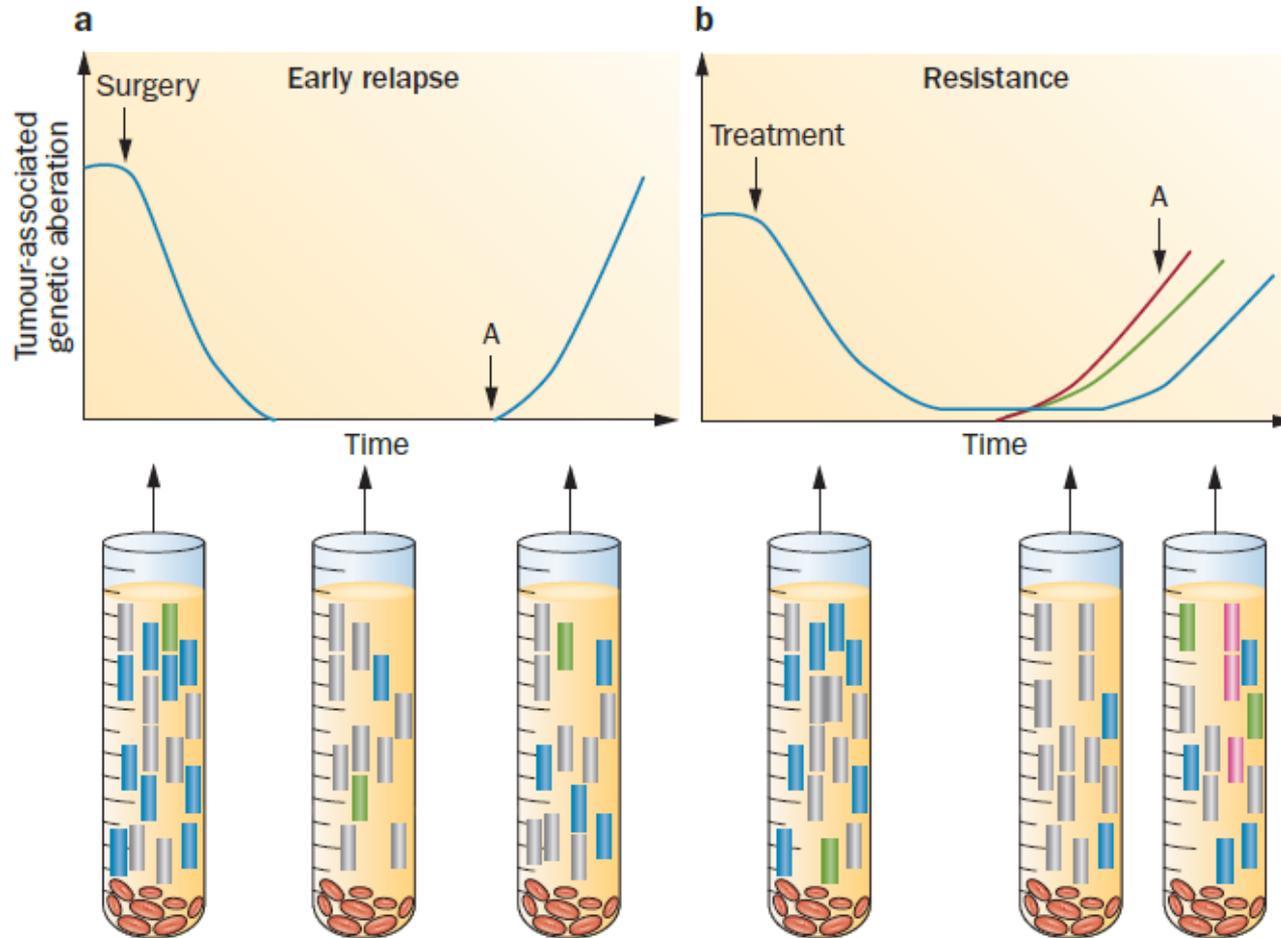
Hétérogénéité tumorale;
 Cancer du rein

Gerlinger M et al. N Engl J Med 2012

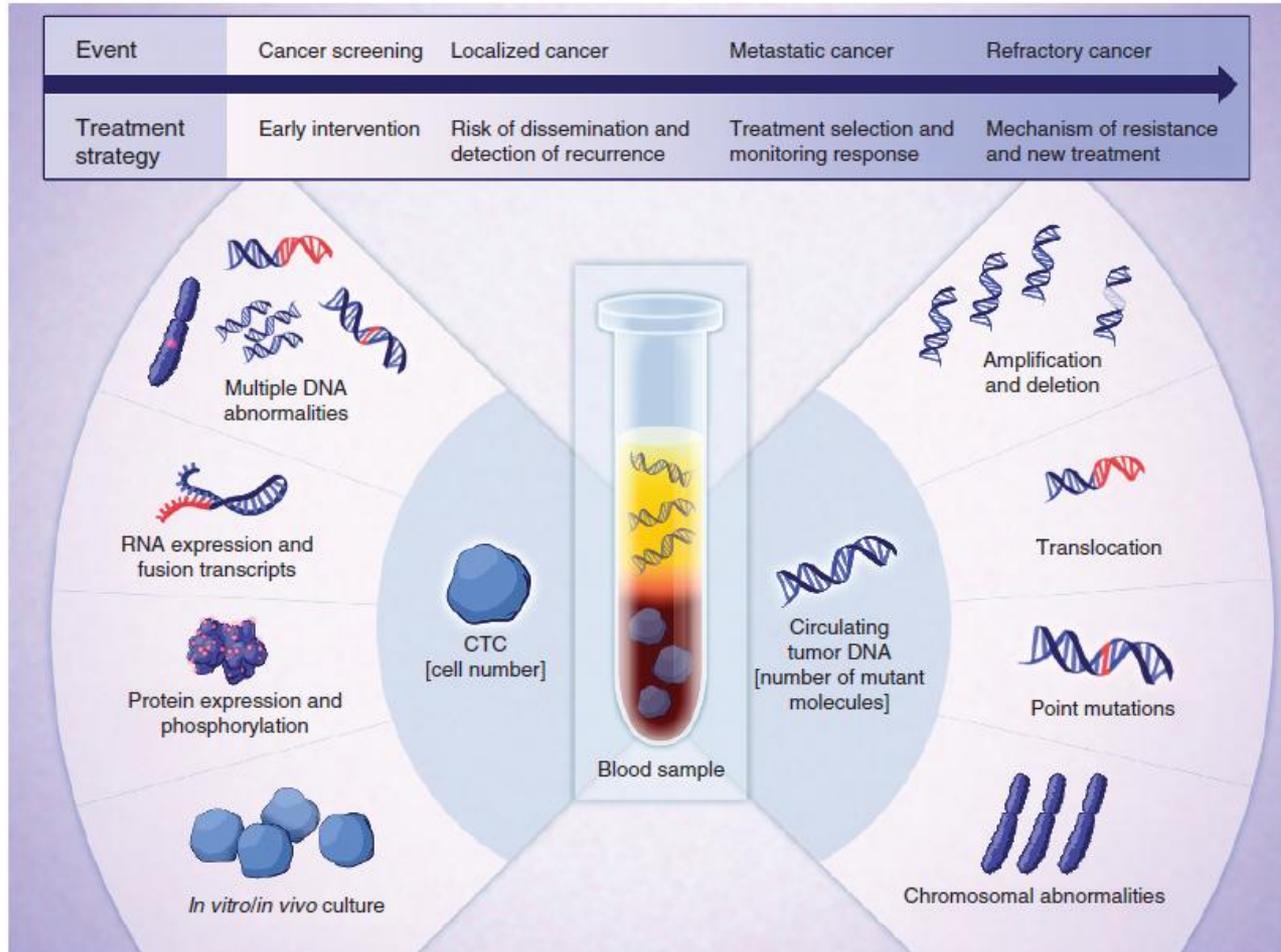
Hétérogénéité tumorale



Concept de biopsie liquide

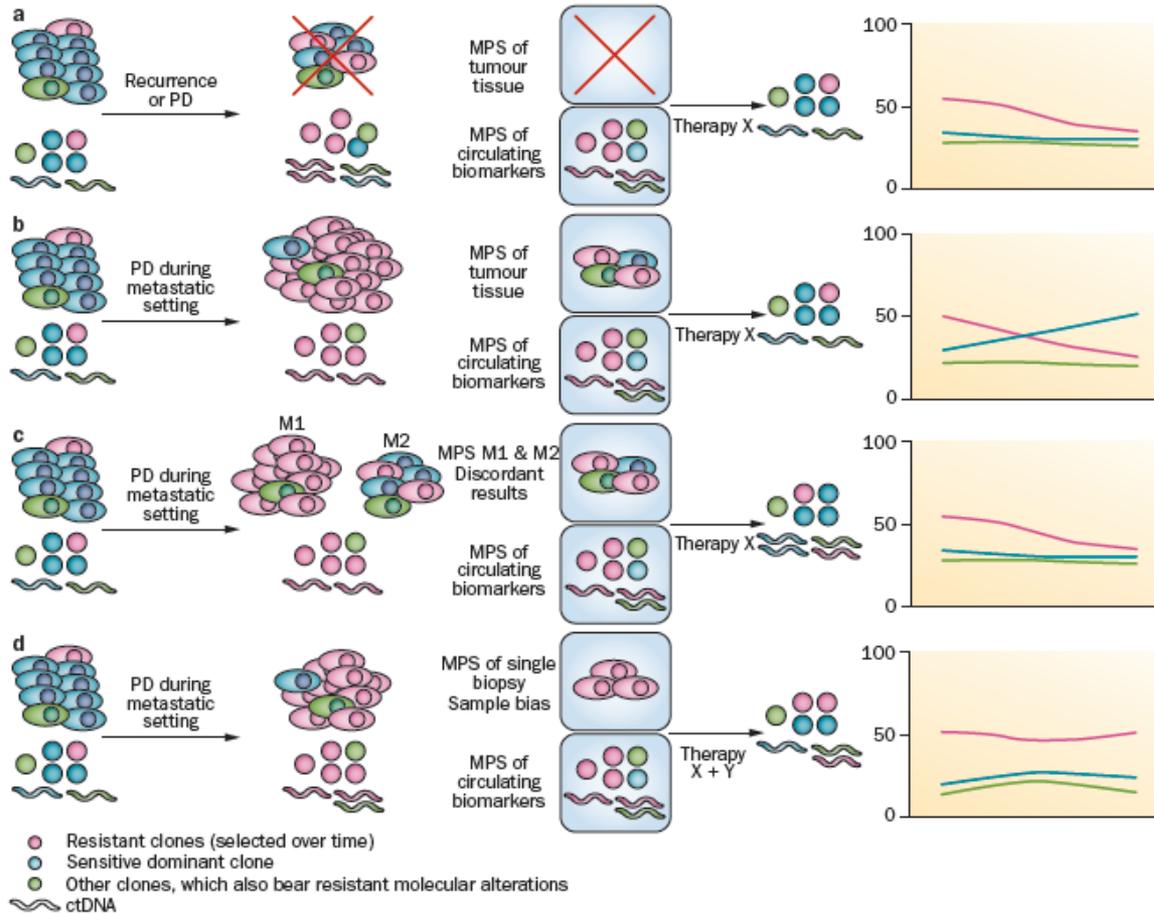


Analyses possibles et situation d'intérêt



Haber et al Cancer Discov 2014

Situations schématiques



Pas de lésion individualisable

Evolutivité sous TT

Résultats discordants

« biais » de prélèvement

De Mattos-Arruda Nat Rev clin Oncol 2013

Cellules tumorales circulantes CTC;

considérations techniques

EpCAM-affinity based

- CellSearch® system
- AdnaTest BreastCancerDetect
- CTC-Chip
- Dynal®
- MACS®
- MagSweeper
- On-Q-Ity
- CTC-ETI

Physical properties-based

- ISET
- ScreenCell®
- ApoStream™
- Density Gradient Centrifugation

Other methods

- FAST
- EPISPOT
- Flow cytometry (FACS)
- PRO Onc Assay

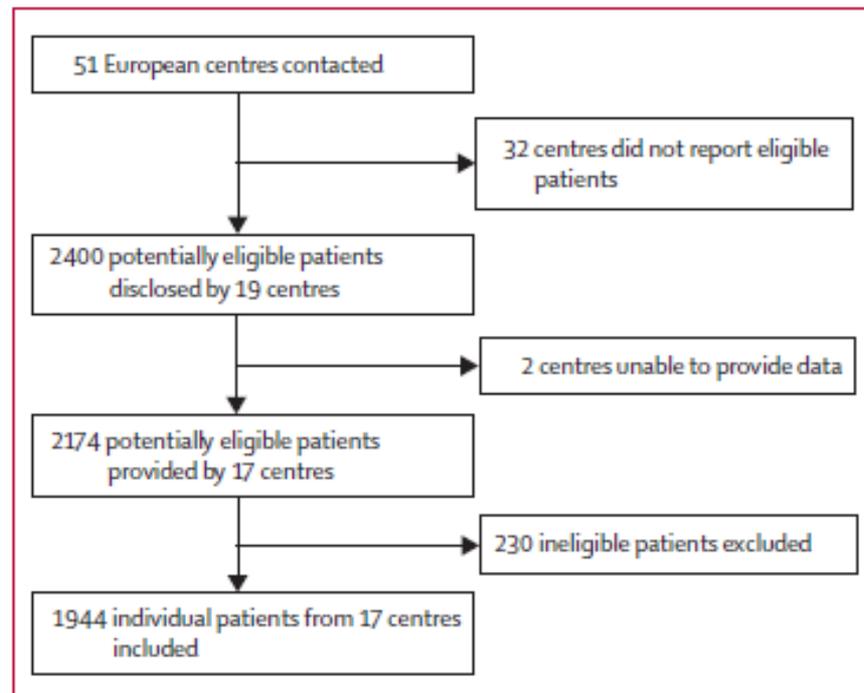
Expression
marqueurs
membranaires

Propriétés
biophysiques

De Mattos-Arruda Nat Rev clin Oncol 2013

CTC en 2014

Facteur pronostique indépendant en situation métastatique confirmation européenne



Système
Cellsearch

Données sur la
mesure des CTC.

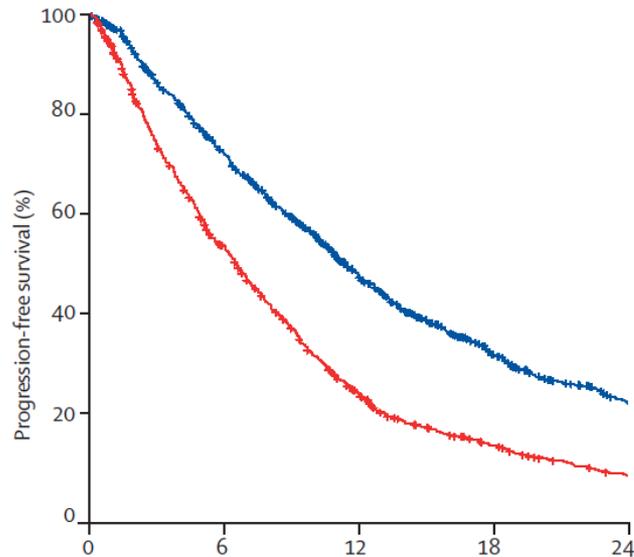
Non
interventionnel.

Méta-analyse des données de centres européens, données publiées et non publiées

Bidard FC et al, Lancet Oncol 2014

Mesure CTC à l'initiation du traitement

Facteur pronostic indépendant en situation métastatique

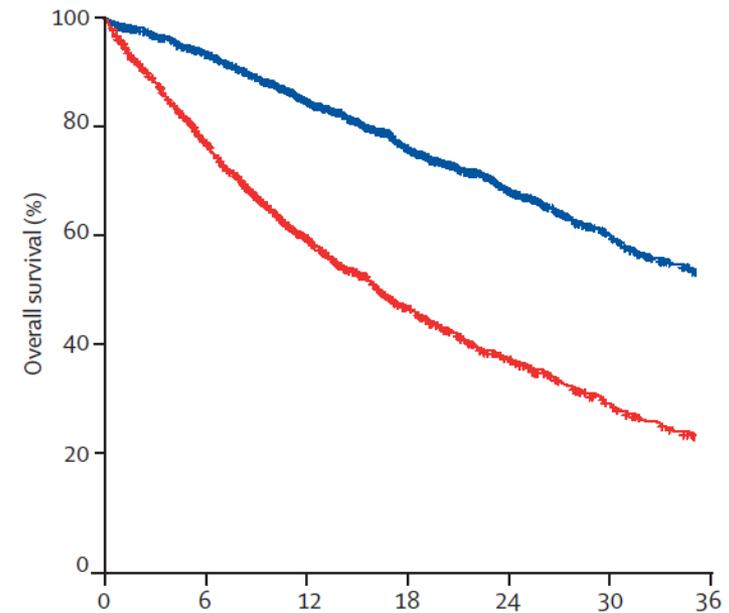


Number at risk		0	6	12	18	24
CTC <5	1014	685	394	211	115	
CTC ≥5	885	439	174	79	35	

	Patients	Events	Median progression-free survival in months (95% CI)
— CTC <5	1014	735	11.4 (10.6–12.1)
— CTC ≥5	885	772	6.5 (5.9–7.0)

PFS

Baseline seuil CTC 5 cellules/7.5ml



Number at risk		0	6	12	18	24	30	36
CTC <5	1033	896	701	496	333	230	162	
CTC ≥5	911	639	396	237	147	85	53	

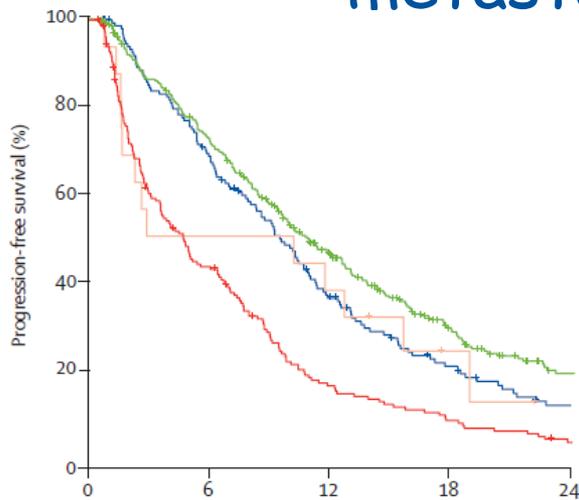
	Patients	Events	Median overall survival in months (95% CI)
— CTC <5	1033	371	37.1 (32.8–41.9)
— CTC ≥5	911	558	15.5 (13.5–16.8)

OS

Bidard FC et al, Lancet Oncol 2014

Variation précoce des CTC sous traitement après 5 semaines

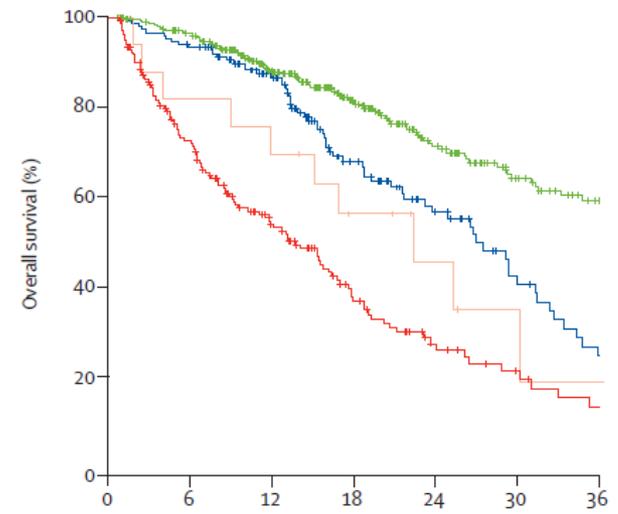
Facteur pronostic indépendant en situation métastatique



Number at risk					
	0	6	12	18	24
Decrease	149	101	49	24	11
Increase	17	8	6	2	..
Stable negative	327	226	126	59	25
Stable positive	179	73	25	12	3

	Patients	Events	Median progression-free survival in months (95% CI)
Decrease ≥ 5 - < 5	149	131	9.6 (8.2-11.1)
Increase < 5 - ≥ 5	17	13	6.7 (1.8-NA)
Stable negative < 5 - < 5	327	243	10.7 (9.7-12.7)
Stable positive ≥ 5 - ≥ 5	179	166	4.8 (3.7-6.5)

PFS



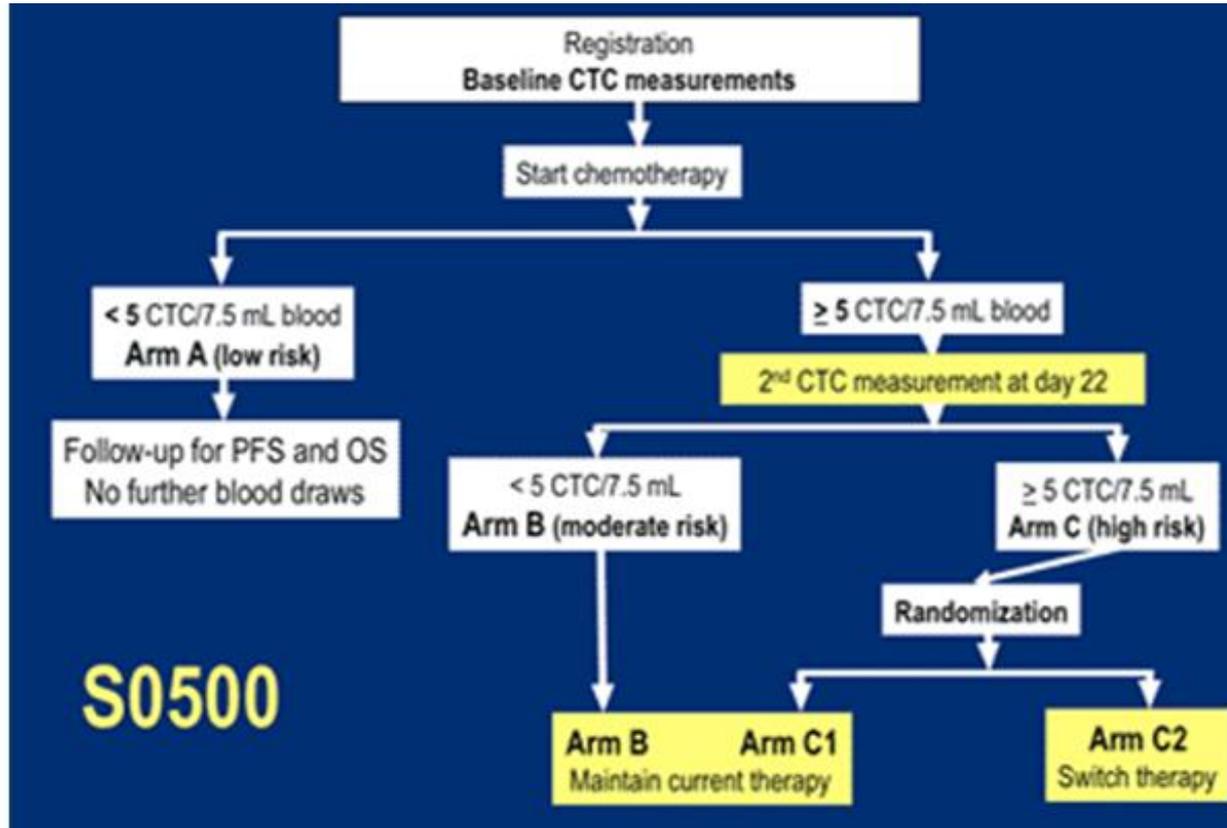
Number at risk							
	0	6	12	18	24	30	36
Decrease	149	135	104	59	36	20	11
Increase	17	13	11	7	4	2	1
Stable negative	327	296	231	160	102	68	50
Stable positive	179	116	68	36	18	10	5

	Patients	Events	Median overall survival in months (95% CI)
Decrease ≥ 5 - < 5	149	70	27.0 (21.7-31.5)
Increase < 5 - ≥ 5	17	10	22.4 (11.9-NA)
Stable negative < 5 - < 5	327	104	41.5 (36.8-52.7)
Stable positive ≥ 5 - ≥ 5	179	116	13.1 (9.4-16.4)

OS

Bidard FC et al, Lancet Oncol 2014

Mesure de CTC décisionnelle après 1 cycle de chimiothérapie SWOG S0500



1^{ère} ligne de
chimiothérapie:

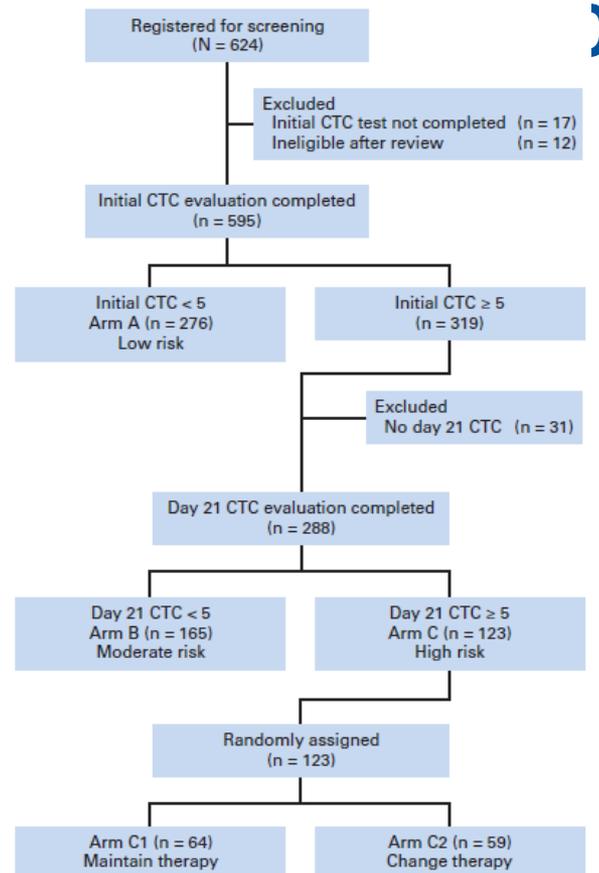
RH-

Ou

Après échec de toute
d'hormonothérapie

Smerage et al JCO 2014 online

Mesure de CTC décisionnelle après 1 cycle

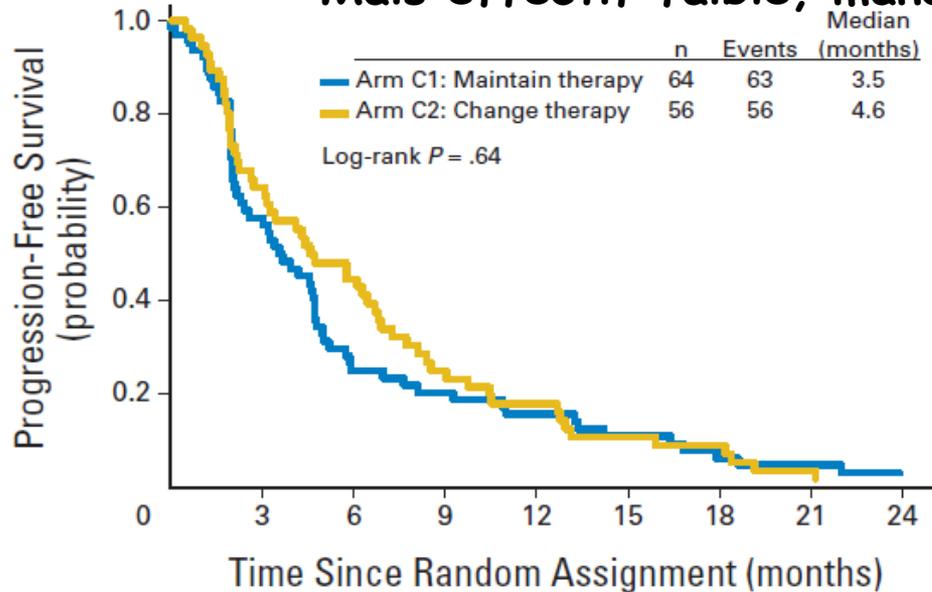


Smerage et al JCO 2014 online

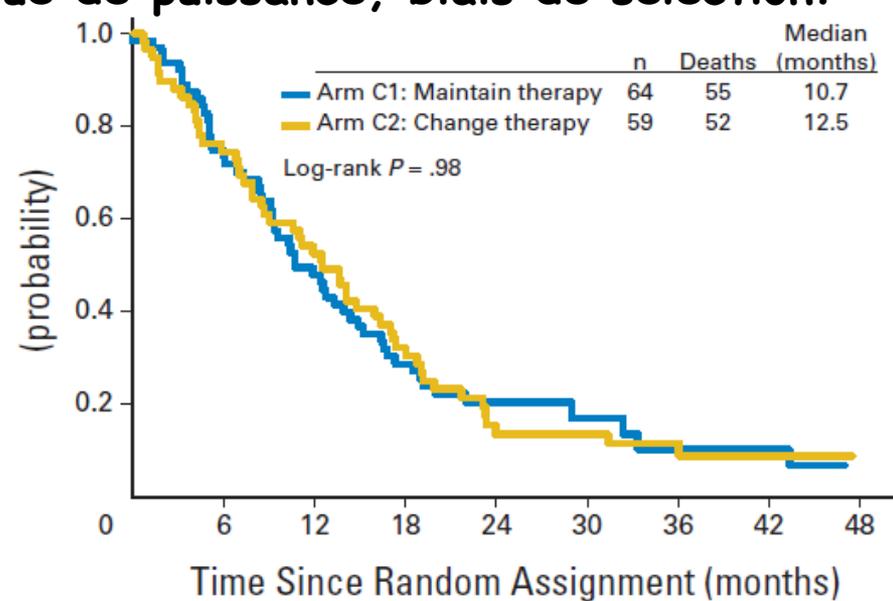
Mesure de CTC décisionnelle après 1 cycle SWOG 50500

Négative

Mais effectif faible, manque de puissance, biais de sélection?



No. at risk	0	3	6	9	12	15	18	21	24
Arm C1	64	37	16	13	10	7	4	3	1
Arm C2	56	36	25	14	10	6	5	2	1



at risk	0	6	12	18	24	30	36	42	48
C1	64	47	30	18	10	5	3	3	1
C2	59	44	31	18	7	7	4	2	1

Smerage et al JCO 2014 online

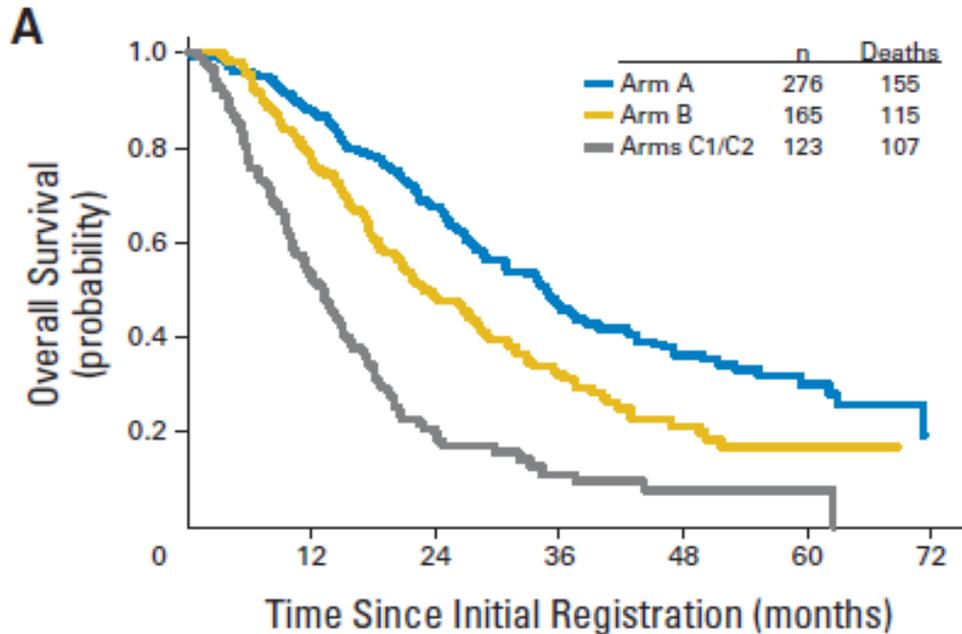
Idem quelque soit le sous type histologique

Biologic Subtype	OS*						PFS					
	Median (months)		HR†	95% CI	P	P _{int‡}	Median (months)		HR†	95% CI	P	P _{int‡}
	C1	C2					C1	C2				
All	10.7	12.5	1.00	0.69 to 1.47	.98	NA	3.5	4.6	0.92	0.64 to 1.32	.64	NA
Hormone receptor positive, HER2 negative	12.4	17.4	0.80	0.50 to 1.28	.35	.21	4.2	5.7	0.86	0.57 to 1.31	.51	.88
Triple negative	9.1	7.9	1.19	0.52 to 2.73	.67		1.9	2.2	0.70	0.31 to 1.56	.38	
HER2 positive	13.3	7.3	4.18	0.45 to 38.5	.16		4.7	7.3	1.44	0.23 to 8.82	.69	

Vérifié même si métastases osseuses
uniquement

Smerage et al JCO 2014 online

SWOG S0500



OS

Bras A (CTC low) 35 mois

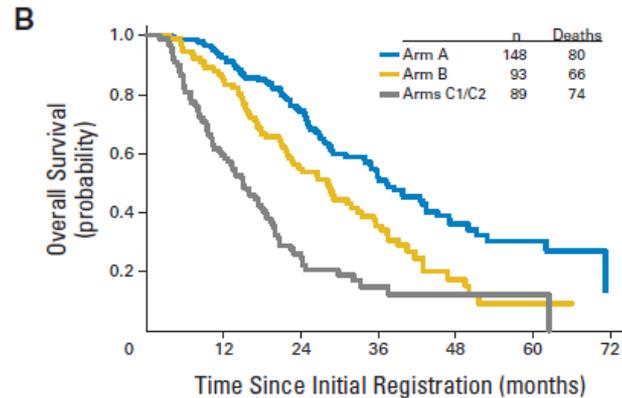
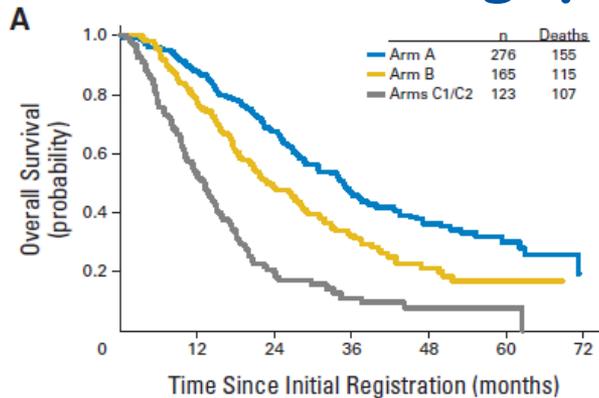
Bras B: 23 mois

Bras C1/C2 13 mois

No. at risk	0	12	24	36	48	60	72
Arm A	276	240	166	87	42	17	2
Arm B	165	123	70	38	16	7	0
Arm C	123	65	21	7	3	2	0

Smerage et al JCO 2014 online

SWOG S0500 selon les sous types histologiques



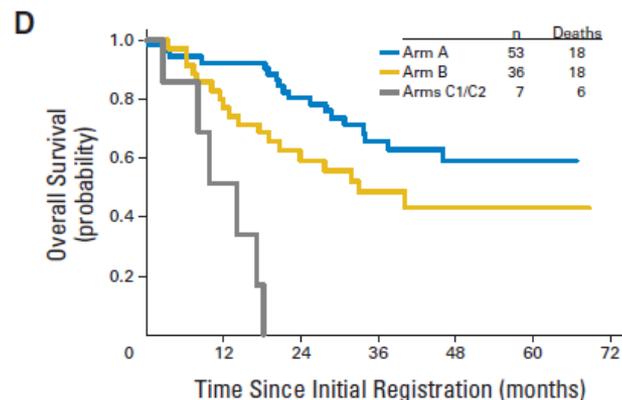
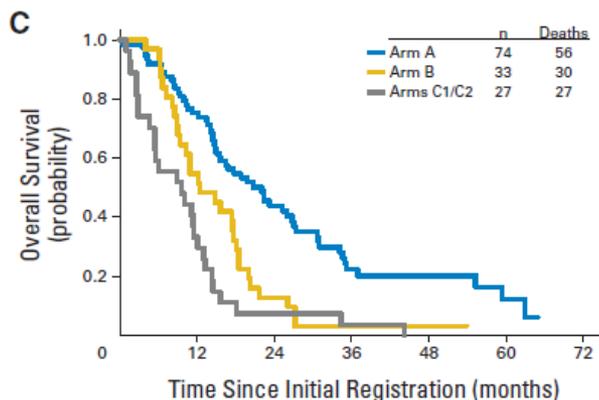
RH+,
HER2 neg

No. at risk

Arm A	276	240	166	87	42	17	2
Arm B	165	123	70	38	16	7	0
Arm C	123	65	21	7	3	2	0

No. at risk

Arm A	148	136	97	51	23	9	0
Arm B	93	76	46	23	7	2	0
Arm C	89	53	19	6	3	2	0



HER2

No. at risk

Arm A	74	55	28	12	7	3	0
Arm B	33	17	4	1	1	0	0
Arm C	27	9	2	1	0	0	0

No. at risk

Arm A	53	48	40	24	12	5	2
Arm B	36	27	18	13	7	4	0
Arm C	7	3	0	0	0	0	0

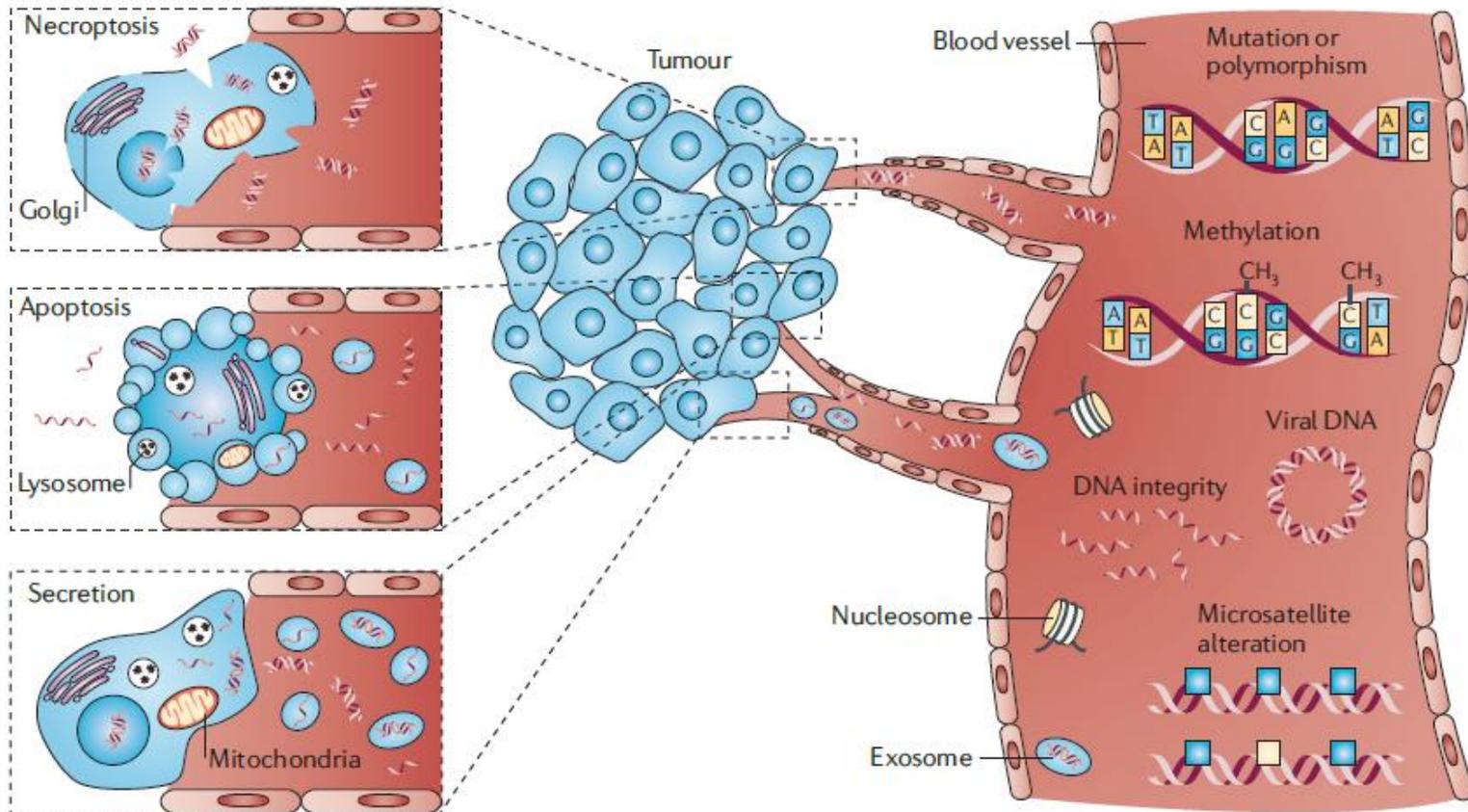
Triple
négative

Smerage et al JCO 2014 online

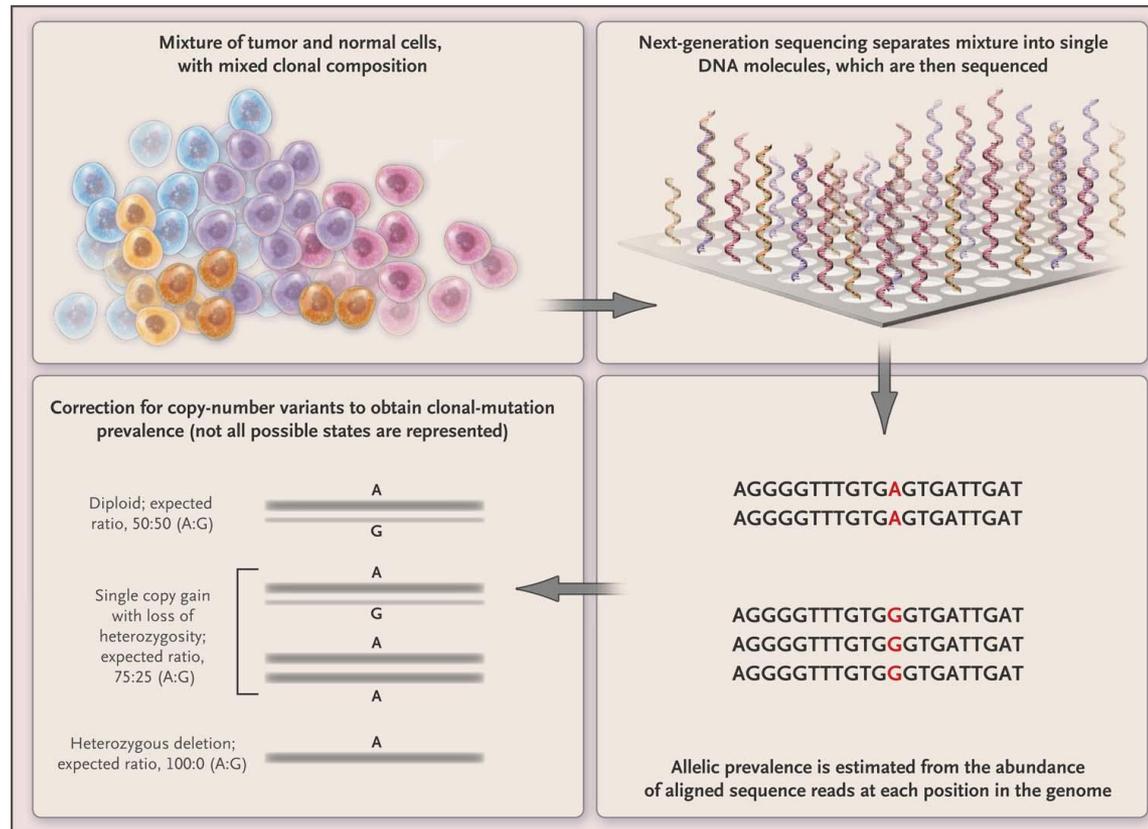
« CTC décisionnelles » études en cours

Clinical trial	Phase of development	Method of CTC detection	Therapeutic intervention	Setting
<i>No selection for breast cancer subtype</i>				
NCT00382018 (SWOG S0500)	III	CellSearch®	Change vs maintenance of chemotherapy, based on CTC counts: stratification for HER2 status	Metastatic (1 st line)
NCT01710605 (STIC CTC METABREAST trial)	III	CellSearch®	Clinician vs CTC count-driven choice (≥5 CTC: chemotherapy; <5 CTC: endocrine therapy)	Metastatic (1 st line)
NCT01349842 (CirCe01)	III	CellSearch®	Change vs maintenance of chemotherapy, based on CTC counts	Metastatic (3 rd line and beyond)
<i>HER2-positive CTCs and HER2-negative primary tumours</i>				
NCT01548677 (TREAT CTC Trial)	II	CellSearch®	Trastuzumab vs observation	Adjuvant
NCT00820924	II	CellSearch®	Lapatinib	Advanced or metastatic
NCT01048099	NA	PRO Onc Assay	Trastuzumab or pertuzumab	Metastatic
NCT01185509	II	CellSearch®	Trastuzumab and vinorelbine	Advanced or metastatic
NCT01619111 (DETECT III trial) ⁹⁷	III	CellSearch®	Standard therapy alone vs standard therapy plus lapatinib	Metastatic
Abbreviations: CTCs, circulating tumour cells; NA, not applicable.				

ADN tumoral libre circulant

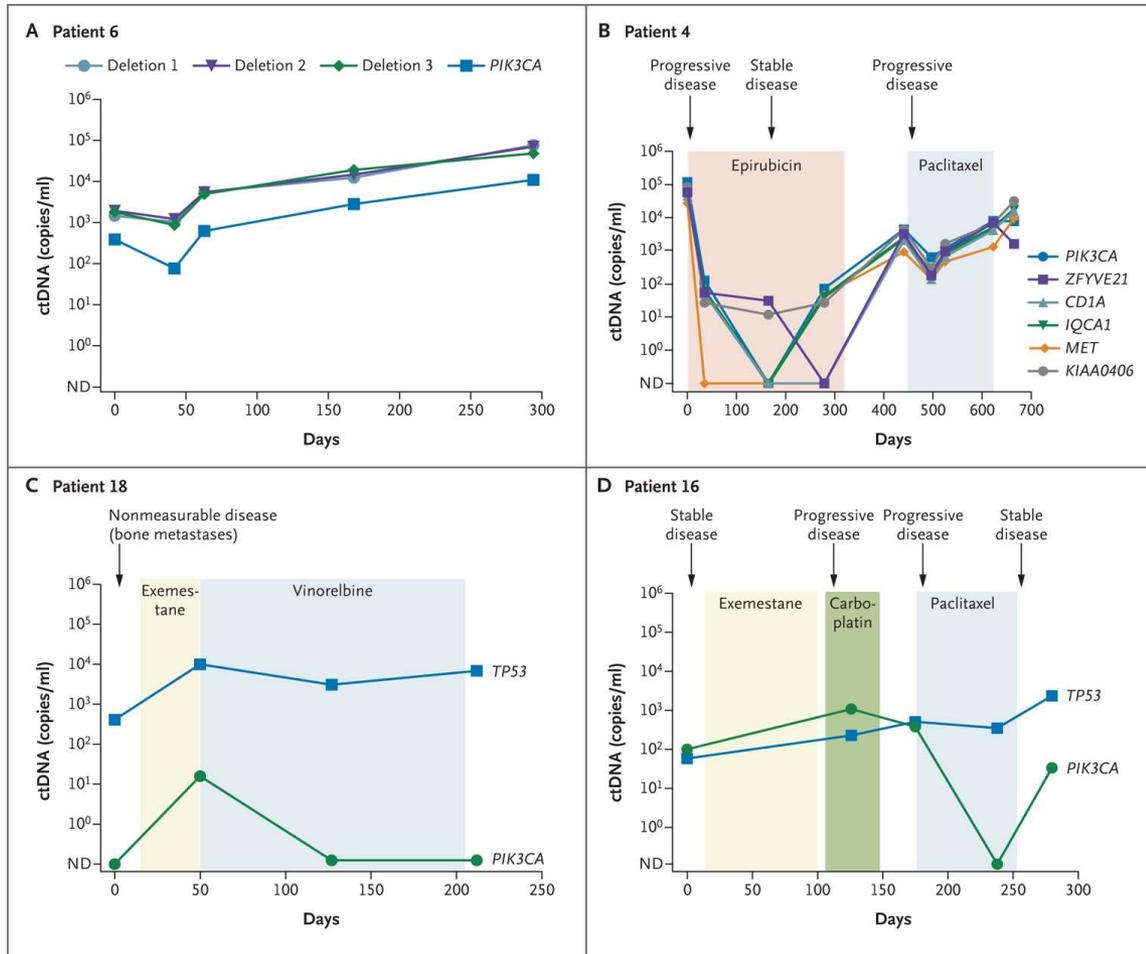


Considérations techniques: techniques séquençage à haut débit



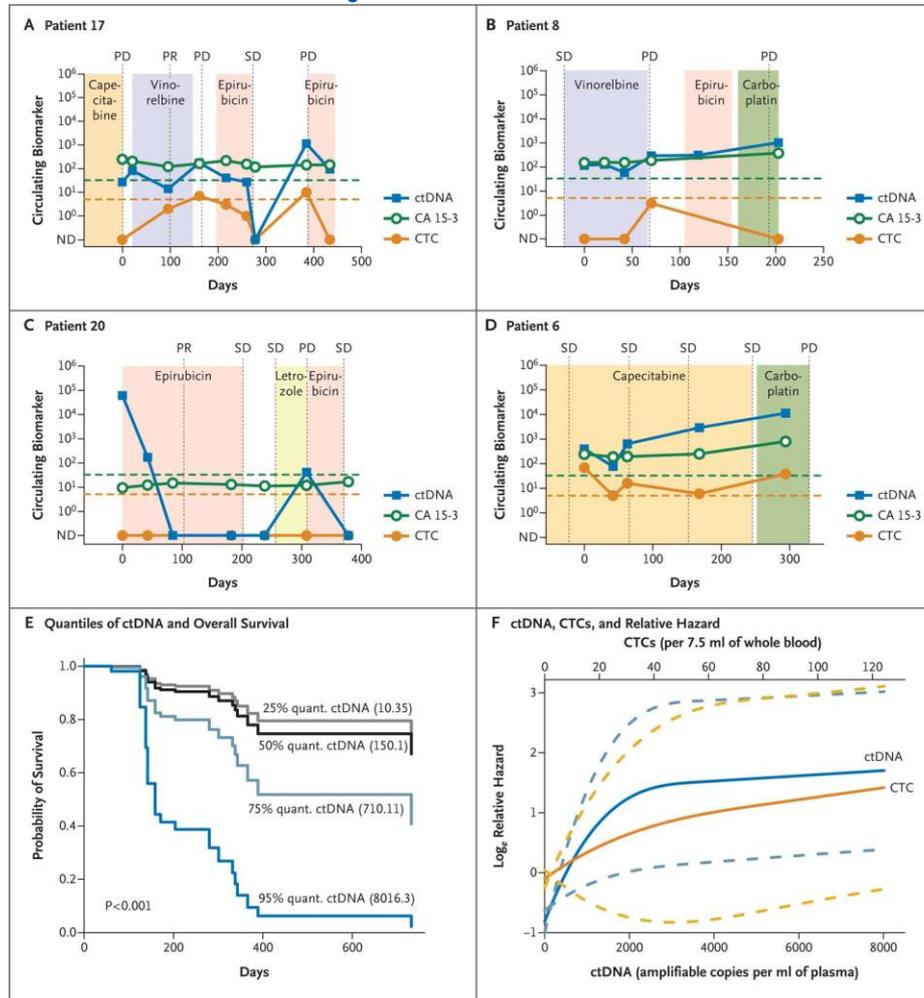
Aparicio S, Caldas C. N Engl J Med 2013

ADN tumoral libre circulant



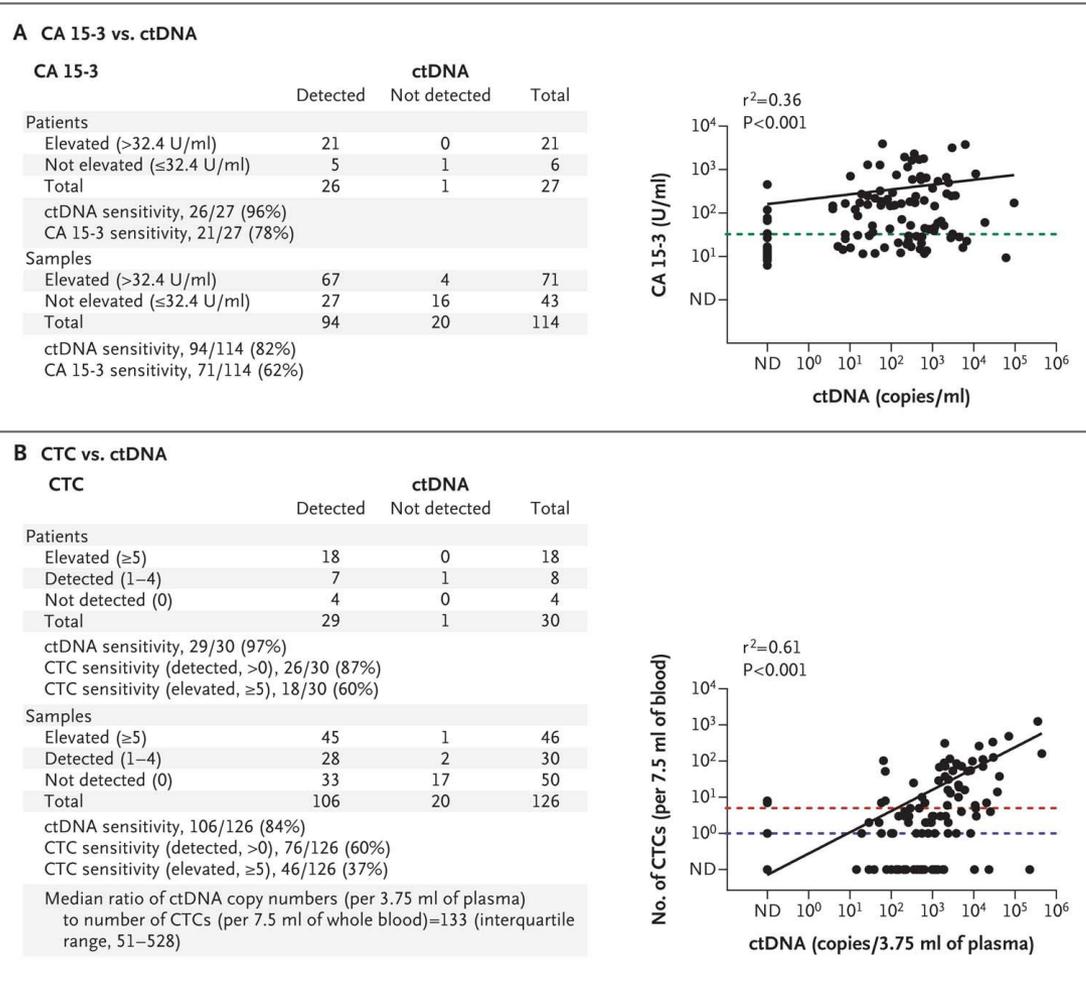
Dawson S-J et al. N Engl J Med 2013

Facteur pronostic



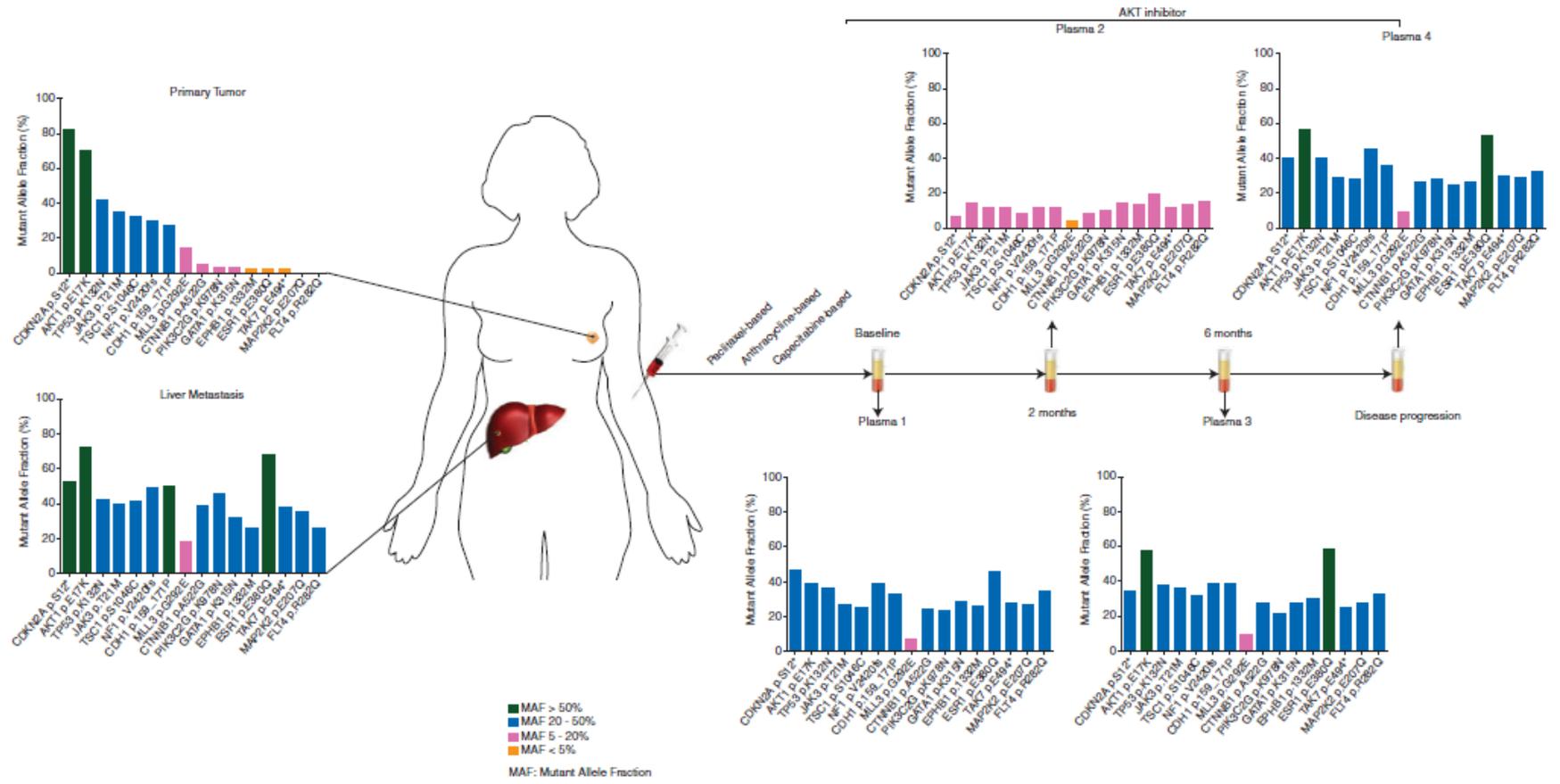
Dawson S-J et al. N Engl J Med 2013

ADN tumoral libre circulant vs. CTC



Dawson S-J et al. N Engl J Med 2013

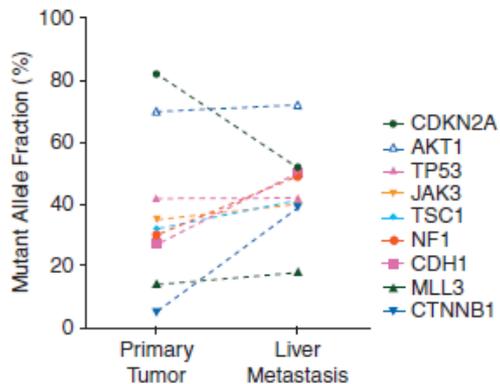
Hétérogénéité tumorale et médecine de précision: preuve de concept



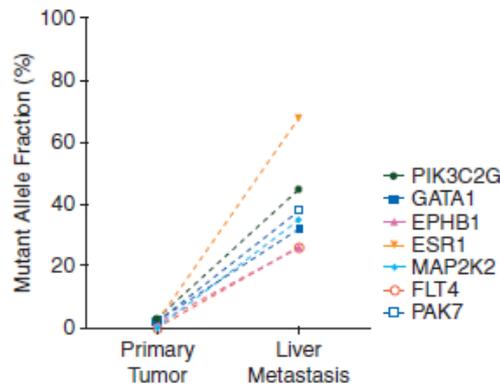
De Mattos-Arruda Ann Oncol 2014 sous presse

Hétérogénéité tumorale et médecine de précision: preuve de concept

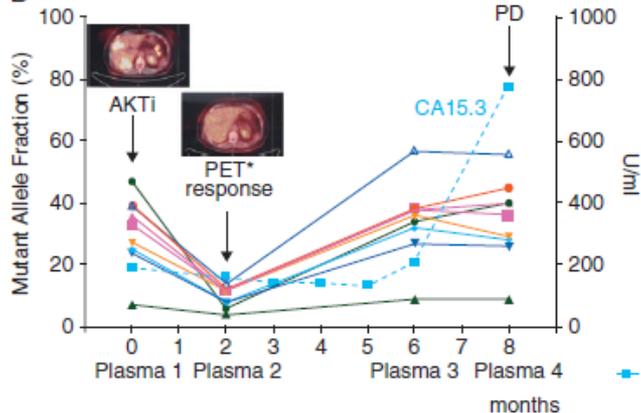
A Mutant allele fraction $\geq 5\%$ in primary tumor



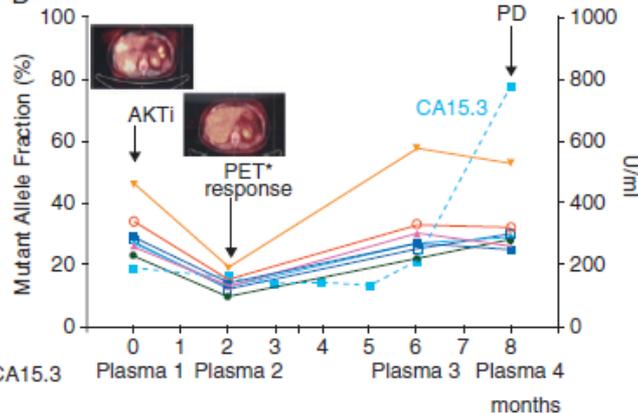
C Mutant allele fraction $< 5\%$ in primary tumor



B Plasma/CA15.3

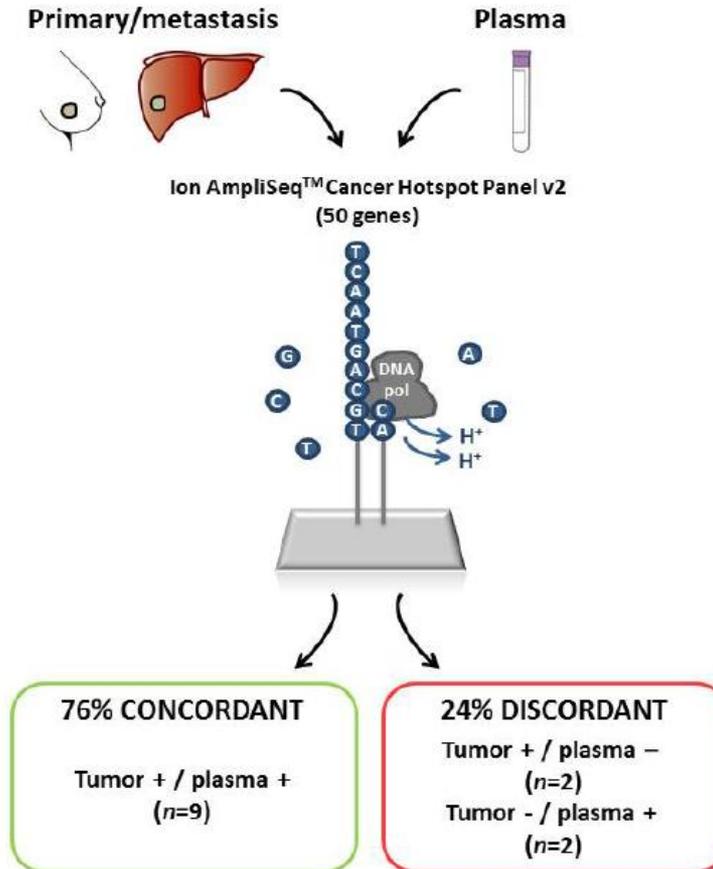


D Plasma/CA15.3



De Mattos-Arruda Ann Oncol 2014 sous presse

Taux de discordance selon les techniques



Rothé et al, Ann Oncol 2014

Perspectives

■ Informations différentes selon les techniques

- Concernant les CTC intérêt théorique de pouvoir analyser/étudier ces cellules tumorales (Protéomique, plusieurs « omics » etc...)
- ADN tumoral circulant pour détection/suivi en cours de traitement, analyse génomique n'est qu'une seule dimension.
Mais techniquement probablement plus simple.

L'avenir nous dira si l'ADN tumoral libre circulant se substituera au CTC

■ Techniques complémentaires; Idéalement faire les 2 ?

Merci pour votre attention

luis.teixeira@sls.aphp.fr