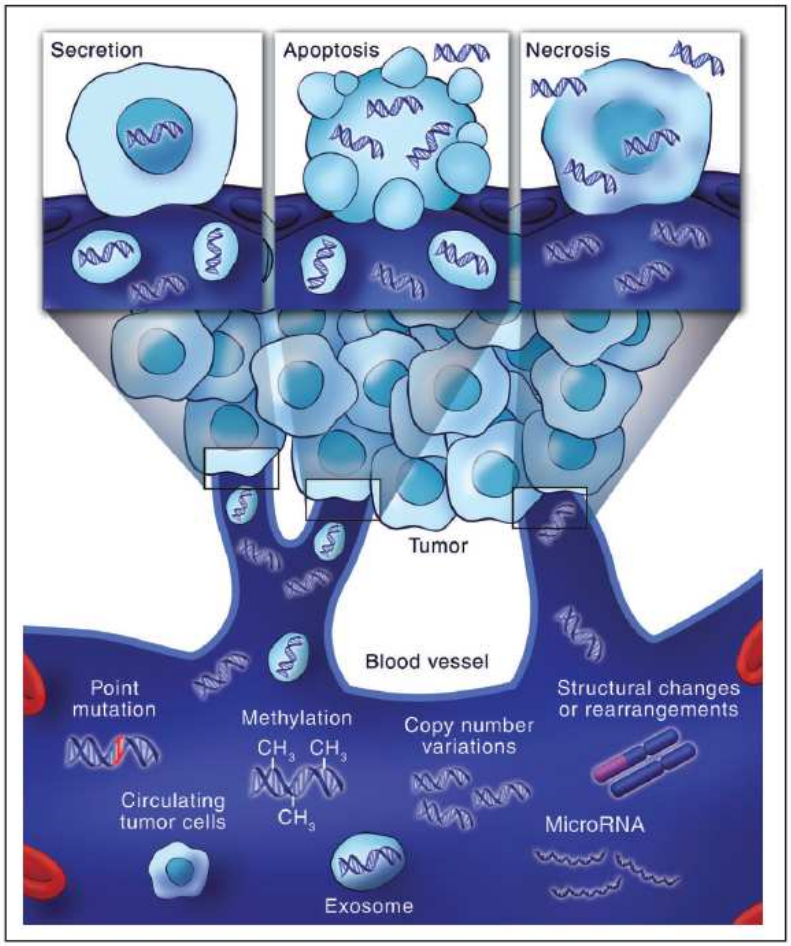
Vloeibare Biopsie bij patiënten met andere vaste tumoren

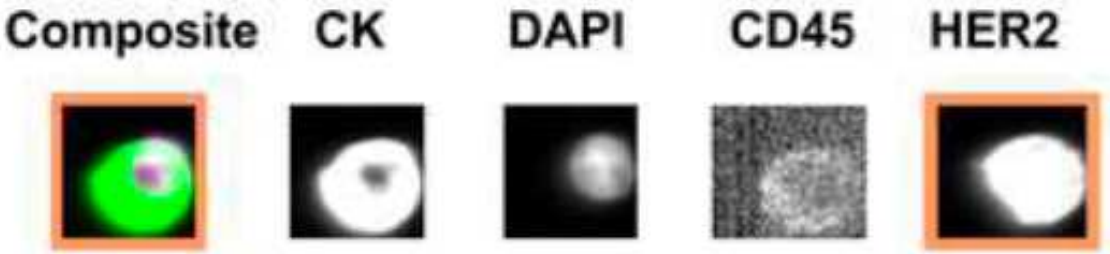
Luc Dirix

Mechanisme van tumor DNA shedding

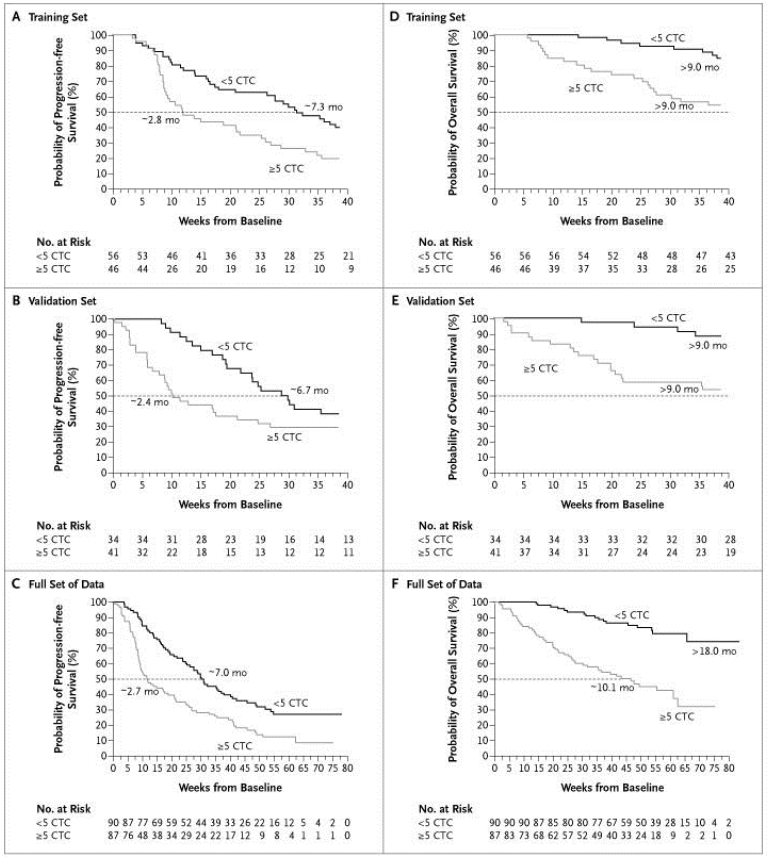


Belang van Circulerende Tumor cellen bij Patienten met Borstkanker

CellSearch® (FDA-cleared)



PFS and OS in Patients with MBC with <5 CTC and with ≥5 CTC



Cristofanilli M et al. N Engl J Med 2004;351:781-791.

Studies included

CONSORT

Letter of intent

#2,400 potentially eligible pts in 18 centers

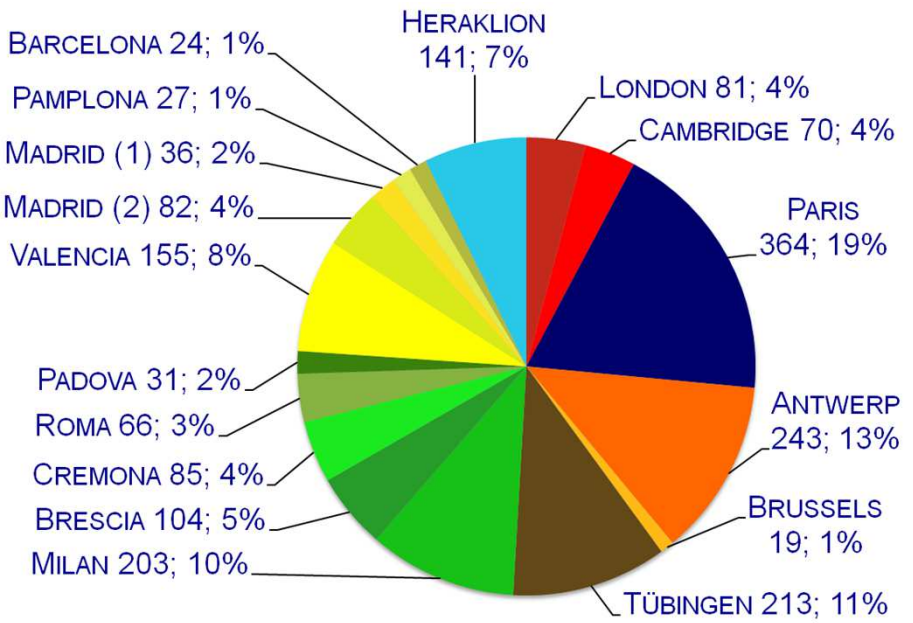
Call for data → **1 center off study**

2,174 pt data received

Data cleaning → **230 ineligible pts**

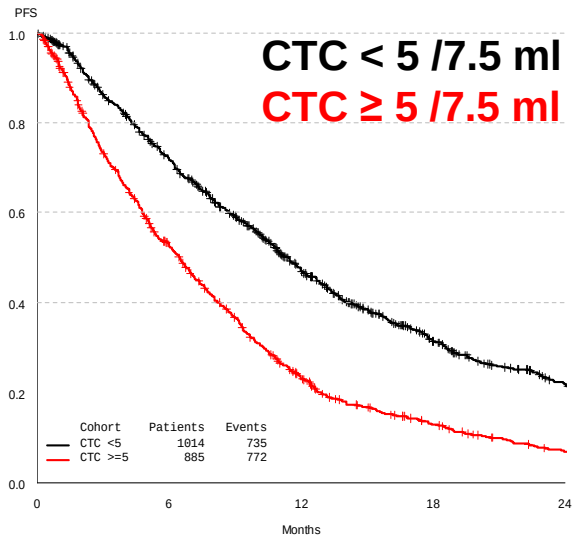
1,944 individual patient data from 17 centers included

Patients / Centres



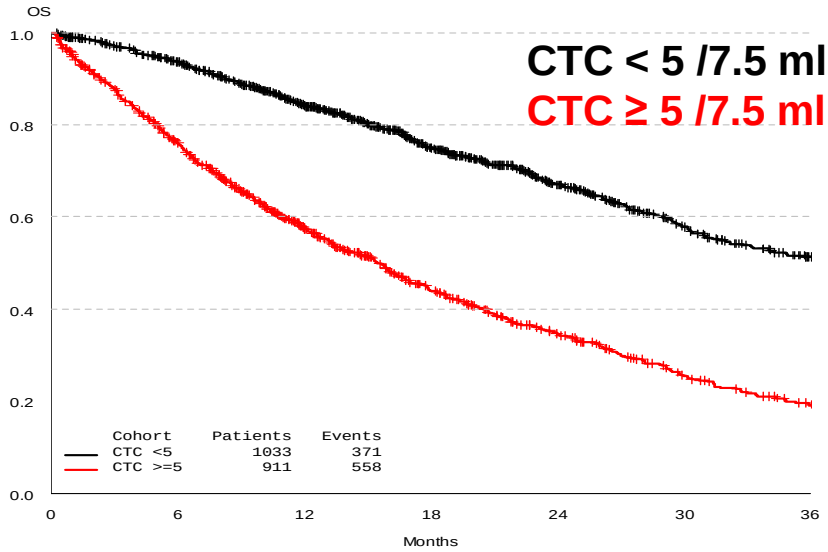
Results – *CTC at baseline*

Prognostic value – univariate analysis



Progression-Free Survival

N= 1,899 patients
HR = 1.92
p<0.0001

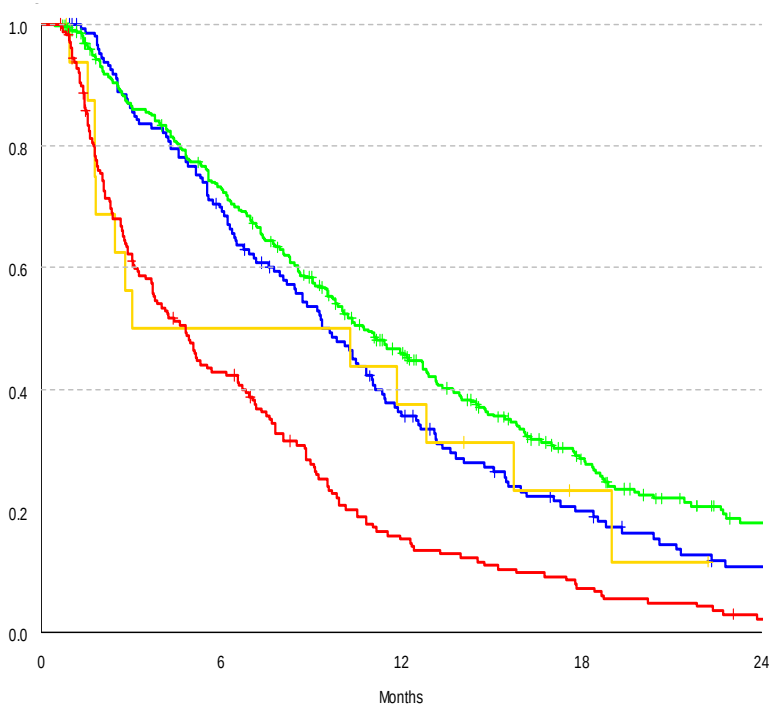


Overall Survival

N= 1,944 patients
HR = 2.77
p<0.0001

Results – *Early CTC changes during treatment*

Baseline & week 3-5

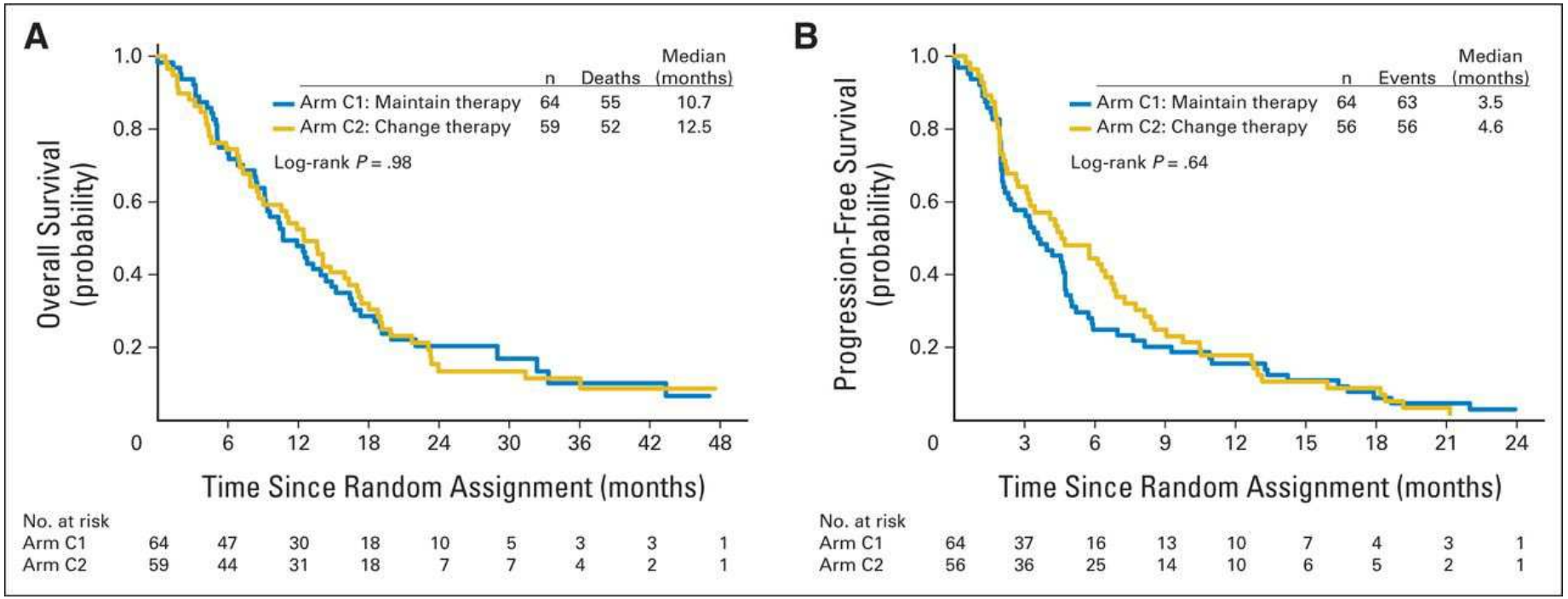


Progression-Free Survival

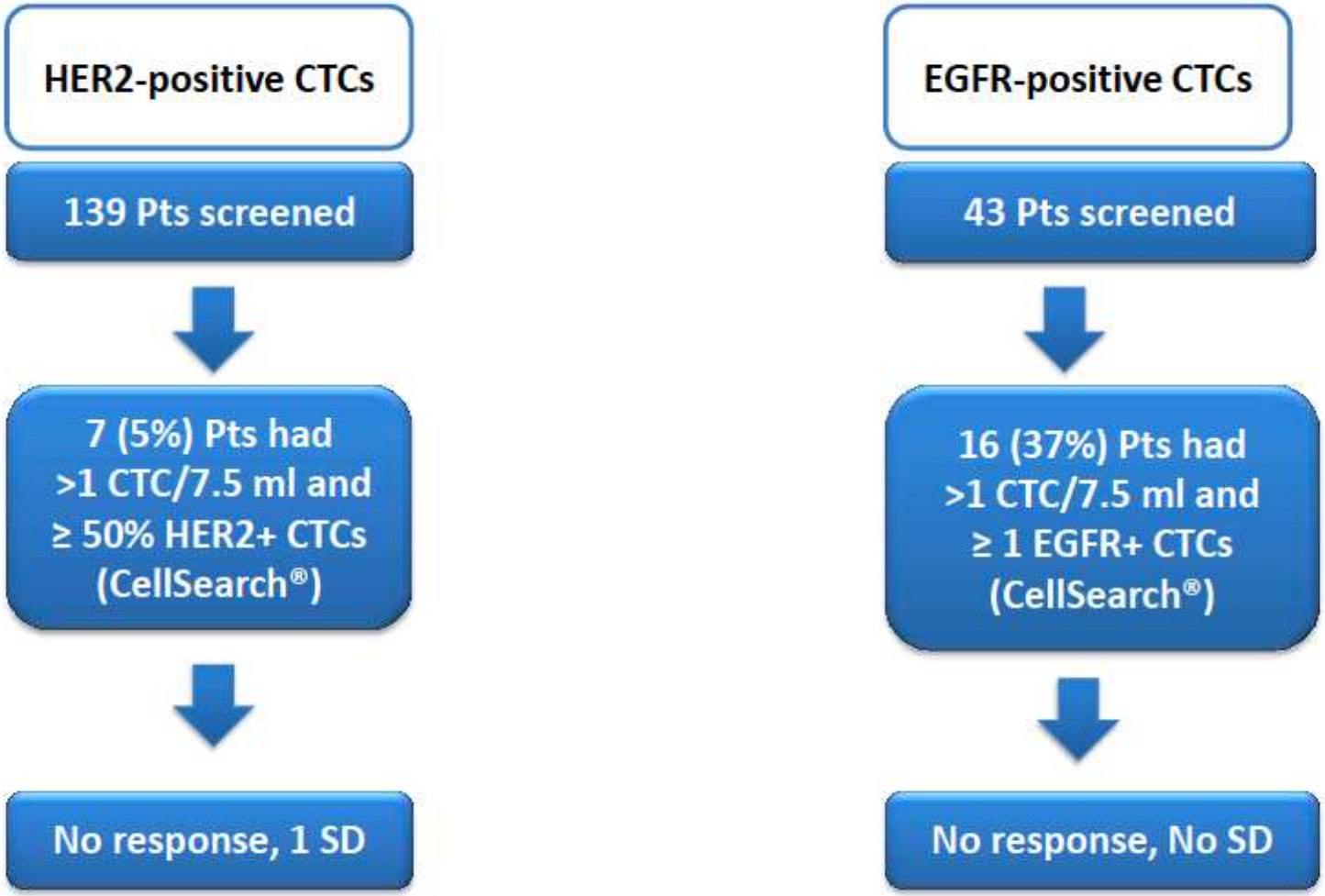
N= 672 patients; p<0.0001

	N Pts	N Events	Median PFS months [95%CI]
Stable neg: <5 - <5	327	243	10.7 [9.7-12.7]
Decrease: ≥5 - <5	149	131	9.6 [8.2-11.1]
Increase: <5 - ≥5	17	13	6.7 [1.9-NE]
Stable pos: ≥5 - ≥5	179	166	4.8 [3.7-6.5]

Similar PFS curves were obtained with later CTC changes (6-8 weeks)


A
Overall Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
n Deaths Median (months)
Arm C1: Maintain therapy 64 55 10.7
Arm C2: Change therapy 59 52 12.5
Log-rank P = .98
6 12 18 24 30 36 42 48
Time Since Random Assignment (months)
No. at risk
Arm C1 64 47 30 18 10 5 3 3 1
Arm C2 59 44 31 18 7 7 4 2 1
B
Progression-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
n Events Median (months)
Arm C1: Maintain therapy 64 63 3.5
Arm C2: Change therapy 56 56 4.6
Log-rank P = .64
3 6 9 12 15 18 21 24
Time Since Random Assignment (months)
No. at risk
Arm C1 64 37 16 13 10 7 4 3 1
Arm C2 56 36 25 14 10 6 5 2 1

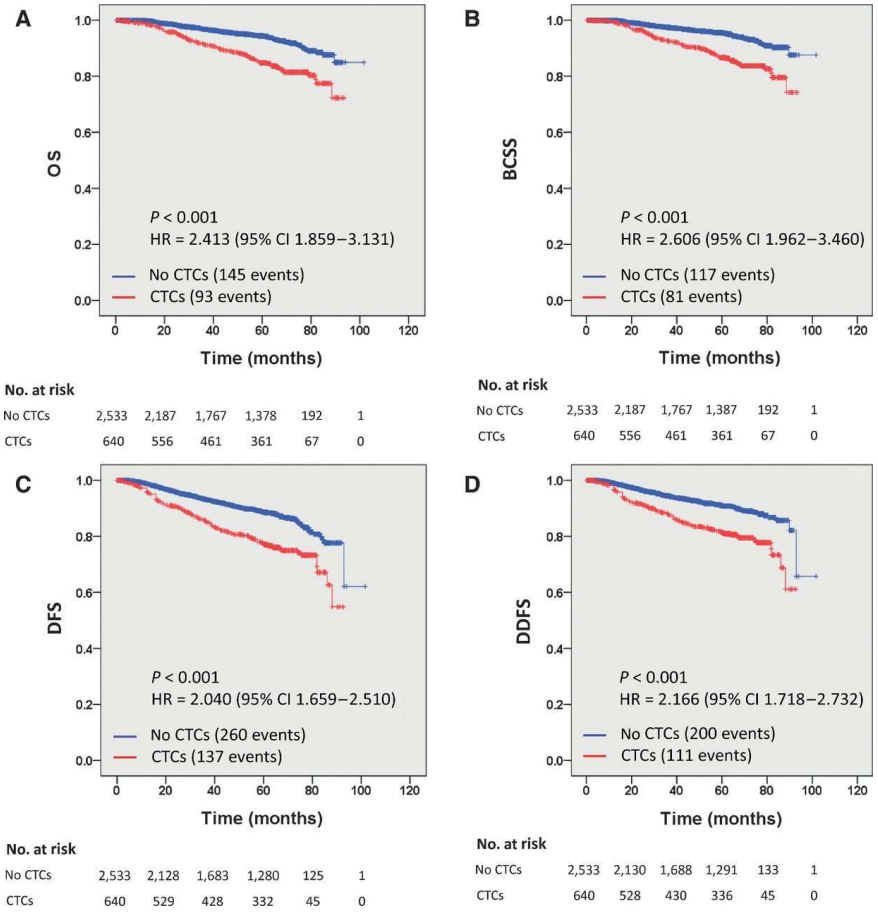
Lapatinib monotherapy in HER2-neg MBC



Pestrin et al BCRT 2012

Stebbing et al Plos One 2013

OS according to presence of CTCs at the time of primary diagnosis.



Wolfgang J. Janni et al. Clin Cancer Res 2016;22:2583-2593

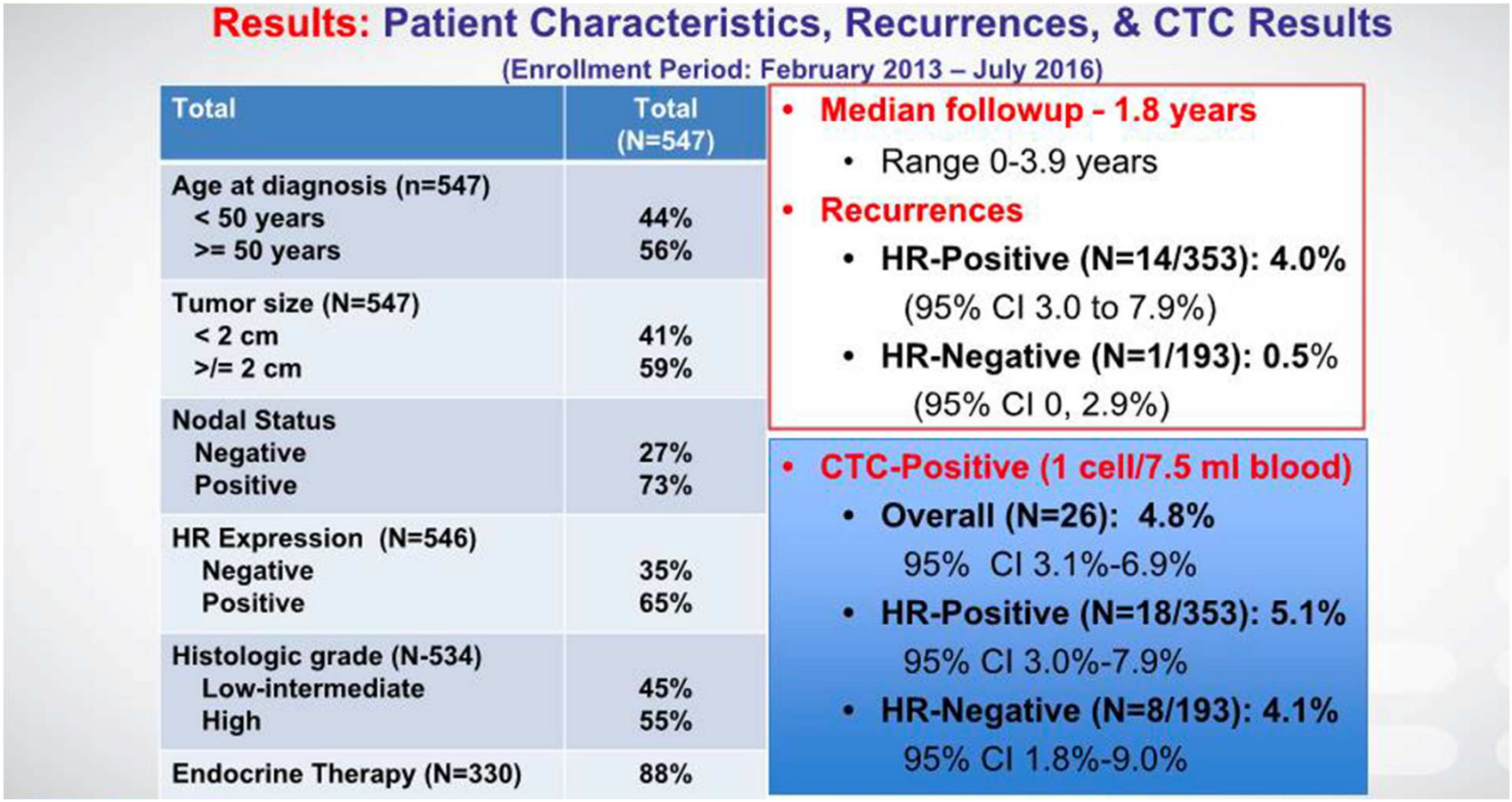
Clinical Cancer Research
AACR American Association for Cancer Research

Voorspellen van Laattijdig Herval

Methods: Study Design

- **Population:** Stage II-III HER2-negative enrolled in E5103 (NCT00433511)
- **Treatment:** AC-weekly paclitaxel ± bevacizumab + endocrine therapy if ER+
- **Selection:** Recurrence-free 4.5-7.5 years after diagnosis & informed consent
- **CTC Assay:** Whole blood (7.5 ml) drawn into fixative-containing tube for CTC identification and enumeration using the CellSearch® system at entry
- **Assay results:** not reported to clinicians or patients due to uncertainty regarding prognostic information

Laattijdig Herval

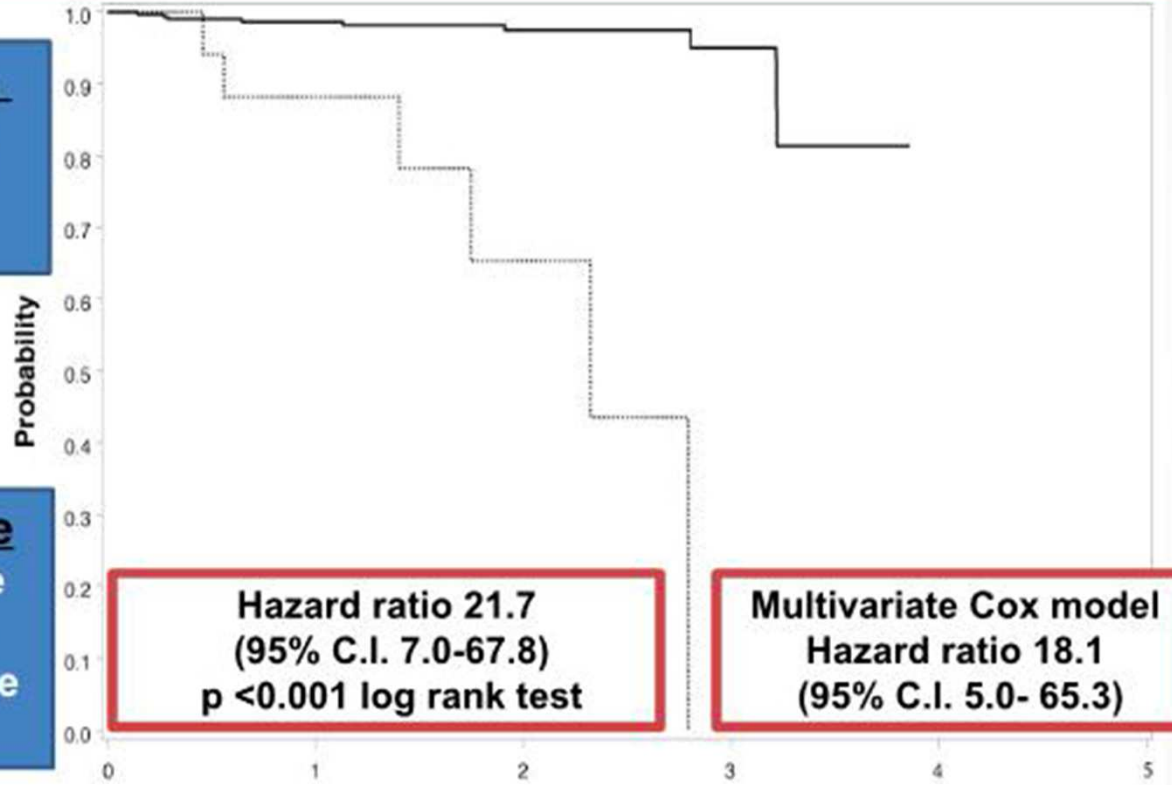


Results: Time to Recurrence in HR+ Disease (N=353)

Median time to recurrence in CTC+: 1.6 years (range 0.5-2.8 years)

Recurrence rates per person-year
- CTC-Pos: 24.7%
- CTC-Neg: 1.5%

2-Year Recurrence
- Positive Predictive Value = 35%
- Negative Predictive Value = 98%



Hazard ratio 21.7
(95% C.I. 7.0-67.8)
p <0.001 log rank test

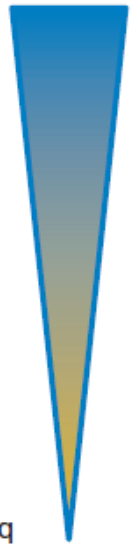
Multivariate Cox model
Hazard ratio 18.1
(95% C.I. 5.0- 65.3)

Challenges for ctDNA in oncology

- Discriminating circulating tumor DNA (ctDNA) from normal cfDNA
- Presence of sometimes extremely low levels of ctDNA
- Accurate quantification of the number of mutant fragments in a sample
  - T1/2 estimated 2 hours
  - (<1.0% of total cfDNA in general; wide range)
  - 180-200 bp cfDNA < apoptosis
  - Plasma > serum
  - Time ?

Methodologies for detecting ctDNA

Technique	Sensitivity	Optimal Application
Sanger sequencing	> 10%	Tumor tissue
Pyrosequencing	10%	Tumor tissue
Next-generation seqeuncing	2%	Tumor tissue
Quantative PCR	1%	Tumor tissue
ARMS	0.10%	Tumor tissue
BEAMing, PAP, Digital PCR, TAM-Seq	0.01% or lower	ctDNA, rare variants in tumor tissue

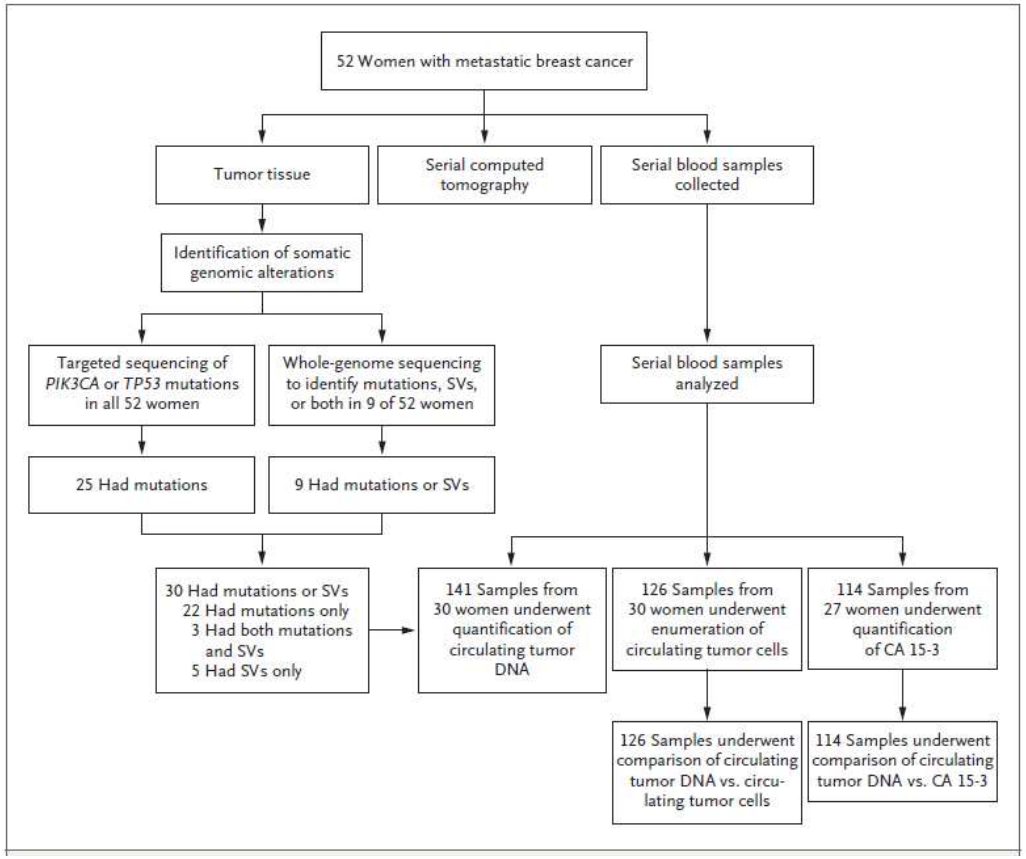


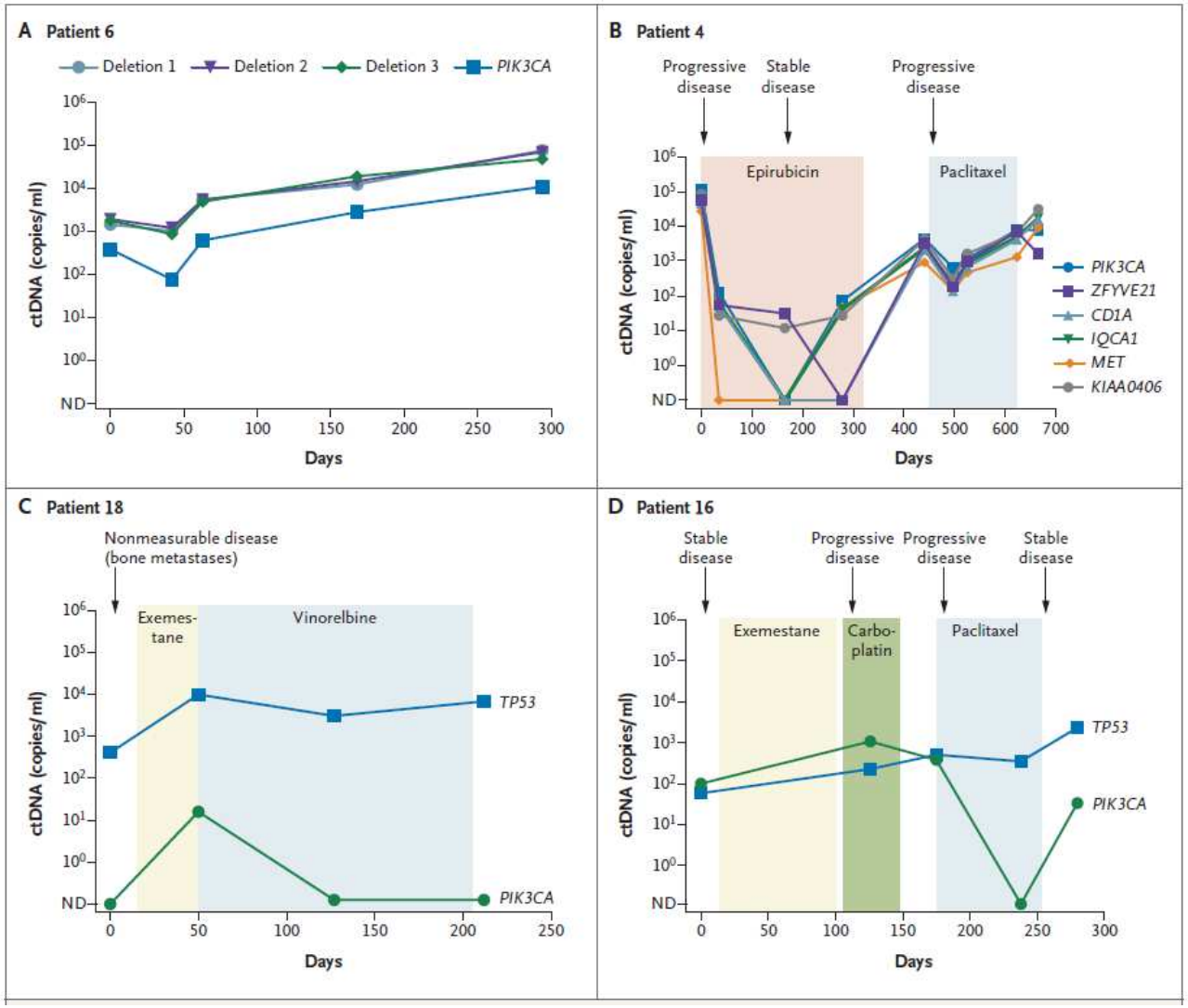
Applications of ctDNA

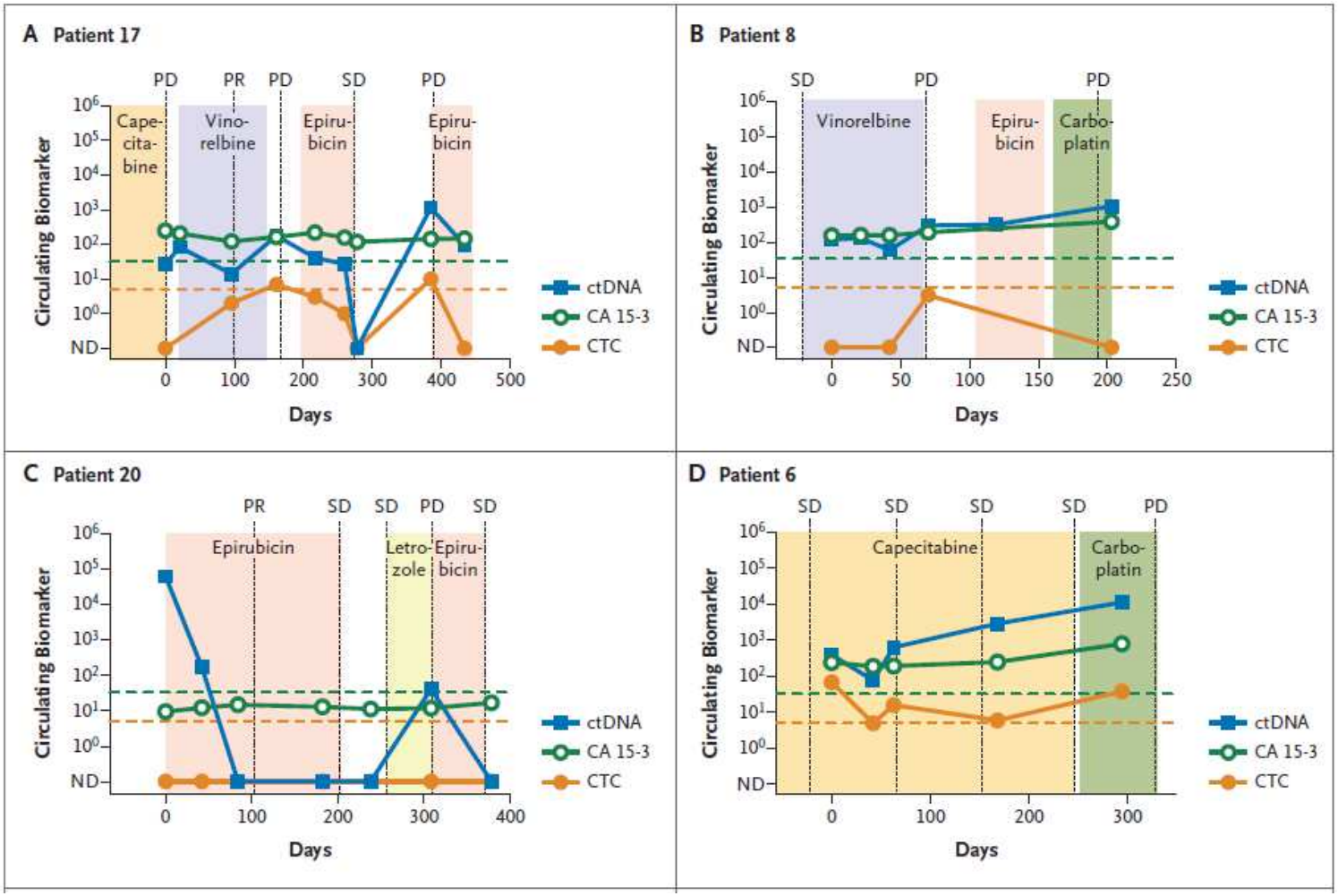
- Monitor tumour burden
- Diagnose minimal residual disease
- Resistance to treatment

The NEW ENGLAND JOURNAL of MEDICINE

Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer




A Patient 6
Deletion 1
Deletion 2
Deletion 3
PIK3CA
ctDNA (copies/ml)
Days
B Patient 4
Progressive disease
Stable disease
Progressive disease
Epirubicin
Paclitaxel
PIK3CA
ZFYVE21
CD1A
IQCA1
MET
KIAA0406
C Patient 18
Nonmeasurable disease (bone metastases)
Exemes-tane
Vinorelbine
TP53
PIK3CA
D Patient 16
Stable disease
Progressive disease
Progressive disease
Stable disease
Exemestane
Carbo-platin
Paclitaxel
TP53
PIK3CA


A Patient 17
PD
PR
PD
SD
PD
Cape-cita-bine
Vino-relbine
Epiru-bicin
Epiru-bicin
Circulating Biomarker
10^6
10^5
10^4
10^3
10^2
10^1
10^0
ND
0
100
200
300
400
500
Days
ctDNA
CA 15-3
CTC
B Patient 8
SD
PD
PD
Vinorelbine
Epiru-bicin
Carbo-platin
0
50
100
150
200
250
C Patient 20
PR
SD
SD
PD
SD
Epirubicin
Letro-zole
Epiru-bicin
D Patient 6
SD
SD
SD
SD
PD
Capecitabine
Carbo-platin

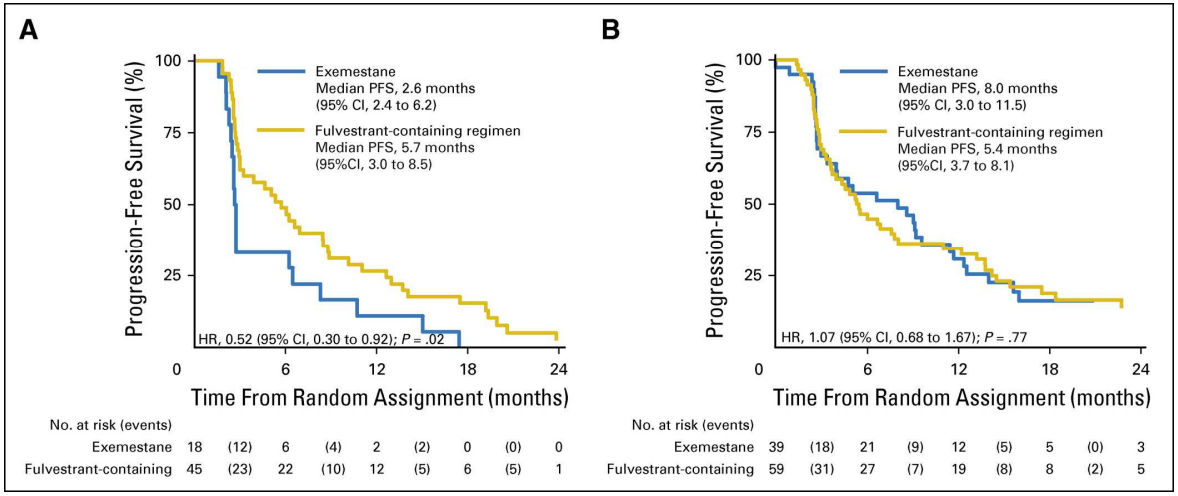


Fig 2. Progression-free survival (PFS) in SoFEA by ESR1 mutation status. (A) PFS of patients with ESR1 mutant cancers who received exemestane or a fulvestrant-containing regimen. (B) PFS of patients without detected ESR1 mutation who received exemestane or a fulvestrant-containing regimen. HR, hazard ratio.

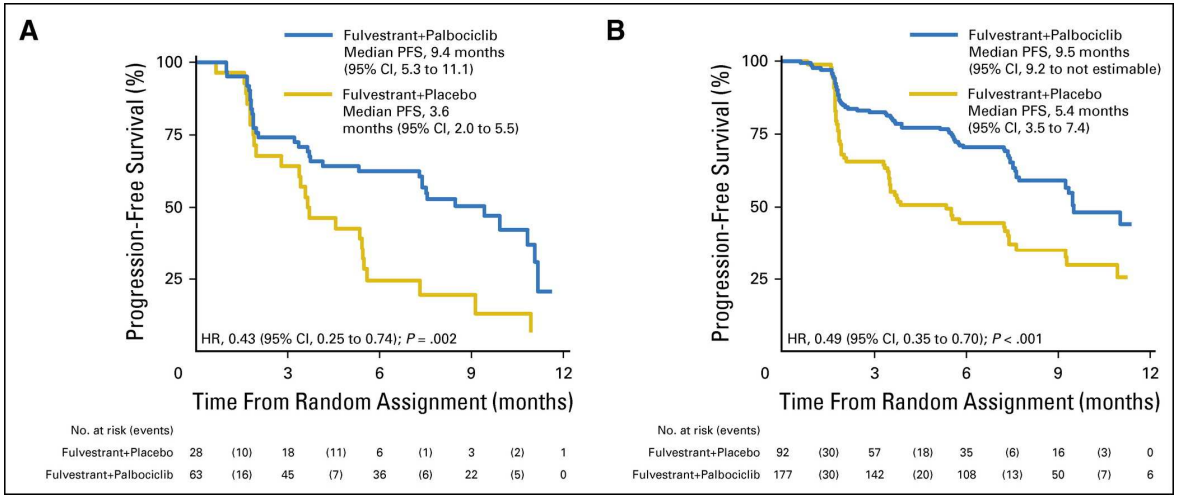


Fig 3. Progression-free survival (PFS) in PALOMA3 by ESR1 mutation status. (A) PFS for patients with ESR1 mutant cancers who received fulvestrant and placebo or fulvestrant and palbociclib. (B) PFS for patients without detected ESR1 mutation who received fulvestrant and placebo or fulvestrant and palbociclib. HR, hazard ratio.

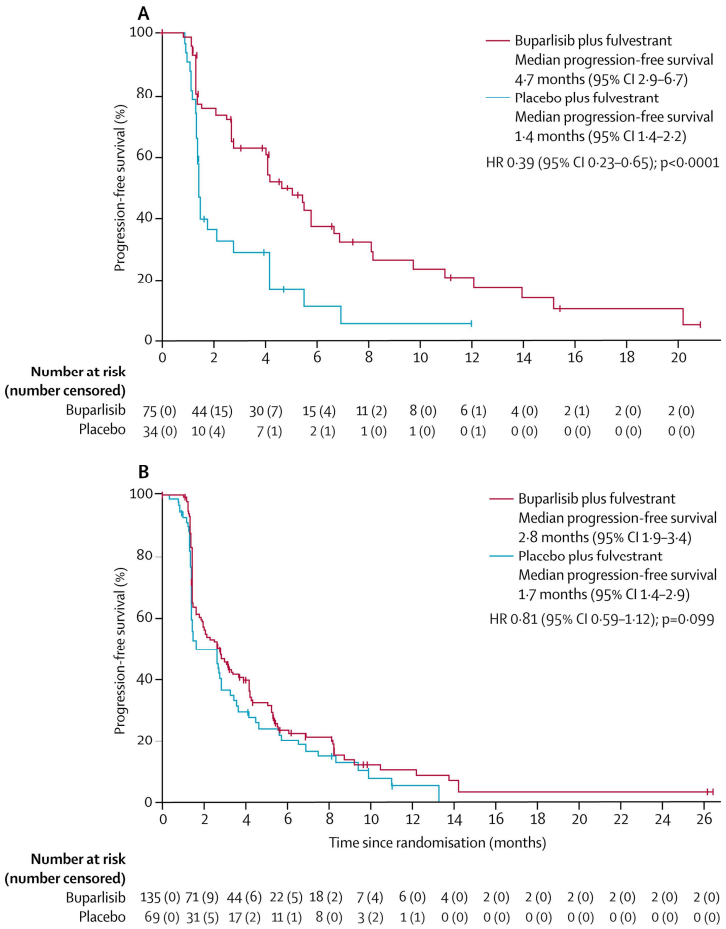
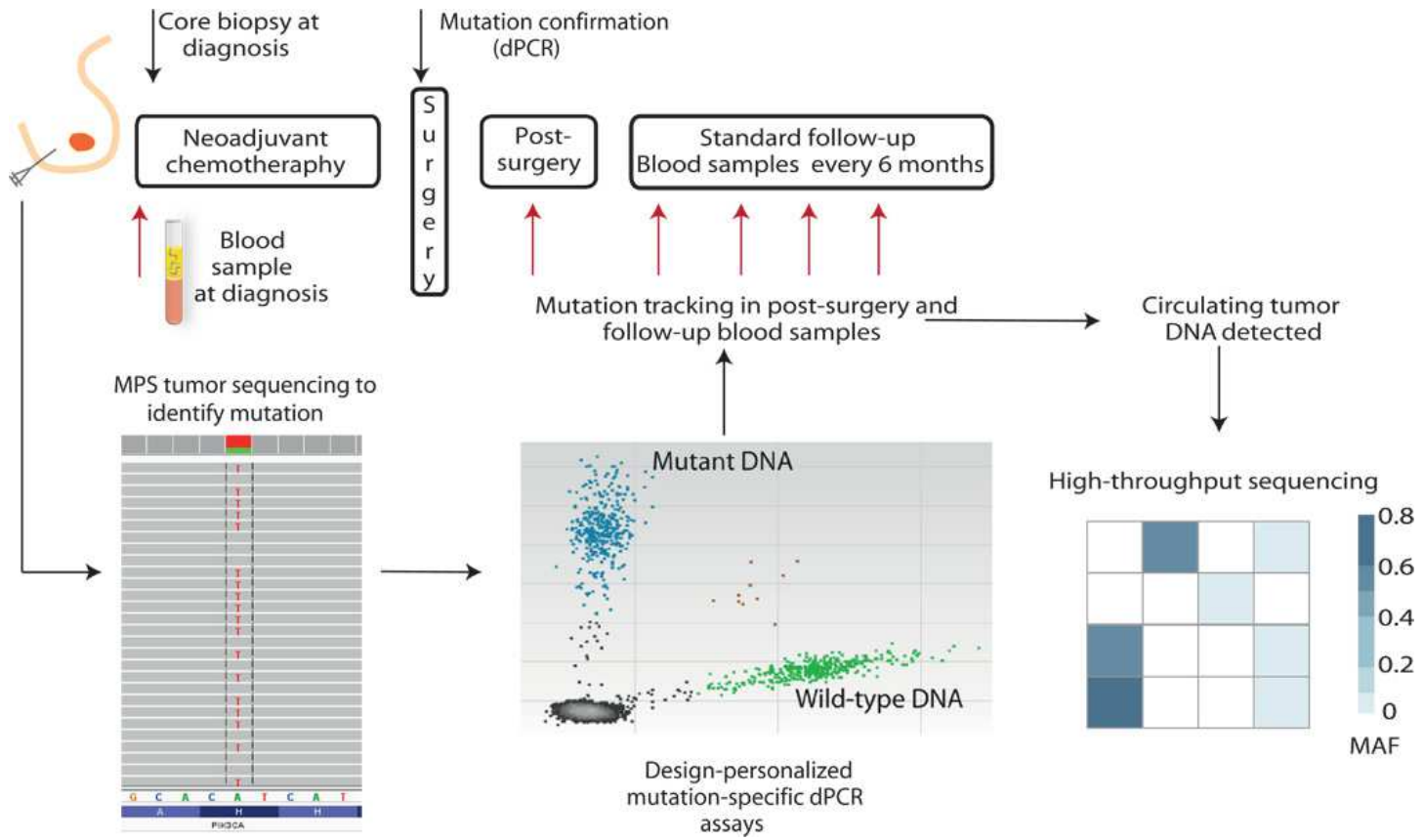


Fig. 1. Personalized dPCR assays for mutation tracking of ctDNA in plasma of patients with early breast cancer.



Isaac Garcia-Murillas et al., Sci Transl Med 2015;7:302ra133

Science Translational Medicine
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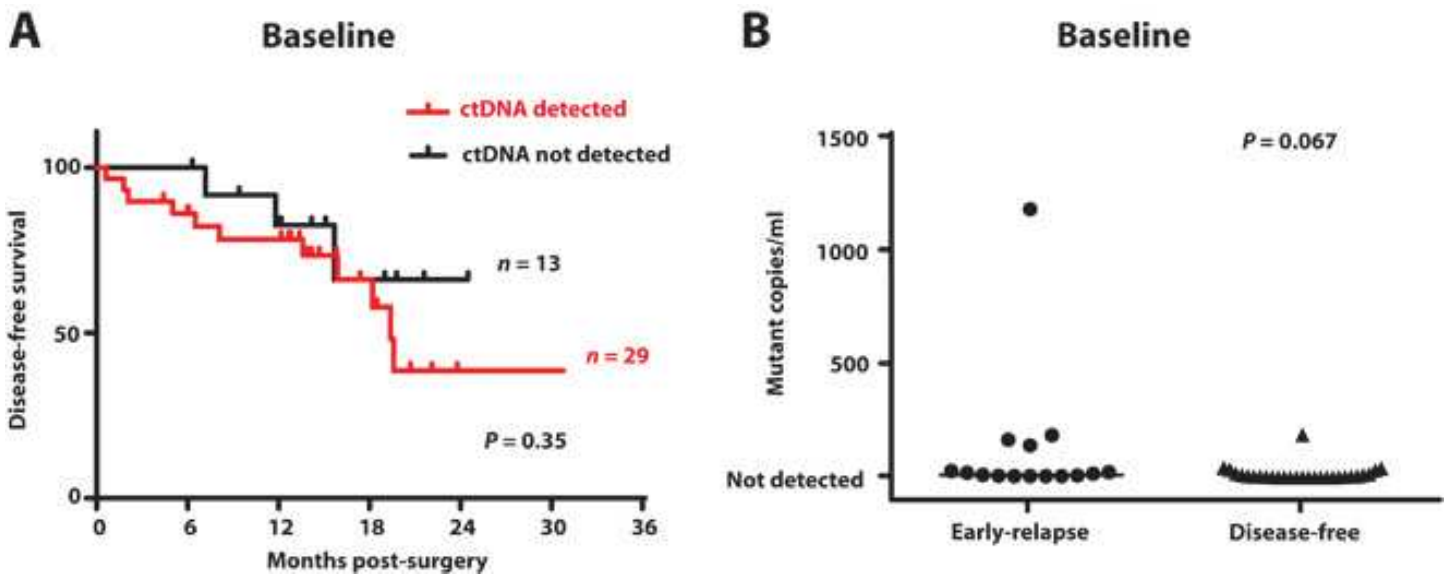
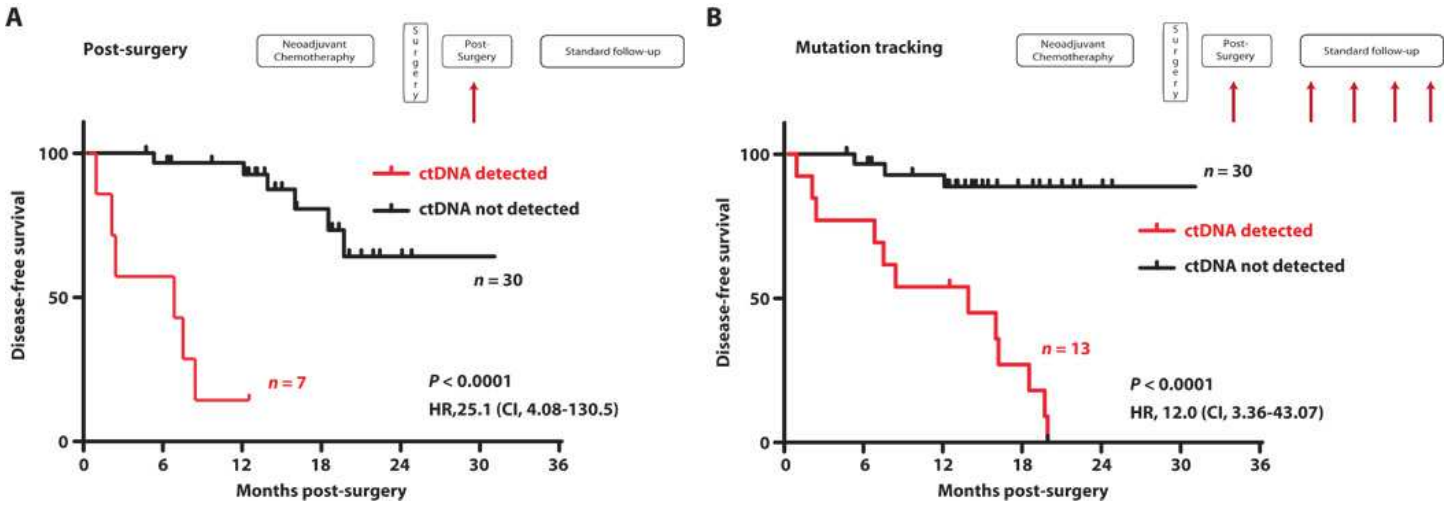
Fig. 3. Early relapse is not predicted by analysis of baseline ctDNA. (A) Disease-free survival according to the detection of ctDNA in the baseline plasma sample.



Isaac Garcia-Murillas et al., Sci Transl Med 2015;7:302ra133

Fig. 4. Mutation tracking in serial plasma samples predicts early relapse.



Isaac Garcia-Murillas et al., Sci Transl Med 2015;7:302ra133

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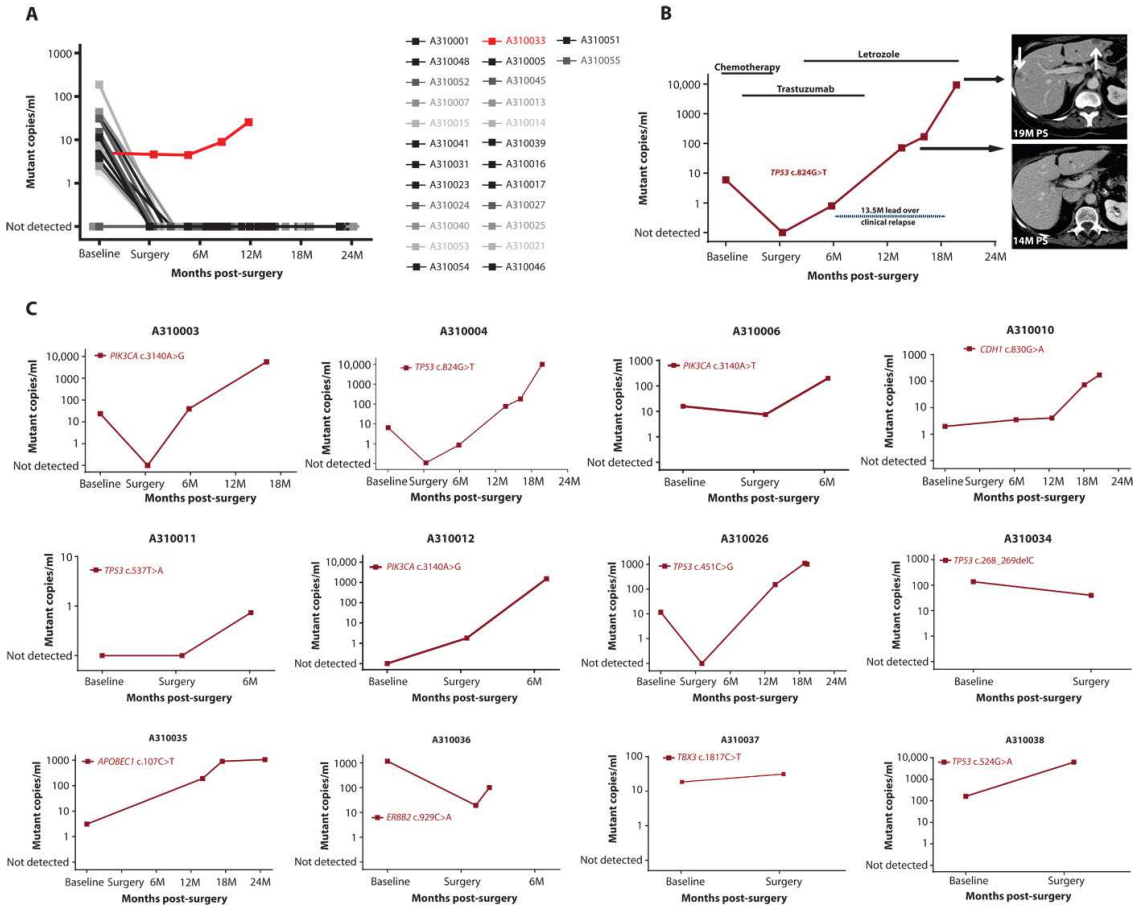
Fig. 5. Mutation tracking in early-relapse and disease-free patients.



Isaac Garcia-Murillas et al., Sci Transl Med 2015;7:302ra133

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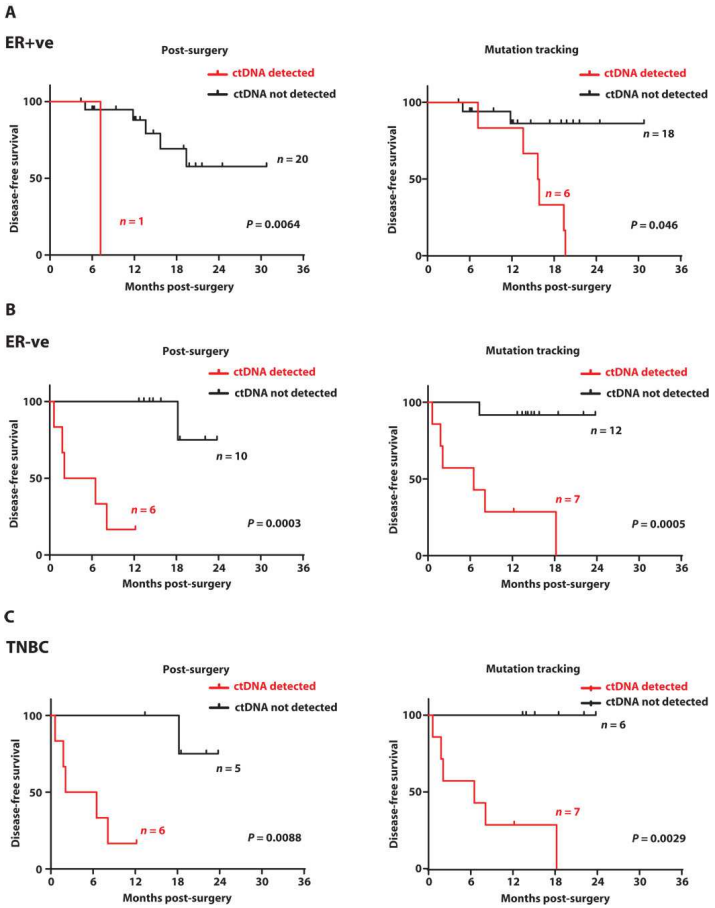
Fig. 6. Disease-free survival prediction based on single post-surgery ctDNA and mutation tracking in serial plasma samples according to tumor subtype.



Isaac Garcia-Murillas et al., Sci Transl Med 2015;7:302ra133

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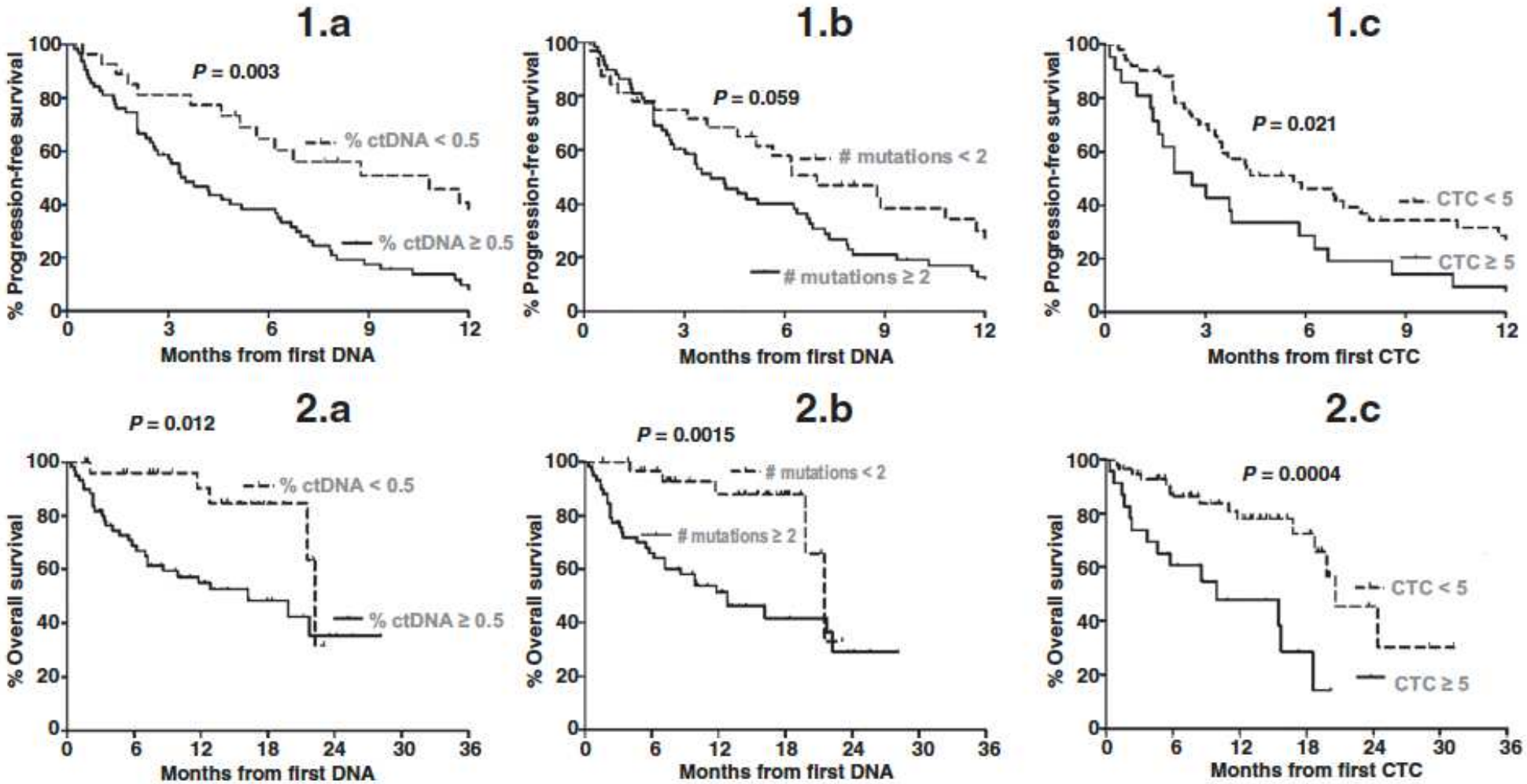
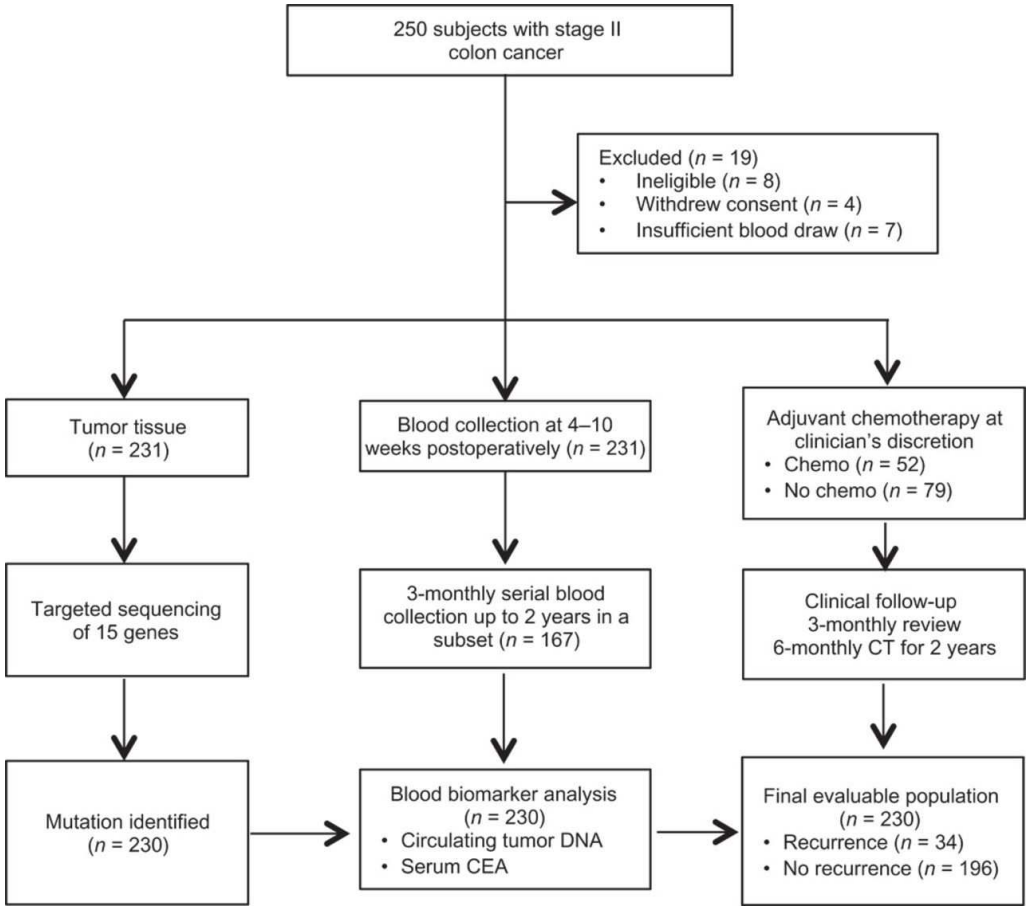

1.a
P = 0.003
% ctDNA < 0.5
% ctDNA ≥ 0.5
% Progression-free survival
Months from first DNA
1.b
P = 0.059
# mutations < 2
# mutations ≥ 2
% Progression-free survival
Months from first DNA
1.c
P = 0.021
CTC < 5
CTC ≥ 5
% Progression-free survival
Months from first CTC
2.a
P = 0.012
% ctDNA < 0.5
% ctDNA ≥ 0.5
% Overall survival
Months from first DNA
2.b
P = 0.0015
# mutations < 2
# mutations ≥ 2
% Overall survival
Months from first DNA
2.c
P = 0.0004
CTC < 5
CTC ≥ 5
% Overall survival
Months from first CTC

Fig. 1. Patient enrolment and sample collection.



Jeanne Tie et al., Sci Transl Med 2016;8:346ra92

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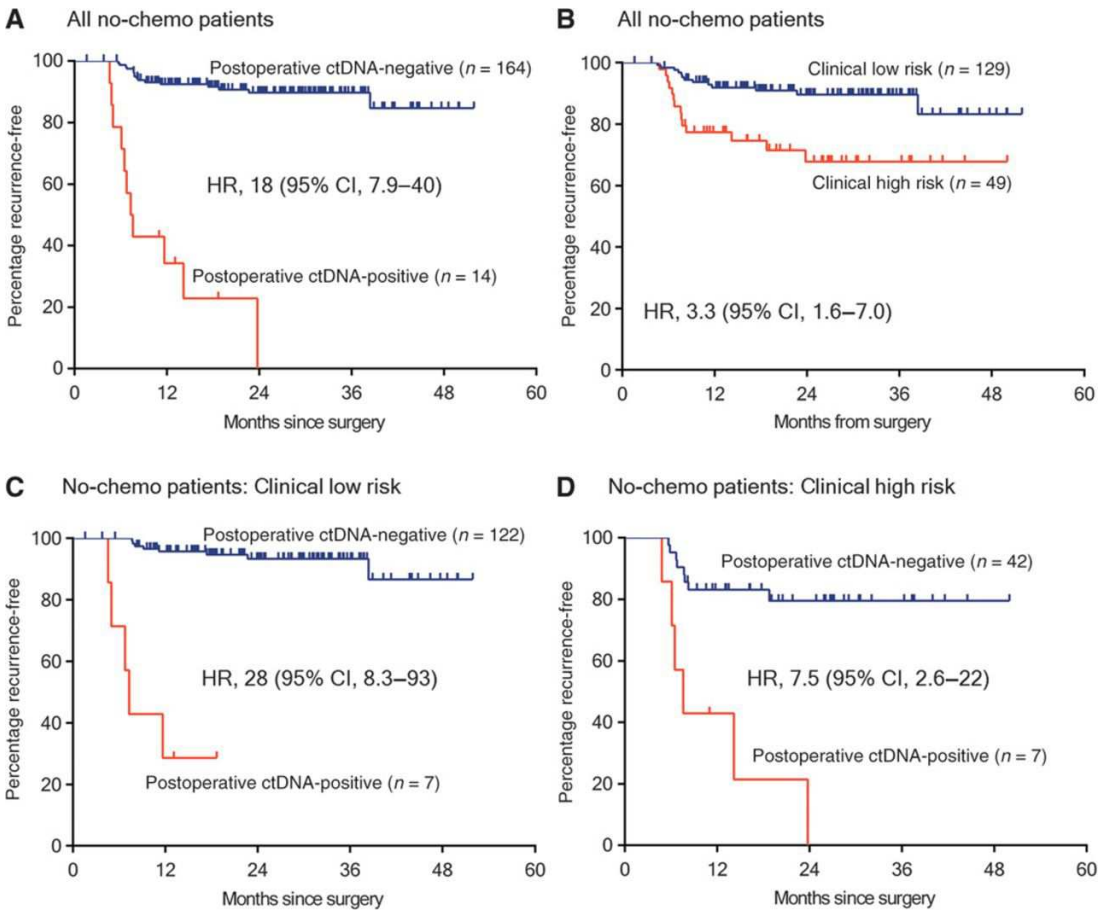
Fig. 2. RFS in patients not treated with adjuvant chemotherapy.



Jeanne Tie et al., Sci Transl Med 2016;8:346ra92

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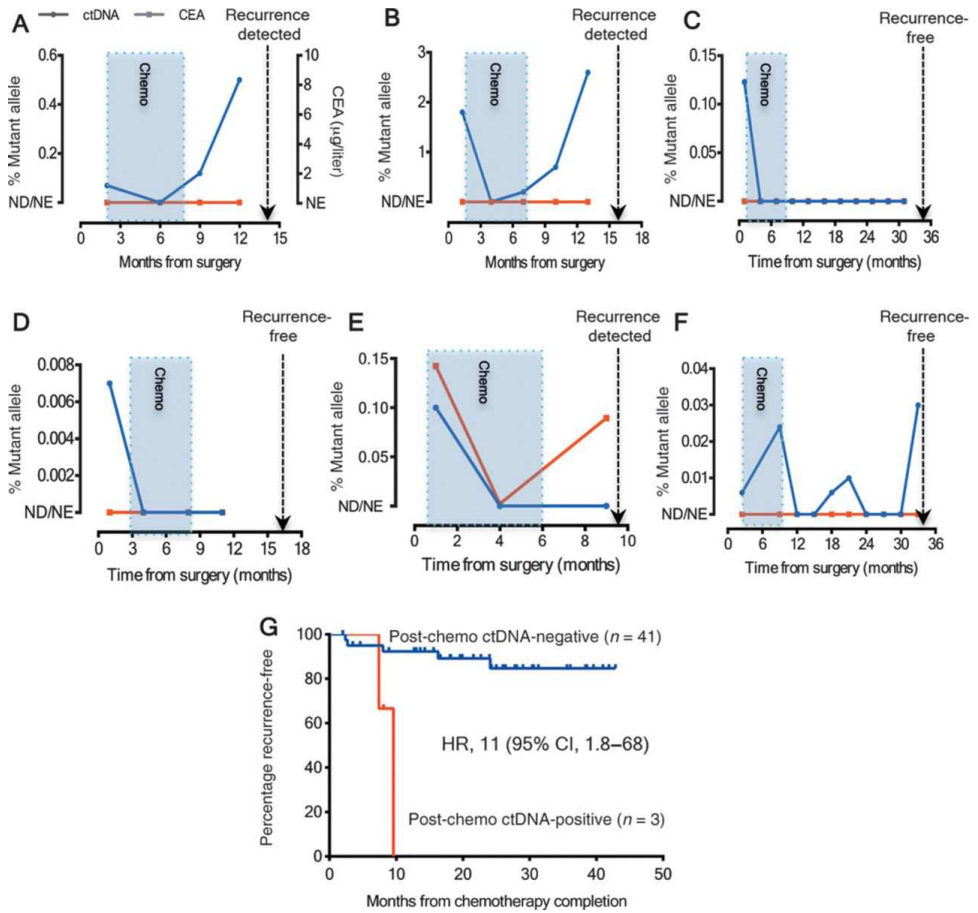
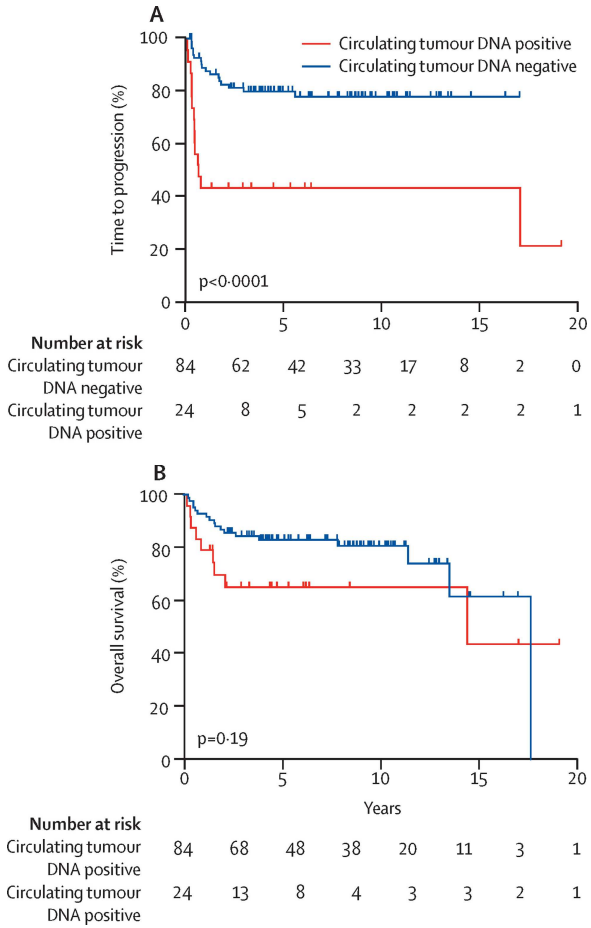
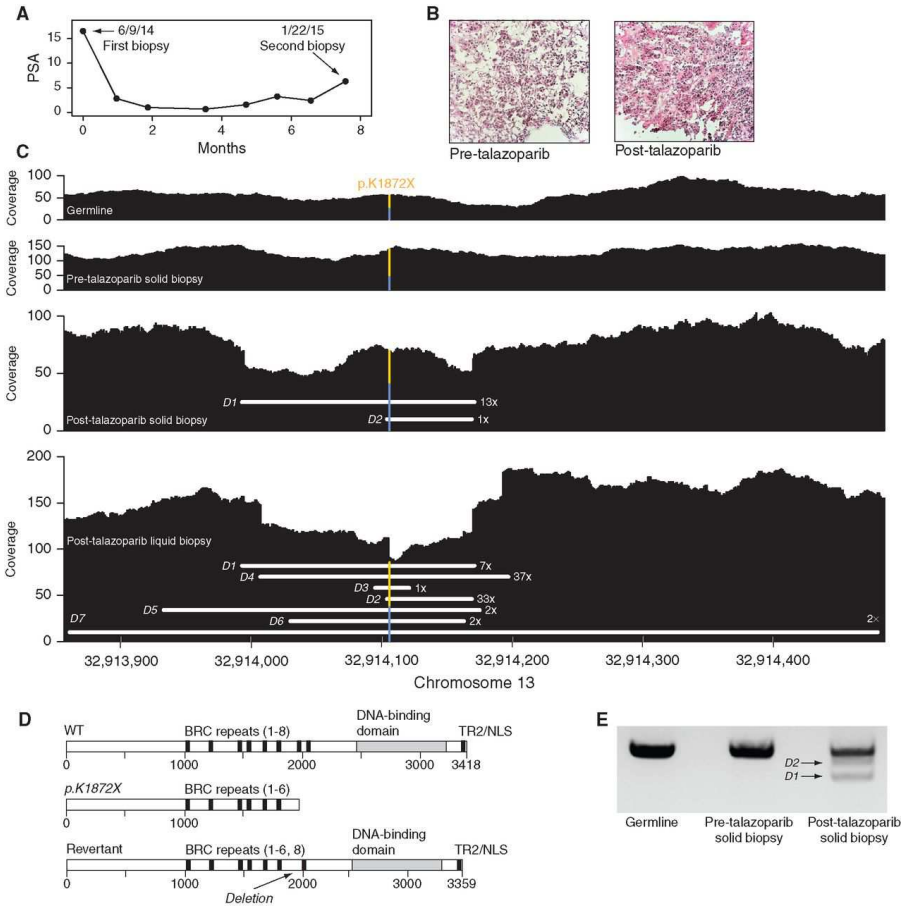
Fig. 3. ctDNA status before, during, and after adjuvant chemotherapy.



Jeanne Tie et al., Sci Transl Med 2016;8:346ra92


A
Circulating tumour DNA positive
Circulating tumour DNA negative
Time to progression (%)
100
80
60
40
20
0
p<0·0001
0
5
10
15
20
Number at risk
Circulating tumour DNA negative 84 62 42 33 17 8 2 0
Circulating tumour DNA positive 24 8 5 2 2 2 2 1
B
Overall survival (%)
100
80
60
40
20
0
p=0·19
0
5
10
15
20
Years
Number at risk
Circulating tumour DNA positive 84 68 48 38 20 11 3 1
Circulating tumour DNA positive 24 13 8 4 3 3 2 1

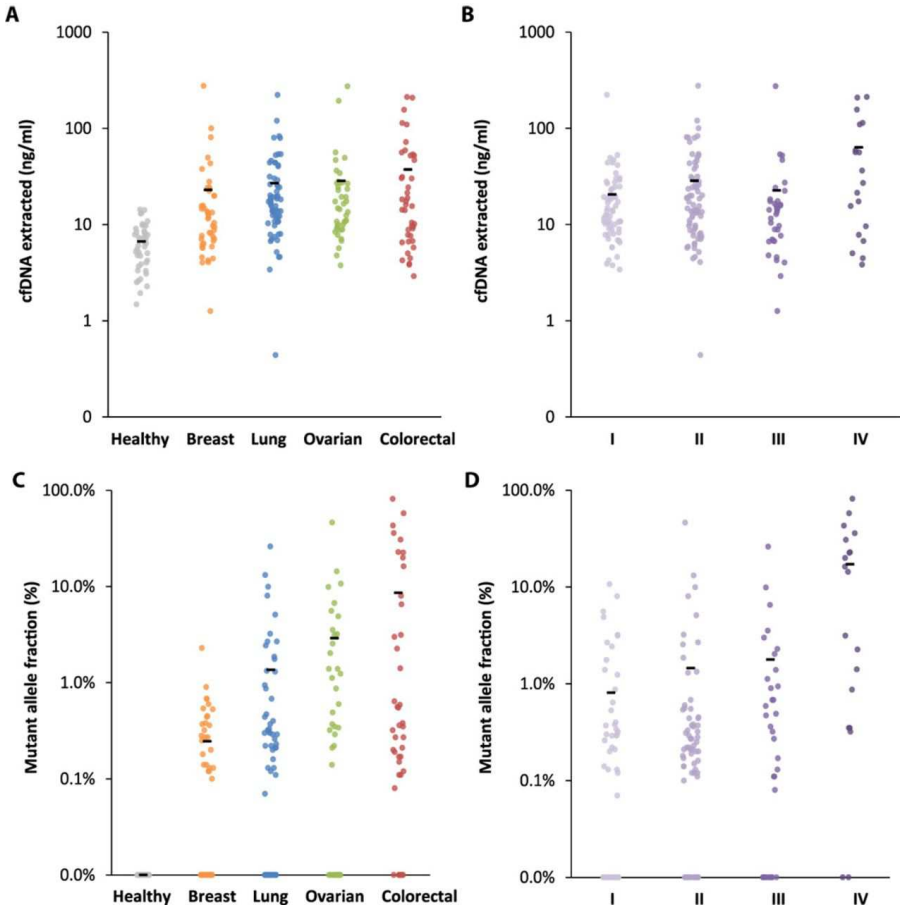
PARPi resistance by multiple large deletions.



David Quigley et al. Cancer Discov 2017;7:999-1005

AACR American Association for Cancer Research
CANCER DISCOVERY

Fig. 3. cfDNA and ctDNA in healthy individuals and patients with cancer.



Jillian Phallen et al., Sci Transl Med 2017;9:eaan2415

Science Translational Medicine
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Table 2. Cancer patients detected using TEC-Seq. NA, not applicable.

Cancer type	Patients (*n*)	Patients with ctDNA alterations (*n*)	Fraction of patients with ctDNA alterations (%)
Colorectal			
I	8	4	50
II	9	8	89
III	10	9	90
IV	15	14	93
I–IV	42	35	83
Lung			
I	29	13	45
II	32	23	72
III	4	3	75
IV	6	5	83
I–IV	71	44	62
Ovarian			
I	24	16	67
II	4	3	75
III	8	6	75
IV	6	5	83
I–IV	42	30	71
Breast			
I	3	2	67
II	29	17	59
III	13	6	46
IV	0	NA	NA
I–IV	45	25	56
All			
I and II	138	86	62
III and IV	62	48	77
I–IV	200	134	67