癌症診療指引簡介及臨床應用

New strategies in anticancer therapy

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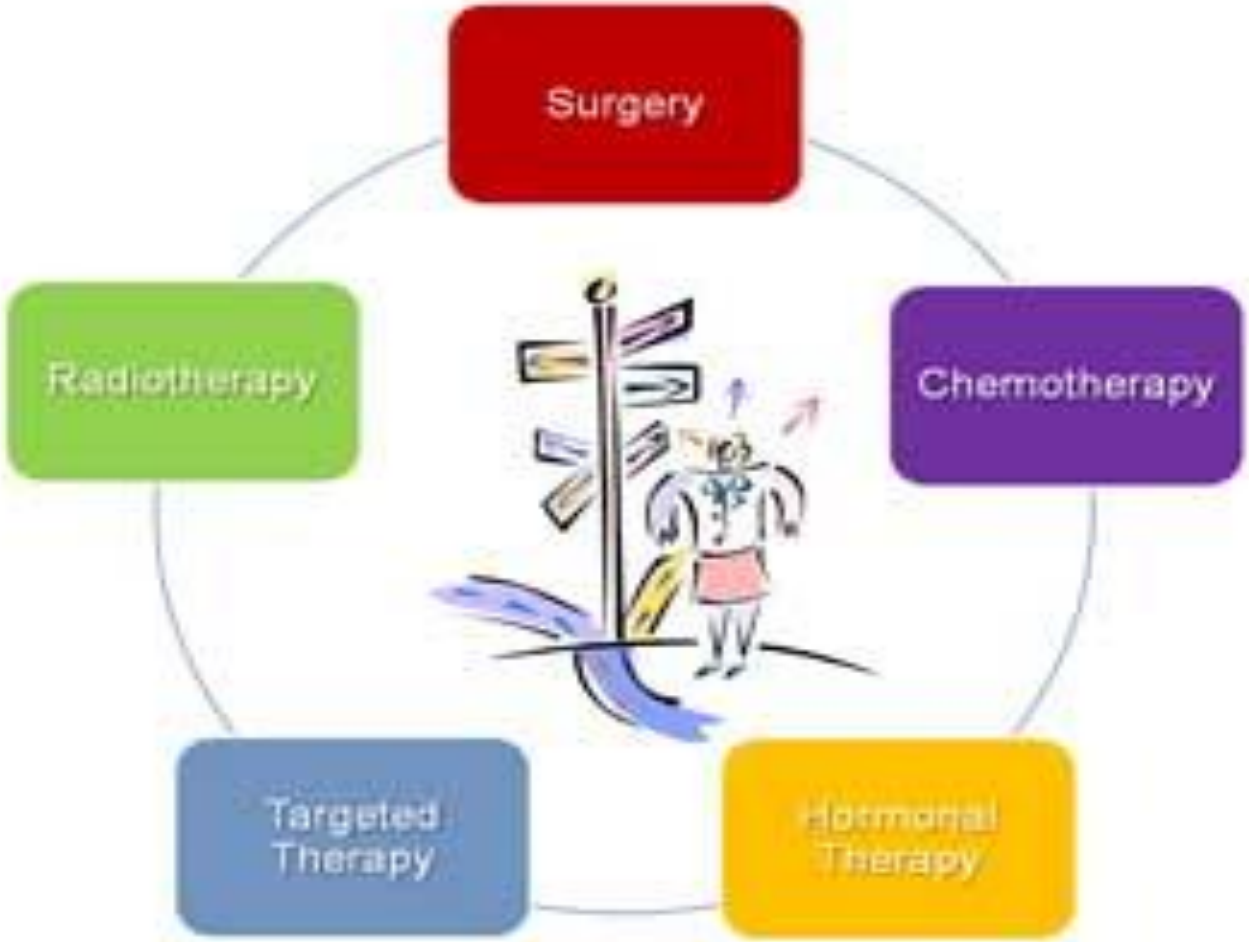
2014/3/29

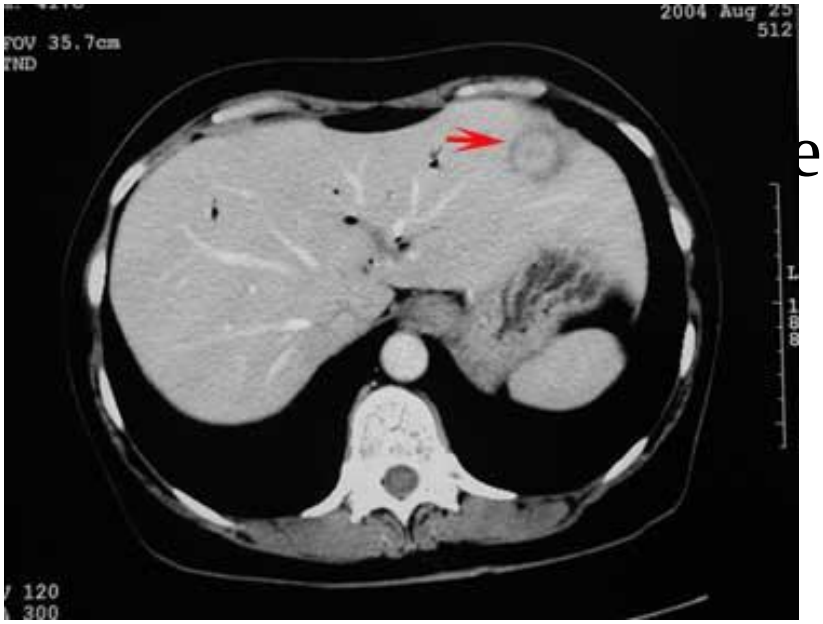
Anti-Cancer Therapy



Surgery

- To diagnose cancer
- As a treatment to cure cancer
- To reconstruct a part of your body
- To prevent or reduce the risk of cancer
- To control symptoms or extend life

Surgery



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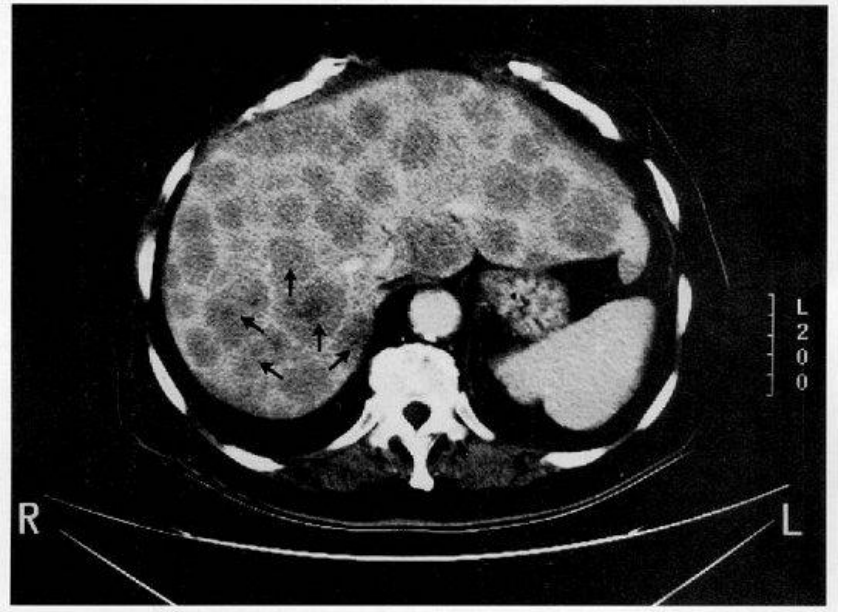
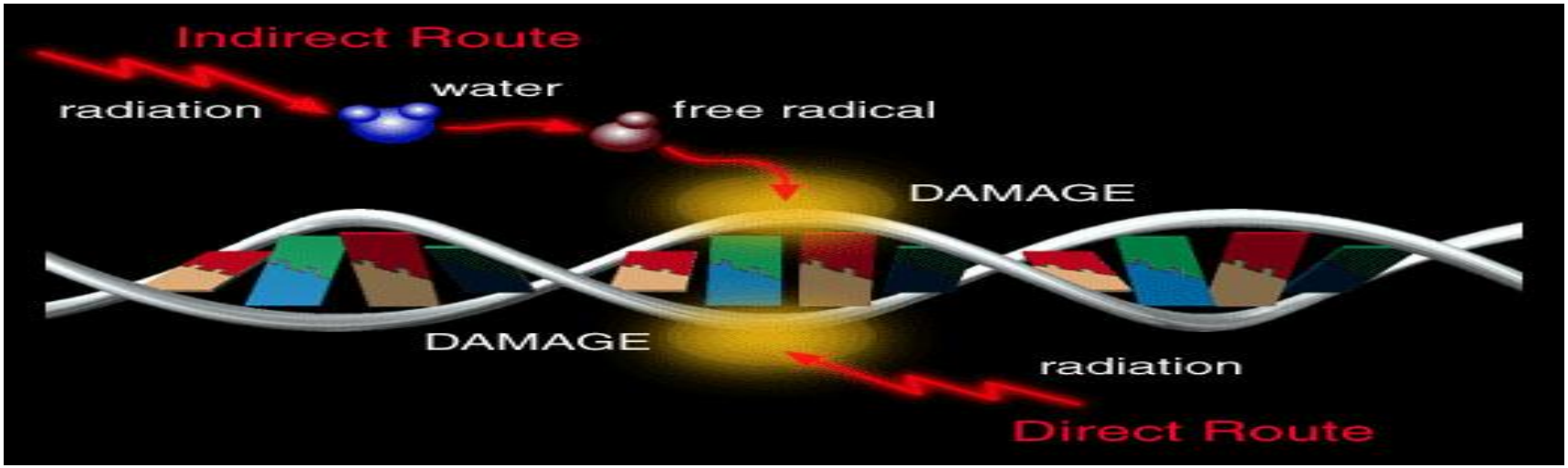


- Not solve the problem of recurrence and most of metastasis.

Radiotherapy

- Radiotherapy: ionizing radiation destroys tumor cells



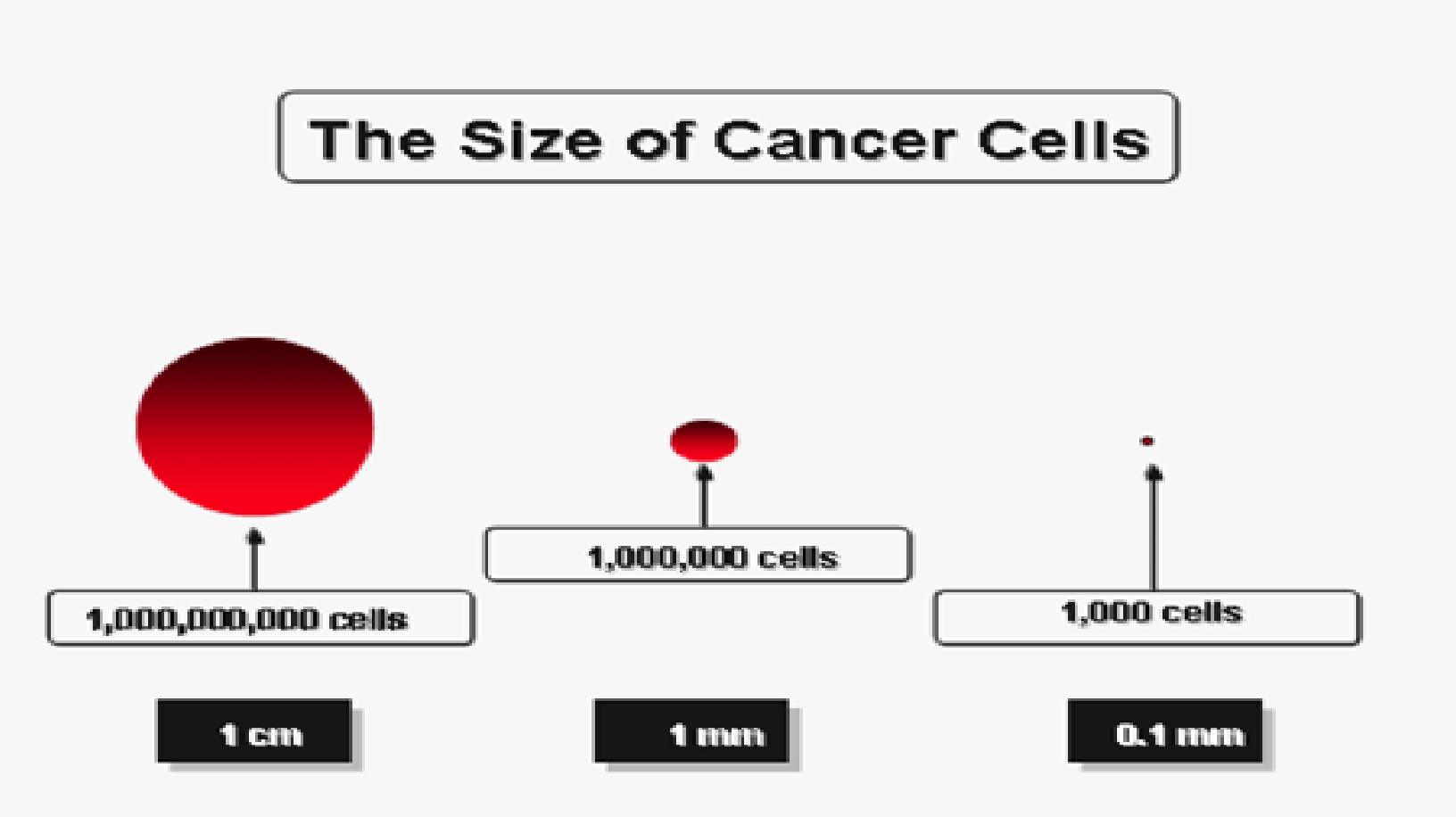
- Curative radiotherapy
- Adjuvant radiotherapy
- Palliative radiotherapy

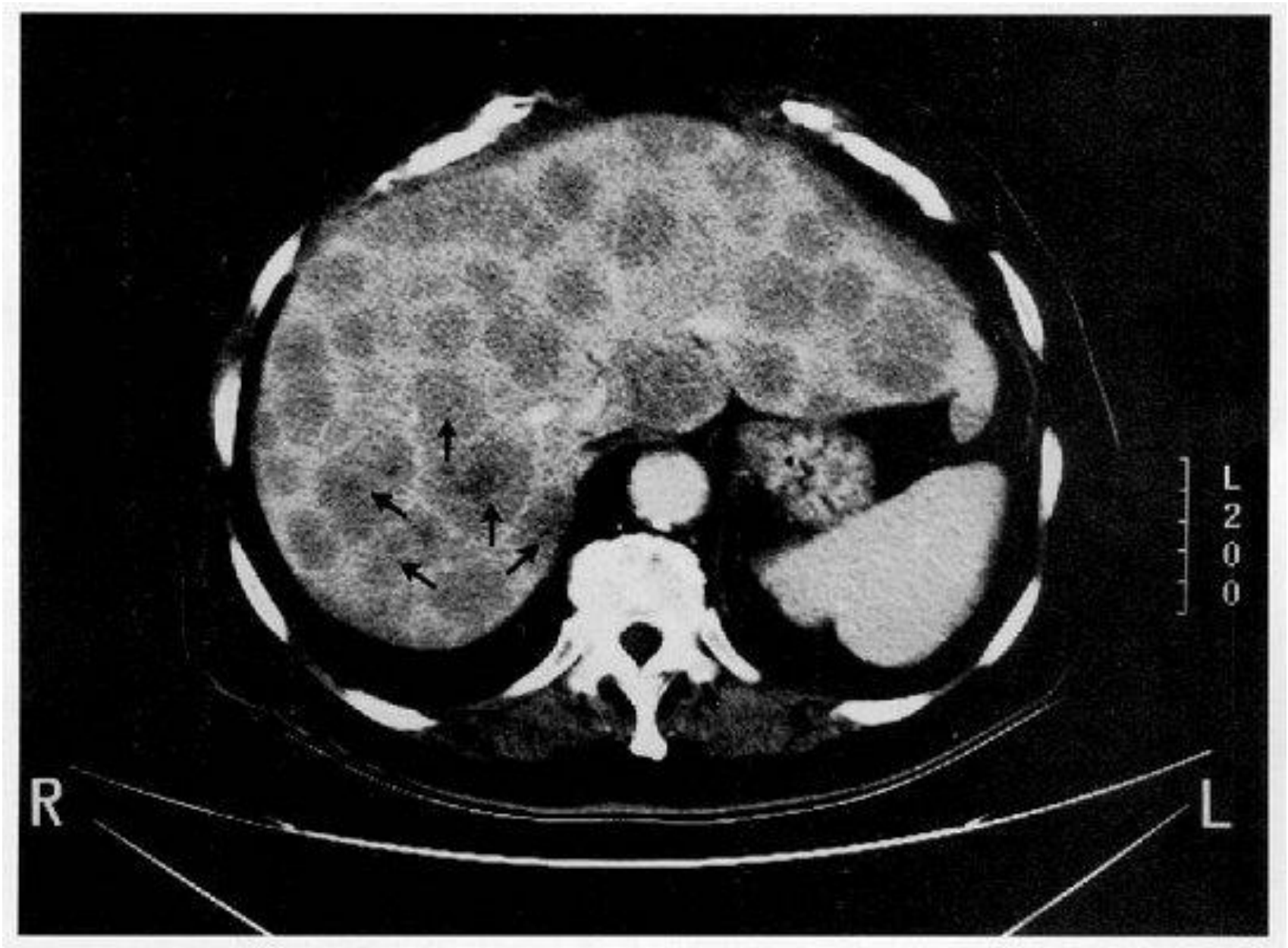
Radiotherapy

- Non-resectable tumors or in the case of recurrences.

Acute side effects	Late side effects
Nausea and vomiting	Fibrosis
Damage to the epithelial surfaces	hair loss
Mouth, throat and stomach sores	Dryness
Intestinal discomfort	Lymphedema
Swelling (edema or oedema)	Cancer
Infertility	Heart disease
	Cognitive decline
	Radiation proctitis
	Cumulative effects

- A 1 cm tumor contains 10^9 (1 billion) cells

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Systemic therapy (Chemotherapy)

- Chemotherapy: electively on cells in mitosis, and antimitotic agents finally aim to destroy cancer cells.

- These substances have the great advantage : perform a therapy of the potential or disseminated systemic disease.

- Relieves painful symptoms, prolongs life and/or even heals the disease.

Systemic therapy (Chemotherapy)

- Anticancer chemotherapy have been remarkably successful.
  – the perspective of a normal life for some patients with different types of metastasized tumors;
  – increased recovery rates, in the case of the use of an adjuvant in surgical therapy or radiotherapy;
  – total remission in more than 25% of the treated patients;
  – an increased rate of response, with a significant prolongation of life duration;
  – objective regression in 30–50% of patients treated for the first time with a chemical product.

Systemic therapy (Chemotherapy)

- Anticancer drugs particularly affect cells in active division and, in normal and neoplastic cells.

- The maximal therapeutic effect is obtained in the case of moderate drug toxicity

- The toxic effects of anticancer drugs :

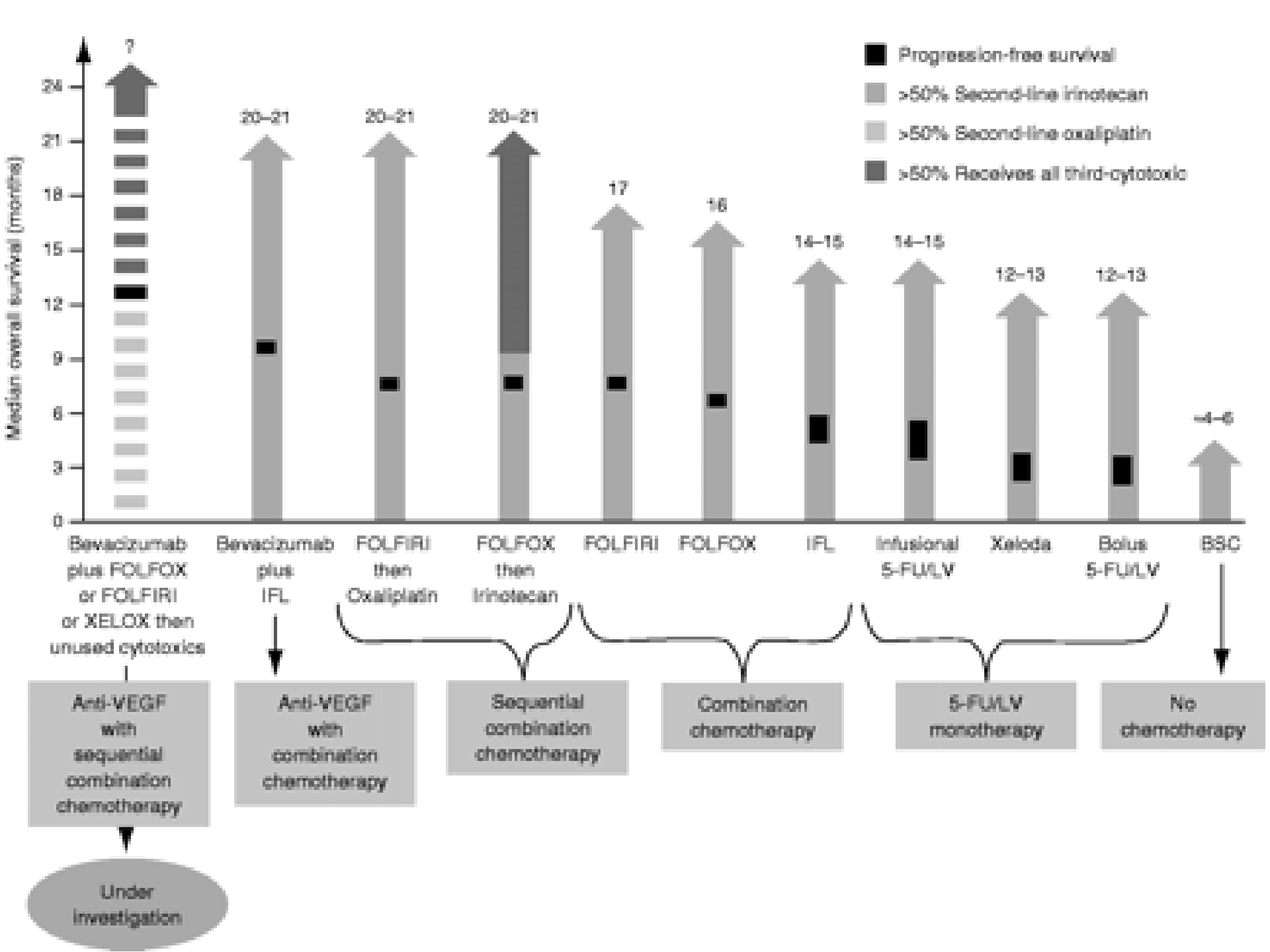
  a.peduncle cells of the bone marrow and lymphocytes;

  b.mucous cells of the gastrointestinal tract;

  c.liver and kidney cells;

  d.cells of the basal epithelial layer;

  e.nervous system cells.


Progression-free survival
>50% Second-line irinotecan
>50% Second-line oxaliplatin
>50% Receives all third-cytotoxic
Median overall survival (months)
0
3
6
9
12
15
18
21
24
?
20–21
20–21
20–21
17
16
14–15
14–15
12–13
12–13
~4–6
Bevacizumab plus FOLFOX or FOLFIRI or XELOX then unused cytotoxics
Bevacizumab plus IFL
FOLFIRI then Oxaliplatin
FOLFOX then Irinotecan
FOLFIRI
FOLFOX
IFL
Infusional 5-FU/LV
Xeloda
Bolus 5-FU/LV
BSC
Anti-VEGF with sequential combination chemotherapy
Anti-VEGF with combination chemotherapy
Sequential combination chemotherapy
Combination chemotherapy
5-FU/LV monotherapy
No chemotherapy
Under investigation

Systemic therapy (Chemotherapy)

- The usual toxic hematological signs include: thrombocytopenia, neutropenia, reticulocytopenia; anemia and lymphopenia.

- The effects of toxicity on the gastrointestinal tract are anorexia, nausea, vomiting, diarrhea, stomatitis and intestinal mucosal ulcers; hair loss, especially in dogs with curly hair.

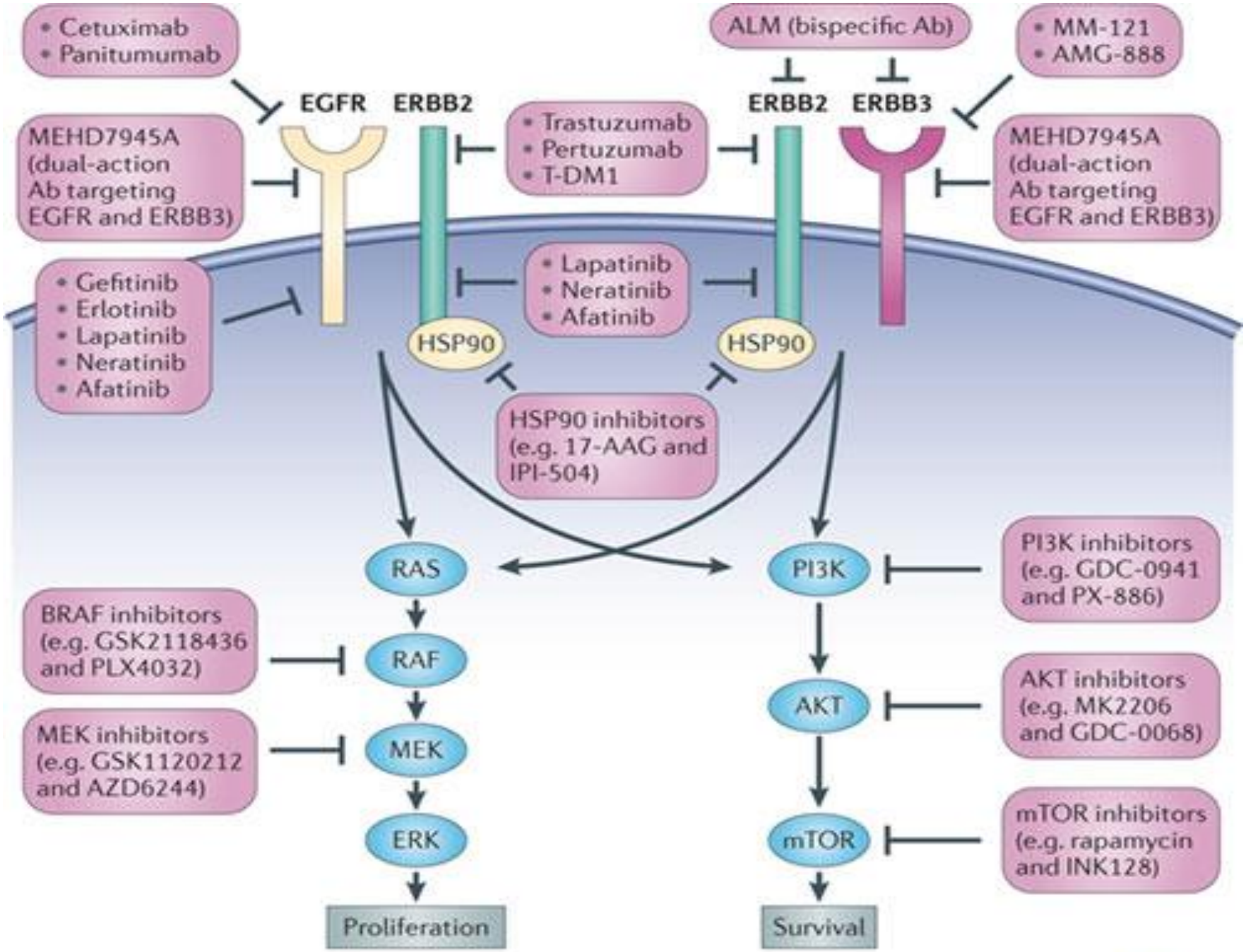
- Anticancer agents act by disturbing cell multiplication or normal functioning, DNA synthesis or chromosomal migration, and by blocking or changing RNA and protein metabolism.

Target therapy

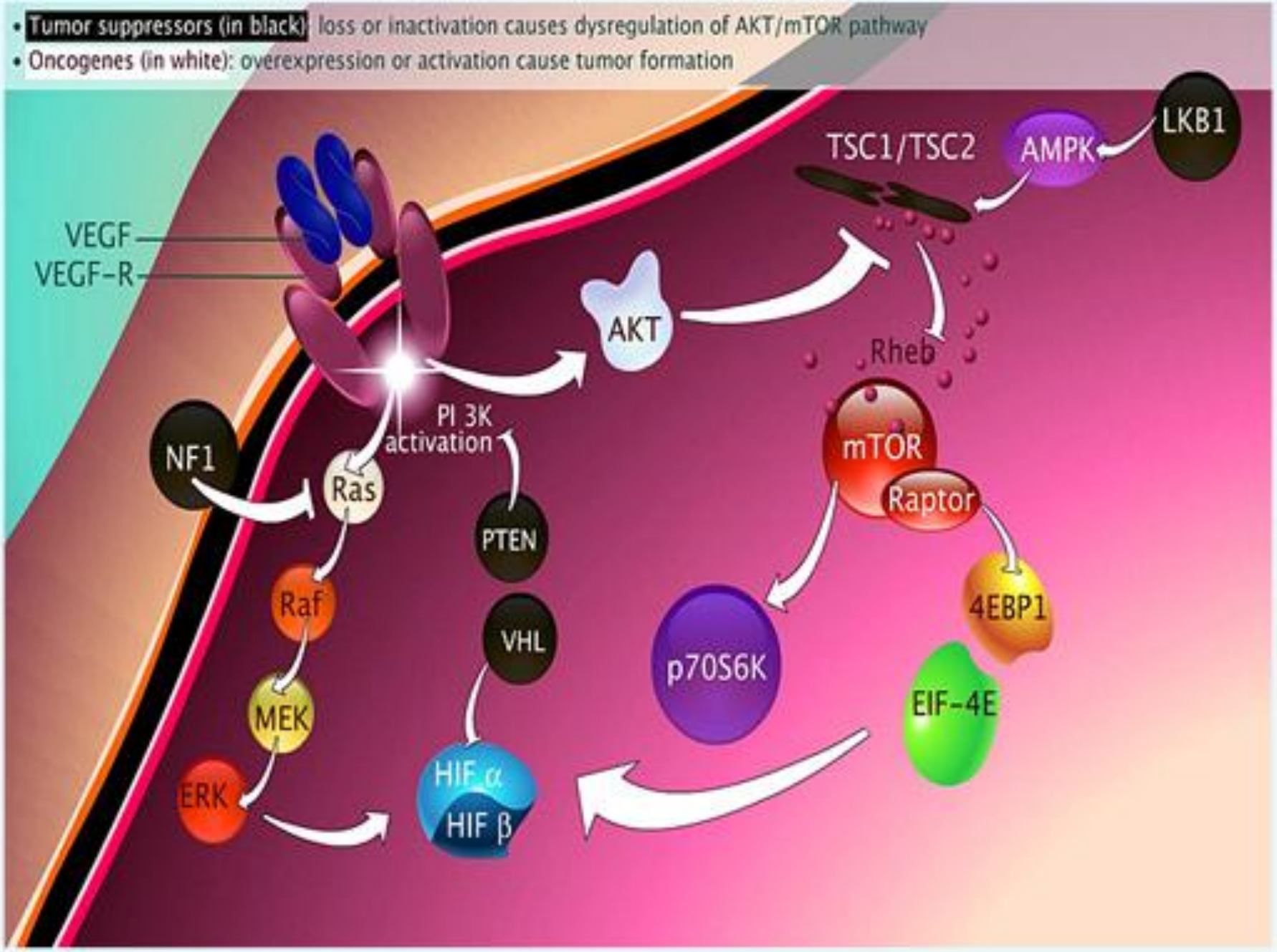
- Late 1990s: nearly all drugs used in cancer treatment worked by killing cells.

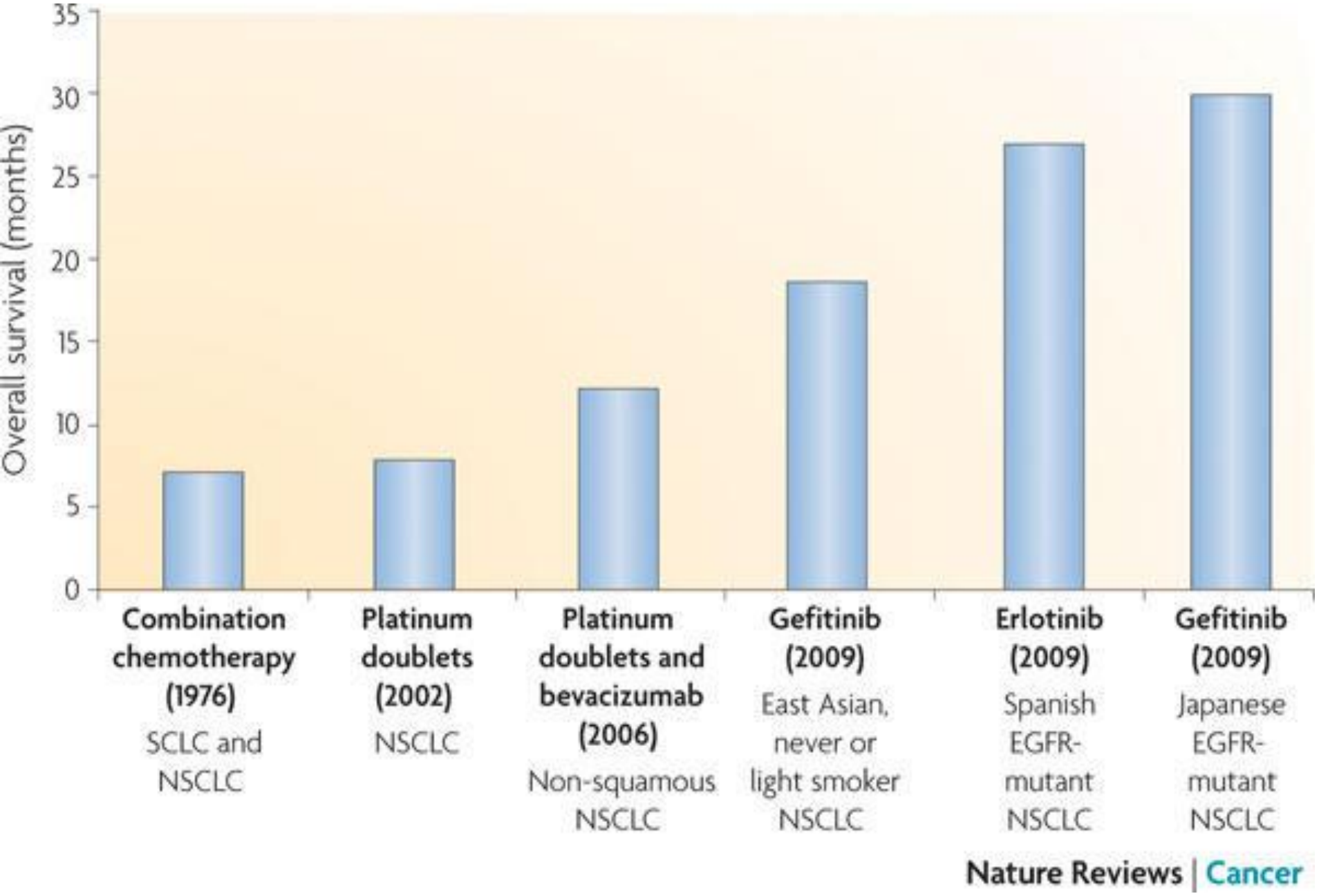
- These chemotherapy drugs also killed some normal cells but had a greater effect on cancer cells.

- Targeted therapies work by influencing the processes that control growth, division, and spread of cancer cells, as well as the signals that cause cancer cells to die naturally.



Nature Reviews | Cancer


• Tumor suppressors (in black): loss or inactivation causes dysregulation of AKT/mTOR pathway
• Oncogenes (in white): overexpression or activation cause tumor formation
LKB1
AMPK
TSC1/TSC2
VEGF
VEGF-R
AKT
Rheb
PI 3K
activation
NF1
Ras
PTEN
mTOR
Raptor
Raf
VHL
4EBP1
p70S6K
MEK
EIF-4E
ERK
HIF α
HIF β


Overall survival (months)
35
30
25
20
15
10
5
0
Combination chemotherapy (1976)
SCLC and NSCLC
Platinum doublets (2002)
NSCLC
Platinum doublets and bevacizumab (2006)
Non-squamous NSCLC
Gefitinib (2009)
East Asian, never or light smoker NSCLC
Erlotinib (2009)
Spanish EGFR-mutant NSCLC
Gefitinib (2009)
Japanese EGFR-mutant NSCLC
Nature Reviews | Cancer

老 藥 新 用

Her2/neu

- HER2 in the development of numerous types of human cancer.
- HER2 overexpression and/or amplification have been detected in 10%-34% of invasive breast cancers and correlate with the clinical outcome.
- HER2 overexpression and/or amplification have also been observed in colon, bladder, ovarian, endometrial, lung, uterine cervix, head and neck, esophageal, and gastric carcinomas.

Colon cancer (Her2: 0-83%)

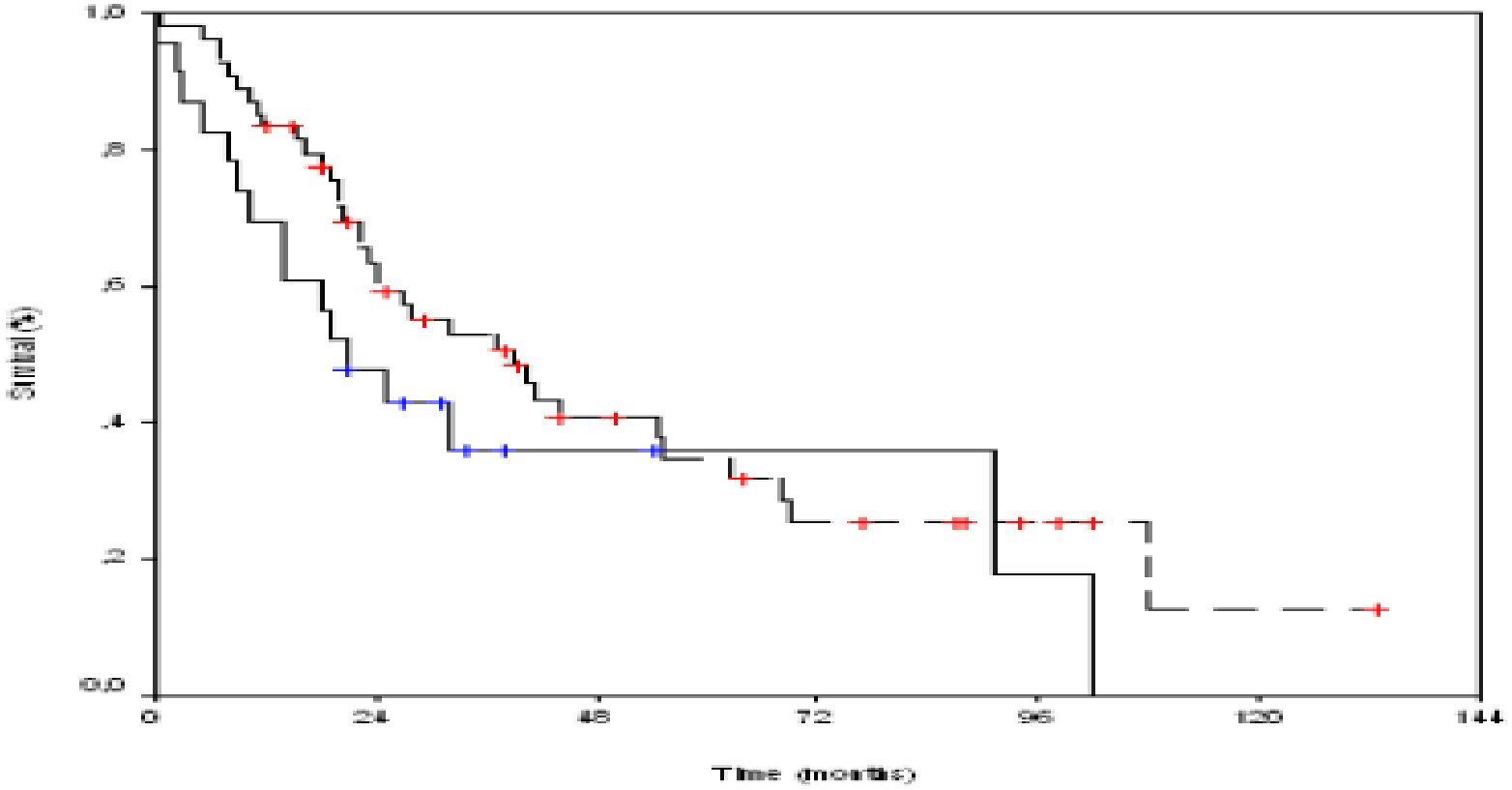


Figure 1

Survival according to Her-2/neu status. ---- HER-2/Neu neg. ——— HER-2/Neu pos.

BMC Cancer 2006, 6:123

Urothelial carcinoma (Her2: 30-40%)

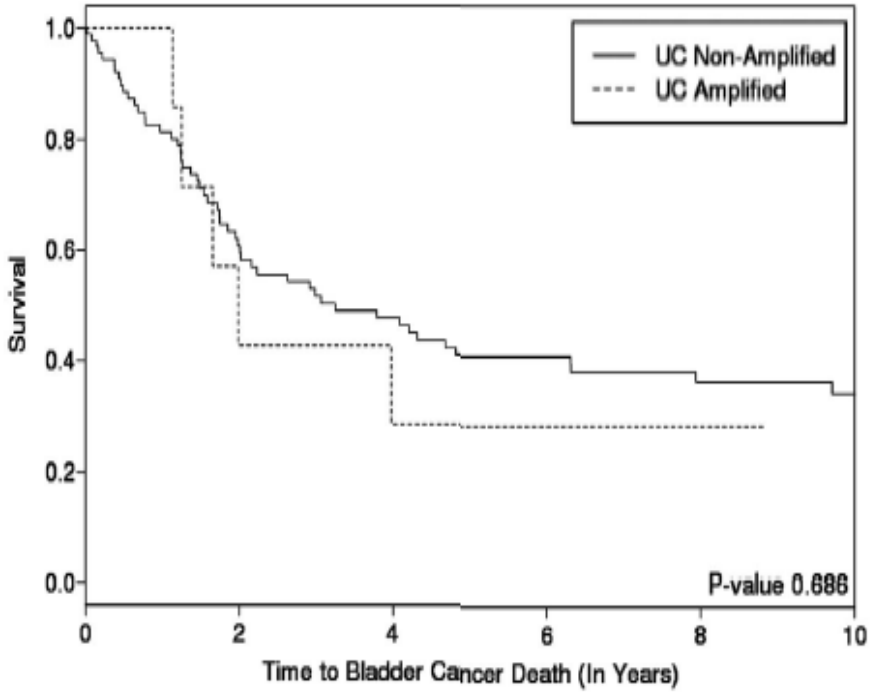
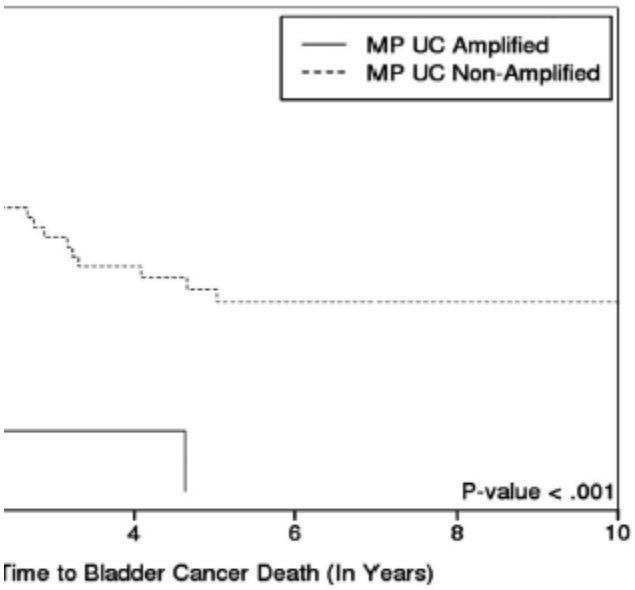


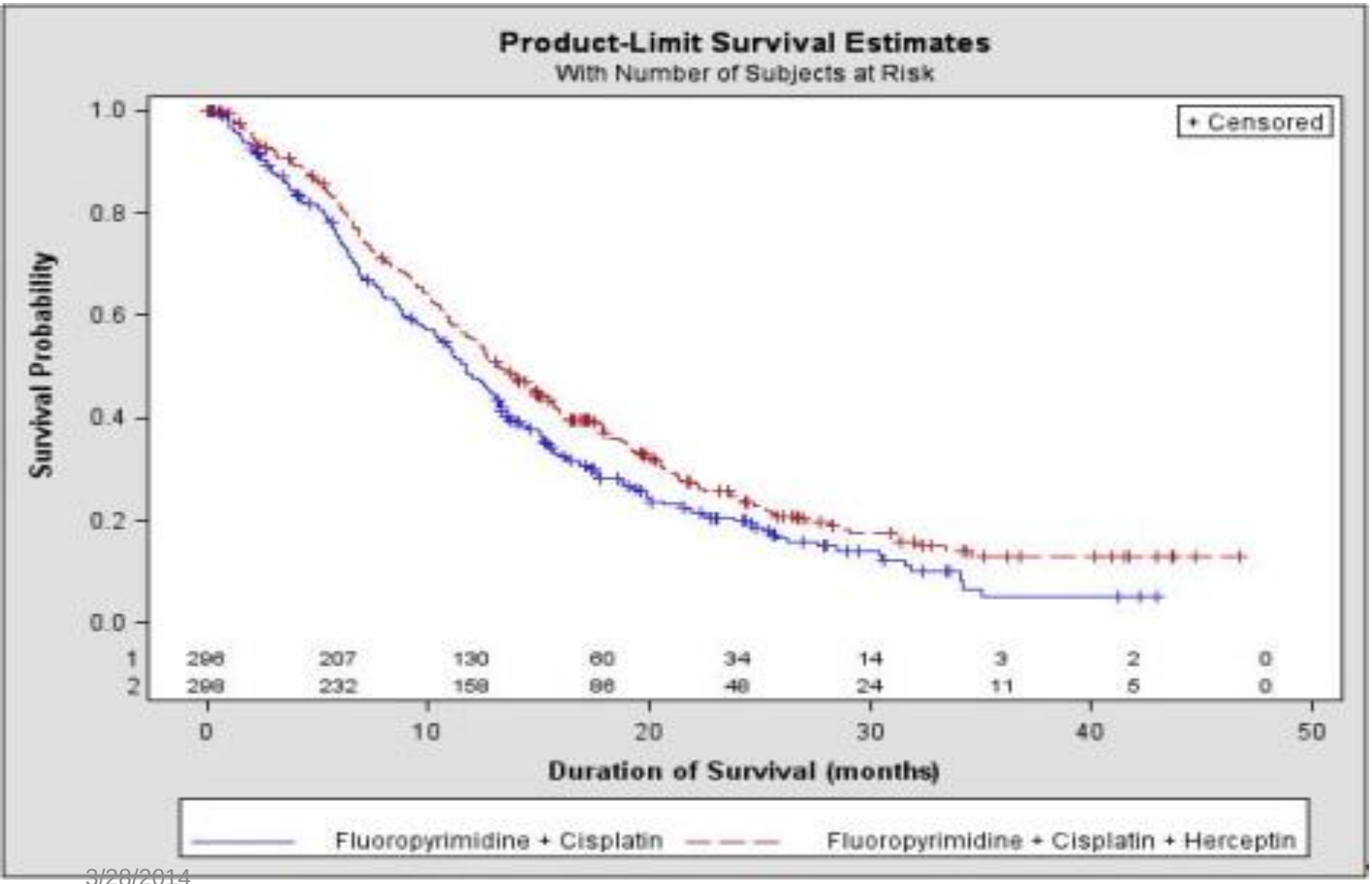
Figure 3 Cancer-specific survival of patients with *ERBB2*-amplified typical urothelial carcinoma (UC) compared to patients with non-amplified typical urothelial carcinoma.



ific survival of patients with *ERBB2*-amplirothelial carcinoma (MP UC) compared to plified micropapillary carcinoma.

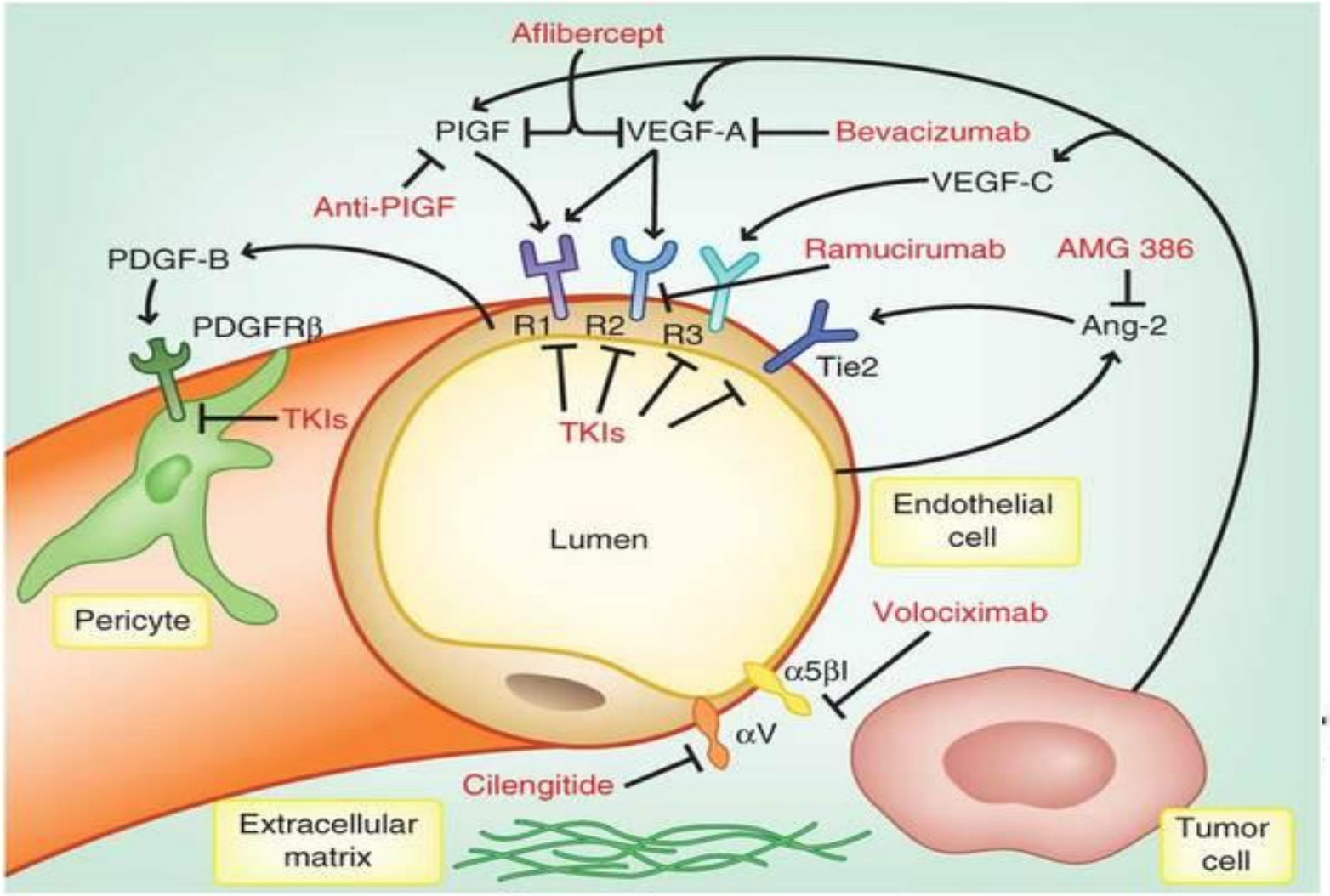
Modern Pathology (2013), 1–7

Gastric cancer (Her2: 10-34%)



Lancet 2010; 376: 687–97

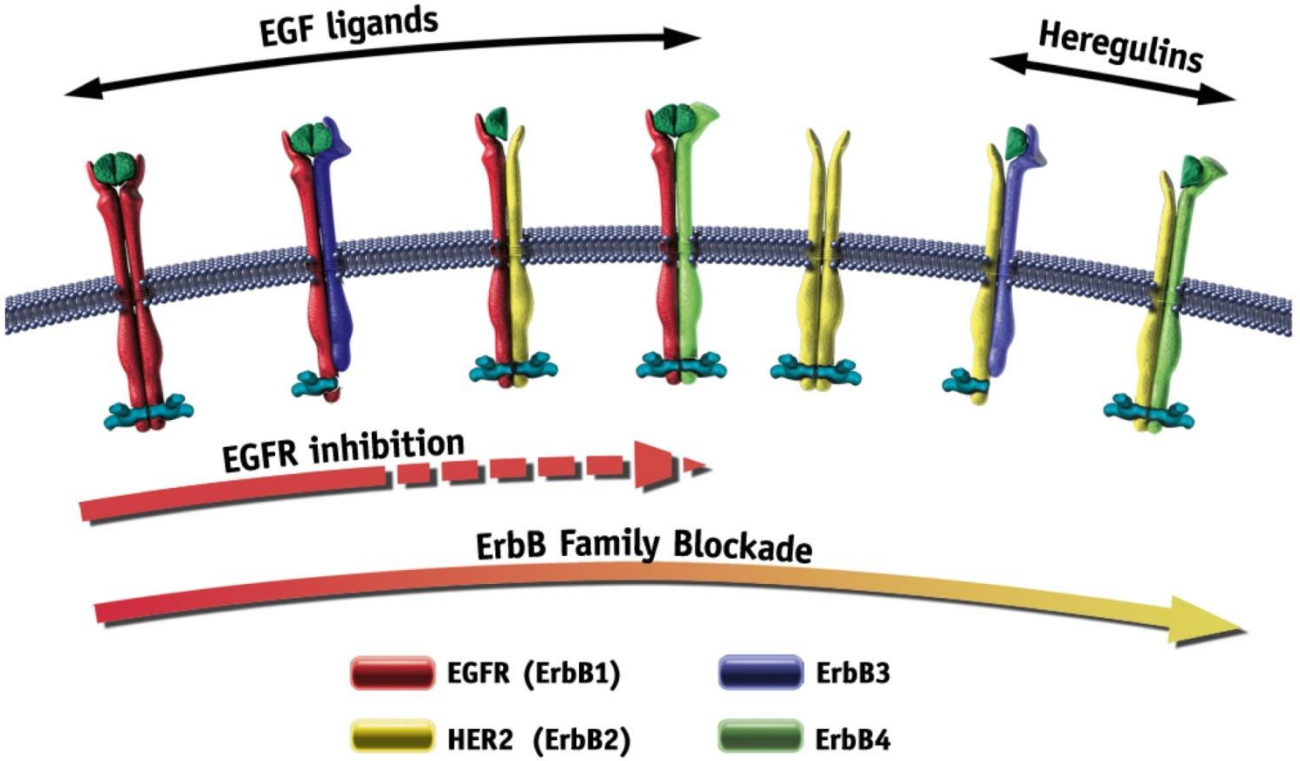
Sutent in Pancreatic neuroendocrine tumor (pNET)



http://www.drugs.com/pro/sutent.html

抗 藥 性

Afatinib: an irreversible ErbB Family Blocker



- Afatinib is an orally available, irreversible ErbB Family Blocker, with high efficacy potential
  - Inhibition of ErbB Family receptor heterodimerization
  - *In vitro* activity against EGFR-resistant T790M mutation

Li D, et al. *Oncogene* 2008;**27**:4702–11.

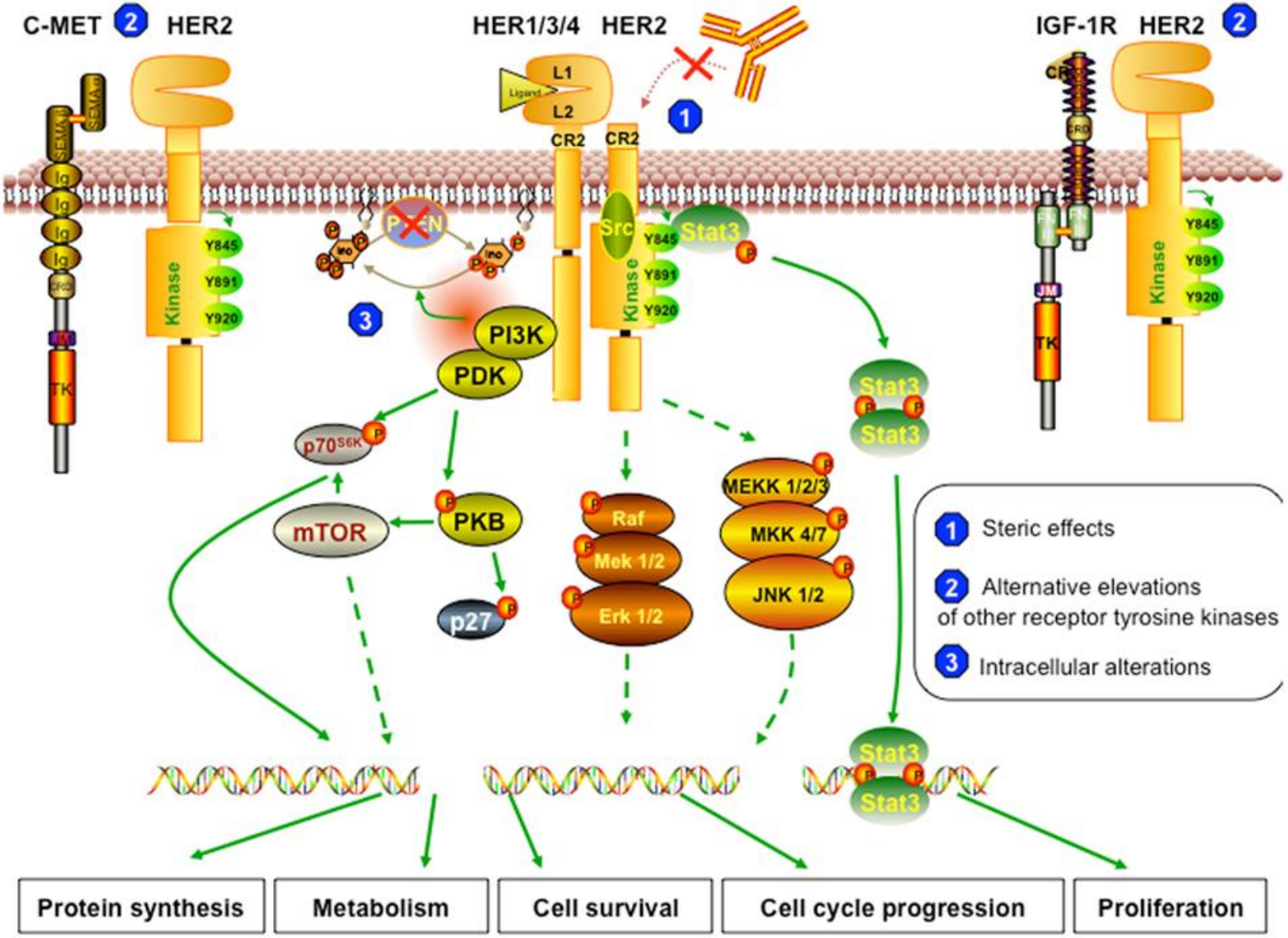

C-MET
2
HER2
HER1/3/4
HER2
IGF-1R
HER2
2
L1
L2
Ligand
CR2
CR2
1
Kinase
Y845
Y891
Y920
TK
JM
PTEN
3
PI3K
PDK
Src
Stat3
Stat3
Stat3
p70S6K
mTOR
PKB
p27
Raf
Mek 1/2
Erk 1/2
MEKK 1/2/3
MKK 4/7
JNK 1/2
1 Steric effects
2 Alternative elevations of other receptor tyrosine kinases
3 Intracellular alterations
Protein synthesis
Metabolism
Cell survival
Cell cycle progression
Proliferation

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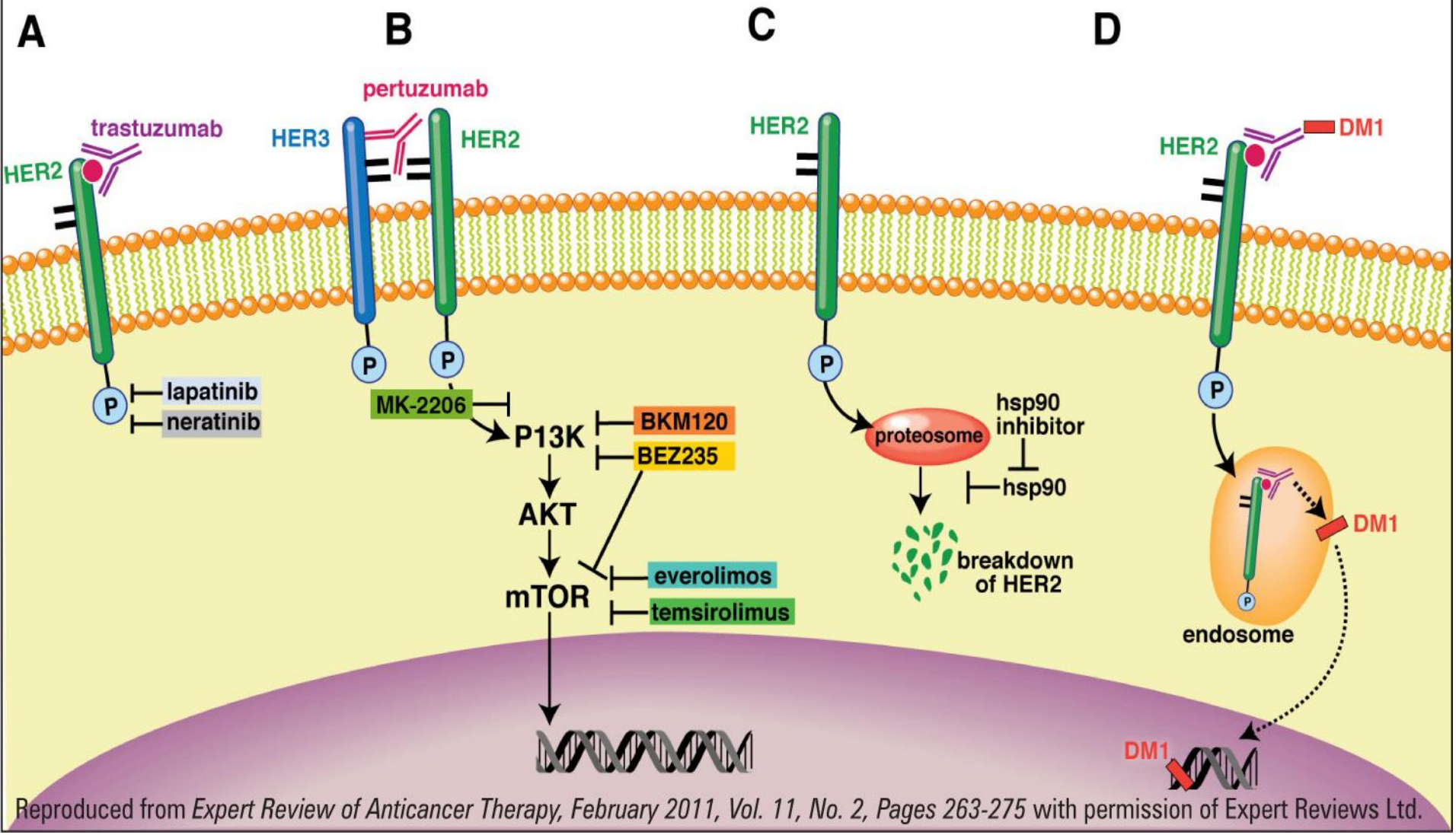
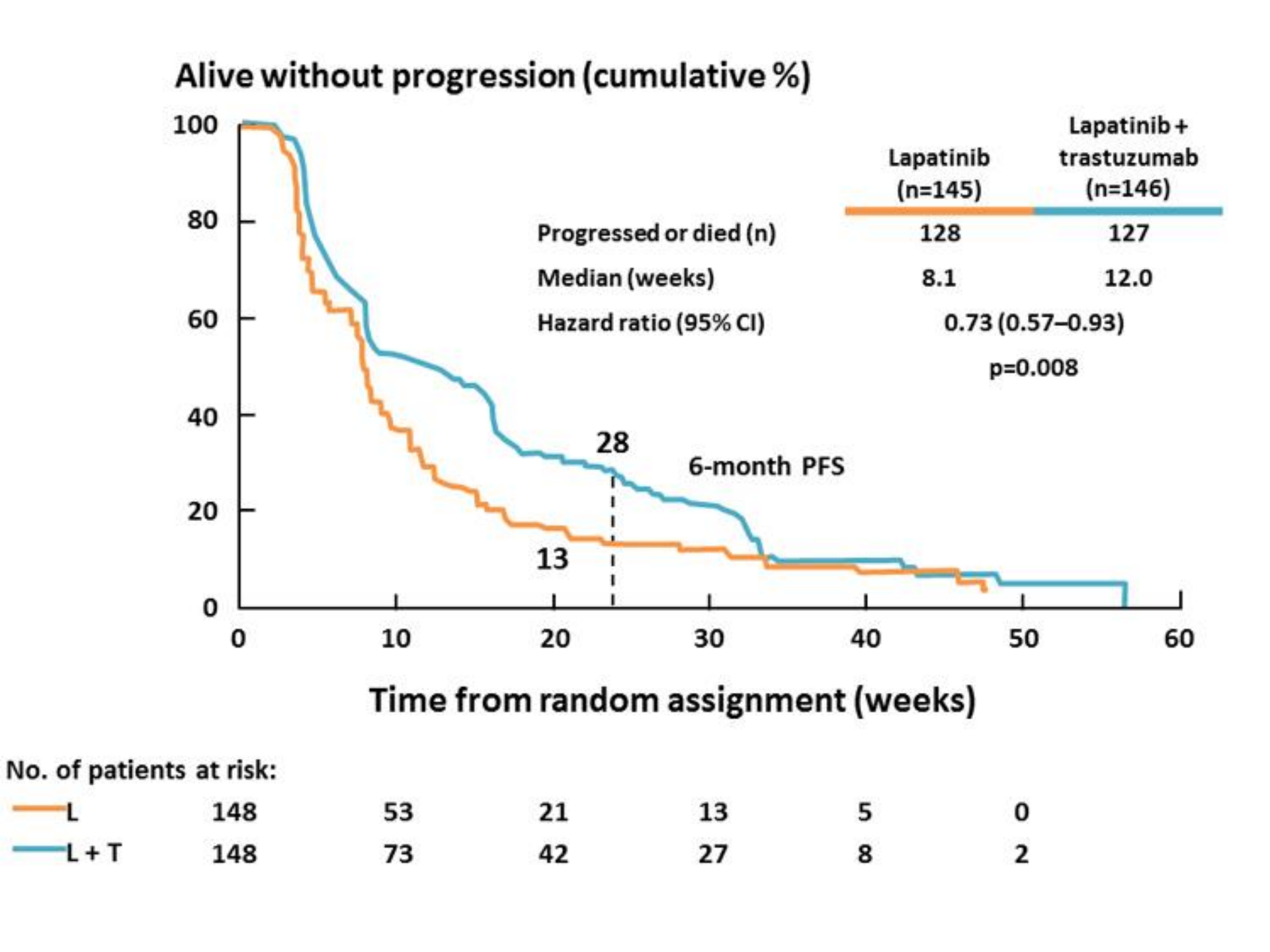
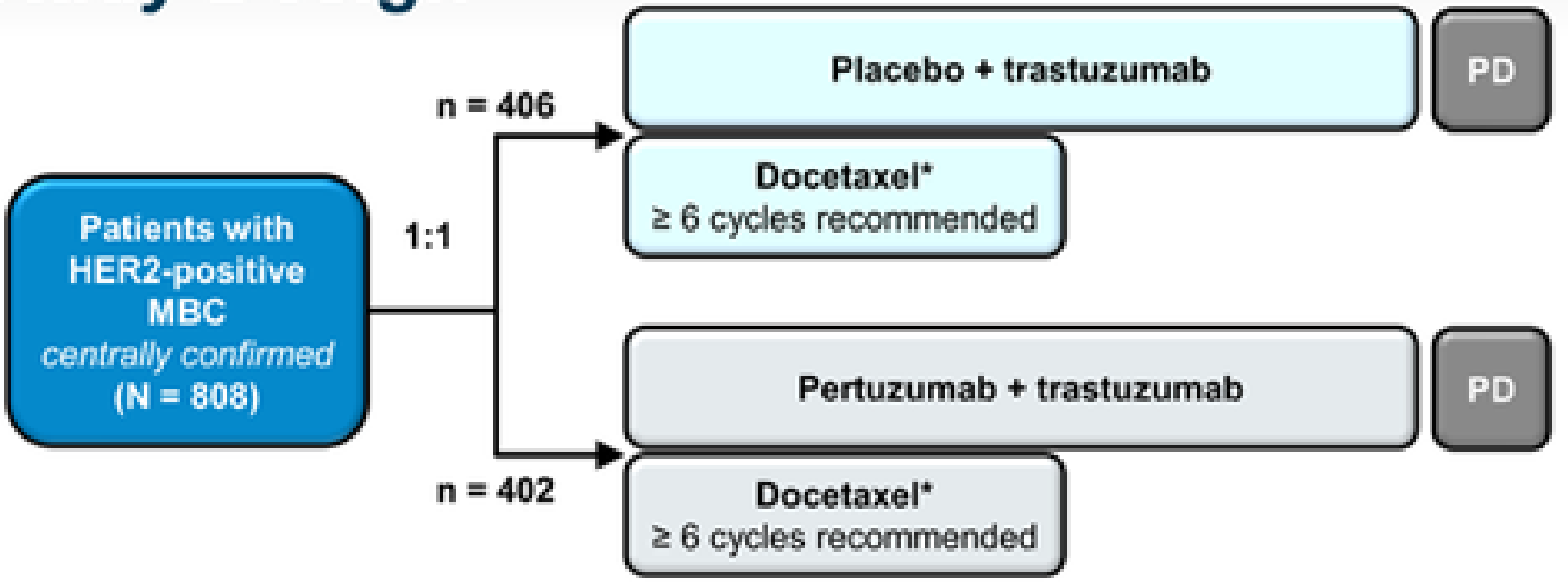
Fig. 1.

HER2 Pathway and Targets




Alive without progression (cumulative %)
100
80
60
40
20
0
0
10
20
30
40
50
60
Time from random assignment (weeks)
Lapatinib (n=145)
Lapatinib + trastuzumab (n=146)
Progressed or died (n)
128
127
Median (weeks)
8.1
12.0
Hazard ratio (95% CI)
0.73 (0.57–0.93)
p=0.008
28
6-month PFS
13
No. of patients at risk:
L
148
53
21
13
5
0
L + T
148
73
42
27
8
2

CLEOPATRA
Study Design



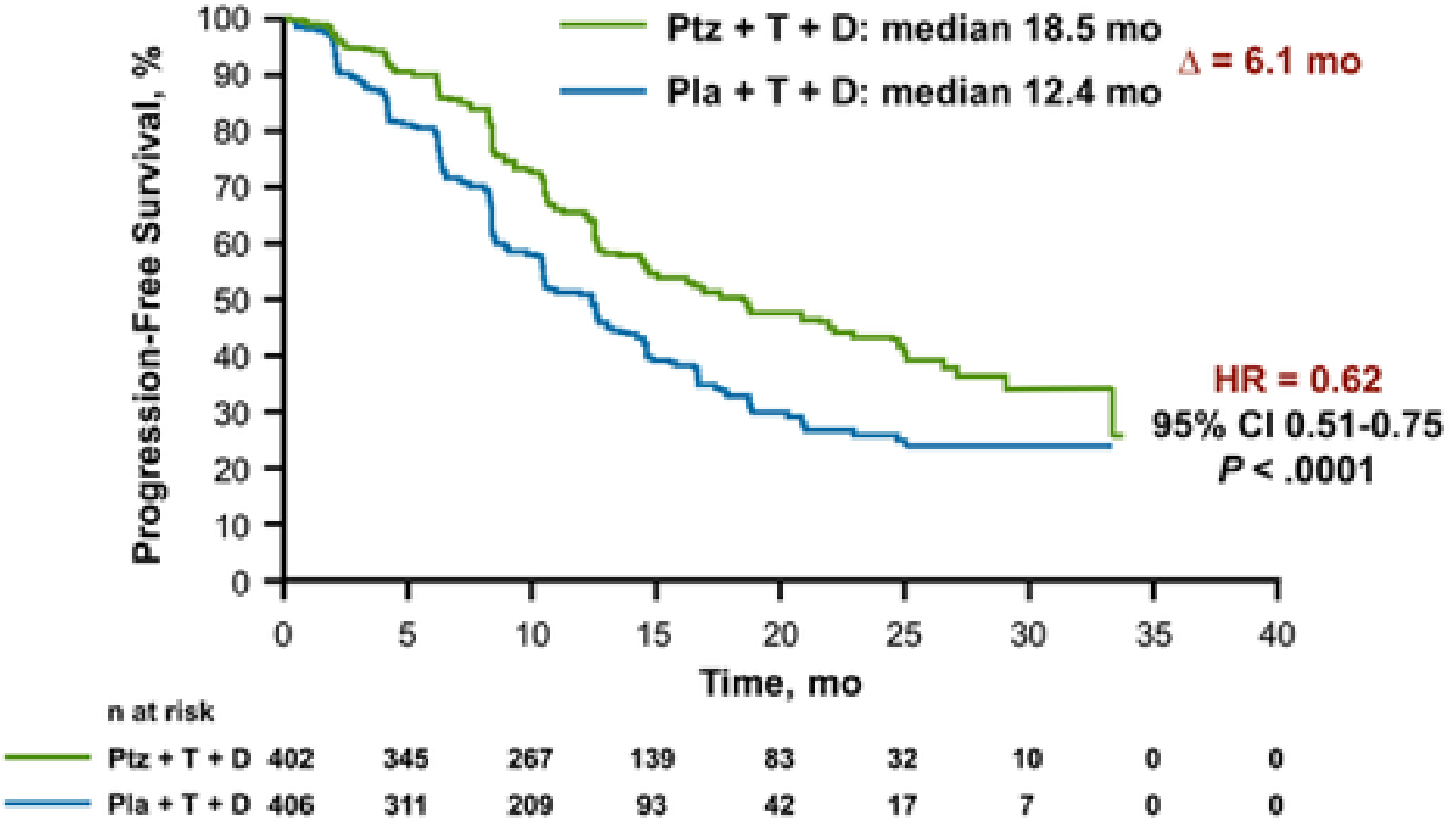
- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated

* < 6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion

Baselga J, et al.[4]

CLEOPATRA

Primary End Point

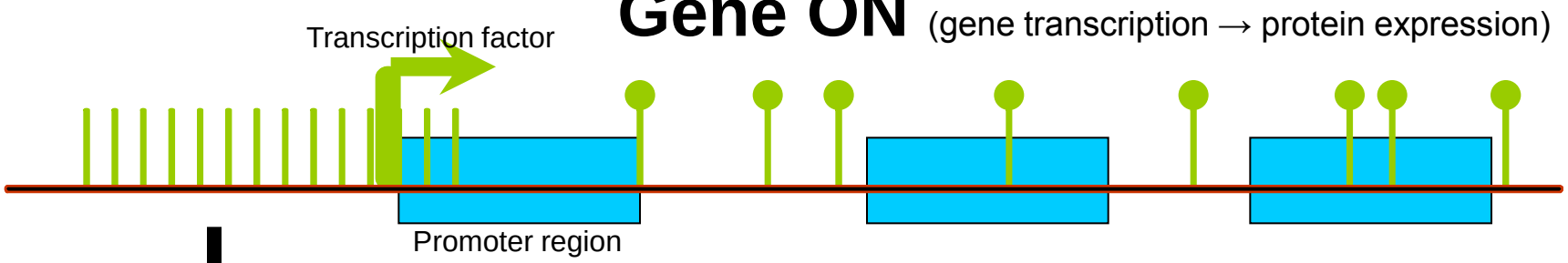


Baselga J, et al.[4,6]

Epigeneic control

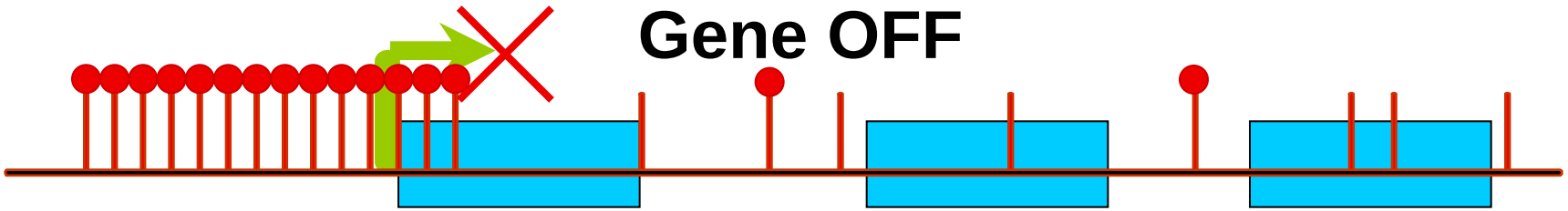
DNA methylation silences genes in cancer including tumor-suppressor genes

Normal tissue



Many hundreds of CpG Islands become aberrantly methylated in all types of cancer cells

Tumour



Esteller M. N Engl J Med 2008;358:1148–59