New Developments in Cancer Treatment

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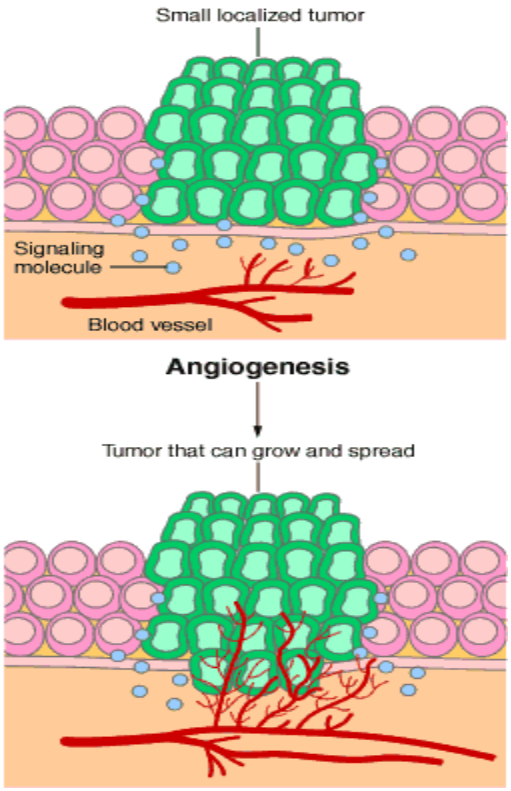
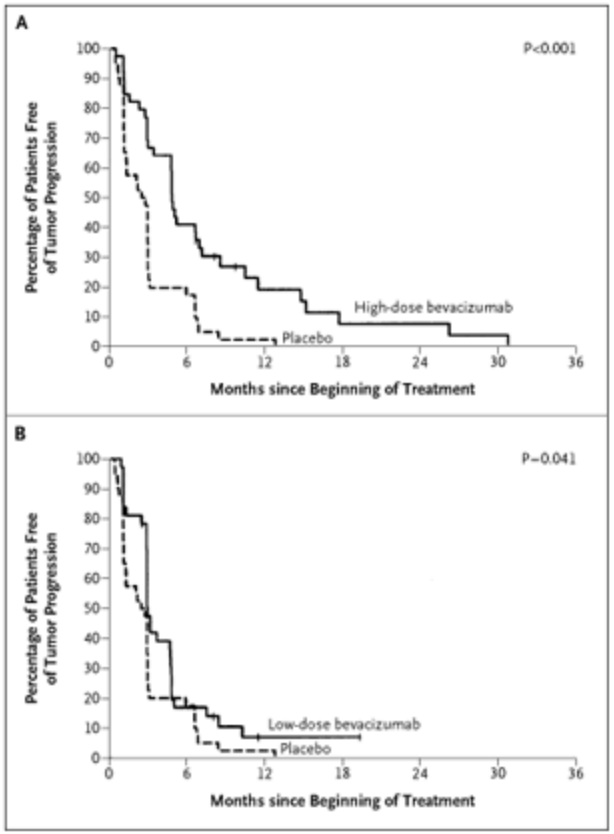
Treatment Outline

- Angiogenesis inhibition
- Targeted therapy
- Immunotherapy
- Personalization of therapy
- Genomics and cancer
- Stem cells and cancer

Angiogenesis in tumors



Bevacizumab in Renal Cancer



- Bevacizumab, a neutralizing antibody against vascular endothelial growth factor
- A randomized, double-blind, phase 2 trial was conducted comparing placebo with bevacizumab at doses of 3 and 10 mg/ kg, given q2 weeks
- After 116 patients randomly assigned to treatment groups, the trial was stopped early

Yang et al, NEJM 2003

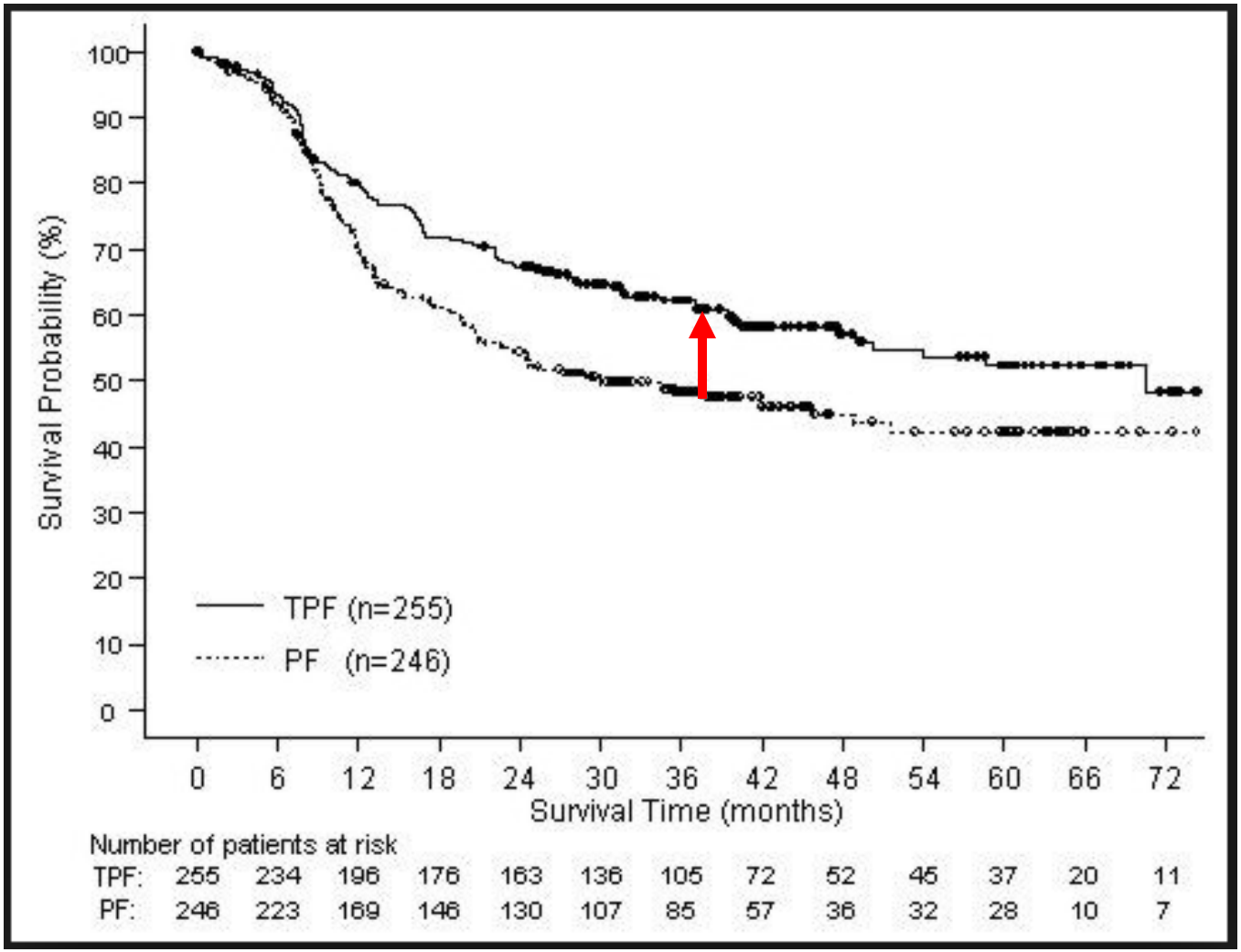
Bevacizumab

- Improve survival in:
  - Colon cancer
  - Lung cancer
  - Renal cancer

Many other angiogenesis inhibitors are in the clinic today

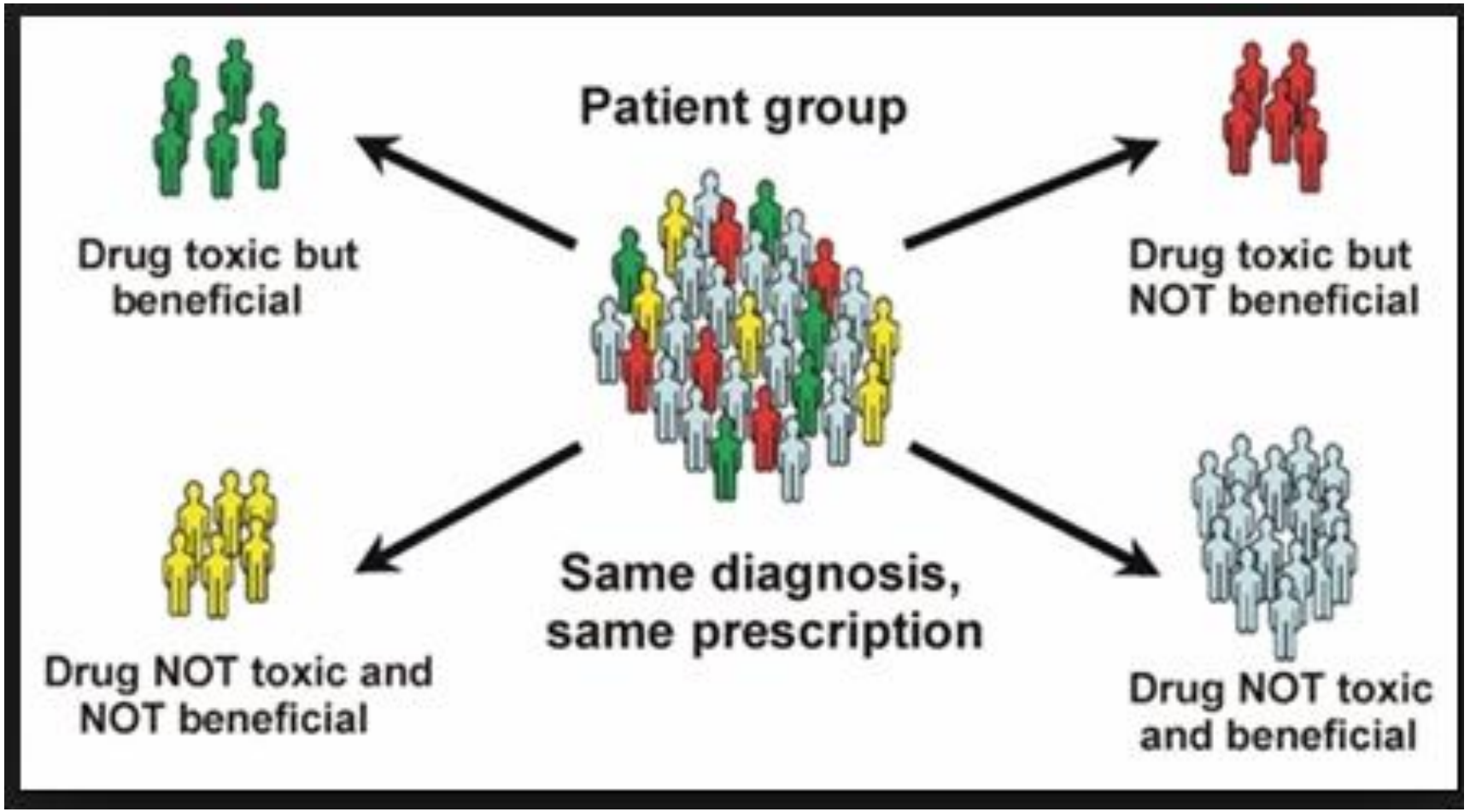
Advances can come in two flavors

Improve the efficacy of treatments



Advances can come in two flavors

Personalized treatment



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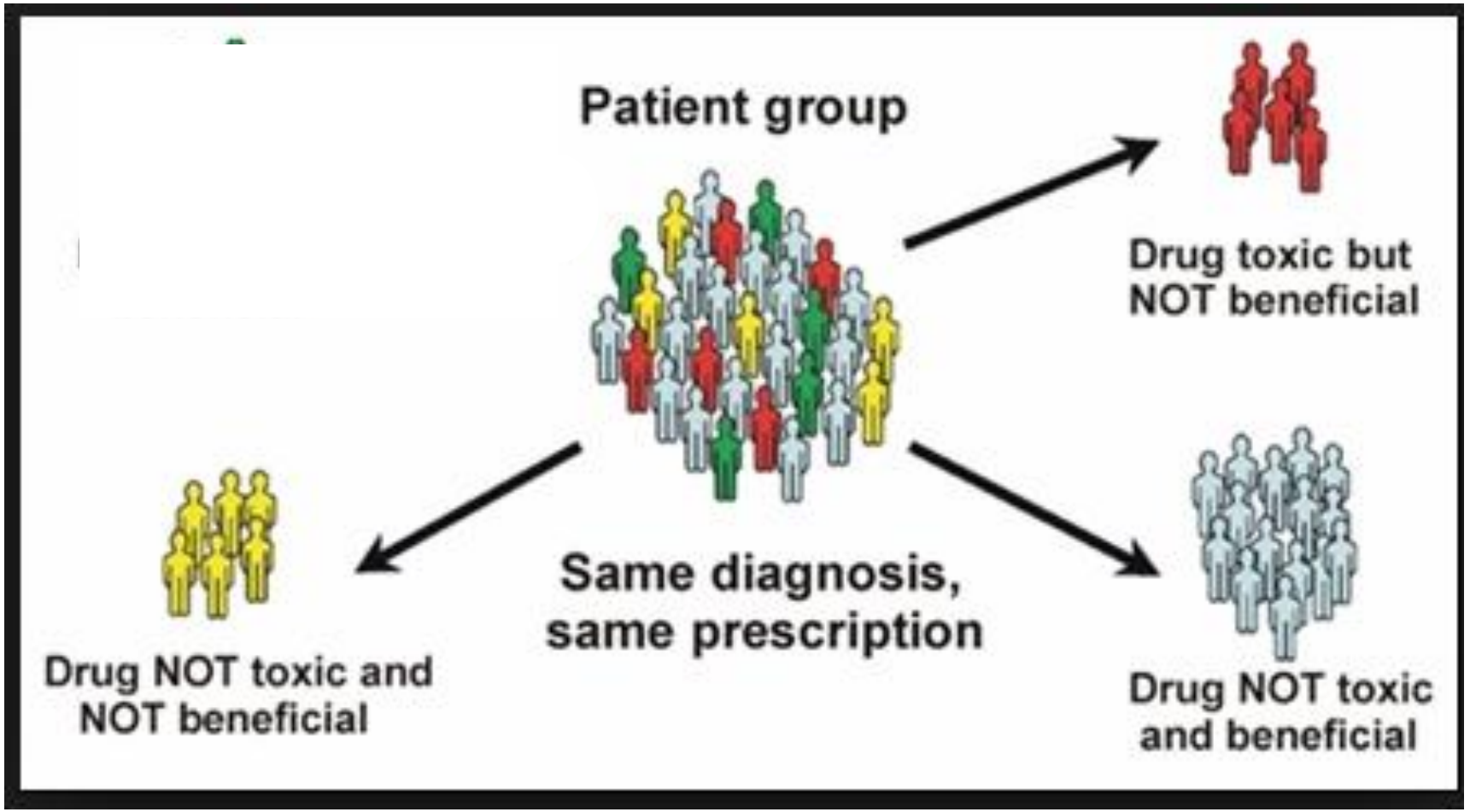

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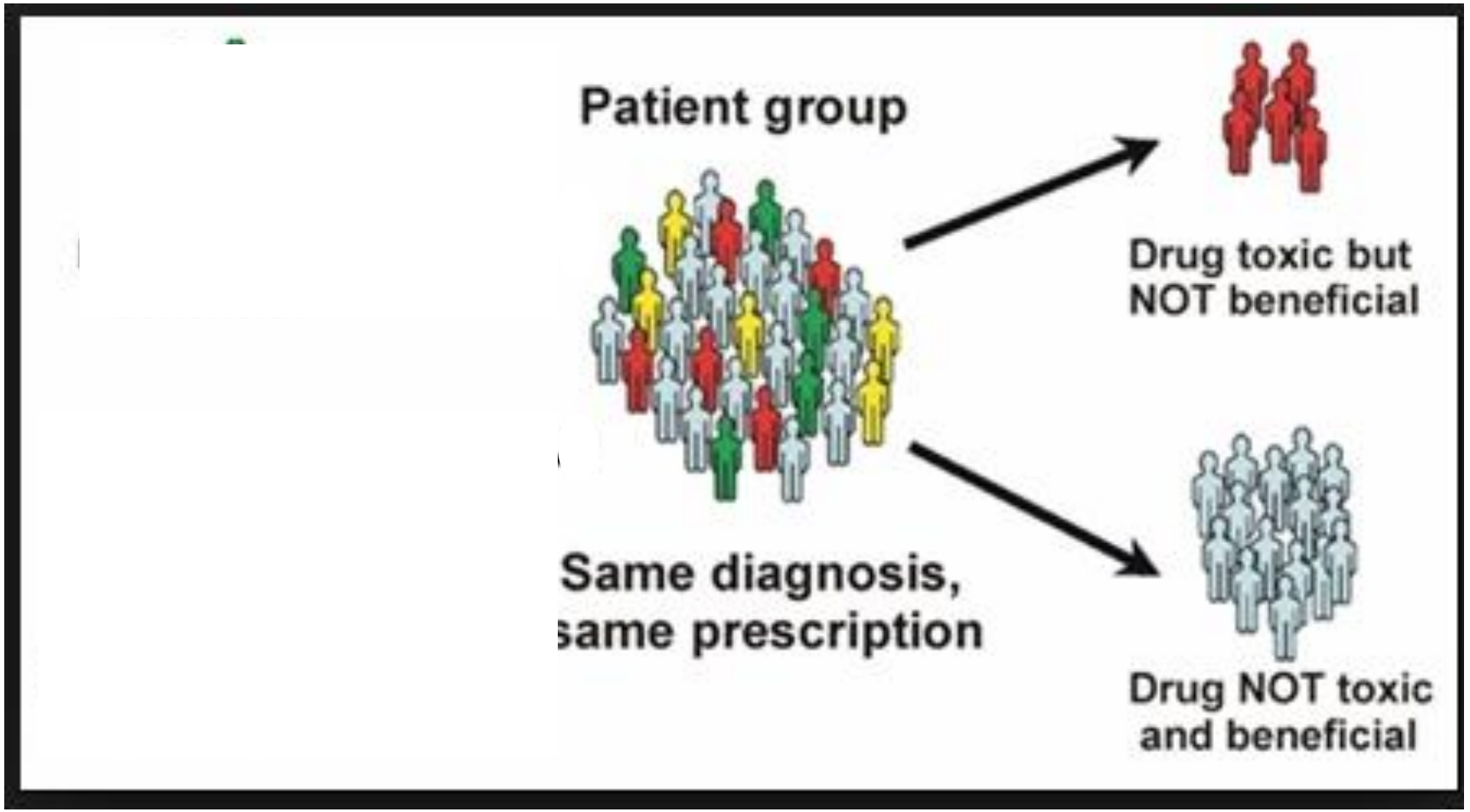

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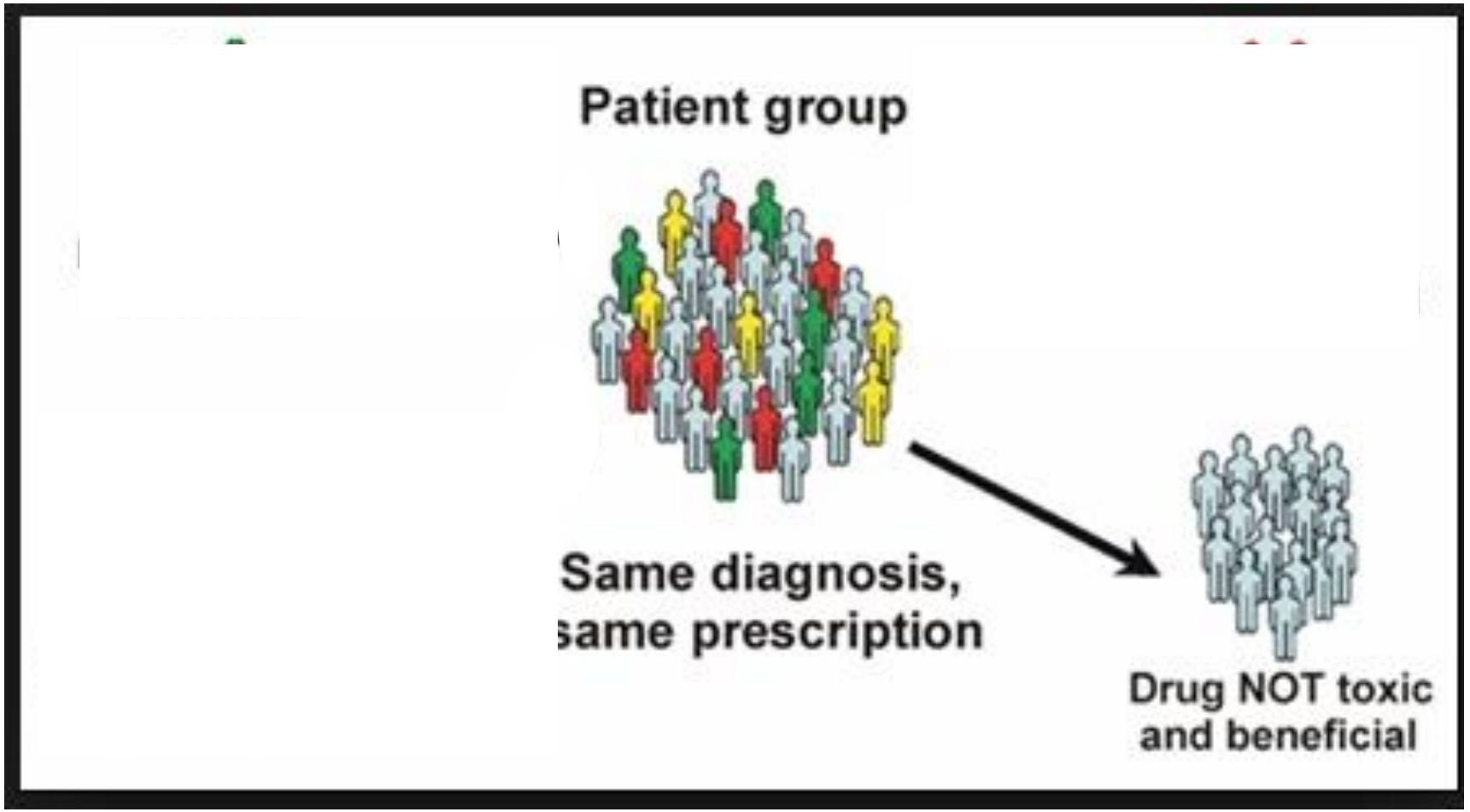
Personalized treatment



Targeted therapy in Lung cancer

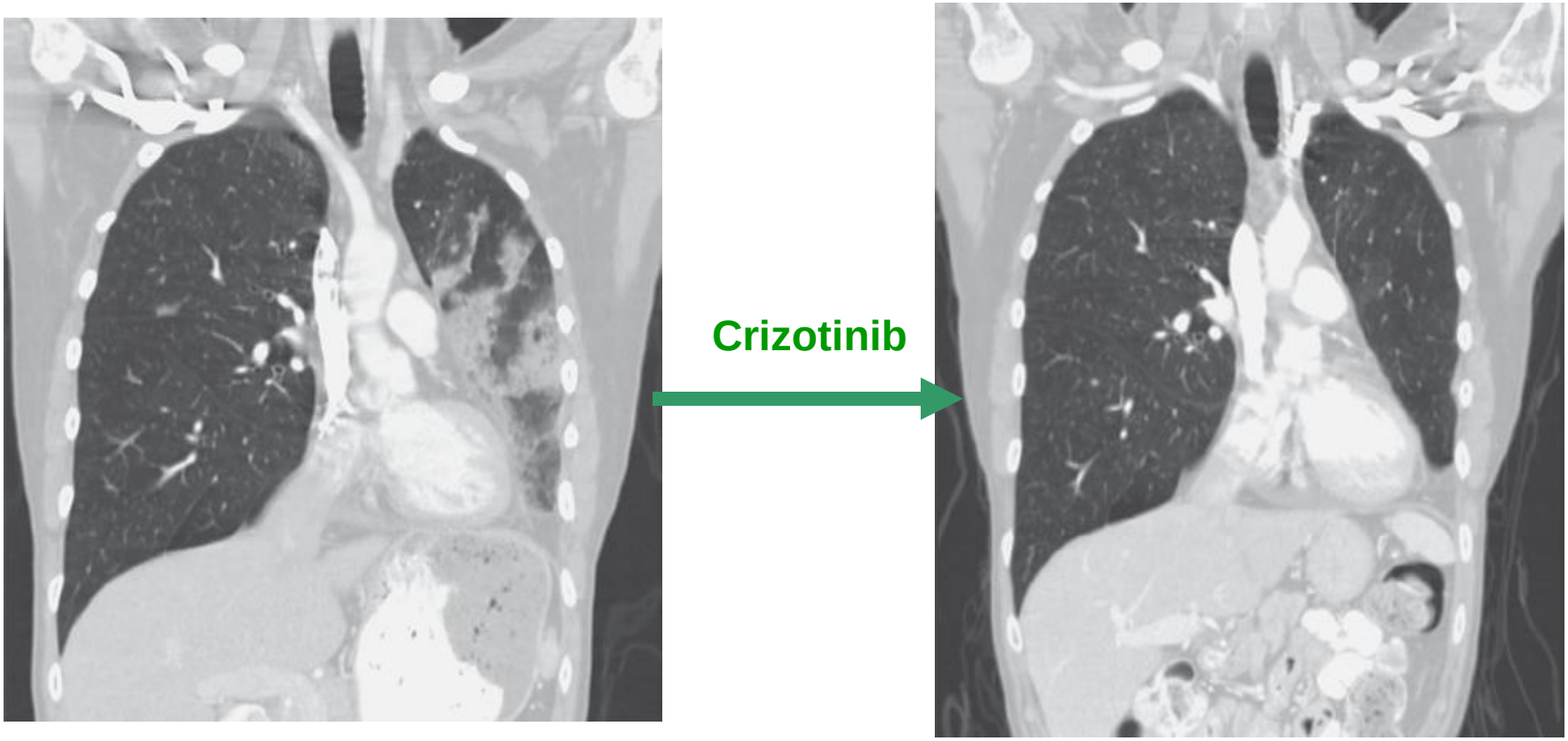
10% of patients

- Patients with NSCLC expressing mutated epidermal growth factor receptors (EGFRs) were randomly assigned to receive either the EGFR kinase inhibitor gefitinib or standard chemotherapy.
- The gefitinib group had a higher response rate (73.7%, vs. 30.7%) and significantly longer median survival (30 vs. 23 months). (NEJM June 2010)

~5% of patients

- A small group of patients with NSCLC have genetic lesions that activate anaplastic lymphoma kinase (ALK).
- Crizotinib, an oral ALK kinase inhibitor, produced a 57% response rate in this subgroup, (NEJM Oct 2010)

CT scan in a representative ALK +ve patient at baseline and after two cycles of therapy.



Examples of mutations guiding therapy in the clinic today

- **+ve**
- EGFR mutations in lung cancer- erlotinib
- B-raf mutations in melanoma- vemurafenib
  BRACA mutations in breast cancer- PARP inhibitors such as olaparib
- Alk translocation in lung cancer/lymphoma- crizotinib
- **-ve**
- K-ras mutations in colon cancer- cetuximab

Immunotherapy

- Use the immune system to prevent or treat neoplasms.
- Goal is to enhance the bodies immune response against weakly immunogenic tumors

Antibodies recognizing tumor associated antigens

3) Treatment of Cancer

- Cancer cells carry specific tumour-associated antigens (TAA) on their plasma membrane.
- Monoclonal anti-TAA antibodies have been produced.

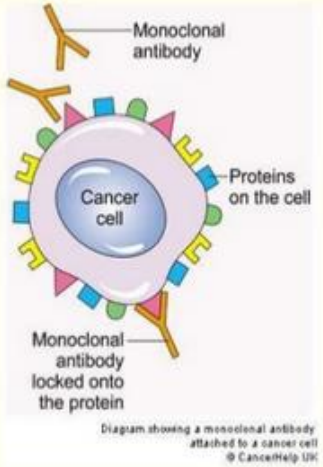
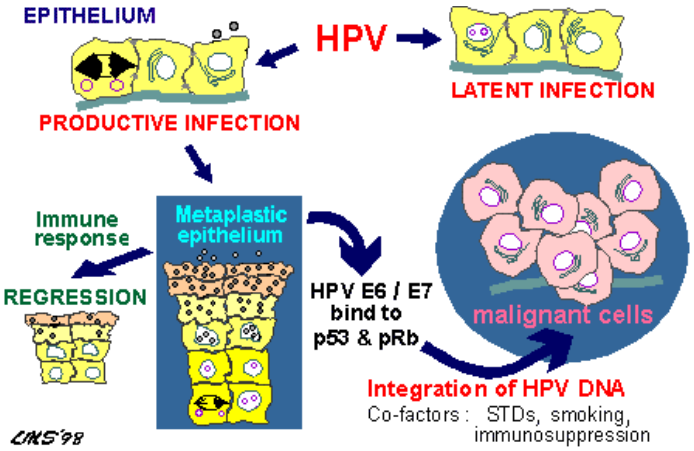


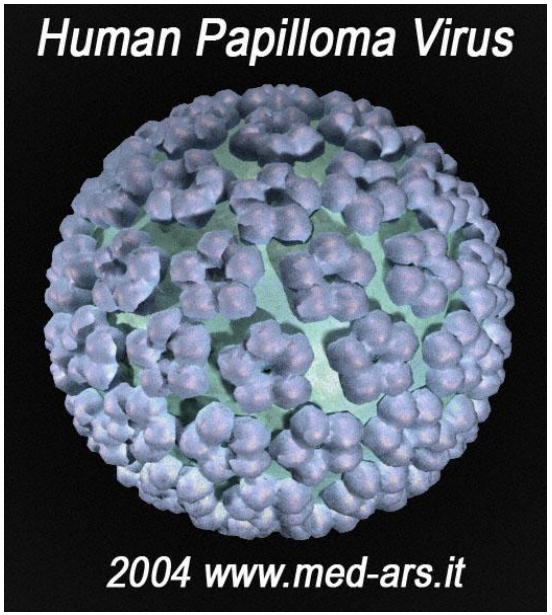
Diagram showing a monoclonal antibody attached to a cancer cell
© CancerHelp UK

- *Herceptin* Breast cancer, useful in ~30% of patients
- *Rituximab* B cell lymphoma, used as a single agent or in combination with chemotherapy.
- *Zevalin* is a radio-labelled conjugates of CD20 useful in NHL
- *Brentuximab* used to treat relapsed Hodgkin's lymphoma

Vaccine as Primary Prevention

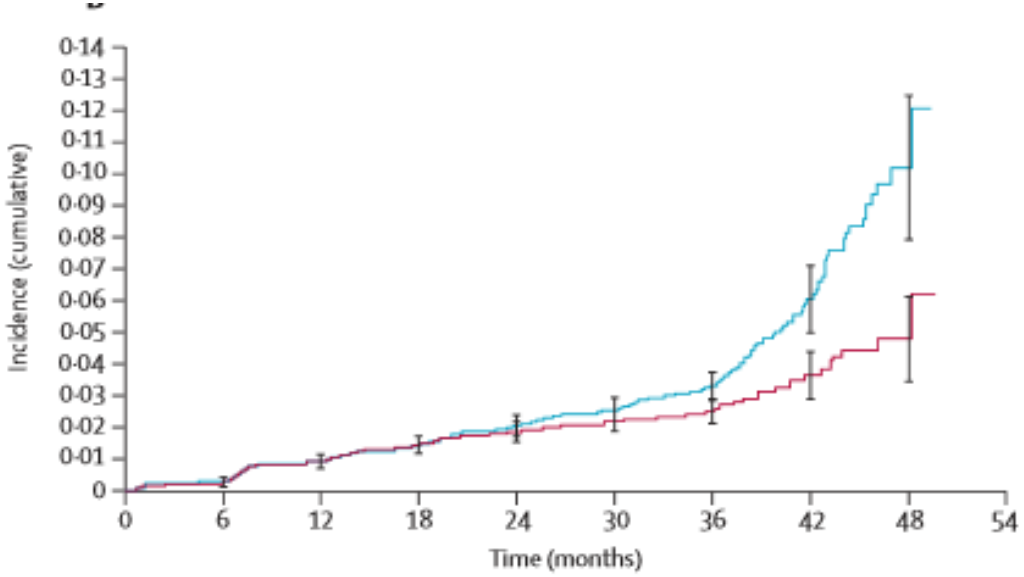
- HPV causes cervical, anal cancer and a subset of head and neck cancers
- Sexually transmitted cancer
- Recently approved vaccine is extremely effective at preventing infection with the two most common strains of HPV





NEJM 2002

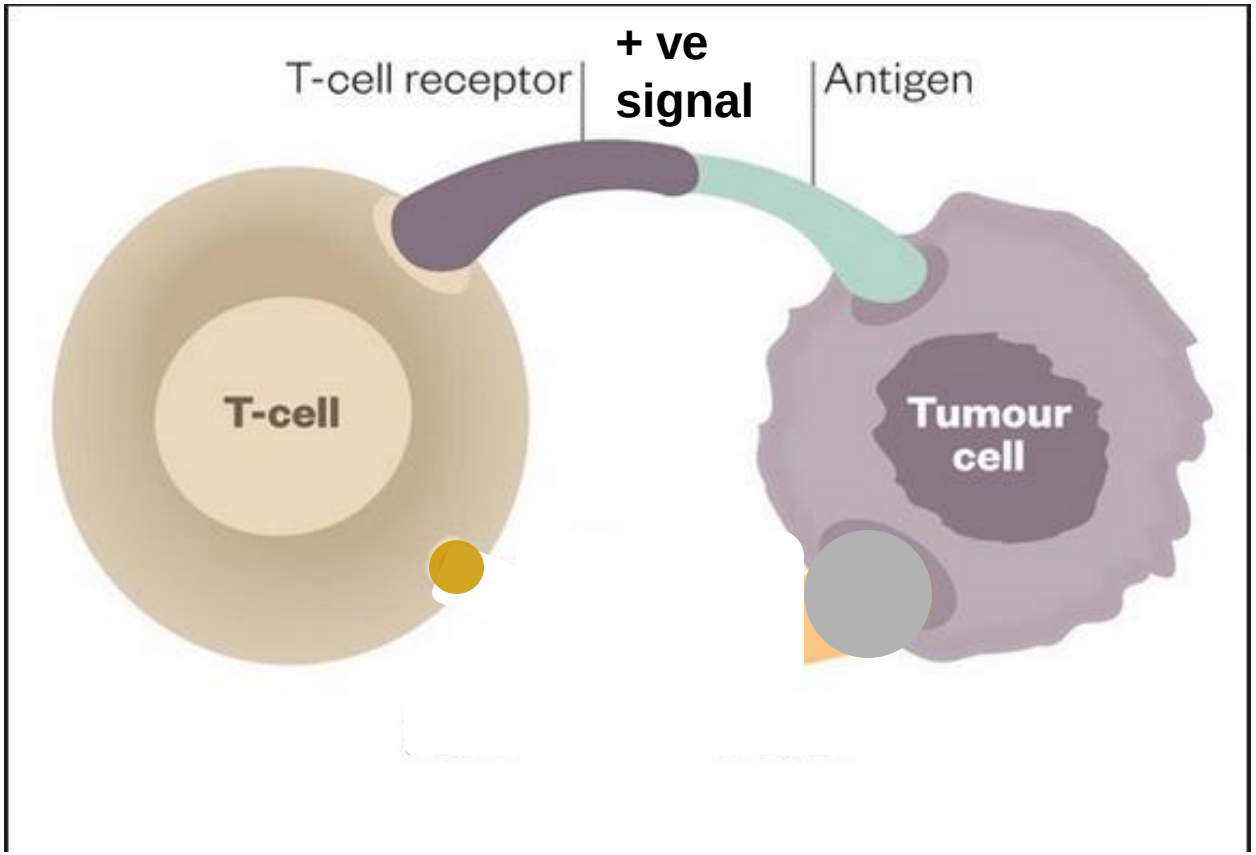
Reduction of the incidence of pre-cervical cancer with a HPV vaccine vs control



Number at risk										
Vaccine	8667	8628	8414	8190	7796	7319	3400	622	72	0
Control	8682	8634	8412	8170	7795	7321	3391	700	62	0
Number of cases (cumulative)										
Vaccine	0	19	79	124	158	181	202	218	223	224
Control	0	26	81	122	173	212	261	301	321	322

Lancet 2009; 374: 301–14

Check point inhibitors



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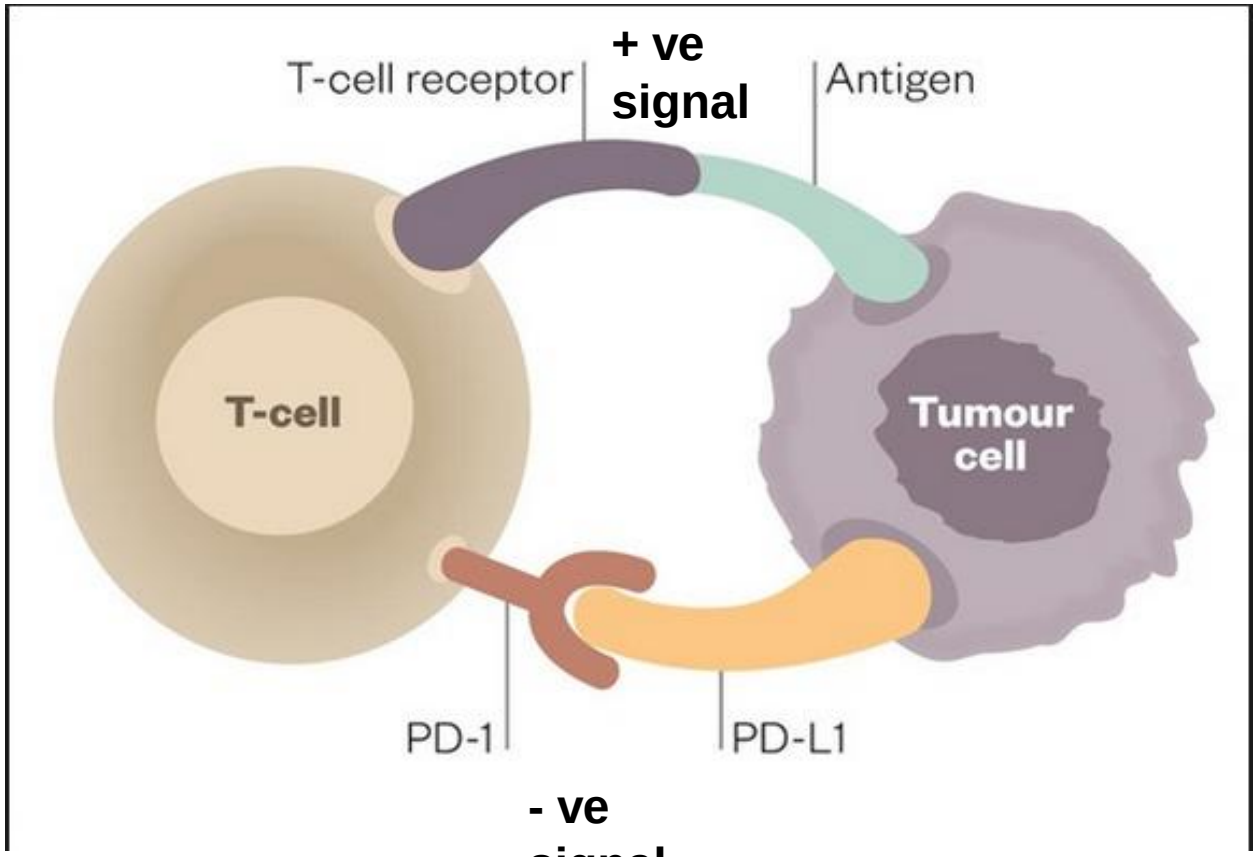

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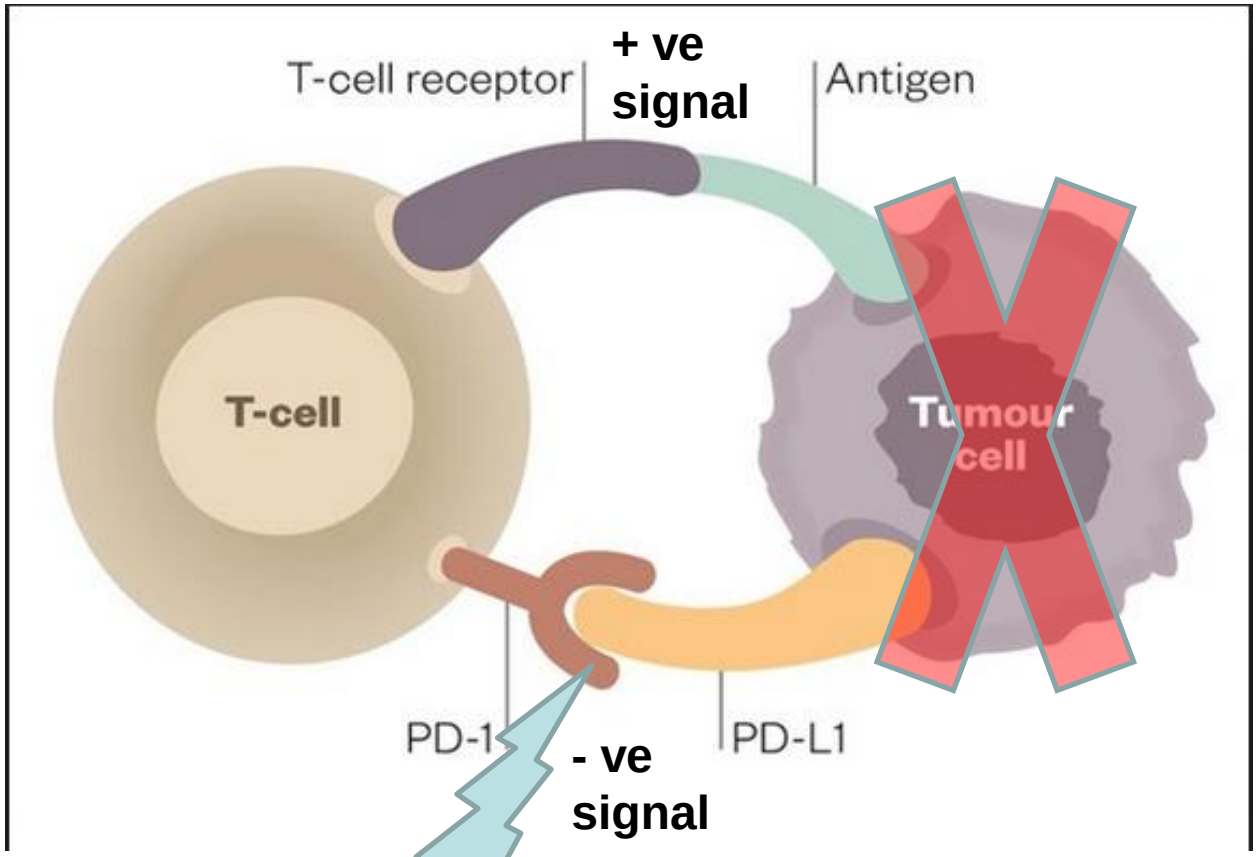


PD1 inhibitors in the clinic

- Melanoma
- NSCLC (lung cancer)
- Kidney cancer
- Many more to come

PD1 inhibitor improves survival over standard chemotherapy in NSCLC

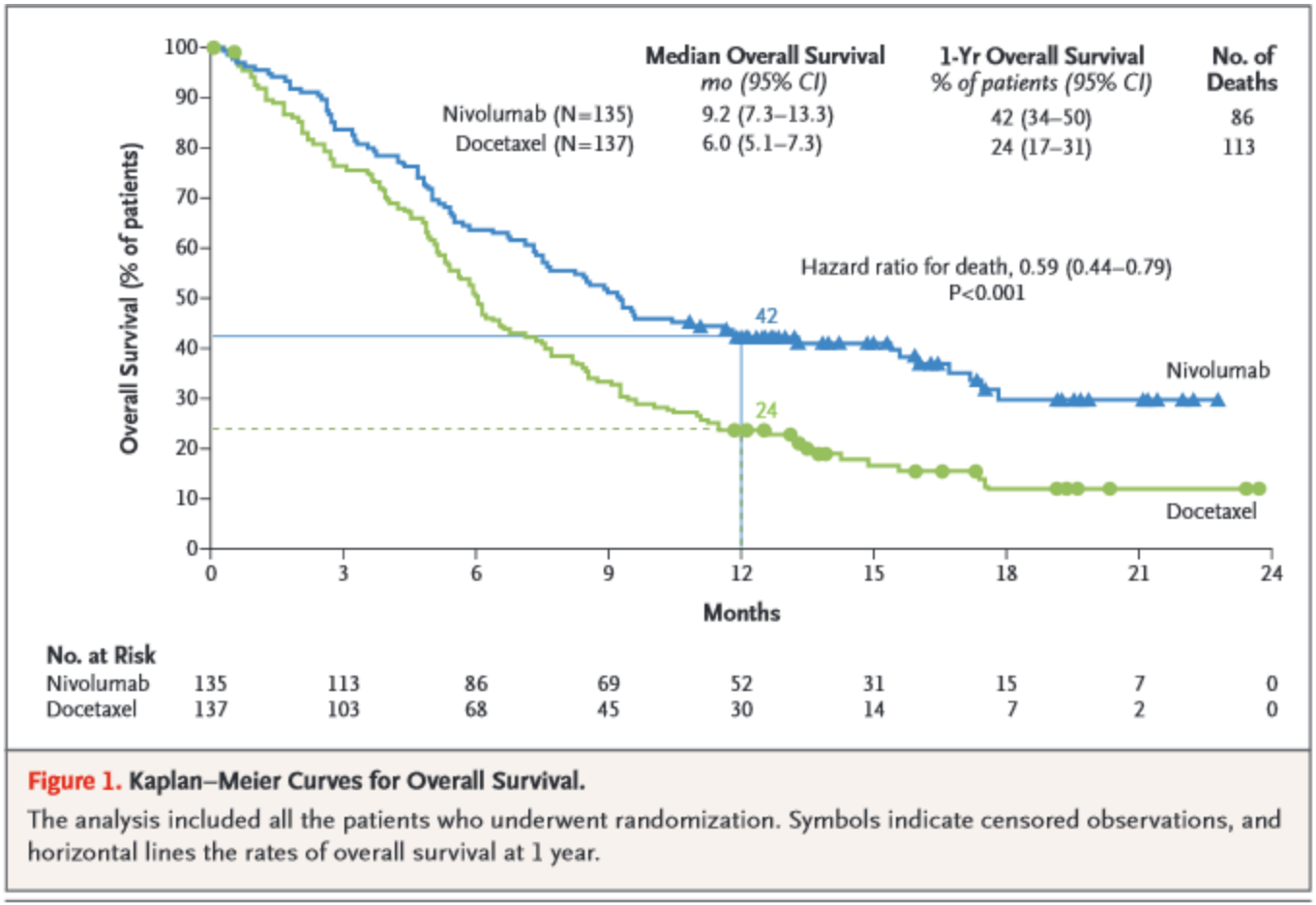


Figure 1. Kaplan–Meier Curves for Overall Survival.

The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

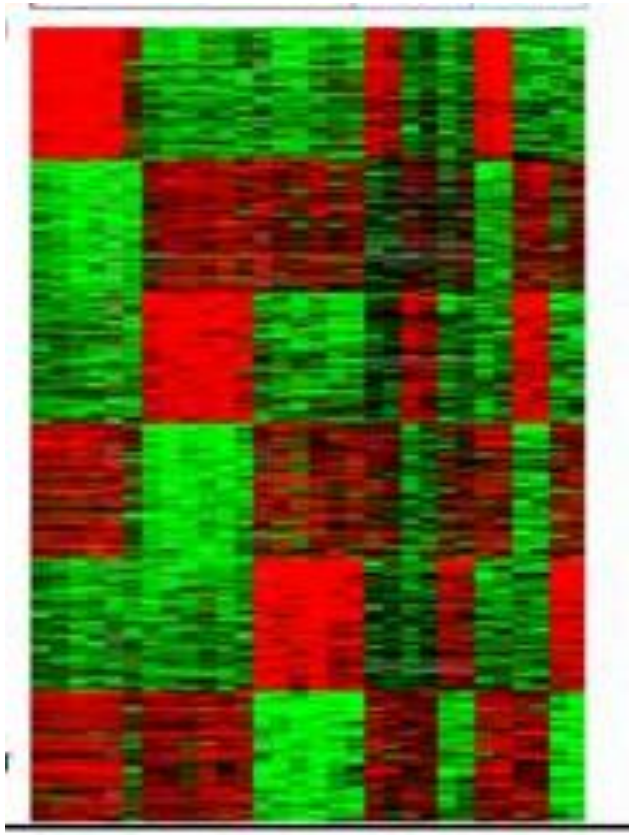
N Engl J Med 2015;373:123-35

New Developments in Cancer Treatment

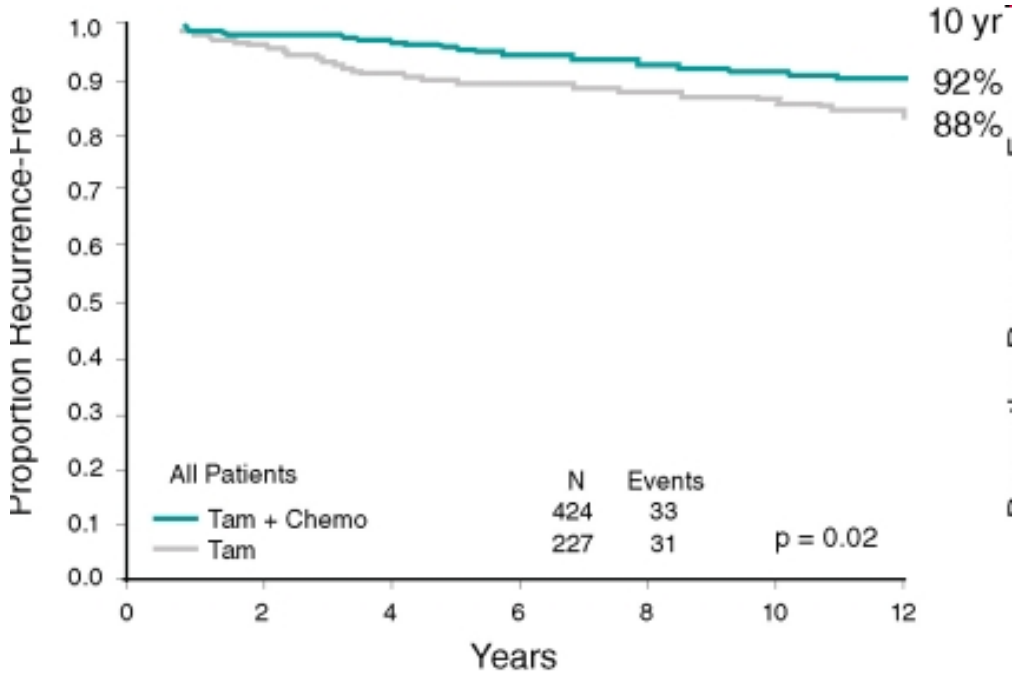
4. Prognosis

Micro-array and Oncotype dx

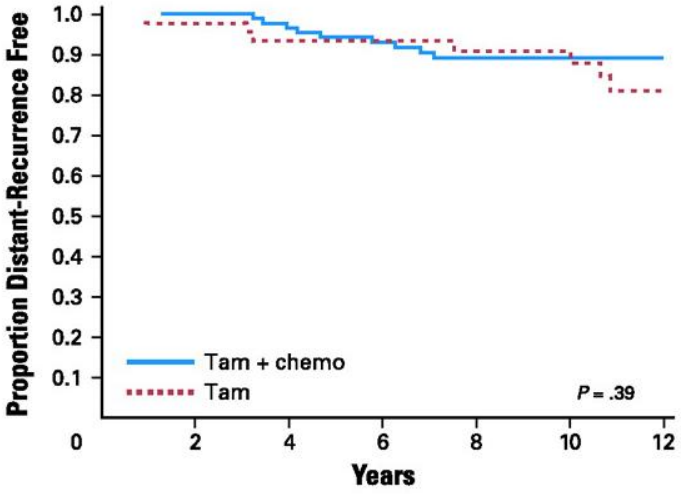
- Women with breast cancer are often offered chemo after definitive surgery removing the primary tumor
- Not all of these patients actually derive benefit from this toxic therapy

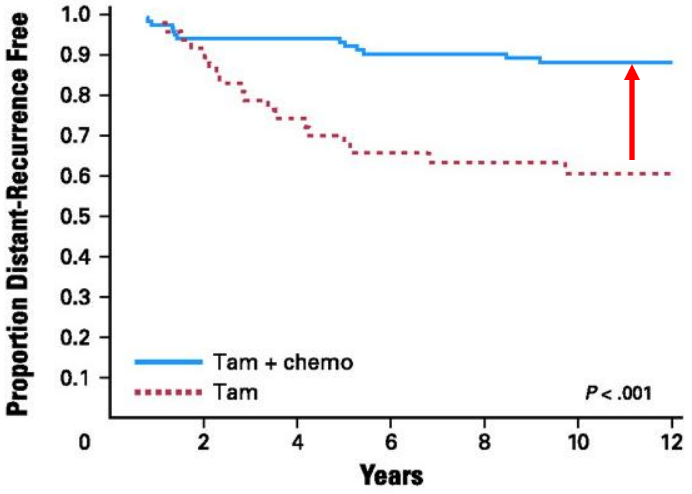


NSABP B-20 clinical trial (1988-1997). Tamoxifen vs. Tamoxifen + Chemotherapy—All 651 patients.



Oncotype Dx in Breast Cancer





30%

Low risk subtype:

Chemo does not help

High risk subtype:

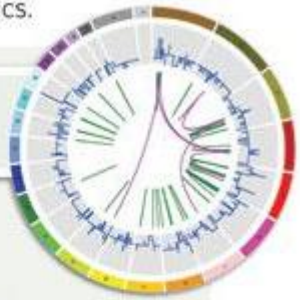
Chemo helps a lot!

Reading All the Tumor DNA

- We can find specific mutations in the tumor that could be targeted
- We can classify tumors based on the tumor DNA. This may enable us to find the target that is driving that specific cancer

CANCER GENOMES COMING FAST

A few examples of fully and partially sequenced cancer genomes and their defining characteristics.



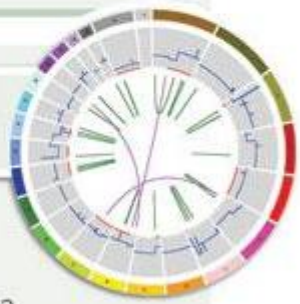
LUNG CANCER

Cancer: small-cell lung carcinoma

- Sequenced: full genome
- Source: NCI-H209 cell line
- Point mutations: 22,910
- Point mutations in gene regions: 134
- Genomic rearrangements: 58
- Copy-number changes: 334

Highlights:
Duplication of the *CHD7* gene confirmed in two other small-cell lung carcinoma cell lines.

Source: E. D. Pleasance *et al. Nature* **463,** 184–190 (2010).



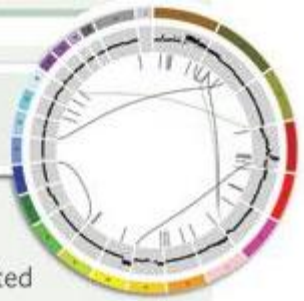
SKIN CANCER

Cancer: metastatic melanoma

- Sequenced: full genome
- Source: COLO-829 cell line
- Point mutations: 33,345
- Point mutations in gene regions: 292
- Genomic rearrangements: 51
- Copy-number changes: 41

Highlights:
Patterns of mutation reflect damage by ultraviolet light.

Source: E. D. Pleasance *et al. Nature* **463,** 191–196 (2010).



BREAST CANCER

Cancer: basal-like breast cancer

- Sequenced: full genome
- Source: primary tumour, brain metastasis, and tumours transplanted into mice
- Point mutations: 27,173 in primary, 51,710 in metastasis and 109,078 in transplant
- Point mutations in gene regions: 200 in primary, 225 in metastasis, 328 in transplant
- Genomic rearrangements: 34
- Copy-number changes: 155 in primary, 101 in metastasis, 97 in transplant

Highlights:
The *CTNNA1* gene encodes a putative suppressor of metastasis that is deleted in all tumour samples.

Source: L. Ding *et al. Nature* **464,** 999–1005 (2010).

BRAIN CANCER

Cancer: glioblastoma multiforme

- Sequenced: exome (no complete Circos plot)
- Source: 7 patient tumours, 15 tumours transplanted into mice (follow-up sequencing on 21 genes for 83 additional samples)
- Genes containing at least one protein-altering mutation: 685
- Genes containing at least one protein-altering point mutation: 644
- Copy-number changes: 281

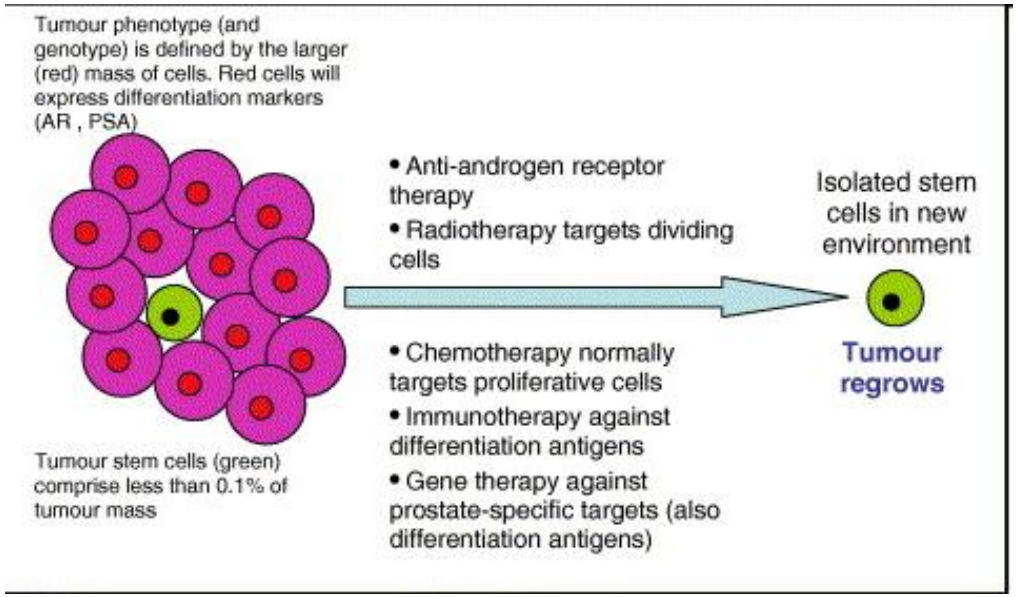
Highlights:
Mutations in the active site of *IDH1* have been found in 12% of patients.

Source: E. R. Mardis *et al. N. Engl. J. Med.* **361,** 1058–1066 (2009).

Cost of Genome Sequencing

- Human Genome Project cost U.S. taxpayers, about $2.7 billion in FY 1991 dollars.
- Cost of sequencing a human genome today is ~$1000-$5000

Cancer Stem cell

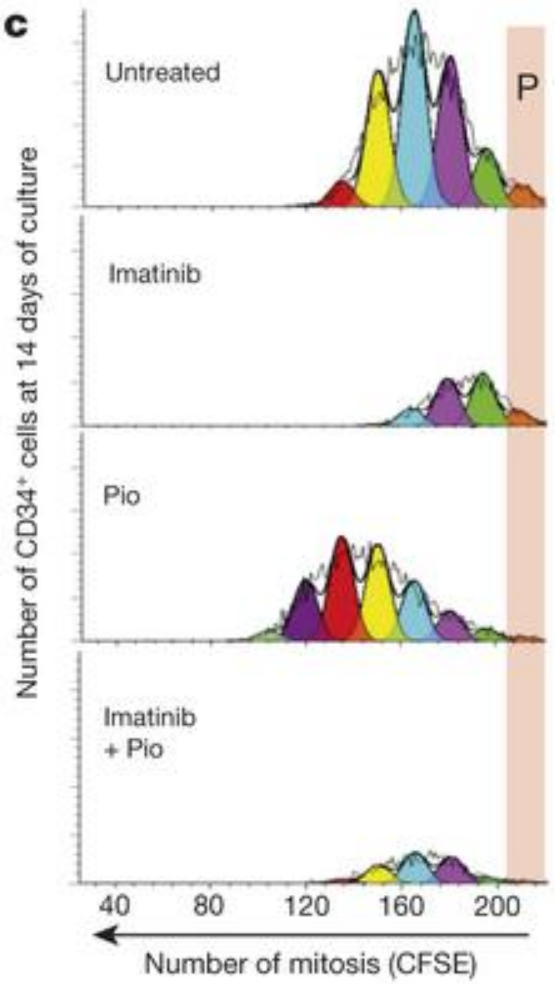


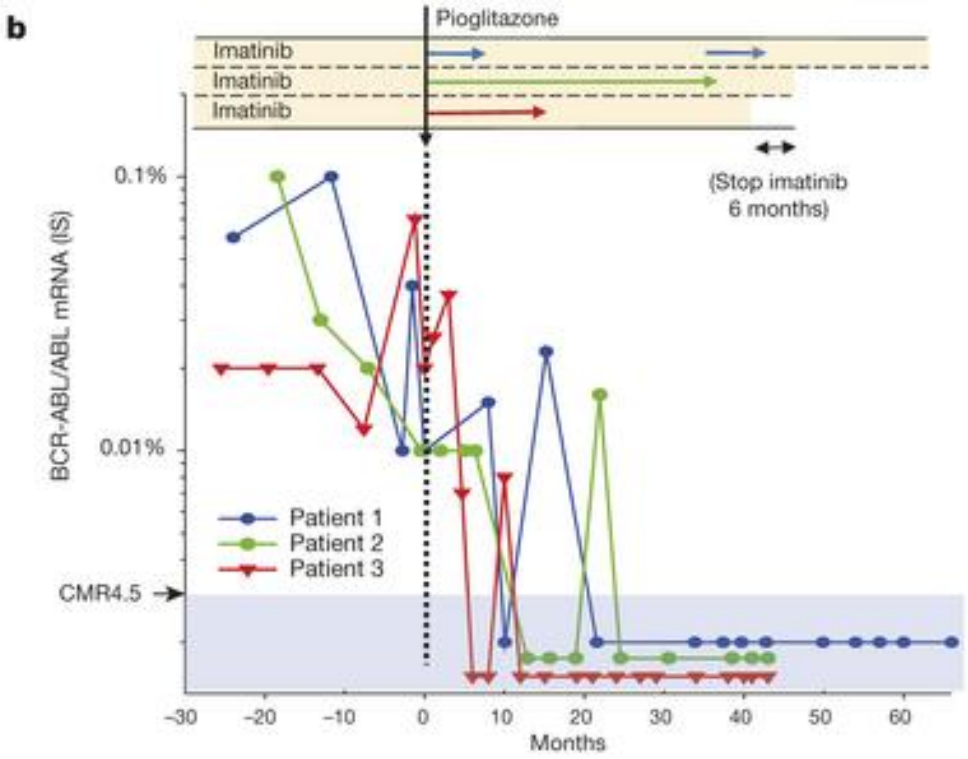
The root of the cancer tree

Cancer stem cells

- Cancer stem cells have been identified for breast, lung, prostate, brain, and leukemia
- Much work needs to be done:
  - characterizing these cells
  - examining their differences to their normal counterparts
  - Developing treatments to eradicate these cells

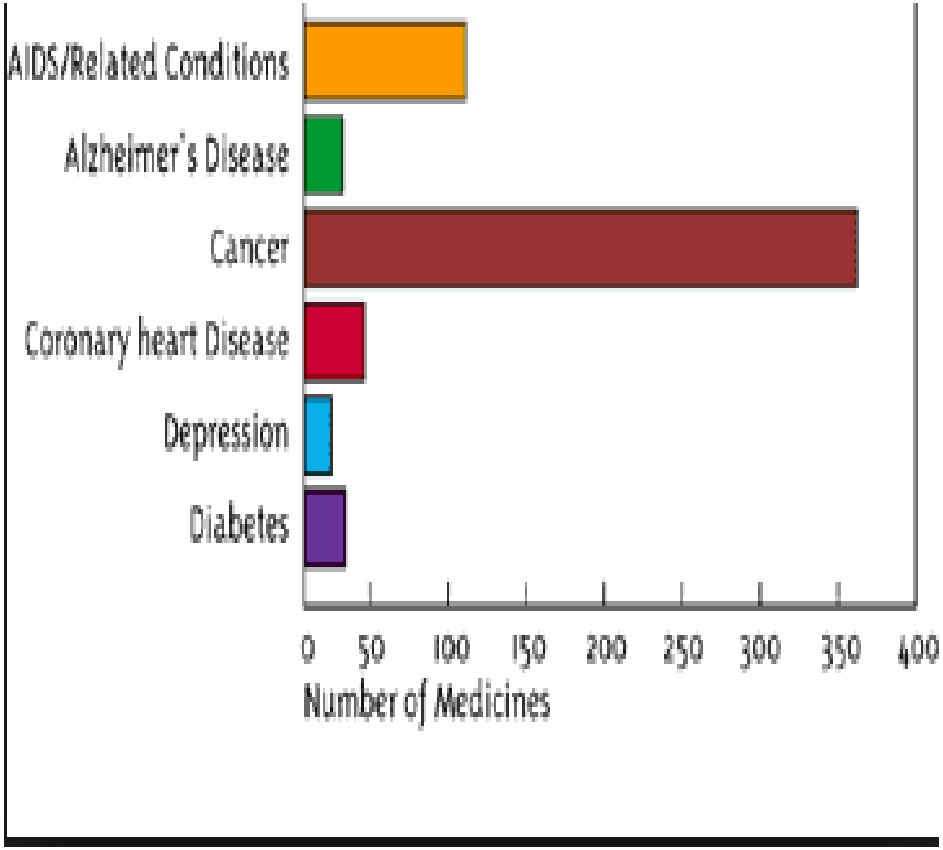
Imatinib and pioglitazone deplete the CML stem cell

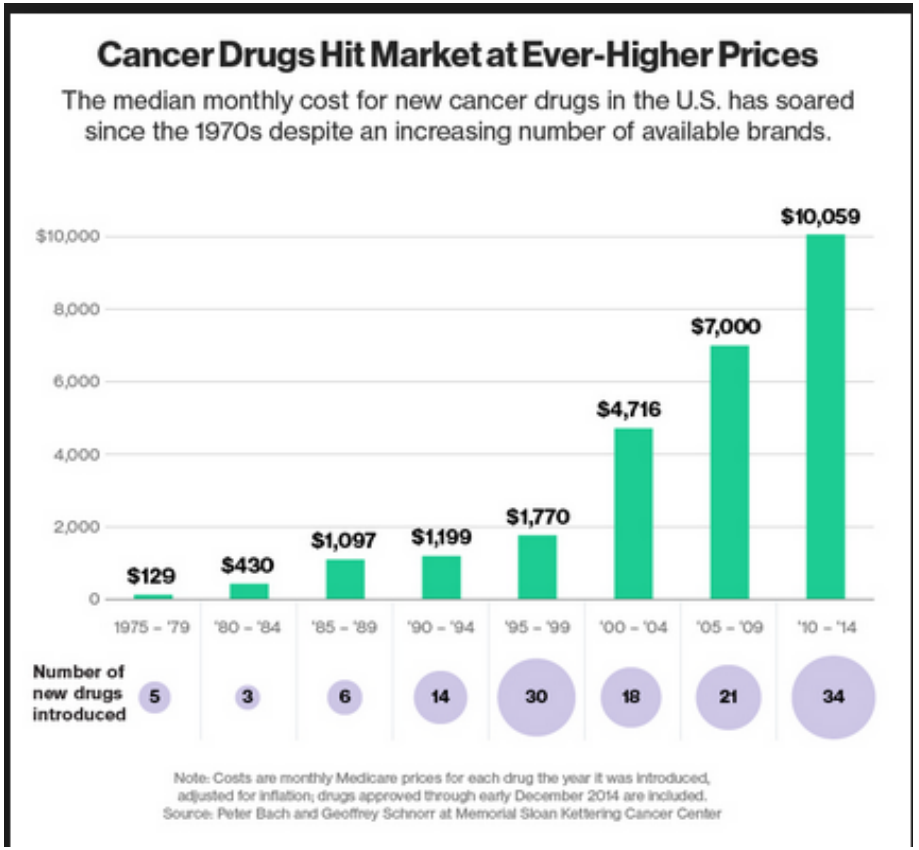




Nature 525,380-383, 2015

Hope is on the way
(but at a cost $$$)





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