CDx in oncology

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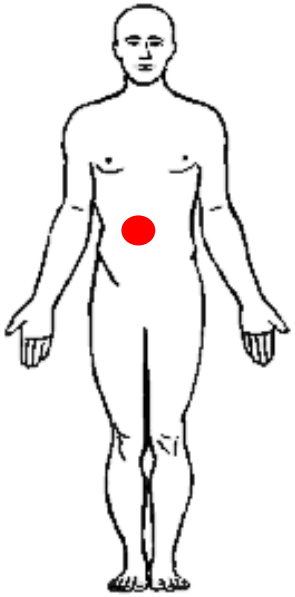
INSERM U900 Research unit

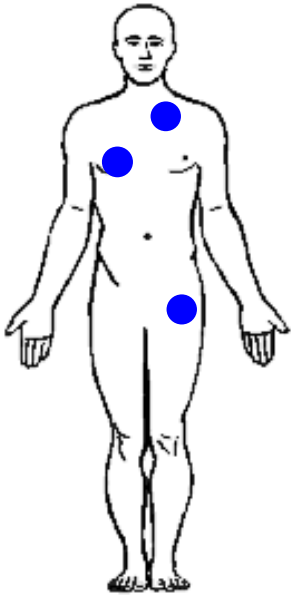
Versailles Saint-Quentin-en-Yvelines University

FEAM – Geneva – September 27, 2018

Treatment of cancer



● Primary tumor



● Metastases

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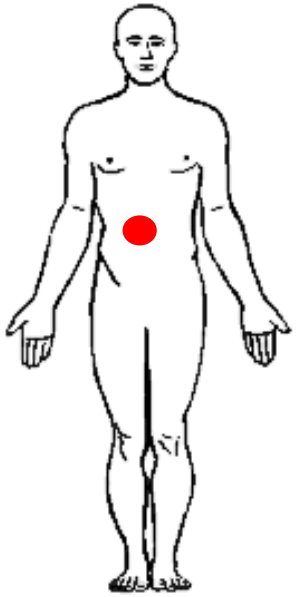
Treatment of cancer



→ Aim = cure

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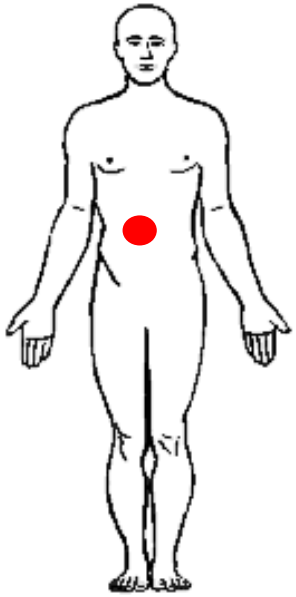
Treatment of cancer



Surgery

Radio-therapy

Local treatments

Drugs

For a limited time

→ **Aim = cure**

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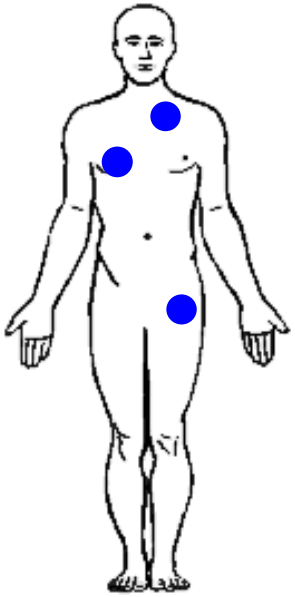
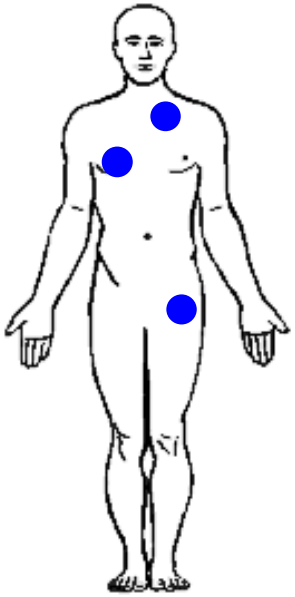
Treatment of cancer



Treatment of cancer



Drugs

Surgery

Radio-therapy

Treatment for life

Curable situation in ~5% of cases (exception of germline tumors [95%])
Chronic disease

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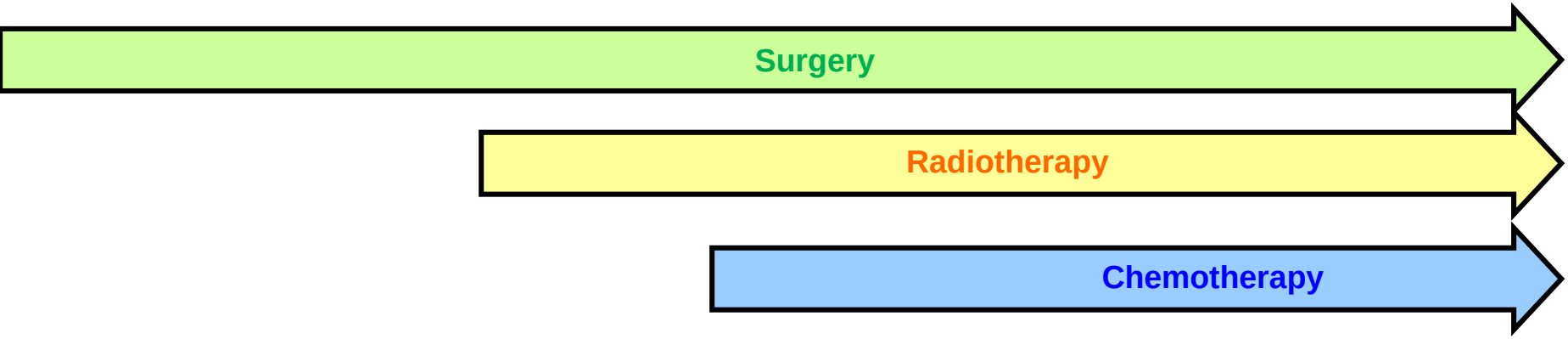
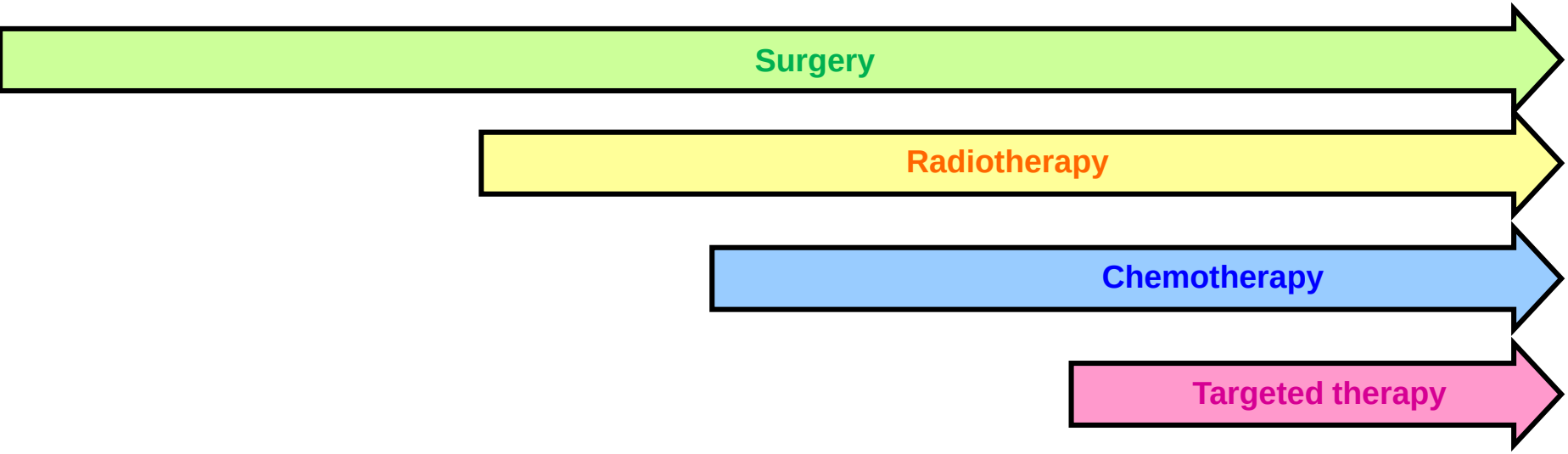
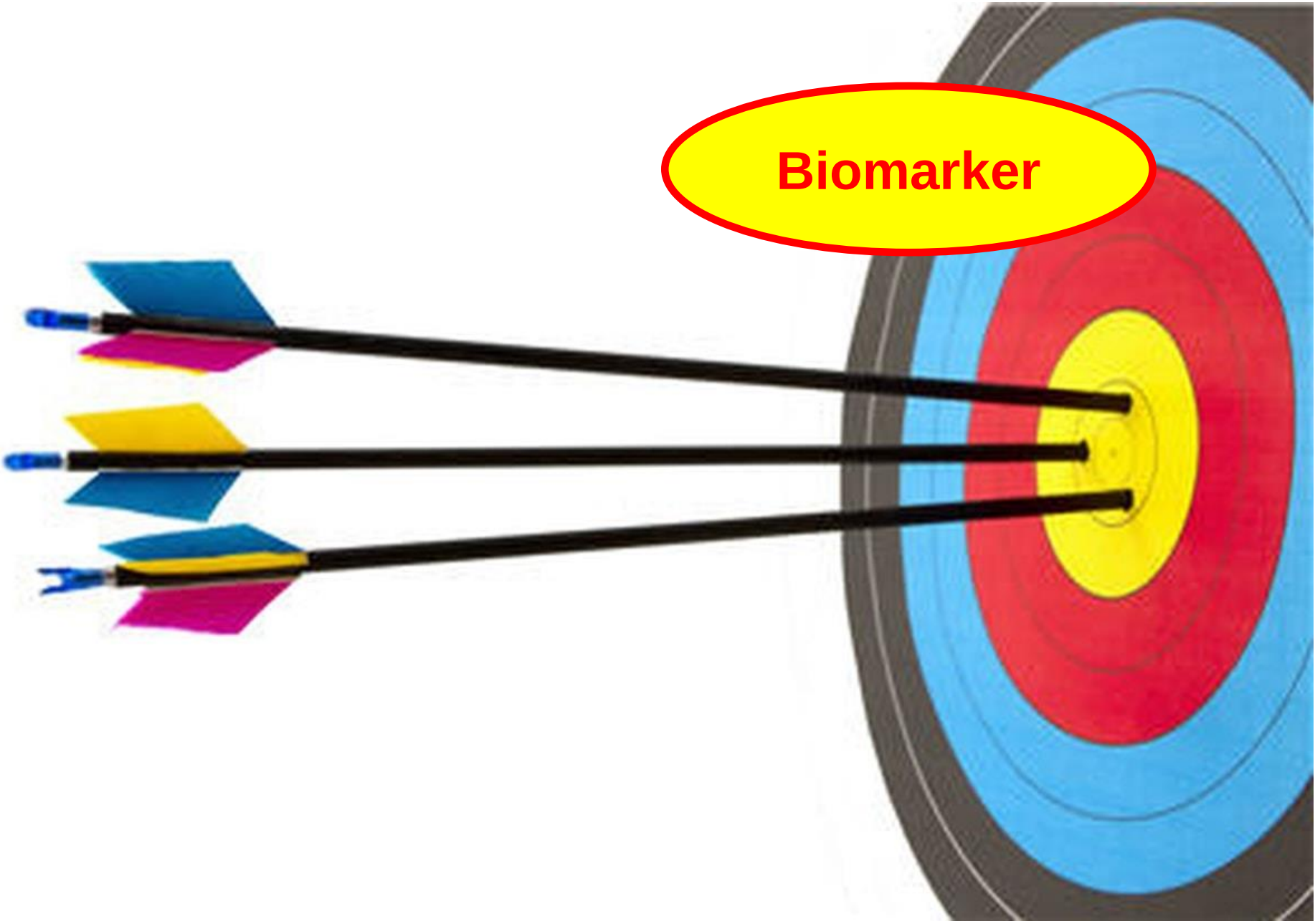
Treatment of cancer




No biomarkers

Treatment of cancer




Biomarker

Treatment of cancer

Targeted therapies	Tumor type	Biomarker
EGFR tyrosine kinase inhibitors	Lung	EGFR mutations
HER2-targeting agents	Breast Gastric	HER2 amplifications HER2 amplifications
EGFR monoclonal antibodies	Colorectal	KRAS mutations
BRAF inhibitors	Melanoma	BRAF mutations
ALK inhibitors	Lung	ALK translocations
ROS1 inhibitors	Lung	ROS1 translocations
KIT inhibitors	GIST	KIT expression

Treatment of cancer

Targeted therapies	Tumor type	Biomarker	Survival benefit
EGFR tyrosine kinase inhibitors	Lung	EGFR mutations	Years
HER2-targeting agents	Breast Gastric	HER2 amplifications HER2 amplifications	Years Months
EGFR monoclonal antibodies	Colorectal	KRAS mutations	Months
BRAF inhibitors	Melanoma	BRAF mutations	Months
ALK inhibitors	Lung	ALK translocations	Years
ROS1 inhibitors	Lung	ROS1 translocations	Years
KIT inhibitors	GIST	KIT expression	Years

Treatment of cancer

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ALK inhibitors	Lung	ALK translocations	**Years**
ROS1 inhibitors	Lung	ROS1 translocations	**Years**
KIT inhibitors	GIST	KIT expression	**Years**
Hormone therapy	Breast	ER/PR expression	**Years**

Treatment of cancer

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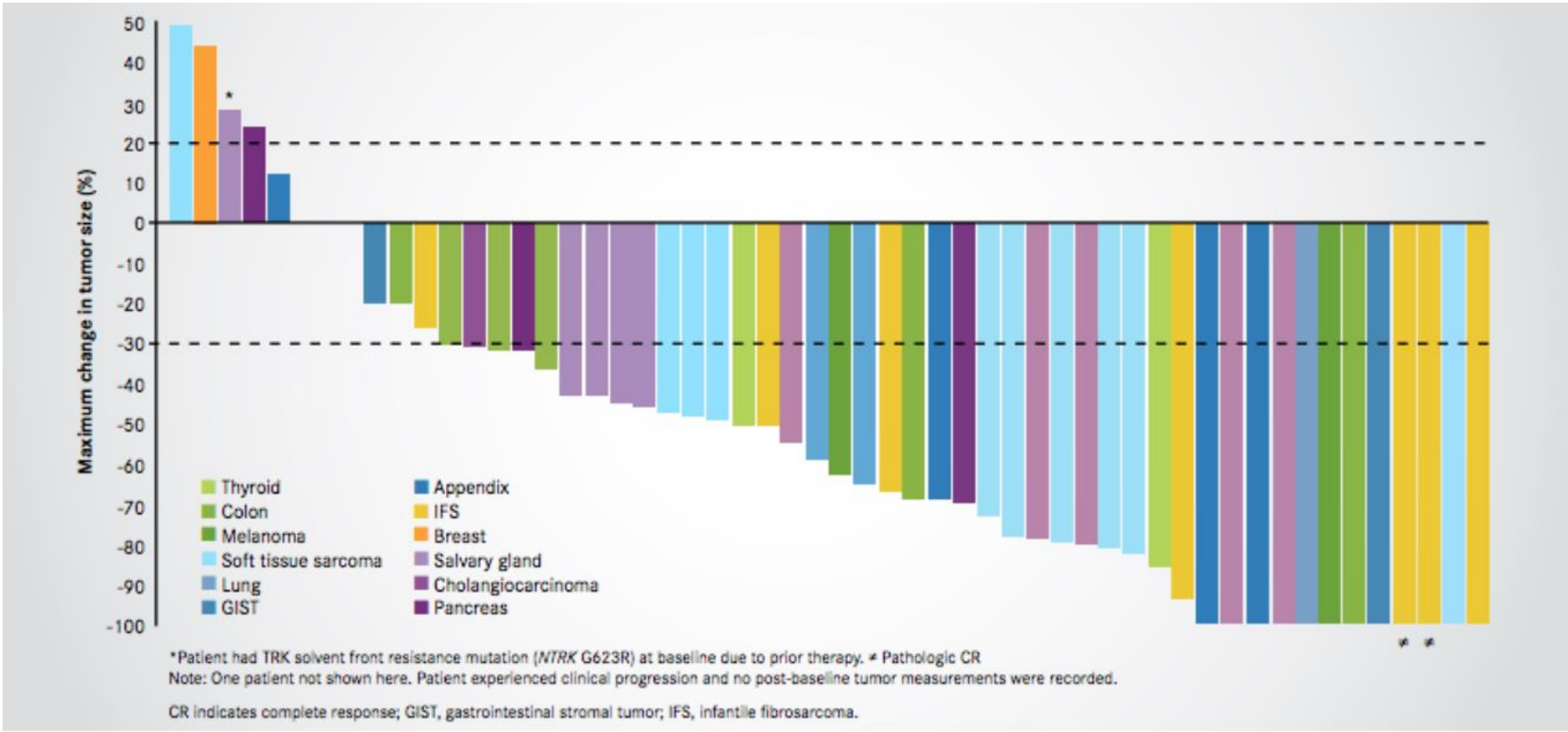
BRAF inhibitors	Melanoma	BRAF mutations	Months
ALK inhibitors	Lung	ALK translocations	Years
ROS1 inhibitors	Lung	ROS1 translocations	Years
KIT inhibitors	GIST	KIT expression	Years
Hormone therapy	Breast	ER/PR expression	Years
NTRK inhibitors	All	NTRK translocations	Years

Treatment of cancer



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Treatment of cancer

Targeted therapies	Tumor type	Biomarker	Survival benefit
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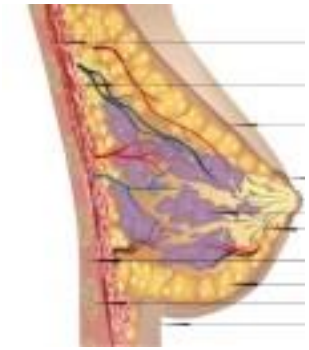
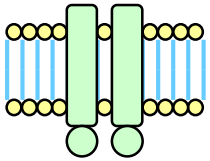
ALK inhibitors	Lung	ALK translocations	Years
ROS1 inhibitors	Lung	ROS1 translocations	Years
KIT inhibitors	GIST	KIT expression	Years
Hormone therapy	Breast	ER/PR expression	Years
NTRK inhibitors	All	NTRK translocations	Years
mTOR inhibitors	Breast/Kidney/Endocrine	-	Months
VEGF(R) inhibitors	Lung/Breast/Colorectal/ Glioblastoma/Kidney/ Ovarian/Gastric	-	Months
CDK4/6 inhibitors	Breast	-	Months

Treatment of cancer



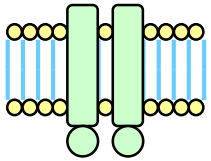
HER-2



Amplification

20%

Trastuzumab
(Herceptin®)



Lapatinib
(Tykerb®)

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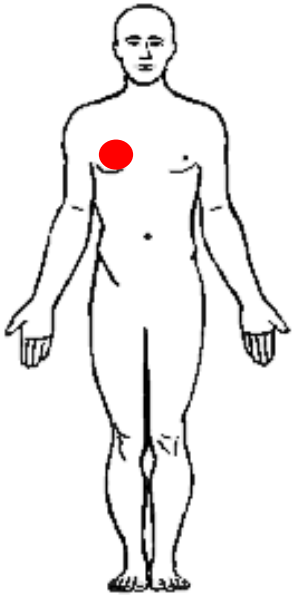
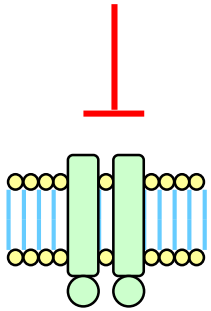
Treatment of cancer



● HER2+ breast cancer

Trastuzumab
(Herceptin®)



→ Risk of recurrence decreased by 50%

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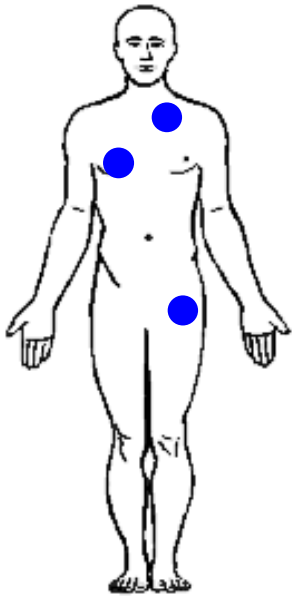
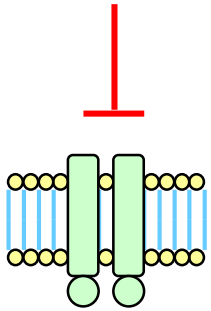
Treatment of cancer



- **HER2+ metastasic breast cancer**

Trastuzumab (Herceptin®)



→ Median overall survival increased from <2 to >6 years

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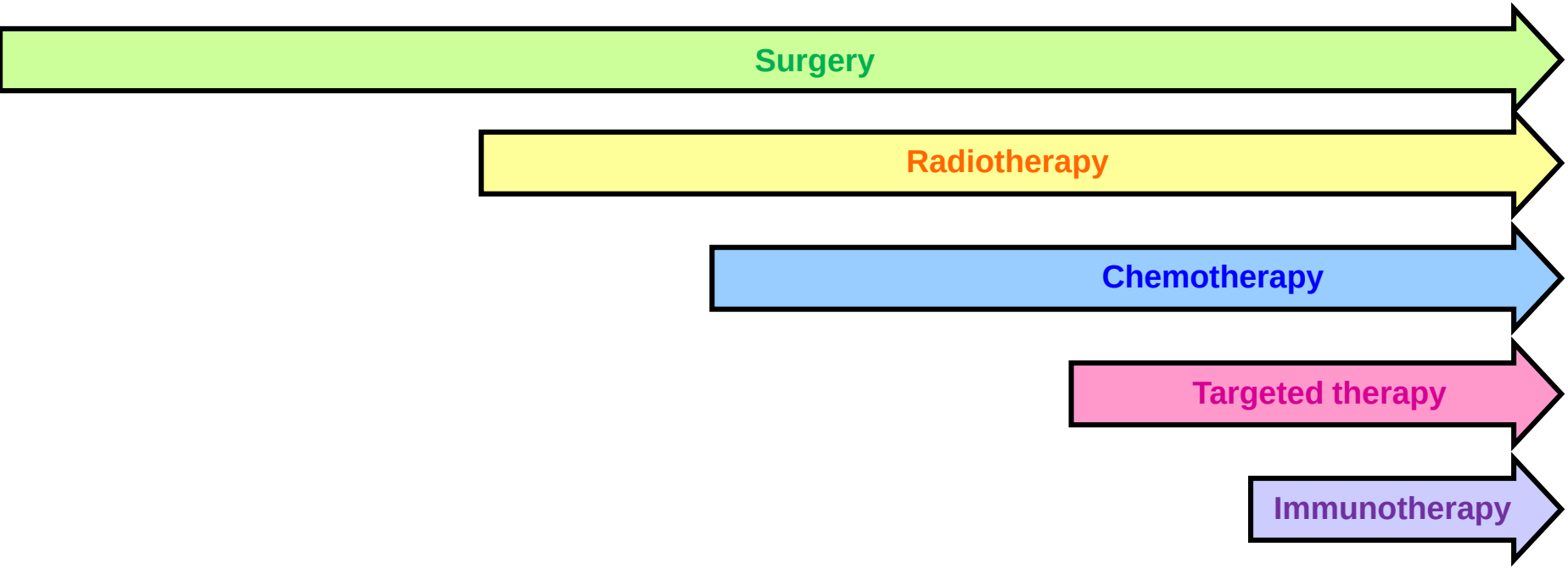
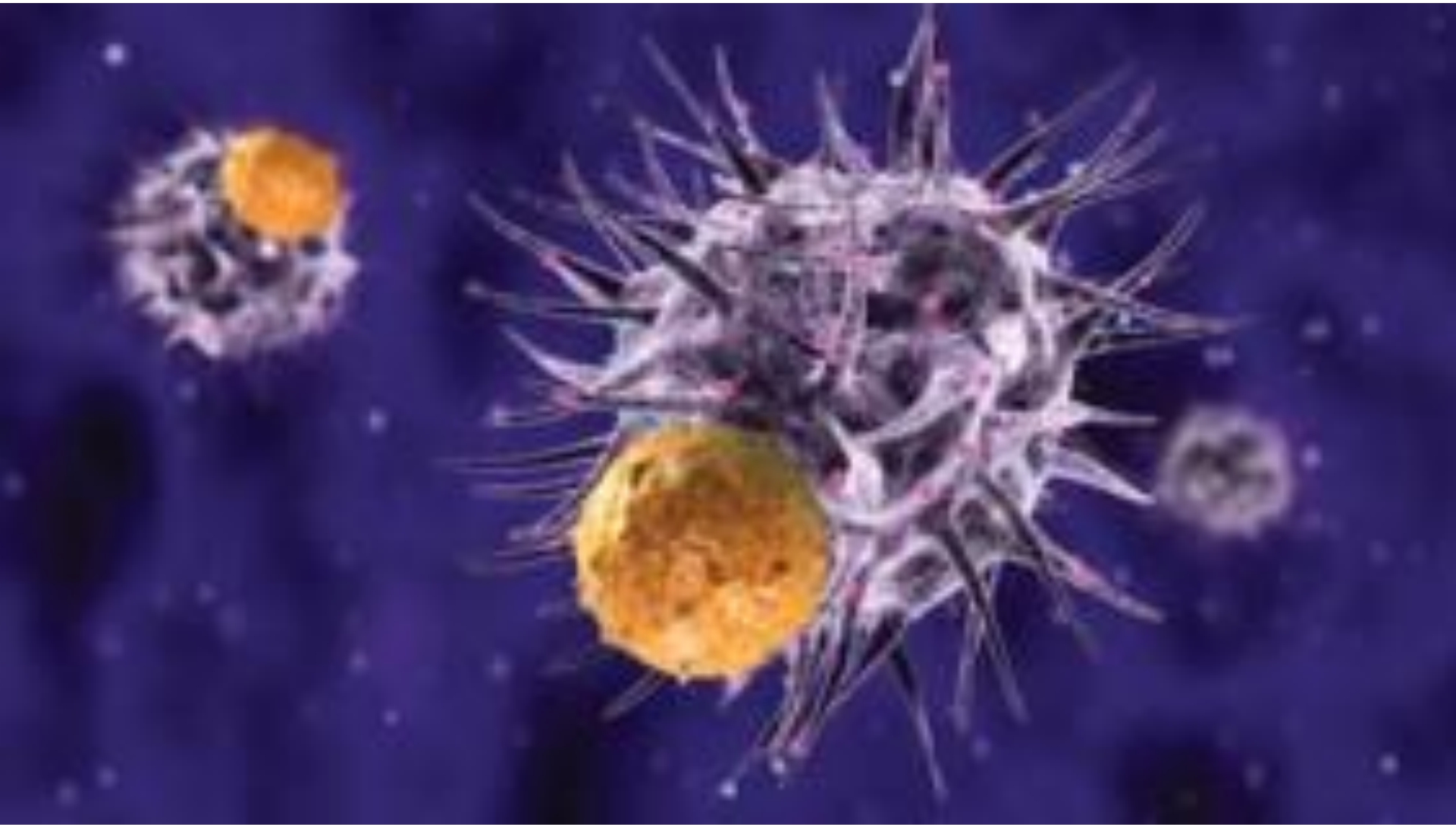
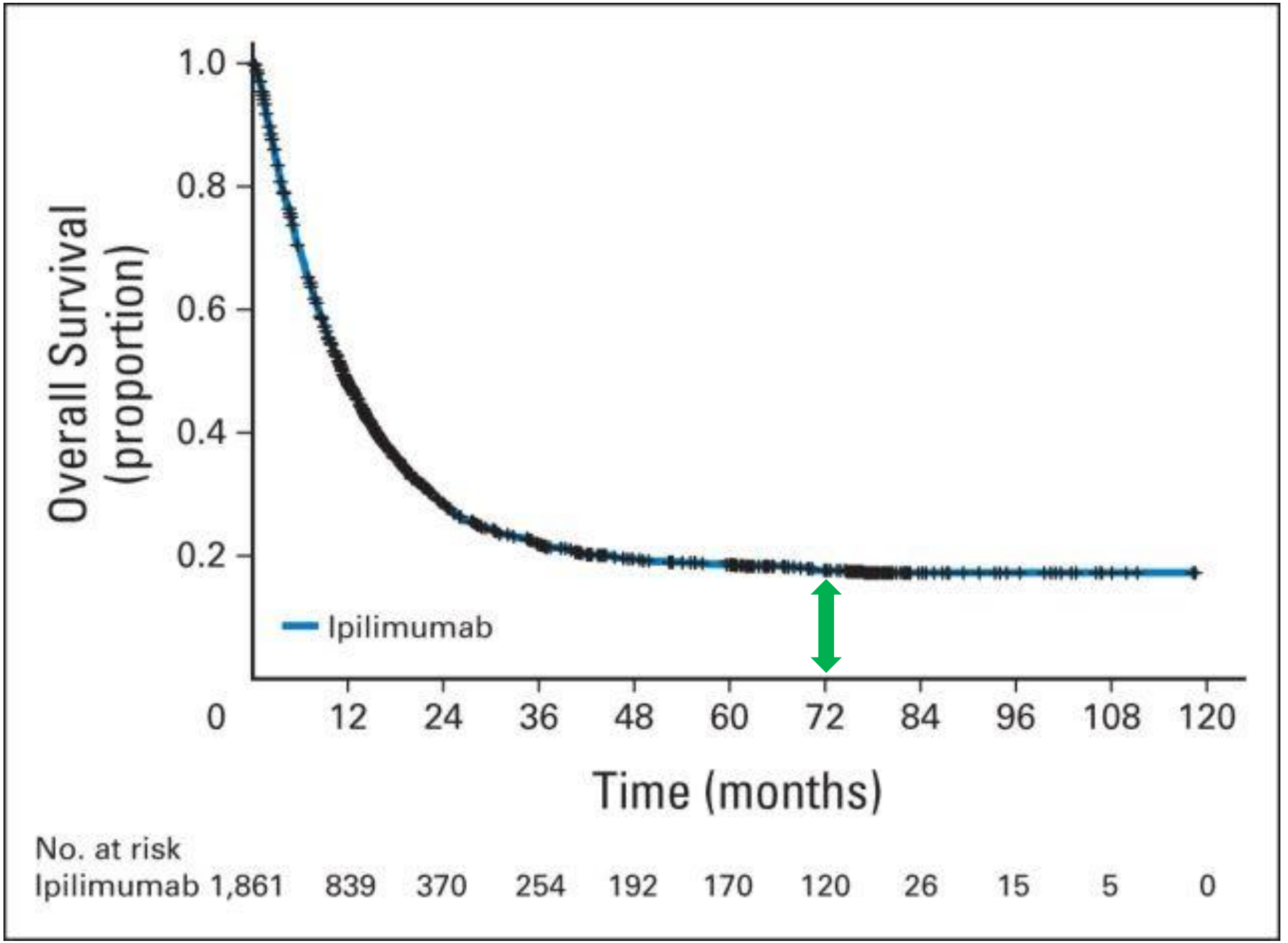
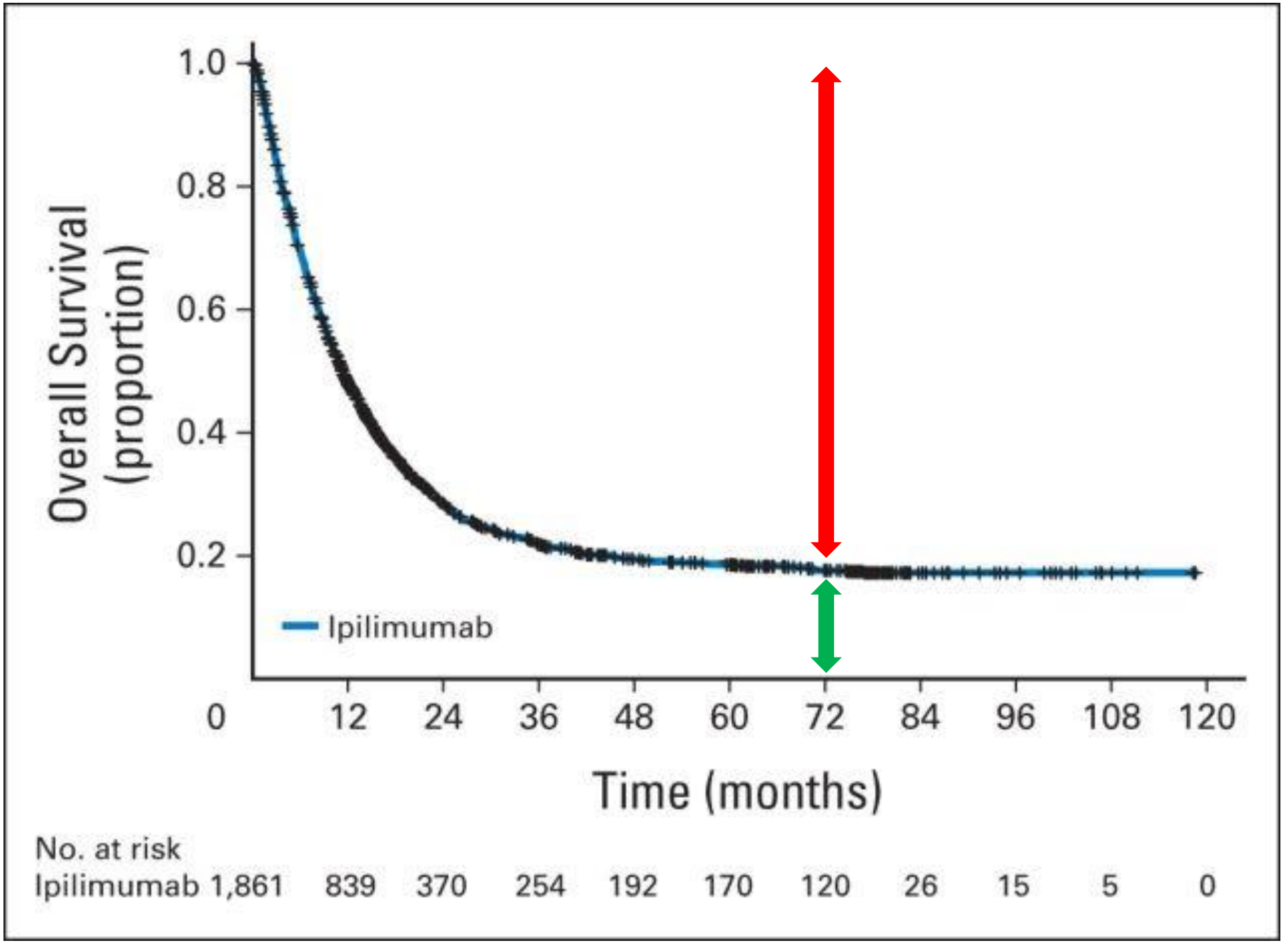
Treatment of cancer






Overall Survival (proportion)
1.0
0.8
0.6
0.4
0.2
Ipilimumab
0
12
24
36
48
60
72
84
96
108
120
Time (months)
No. at risk
Ipilimumab 1,861 839 370 254 192 170 120 26 15 5 0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Treatment of cancer

Tumor type	Setting	Biomarker
Lung	1st line single agent 1st line + chemo 2nd line single agent Adjuvant post CRT	PD-L1 expression - - -
Head and Neck	2nd line single agent	-
Bladder	2nd line single agent	-
Kidney	1st line single agent	-
Melanoma	Any line single agent	-
Lymphoma	2nd line single agent	-
Merckel cell	2nd line single agent	-

Treatment of cancer

Tumor type	Setting	Biomarker	% responders	Survival benefit
Lung	1st line single agent 1st line + chemo 2nd line single agent Adjuvant post CRT	PD-L1 expression - - -	50% NA 20% NA	**Months** **Months** **Months** **Months**
Head and Neck	2nd line single agent	-	20%	**Months**
Bladder	2nd line single agent	-	20%	**Months**
Kidney	1st line single agent	-	20%	**Months**
Melanoma	Any line single agent	-	40%	**Months**
Lymphoma	2nd line single agent	-	80%	**Months**
Merckel cell	2nd line single agent	-	30%	**Months**

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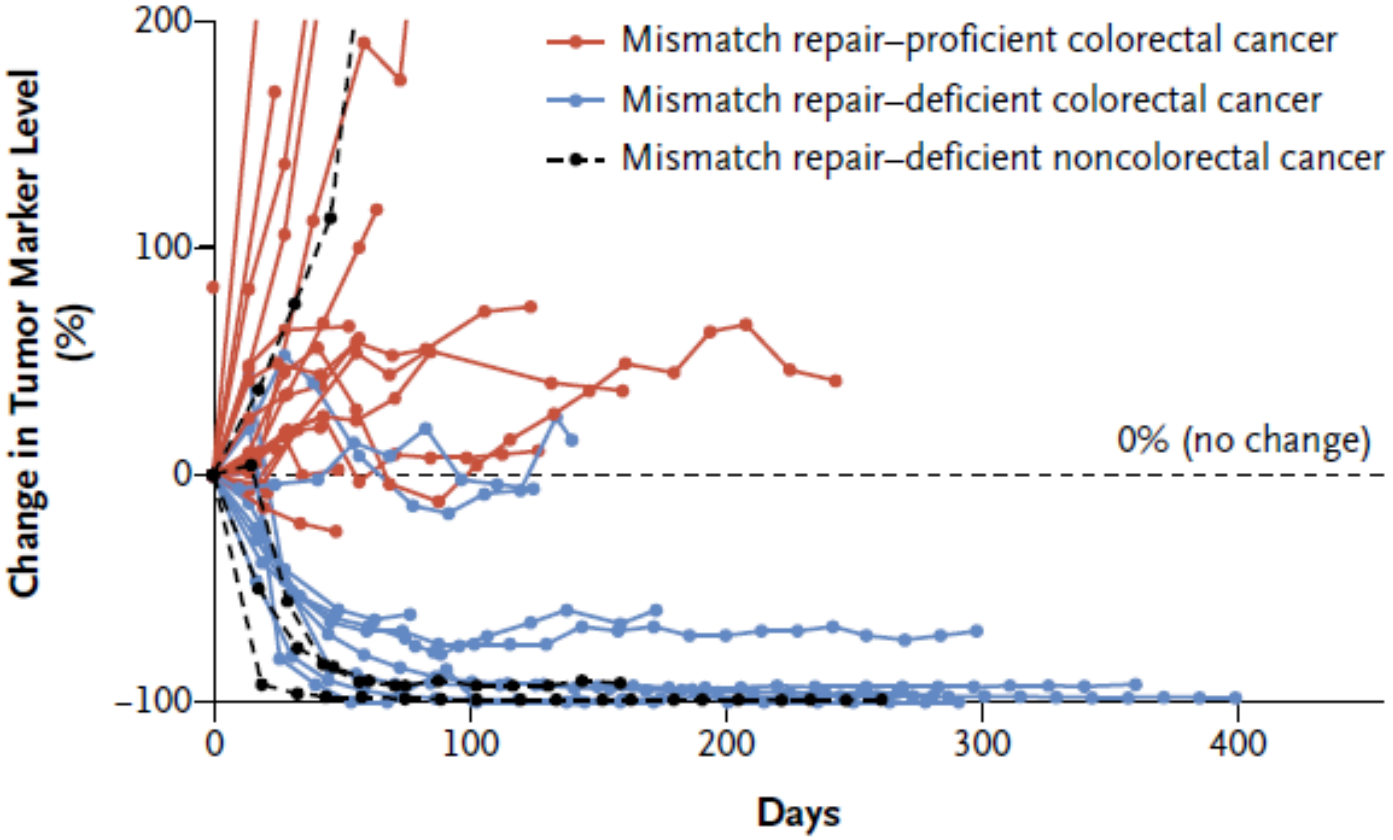
Treatment of cancer



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Melanoma	Any line single agent	-	40%	**Months**
Lymphoma	2nd line single agent	-	80%	**Months**
Merckel cell	2nd line single agent	-	30%	**Months**
All	Any line single agent	MSI	40%	**Years**

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Challenges

1) Identification of **resistance biomarkers** to targeted therapies/immunotherapy

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- **T790M** EGFR mutation in EGFR-mutated **lung** cancer patients treated with **EGFR inhibitors**

- **ESR1** mutations in **breast** cancer patients treated with **aromatase inhibitors**

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Challenges

1) Identification of **resistance biomarkers** to targeted therapies/immunotherapy

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→ **Sequential** analyses of tumor DNA

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Challenges

1) Identification of **resistance biomarkers** to targeted therapies/immunotherapy

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- **ESR1** mutations in **breast** cancer patients treated with **aromatase inhibitors**

→ **Sequential** analyses of tumor DNA

→ **ctDNA** analysis might be a solution to avoid tumor **biopsies**

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Challenges

2) Identification of biomarkers of efficacy of **immunotherapy**

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- a **minority** of cancer patients **benefit** from immunotherapy although **survival benefits** are reported **without using biomarkers**

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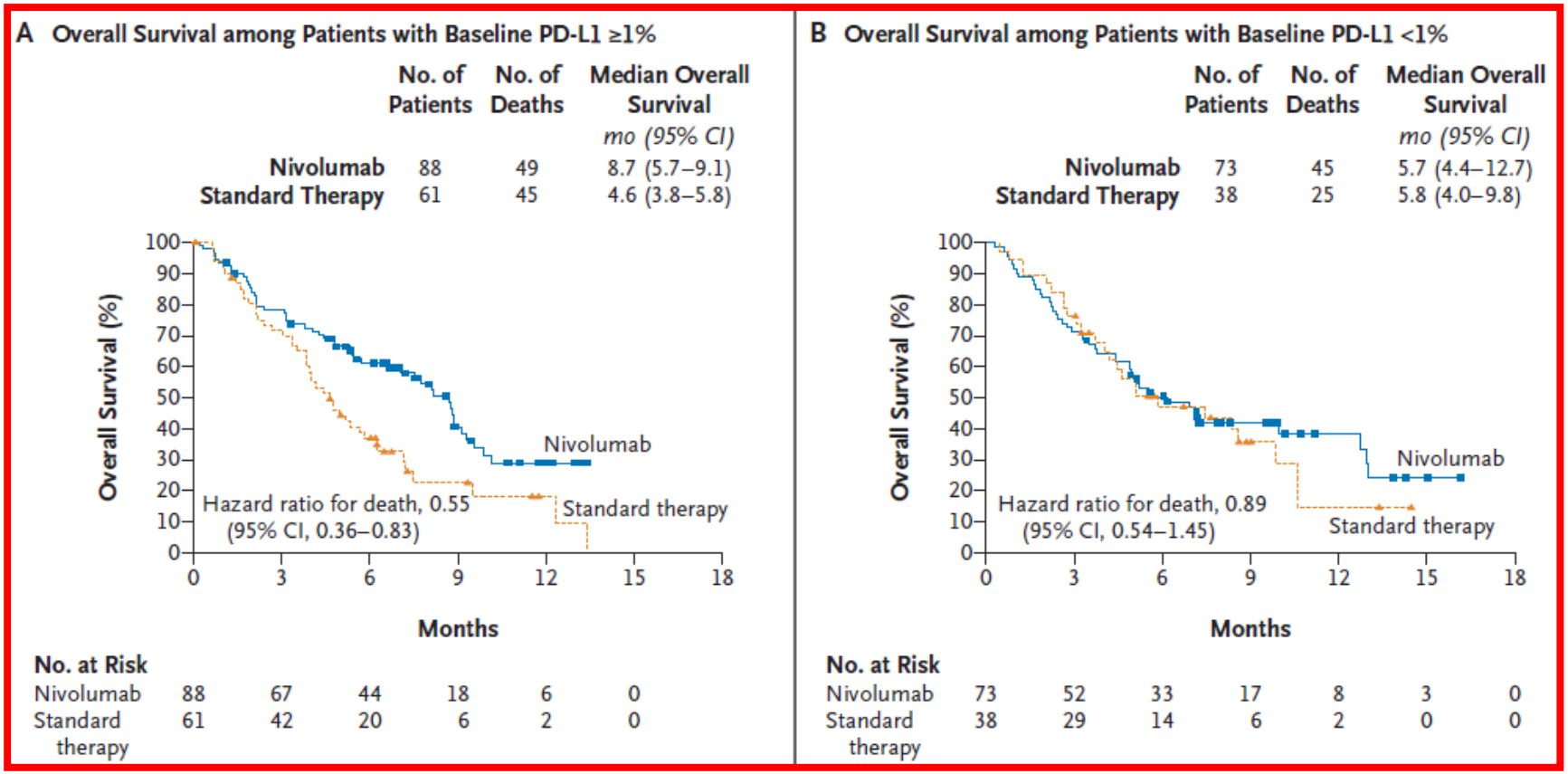
Challenges



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Ferris *et al*. *NEJM* 2016;375:1856-67

Challenges

2) Identification of biomarkers of efficacy of **immunotherapy**

- a **minority** of cancer patients **benefit** from immunotherapy although **survival benefits** are reported **without using biomarkers**

→ Need for identifying **biomarkers** to avoid **ineffective treatments** to patients and to preserve the **financial health** of our systems

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Challenges

3) Democratization of **high throughput technologies** to identify targets

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Challenges

3) Democratization of **high throughput technologies** to identify targets

- analysing multiple biomarkers in a **single assay** is a gain of **time**, **tissue** and likely **money**

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Challenges

3) Democratization of **high throughput technologies** to identify targets

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→ **Concordance** between the results of a single gene CDx and NGS?

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Challenges

3) Democratization of **high throughput technologies** to identify targets

- analysing multiple biomarkers in a **single assay** is a gain of **time**, **tissue** and likely **money**

→ **Concordance** between the results of a single gene CDx and NGS?

→ How **CDx companies** get their money back?

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Conclusions

- The development of **biomarkers** has emerged with the advent of **targeted therapies** leading to **impressive efficacy** in **enriched** patient populations

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Conclusions

- The development of **biomarkers** has emerged with the advent of **targeted therapies** leading to **impressive efficacy** in **enriched** patient populations
- The development of **biomarkers** for **immunotherapy** is key since only a **minority** of patients benefit from these drugs

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Conclusions

• The democratization of **NGS** is a gain of **time**, **tissue**, and likely **money**. However, the **quality** of the data has to be ensured and the impact on **CDx companies** be discussed.