



Clinical utility of precision medicine in oncology

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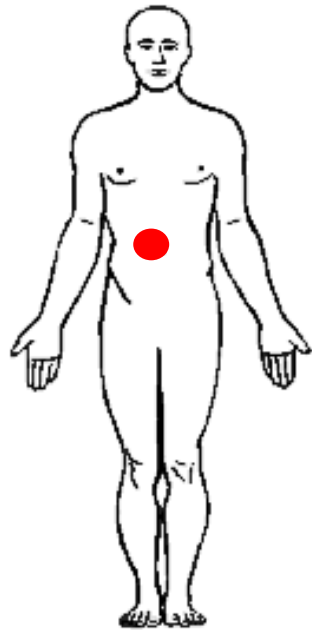
Head, Department of Drug Development and Innovation (D³i)

INSERM U900 Research unit

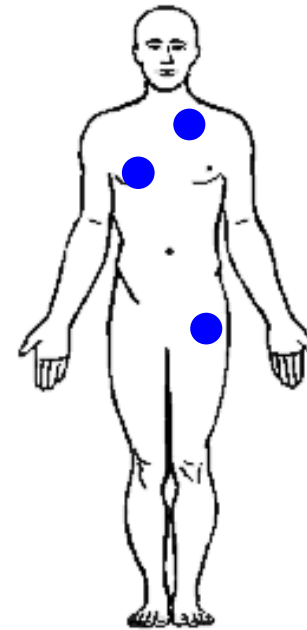
Versailles Saint-Quentin-en-Yvelines University

FEAM – Geneva – September 28, 2018

Treatment of cancer

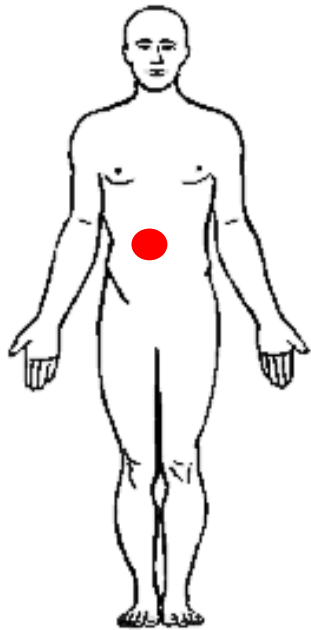


● Primary tumor



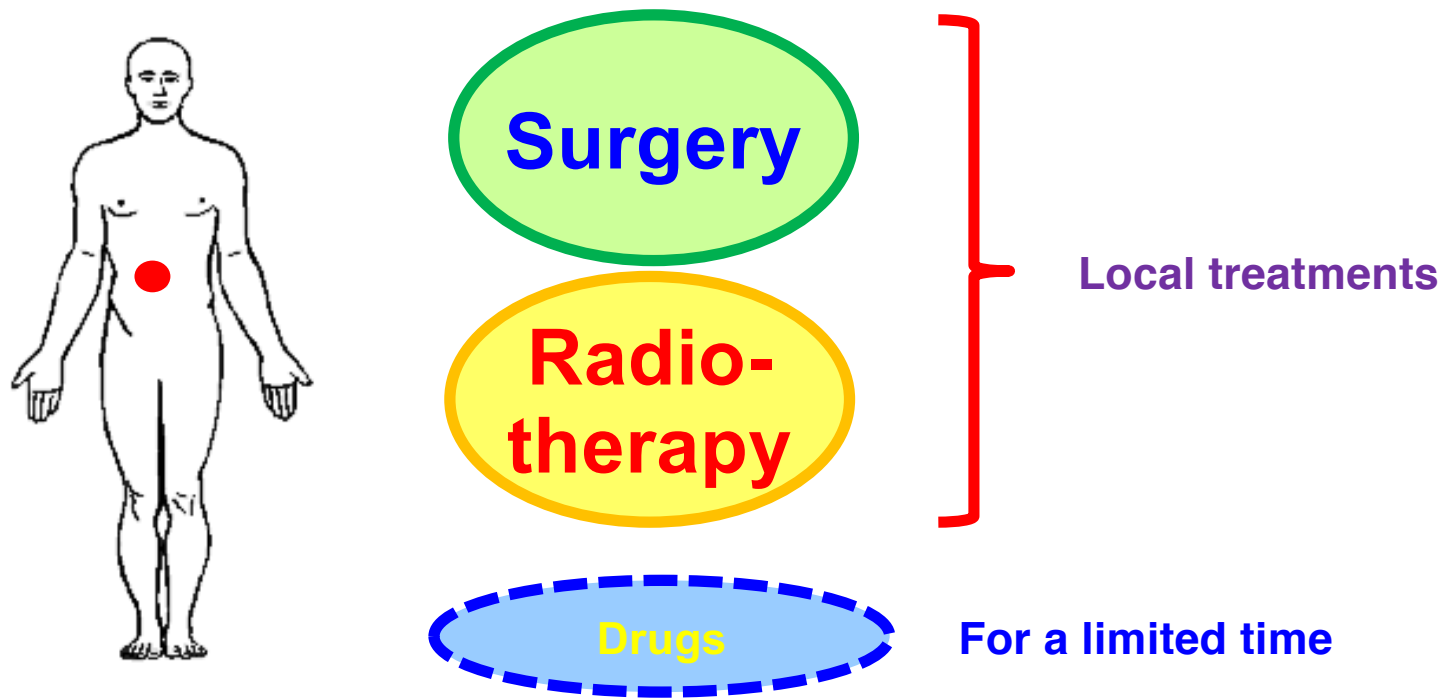
● Metastases

Treatment of cancer



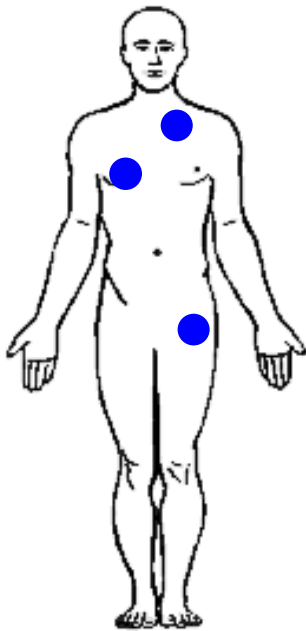
→ Aim = cure

Treatment of cancer

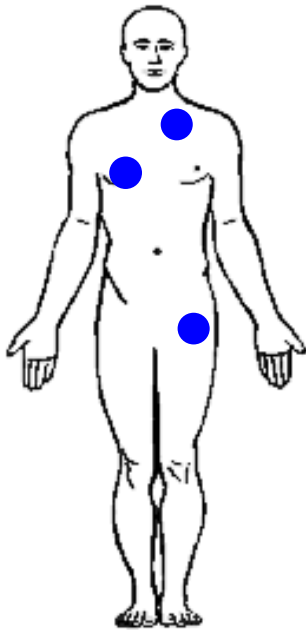


→ Aim = cure

Treatment of cancer



Treatment of cancer



Drugs

Treatment for life

Surgery

Radio-therapy

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

Treatment of cancer

Surgery

Radiotherapy

Chemotherapy

20th century

21st century



Treatment of cancer

Surgery

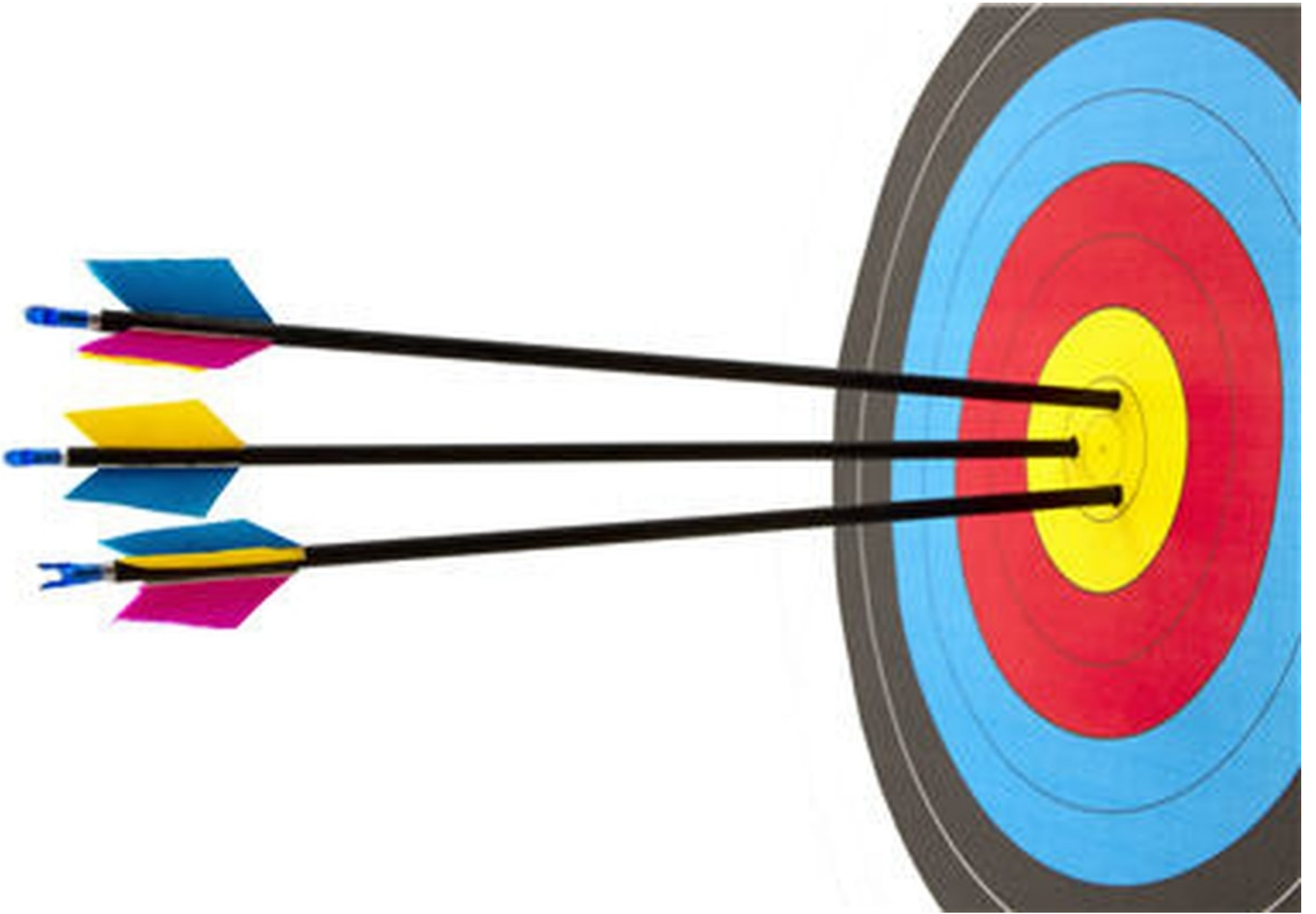
Radiotherapy

Chemotherapy

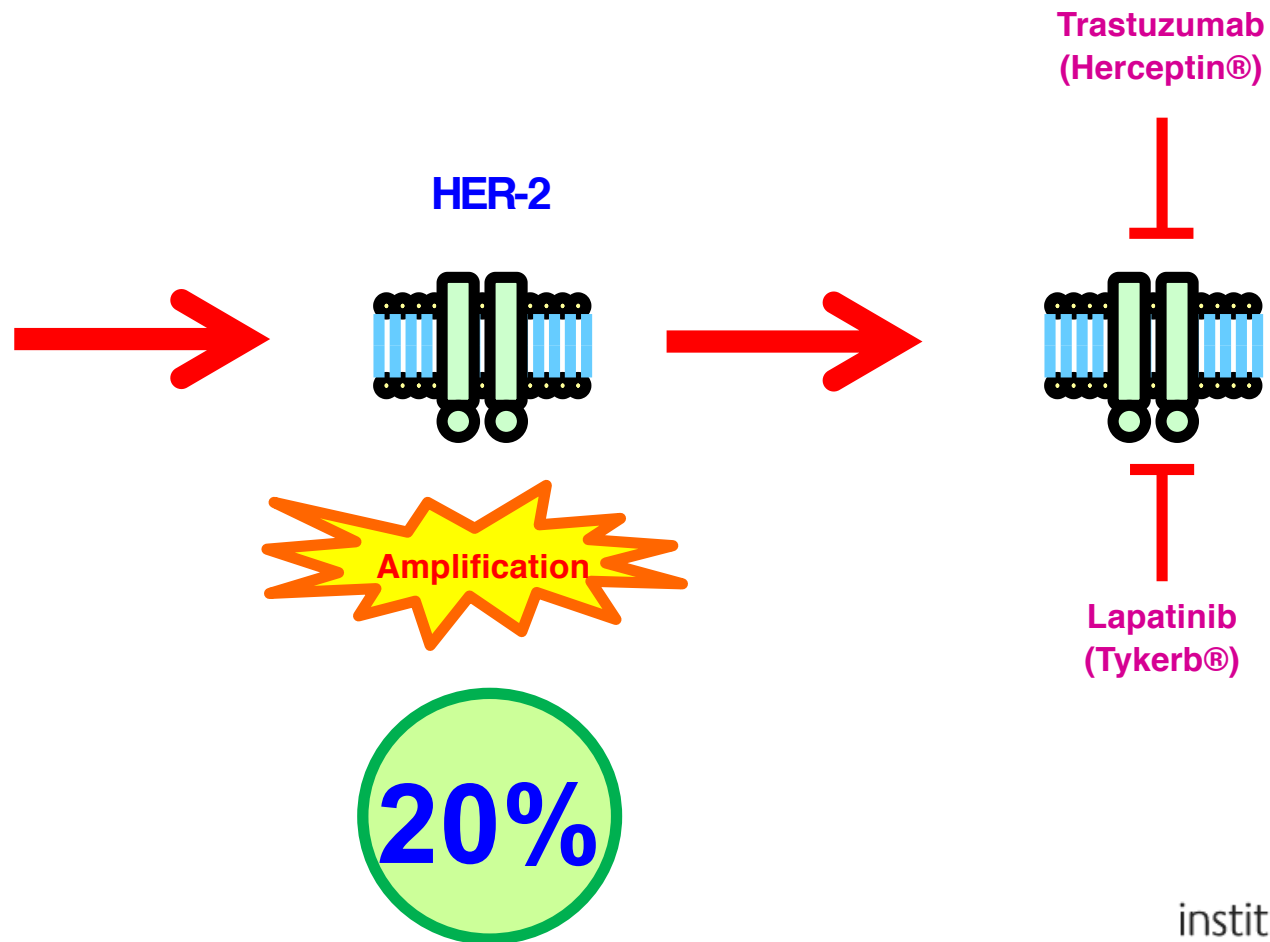
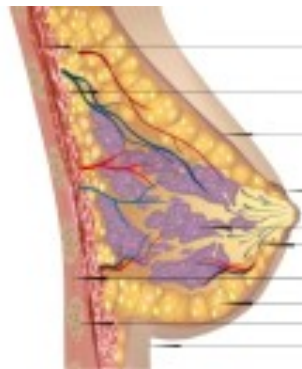
Targeted therapy

20th century

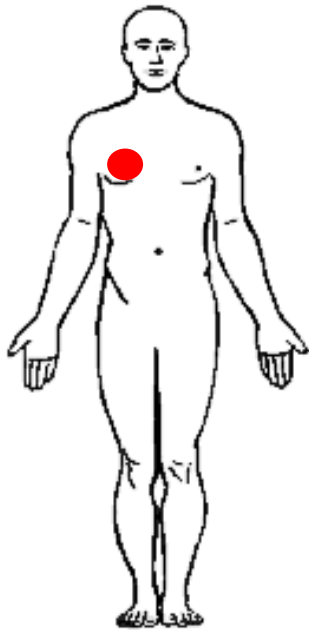
21st century



Treatment of cancer

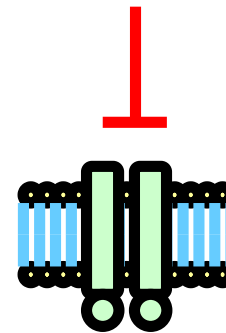


Treatment of cancer



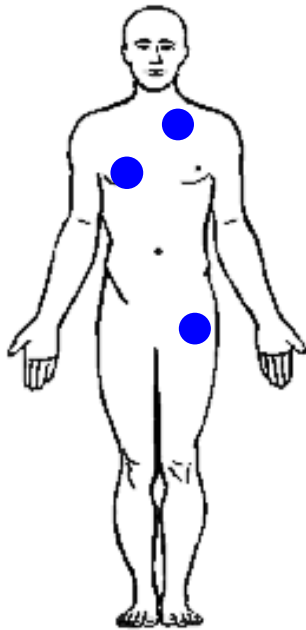
● HER2+ breast cancer

Trastuzumab
(Herceptin®)



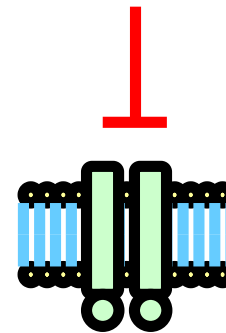
→ Risk of recurrence
decreased by 50%

Treatment of cancer



- HER2+ metastatic breast cancer

Trastuzumab
(Herceptin®)



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

Treatment of cancer

Surgery

Radiotherapy

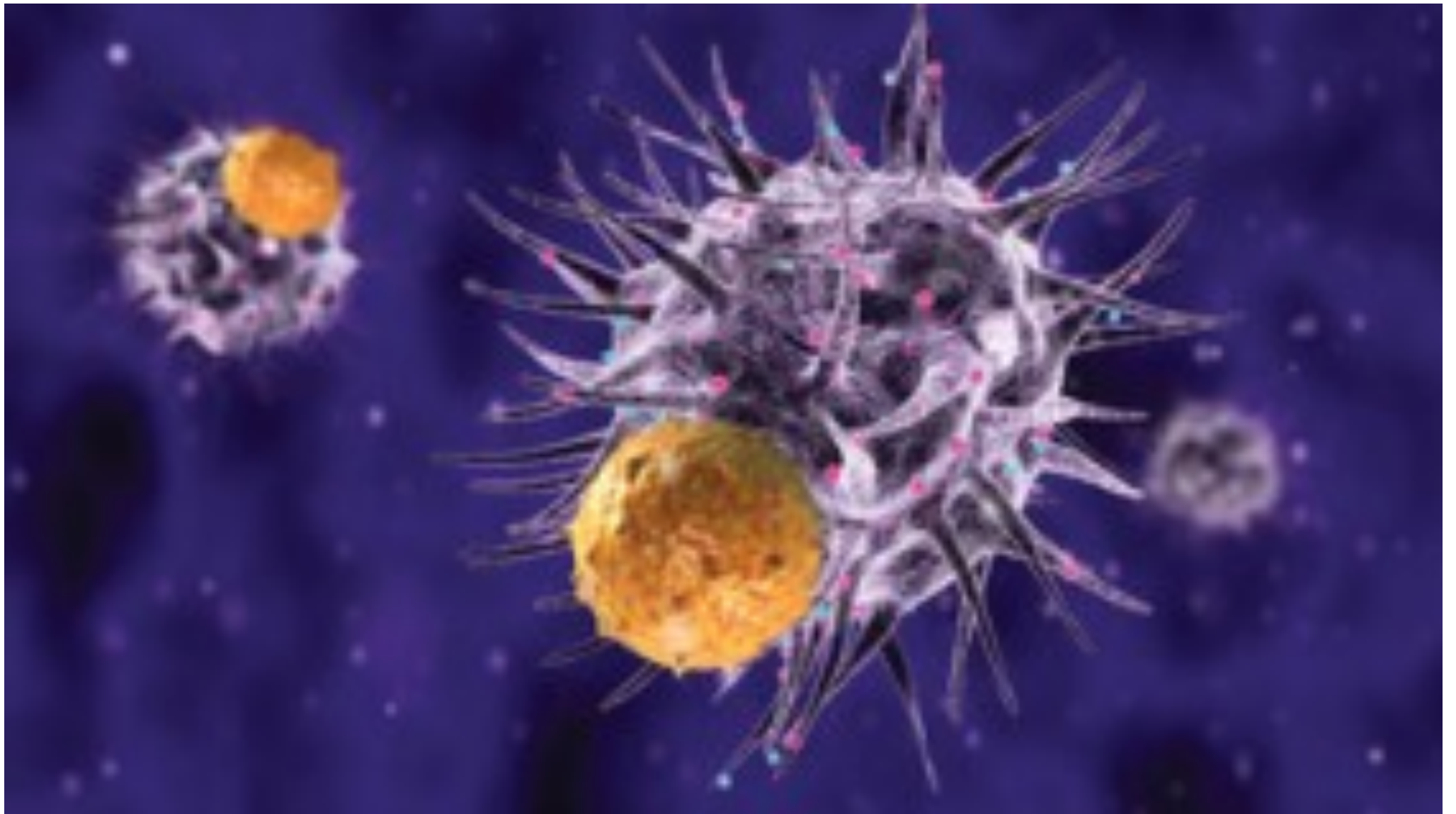
Chemotherapy

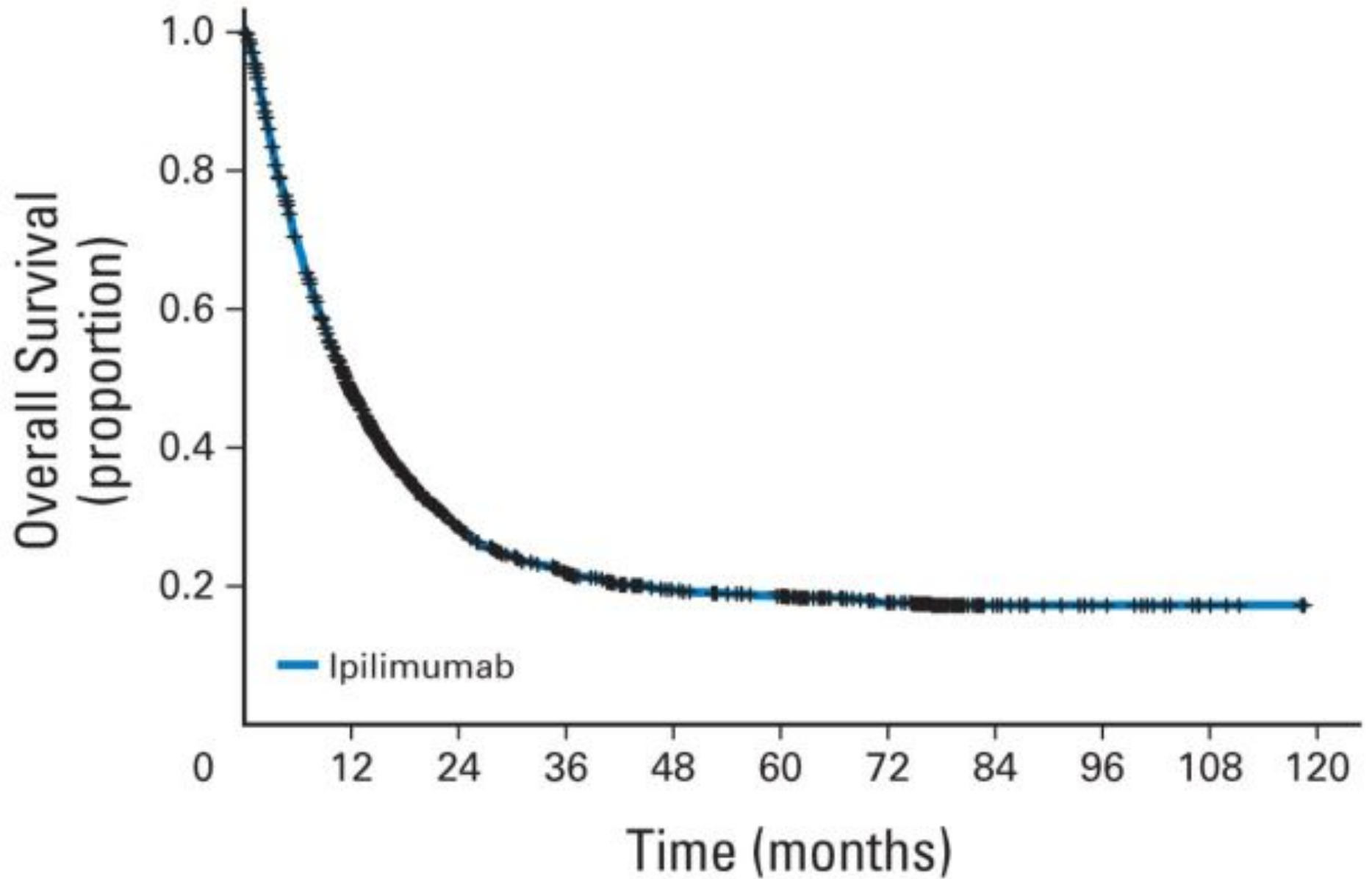
Targeted therapy

Immunotherapy

20th century

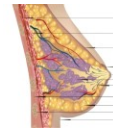
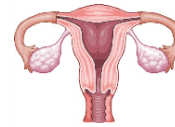
21st century





No. at risk
Ipilimumab 1,861 839 370 254 192 170 120 26 15 5 0

Treatment of cancer



Chemotherapy

Chemotherapy

Chemotherapy

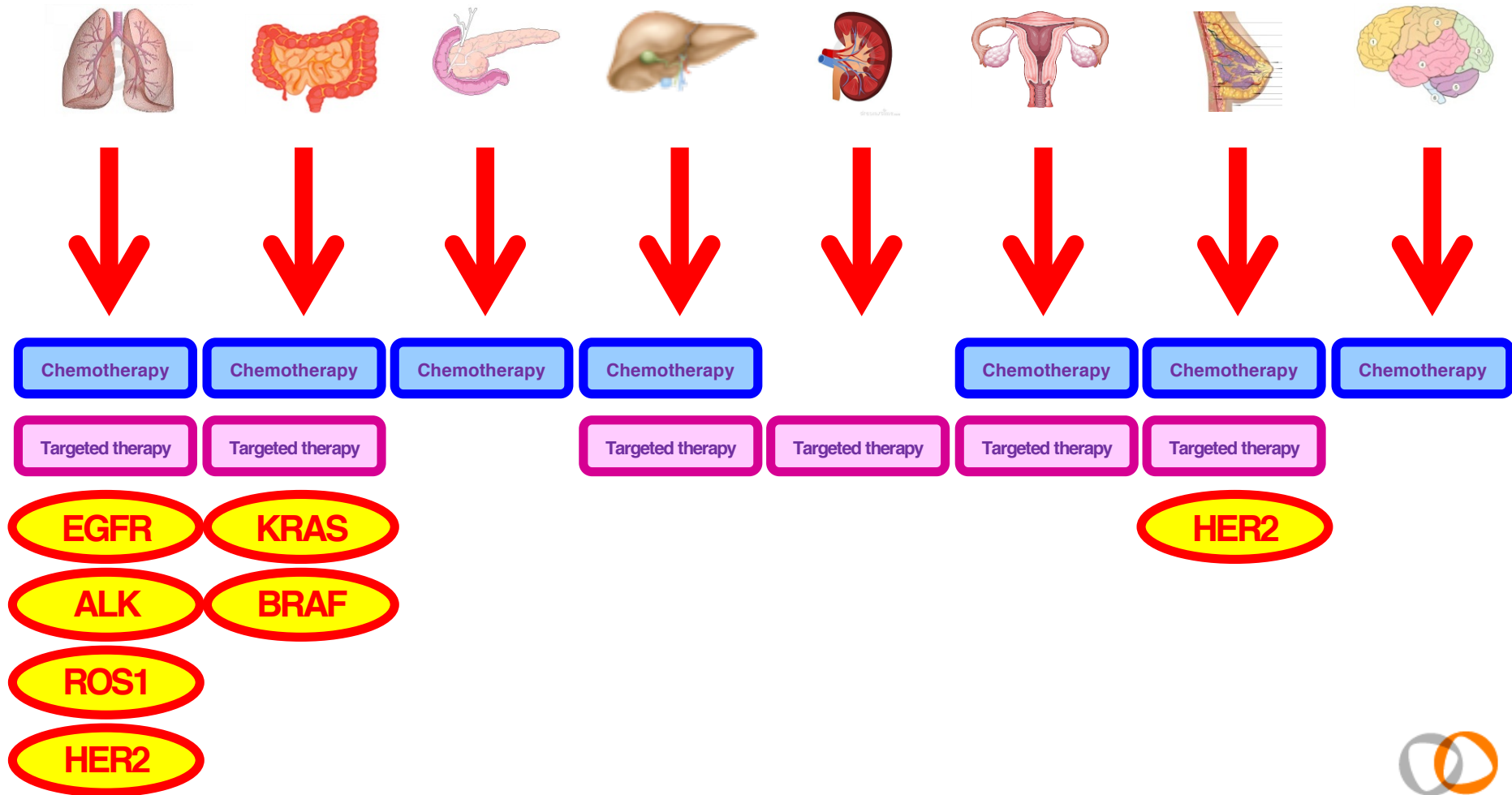
Chemotherapy

Chemotherapy

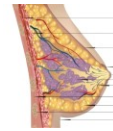
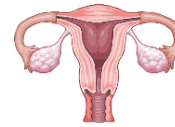
Chemotherapy

Chemotherapy

Treatment of cancer



Treatment of cancer



Chemotherapy

Chemotherapy

Chemotherapy

Chemotherapy

Chemotherapy

Chemotherapy

Chemotherapy

Targeted therapy

Targeted therapy

Targeted therapy

Targeted therapy

Targeted therapy

Targeted therapy

Immunotherapy

Immunotherapy

Immunotherapy

PD-L1





Utility of sequencing



Prognostic value

Predictive value

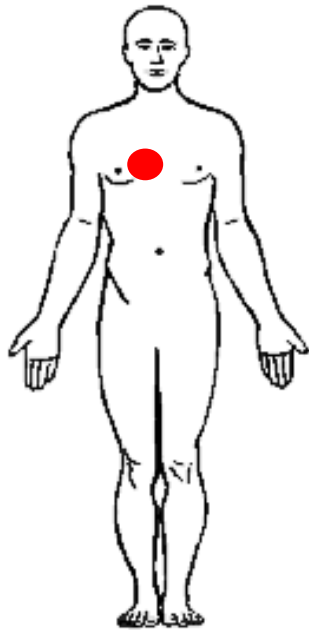
Utility of sequencing



Prognostic value



Utility of sequencing



Early breast cancer

Surgery

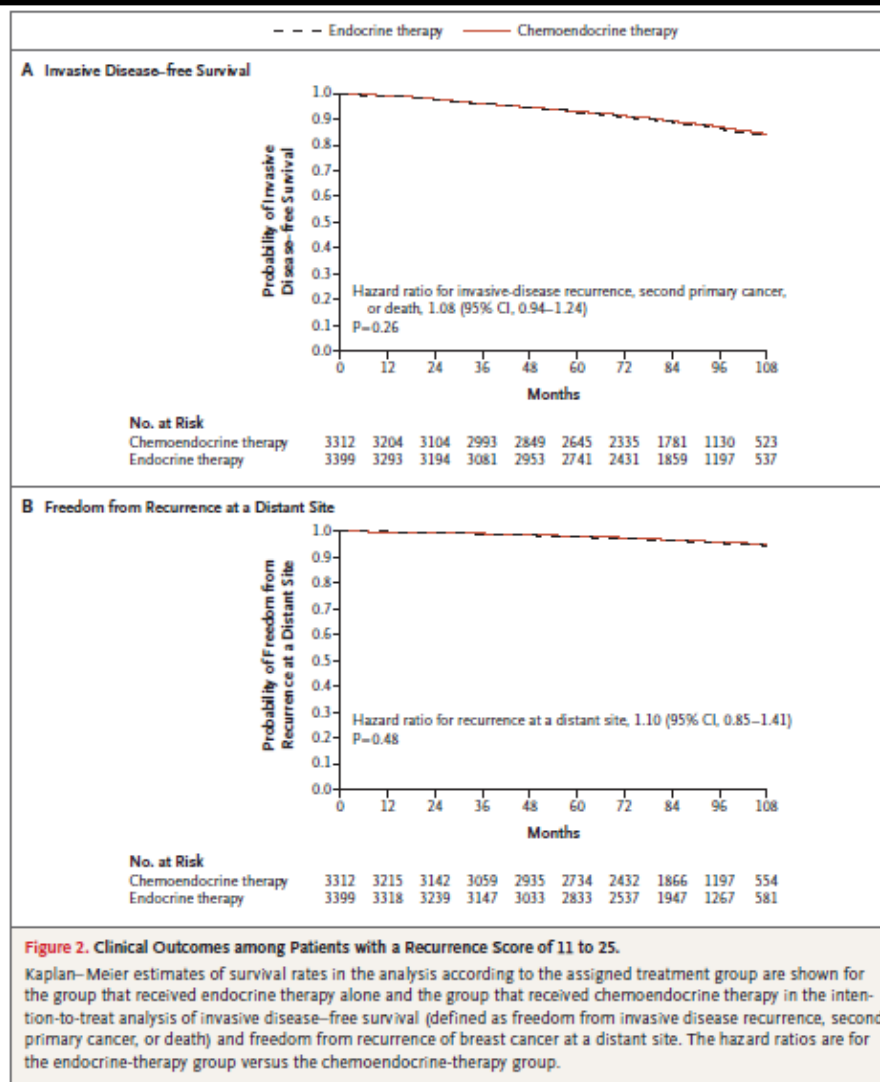
Radio-therapy



Chemotherapy

No chemotherapy

Utility of sequencing



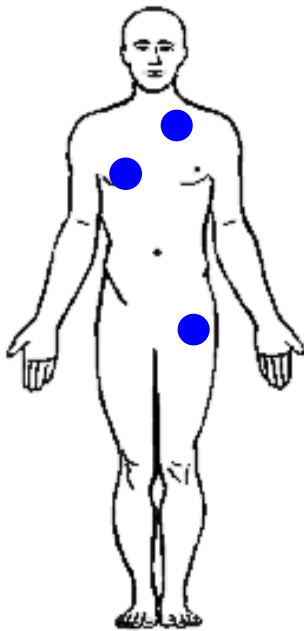
Utility of sequencing



Prognostic value ✓

Predictive value

Utility of sequencing



What drugs?

Surgery

Radiotherapy

Recurrent/metastatic cancer

SHIVA01

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Lancet Oncol 2015; 16: 1324-34

Published Online

September 3, 2015

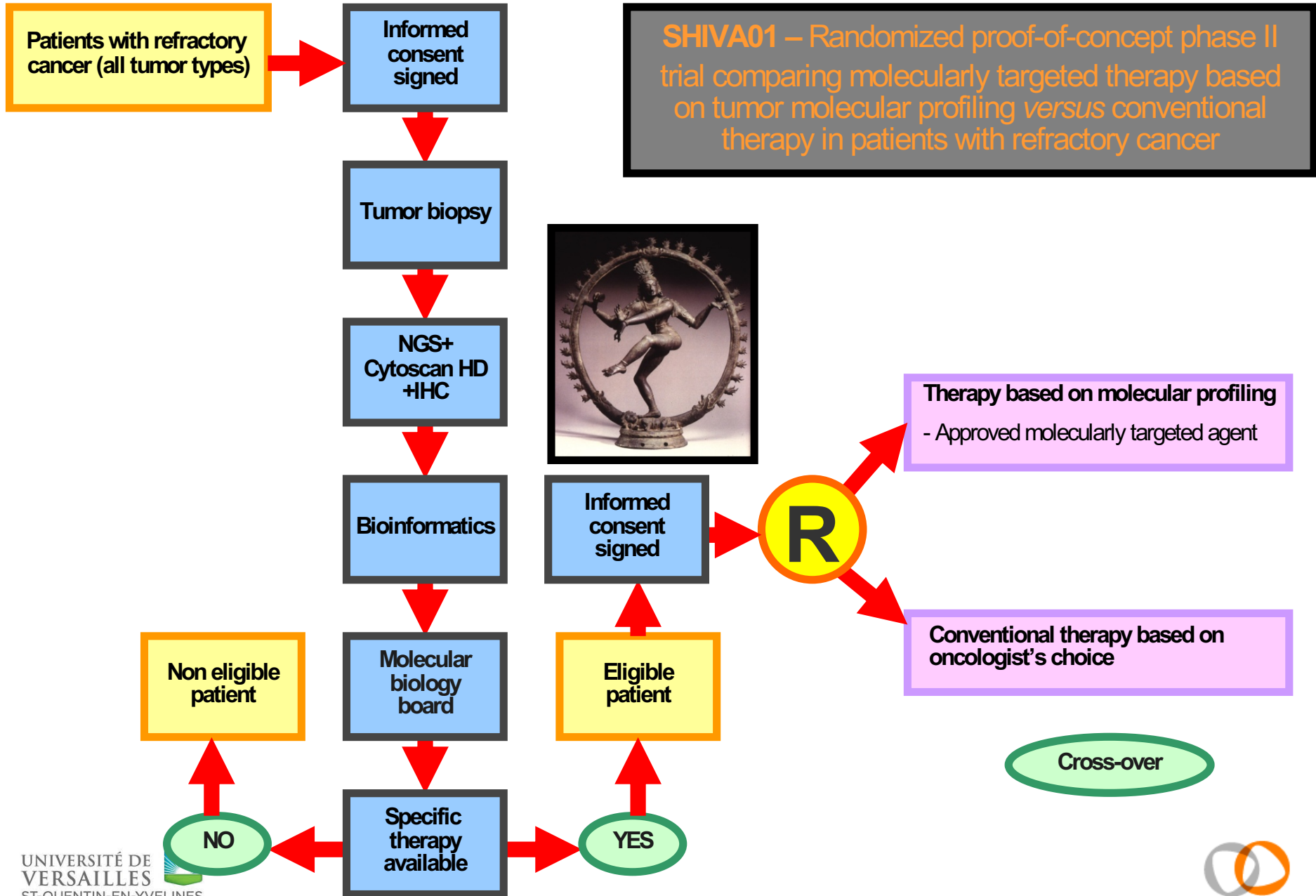
[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S1470-2045(15)00188-6)

[S1470-2045\(15\)00188-6](http://dx.doi.org/10.1016/S1470-2045(15)00188-6)

See Comment page 1276

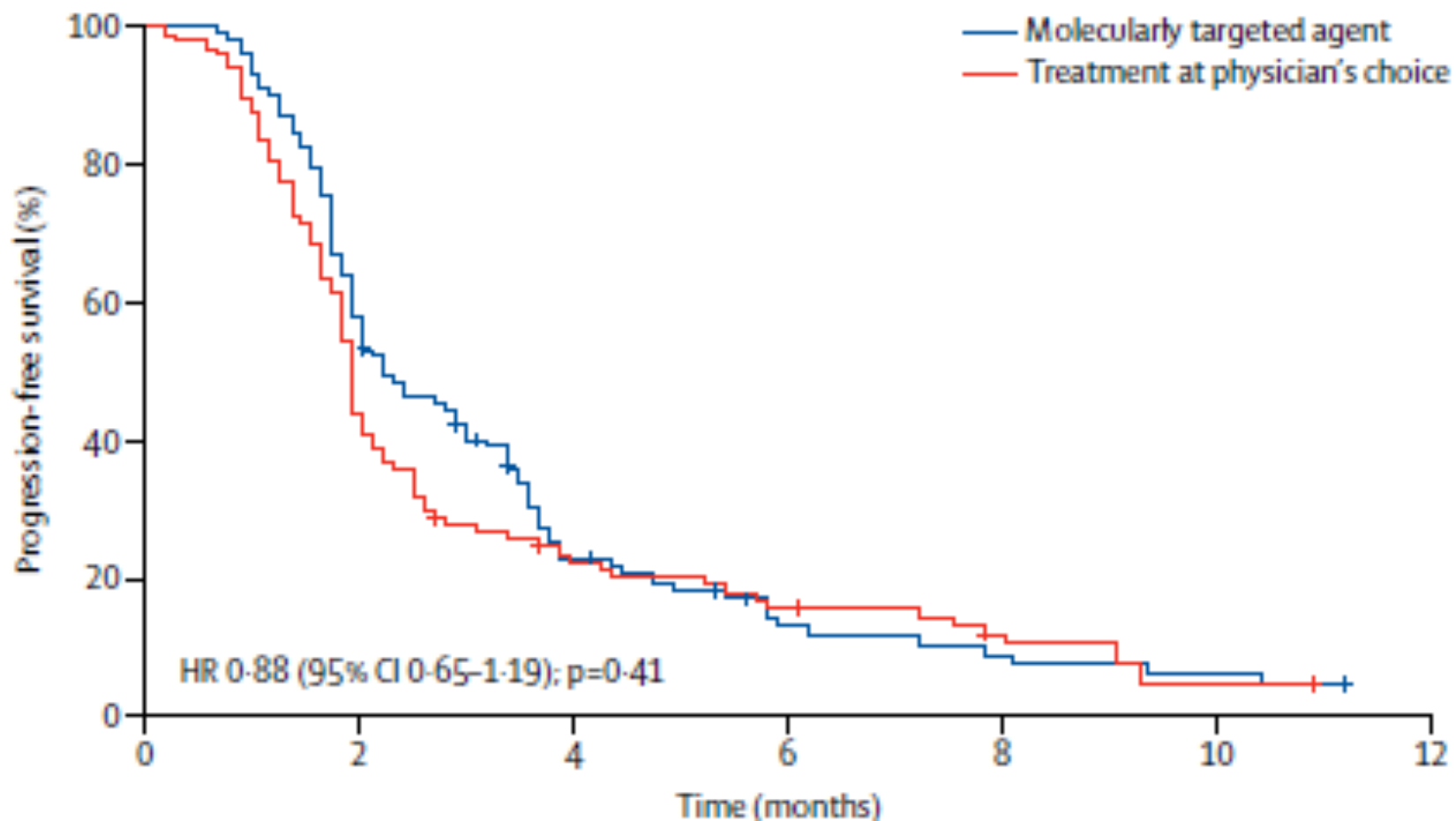
Department of Medical
Oncology, Institut Curie, Paris
& Saint-Cloud, France
(C Le Tourneau MD);

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Camponé, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sébastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators



SHIVA01

PFS – WHOLE POPULATION



Challenges



JNCI J Natl Cancer Inst (2016) 108(4): djv362

doi:10.1093/jnci/djv362

First published online November 23, 2015

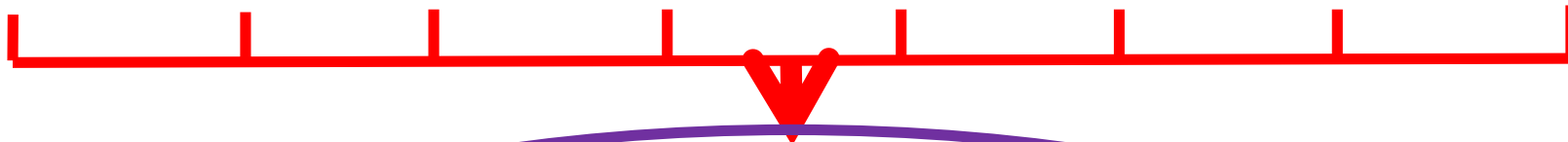
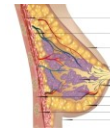
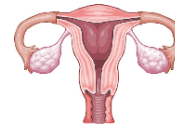
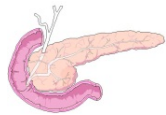
Review

REVIEW

Treatment Algorithms Based on Tumor Molecular Profiling: The Essence of Precision Medicine Trials

Christophe Le Tourneau*, Maud Kamal*, Apostolia-Maria Tsimberidou, Philippe Bedard, Gaëlle Pierron, Céline Callens, Etienne Rouleau, Anne Vincent-Salomon, Nicolas Servant, Marie Alt, Roman Rouzier, Xavier Paoletti, Olivier Delattre, Ivan Bièche

Challenges



= TREATMENT ALGORITHM

Targeted agent

Targeted agent

Targeted agent

Targeted agent

Targeted agent

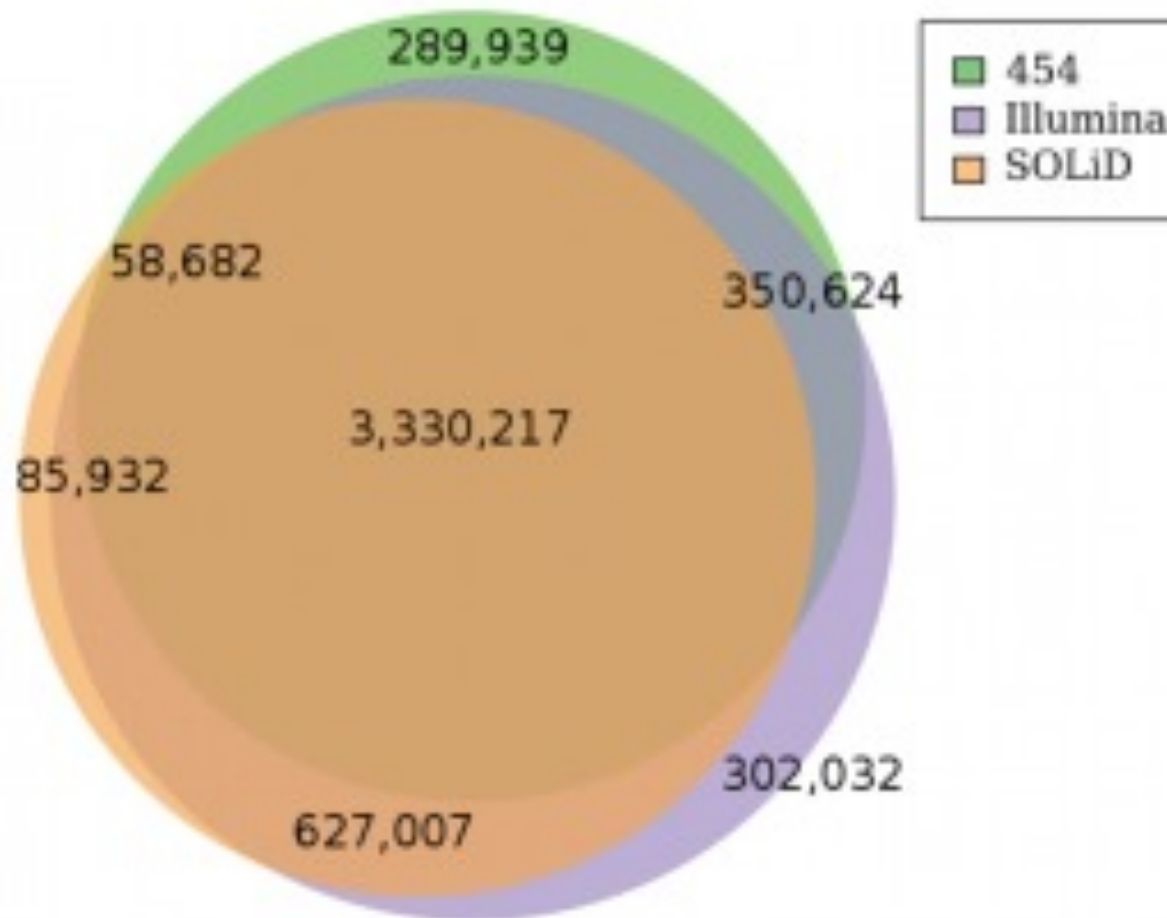
Targeted agent

Targeted agent

Challenges

- **Treatment algorithm:**
 - **technology** used to identify molecular alterations

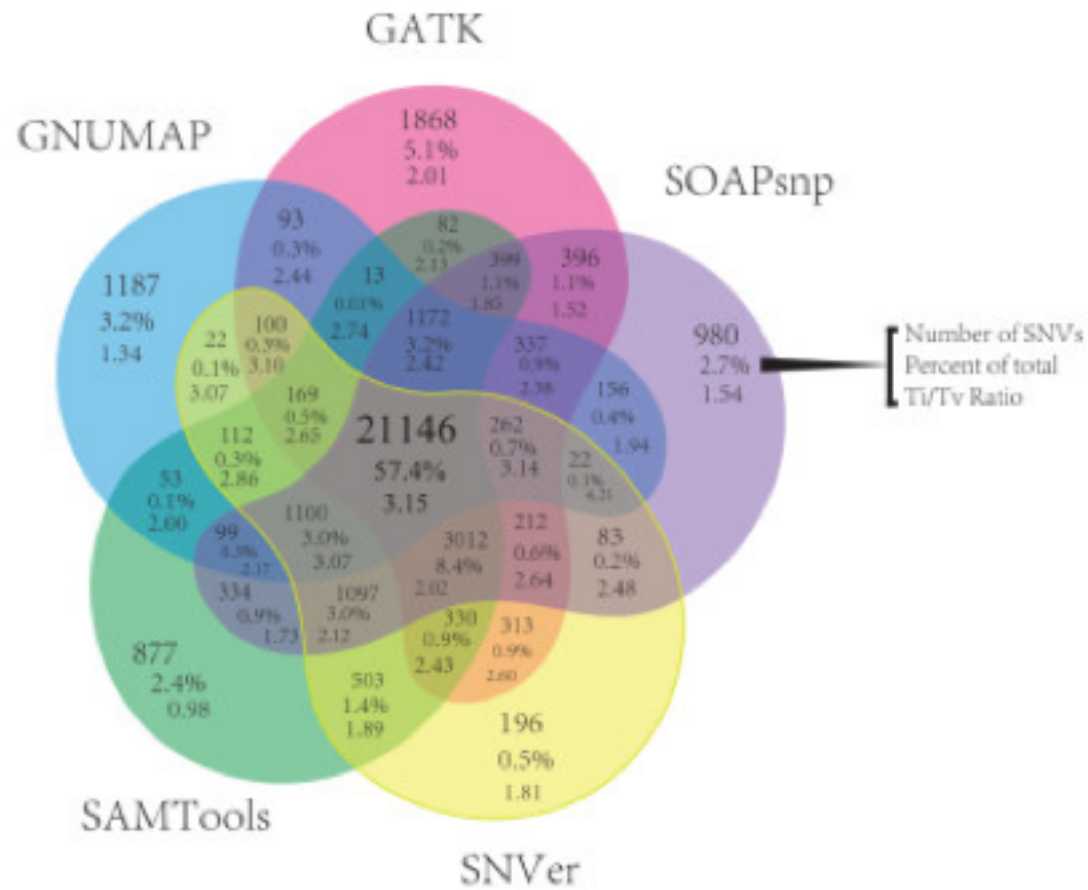
Challenges



Challenges

- **Treatment algorithm:**
 - **technology** used to identify molecular alterations
 - **thresholds** used

Challenges



Challenges

- **Treatment algorithm:**
 - **technology** used to identify molecular alterations
 - **thresholds** used
 - molecular alterations/drugs **matching**

Challenges

- **Treatment algorithm:**
 - **technology** used to identify molecular alterations
 - **thresholds** used
 - molecular alterations/drugs **matching**
 - molecular alterations **priorization**

Utility of sequencing

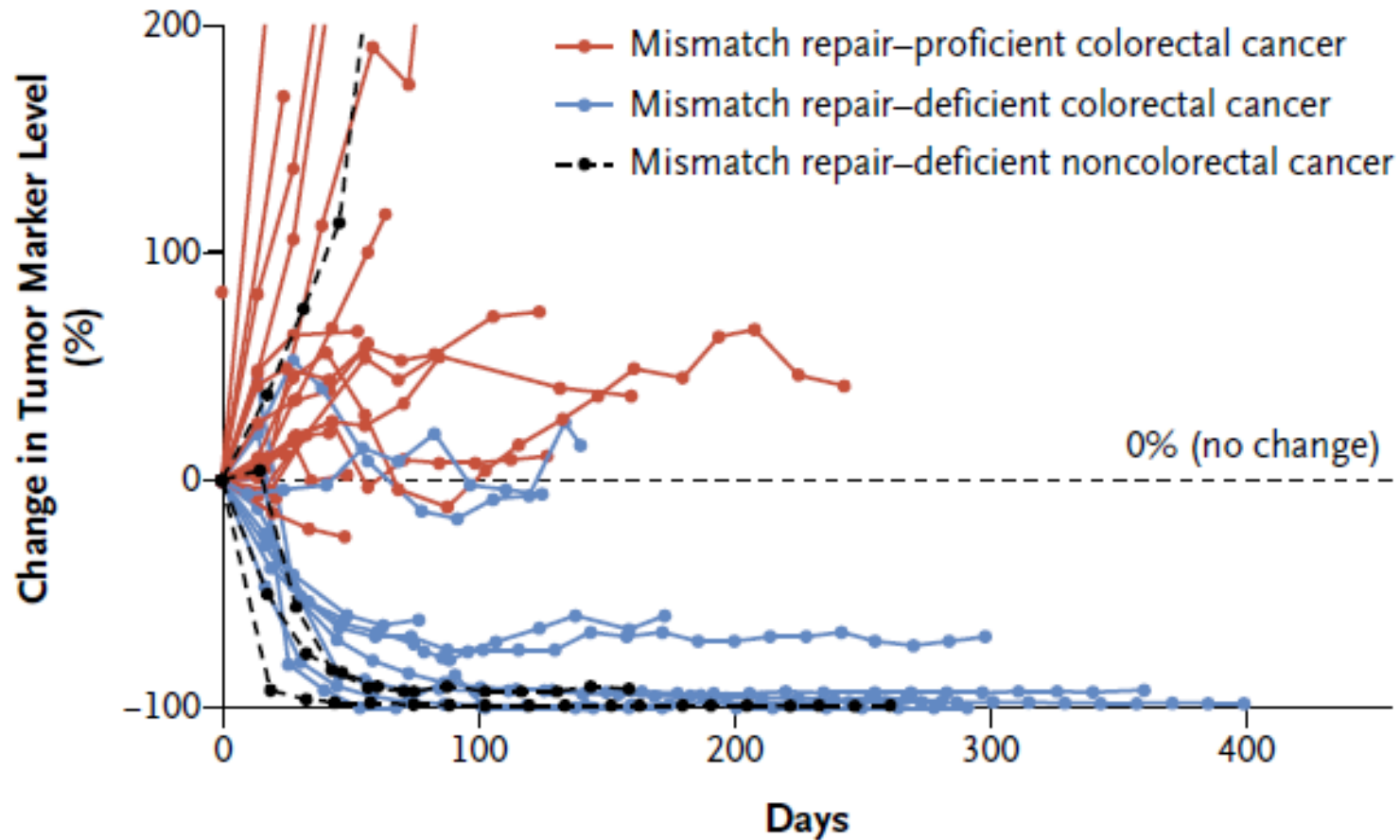
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

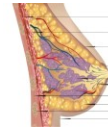
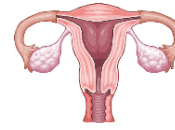
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Lubner, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

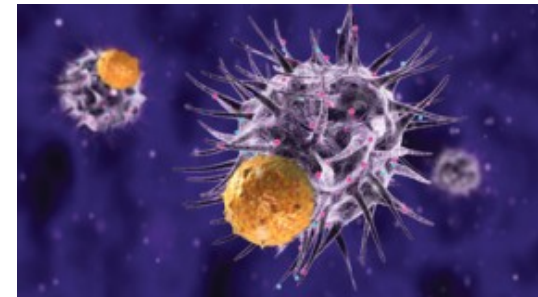
Utility of sequencing



Utility of sequencing



Pembrolizumab



Utility of sequencing

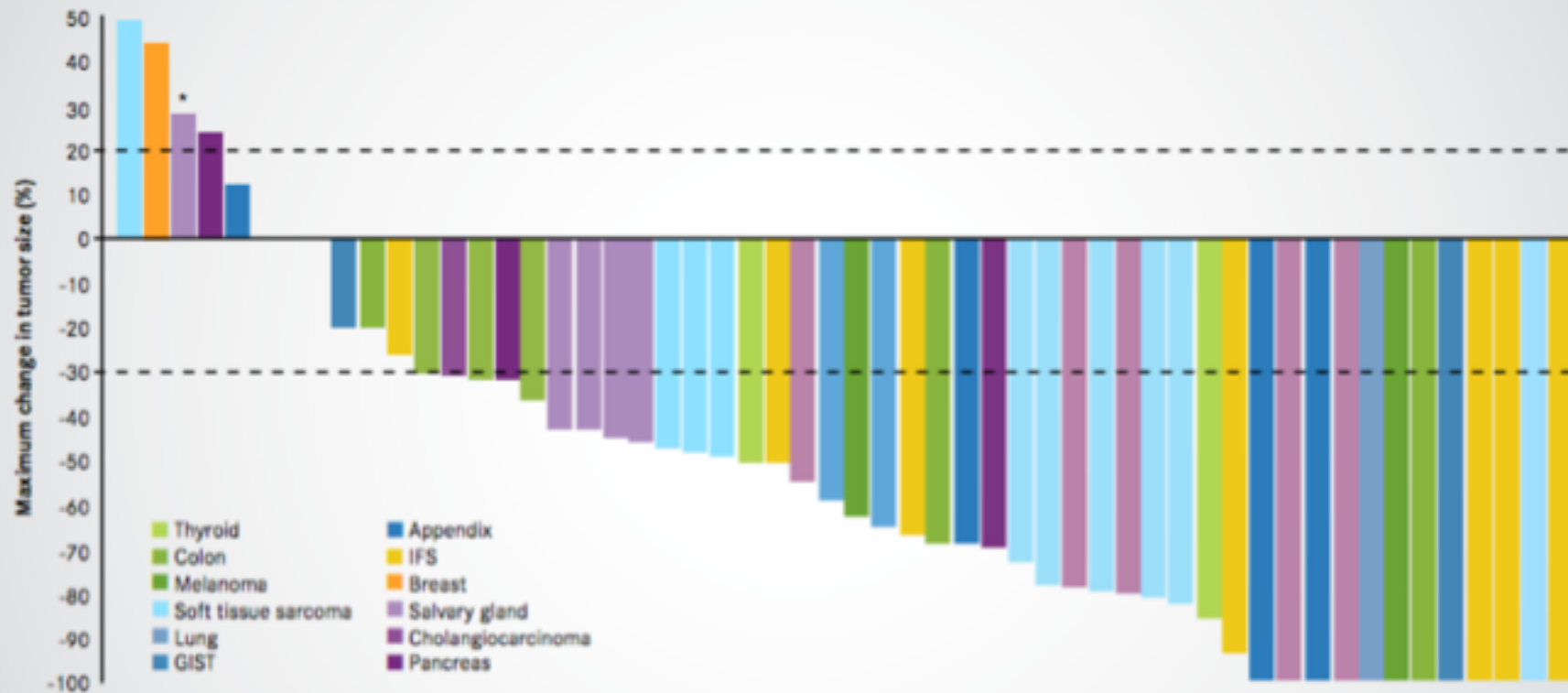
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

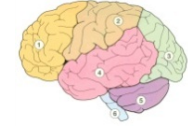
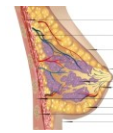
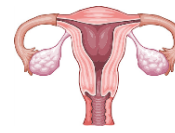
A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

Utility of sequencing

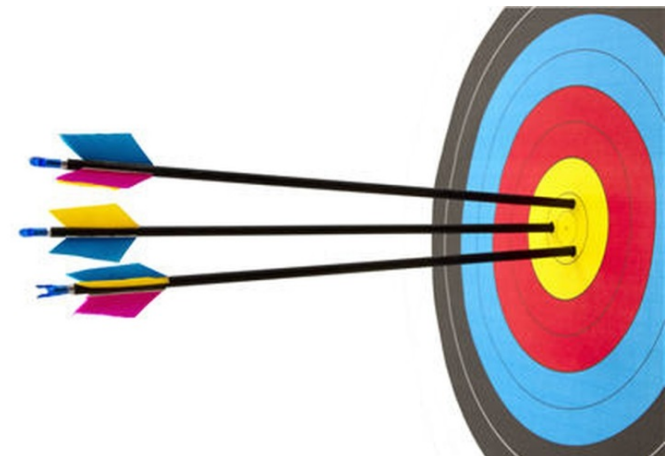


*Patient had TRK solvent front resistance mutation (NTRK G623R) at baseline due to prior therapy. * Pathologic CR
 Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
 CR indicates complete response; GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma.

Utility of sequencing



Larotrectinib



Conclusions

- **Sequencing** has been demonstrated to successfully guide the need of **adjuvant** therapy in hormone-positive **early breast cancer**

Conclusions

- **Sequencing** has been demonstrated to successfully guide the need of **adjuvant** therapy in hormone-positive **early breast cancer**
- The **predictive** value of **sequencing** to guide **therapy** in cancer patients has not been demonstrated with a level 1 **evidence**

Conclusions

- All **recurrent/metastatic** cancer patients should be sequenced for **MSI** and **NTRK fusions**, and potential inclusion into **clinical trials**