The drug therapy journey:

learned clinical needs for modern treatments

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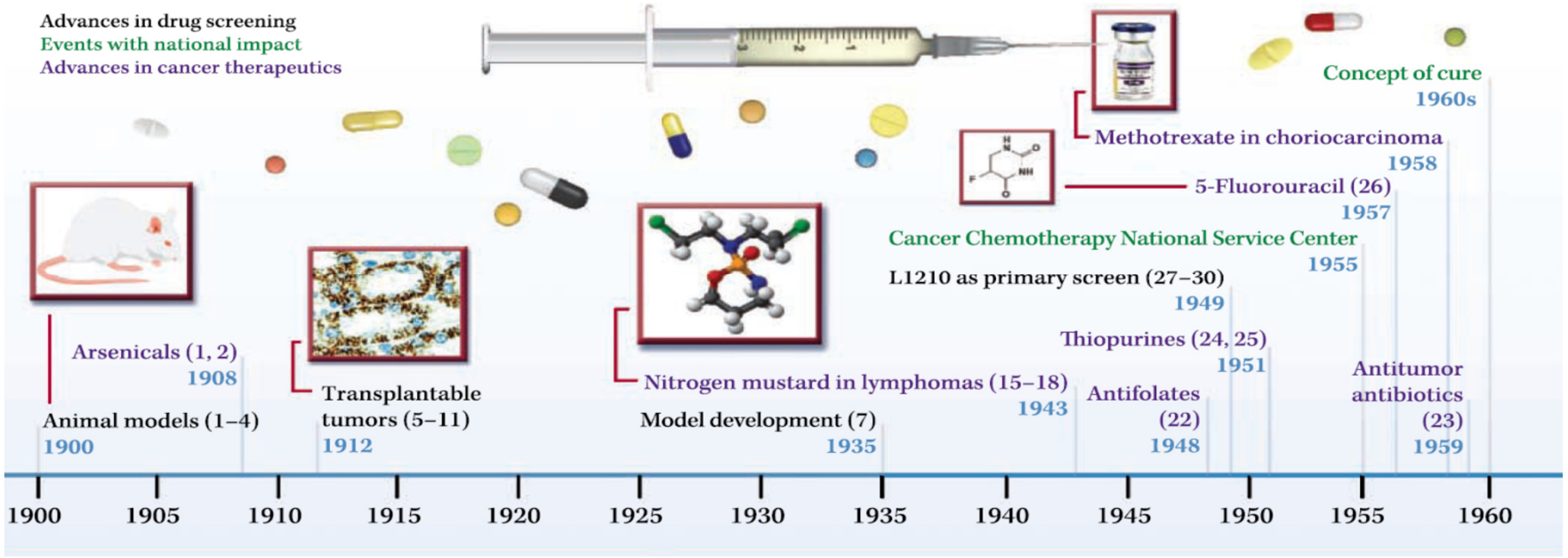
Rome

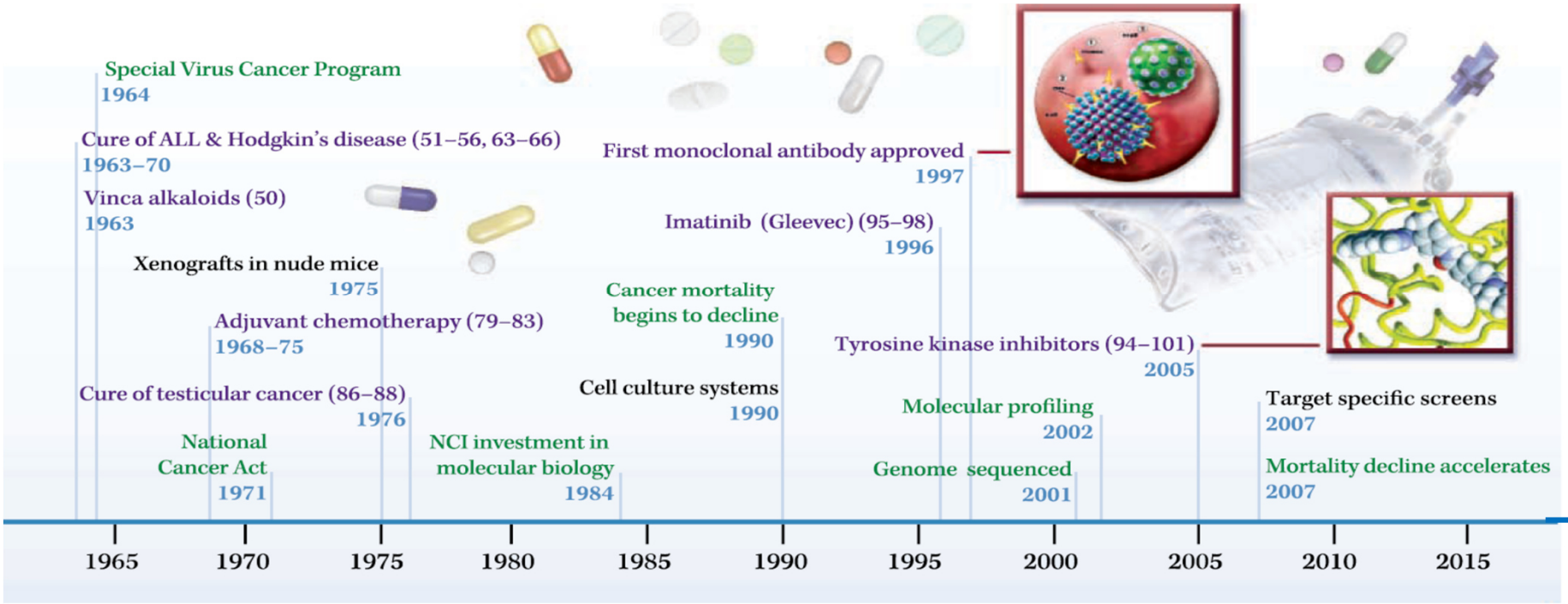
Gemelli

Comprehensive Cancer Center

UNIVERSITÀ CATTOLICA del Sacro Cuore

Key Advances in the History of Cancer Research





Immunetherapy
ADC
Vaccines
PARPi

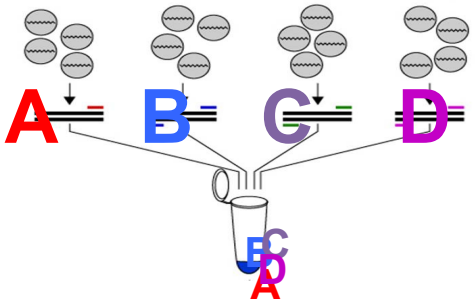
2020'

New technologies of Next generation sequencing

blood

paraffin

Genomic DNA

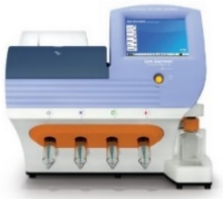


Sanger

350 bp for each sequence
8,538/350 = 25 reactions

Costs: ~ 2,000 €
Time: ~ 1 month

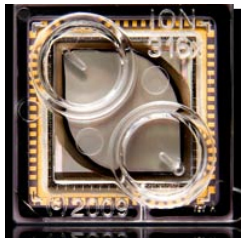
ION Torrent

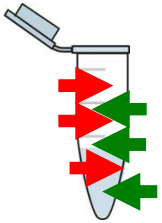


1 reaction

Multiple genes and samples

Costs: ~ 600 €
Time: ~ 5 days





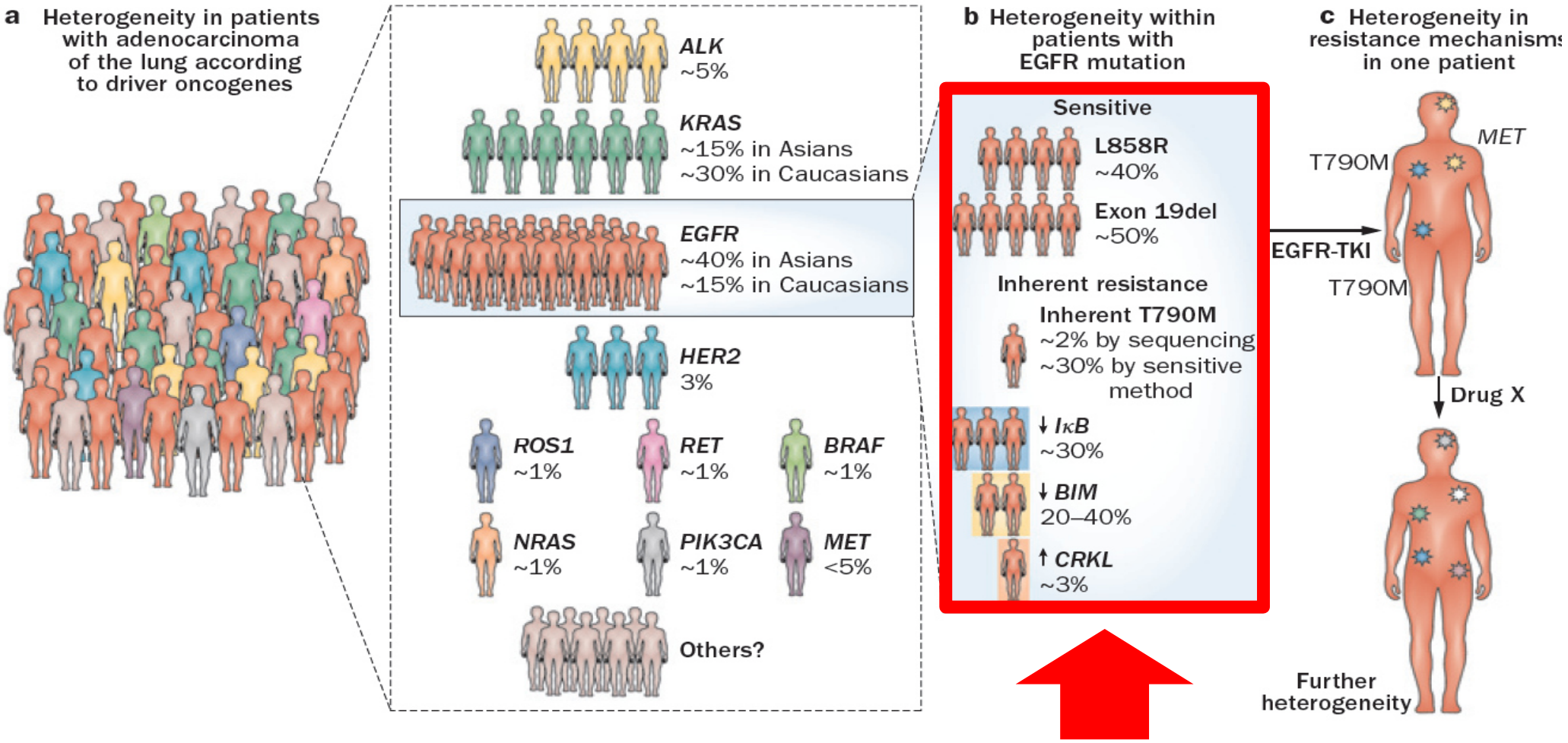
~ 500 genes

Bar Code – many patients simultaneously

3.5 hrs - 1 hr manual work

Courtesy of Prof. Aldo Scarpa

Selection of patients based on specific targets



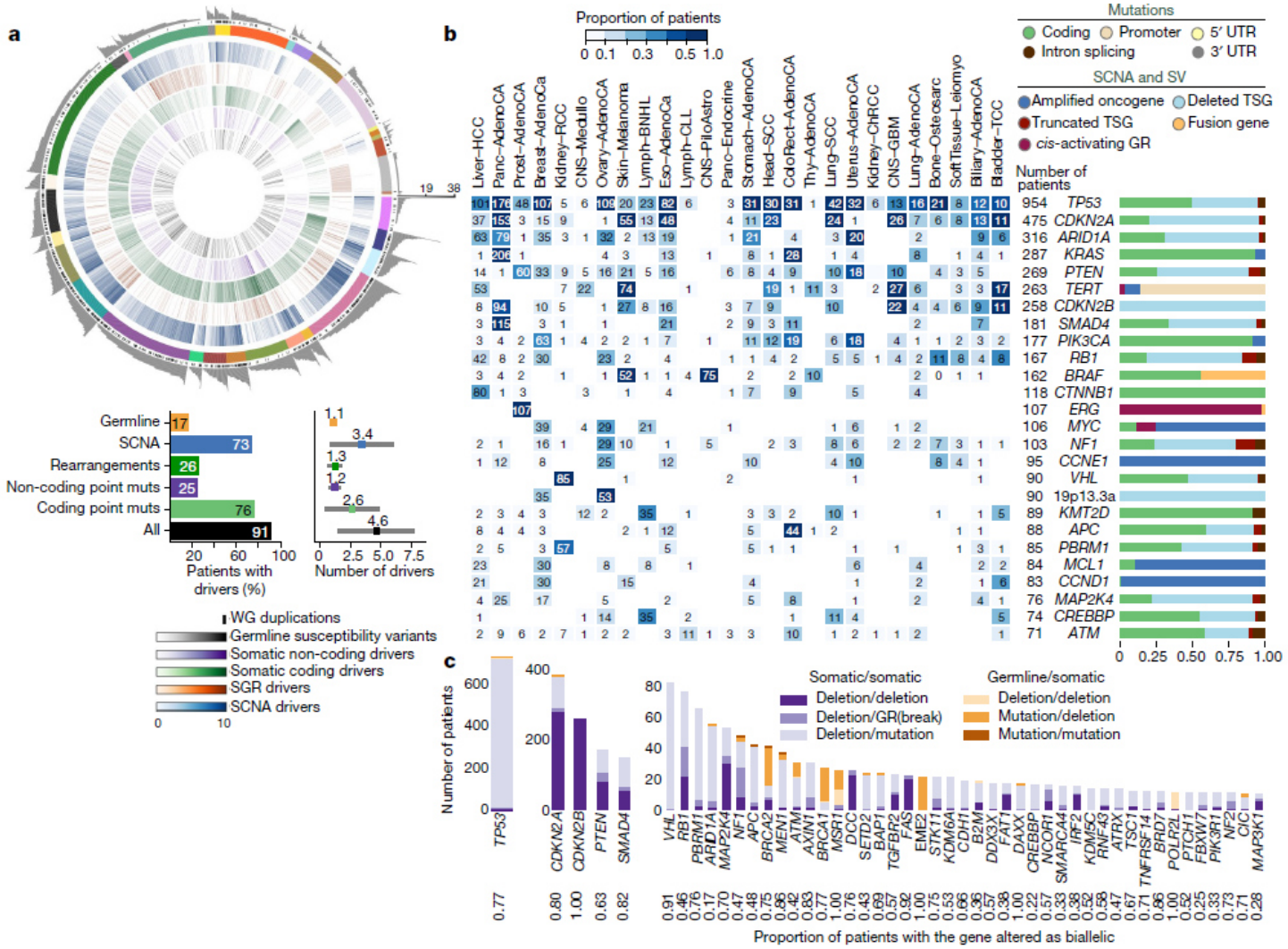
Mitsudomi T, Nat Rev Clin Oncol 2013

Pan-cancer analysis of whole genomes

https://doi.org/10.1038/s41586-020-1969-6
Received: 29 July 2018
Accepted: 11 December 2019
Published online: 5 February 2020

The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium

Cancer is driven by genetic change, and the advent of massively parallel sequencing has enabled systematic documentation of this variation at the whole-genome scale[1–3]. Here



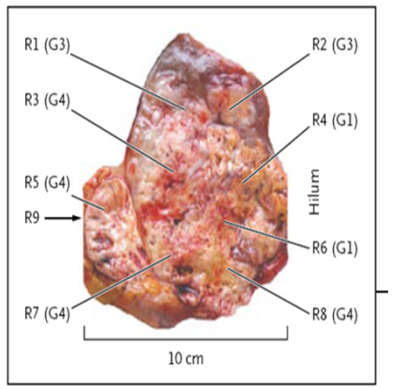
Panorama of driver mutations in PCAWG

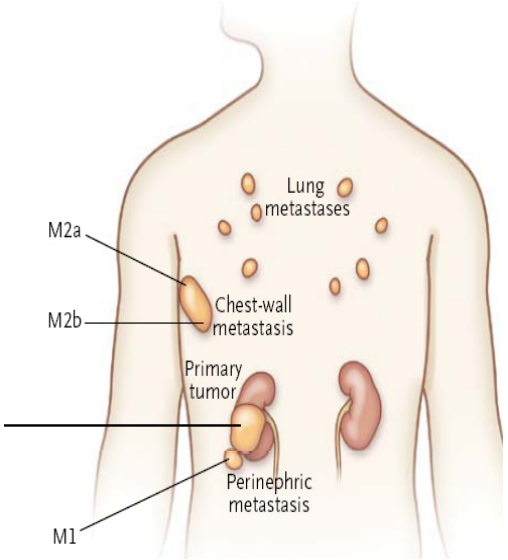
a, Top, putative driver mutations in PCAWG

b, Genomic elements targeted by different types of mutations in the cohort altered in more than 65 tumours. Both germline and somatic variants are included.

c, Tumour-suppressor genes with biallelic inactivation in 10 or more patients.

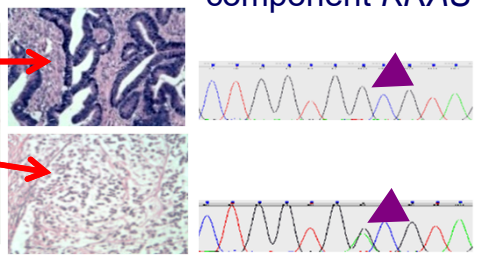
Tumor Heterogeneity



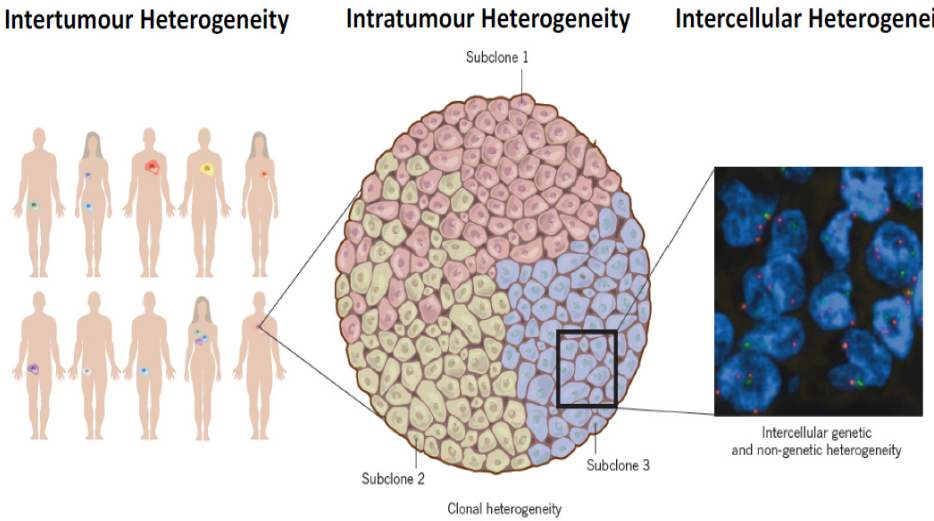


Colon cancer

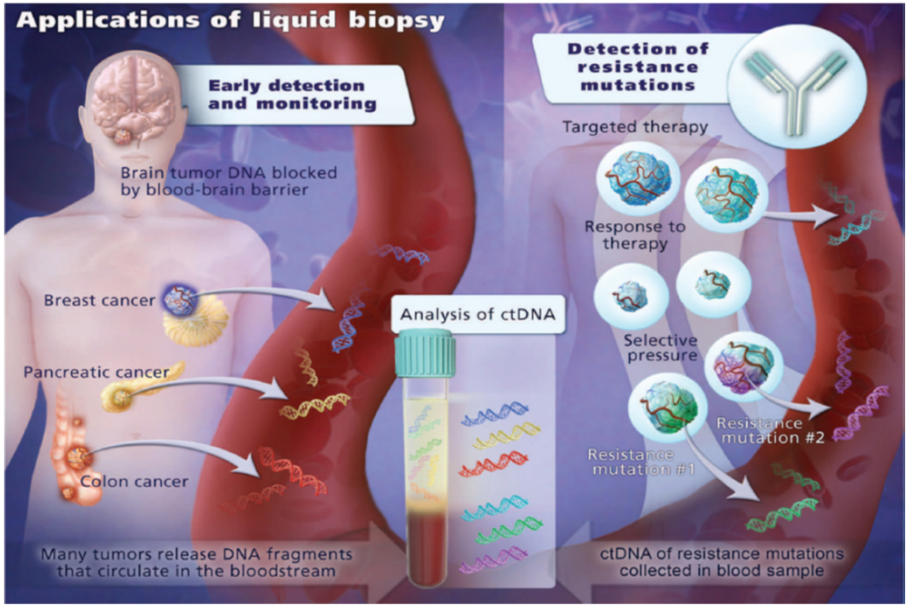
Adenocarcinomatous component *KRAS wt*

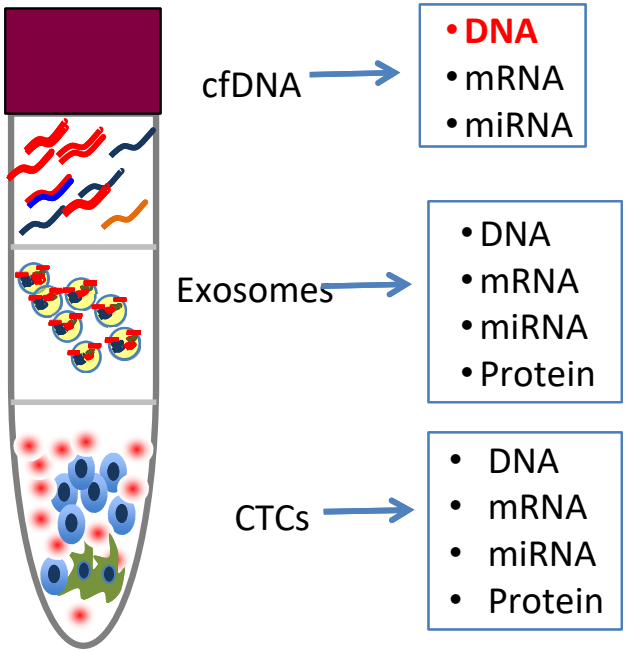


Signet ring cell component with *KRAS* mutation



Liquid Biopsy





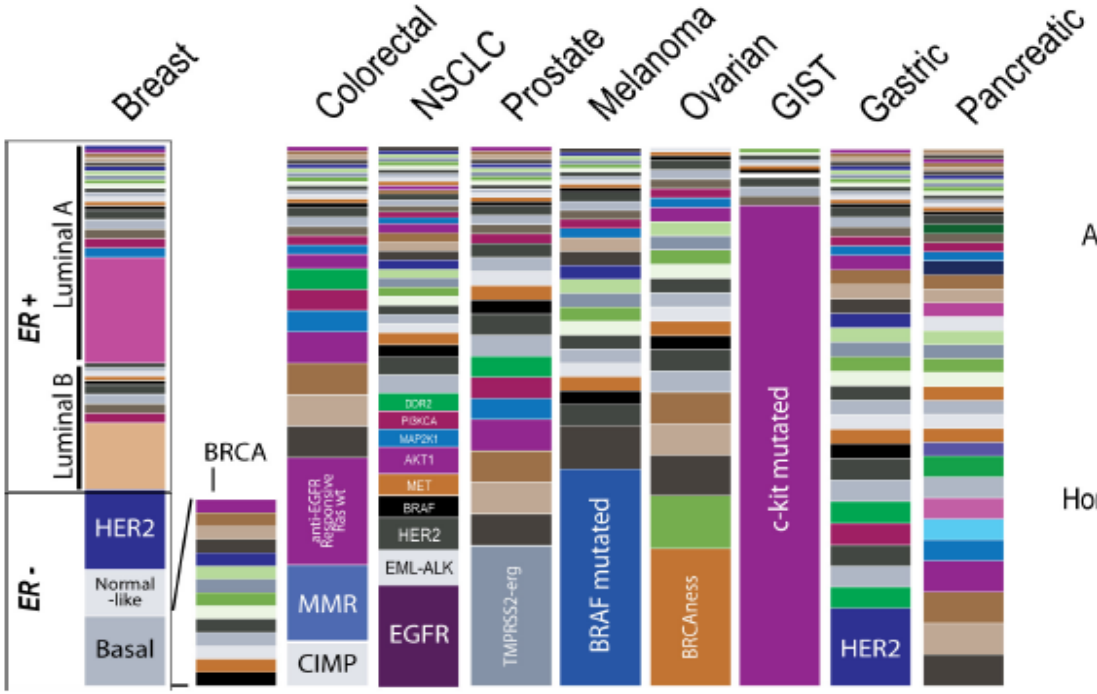
Sample Type	n	Objective Response Rate* % (95% confidence interval)
Tissue	443	33.9 (29.5–38.5)
Plasma	374	32.1 (27.4–37.1)
Urine	169	36.7 (29.4–44.4)

Anticipated diagnosis: 3 to 9 months compared to imaging (TC, MR ec.)

Different classification of tumours, different study design

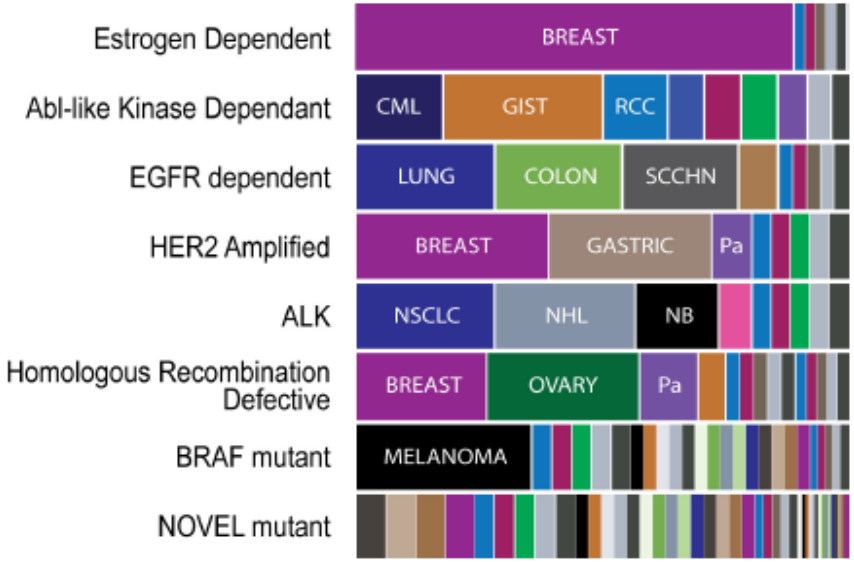
Site of tumor origin

Umbrella studies



Molecular Alteration

Basket studies

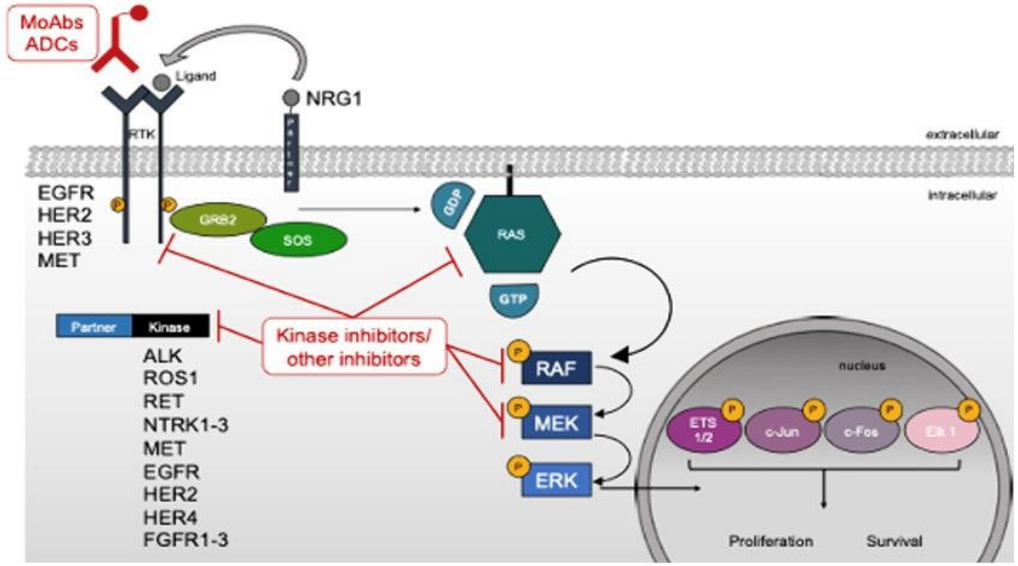


Biankin A, and ESMO E-learning module, prof. A. Scarpa

Tumor Agnostic approach: from Basket trials to Drug Approval

Tumor-specific
(anatomical/empiric/biologic)

Tumor-agnostic
(biologic only)



Therapy	Biomarker	FDA approval date[a]
Pembrolizumab (Keytruda)	MSI-H or dMMR	May 2017
Pembrolizumab	TMB-H[b]	June 2020
Larotrectinib (Vitrakvi)	*NTRK* gene fusion	November 2018
Entrectinib (Rozlytrek)	*NTRK* gene fusion	August 2019
Dostarlimab-gxly (Jemperli)	dMMR	February 2022
Dabrafenib (Tafinlar) + trametinib (Mekinist)	*BRAF* V600E mutation	June 2022

Adapted from Doebele et al 2019

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 0: 1–8, 2018
doi:10.1093/annonc/mdy263

SPECIAL ARTICLE

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J. -Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12]* & L. Pusztai[13]

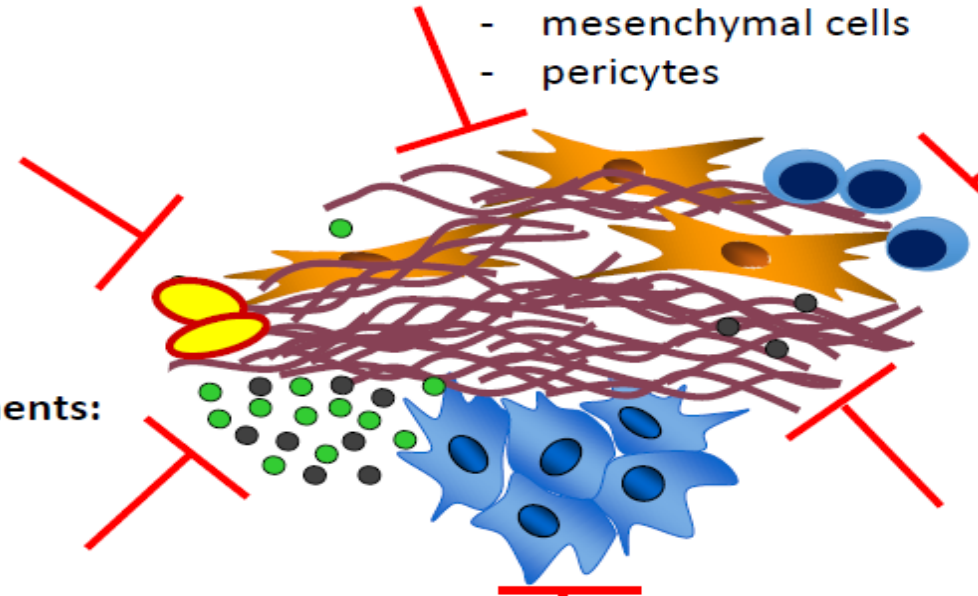
	Readiness for use in clinical practice	**Current examples of genomic alterations**
Tier I (I-A, I-B, I-C)	Targets ready for implementation in routine clinical decisions	HER2 in breast cancer BRCA1/2 in ovarian and breast cancer EGFR, ROS1/ALK in NSCLC TRK, PD1 in multiple cancers BRAF in metastatic melanoma
Tier II (II-A, II-B)	Investigational targets likely to define patients who benefit from a targeted drug, but additional data needed	PTEN pathway (PIK3CA, AKT1)
Tier III (III-A, III-B)	Clinical benefit previously demonstrated in other tumour type or for similar molecular targets	BRAF in non-melanoma cancers PALB2 and other non-BRCA DNA repair mutations
Tier IV (IVA, IVB)	Preclinical evidence of actionability	Hypothetical targets for future clinical testing
Tier V	Evidence supporting co-targeting approaches	PIK3CA in ER+, HER- breast cancer
Tier X	Lack of evidence for actionability	

The tumor microenvironment

Cellular components
- CAFs
- FAP$^+$, α-SMA, FSP-1, PDGF-R fibroblasts
- PSCs
- myofibroblasts
- mesenchymal cells
- pericytes

Matricelullar proteins
- SPARC
- Periostin
- Tenascin
- Osteopontin

Immune cells
e.g. CD40



Soluble components:
- CTGF
- FGF
- VEGF
- HGF
- EGF
- TGF-β
- IL-6
- IL-8

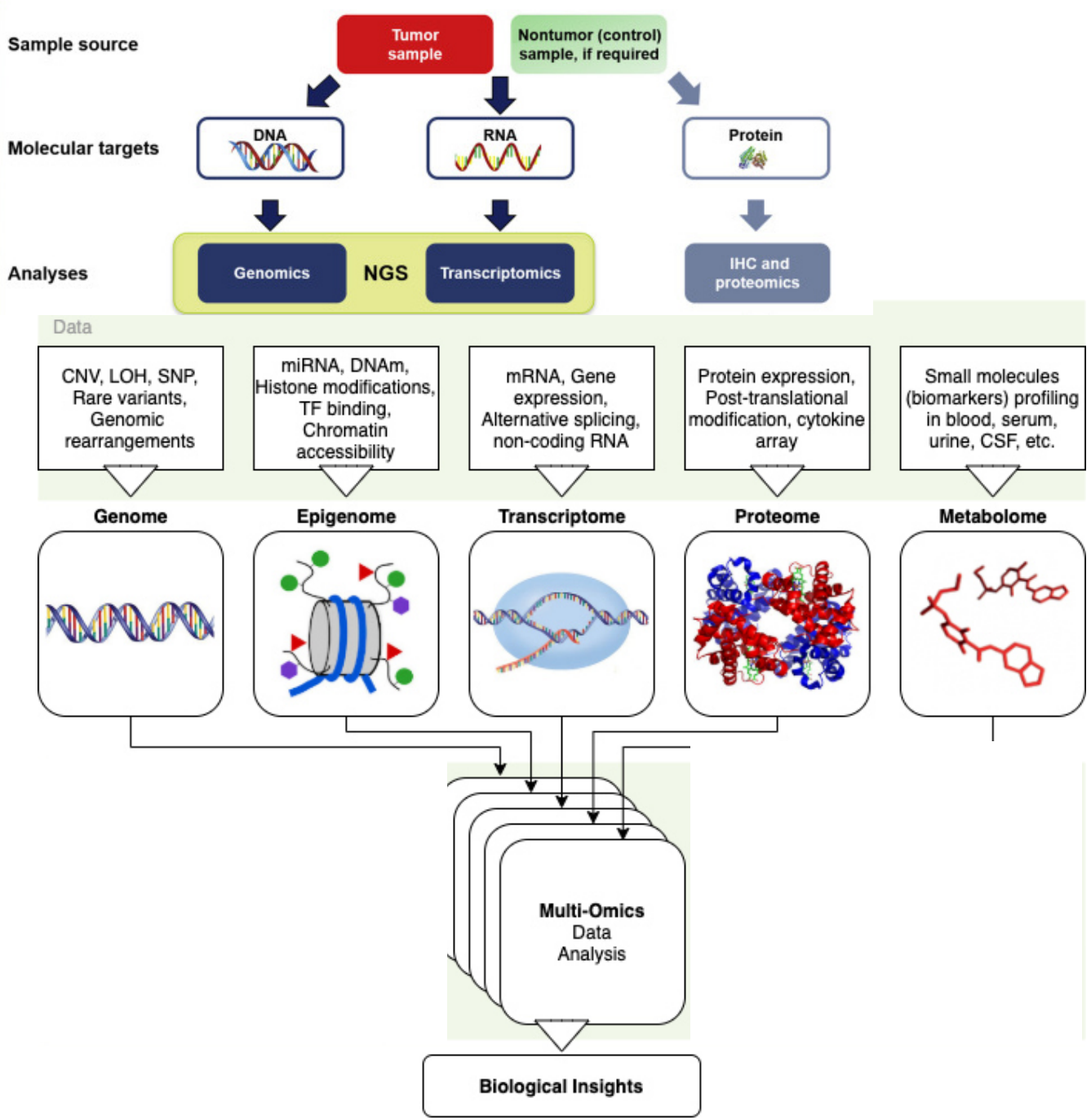
Pathways
- SHH

Solid components
- hyaluronic acid
- collagen I-IV
- laminin
- fibronectin

Multiomics in Cancer

- While a single type of *omics* can provide a significant amount of information at a specific level, the complexity of intra and extracellular mechanisms can only be addressed by combining several *omics* approaches to provide a complete picture of cancer pathogenesis and progression

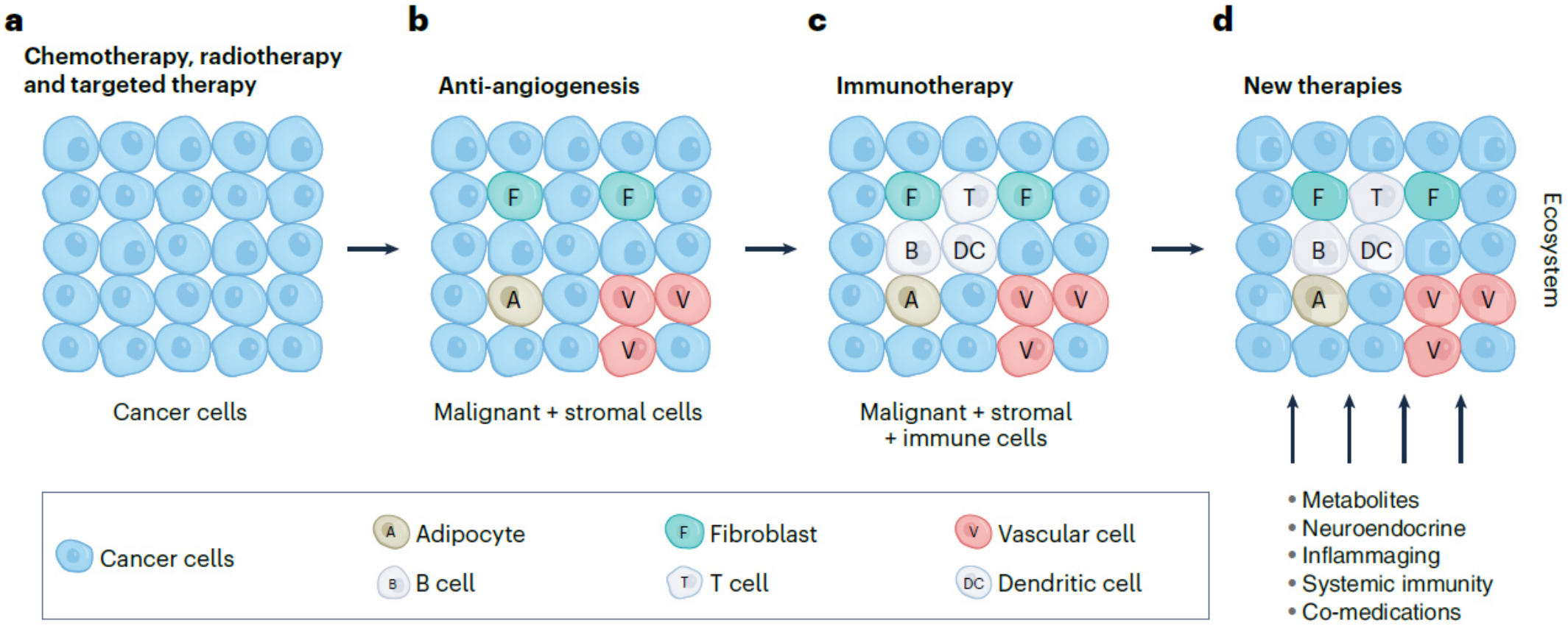
- With Multiomics (the combined use of genomics, transcriptomics, proteomics, metabolomics, and other technologies yet to fully unfold) we can obtain a complete dynamic vision of cancer.



Perspective https://doi.org/10.1038/s41591-022-02193-4

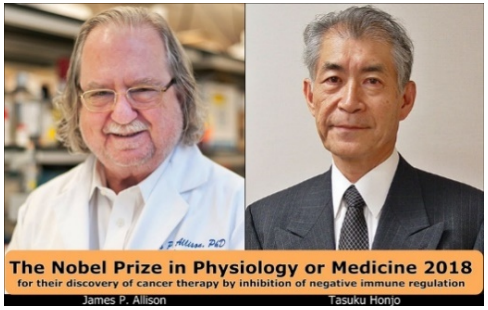
Bodywide ecological interventions on cancer

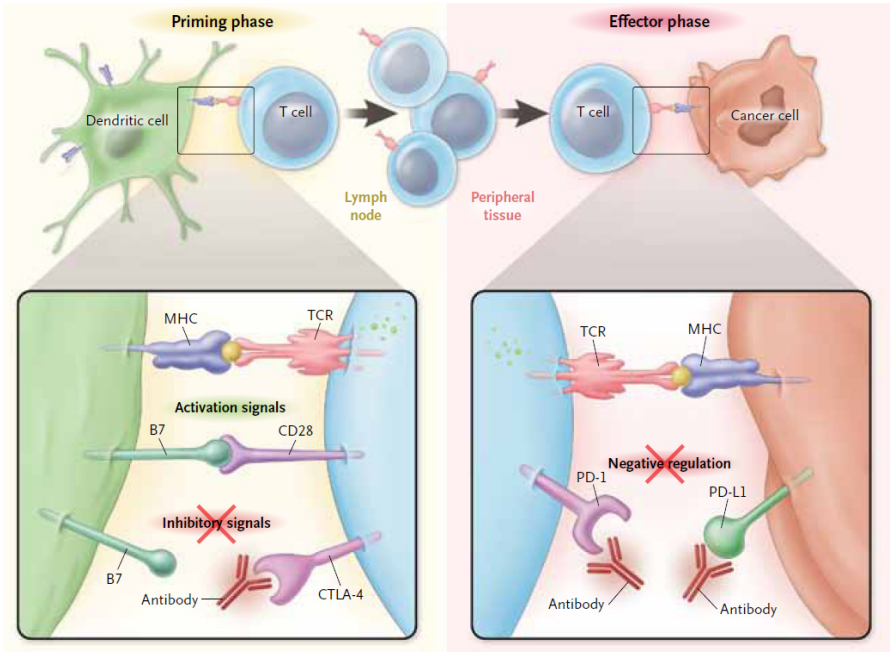
Guido Kroemer[1,2,3] ✉, Jennifer L. McQuade[4], Miriam Merad[5], Fabrice André[6] & Laurence Zitvogel[7,8,9,10]



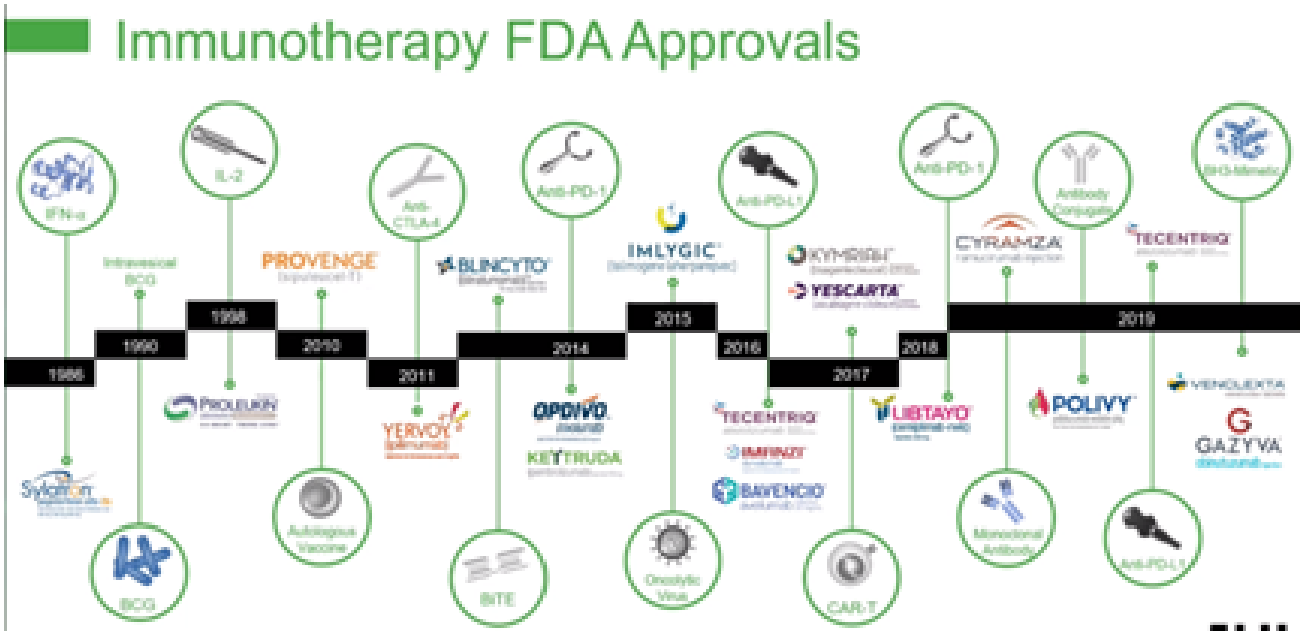
Kroemer et al. *Nature Medicine* Jan 2023

The revolution of Immunetherapy

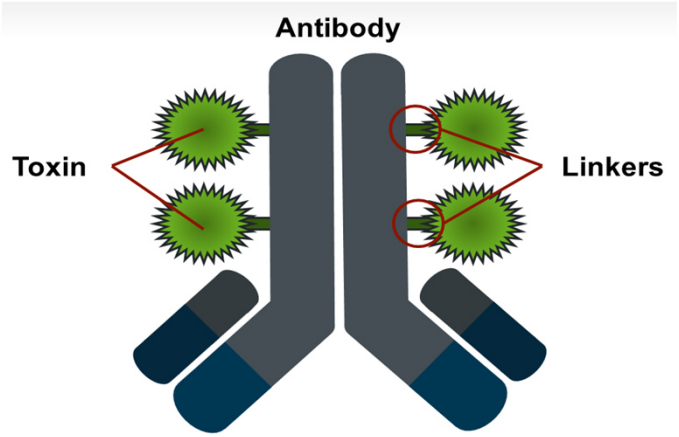




Drug	Target
Nivolumab	PD-1
Pembrolizumab	PD-1
Avelumab	PD-L1
Atezolizumab	PD-L1
Durvalumab	PD-L1
Ipilimumab	CTLA-4
Tremelimumab	CTLA-4

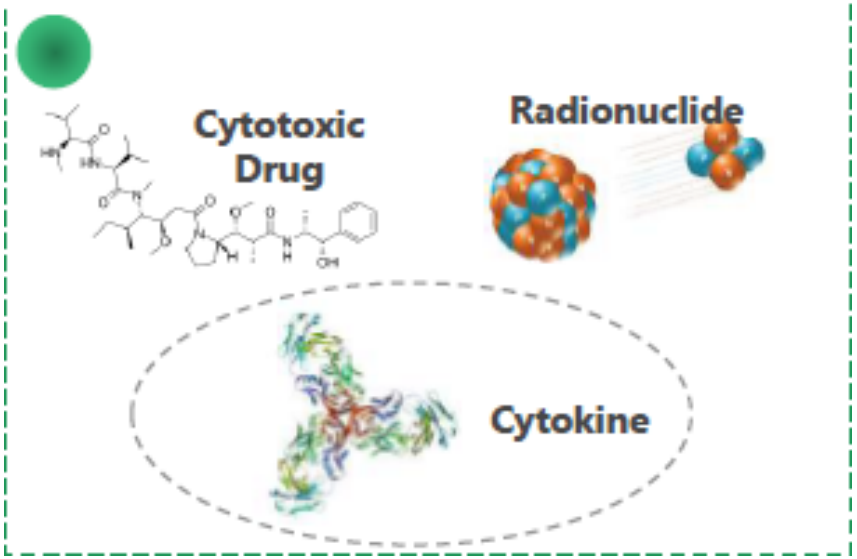


Antibody-Drug Conjugated (ADC) : new payloads



The poison

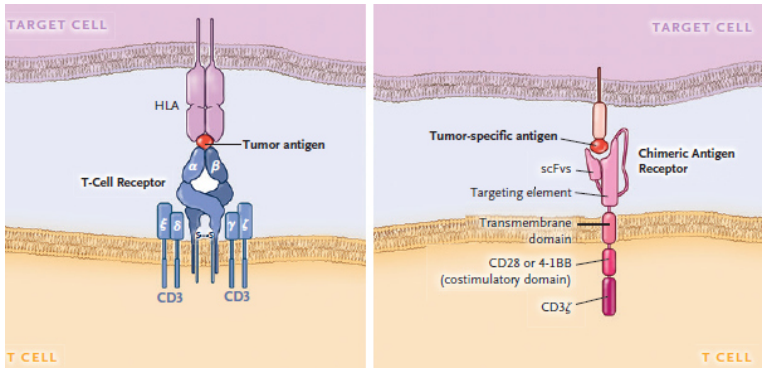
- Auristatin derivatives (MMAE, MMAF)
- Maytansine derivatives (DM1, DM4)
- Calicheamicin derivatives
- Highly potent cytotoxicity
- IC_{50} at a nM level

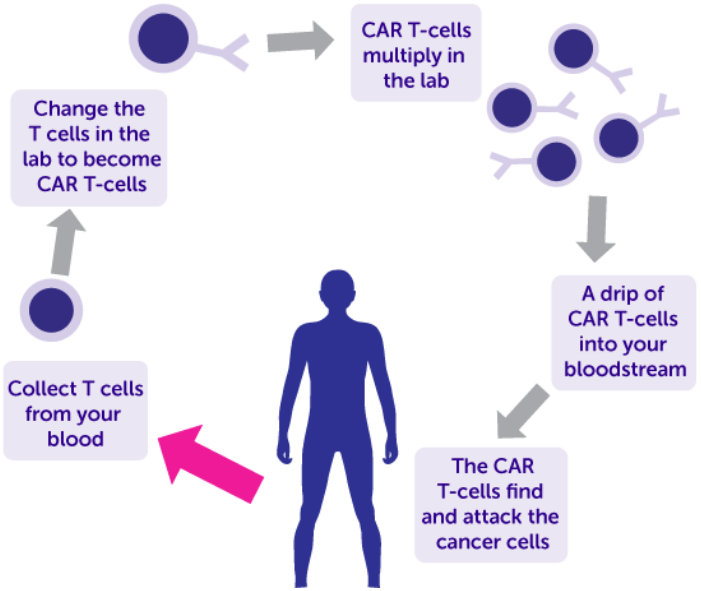


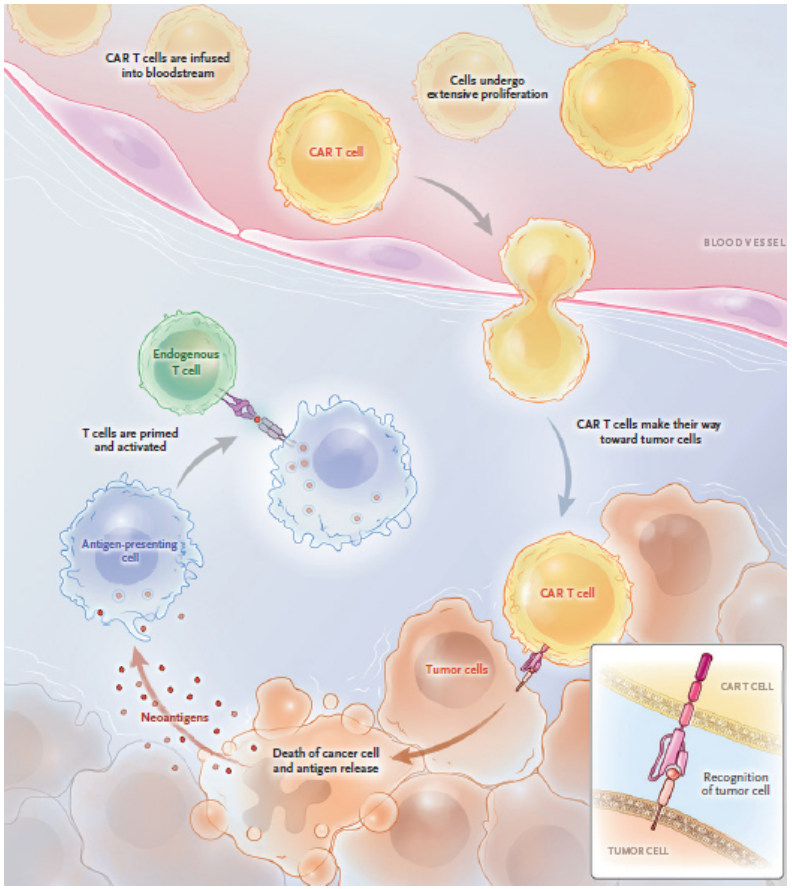
CYTOKINES	**IL1b** (Hess, 2014) **IL2** (Carnemolla, 2002) **IL3** (Schmid, 2018) **IL4** (Hemmerle, 2014) **IL5** (unpublished) **IL6** (Hess, 2014) **IL7** (Pasche, 2012) **IL9** (Venetz, 2015) **IL10** (Trachsel, 2007) **IL12** (Halin, 2002) **4-1BBL** (Mock, 2020)	**IL13** (Hess, 2015) **IL15** (Kaspar, 2007) **IL17** (Pasche, 2012) **IL18** (unpublished) **IL22** (Bootz, 2016) **IFNa** (Frey, 2010) **IFNb** (unpublished) **IFNg** (Ebbinghaus, 2005) **TNF** (Borsi, 2003) **TRAIL** (Hemmerle, 2014)	**TRAILtrunc** (Hemmerle, 2014) **CD40L** (Hemmerle, 2014) **FasL** (Hemmerle, 2014) **LiGHT** (Hemmerle, 2014) **VEGI** (Hemmerle, 2014) **VEGItrunc** (Hemmerle, 2014) **LT-a** (Hemmerle, 2014) **LT-b** (Hemmerle, 2014) **LT-a1b2** (Hemmerle, 2014) **G-CSF** (Schmid, 2018) **GM-CSF** (Kaspar, 2007)
CHEMOKINES	**CCL5** (Hess, 2014) **CCL17** (Hess, 2014) **CCL19** (Hess, 2014)	**CCL20** (Hess, 2014) **CCL21** (Hess, 2014) **CXCL4** (Hess, 2014)	**CXCL9** (Hess, 2014) **CXCL10** (Hess, 2014) **CXCL11** (Hess, 2014) **ITIP** (Hess, 2014)
OTHER PAYLOADS	**B7.2** (Hemmerle, 2012) **tTF** (Nilsson, 2001)	**TNFR** (Schwager, 2009) **VEGF-A^{120}** (Halin, 2002)	**VEGF-A^{164}** (Halin, 2002) **VEGF-C** (Schwager, 2018) **other undisclosed payloads**

Chimeric Antigen Receptor T cells (CAR-T) Therapy

Struttura dei recettori T e CAR







June C. and Sadelein M, New Engl J Med 2018;379:64-73

Vaccines (mRNA)

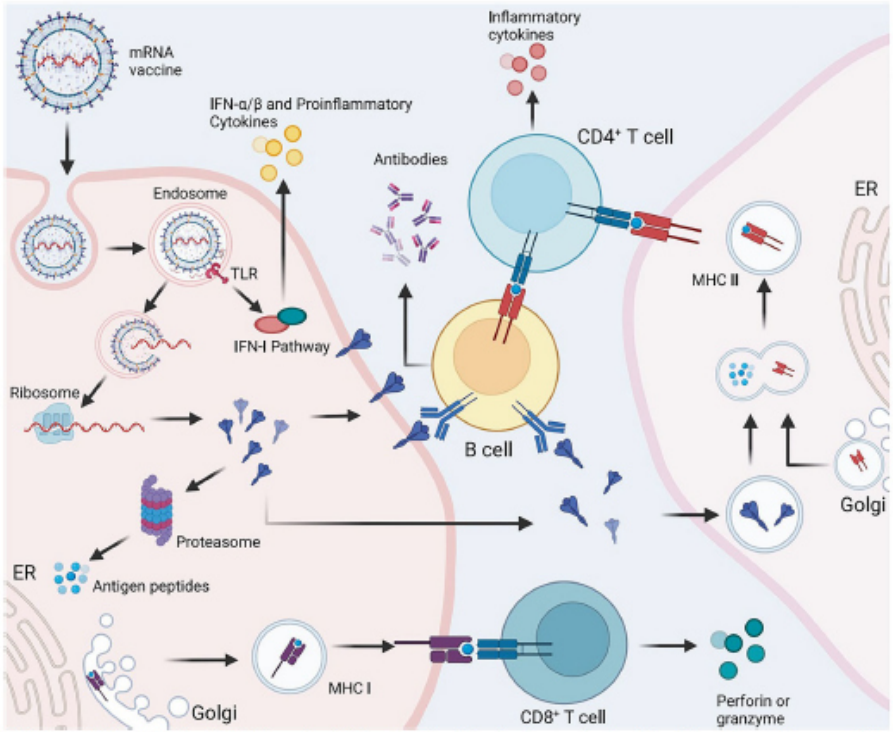


Fig. 6 In an mRNA vaccine, the mRNA is taken up by cells through endocytosis and subsequently released from the endosome to be converted

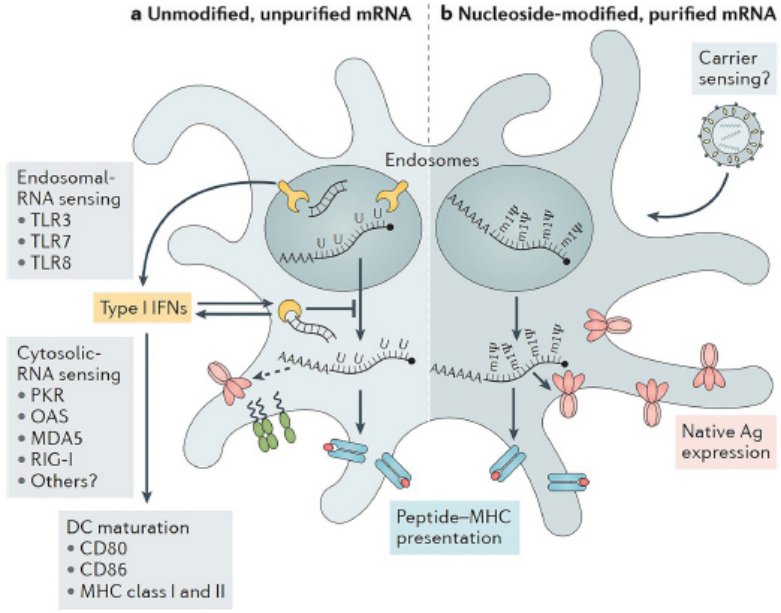
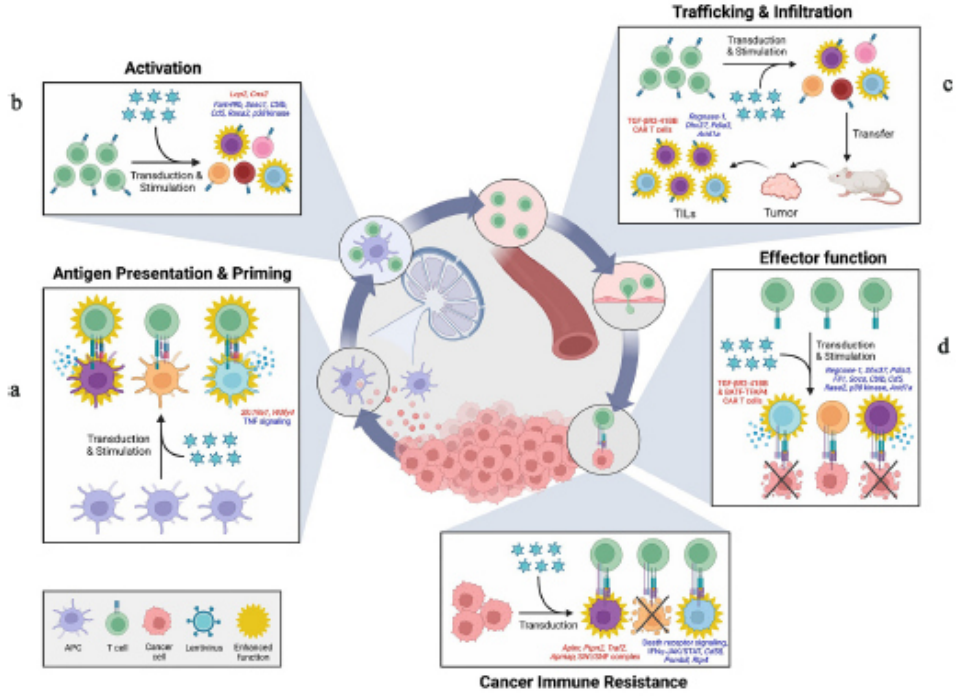


Fig. 11 Natural immune detection of mRNA vaccines. DC recognizes two types of mRNA vaccines, with RNA sensors in yellow, antigens in red.



OPINION

Integrated molecular and clinical staging defines the spectrum of metastatic cancer

Nature Rev Clinical Oncology, 16: 581, 2019

Sean P. Pitroda and Ralph R. Weichselbaum

Box 1 | Characteristics of indolent clinical metastases

Clinical

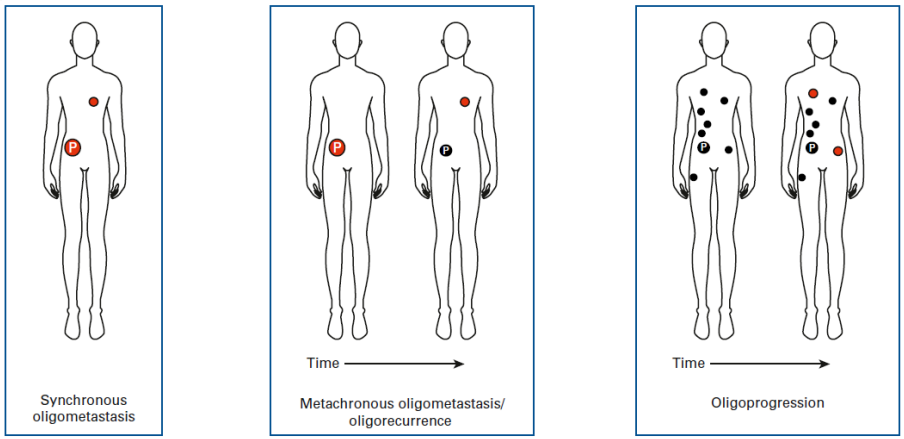
- Low number (typically 1–5 lesions)
- Metachronous presentation
- No involvement of lymph nodes
- Slow rate of progression (typically <0.6 new lesions per year)
- Limited organ sites (typically 1–2 sites)
- Favourable histology (including, but not limited to, breast, prostate and kidney)

Biological

- Activation of innate and adaptive immunity
- Absence of mesenchymal features
- Low degree of tumour aneuploidy
- Low degree of intratumoural heterogeneity
- Intact 14q chromosomal arm
- Expression of microRNAs that suppress genes associated with metastasis

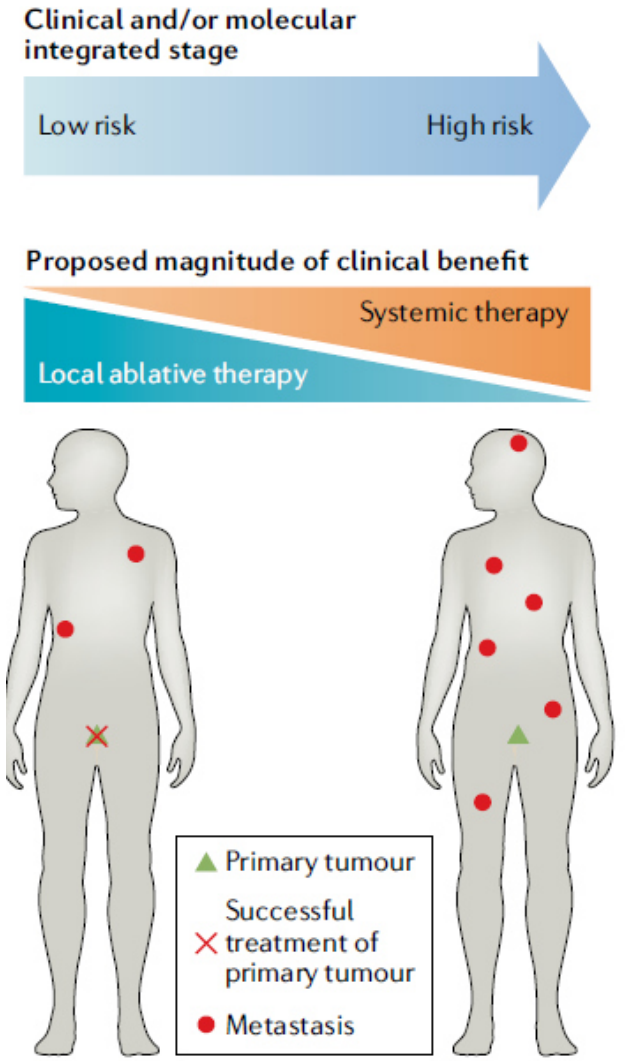
Treatment

Local ablative interventions (with stereotactic body radiotherapy, radiofrequency ablation or surgery) tend to be more beneficial for these patients than systemic therapy



Liu W.JCO 40:4250, 2022

Personalized treatment along the metastasis spectrum




David A. Karnofsky Memorial Lecture

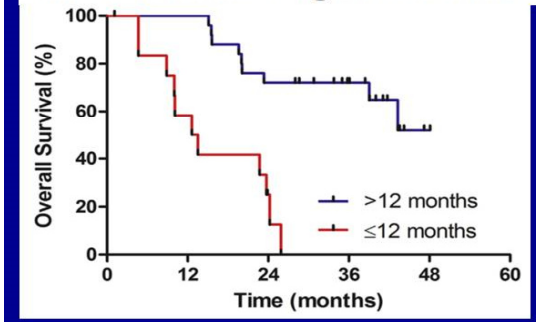
Ralph R. Weichselbaum, MD
Department of Radiation and Cellular Oncology
Ludwig Center for Metastasis Research
The University of Chicago

ASCO 2018

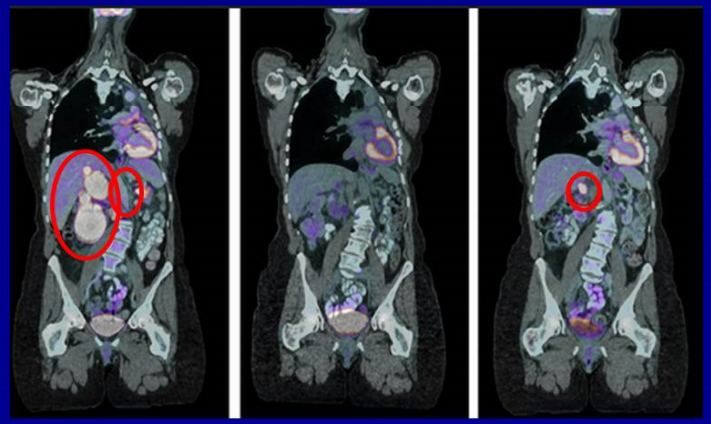
Ablative Therapy Can Be Integrated with (some) Systemic Therapies

Crizotinib (TK-inhibitor)

Stereotactic Radiation Therapy can Safely and Durably Control Sites of Extra-Central Nervous System Oligoprogressive Disease in Anaplastic Lymphoma Kinase-Positive Lung Cancer Patients Receiving Crizotinib



Length of time taking crizotinib (≤12 vs >12 months) and its effect on overall survival.



ALK+ NSCLC | CR to Crizotinib | Oligo-Progression

SBRT+**Erlotinib:** (EGFR-inhibitor)

resulted in dramatic changes in patterns of failure, and high PFS and OS.

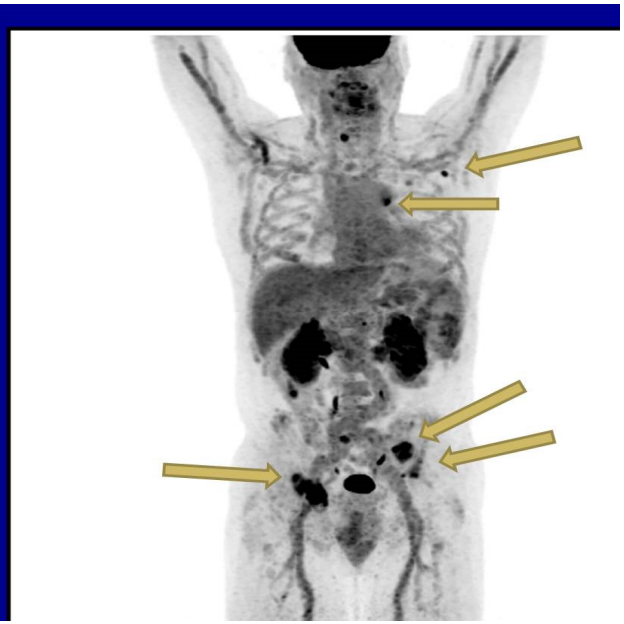
- Phase 2 trial of SBRT+Erlotinib for limited (but progressive) metastatic NSCLC

Iyengar P, et al. J Clin Oncol 32(34):3824-30;2014.

Treat all sites!

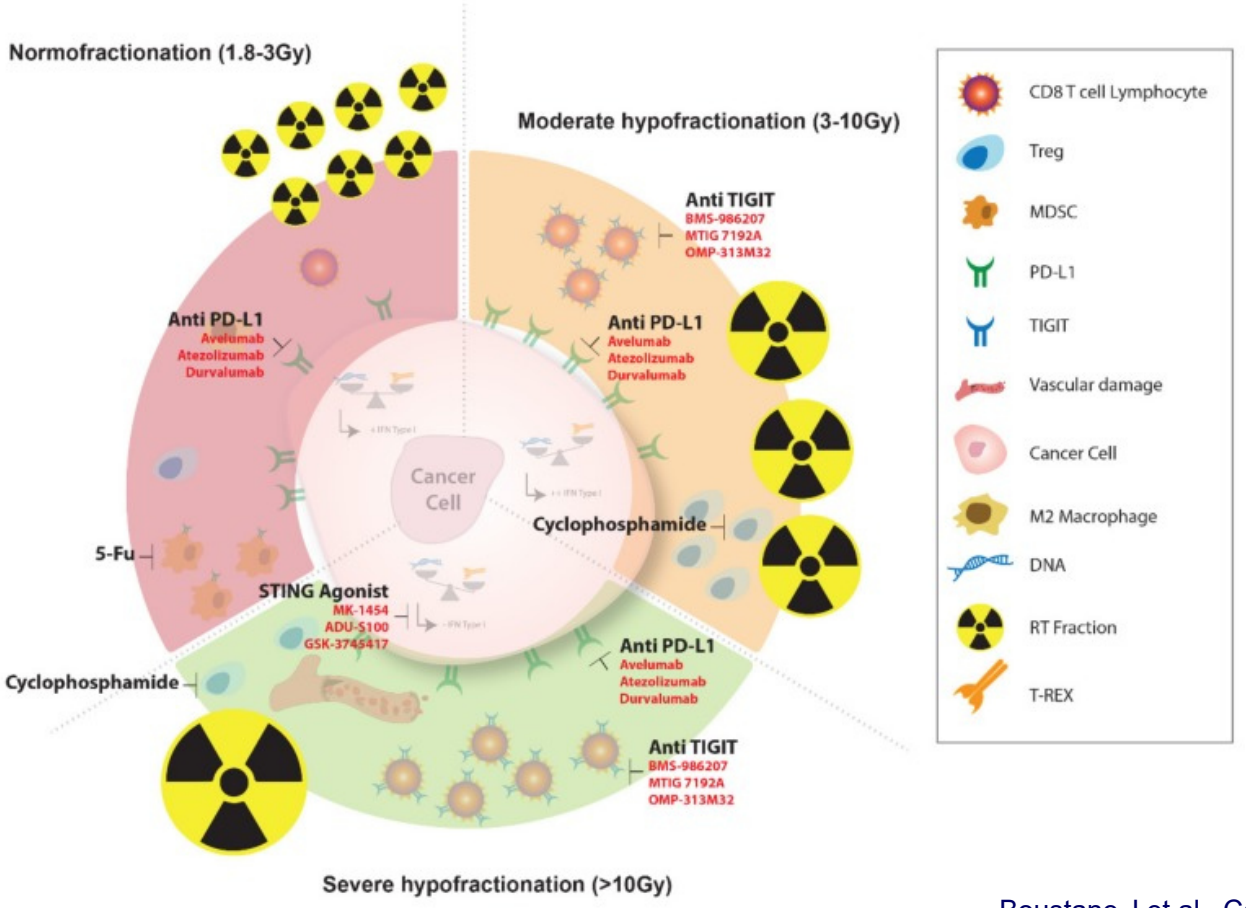
(or most) of visible disease with image-guided SBRT and/or image-guided surgery, and thereby amplify local and systemic immunity.

Barriers:
Limitations in imagination, software, software/hardware integration



Radiotherapy and Immune response

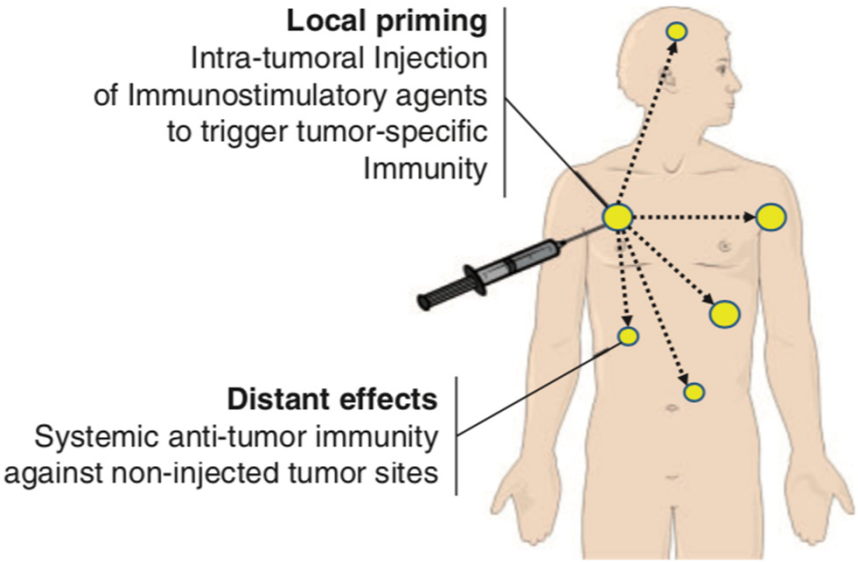
Optimized radio-chemo-immunotherapy protocols according to the immune response induced by three types of fractionation schedules

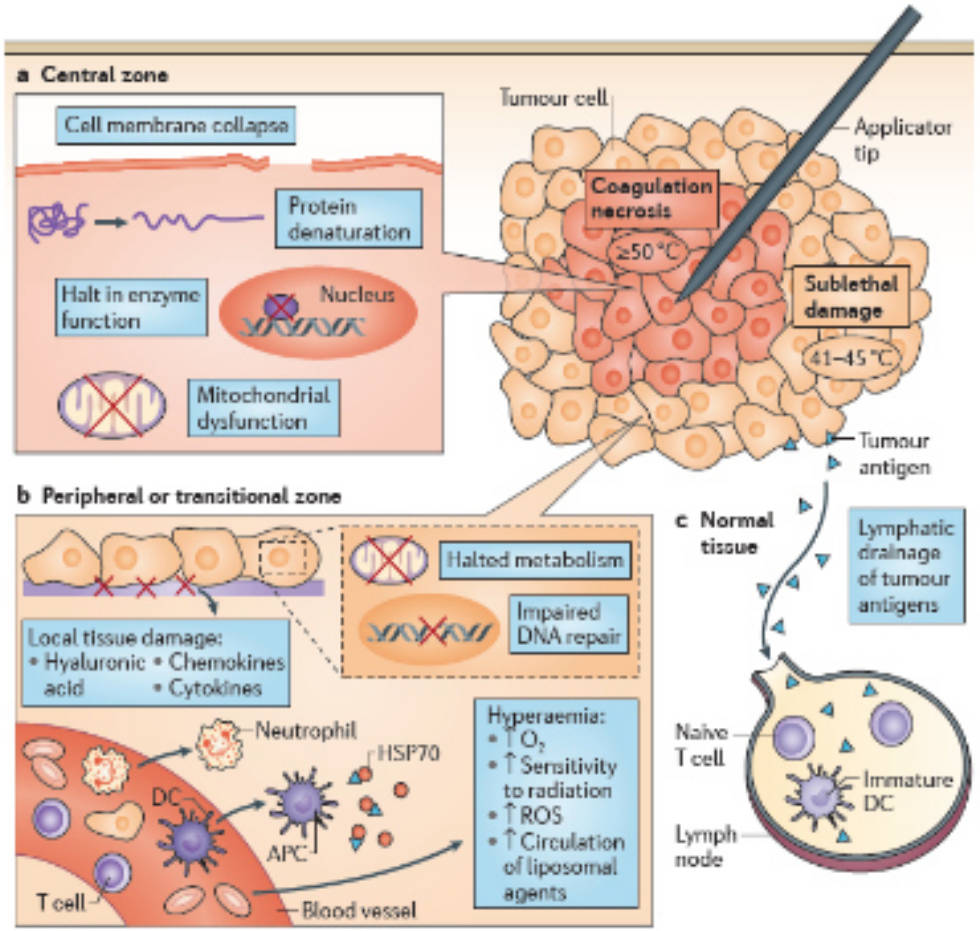


Boustane J et al., Cancers 11: 860, 2019

Intratumoral immunotherapy: using the tumor as the remedy

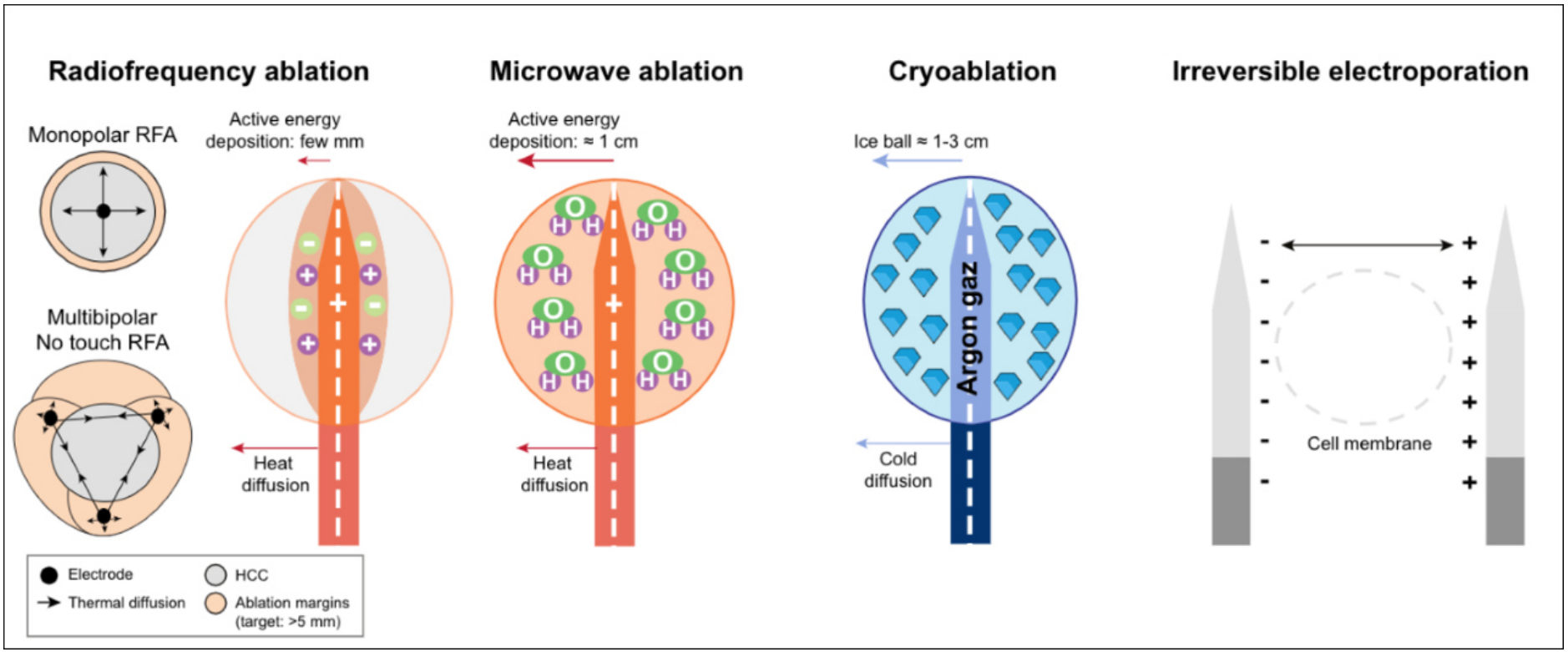
A. Marabelle[1,2,3*], L. Tselikas[4], T. de Baere[4] & R. Houot[5,6]





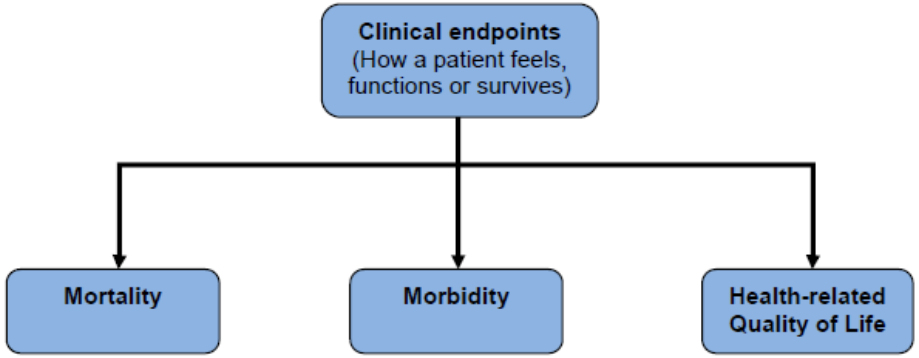
Ann Oncol 2017;28(suppl 12):xii33-xii43.

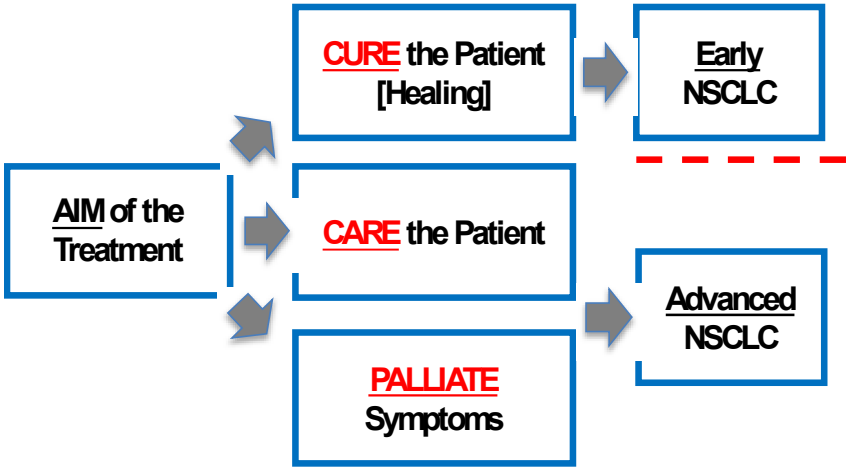
Techniques for ablation : possible combination with chemo-, radiation and immunetherapy

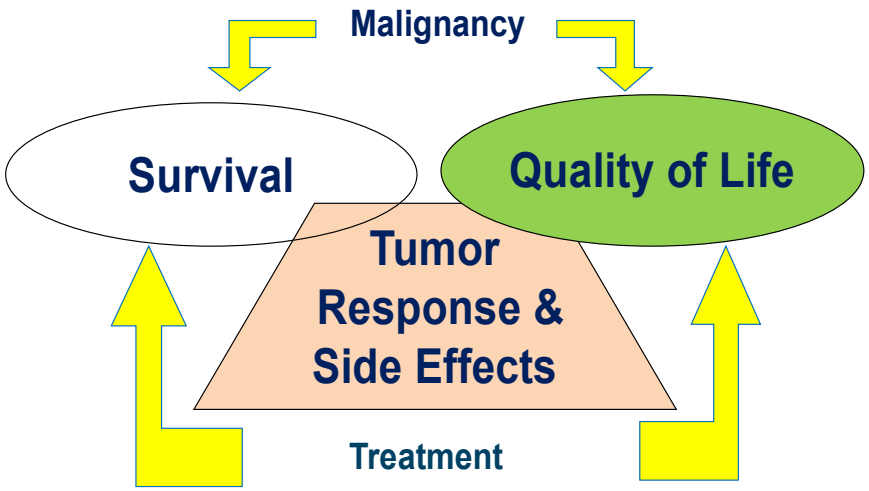


Courtesy of Prof. Roberto Iezzi

Reconciliate Survival and QoL Patient Reported Outcomes







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