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ONCODISTINCT NETWORK

Therapies progress in oncology (and imaging implications)

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Disclosures

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Roche, Lilly, Amgen, EISAI, BMS, Pfizer, Novartis, MSD, Genomic Health, Ipsen, AstraZeneca, Bayer, Leo Pharma, Merck

Therapeutic approaches of cancer : Innovations
Role of imaging is crucial!

- Surgery (robotic…)
- Radiotherapy (targeted, proton…)
- Therapeutic radionuclides (I* (thyroid); PSMA* (prostate); NET;…)
- Chemotherapy (targeted via antibody drugs conjugates)
- Molecular – targeted therapies
- Immunotherapy

} A huge development (tsunami of new drugs)

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CURRENT DRUGS-BASED STRATEGY IN CLINICAL RESEARCH

- New chemotherapy agents are less and less developed *(except antibody drugs conjugates (ADC))*

↓

- Molecular-targeted therapies have been developed but rarely have cured patients *(except for endocrine agents and trastuzumab in breast cancer and B-RAF inhibitors in melanoma)*

↓

- Recently the hype of immunotherapy slows significantly the development of other anti-cancer treatments

Targeted chemotherapy:
The Example of Trastuzumab-DM1 in HER2+ MBC

Trastuzumab-DM1 → **Antibody Drug Conjugate (ADC)**

DM1 — **Maytansine (inhibitor of microtubule assembly)**

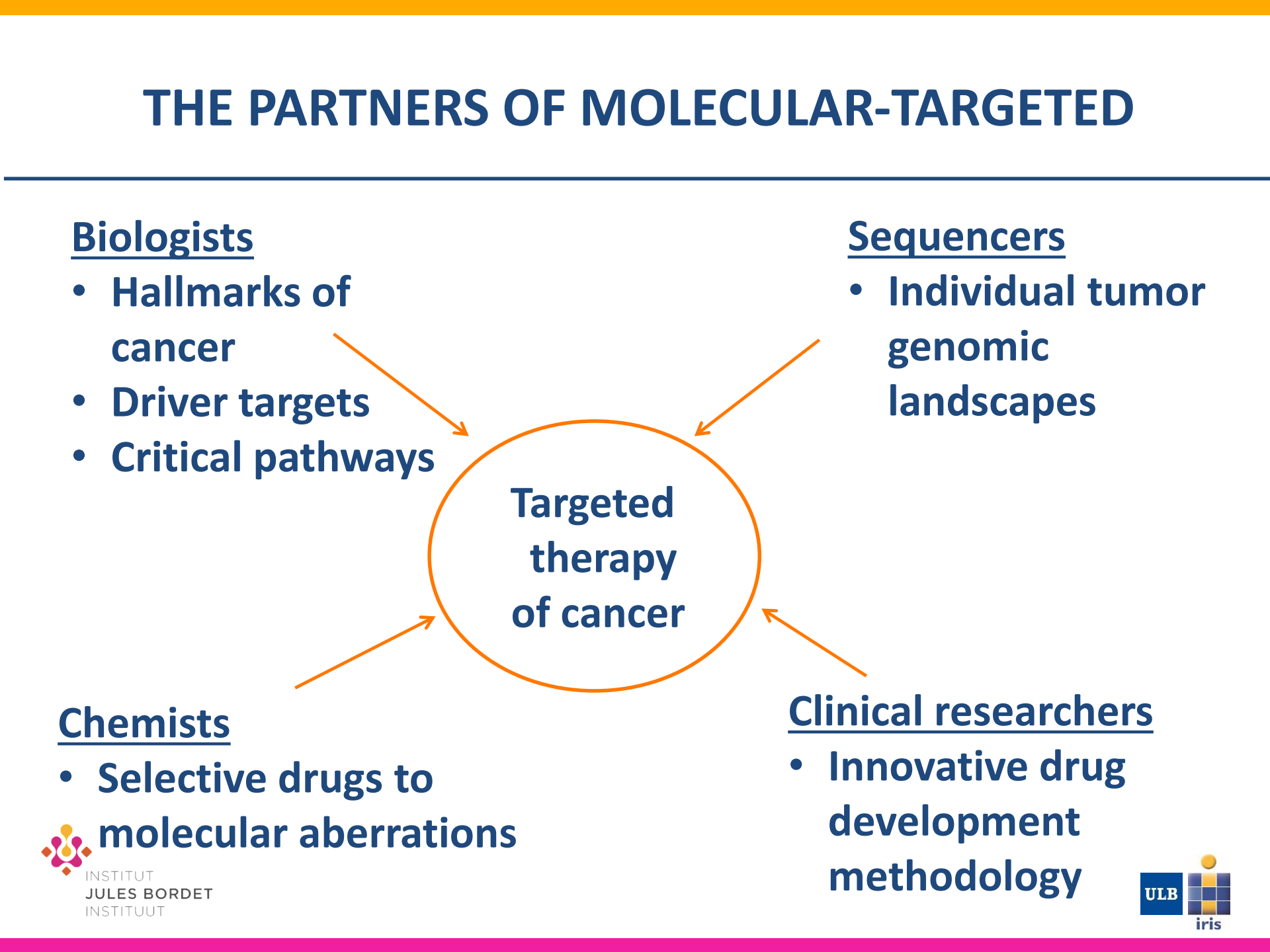
Lewis-Phillips GD et al., Cancer Res 68:9280-9290, 2008

New generations of ADCs targeting HER2

Agent	Target	Phase of development	Initial Phase I Results	Main Side Effects
DS8201a	Humanized HER2 antibody + topoisomerase-I inhibitor exatecan	Ongoing phase II (DESTINY-Breast01) and III (NCT03529110)	RR: 64.2%[46] PFS:10.4 mo.[46] (heavily pre-treated patients)	Gastrointestinal and haematological
SYD985	Trastuzumab + duocarmazine	Ongoing phase III (TULIP)	RR: 33%[48] PFS: 9.4 mo.[48]	Ophthalmologic effects (conjunctivitis and keratitis)
RC48- ADC	HER2 antibody + MMAE	Ongoing phase II (NCT03500380)	RR: 36.7%[49]	Transaminases elevations Neutropenia
MM-302	HER2 antibody + liposomal doxorubicin	Failed to demonstrate activity in the phase 2 HERMIONE study[50]	RR: 24%[51] PFS: 11 mo.[51]	Development interrupted after phase II results

[46] Iwata H et al. J Clin Oncol. 2018, [48] Saura C et al. J Clin Oncol. 2018, [49] Xu B et al. J Clin Oncol. 2018 [51] Munster P et al. Br J Cancer. 2018 Miller K et al. BMC Cancer 2016

THE PARTNERS OF MOLECULAR-TARGETED



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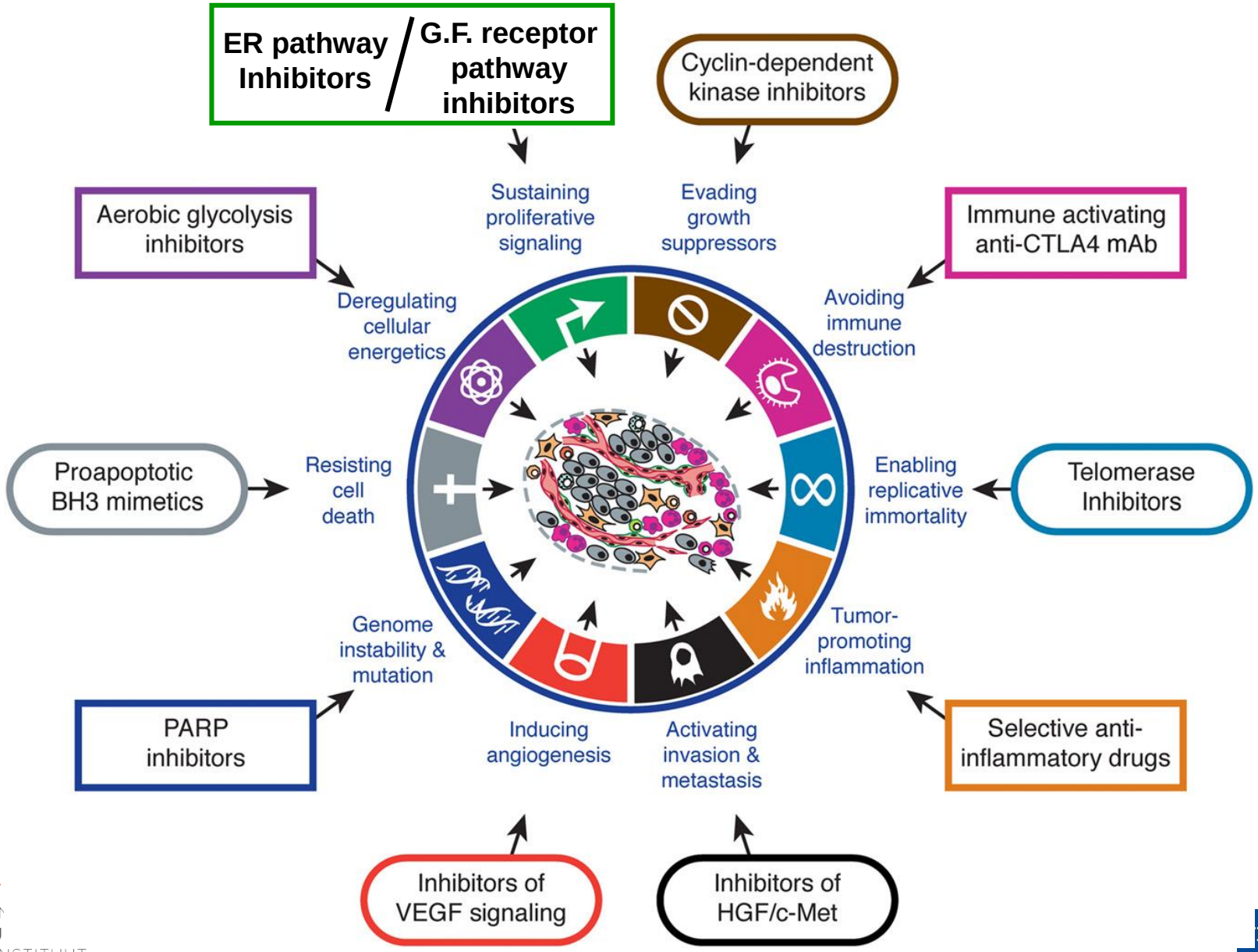
THERAPEUTIC TARGETING OF THE HALLMARKS OF CANCER



Hanahan D. and Weinberg R.A., Cell 144, March 4, 2011

Targets importantly involved in carcinogenesis and their inhibitors (1)

PROLIFERATION

Target	Tumor	Inhibitor	Predictive markers of sensitivity/resistance	Disease setting
ER	Breast	Tamoxifen, AI, fulvestrant, SERD	ER expression ER mutation (Resistance)	Adjuvant & advanced disease
EGFR	Head&neck	Cetuximab	-	Locally/advanced H&N cancer
EGFR	NSCLC	Gefitinib/Erlotinib / Dacomitinib/Afatinib/Osimertinib	Mutation of EGFR (T790M)	Metastatic NSCLC
EGFR	Colorectal	Cetuximab Panitumumab	Ras status	Metastatic colorectal cancer
HER-2/neu	Breast, gastric	Trastuzumab, Pertuzumab Lapatinib Neratinib T-DM1	HER-2/neu amplification	Adjuvant (breast) & advanced disease (breast, gastric)

Targets importantly involved in carcinogenesis and their inhibitors (2)

ANGIOGENESIS

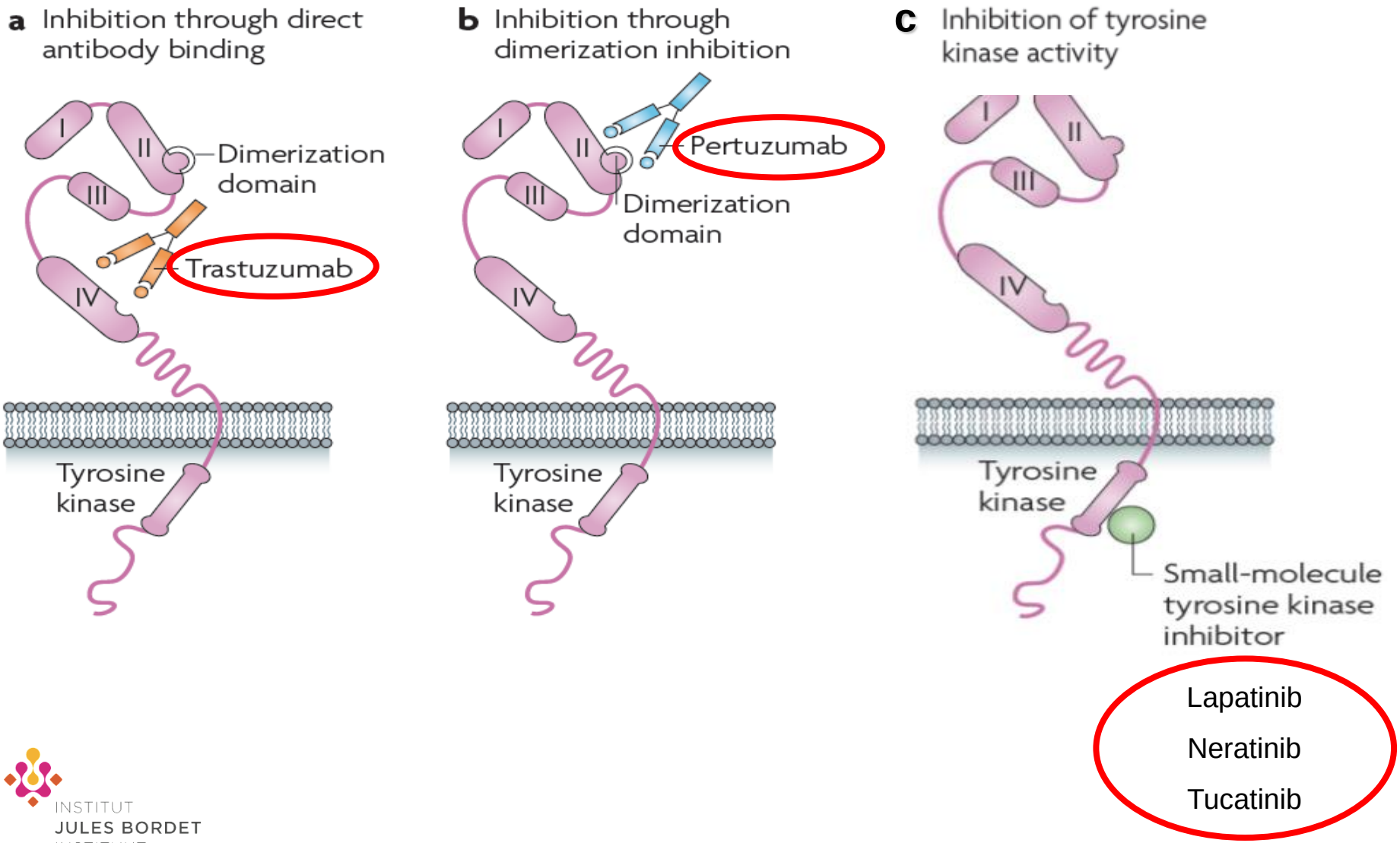
Target	Tumor	Inhibitor	Predictive markers of sensitivity	Disease setting
VEGF	NSCLC, colorectal, renal, breast, ovary, cervix	Bevacizumab, Aflibercet (colon)	-	Advanced disease
VEGFR	Hepatocarcinoma Colorectal Gastric	Sorafenib, Lenvatinib, Cabozantinib Regorafenib Ramucirumab	Regorafenib	Advanced disease
VEGF(R); M-TOR	Renal	MTKs, Bevacizumab Everolimus, Temsirolimus	-	Advanced disease
VEGFR; M-TOR; PDGFR	Neuroendocrine, Soft tissue sarcomas	Sinutinib, Everolimus Pazopanib, Olaratumab	-	Advanced disease
VEGFR, RET	Thyroid	Vandetanib, Sorafenib Lenvatinib, Cabozantinib	-	Advanced disease
M-TOR PI3K	Breast	Everolimus Alpelisib	- Mutated PI3K	Advanced disease
CDK 4/6	Breast	Palbociclib, ribociclib, abemaciclib	-	Advanced disease

Targets importantly involved in carcinogenesis and their inhibitors (3)

Target	Tumor	Inhibitor	Predictive markers of sensitivity/resistance	Disease setting
C-Kit	GIST	Imatinib Sunitinib, Regorafenib, …	C-Kit mutation PDGFR mutation	High risk or metastatic GIST
EML4-ALK R0S1	NSCLC	Crizotinib, Ceritinib, Alectinib	EML4-ALK translocation R0S1	Advanced NSCLC
RANKL	Bone metastases; Giant cell tumors	Denausumab	-	Advanced disease
Hedgehog	Basal cell carcinoma	Vismodegib	-	Advanced disease
BRAF, MEK	Melanoma, NSCLC (BRAF)	Vemurafenib Dabrafenib Trametinib, Cobimetinib	BRAF mutation	Adjuvant Advanced disease
PARP	Breast, ovary, … (BRCA tumors)	Olaparib, niraparib, Talazoparib	BRCA mutation	Advanced disease
CTLA4, PD-1	Melanoma	Ipilimumab, Larotrectinib, Entrectinib	-	Adjuvant Advanced disease
PD-1/PD-L1	Melanoma, NSCLC, RCC, H&N, urothelial, MCC, MSI tumors	Nivolumab, Pembrolizumab, Atézolizumuab, Avelumab…	(PD-L1 protein) ? TMB? …	Adjuvant (melanoma) Advanced disease
Androgen receptor; immune system	Prostate	Aberaterone, Enzalutamide, Sipuleucel-T	Androgen receptor variant 7 (Resistance)??	Advanced disease
TRK	Solid tumors	Larotrectinib, Entrectinib	TRK fusion	

IMMUNE FUNCTION

Anti HER2 therapies = Anti-proliferation in HER2+ breast cancer



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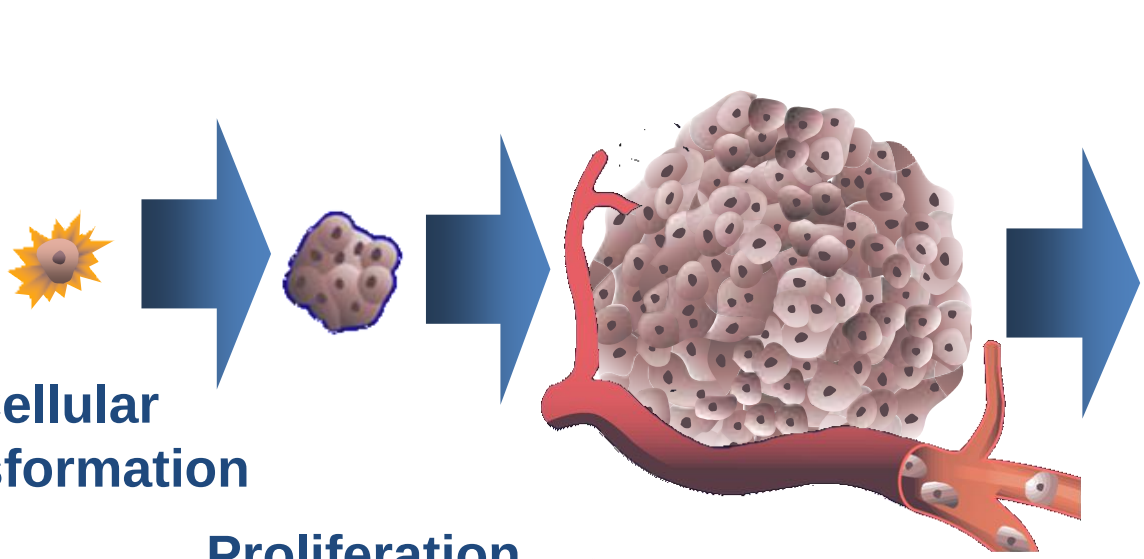
J Baselga, S Swain, Nature Reviews Cancer, 2009

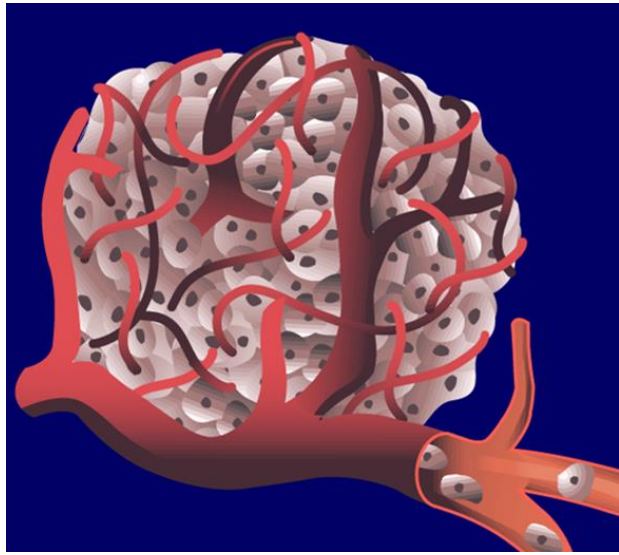
Characteristic of Cancer: Angiogenesis



Cellular transformation

Proliferation = apoptosis

Proliferation > apoptosis



Increased and abnormal vascularization

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Ten agents have been approved in RCC over last 10 years [Med survival (mo.) : 28-30!!]

- Sorafenib (2006)
- Temsirolimus
- Beva + IFNX
- Sunitinib

(2007)

- Everolimus (2009)
- Pazopanib (2010)
- Axitinib (2012)
- Lenvatinib
- Carbozantinib
- Nivolumab

(2016-2017)

Seven agents = Antiangiogenic agents !

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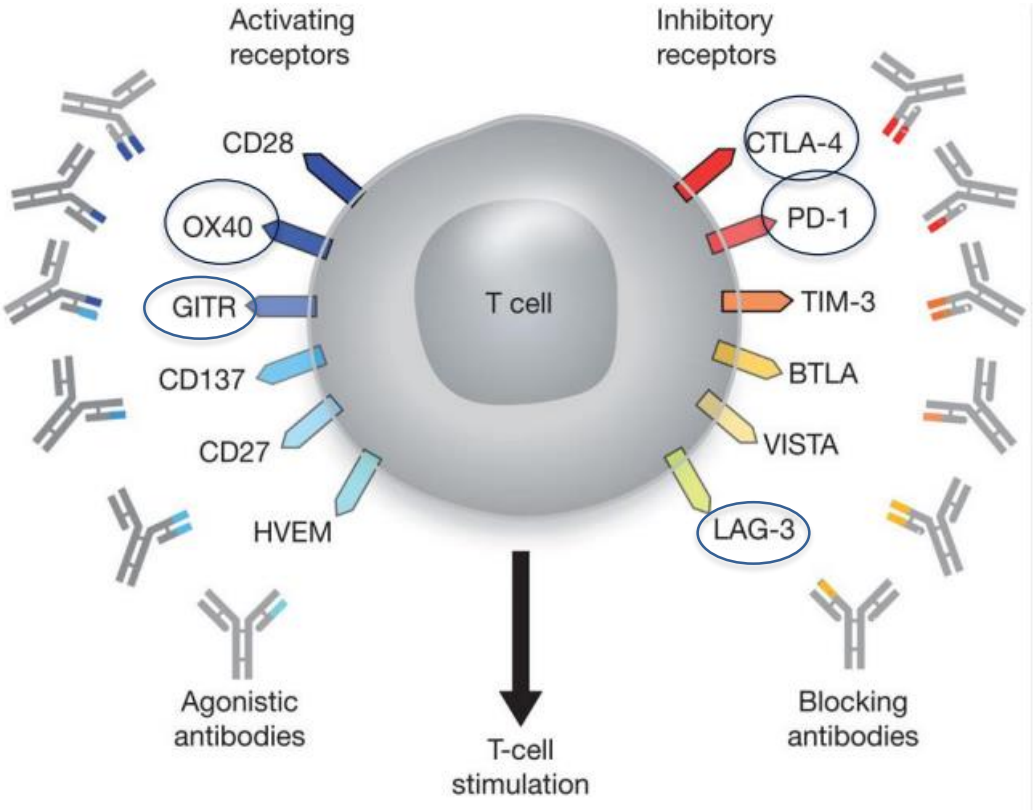
Activating and inhibitory receptors on T cells : Basis of modern immunotherapy



Mellman et al., Nature 2011

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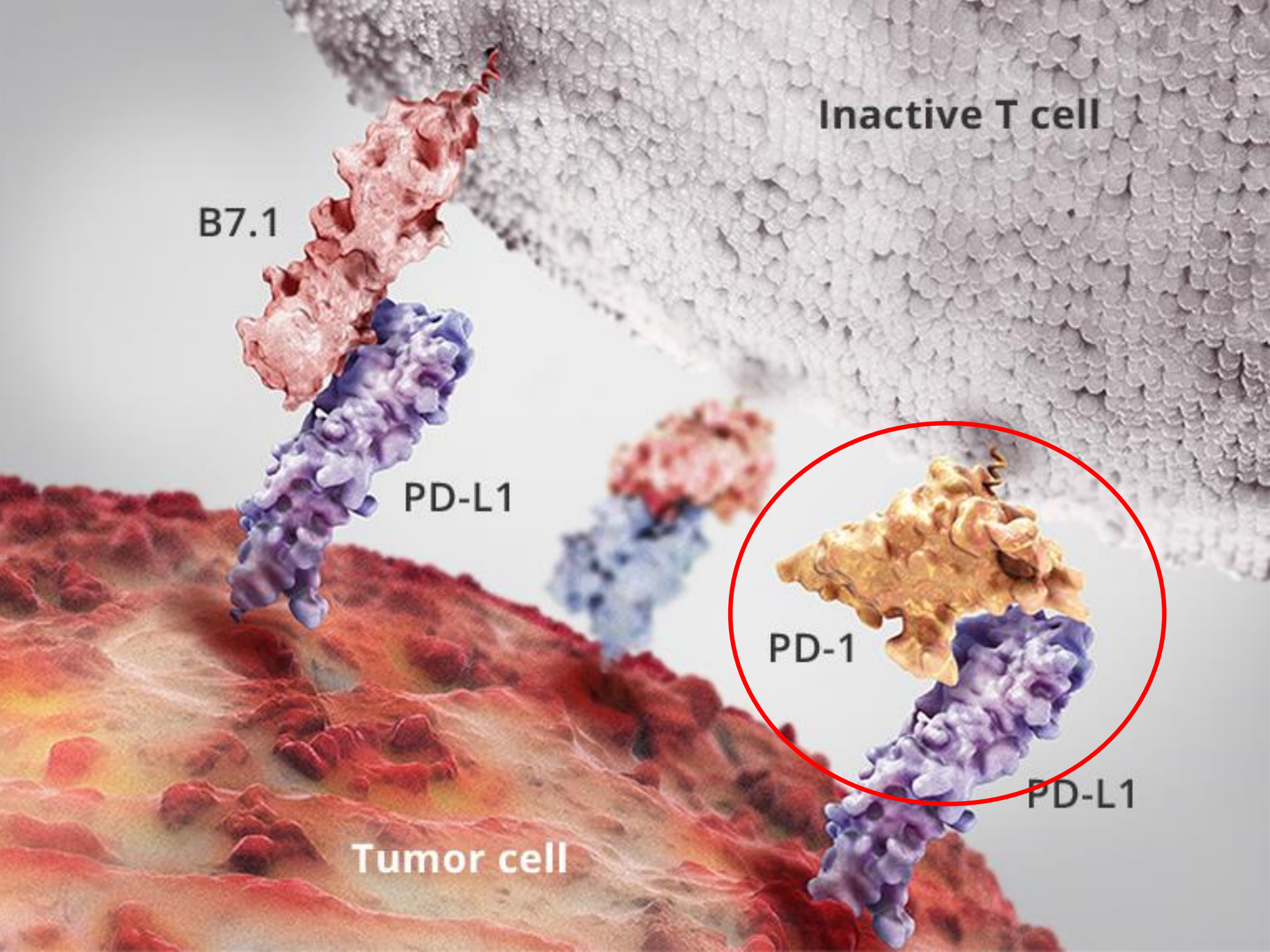
Inactive T cell
B7.1
PD-L1
PD-1
PD-L1
Tumor cell

Established activity of CPIs in:	Activity reported with CPIs in:
Melanoma	HCC
NSCLC	Cervical Cancer
RCC	Esophageal
Urothelial	Gastric / GEJ
H & N	NET (Lung)
Merkel Cell	Ovarian
MSI high	SCLC
TNBC	

Question: How to move further (adjuvant, …)?

Question: How to improve the tumor activity?

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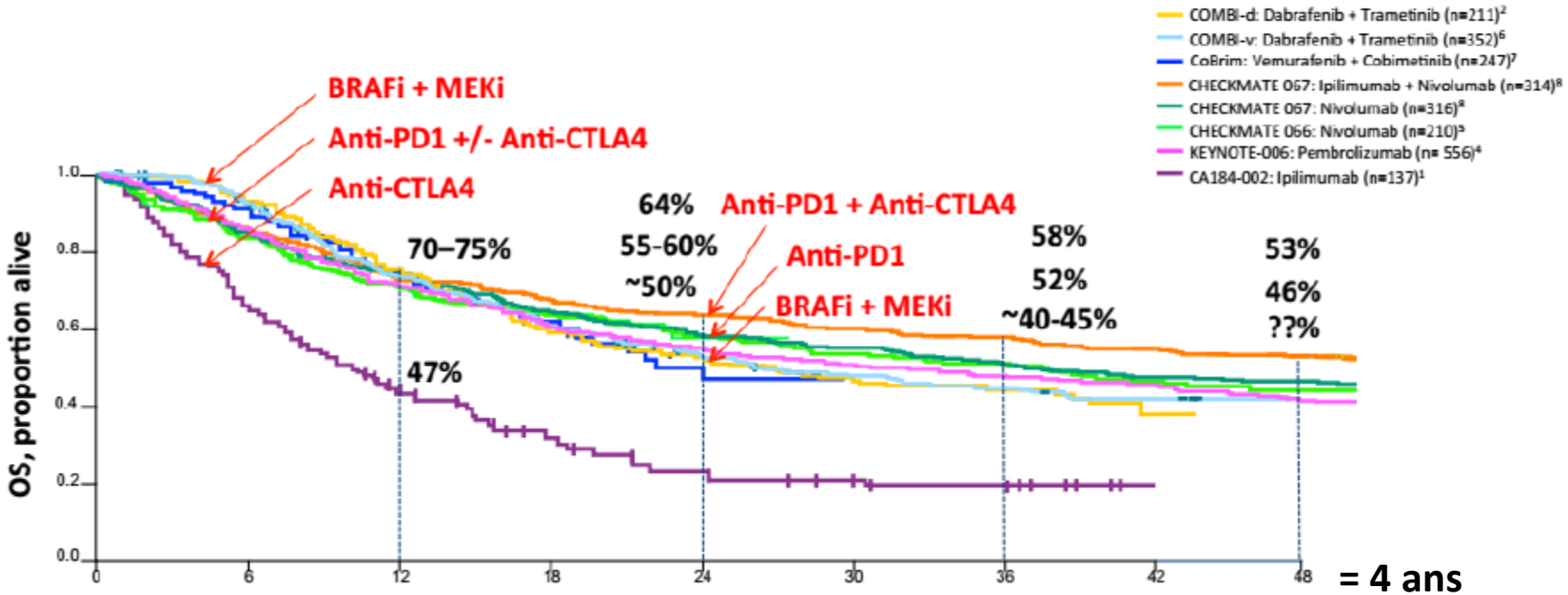
No convincing activity of CPIs in:

- Prostate
- Sarcoma (all disease)
- NET (other than lung)
- Colon (outside MSI)
- Endometrium (outside MSI)
- ER+ BC
- Pancreas
- Glioblastoma
- Mesothelioma
- Germ cell tumors

Question: How to transform these « Cold » tumors in « Hot » tumors?

Overall survival in metastatic melanoma – now we have 5 years data! : 52% of pts are alive with IPI + Nivo therapy



= 4 ans

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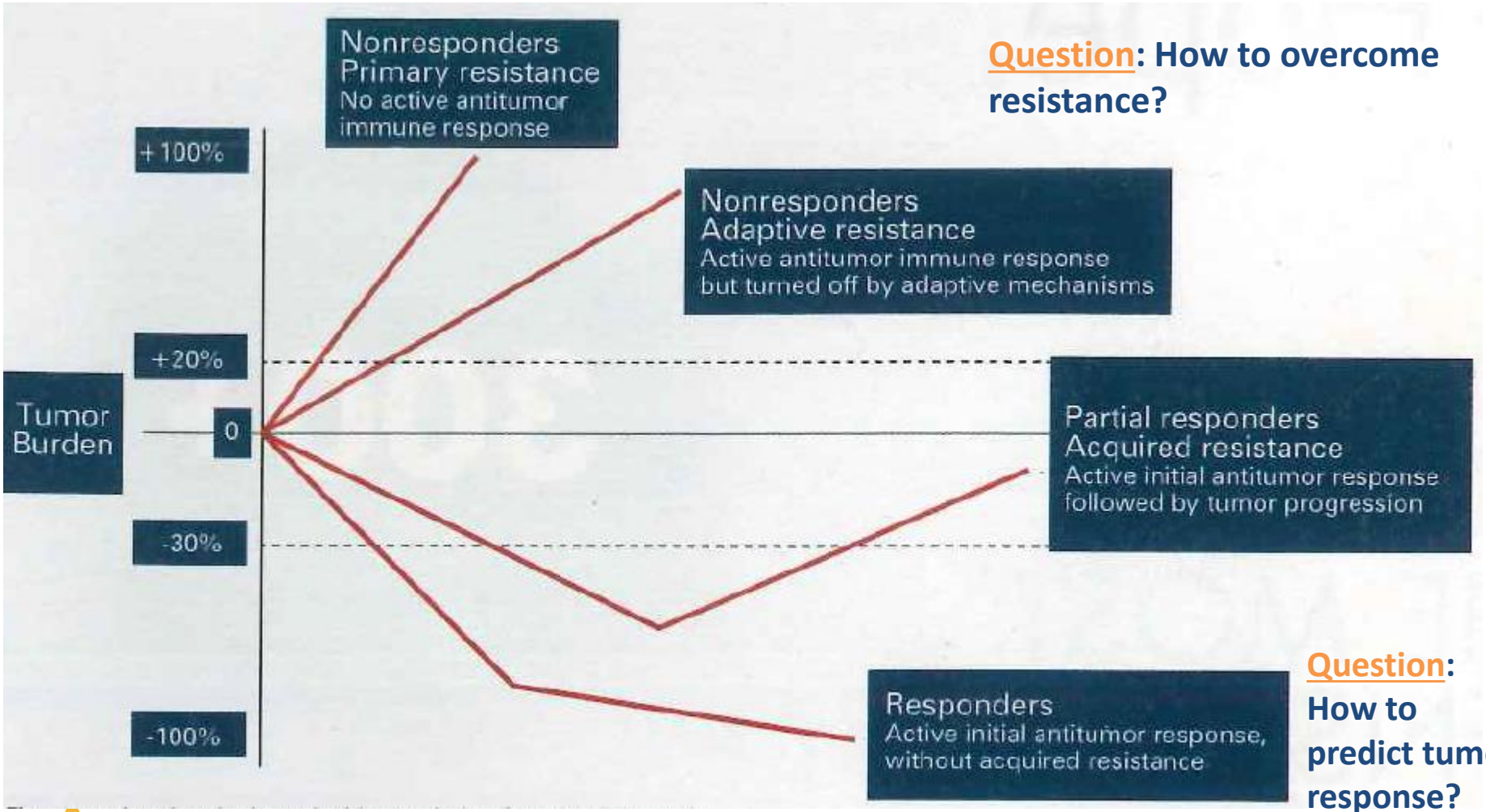
Spider Plot of Clinical Scenarios Demonstrating Response and Resistance to Immunotherapy



Question: How to overcome resistance?

Question: How to predict tumor response?

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Hyperprogression and Pseudoprogression: Role of Imaging?

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Hyperprogression and pseudoprogression

- Hyperprogression (HP) is a rapid increase in tumor growth rate after starting a checkpoint inhibition (CPI).
- Concept of HP is still evolving, not yet fully understood and still controversial.
- Pseudoprogression (PP) is an initial flare-up followed by tumor shrinkage after starting a CPI (Saada-Bouzid et al, 2017)
- No consensus exist on the quantitative definition of HP or PP with ICI
- iRECIST is a consensus-guideline for consistent conduct, interpretation, and analysis of objective change in tumour size in trials with ICIs (Seymour L. et al, 2017)

Hyper/Pseudoprogression in NSCLC tumors treated with ICI

- 242 patients, multicenter, retrospective French study

16% Hyperprogression

1,2% Pseudoprogression

- Results independent of tumor burden baseline, clinical, molecular, pathological characteristics, PD-L1 status

Ferrara R et al, Annals of Oncology (2017) 28 (suppl_5): v460-v496. 10.1093/annonc/mdx380

Hyper/Pseudoprogression in Head&Neck tumors treated with ICI

- 34 patients, Four French centers
- Hyperprogression defined as a TGKr* ≥ 2

29% Hyperprogression

0% Pseudoprogression

- Hyperprogression associated with shorter OS but non statistical significance (6.1 months versus 8.1 months, p=0.77)

*TGKr: Tumor growth kinetics ratio (pre and post treatment)

Saâda-Bouzid E, et al, Ann Oncol. 2017 Jul 1;28(7):1605-1611

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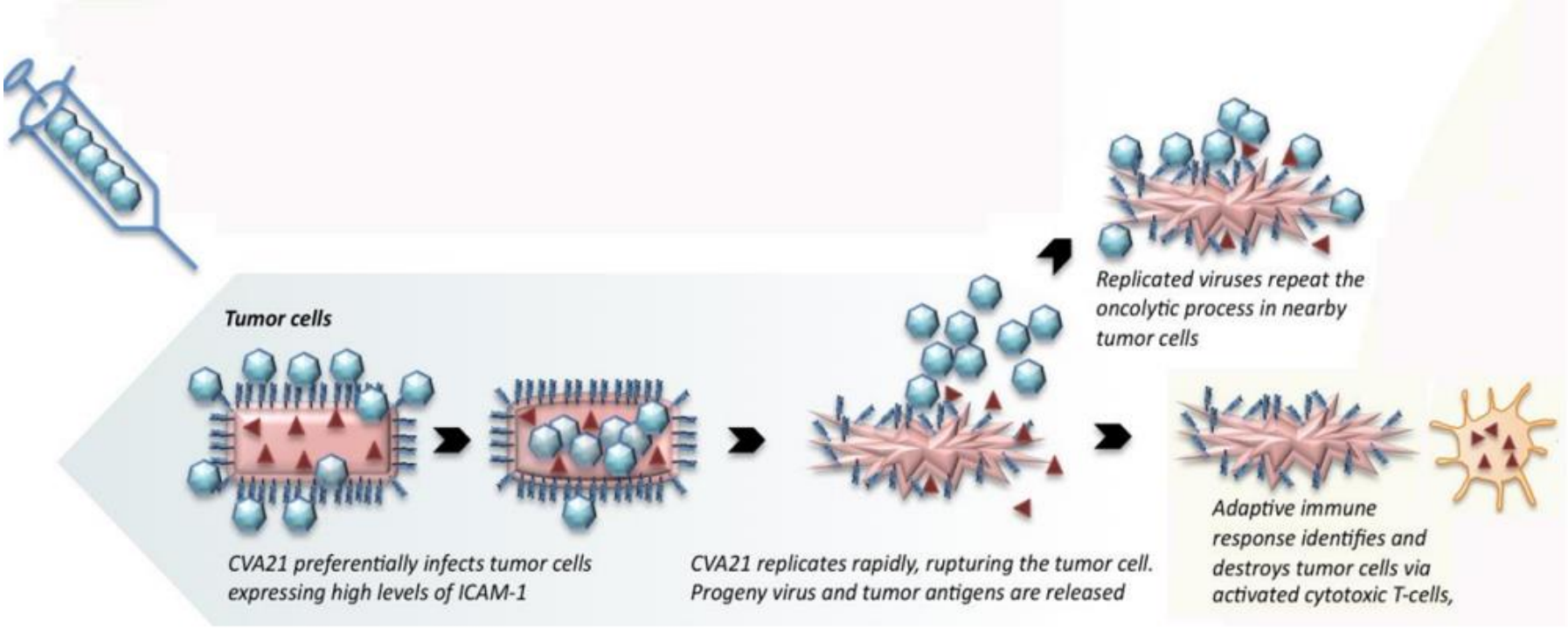
Emerging Immune Therapy Approaches

- Adoptive cells therapy approaches (TILs, TCR, CAR)
- Intratumoral: Oncolytic viruses (e.g., T-VEC)
- IDO inhibitors
- Bispecific antibodies
- Vaccines

Mode of action of oncolytic CVA 21, an Oncolytic virus



Example: Antitumor activity of T-VEC in melanoma

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Cell therapy: CAR-Ts CYAD-01 program at JB Institute

- **CYAD-01: A NKG2D receptor-based CAR-T targets 8 stress ligands expressed across the hematological/solid tumors**
- **CYAD-01: Multiple administrations (safe) in ≠ solid tumors**
- **CYAD-01: combination with FOLFOX in CRC**

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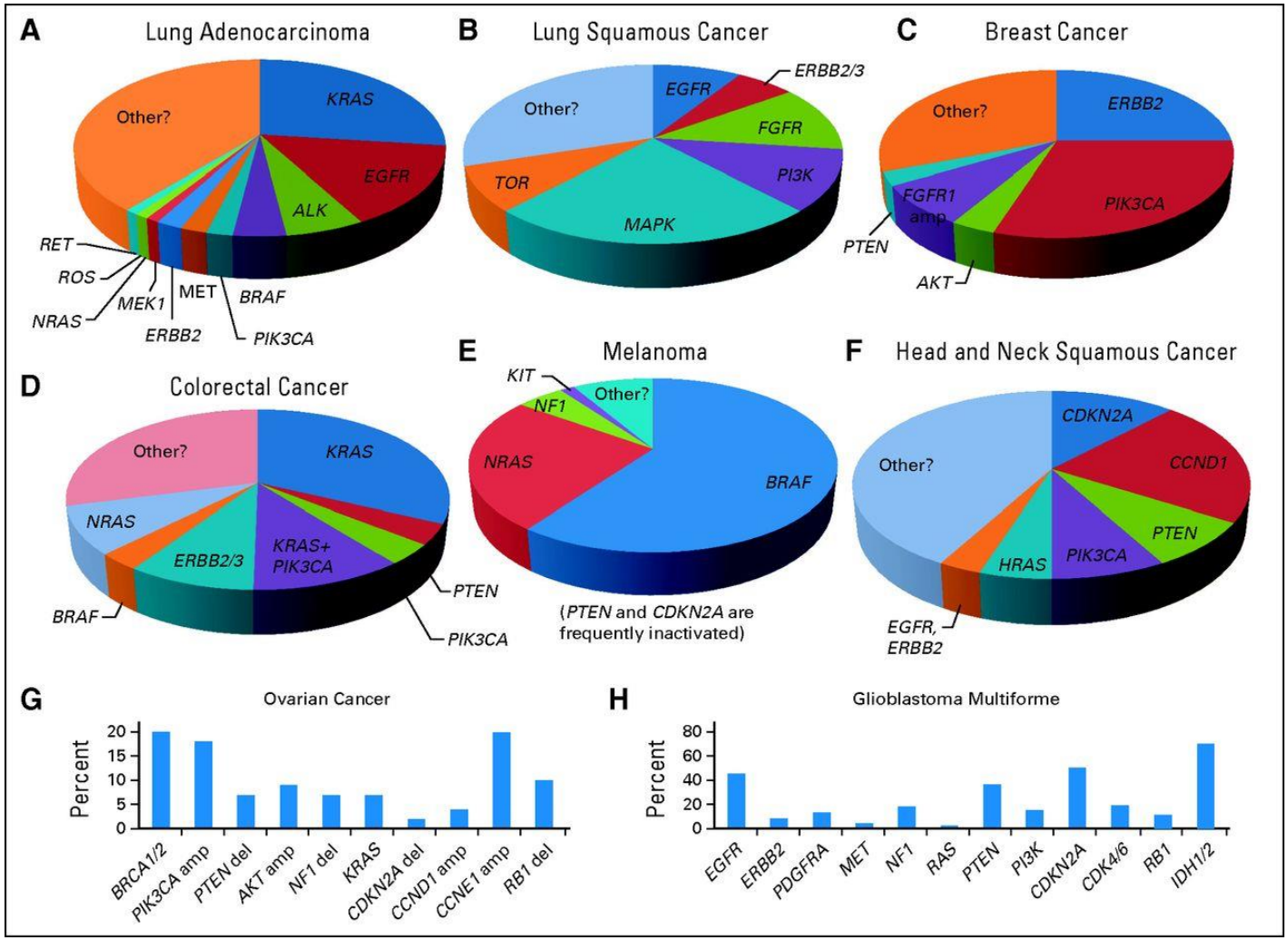
Cancer Therapy: Evolution of Concepts

- Escalation/de-escalation therapeutic strategies and role of genomics (e.g., breast cancer)
- Local therapy (RT, surgery) for oligometastatic diseases (prostate, CRC, ..)
- Molecular tumor segmentation using tumor genome sequencing
- Organ-agnostic therapies

Why to perform whole genome sequencing on solid tumors ? (Multiple tumor biopsies !)

- Understand tumor biology & evolution
- Guide therapy (e.g., BRCA tumors, MMR deficient tumors, …) = Personalized oncology

Common tumors segmentation = rare tumors !



Garraway L A JCO 2013;31:1806-1814

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JOURNAL OF CLINICAL ONCOLOGY ASCO

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Selected Clinical Studies That Have Evaluated Personalized Oncology Based on NGS

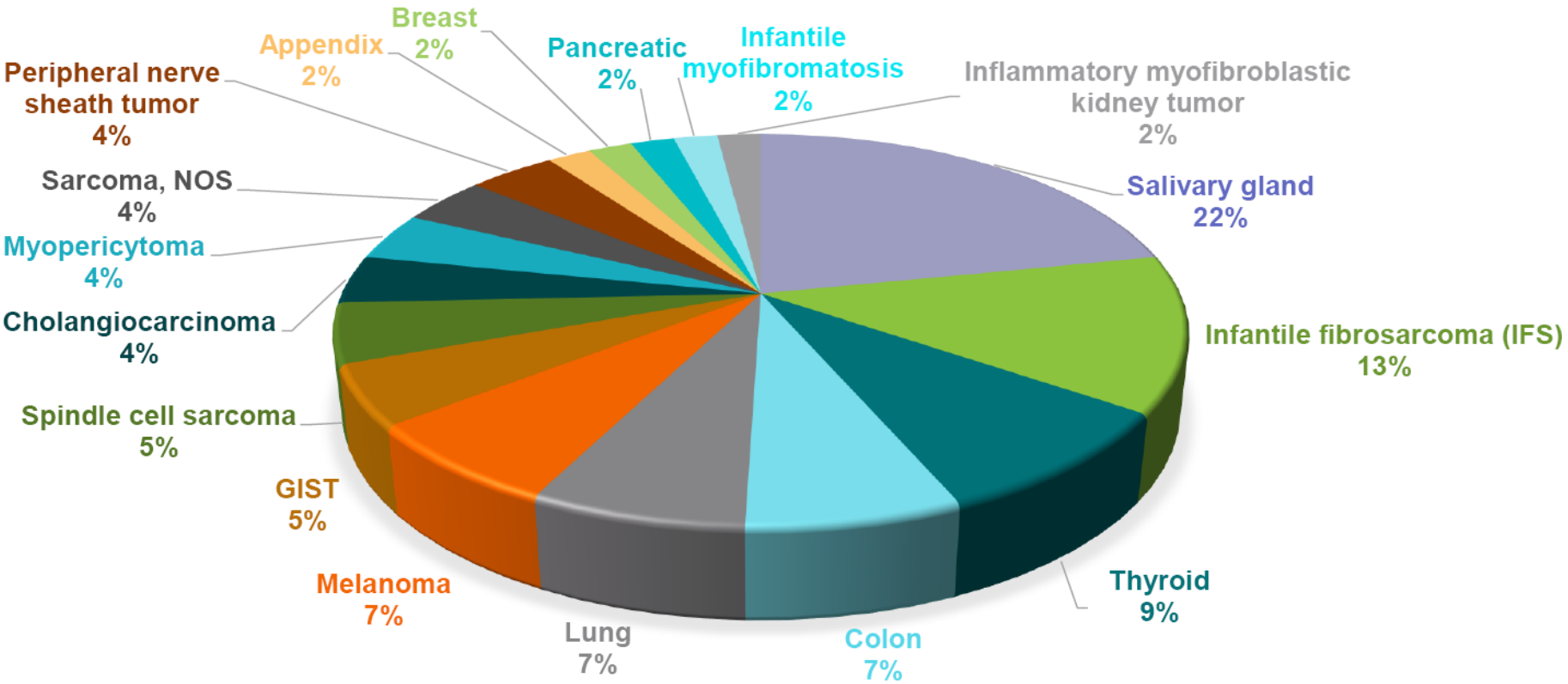
Table 1. Clinical Studies That Have Evaluated Personalized Cancer Medicine.*

Clinical Study	Design	Screened Sample	Patients with Genetic Profile	Patients with Mutation That Might Be Targeted by Drugs	Patients Receiving Matched Drug	Main Outcome Result
SHIVA trial[8]	Randomized, controlled trial of matched molecular targeted agent or physician's choice	741 patients with metastatic solid tumors who were amenable to biopsy	496 (67%)	293 (40%), of whom 195 underwent randomization	96 (100% of experimental-therapy group)	No significant difference in progression-free survival (primary end point); hazard ratio for death or disease progression, 0.88 (95% CI, 0.65–1.19)
Lung Cancer Mutation Consortium	Testing for driver mutations in metastatic lung adenocarcinomas at multiple centers				Many treated as per guidelines for an approved biomarker	Longer overall survival in the subgroups with a mutation treated with directed therapy than in those without the mutation or those that do not receive directed therapy
Study I[5]		1007 patients	733 (73%) tested for ≥10 genes	466 (46%)	260 (26%)	
Study II[6]		1315 patients	919 (70%) tested for ≥8 genes	529 (40%) had mutations, with 187 (14%) of them that could be targeted by drugs and had follow-up	127 (10%)	
SAFIR-01[9]	Treatment chosen after genetic profiling by comparative genomic hybridization and gene sequencing	423 women with metastatic breast cancer	299 (71%)	195 (46%)	55 (13%)	4 patients had a partial response and 9 had stable disease for >16 wk (3% of screened sample)
M.D. Anderson Study[10]	Treatment chosen after gene sequencing of patients with advanced cancer	2601 patients	2000 (77%)	789 (30%)	83 (3%) in genotype-matched trials; 116 (4%) with common mutations not in trial	Not stated
Princess Margaret IMPACT–COMPACT study[11]	Treatment chosen after gene sequencing of archival tissue	1893 patients with advanced solid tumors	1640 (87%)	938 (50%) had mutations, approximately 20% of which could be targeted by drugs	84 (4%) treated in genotype-matched trials	Response rate of 20% in genotype-matched trial vs. 11% in unmatched trials
y[12]	Treatment chosen after gene sequencing	250 patients	223 (89%)	109 (44%)	24 (10%)	Not stated

e interval, COMPACT Community Oncology Molecular Profiling in Advanced Cancers Trial, and IMPACT Integrated Molecular Profiling in Advanced Cancers Tri

Tannock IF, Hickman JA. N Engl J Med 2016;375:1289-1294.

Organ-agnostic Therapies: The Example of Larotrectinib (TRK fusion inhibitor)
Diversity of pediatric & adult cancers treated – 17 unique types



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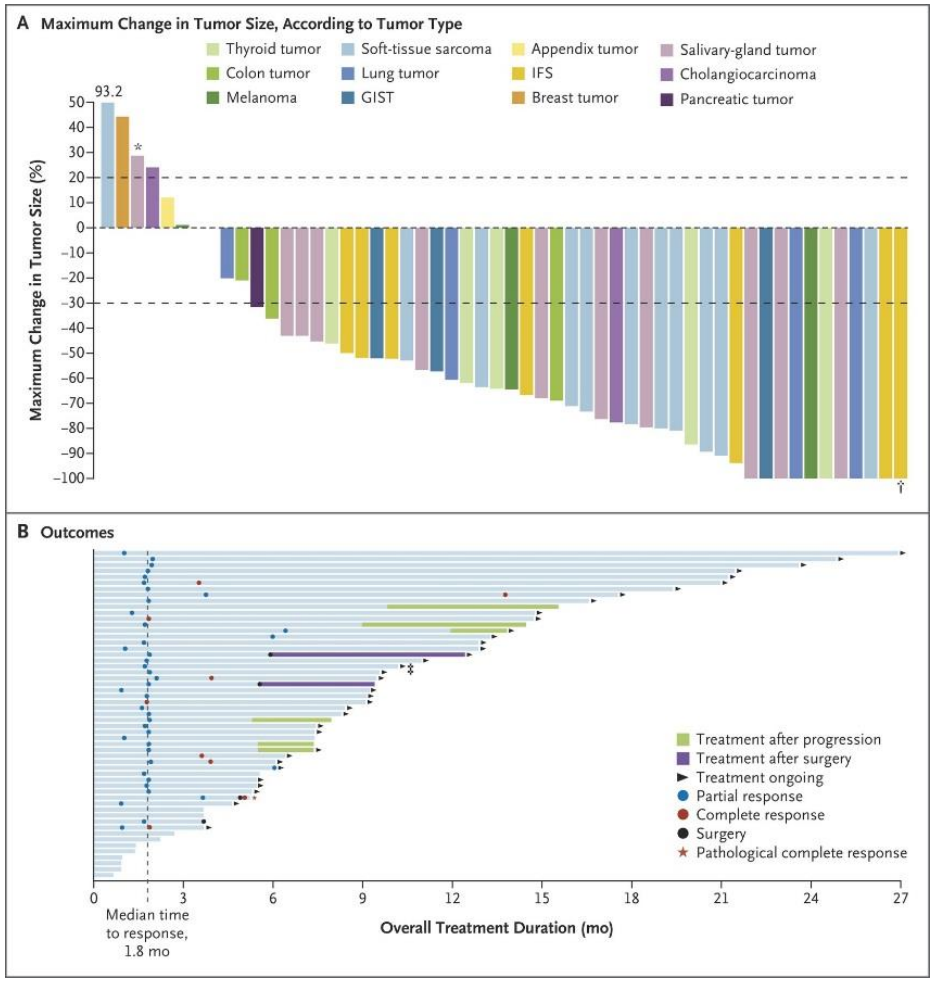
Larotrectinib (TRK inhibitor): Huge Efficacy



Drilon A et al. N Engl J Med 2018;378:731-739

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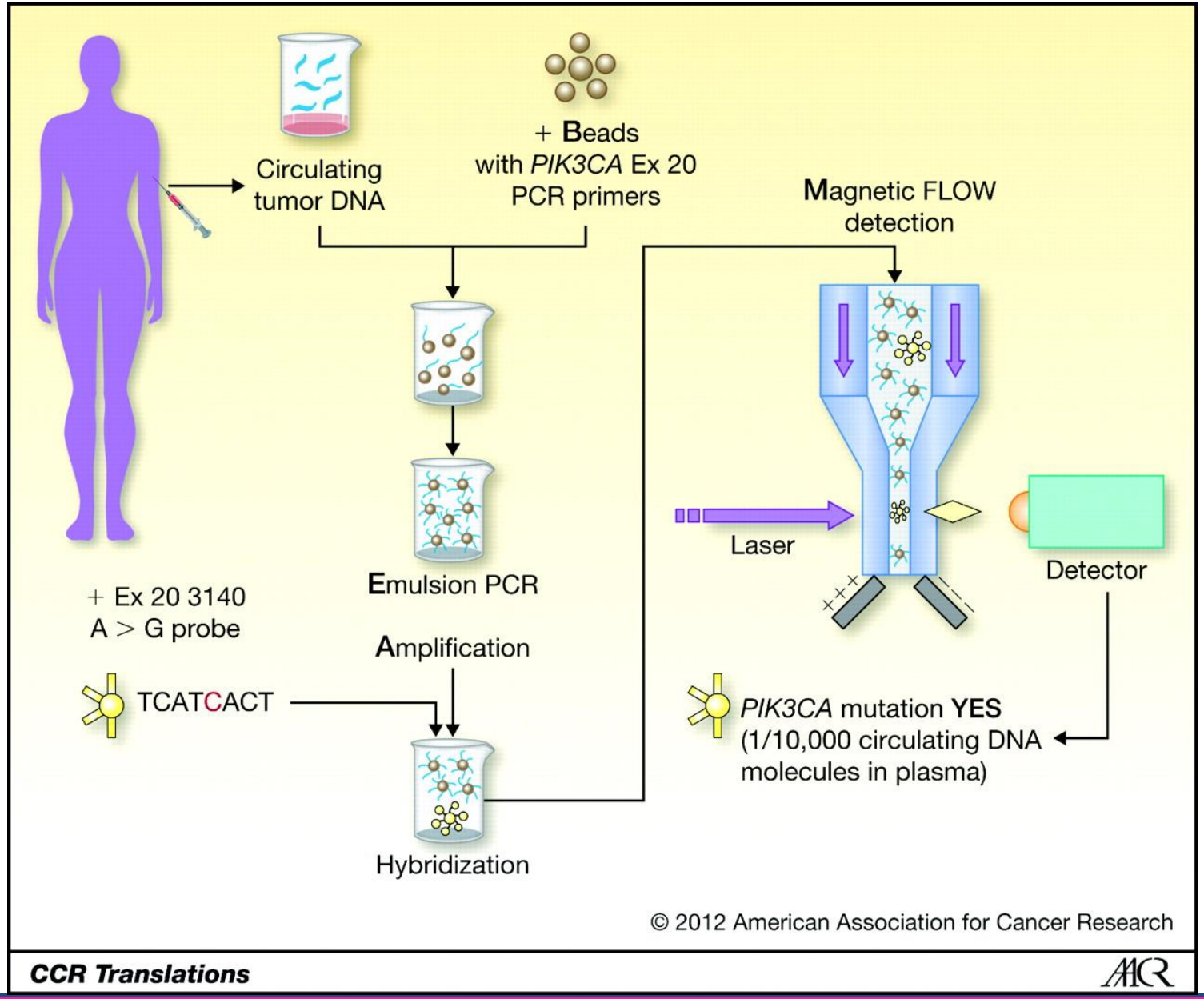
Circulating tumor cells or DNA to map clonal evolution, tumor heterogeneity and avoid serial invasive biopsies ?!



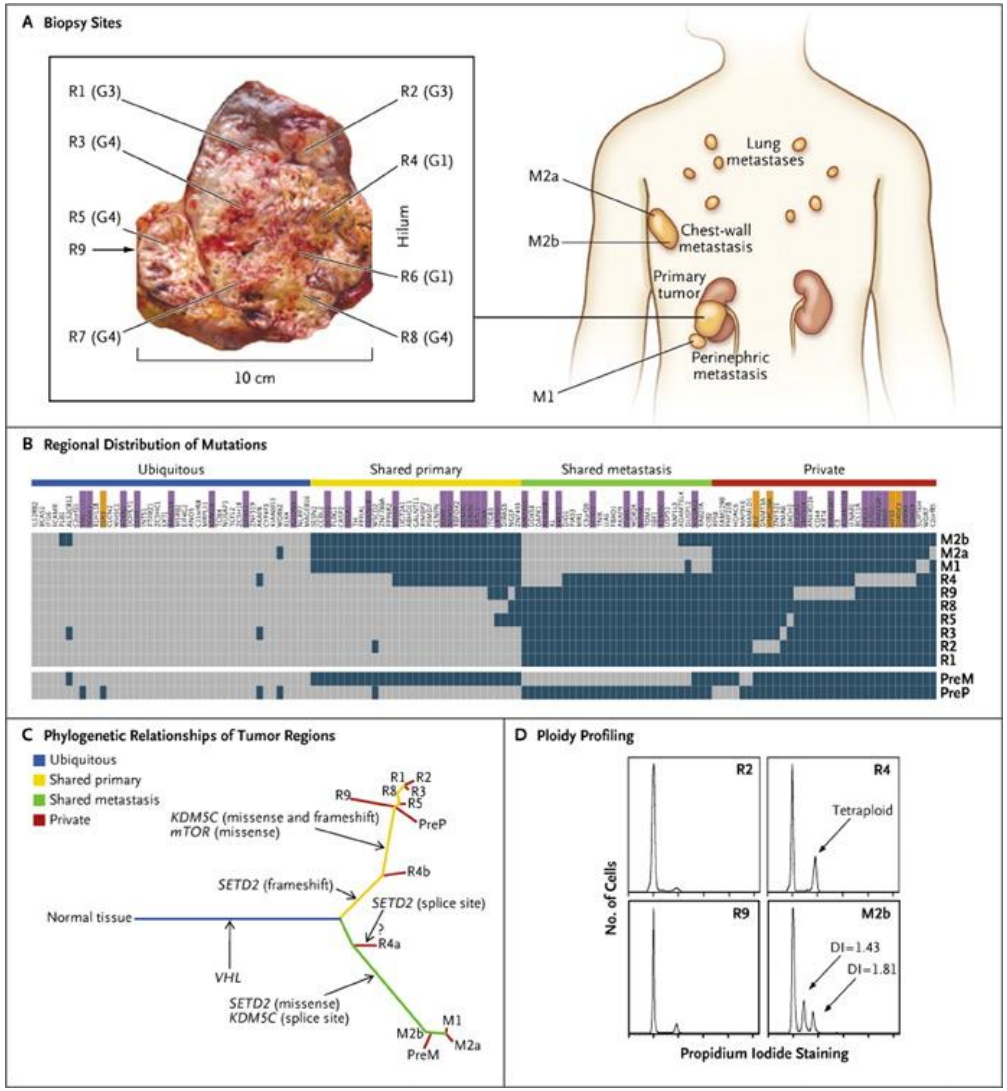
Potential clinical applications of circulating tumor DNA (liquid biopsies !)

- Early detection of cancer (e.g., NPC, …)
- Prognostic indicator
- Tumor mutation burden
- Minimal residual disease monitoring
- Predictor of response to therapy
- Treatment response monitoring
- Resistance mechanisms

Cancer Therapy: Challenges

- Molecular tumor heterogeneity→ Mixed tumor responses
- Resistance → Tumor disease progression
- Emerging of cerebral metastases

Dynamic intratumor heterogeneity revealed by multiregion sequencing in a patient with renal cancer



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M. Gerlinger et al. N. Engl J Med March 8 2012

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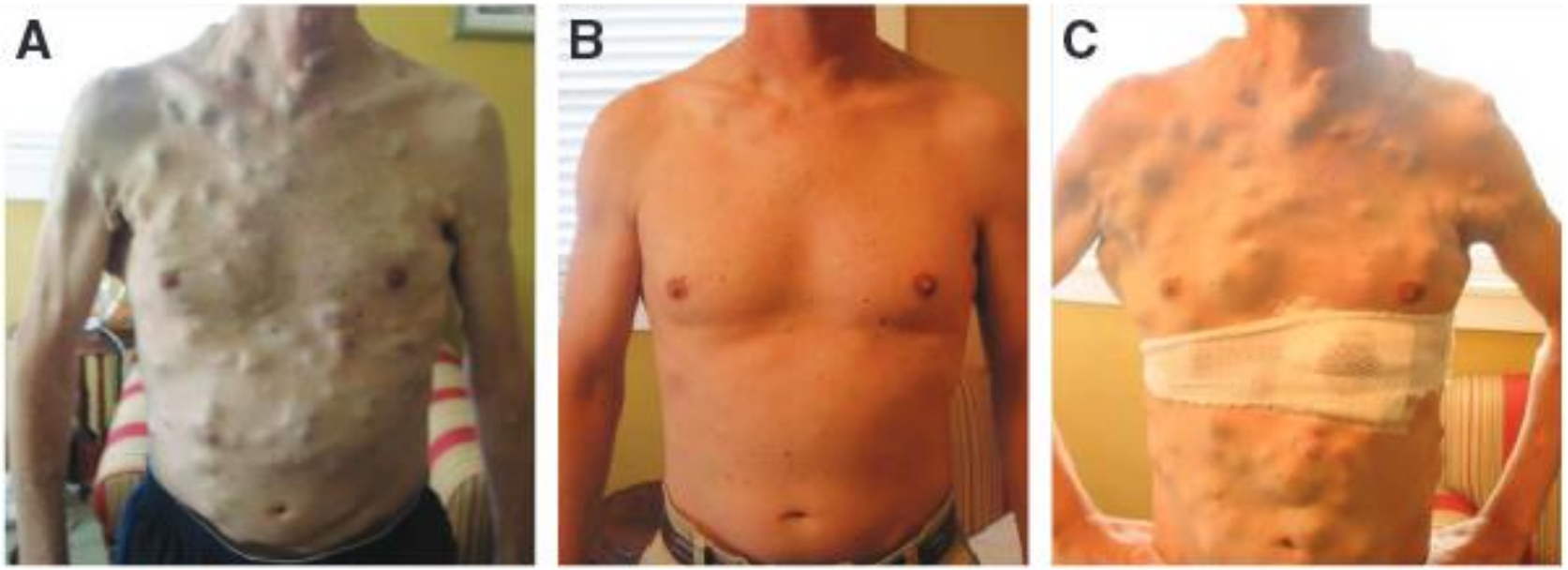
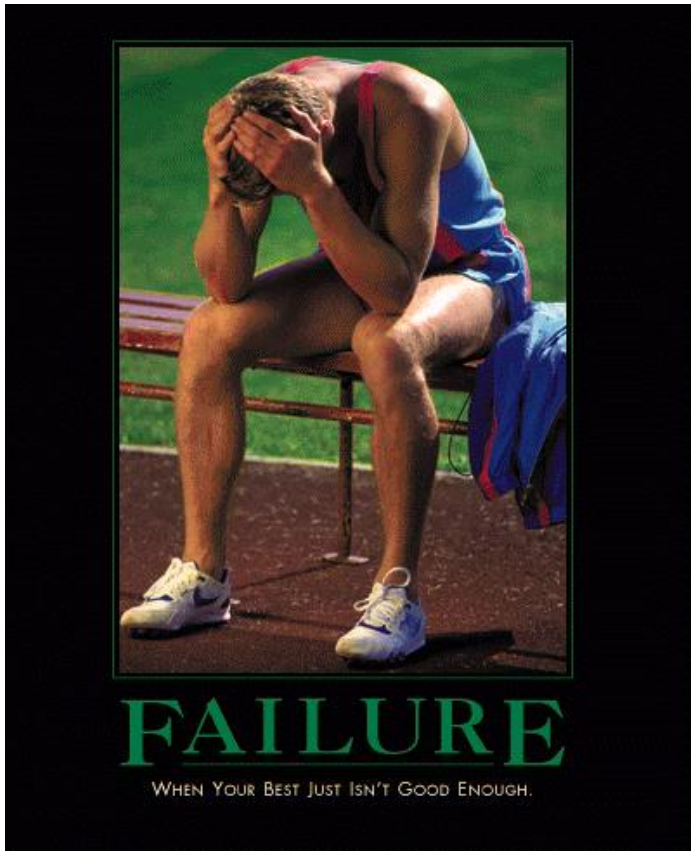
Dramatic response followed by « escape » to a mutated BRAF inhibitor in a patient with melanoma



Targeted therapy in selected tumors failed so far : the examples of pancreatic cancer and glioblastoma



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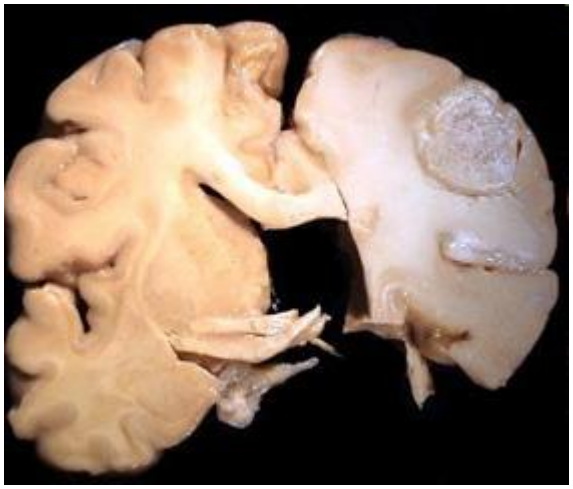
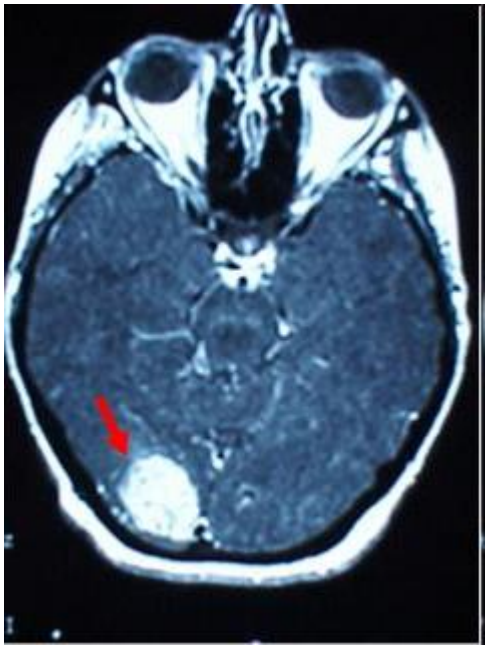
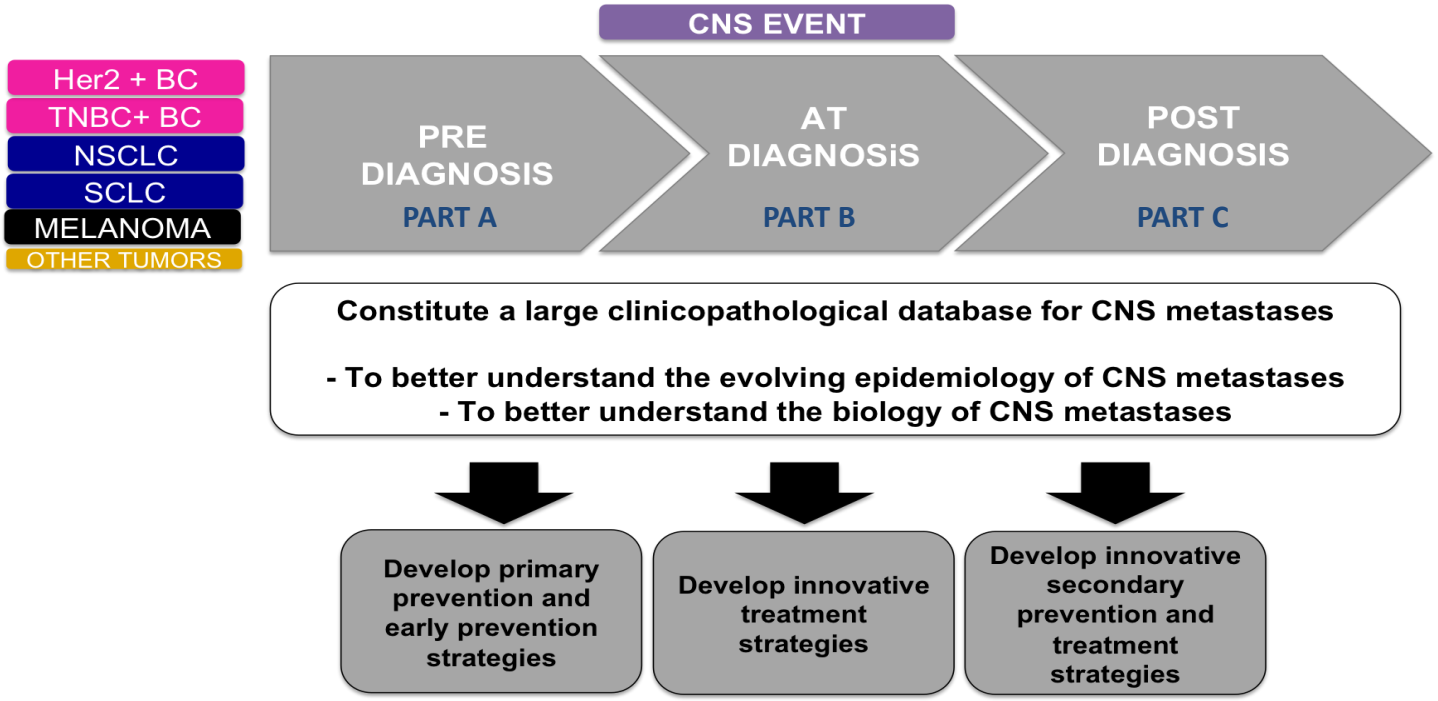
Emergence of brain metastases is a major challenge in some tumors

- **Breast HER-2, TNBC and other solid tumors**





BRAINSTORM Program at JBI: STUDY DESIGN AND OBJECTIVES



N. Kotecki & A. Awada

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Looking to the future (1)

- Innovations in science and technology will shape the future of clinical cancer care from diagnosis to surgery to supportive care
- Integration and mining of health care data from various sources (artificial intelligence) will probably improve patient management and outcomes

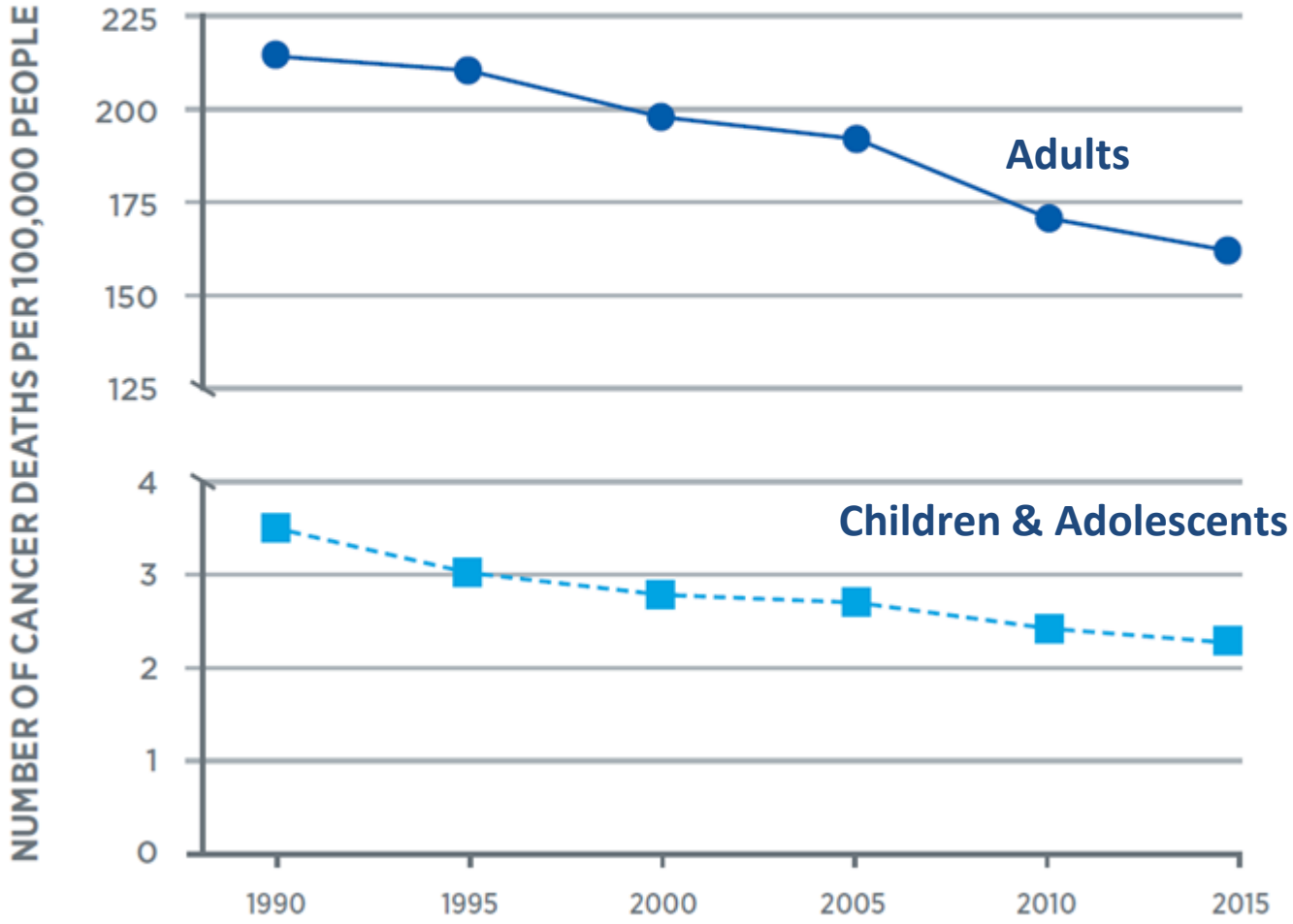
Looking to the future (2)

- Liquid biopsies have the potential to transform early detection, diagnosis and treatment of cancer
- How to manage life during and after cancer : the major role of psychological and social support

Innovative anticancer approaches

New therapeutic approaches without access to cancer patients aren't innovation – they are just an invention!

Making Progress against Cancer



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THANK YOU

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