Definition of a driver. Cellular/tissular mechanisms supporting that a driver becomes a target Multiple drivers, mechanisms of resistance

Prof. Dr. Christian Rolfo, MD, PhD, MBAh
Head of Phase I – Early Clinical Trials Unit
Director of Clinical Trials Management Program
Antwerp University Hospital & Center for Oncological Research (CORE), Antwerp University
Belgium

Kennis / Ervaring / Zorg

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Disclosures

- Novartis International Speaker bureau
- Boeringher Speaker Bureau
- MSD – Merck Speaker Bureau
- Oncompass Molecular Profile Steering Committee board Member
- Mylan Biosimilars Advisor for NSCLC
- Guardant Health speaker bureau
- OncoDNA research grant for exosomes

Biomarker Definition by NCI

"A biological molecule found in blood, other fluids or tissues, that is a sign of a normal or abnormal process, or a condition or disease"

Prognostic Biomarker

Disease Related

Predictive Biomarker

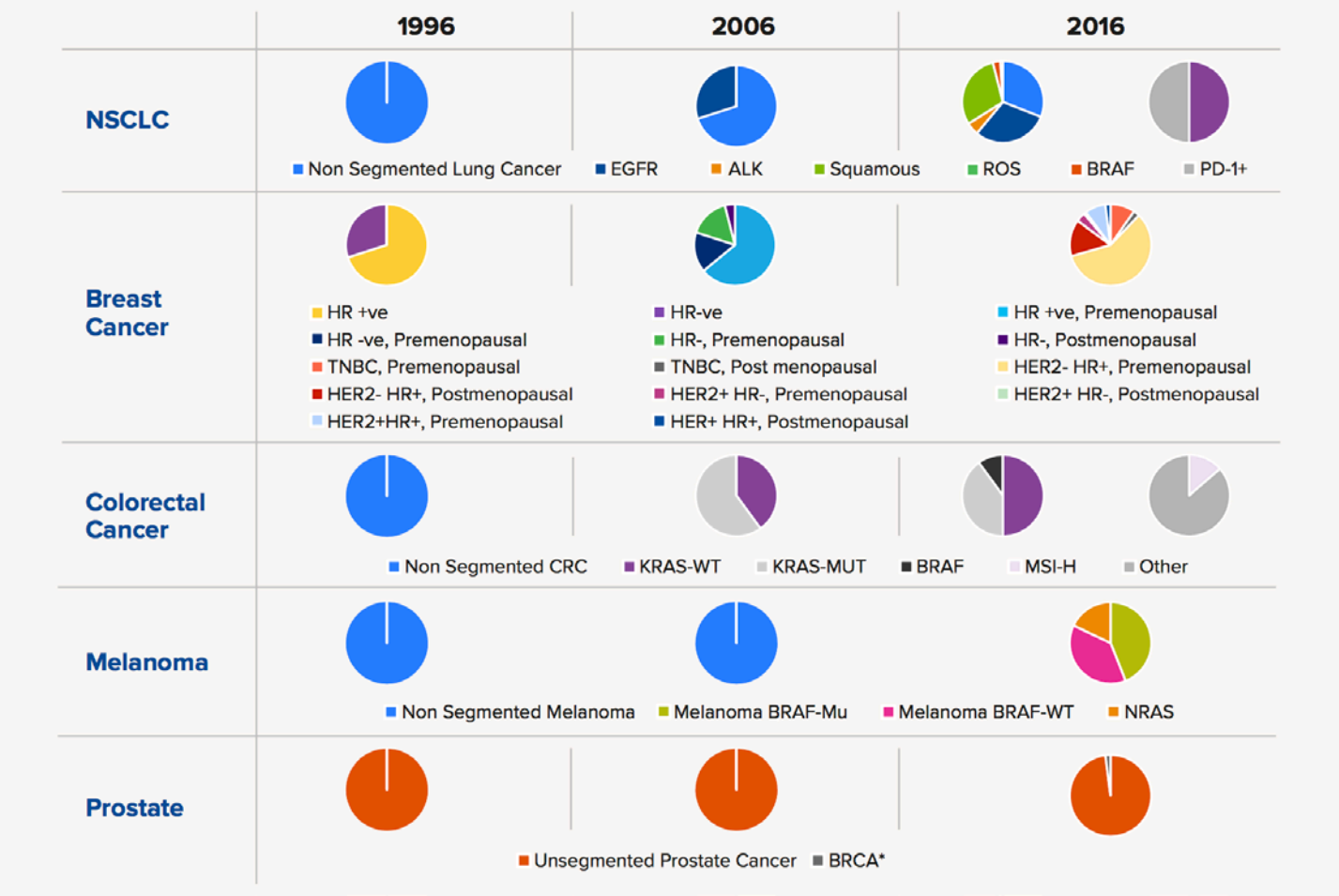
Drug Related

State of the Science in Biomarker Research

- More than 40,000 papers on cancer biomarkers each year
- Around 4000–5000 on biomarkers for early detection, diagnosis and prognosis
- **99% claims >90% sensitivity and specificity**
- But, very few are supported by evidence sufficient for regulatory approval
  - Rigorous standards for validation of clinical relevance in appropriate populations (i.e., in detecting preclinical disease, predicting progression/extent of disease)

Cancer treatment over the last past 20 years

Percent of Biomarker-Based Segmentation in Selected Tumor



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Global Oncology Trends 2017: Advances, Complexity, and Cost. QuintilesIMS Institute. June 2017.

The Hallmarks of a Precision-Oncology Study

Kennis / Ervaring / Zorg

Hyman et al, Cell. 2017 Feb 9;168(4):584-599

Biomarker Development

Clinical validity:
The test result shows an association with a clinical outcome of interest.

Analytical validity:
The test's performance is established to be accurate, reliable, and reproducible.

Clinical utility:
Use of the test results in a favorable benefit to risk ratio for the patient

Cancer Biomarkers: Missing the Mark

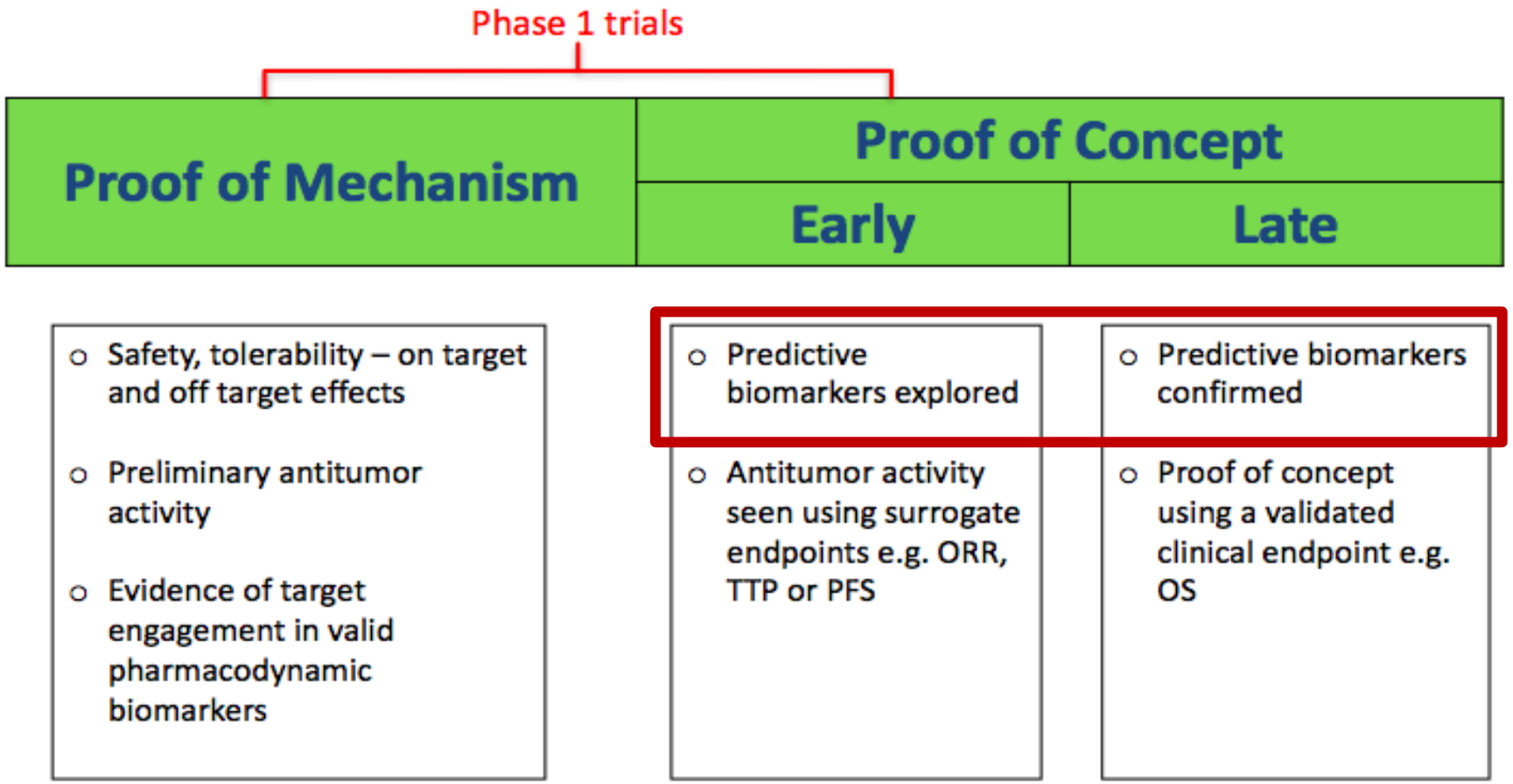
- **Biology of early disease not fully explored**
- Differences in **analytical techniques**
- Differences in **statistical methods** (study designs)
- Unintentional selective reporting
- Incomplete protocol reporting
- **Lack of appropriate specimens and reagents**
- **Variations in interpretation**
- Bias, chance and overfitting
- Lack of appropriate **controls**
- Need for additional knowledge in translation of laboratory tests into clinical tests
- **Need for more collaboration**

Phases of Biomarker Discovery and Validation

Preclinical Exploratory	PHASE 1	Promising directions identified
Clinical Assay and Validation	PHASE 2	Clinical assay detects established disease
Retrospective Longitudinal	PHASE 3	Biomarker detects preclinical disease and a "screen positive" rule defined
Prospective Screening	PHASE 4	Extent and characteristics of disease detected by the test and the false referral rate are identified
Cancer Control	PHASE 5	Impact of screening on reducing burden of disease on population is quantified

Margaret Sullivan Pepe et al. J Natl Cancer Inst, Vol. 93, No. 14, July 18, 2001

The Current Drug Development Paradigm



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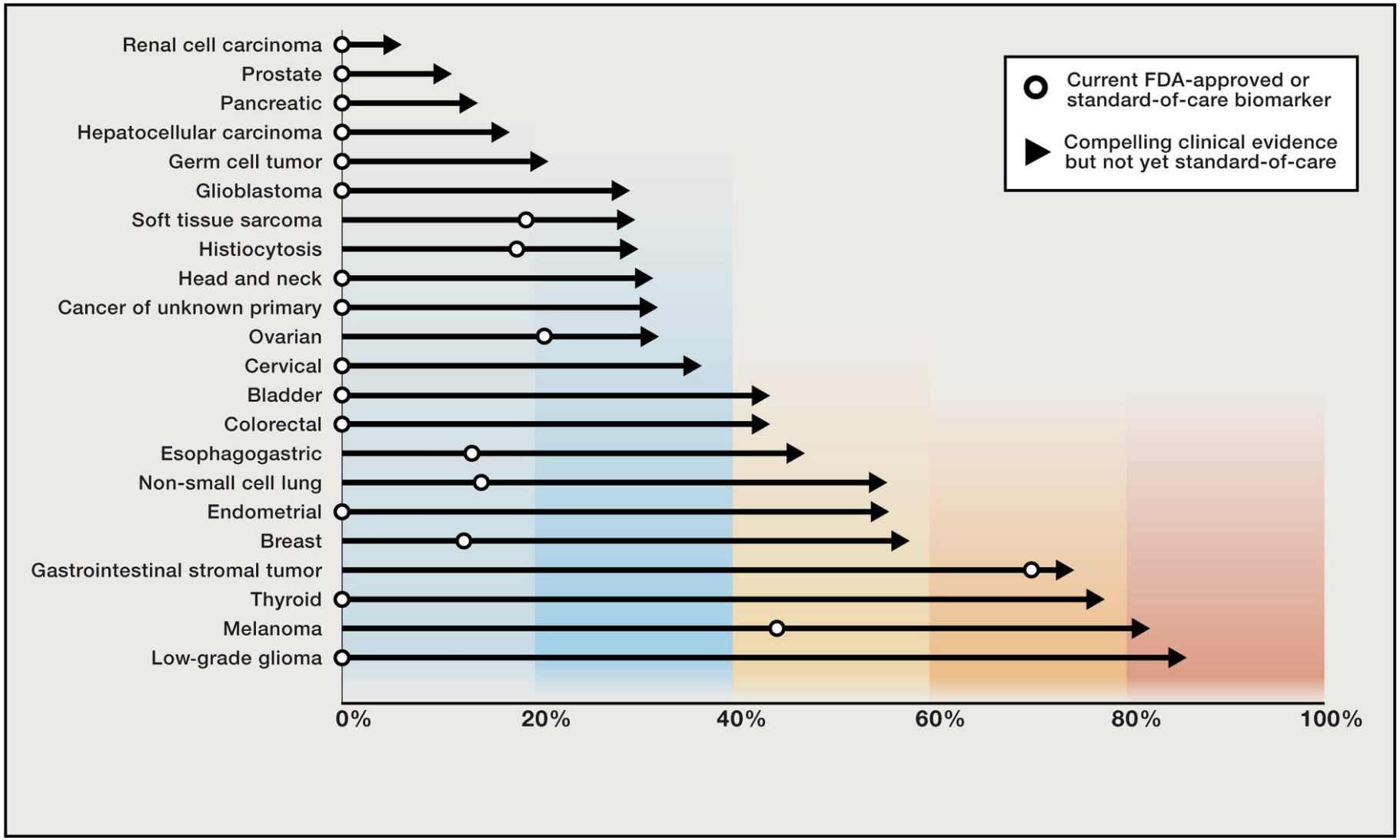
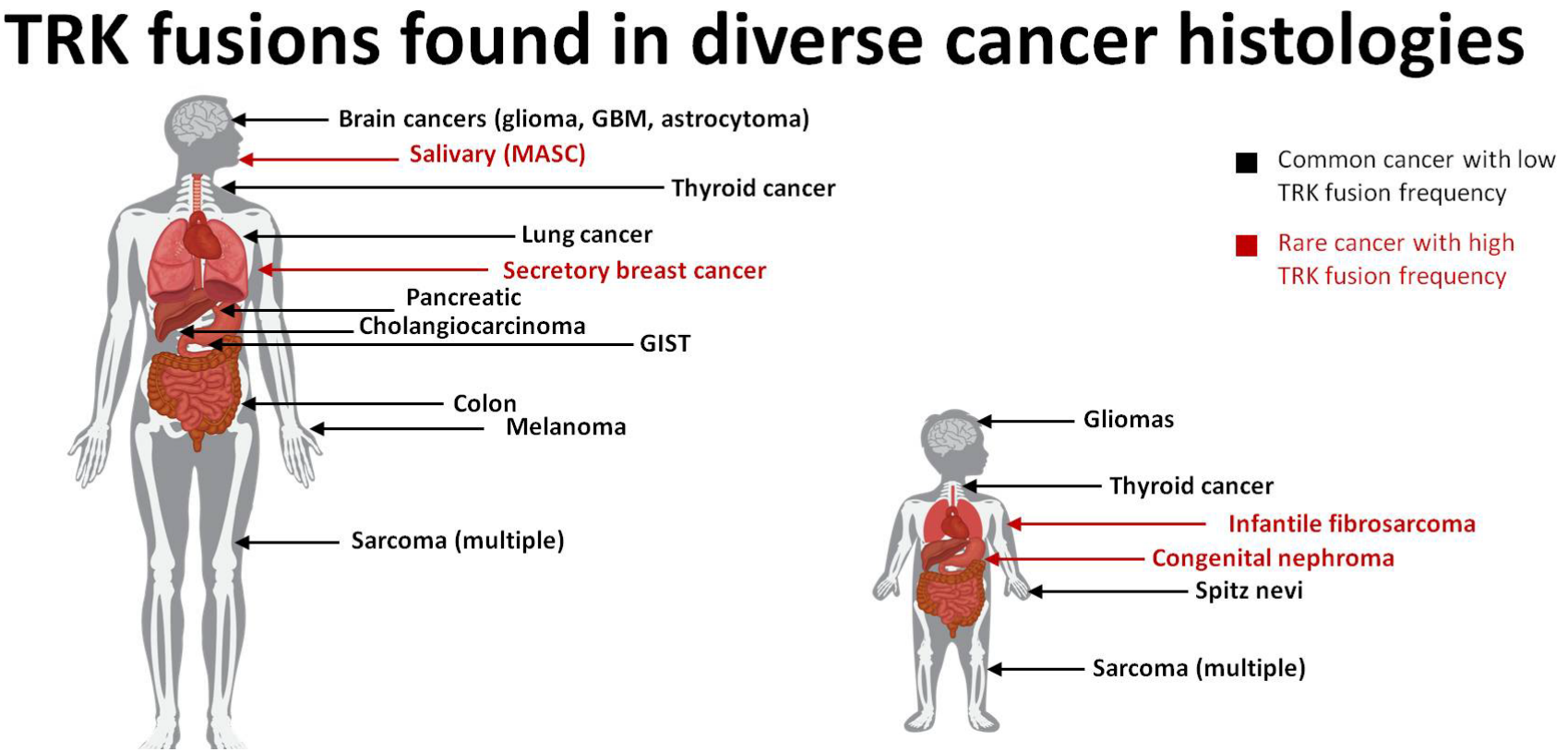
Courtesy of David Hong

Druggable Alterations in Oncology Today and in the Near Future



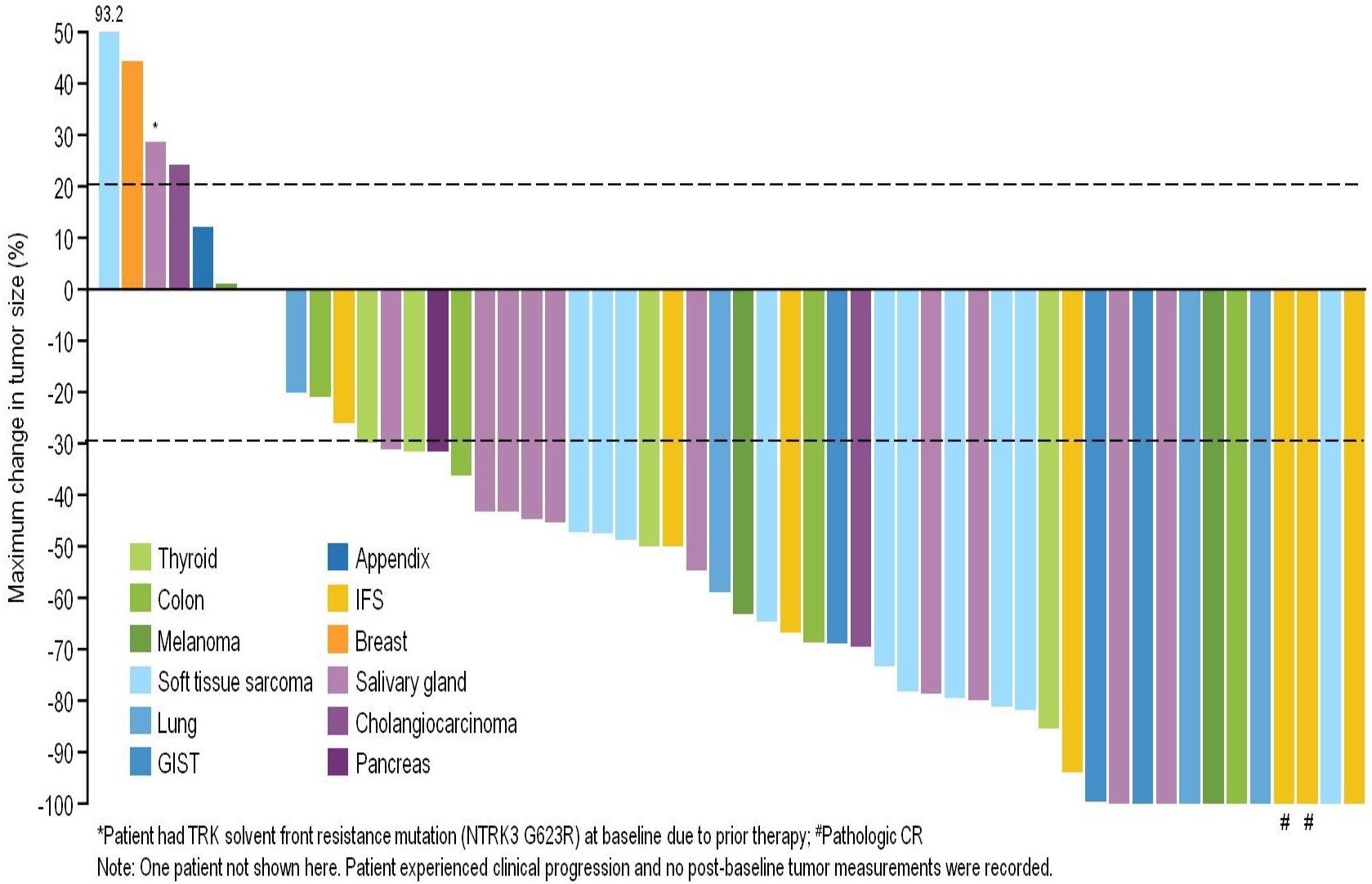
Hyman et al, Cell. 2017 Feb 9;168(4):584-599

TRK fusions found in diverse cancer histologies



Presented By David Hyman at 2017 ASCO Annual Meeting

NTRK Inhibitor
Efficacy regardless of tumor type

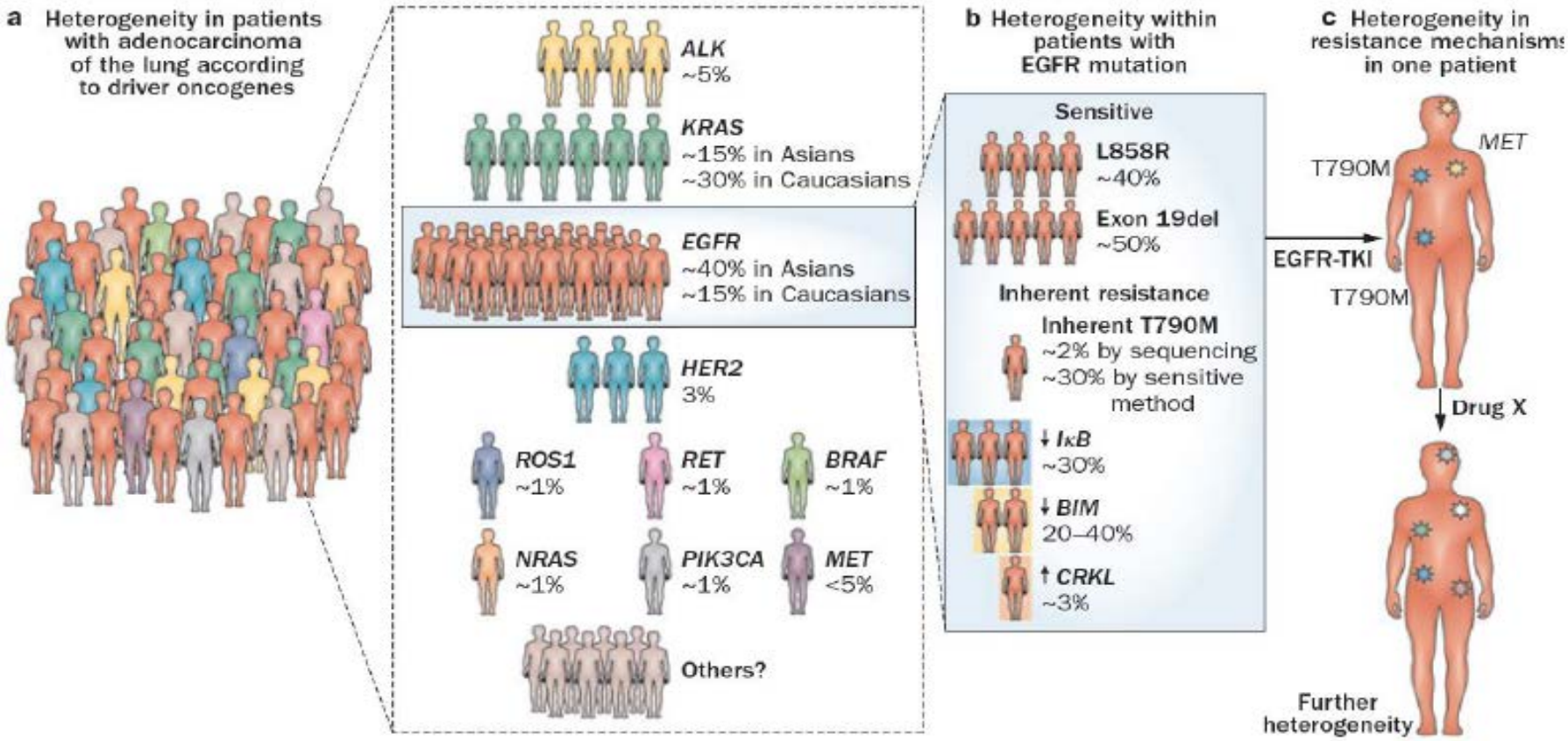


*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

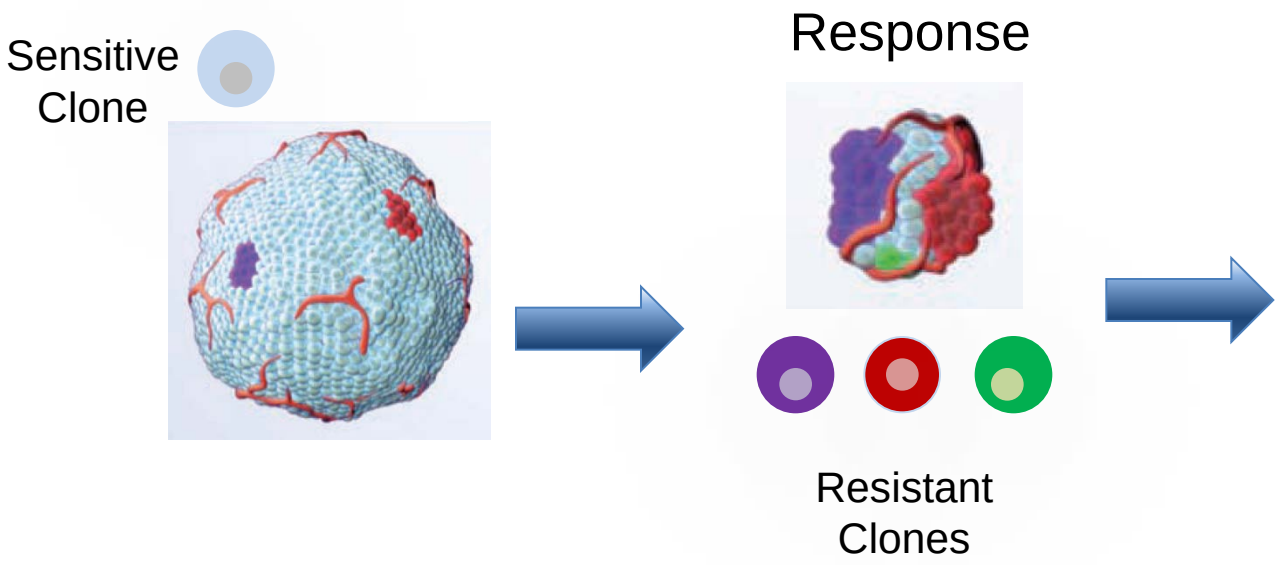
The efficacy of target therapy is affected by…

TUMOR HETEROGENEITY



Mitsudomi Nat Rev Clin Oncol 2013

Molecular Issues regarding T790M



- **T790M-positive and T790–wild-type clones may coexist** in some cancers with acquired resistance to initial EGFR TKIs
- Concept of **cancer's "loss" of T790M** suggests that the original lesion, although testing "positive" for T790M, may have contained both T790M-positive and T790–wild-type clones
- **Spatial heterogeneity** indicates **inter-/intratumor** differences at the genomic, epigenetic, and proteomic levels, whereas **temporal heterogeneity** reflects dynamic tumor evolution over time

Multiple Tests Require Large Tissue Volume

Tumor Biopsy

Finite tissue

Histology

↓

Cancer

≥2 slides

Anatomy

↓

Adeno-carcinoma

≥1 slide

cMET

EGFR

5 µm tissue

BRAF

PI3K

FGFR

≥5 slides

IHC (ALK+)

≥2 slides but no tissue

Confirmatory FISH

≥2 slides

RELAPSE

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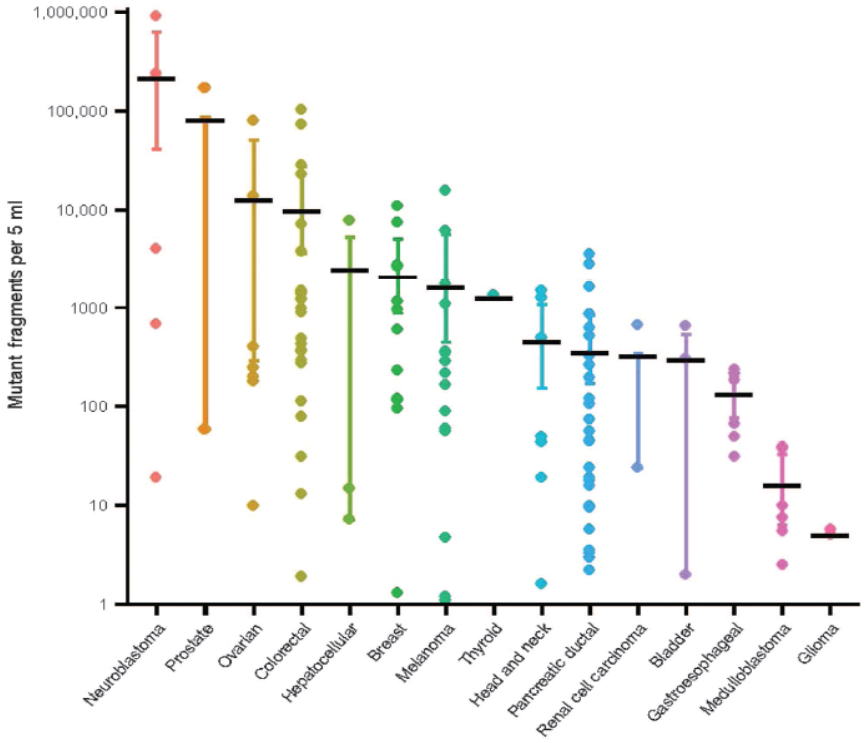
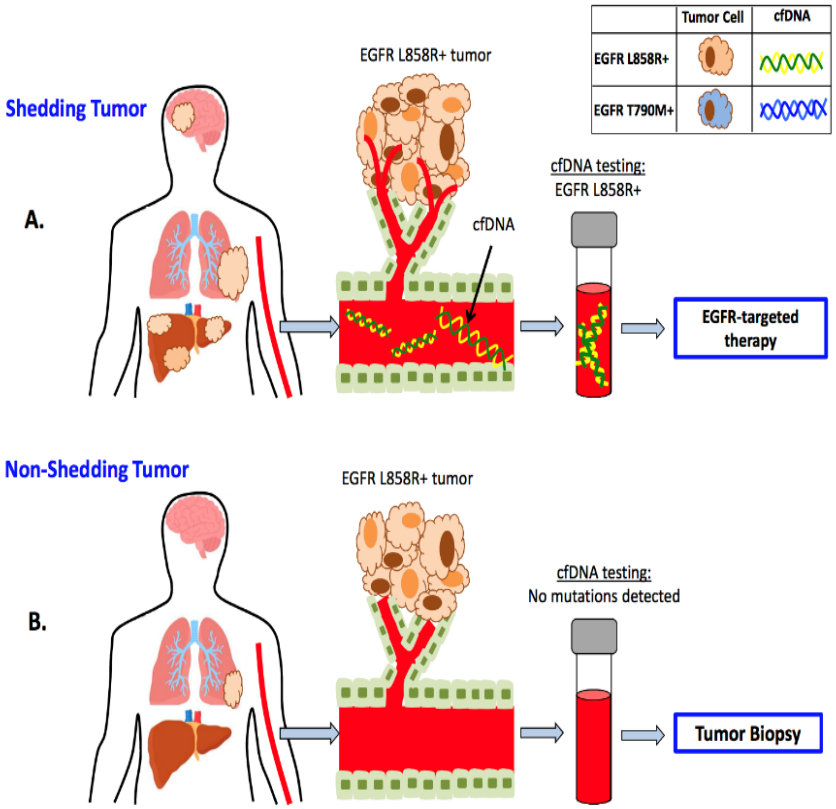
Liquid biopsy: ctDNA

Does ctDNA concentration is the same among patients with the same tumor?



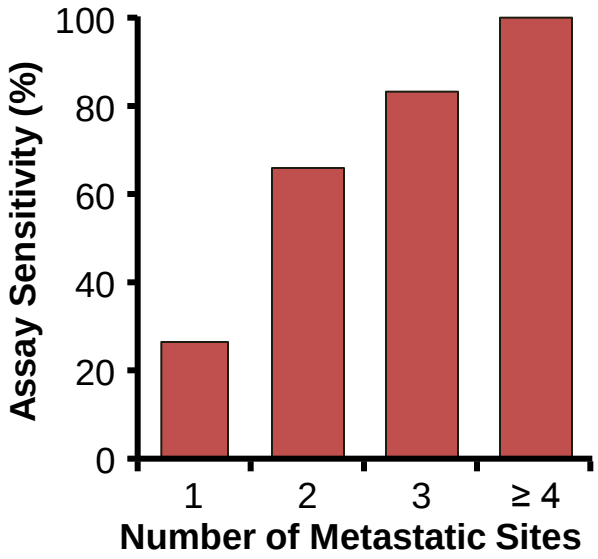


Bettegowda et al., Sci Trans Med, 2014

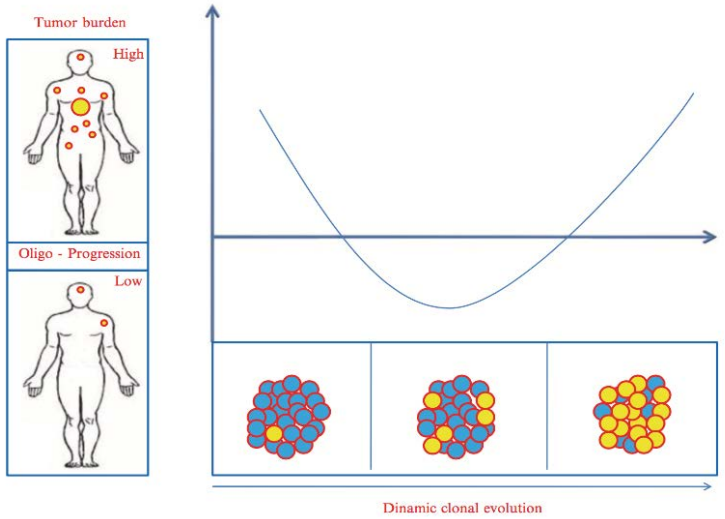
Sacher, Komatsubara,Oxnard J Thorac Oncol. 2017 Sep;12(9):1344-1356

Some considerations

Sensitivity of Plasma ddPCR Higher in Pts With Metastases



Correlation between tumor burden (*y*-axis) and dynamic clonal evolution of the tumor



Increasing number of metastatic sites (*P* = .001) and presence of bone (*P* = .007), hepatic (*P* = .001) metastases significantly associated with assay sensitivity

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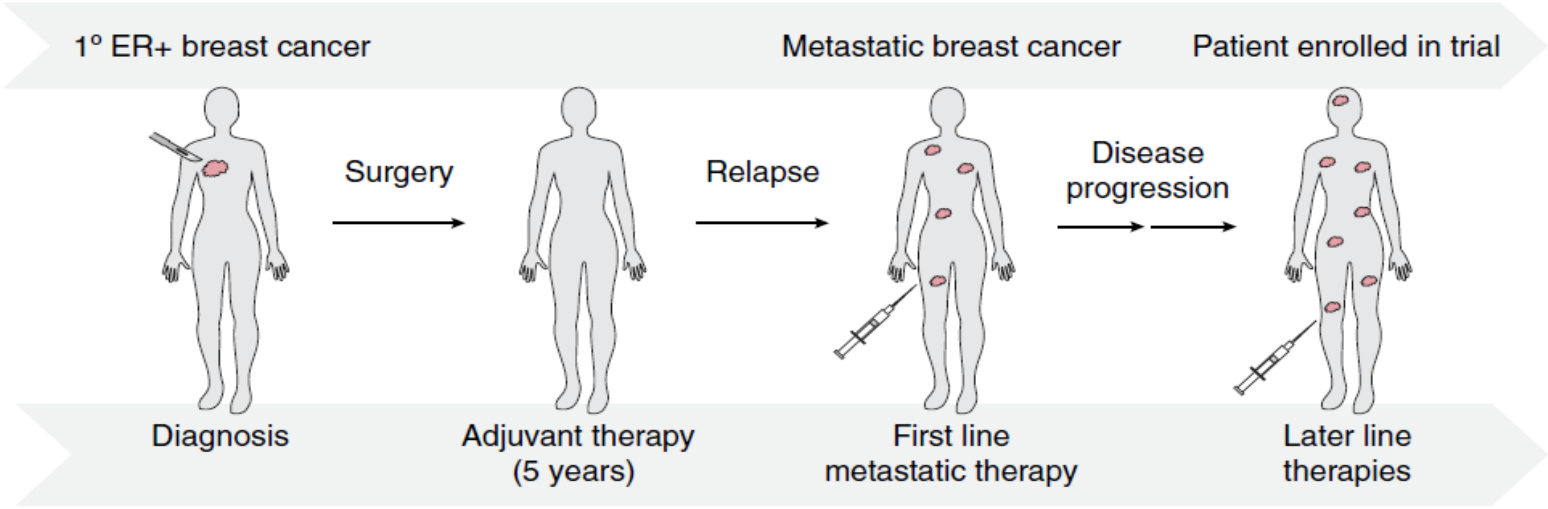
Sacher AG, et al. JAMA Oncol. 2016

Pisapia, Malapelle, Troncone, Springer Book 2017

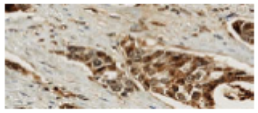
Special considerations...

The Role of Next-Generation Sequencing in Enabling Personalized Oncology Therapy



Tumor tissue collection

Surgical resection



Use for Dx (ER, PR, HER2)
Archive for later NGS profiling

Biopsy

NGS to identify genomic drivers

Biopsy

NGS to identify resistance mechanisms

Blood collection

Screening for early cancer detection

Detection of residual disease post surgery to predict risk of relapse

Dissecting heterogeneity of metastatic disease

Monitoring response and detecting resistance mutations

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Cummings et al, Clin Transl Sci (2016) 9, 283–292

Guardant360 Panel

All NCCN Somatic Genomic Targets in a Single Test

Point Mutations - ***Complete**** *or Critical Exon Coverage in 73 Genes*

AKT1	*ALK*	***APC***	***AR***	*ARAF*	***ARID1A***	*ATM*	***BRAF***	***BRCA1***	***BRCA2***
CCND1	***CCND2***	***CCNE1***	*CDH1*	***CDK4***	***CDK6***	***CDKN2A***	***CDKN2B***	*CTNNB1*	***EGFR***
ERBB2	*ESR1*	*EZH2*	*FBXW7*	***FGFR1***	***FGFR2***	*FGFR3*	*GATA3*	*GNA11*	*GNAQ*
GNAS	*HNF1A*	***HRAS***	*IDH1*	*IDH2*	*JAK2*	*JAK3*	***KIT***	***KRAS***	*MAP2K1*
MAP2K2	***MET***	*MLH1*	*MPL*	***MYC***	***NF1***	*NFE2L2*	*NOTCH1*	*NPM1*	***NRAS***
NTRK1	***PDGFRA***	***PIK3CA***	***PTEN***	*PTPN11*	***RAF1***	***RB1***	*RET*	*RHEB*	*RHOA*
RIT1	*ROS1*	*SMAD4*	*SMO*	*SRC*	*STK11*	*TERT*	***TP53***	*TSC1*	*VHL*

AMPLIFICATIONS

AR	*BRAF*	*CCND1*	*CCND2*	*CCNE1*	*CDK4*	*CDK6*	*EGFR*	*ERBB2*
FGFR1	*FGFR2*	*KIT*	*KRAS*	*MET*	*MYC*	*PDGFRA*	*PIK3CA*	*RAF1*

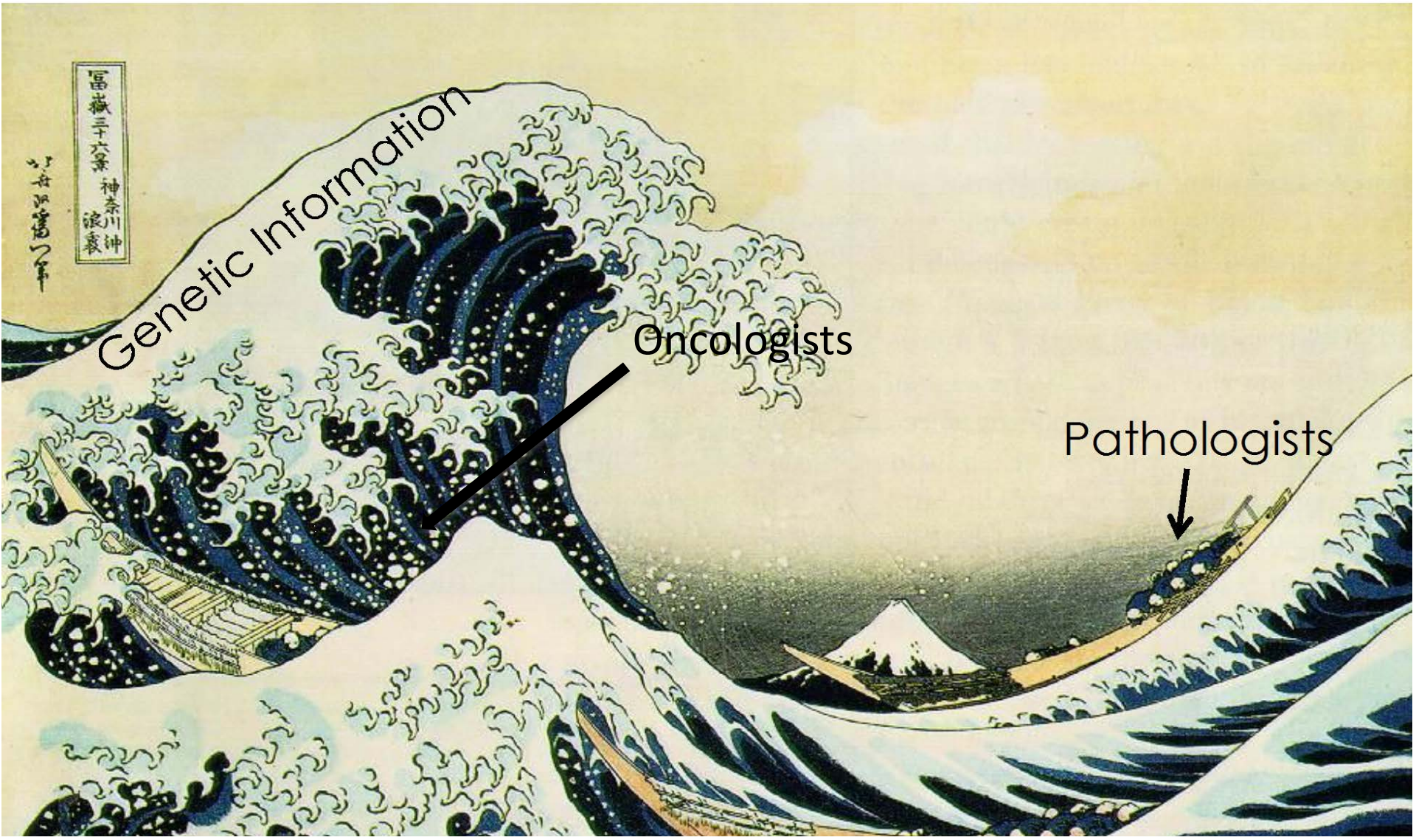
FUSIONS

ALK	*FGFR2*	*FGFR3*	*RET*	*ROS1*	*NTRK1*

INDELS

EGFR exons 19/20	*ERBB2* exons 19/20	*MET* exon 14 skipping

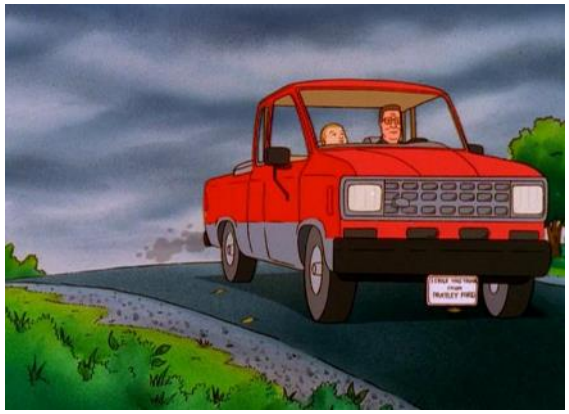
Data Tsunami

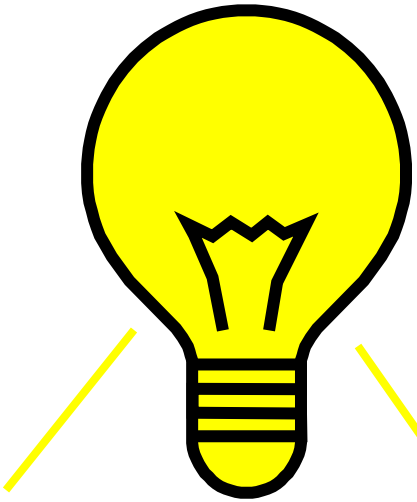


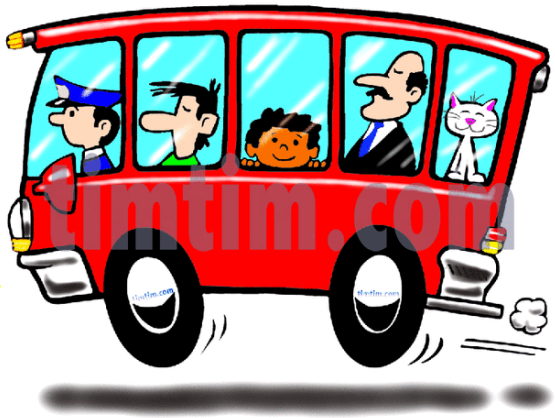
Classifying a mutation by frequency

- **Mountain**: number of mutations in a gene is very high. Any reasonable statistic will indicate that the gene is a driver
- **Hill**: few mutations.

Discriminating a Driver and a Passenger Mutation in Early Phases Can Be Difficult

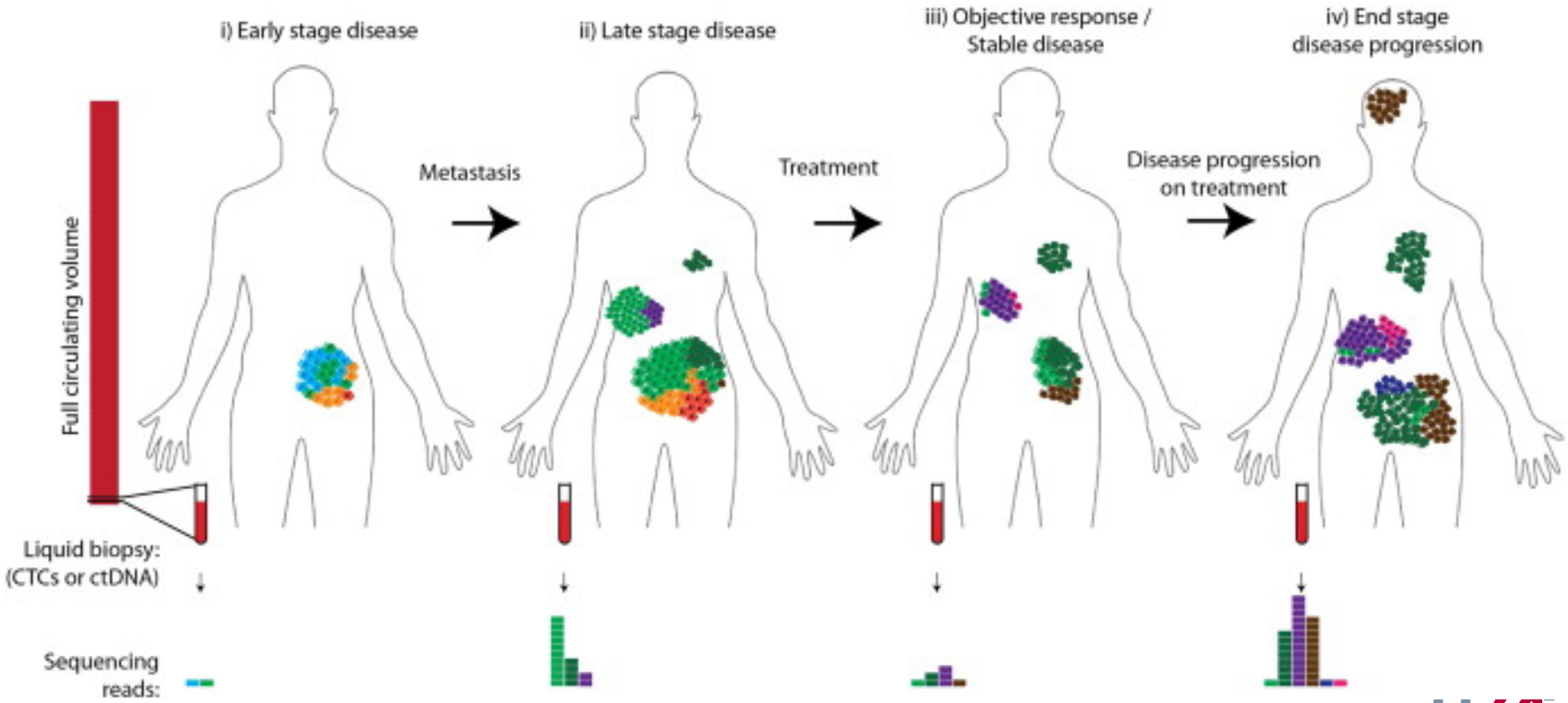






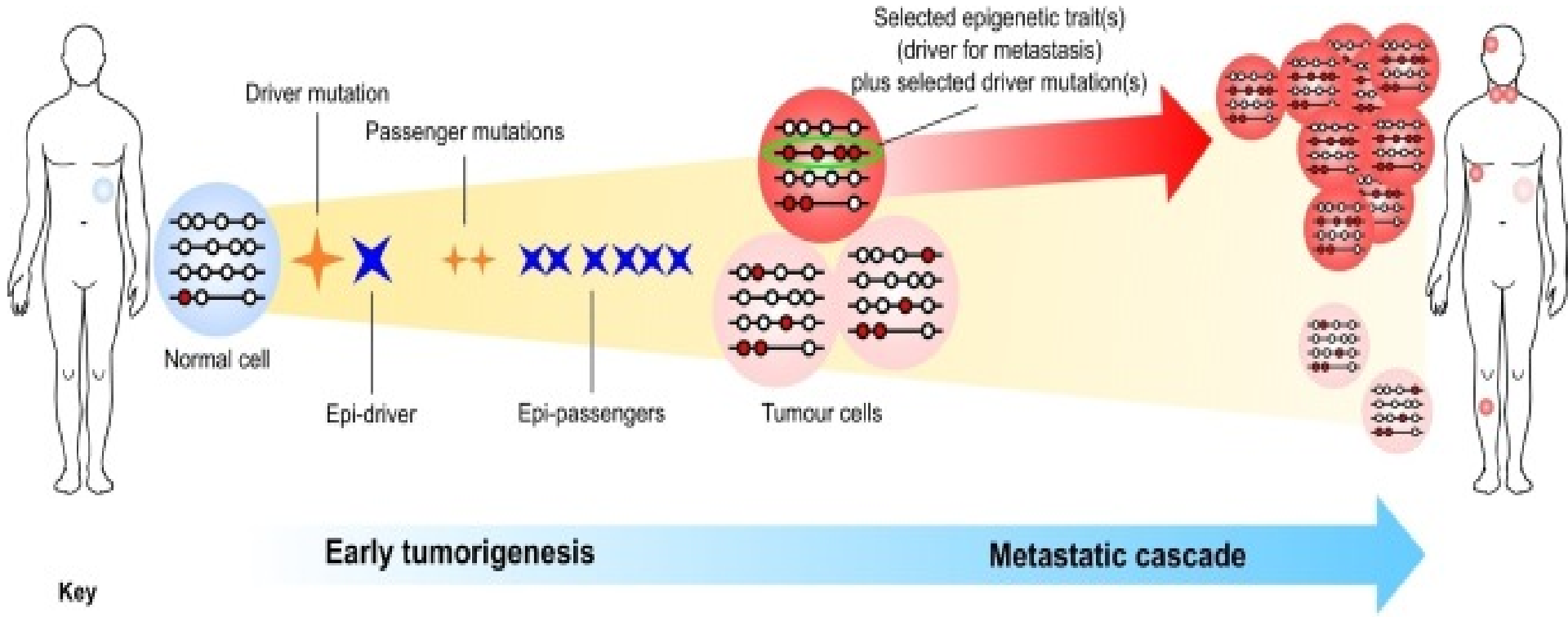
DRIVER MUTATIONS

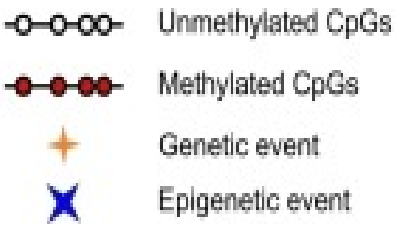
- Passenger mutations can transform into driver mutations (“latent drivers” or “mini-drivers”)
- In the context of resistant and/or recurrent disease.



R. Burrell, C. Swanton Mollecular Oncology. 2014

DRIVER GENE MUTATION





➢**Epi-driver genes**: are expressed aberrantly in tumors but not frequently mutated. Changes in DNA methylation or chromatin modification that persist as the tumor cell divides

Chatterjee,E.J. Rodger,M. Eccles. Seminars in Cancer Biology, 2017

Multidisciplinary Molecular Tumour Board: a tool to improve Clinical Practice and selection accrual for Clinical Trials in Cancer Patients

Christian Rolfo, Paolo Manca, Andreia Coelho, Jose Ferri, Peter Van Dam, Amelie Dendooven, Christine Weyn, Marika Rasschaert, Lucas Van Houtven, Xuan Bich Trinh, Jan Van Meerbeeck, Roberto Salgado, Marc PeetersPatrick Pauwels

On behalf of Molecular Tumour Board of Antwerp University Hospital, Edegem, Belgium.

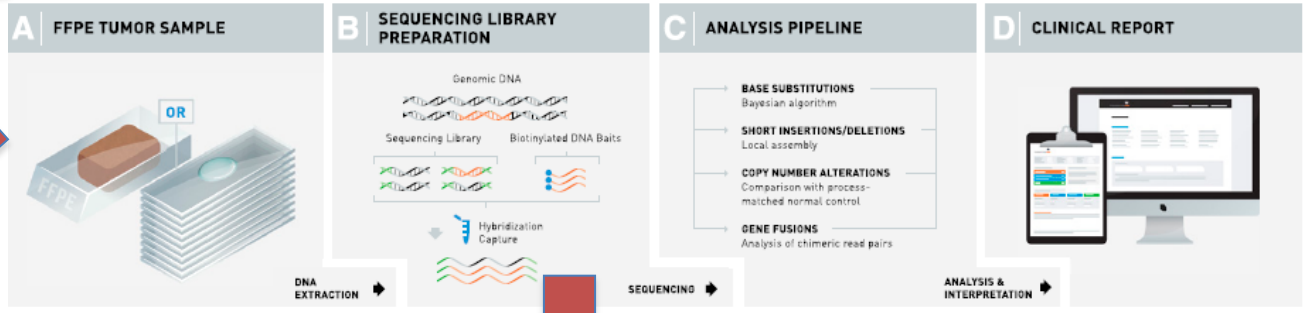
Molecular Tumor Board

Patient case is derived from his doctor

Molecular Tumor Board

Oncologist | Mol. Pathol | Surgeon

Gyneco | Thorax | Geneticist | Pediat | Nav. nurse



Molecular Tumor Board → **Report with therapeutic proposal** → Referral Doctor Discussion

MSK Levels of Evidence

OncoKB

Level 1 — **FDA-recognized** biomarker predictive of response to an **FDA-approved** drug **in this indication**

Level 2A — **Standard of care** biomarker predictive of response to an **FDA-approved** drug **in this indication***

Level 2B — **Standard of care** biomarker predictive of response to an **FDA-approved** drug **in another indication**, *but not standard of care for this indication*

Level 3A — **Compelling clinical evidence** supports the biomarker as being predictive of response to *a drug* **in this indication**, *but neither biomarker nor drug are standard of care*

Level 3B — **Compelling clinical evidence** supports the biomarker as being predictive of response to *a drug* **in another indication**, *but neither biomarker nor drug are standard of care*

Level 4 — **Compelling biological evidence** supports the biomarker as being predictive of response to *a drug, but neither biomarker nor drug are standard of care*

Level R1 — **Standard of care** biomarker predictive of **resistance** to an **FDA-approved** drug **in this indication**

Standard Therapeutic Implications
*Includes biomarkers that are recommended as standard of care by the NCCN or other expert panels but not necessarily FDA-recognized for a particular indication

Investigational Therapeutic Implications
possibly directed to clinical trials

Hypothetical Therapeutic Implications
based on preliminary, non-clincial data

Standard Therapeutic Implications

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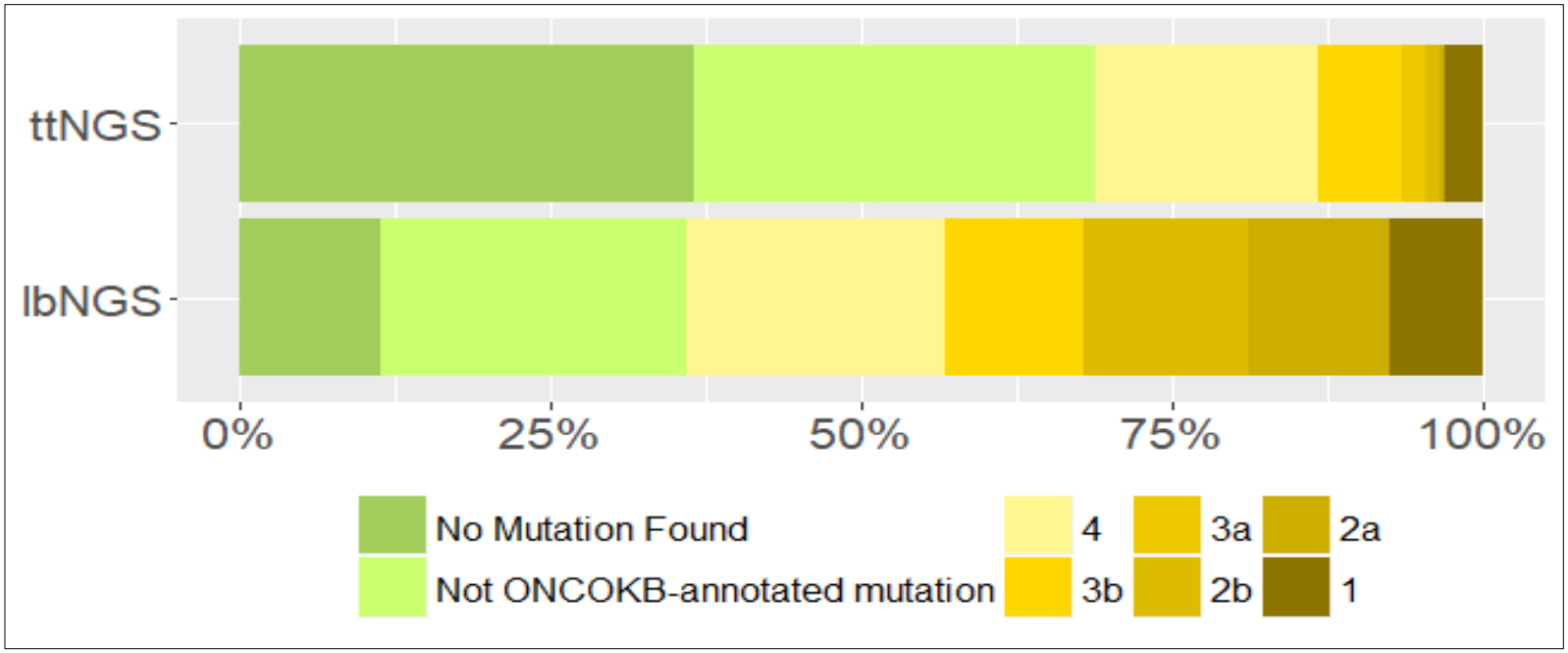
J Clin Oncol 34, 2016 (suppl; abstr 11583)

ONCO KB evidence levels from lbNGS (n=53) and ttNGS (n=195) in all available samples



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Rolfo et al, unpubished data 2017

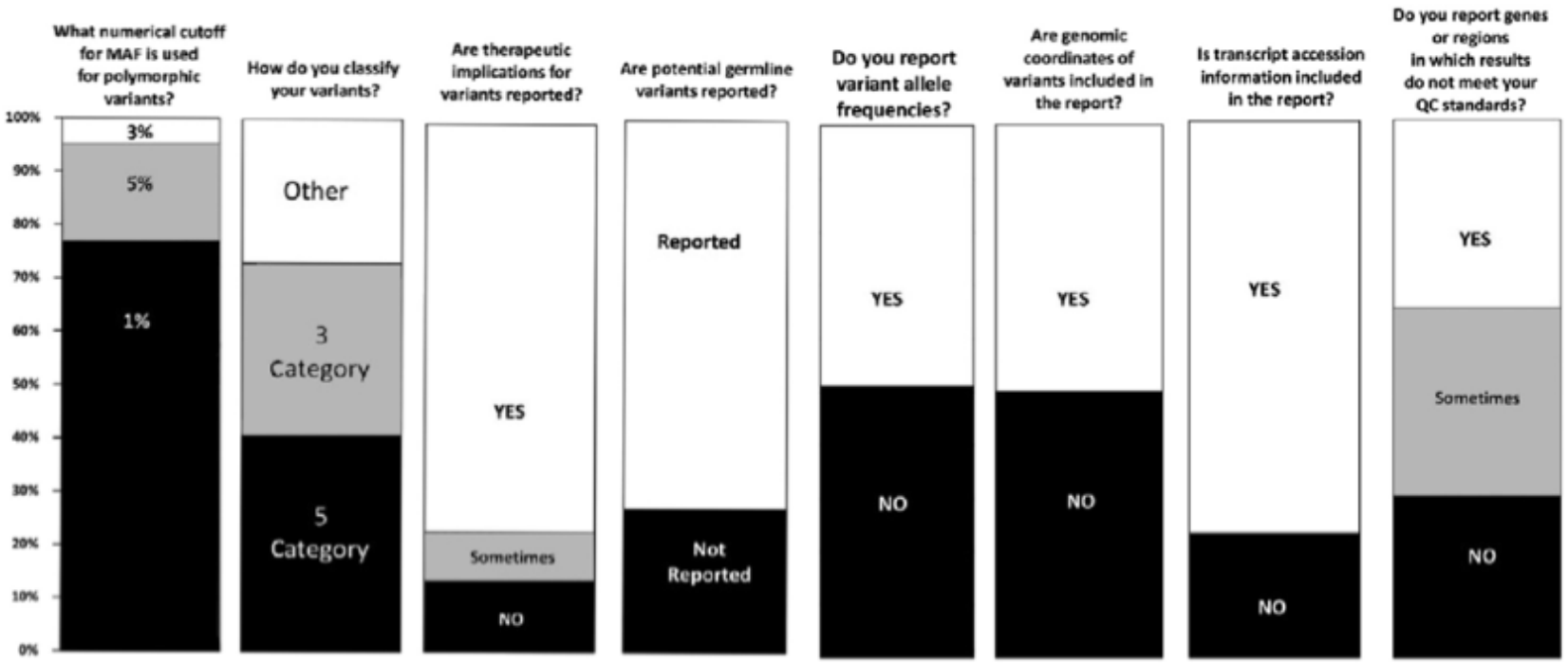
Everybody can do it?

Malapelle et al. Cancer Cytopathology 2017

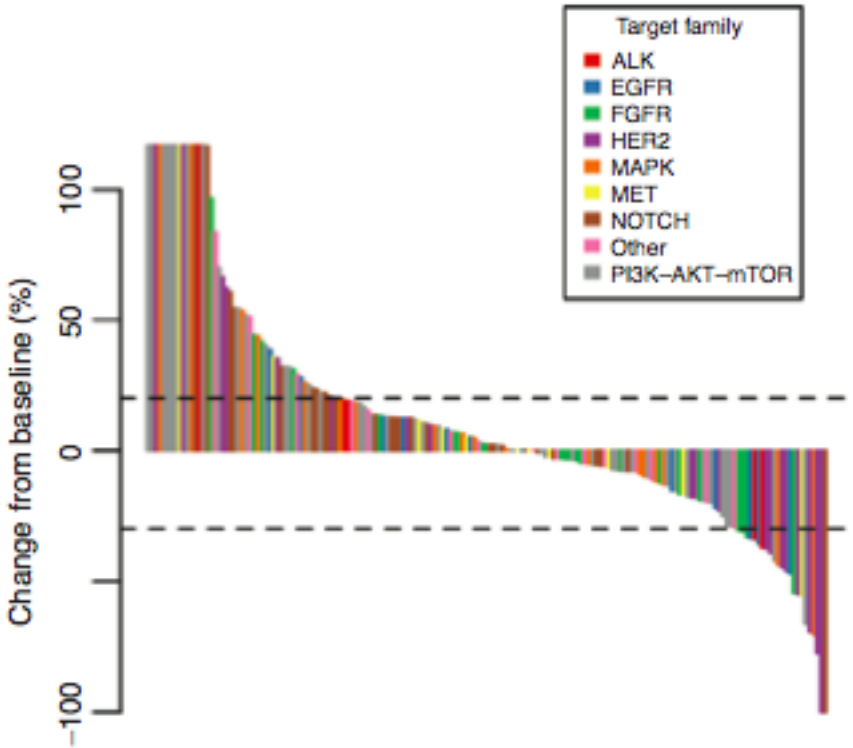
Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists

Marilyn M. Li,[*†] Michael Datto,[*†] Eric J. Duncavage,[*§] Shashikant Kulkarni,[*¶] Neal I. Lindeman,[*‖] Somak Roy,[*,**] Apostolia M. Tsimberidou,[*††] Cindy L. Vnencak-Jones,[*‡‡] Daynna J. Wolff,[*§§] Anas Younes,[*¶¶] and Marina N. Nikiforova[*,**]



High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers:



high-throughput genomics could improve outcomes in a subset of patients with hard-to-treat cancers. Although these results are encouraging, **only 7%** of the successfully screened patients benefited from this approach

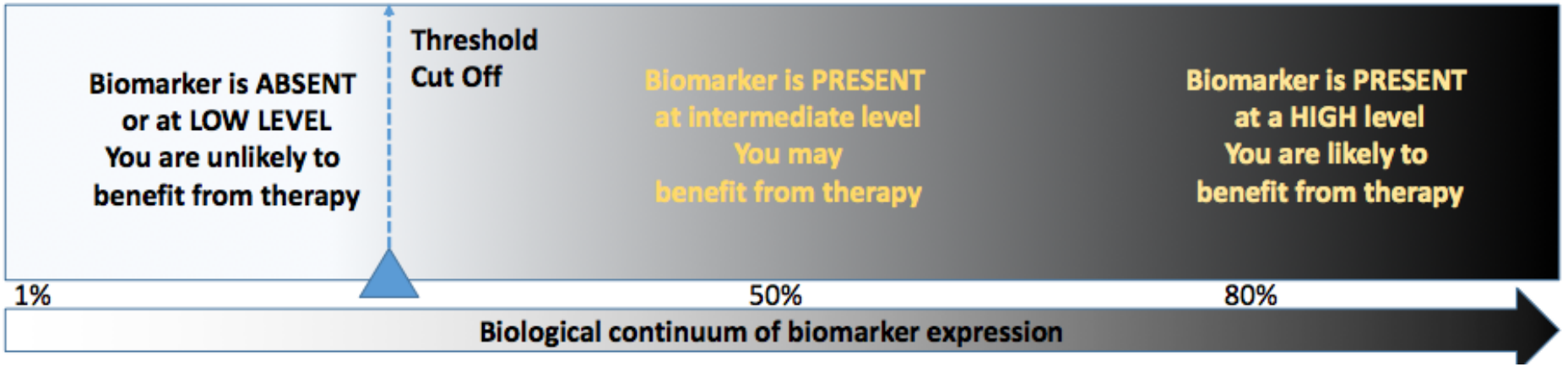
Massard (Soria) Cancer Discov. 2017 Jun;7(6):586-595.

Immunotherapy in Cancer

Binary output vs Biological Continuum

Biomarker is ABSENT
You are unlikely to
benefit from therapy

Biomarker is PRESENT
You are likely to
benefit from therapy



PD-L1 & the Meta-analysis

Systematic Review and Meta-Analysis

Medicine®

OPEN

A meta
of anti
treatm

Cuihua Wang,

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 15

PD-L1 expression as predictive biomarker in patients with NSCLC: a pooled analysis

Francesco Passiglia[1,*], Giuseppe Bronte[1,*], Viviana Bazan[1,*], Clara Natoli[2], Sergio Rizzo[1], Antonio Galvano[1], Angela Listì[1], Giuseppe Cicero[1], Christian Rolfo[3], Daniele Santini[4], Antonio Russo[1]

ELSEVIER

Review

The prognostic value of PD-L1 expression for non-small cell lung cancer patients: A meta-analysis

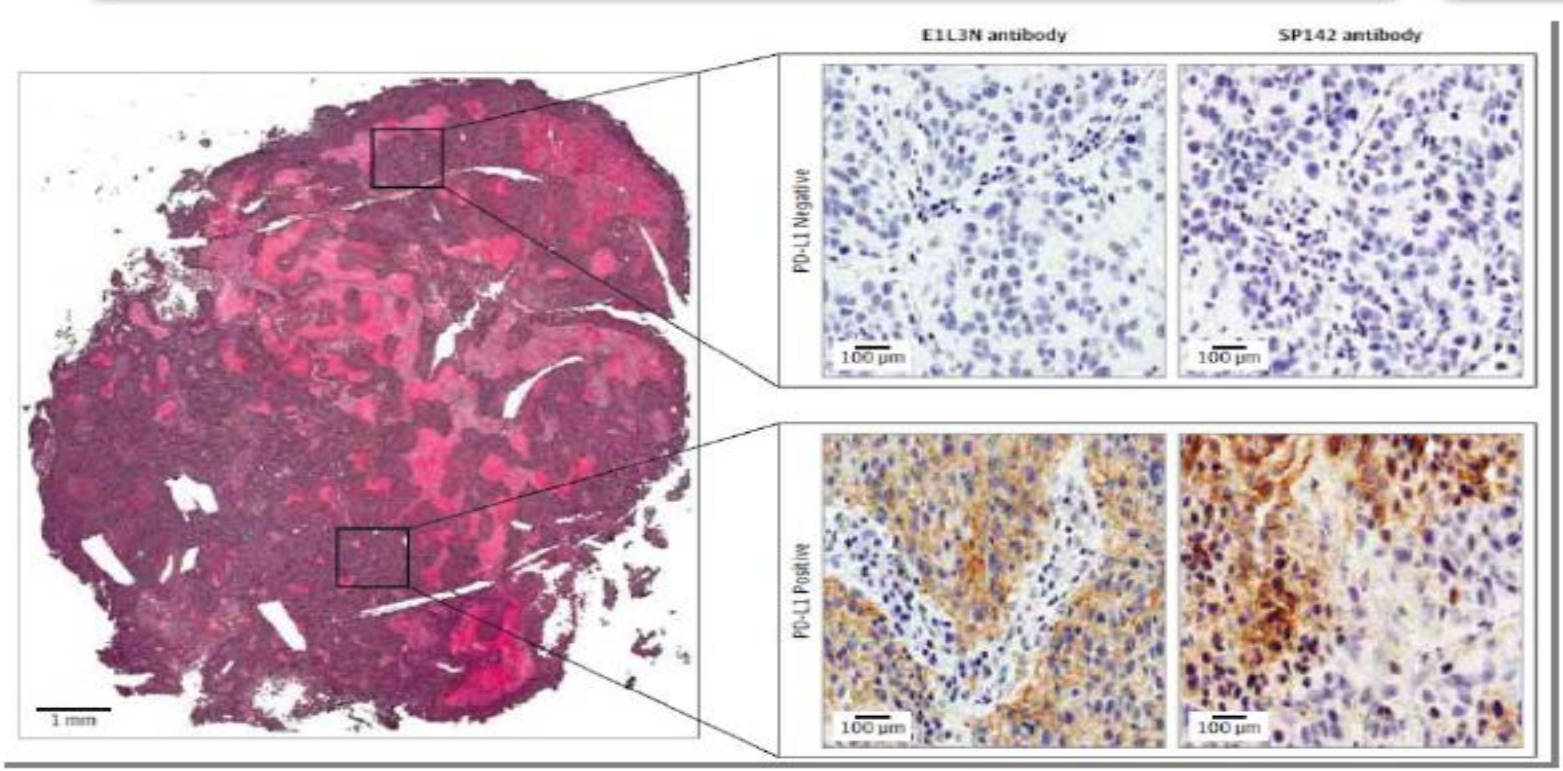
A. Wang [a,f], H.Y. Wang [b,f], Y. Liu [c,f], M.C. Zhao [a], H.J. Zhang [d], Z.Y. Lu [a], Y.C. Fang [a], X.F. Chen [a,d,*], G.T. Liu [c,**]

Systematic Review

Immunotherapy

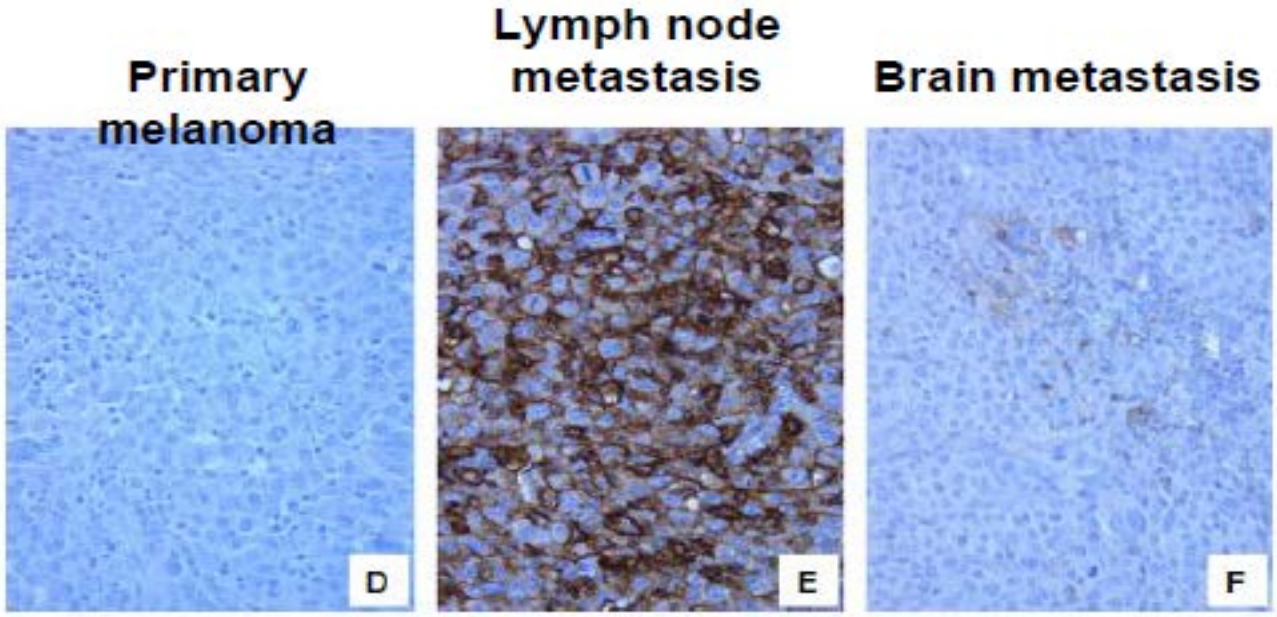
The role of PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: a network meta-analysis

PDL-1 may vary inside the same tissue section



Using the PD-L1 IHC 28-8 pharmDx, 6% discordance was observed in 30 cases of multisamples per case[5]

PDL-1 status



Adapted from Madore et al.[2]

PD-L1 discordance observed within same patient

PD-L1 as a predictive immune biomarker: assays, sample collection and analysis in NSCLC studies

	Pembrolizumab Merck	Nivolumab Bristol-Myers Squibb	Atezolizumab Roche/Genentech	Durvalumab AstraZeneca	Avelumab Pfizer/Merck Serono
PD-L1 assay	• Prototype or clinical trial IHC assay (**22C3** Ab)[1,2]	• Dako automated IHC assay • (**28-8** Ab)[3,4]	• Central laboratory IHC assay • Ventana PD-L1 (**SP142**)	• Ventana automated IHC (BenchMark ULTRA using Ventana PD-L1 (**SP263**) clone)[7,8]	• Dako assay • Clone not known
Sample source and collection	• Surface expression of PD-L1 on tumour specimen[1,2] • Ph I: Fresh or archival tissue[1,2]	• Surface expression of PD-L1 on tumour cells[3,4] • Archival or fresh tissue[3,4]	• Surface expression of PD-L1 on TILs or tumour cells • Archival or fresh tissue	• Surface expression of PD-L1 on tumour cells[7,8] • recent or archival samples	• Surface expression of PD-L1 on tumour cells • Unknown
Definition of positivity†	**IHC staining:** • Strong vs weak expression[1,2] • PD-L1 expression required for NSCLC for enrolment[1] • Note that one arm of KEYNOTE 001 trial requires PD-L1⁻ tumours[1] **Tumour PD-L1 expression:**[1,2] • ≥50% PD-L1⁺ cut-off: 32% (41/129) • 1–49% PD-L1⁺ cut-off: 37% (48/129)	**IHC staining:** • Strong vs weak expression[3,4] • Patients not restricted by PD-L1 status in 2nd- & 3rd-line • Ph III 1st-line trial in PD-L1+[5] **Tumour PD-L1 expression:** • 1% PD-L1 + cut off • 5% PD-L1⁺ cut-off: 59% (10/17)[3] • 5% PD-L1⁺ cut-off: 49% (33/68)[4] • 10% PD-L1 + cut off	**IHC staining intensity (TC: 0, 1, 2, 3):** • IHC 3 (≥50% PD-L1⁺) • IHC 2,3 (≥5% PD-L1⁺) • IHC 1,2,3 (≥1% PD-L1⁺) • IHC 0,1,2,3 (all patients with evaluable status)[5,6] • PD-L1 expression required for NSCLC for enrolment in Ph II trials **IC: TIL PD-L1 expression:** • IHC 3 (≥10% PD-L1⁺): 11% (6/53) • PD-L1 low (IHC 1, 0): 62% (33/53)	**IHC staining intensity:** • proportion of cell staining regardless of intensity **Tumour PD-L1 expression:**[7] • PD-L1 + cut off 25% • PD-L1⁺: 34% (20/58) • PD-L1⁻: 50% (29/58)	**IHC staining intensity:** • Not presented to date **Tumour PD-L1 expression (all doses):** • PD-L1 + cut off 1% • PD-L1⁺: 34% (20/58) • PD-L1⁻: 50% (29/58)

†Definition of PD-L1 positivity differs between assay methodologies

1. Garon EB et al. ESMO 2014. Abs LBA43; 2. Rizvi NA et al. ASCO 2014. Abs 8007; 3. Gettinger S et al. ASCO 2014. Abs 8024; 4. Brahmer JR et al. ASCO 2014. Abs 8112; 5. Rizvi NA et al. ASCO 2014. Abs TPS8123; 6. Soria J-C et al. ESMO 2014. Abs 1322P; 7. Brahmer JR et al. ASCO 2014. Abs 8021; 8. Segal NH et al. ASCO 2014. Abs 3002

The IASLC Blue Print Study

- 39 NSCLC tumor stained with four PD-L1 assays
- Independent review by three expert pathologists
- Similar PD-L1 expression for three assays

1. Blueprint phase 2A involving real-life clinical lung cancer samples and 25 pathologists largely affirms the results of Blueprint phase 1
2. 22C3, 28-8 and SP263 are comparable, SP142 detects less, while 73-10 stains more PD-L1 positive tumor cells
3. PD-L1 scoring on digital images and glass slides show comparable reliability

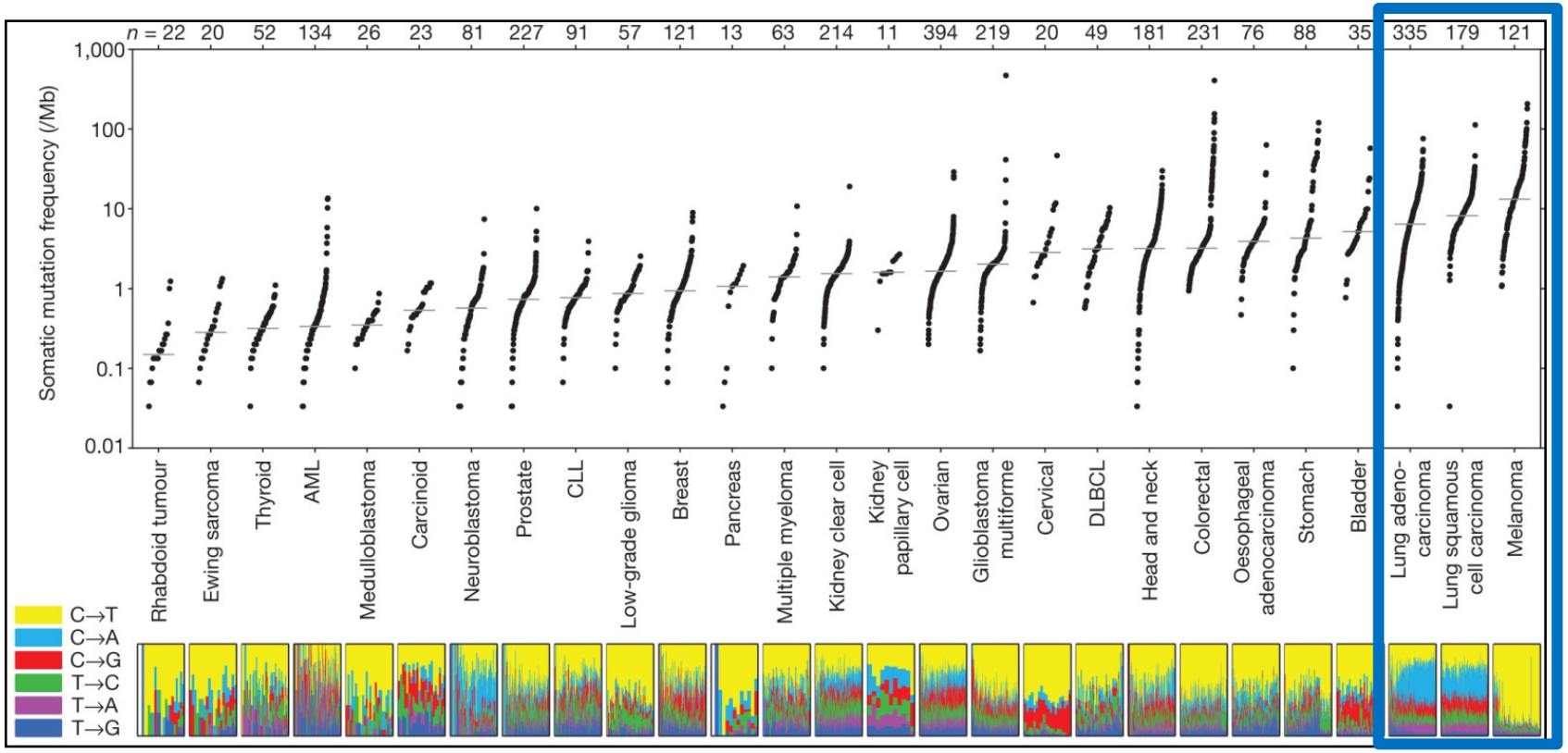
28-8	36/38 (94.7%)	38/38 (100%)	31/38 (81.6%)	33/38 (86.8%)
SP142	24/38 (63.2%)	24/38 (63.2%)	38/38 (100%)	25/38 (65.8%)
SP263	34/38 (89.5%)	34/38 (89.5%)	33/38 (86.8%)	38/38 (100%)

** Tumor cell (TC) and immune cell (IC) scoring ranges are described in chapter 6. TC0 is defined as less than 1% of tumor cells expressing PD-L1, TC1 is 1% to 5% expression, TC2 is 5% to 50% expression, and TC3 is greater than 50% expression. Table adapted from Hirsch FR et al,* J Thorac Oncol. *2017;12(2):208-222.*

Other biomarkers to better select our patients?

Mutational Tumor Burden

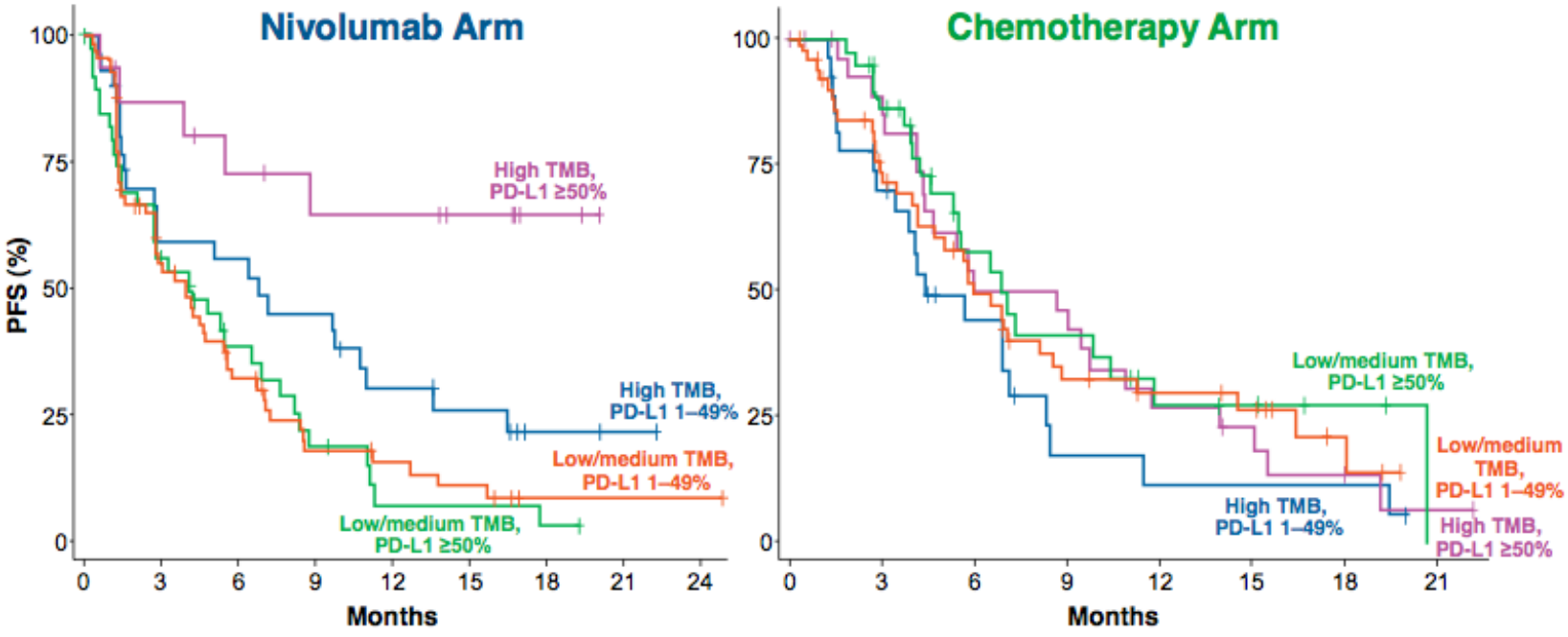
Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.



Mutational Tumor Burden

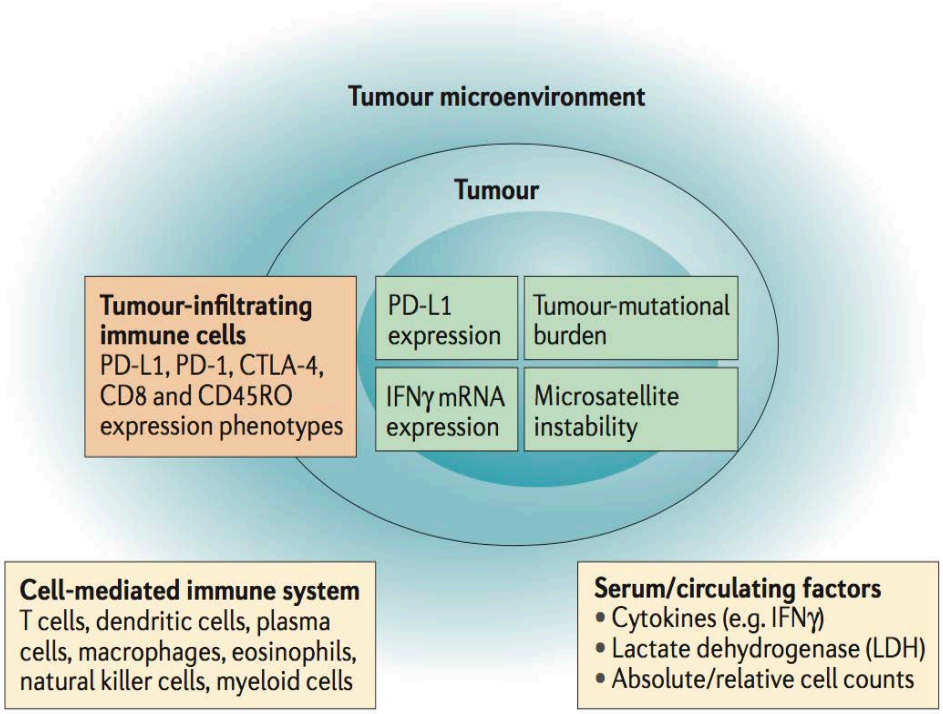
PFS by TMB Subgroup and PD-L1 Expression
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

Peters S et al
AACR 2017



No. at Risk																
High TMB, PD-L1 ≥50%	16	13	10	8	8	6	2	0	0	32	24	13	12	7	5	2	1
High TMB, PD-L1 1–49%	31	17	16	13	8	6	2	1	0	28	18	9	3	2	2	2	0
Low/medium TMB, PD-L1 ≥50%	41	21	12	6	2	2	1	0	0	41	30	14	10	5	4	2	0
Low/medium TMB, PD-L1 1–49%	70	33	18	9	7	5	1	1	1	53	35	23	13	10	8	3	0

Liquid Biopsies in Immunotherapy



Unmeet Medical Need:

Validated Biomarkers in Blood!

Potential Utility of Liquid Biopsy in Immunotherapy

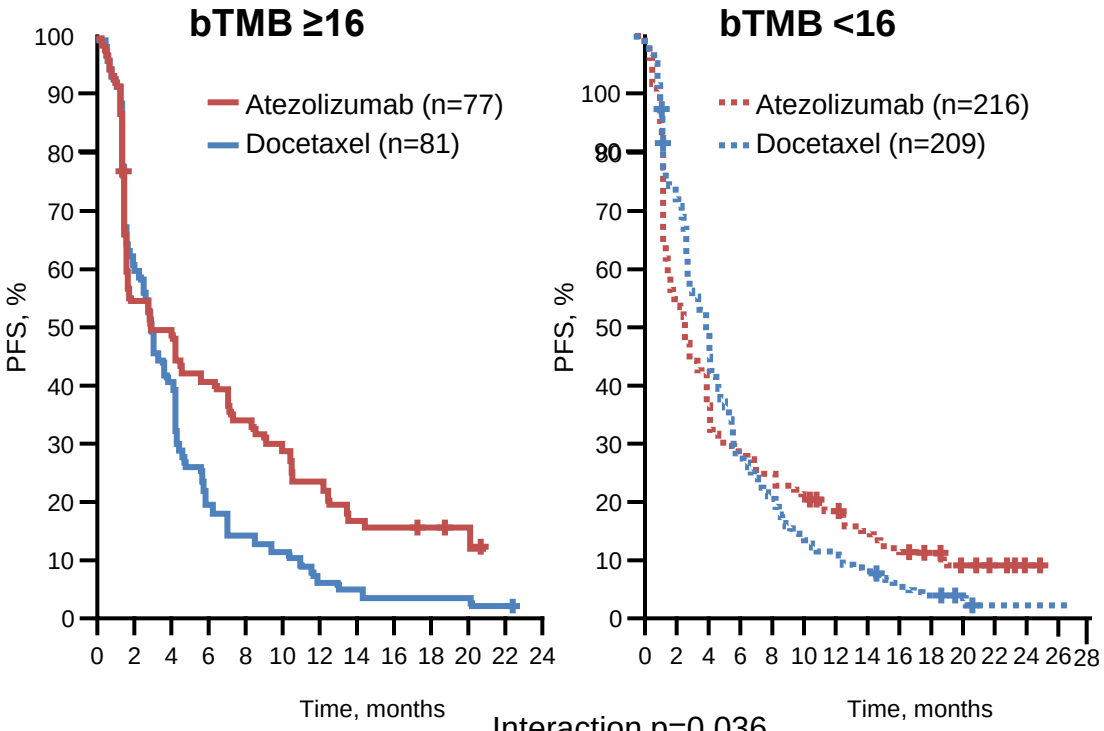
- Diagnostic
- Prognostic
- Predictive of Response
- Monitoring
- Mechanisms if Resistance

Current tools:

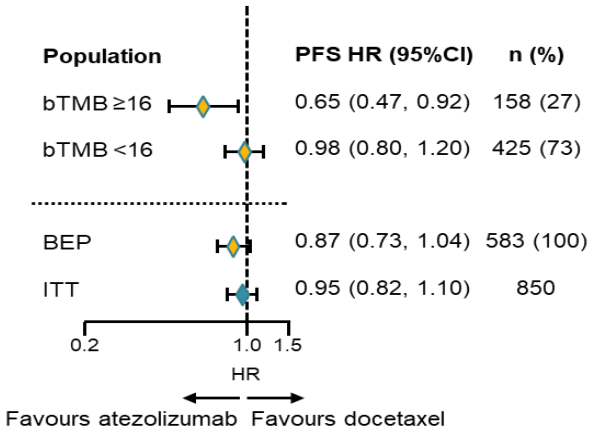
- Calculation of circulating TMB
- Detection of bPDL1
- Alellic Fraction Variation Dynamic

Image from Nishino et al, Nature Reviews Clinical Oncology, June 2017

bMTB



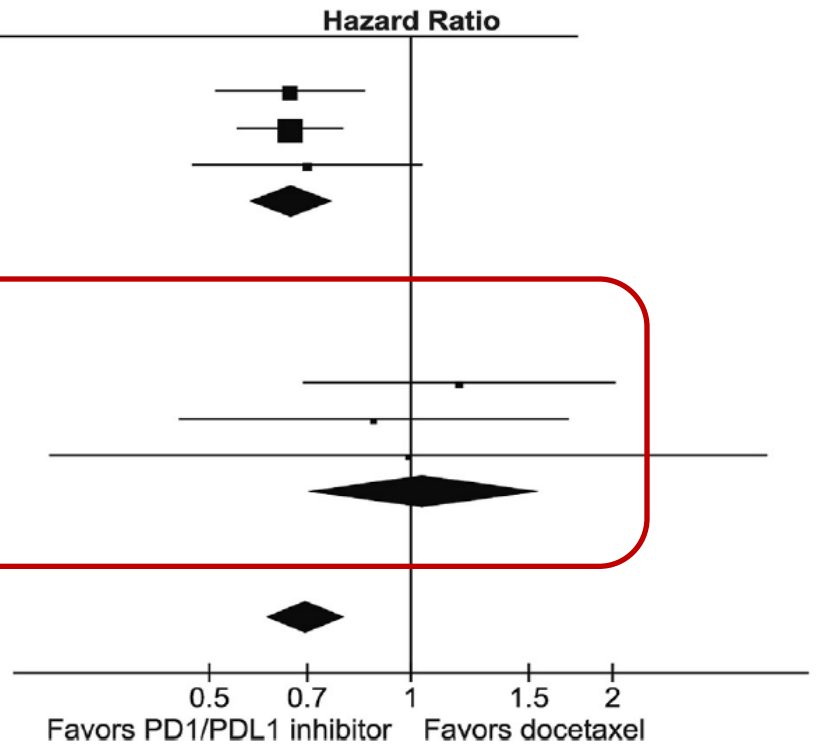
Interaction p=0.036



D. R. Gandara et al., ESMO 2017 abstract 1295O

No Change in Overall Survival with I/O in 2nd Line *EGFR* Mutated Lung Cancer: A Meta-Analysis

Study	Weight	Hazard Ratio [95% CI]
EGFR wild-type		
Checkmate 057	26.0%	0.66 [0.51, 0.86]
Keynote 010	52.0%	0.66 [0.55, 0.80]
POPLAR	11.0%	0.70 [0.47, 1.04]
Subtotal (95% CI)	**89.0%**	**0.66 [0.58, 0.76]**
EGFR mutant		
Checkmate 057	6.0%	1.18 [0.69, 2.00]
Keynote 010	3.8%	0.88 [0.45, 1.70]
POPLAR	1.1%	0.99 [0.29, 3.40]
Subtotal (95% CI)	**11.0%**	**1.05 [0.70, 1.55]**
Total (95% CI)	**100.0%**	**0.70 [0.61, 0.80]**



Key:
Checkmate 057 (N=582) Nivolumab
Keynote 010 (N=1034) Pembrozulimab
POPLAR (N=287) Atezolizumab

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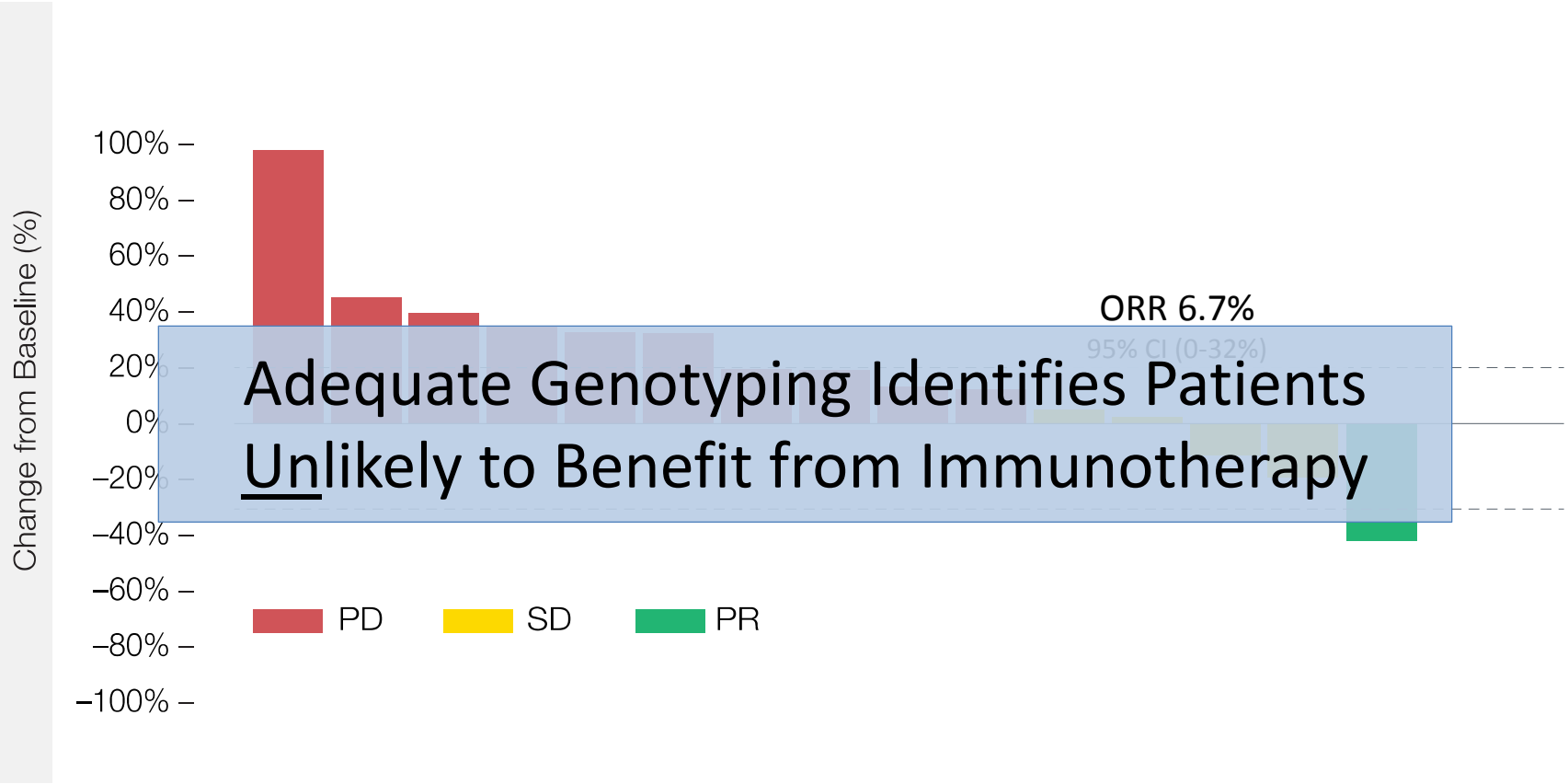
Lee (Yang) et al. 2017 (Oct 2016) Journal of Thoracic Oncology

Poor Response to Immunotherapy in NSCLC Patients with *MET* Exon14 Skipping Mutations



Adequate Genotyping Identifies Patients Unlikely to Benefit from Immunotherapy

Note: PD defined as ≥ 20% growth or appearance of new lesions

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Sabari et al, J Clin Oncol 35, 2017 (suppl; abstr 8512)

BRAF & IO

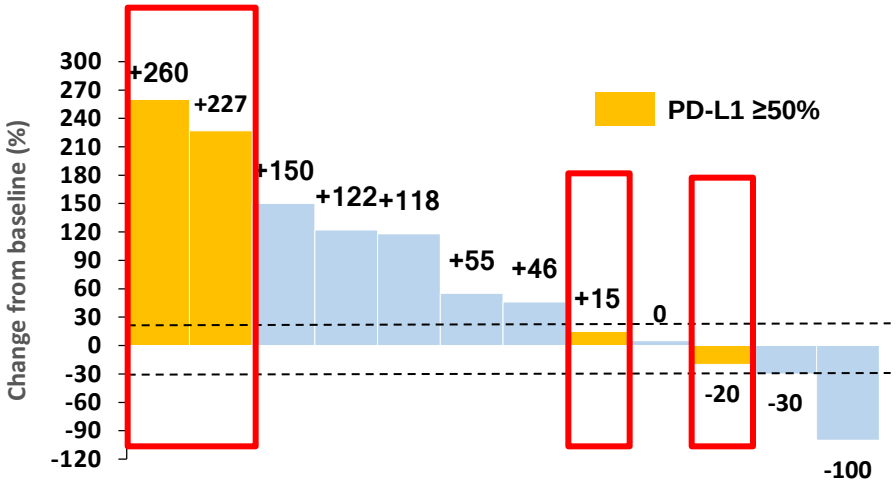
Objective response with ICPi

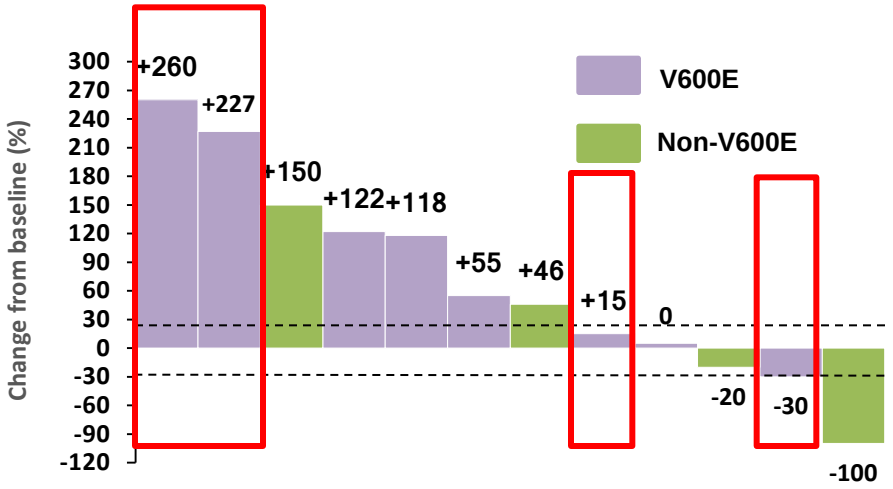
BRAF MUT NSCLC

- n-15 (V600E, n-8; non-V600E, n-7)
- Nivolumab, n-10; pembrolizumab, n-5
- ICPi 1st-line, n-4 (V600E, n-1; non-V600E, n-3); 2nd-line, n-9 (V600E, n-5; non-V600E, n-4); 3rd-line, n-2 (V600E, n-2)

ORR (RECIST 1.1) - 17%

Abbreviations: ICPi - immune check-point inhibitors s, ORR – objective response rate.





How to integrate biomarkers in clinical trials design?

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Why Master Protocols and not Separate Studies?

- Enhanced genomic screening efficiency
- Inclusion of wide array of molecular subtypes
- Use of common genomic platform or diagnostic tests
- Screening for variants of multiple genomic targets in each tumor sample in each tumor sample (**requires sufficient tumor material**)
- ↑ willingness of patients and HCPs to participate
- Deletion/insertion of new subprotocol by amendment instead of completely new protocol developmer
- ↑ and faster accrual c/w separate studies
- More rapid clinical development

Basket Trials: Pros and Cons

Prerequisites:

1. **Drug must sufficiently inhibit target**
2. **Tumor must depend on target**

- **Benefits**:
  - Access to trial for **patients with rare tumors** (bust must have respective molecular marker)
  - Testing could be done locally
  - **Small cohorts** (usually single arm) may suffice to detect activity
  - **Quick results**

- **Challenges**:
  - Molecular variant(s) may not be the only driver of tumor
  - Contextual **complexities in various histologies**
  - Single biomarkers may be inferior to multi-gene signature
  - **Structural variants** may need to be complemented with functional studies
  - **Different tumor types have different prognoses**: single primary endpoint (eg ORR) may skew results

Hallmarks of Umbrella Protocols

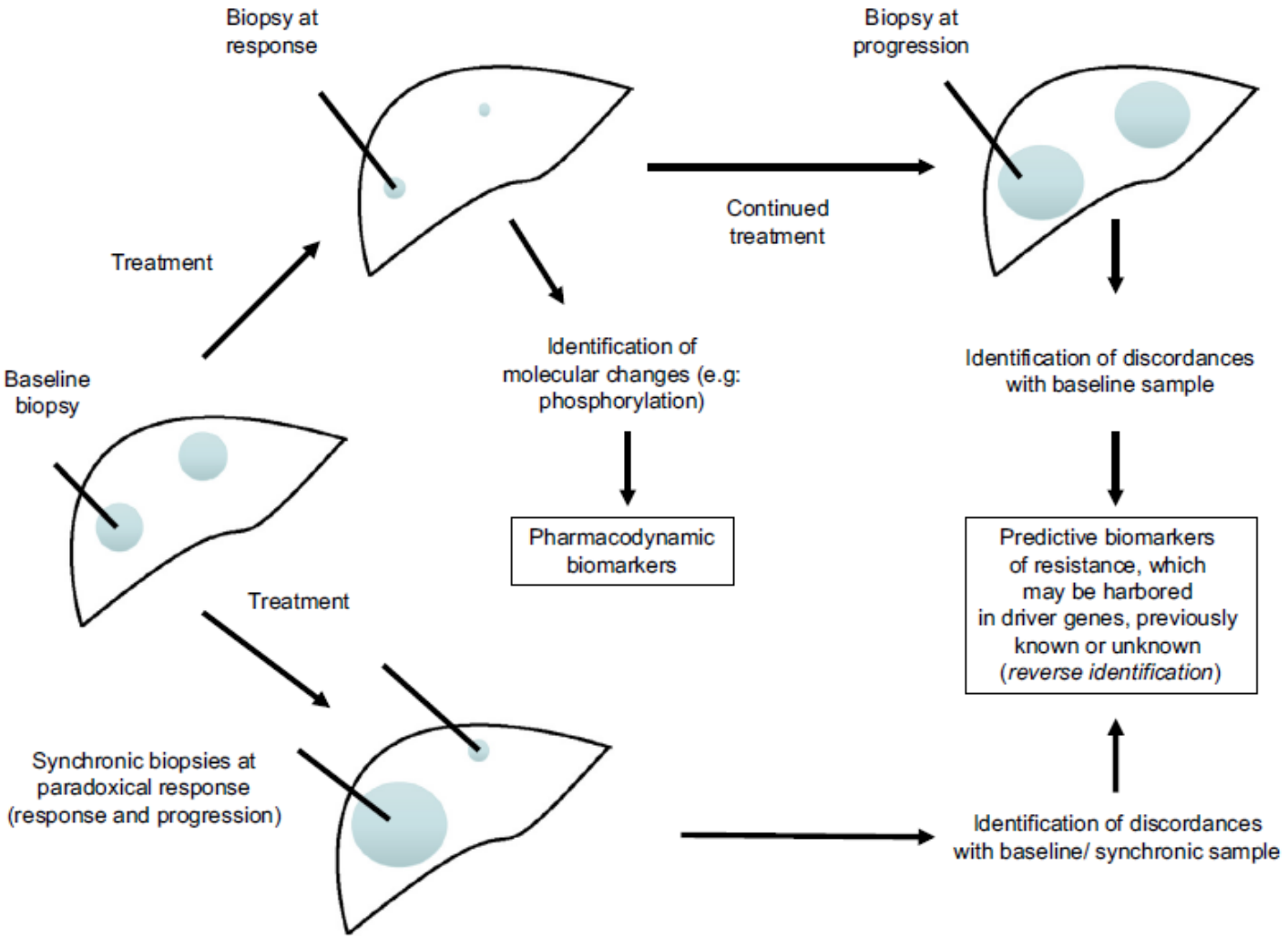
Hypothesis: The response to targeted therapy is primarily determined by histologic context

Umbrella Trials: Pros and Cons

- Benefits:
  - Conclusions are specific for a given tumor type
    - Tumor heterogeneity limited to one tumor type
  - For randomized substudies:
    - Potential to better understand the difference of targeted therapy vs SOC
    - Potential to differentiate between prognostic and predictive markers
    - Easier path to negotiate approval with regulatory agencies

- Challenges:
  - Requires:
    - **Strong collaboration** between academia and industry
    - Consistent marker profile , **comparability of cohorts** (bx, assay, Tx)
  - Feasibility:
    - Subclassification into rare populations (particularly with rare cancers to start out with)
    - →↓ speed of accrual
    - Randomization requiring **a larger sample size** may be challenging
    - **Appearance of new SOCs during trial conduct changes the environment**

Design of studies exploring responses following progression or paradoxical responses



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Perez Gracia et al, Cancer Treatment Reviews 53 (2017) 79–97

Why is Discovery of Clinically Useful Biomarkers Difficult?

- Biology
- Need for Infrastructural Support
- Need for Collaborations Among Stakeholders
  - Basic scientists
  - Clinicians
  - Public Health Professionals
  - Informaticians and Bioinformaticians
  - Advocates
  - Funding organizations
  - Regulatory authorities

Project Team members

Oncology – Phase I Early Clinical Trials Unit
Prof. Dr. Christian Rolfo -
Prof. Dr. Marc Peeters – head oncology and MOCA
Dr. Marika Rasschaert – Dr. Katrine De Block
Fellows: Dr. Helena Oliveres. Dr. Mariana Rocha
Rolfo Lab:
Exosomes: Senior Dr. SimonaTaverna
PhD students: Dr. Pablo Reclusa Asiain
Dr. Marzia Pucci
Dr. Mahafarin Maralani
tFree DNA: Dr. Laura Sober – Karen Zwaenepoel
Cell Lines & cMET: Dr. Nele Van Der Steen
Logistics: Sam Van Gerwen, BsC
Clinical Study –co: Amelie Lyessens, BsC
Molecular Pathology Unit
Prof. Dr. Patrick Pauwels
Dr. Amelie Dendooven
Dr. Karen Zwaenepoel
Tumor - Serum Bank
Dr. Annemieke De Wilde
Dr. Sofie Goethals

Next Generation Sequencing
Dr. Christine Weyn – UZA
Dr. Suzanne Lambin
Dr. Ken Op De Beeck - UA
Database: Dr. R. Mauceri
Dr. Andreia Coelho

Proteomics
Prof. Inge Mertens
Prof. Geert Baggerman
Dr. Evelien Maes

MOCA **2014 Research Grant**

2015

Stichting tegen Kanker

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Dank u voor uw aandacht

Thank you for your attention

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christian.rolfo@uza.be

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