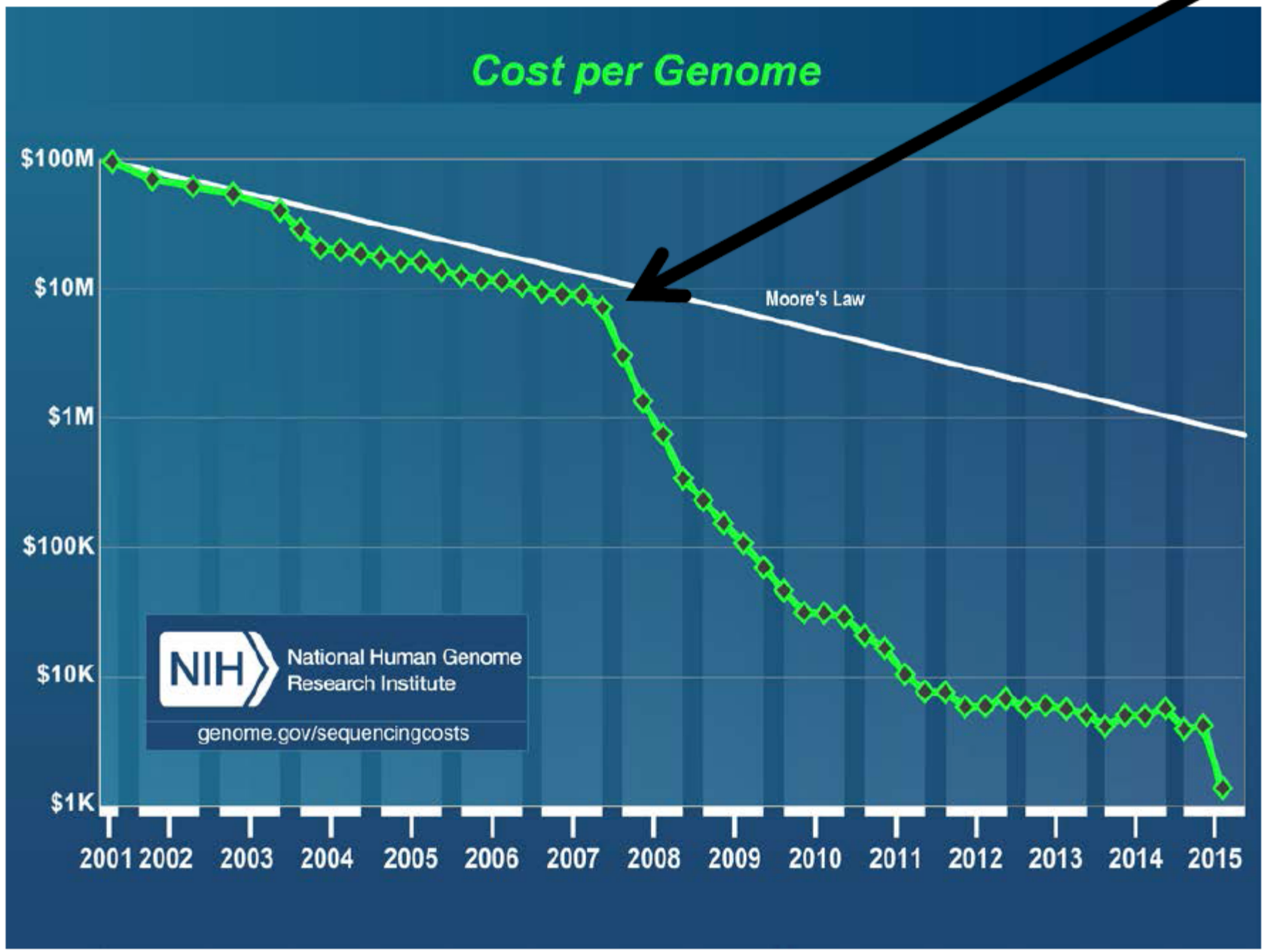
„Next generation sequencing“ v onkologii

Doc. MUDr. Mgr. Marek Mraz, PhD

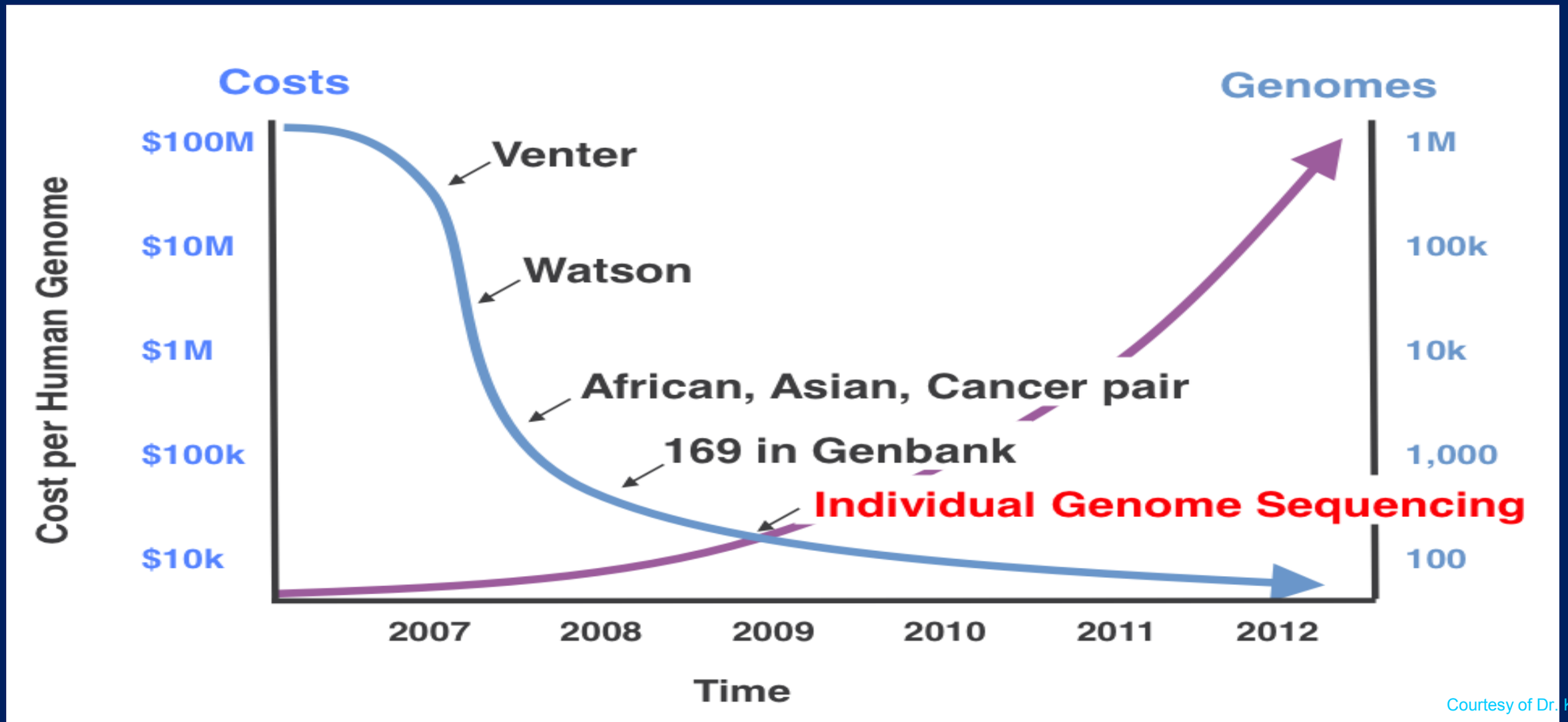
IHOK FN Brno and CEITEC MU

Next Generation Sequencing (NGS)



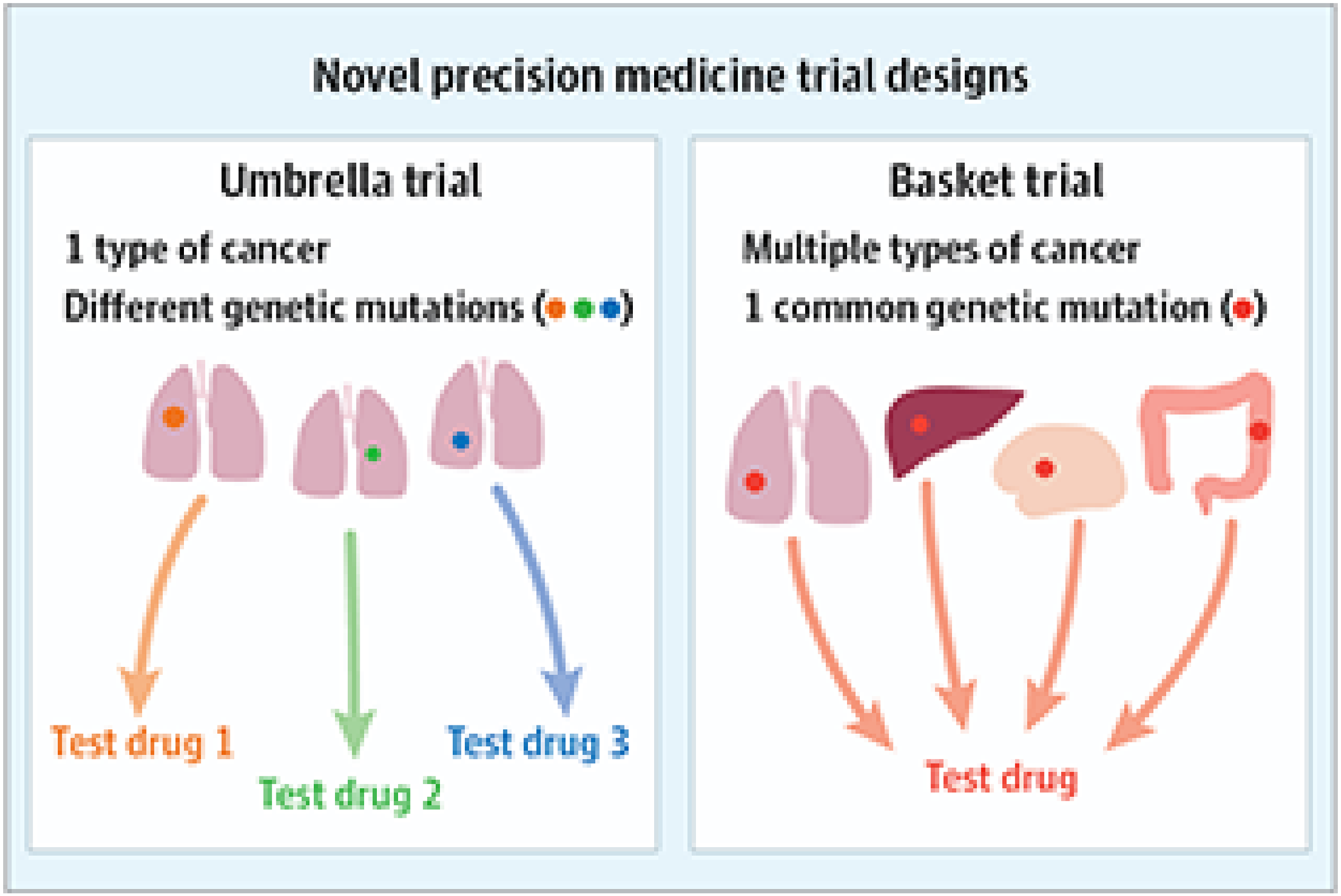
QUICKER, SMALLER, CHEAPER

Genome sequenced (publication year)	HGP (2003)	Venter (2007)	Watson (2008)	Current (2015)
Time taken (start to finish)	13 years	4 years	4.5 months	~1 days
Number of scientists listed as authors	> 2,800	31	27	
Cost of sequencing (start to finish)	$2.7 billion	$100 million	< $1.5 million	~$1000
Coverage	8–10 ×	7.5 ×	7.4 ×	30-50X
Number of institutes involved	16	5	2	
Number of countries involved	6	3	1	



Courtesy of Dr. Kurzrock

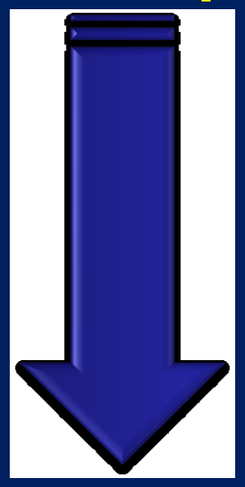
DŮLEŽITÉ!!!



JAMA Oncology: doi:10.1001/jamaoncol.2016.5299

Meta Analýza 32,149 pacientů
Z Fáze II klin. studií

Horší odpověď



Lepší odpověď

	POOLED Analysis			Meta-analysis		
ARMS type	R Rate (%)	PFS (Mos)	OS (Mos)	RR (%)	PFS (Mos)	OS (Mos)
Non-personalized targeted	4	2.6	8.7	7.5	2.5	8.3
Cytotoxic	12	3.3	9.4	16.1	3.3	9.3
Personalized targeted	30	6.9	15.9	31.3	6.1	13.7

Schwaederle……Kurzrock, JCO, 2015

Courtesy of Dr. Kurzrock

Center for Personalized Cancer Therapy at Moores Cancer Center

Developmental Therapeutics
Phase I Trials/Immunotherapy

Discovery to Bedside Enabling Program

Molecular Tumor Board

Adolescent and Young Adult Clinic

Rare Tumor Clinic

Hereditory Cancer Predispositon Genetic Counselling

Molecular Pathway Clinic

Financial Aid

Laboratory Processing

San Diego Biotech, Pharma, Genomics

UCSD Super Computer Center

UCSD, Salk, Scripps, Sanford-Burnham

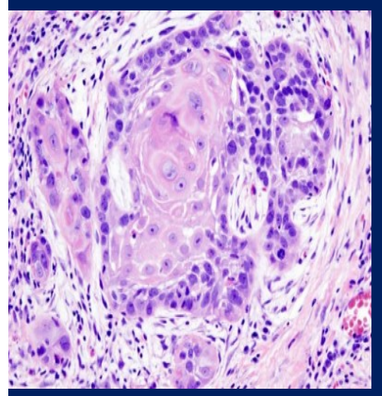
Courtesy of Dr. Kurzrock

Molecular Tumor Board

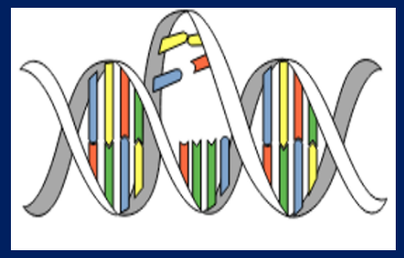
- Multidisciplinární diskuze
- Molekularní profilování (clinical-grade) (N ~ 8000)
- Cílená léčba

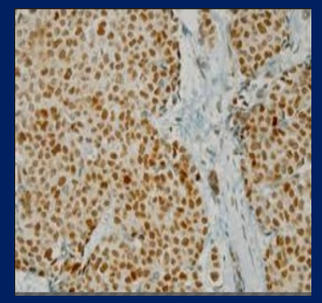
Courtesy of Dr. Kurzrock

komprehensivní profilování



Tumor





PREDICT/ IPREDICT Clinical Trial

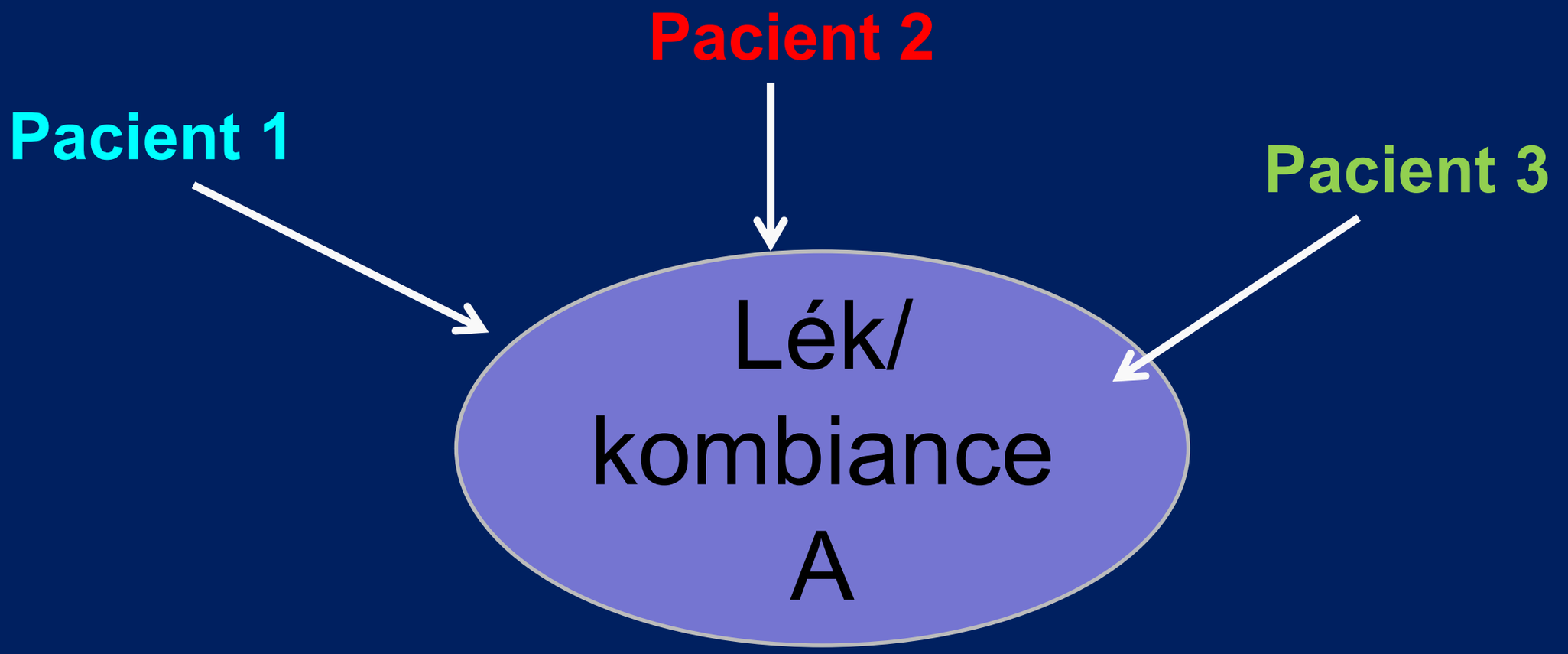
Comprehensive molecular profiling:

- Next-Generation DNA Sequencing
- Protein analysis
- Immune signature analysis
- Liquid biopsy (cancer DNA detection from blood)

“MATCH” the therapy based on the profiling.
Personalized/Precision Medicine approach.

Courtesy of Dr. Kurzrock

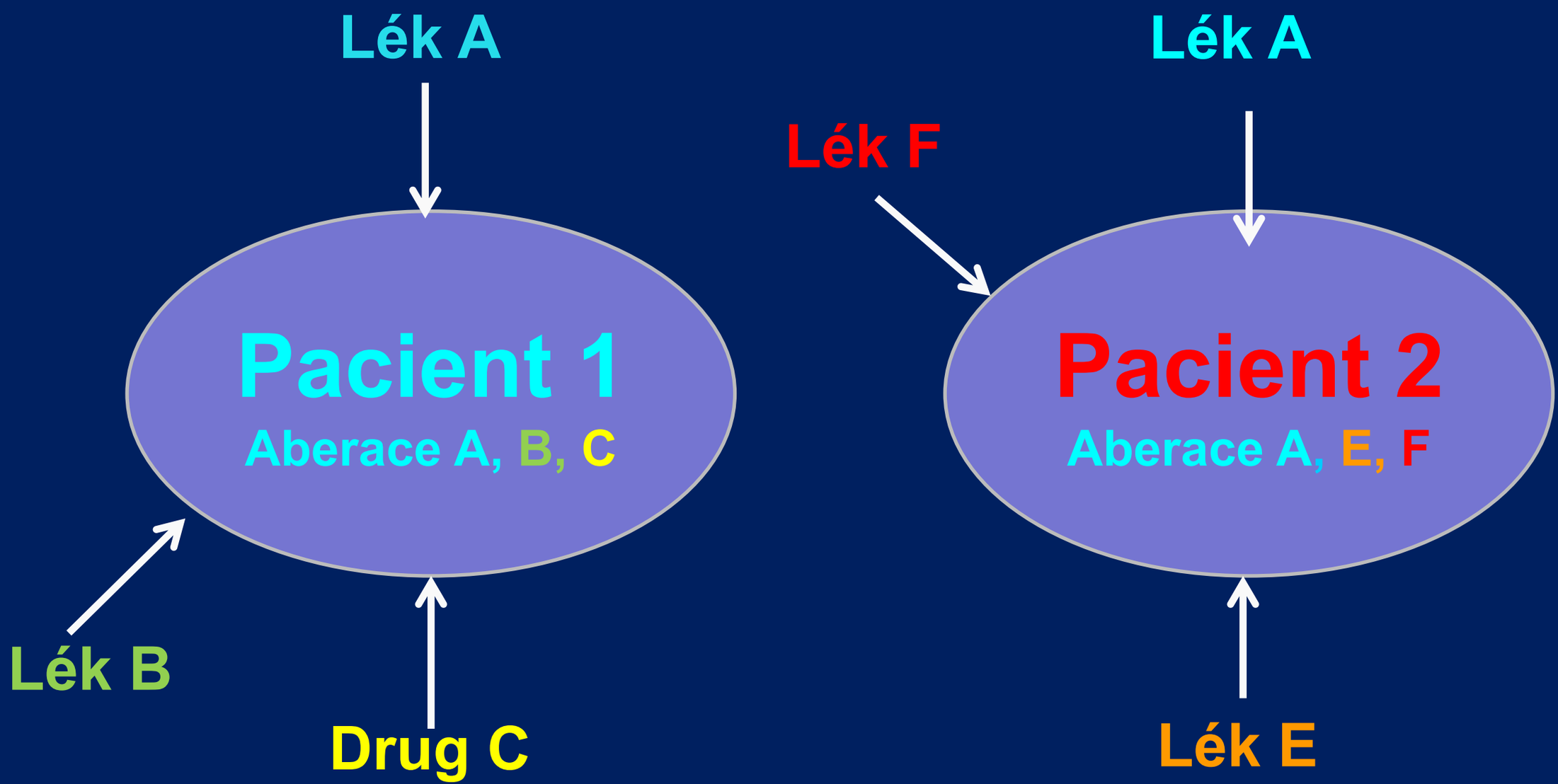
Lék-Centrická studie (Tradiční)



Strategie: Najít sdílenou vlastnost mezi pacienty (např. druh nádoru nebo mol. aberaci) a všem dát stejnou léčbu

Courtesy of Dr. Kurzrock

Pacient-Centrické studie (N=jeden)



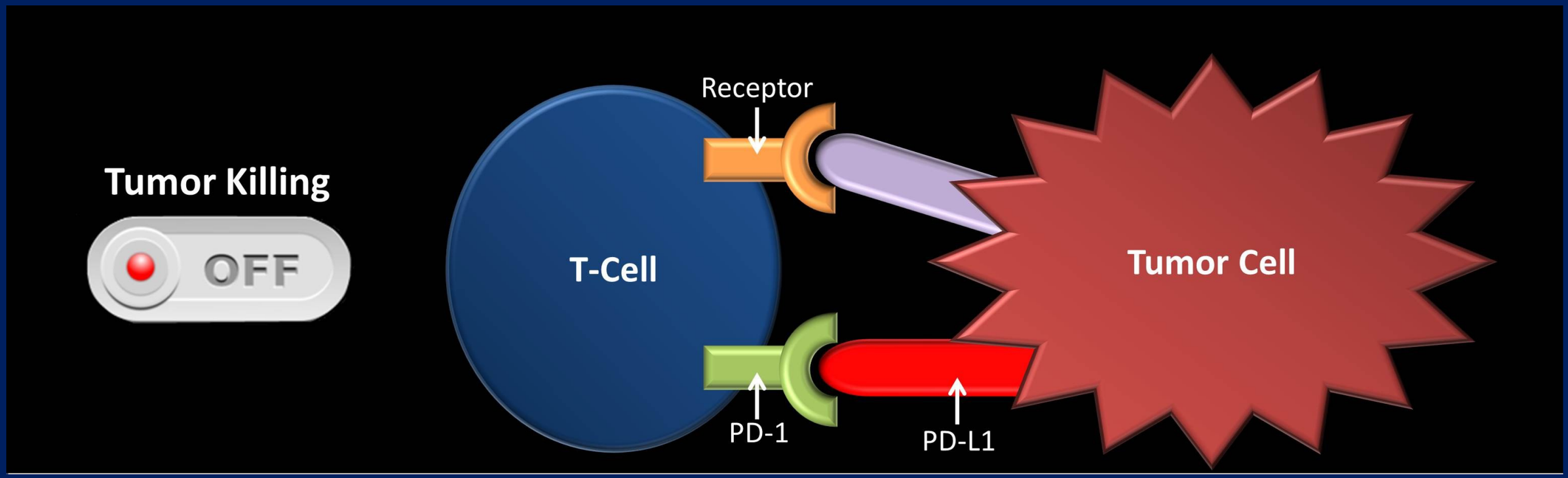
Strategie: Molekulární párování každého pacienta s kombinací léčiv

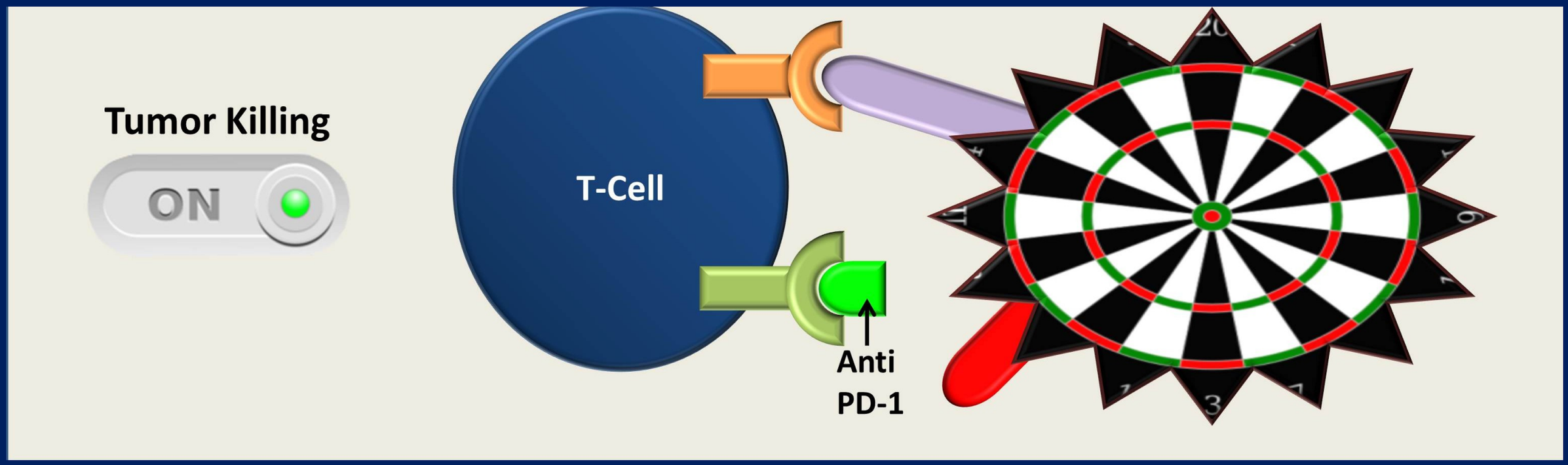
Courtesy of Dr. Kurzrock

Liquid biopsie

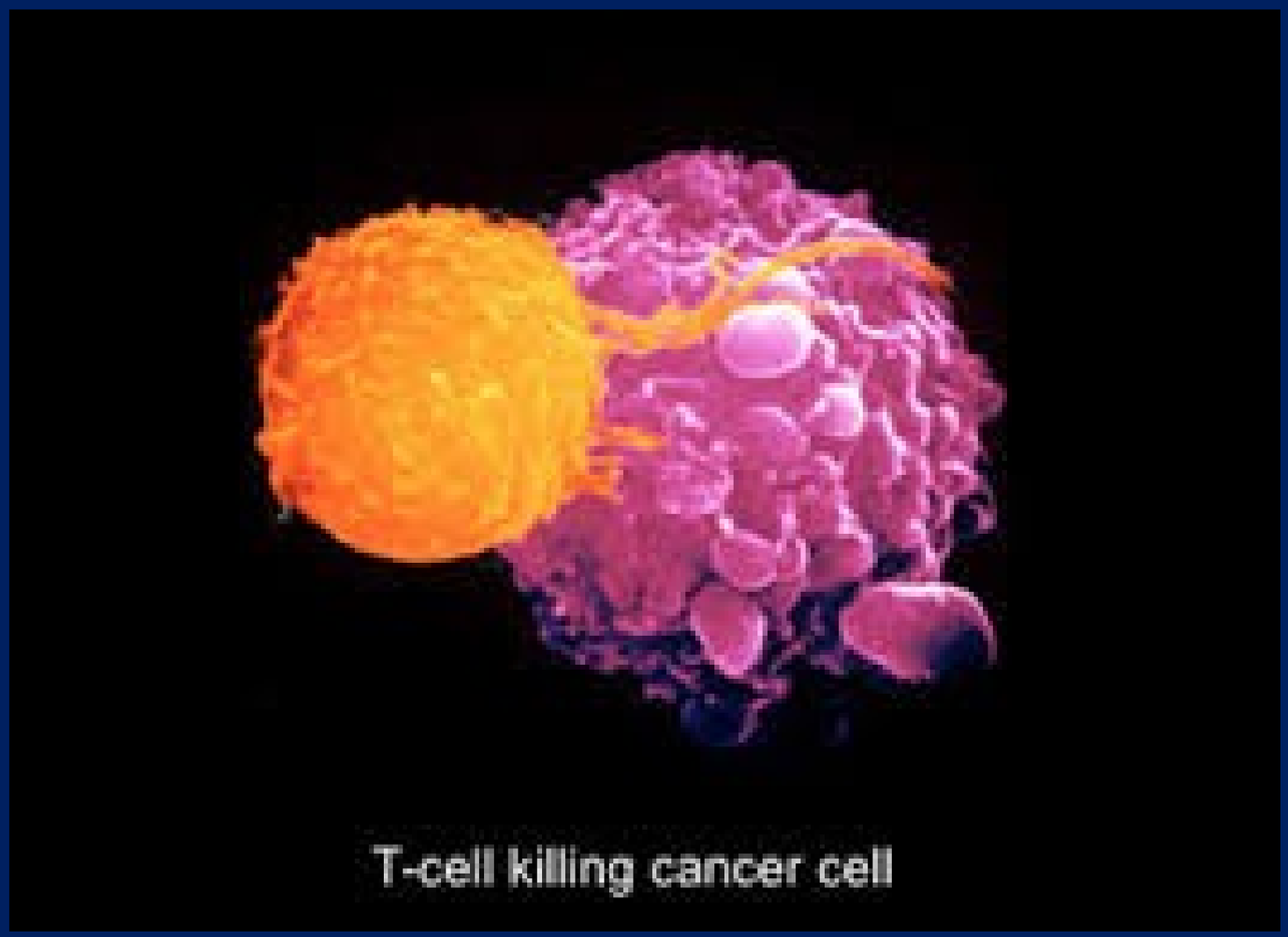
- Časná detekce rezistence
- Časná detekce odpovědi
- Predikce odpovědi na immunoterapii

Checkpoint inhibitory





„Boj“ rovného s rovným



Spojení mezi genomikou a immuno terapií

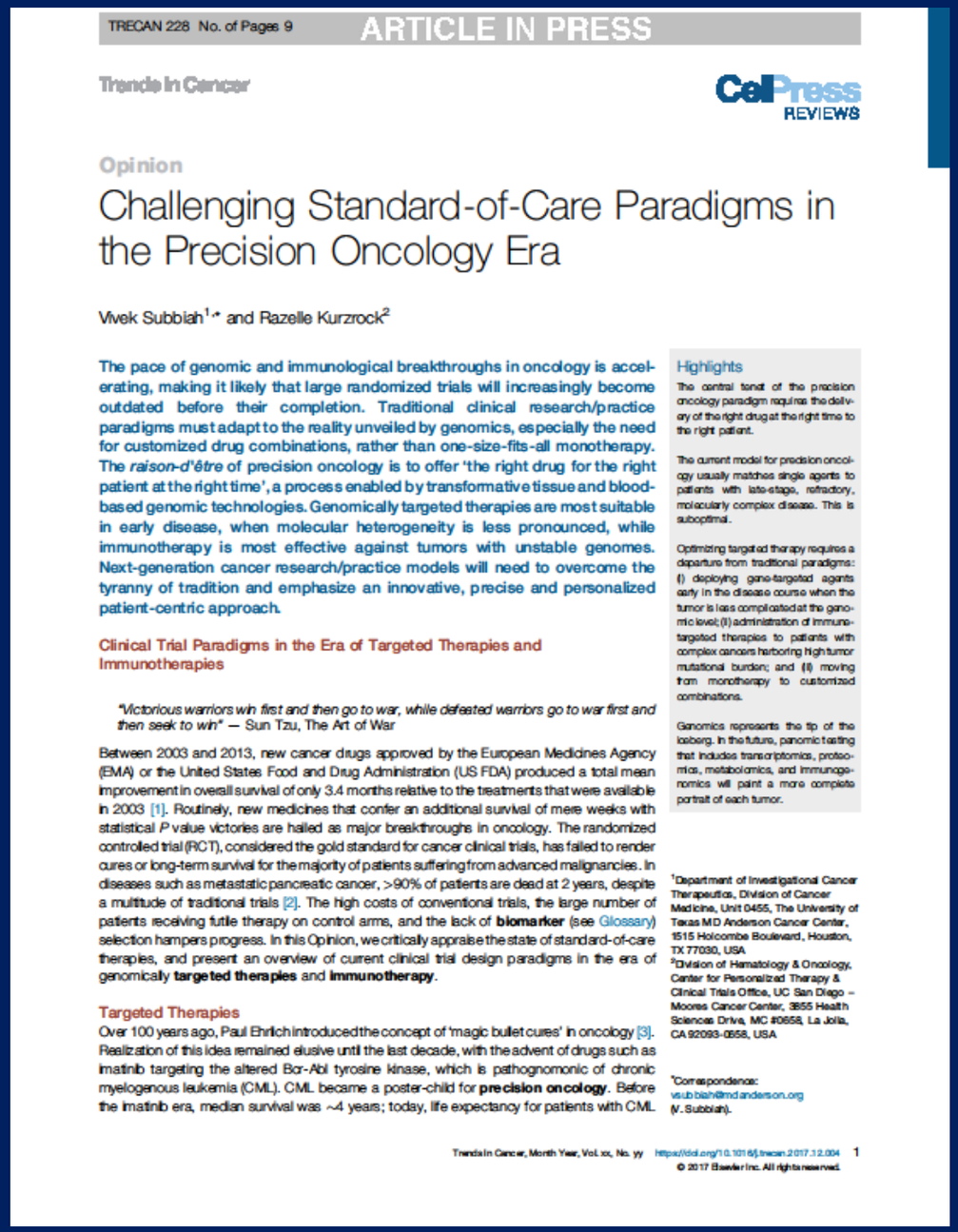
Mutanomem-cílená Immunotherapie

Čím více mutovaný nádor tím lepší odpověď na immunoterapii

- 4% odpovědí u nádorů s málo mutacemi
- 26% odpovědí u nádorů se středně mutacemi
- 45% odpovědí u nádorů s hodně mutacemi
- 67% odpovědí u nádorů s opravdu hodně mutacemi

Courtesy of Dr. Kurzrock

Přečtěte si tento článek..je to krásné a srozumitelné čtení



Trends in Cancer

CellPress REVIEWS

Opinion

Challenging Standard-of-Care Paradigms in the Precision Oncology Era

Vivek Subbiah[1,*] and Razelle Kurzrock[2]

The pace of genomic and immunological breakthroughs in oncology is accelerating, making it likely that large randomized trials will increasingly become outdated before their completion. Traditional clinical research/practice paradigms must adapt to the reality unveiled by genomics, especially the need for customized drug combinations, rather than one-size-fits-all monotherapy. The *raison-d'être* of precision oncology is to offer 'the right drug for the right patient at the right time', a process enabled by transformative tissue and blood-based genomic technologies. Genomically targeted therapies are most suitable in early disease, when molecular heterogeneity is less pronounced, while immunotherapy is most effective against tumors with unstable genomes. Next-generation cancer research/practice models will need to overcome the tyranny of tradition and emphasize an innovative, precise and personalized patient-centric approach.

Highlights

The central tenet of the precision oncology paradigm requires the delivery of the right drug at the right time to the right patient.

The current model for precision oncology usually matches single agents to patients with late-stage, refractory, molecularly complex disease. This is suboptimal.

Optimizing targeted therapy requires a departure from traditional paradigms: (I) deploying gene-targeted agents early in the disease course when the tumor is less complicated at the genomic level; (II) administration of immune-targeted therapies to patients with complex cancers harboring high tumor mutational burden; and (II) moving from monotherapy to customized combinations.

Genomics represents the tip of the iceberg. In the future, panomic testing that includes transcriptomics, proteomics, metabolomics, and immunogenomics will paint a more complete portrait of each tumor.

Clinical Trial Paradigms in the Era of Targeted Therapies and Immunotherapies

> *"Victorious warriors win first and then go to war, while defeated warriors go to war first and then seek to win"* — Sun Tzu, The Art of War

Between 2003 and 2013, new cancer drugs approved by the European Medicines Agency (EMA) or the United States Food and Drug Administration (US FDA) produced a total mean improvement in overall survival of only 3.4 months relative to the treatments that were available in 2003 [1]. Routinely, new medicines that confer an additional survival of mere weeks with statistical *P* value victories are hailed as major breakthroughs in oncology. The randomized controlled trial (RCT), considered the gold standard for cancer clinical trials, has failed to render cures or long-term survival for the majority of patients suffering from advanced malignancies. In diseases such as metastatic pancreatic cancer, >90% of patients are dead at 2 years, despite a multitude of traditional trials [2]. The high costs of conventional trials, the large number of patients receiving futile therapy on control arms, and the lack of **biomarker** (see Glossary) selection hampers progress. In this Opinion, we critically appraise the state of standard-of-care therapies, and present an overview of current clinical trial design paradigms in the era of genomically **targeted therapies** and **immunotherapy**.

Targeted Therapies

Over 100 years ago, Paul Ehrlich introduced the concept of 'magic bullet cures' in oncology [3]. Realization of this idea remained elusive until the last decade, with the advent of drugs such as imatinib targeting the altered Bcr-Abl tyrosine kinase, which is pathognomonic of chronic myelogenous leukemia (CML). CML became a poster-child for **precision oncology**. Before the imatinib era, median survival was ~4 years; today, life expectancy for patients with CML

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5822744/

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