Molecular Profiling
Challenges and Perspectives

Conclusions and Clinical Perspectives

CHRISTIAN DITTRICH

Ludwig Boltzmann Institute for Applied Cancer Research (LBI-ACR VIEnna)
3rd Medical Department – Centre for Oncology and Haematology
Kaiser Franz Josef-Spital, Vienna, Austria

Conflict of Interest Disclosure

I herewith declare that I have potential conflicts of interest with several pharmaceutical companies, the drugs of which will be mentioned during my presentation, predominantly in form of unrestricted research grants donated to the research institutes directed by me, but also as honoraria for consulting.

Summary

- Molecular profiling is increasingly part of patient‘s care (J.-C. Soria; Introduction)
- The use of the most adequate trial design is key; “Tailored design approach” (S. Mandrekar)
- The survey on screening platforms by M. Lolkema is in agreement with Heisenberg‘s uncertainty principle that the instruments used for measurement and the measurement procedure itself exert potential influence on the results. For him and his institution, NGS is ready for „prime time“.
- J.-C. Soria launched a firework on trials testing tumor molecular profiling using the example of lung cancer — the entity, this process has started.
- U. Banerji described how to start with a new target without drug and to end-up with a single patient real-time adaptive combination selection.

Experience with Early Personalized Clinical Trials

SWOG-Study on the Use of the Human Tumor Cloning Assay (HTCA) for Predicting Response in Patients with Ovarian Cancer

168 pretreated patients

R

Treated according to HTCA results		Treated according to physician's choice
4 (22%)	CR	3 (3%)
1 (6%)	PR	7 (8%)
5 (28%)	p=0.03	10 (11%)
6.25 months	OS n.s.	7.0 months

Von Hoff et al; Cancer 67:20-27,1991

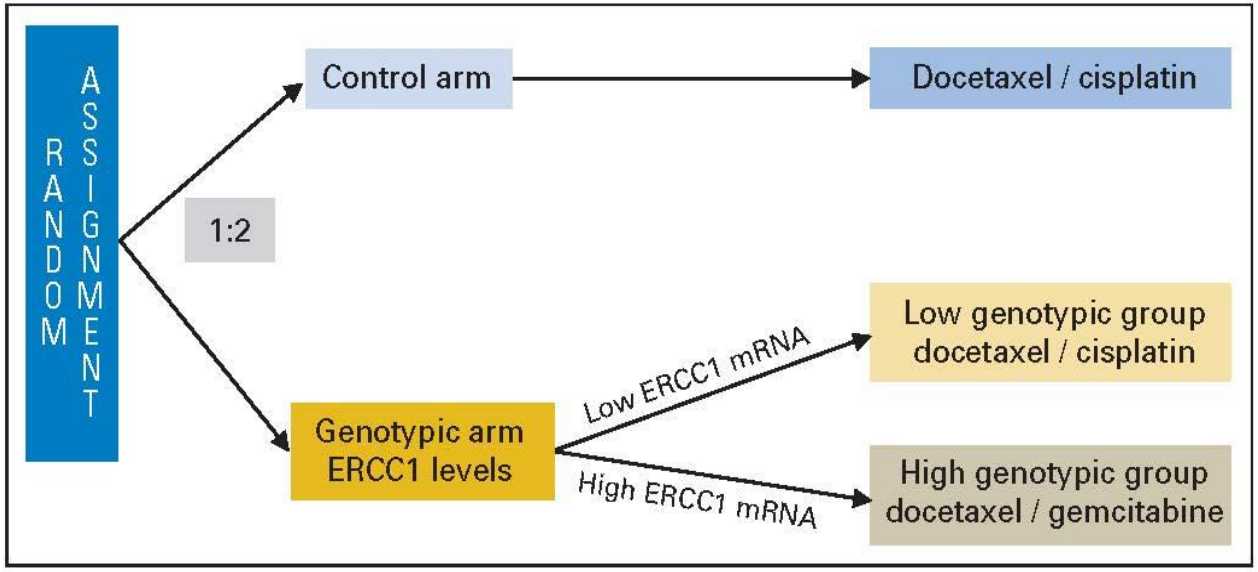
Experience with Early Personalized Clinical Trials

Tumor Chemosensitivity Assay (TCA)-directed Chemotherapy vs Physician's Choice in Patients with Recurrent Platinum-Resistant Ovarian Cancer

ATP-TCA based choice of chemotherapy (12 possible choices)	ATP-TCA	Physician's choice (physicians blinded to ATP-TCA result)
41% (31%)	ORR (ITT-analysis)	32% (26%)
104 days	median PFS HR 0.8; 95%CI:0.59-1.10	93 days
	OS: n.s.	
41% RR	Cross-over to ATP-TCA based	—

Cree et al; Anticancer Drugs 18:1093-1101,2007

Early Molecularly Profiled Prospective Randomized Trial



	ORR	PFS median	OS median
Control arm	39%	5.2 mos	9.8 mos
Low genotypic group	p=0.02	HR 0.9 0.7-1.1 p=0.30	HR 0.9 0.7-1.2 p=0.59
High genotypic group	51%	6.1 mos	9.9 mos

Cobo et al; J Clin Oncol 25:2747-2754,2007

Personalized Medicine Trials – Molecularly/Histology-Stratified

Trial's Name	Tumor Type	Setting	Design	Molecular Alterations	Treatment Arms	Endpoints	Status
BATTLE-1	Lung	≥1 R/M	Equal / Adaptive R	Multiple Specified (4)	4	8 wk DC	Completed
BATTLE-2	Lung	≥1 R/M	Adaptive R	Multiple Specified (11)	4	8 wk DC	Completed
BATTLE-FL	EGFR wt Lung	1 R/M	Adaptive R	Not specified	3	—	Active
FOCUS 4	CRC	FL Maintenance	Adaptive R	Multiple (4)	5	PFS, OS	Active
I-SPY 2	Breast	Neo-adjuvant	Adaptive R	BM: standard BM: qualifying BM: exploratory	Multiple Serial	pCR rate DFS, OS	Active - Veliparib - Neratinib
VE-BASKET	Multiple	R/M	PhII (7)	V600E BRAF mut	Vemurafenib	8 wk RR	Active
CREATE	Multiple	R/M	PhII	ALK/MET activation	Crizotinib	PFS, DCR OS, RR duration	Active
NCI-MATCH	Multiple	R/M	PhII	Any	Matched	ORR, PFS 6	Active

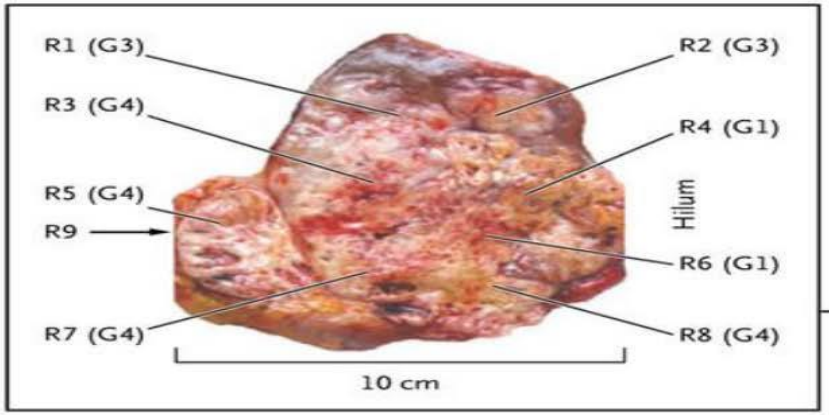
Modified acc. to Le Tourneau et al; Chin Clin Oncol 3:1-14,2014

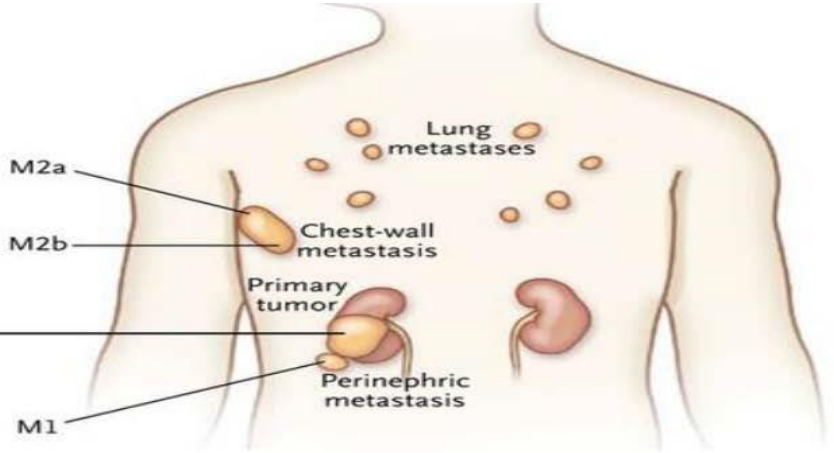
Personalized Medicine Trials – Algorithm-Based

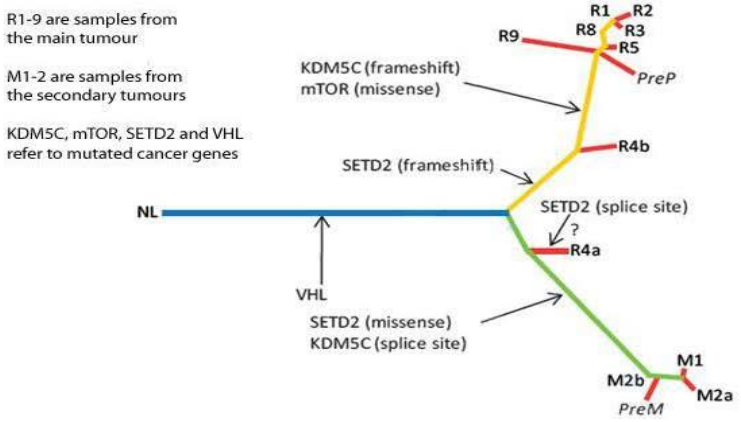
Trial's Name	Tumor Type	Setting	Design	Molecular Alterations	Treatment Arms	Endpoints	Status
Von Hoff Study	All	≥SL	N=1	Multiple	1	PFS ratio	Completed
MOSCATO	All	≥SL	N=1	Multiple	1	PFS ratio	Completed (PR 21%, SD 48%)
WINTHER	All	≥SL	N=1	Multiple	1	PFS ratio	Active
SHIVA	All	≥SL	RPhII	Multiple	Exp vs Ctl	PFS 6	Active
M-PACT	All	>SL	RPhII	Multiple	Exp vs Ctl	ORR, PFS 4	Active
MOST	All	PD on FL	R discontin.	Multiple (7)	2	OS	Active
SAFIR 02	NSCLC Non-EGFR mut ALK-transloc.	FL Maintenance	R: BM-driven vs Ctl	Multiple	Exp vs Ctl (6/2)	PFS	Active
SAFIR 02	Breast ER+/HER2-	FL Maintenance	R: BM-driven vs CTX	Multiple	Exp vs Ctl	PFS	Active
LUNG-MAP	NSCLC SCC	SL	R: BM-driven vs Ctl	Multiple (4)	Exp 5 / Ctl 5	PFS (PhII) OS (PhIII)	Active
TASTE	NSCLC Non-SCC	Adjuvant	R: BM-driven vs CTX	EGFR wt/mut ERCC1 +/-	4	Feasibility (PhII)	Completed; Refinement IHC ERCC1
ALCHEMIST	NSCLC	Adjuvant	Screening trial	EGFR mut ALK translocated	3	OS	Active

Modified acc. to Le Tourneau et al; Chin Clin Oncol 3:1-14,2014

Tumor Heterogeneity







101 nonsynonymous point mutations and 32 indels in seven primary-tumor regions of the nephrectomy specimen (R1 through R5 and R8 through R9), in the perinephric fat of the nephrectomy specimen (M1), and in two regions of the excised chest-wall metastasis (M2a and M2b), as detected by exome sequencing

"Intratumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges to personalized-medicine and biomarker development"

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing.

Gerlinger et al; N Engl J Med 366:883-892,2012

Types of Clinical Molecular Tests and Variants Detected

	Variant types			
Molecular methodology	SNVs	Small duplications, insertions, deletions, indels	Exon duplications, deletions, or gene copy-number changes	SVs
Allele-specific PCR	√			
PCR and Sanger dideoxy sequencing	√	√		*a*
PCR and pyrosequencing	√	•		
PCR and MS	√	•		
PCR and single-base extension	√			
MLPA	√		√	
FISH			*b*	√
NGS—custom panels (amplicon capture)	√	√		
NGS—custom panels (hybridization capture)	√	√	√	•
NGS—WES	√	√	√	•
NGS—WGS	√	√	√	√

√, Variant detected; •, variant detected with difficulty; *a*, variant detected if fusion RNA is extracted first; *b*, variant in gene copy number only.

Abbreviations: Indels, mutations including both insertions and deletions; MS, mass spectrometry. Adapted from Vnencak-Jones et al. "Types of Molecular Testing." My Cancer Genome, http://www.mycancergenome.org/content/other/molecular-medicine/types-of-molecular-tumor-testing. © Copyright 2013 Vanderbilt University.

Meador et al; Clin Cancer Res 20:2264-2275,2014

Ambiguous Attitude of Trialists

- Conservative with respect to expectations/goals

  Molecularly profiled treatment selection

  - NCI-MATCH Trial: ORR 25% vs 5%; PFS 6 35% vs 15%
  - SHIVA Trial: PFS 6 30% vs 15%

- Courageous with respect to choice of setting
  - No proof of algorithm-based treatment selection in advanced disease based on randomization established
  - Trials in adjuvant setting activated (TASTE, ALCHEMIST)

Molecular Profiling

Challenges	Perspectives
Intratumoral heterogeneity	Biomarker panel testing
Secondary resistance	Liquid biopsies for early assessment Molecular imaging Prevention by combination therapy Compounds overcoming secondary mutations Adaptive therapy in response to longitudinal profiling
Discordance in molecular profiling	Validation of “omics“ technologies
Undruggability of targets	Conversion into druggability (direct/indirect)
Histology/organ as common denominator	Genetic aberration as common denominator (basket trials)
Complexity of multiple genetic alterations and of drugs with multiple on-target and off-target effects	Systems biology
Inherent functional variability of cancer cells leading to cancer growth and therapy tolerance	Epigenetic therapy? Modulation of microenvironment? Immunotherapy?

One-size fits all approach: all patients
effective to a certain degree

Stratified approach: average patient
preselected criteria
effective to a higher degree

Personalized approach: individual patient
effective to a high degree

Personalization
The Holy Grail of Oncotherapy

Alex Grey