When patients fail on molecular targeted therapy: what to do in 2013

For 3rd APASAL HCC conference on 23 Nov 2013

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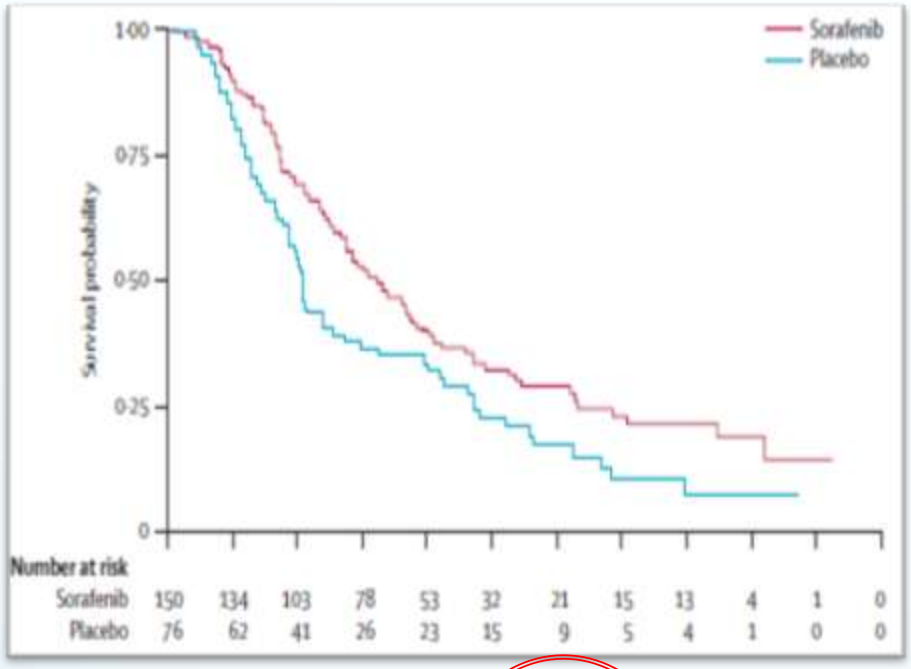
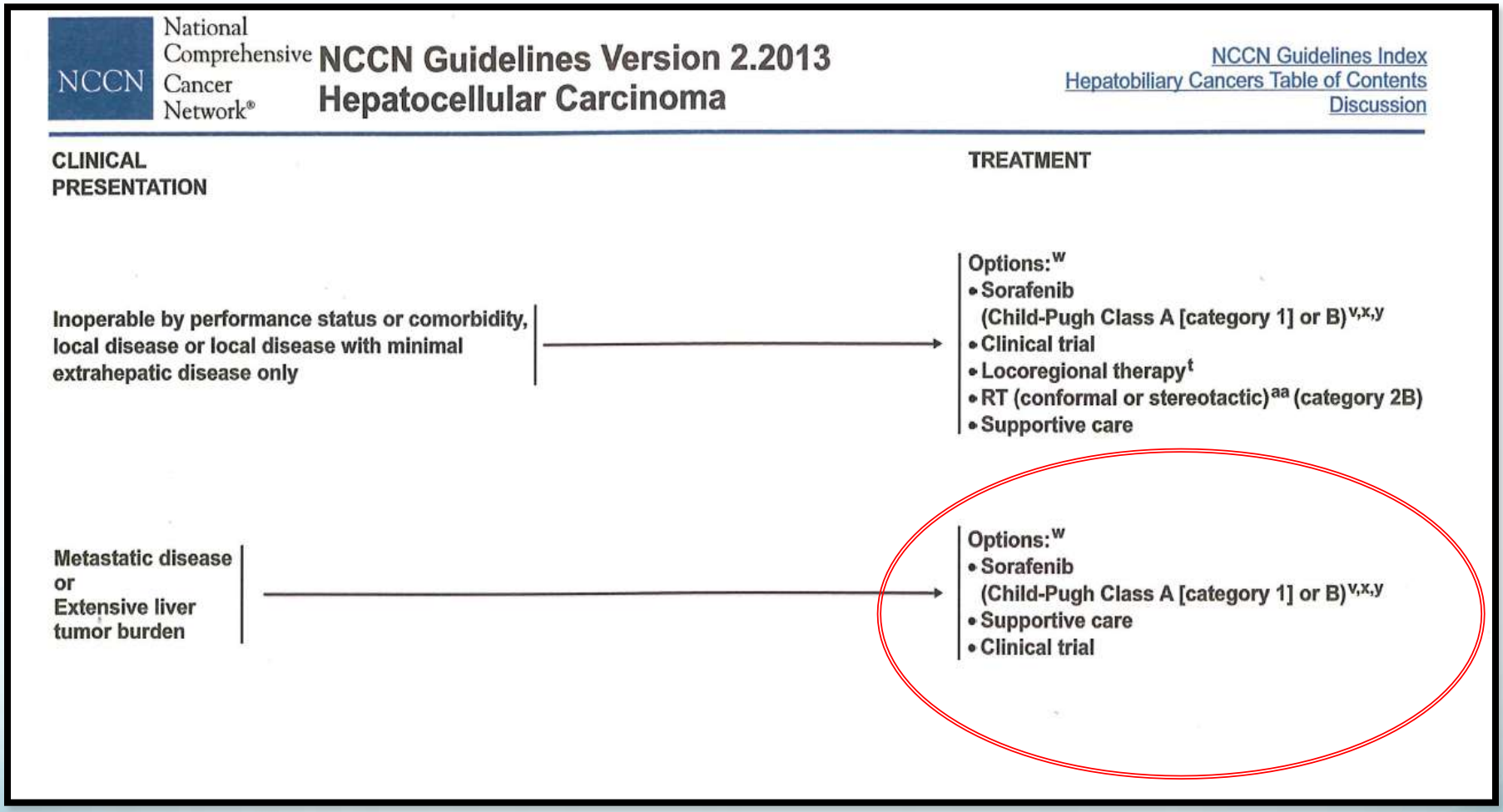
Sorafenib for advanced HCC



	OS	TTP	TTSP
Sorafenib	6.5m	2.8	3.5
Placebo	4.2m	1.4	3.4

Cheng AL et al. Lancet Oncology 2009

The issue of 'what to do next' occurs at a median of ~3-month duration after commencement of treatment.



Simple answer to the question: No, we don't have standard second line agent

Existing weapons

Novel treatment approach

End of the talk

Consensus on the current use of sorafenib for the treatment of hepatocellular carcinoma

Markus Peck-Radosavljevic[a], Tim F. Greten[c], Johannes Lammer[b], Olivier Rosmorduc[d], Bruno Sangro[e], Armando Santoro[f] and Luigi Bolondi[g]

Continuation of sorafenib after disease progression

Patients who experience progression of disease during sorafenib treatment have limited treatment options and the first option for these patients is inclusion in clinical trials, where available. In the absence of alternative therapies with proven efficacy in this setting, continuing sorafenib treatment after disease progression may be beneficial in slowing down tumour growth. Sorafenib may be continued after disease progression for patients with stable performance status, although there is currently no clear evidence supporting the effectiveness of this approach.

In the absence of alternative therapies with proven efficacy….continuing sorafenib treatment after disease progression may be beneficial……

European Journal of Gastro & Hepatol. 2010: 22: 391-98

Hepatology Research

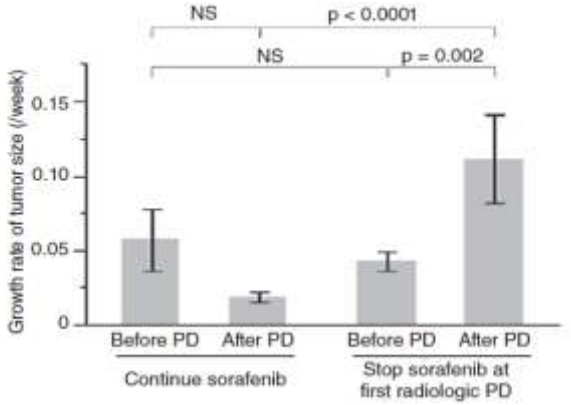
Hepatology Research 2013 doi: 10.1111/hepr.12123

Efficacy of sorafenib beyond first progression in patients with metastatic hepatocellular carcinoma

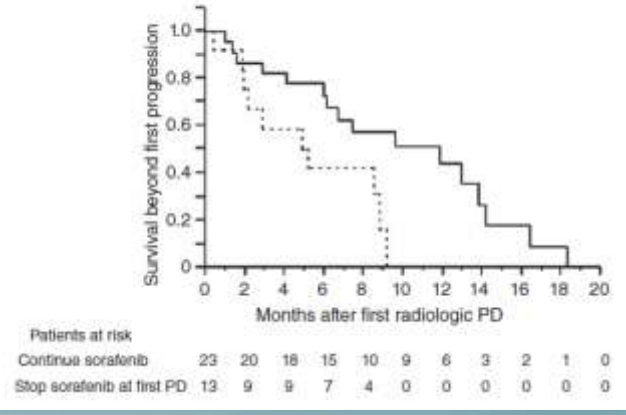
Koji Miyahara,[1] Kazuhiro Nouso,[1,2] Yuki Morimoto,[1] Yasuto Takeuchi,[1] Hiroaki Hagihara,[1]

- Case-control study
- Decision to continue sorafenib beyond progression relies on physicians' decision
- Predominantly HCV infection
- Total sample size
  - 23 continued sorafenib beyond progression
  - 13 stopped sorafenib upon progression

Tumor size



Overall survival



Phase II randomized study on dose escalated sorafenib versus best supportive care after PD to sorafenib: Abstract results

- Child's A/B
- PD (RECIST)
- not suitable for any loco-regional therapy

- 2007-2008, 300 sorafenib-treated patients were registered; 101 (34%) randomized
- 93% Child's A, 58% without extrahepatic spread
- S arm: 46% (full dose); others required dose reduction

End point	S-arm	BSC-arm	p	HR
Median PFS (months)	3.9	2.6	0.07	0.66 (0.41-1.04)
Median OS (months)	6.1	6.0	0.14	0.73 (0.47-1.11)

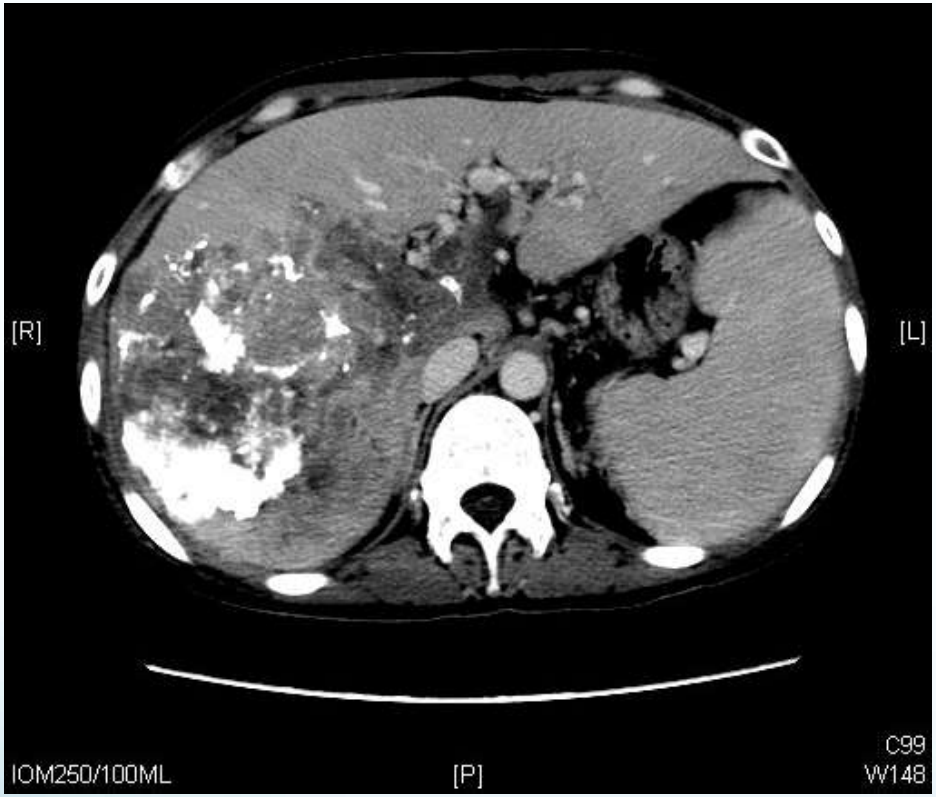
Pressiani T et al. ASCO 2011 abstract 4115

Use of sorafenib beyond progression

- Lack of evidence
  - One small scaled non-controlled study
  - One phase II randomized study (abstract only)
- The benefit is likely negligible to small, even if present
- Reimbursement program/funding policy may also be a limiting factor

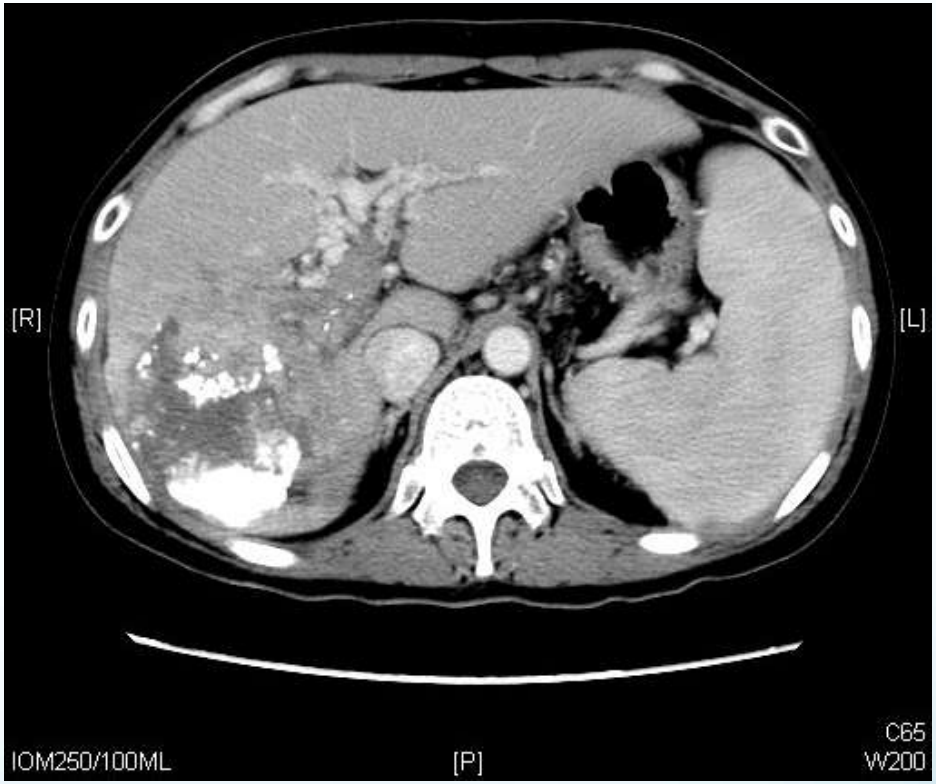
Back to basic: use the old weapon

Cytotoxic chemotherapy



Before chemo

AFP: 120000 ng/ml

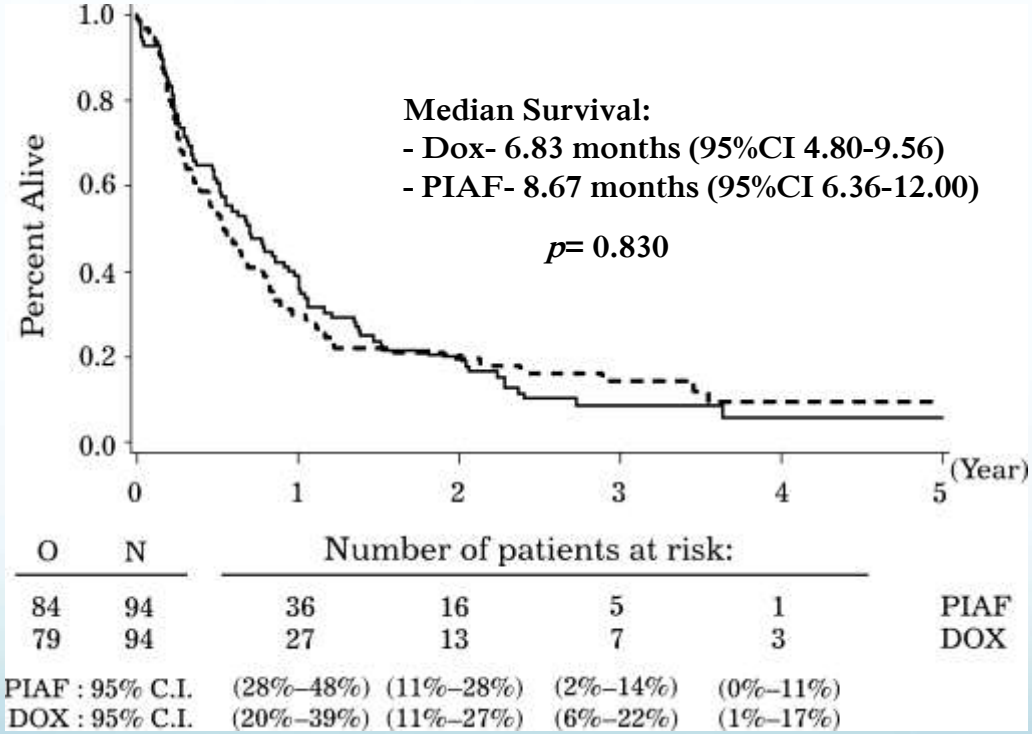


After 3 chemo

AFP: 450 ng/ml

Phase III data on chemotherapy

	Doxorubicin arm	PIAF arm	p
Median no. of cycles	4	3	0.076
Overall responses	10.5% (95% CI 3.9-16.9%)	20.9% (95% CI 12.5-29.2%)	0.0578



Yeo W et al, J Natl Cancer Inst 2005

VOLUME 31 · NUMBER 28 · OCTOBER 1 2013

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ORIGINAL REPORT

Randomized, Multicenter, Open-Label Study of Oxaliplatin Plus Fluorouracil/Leucovorin Versus Doxorubicin As Palliative Chemotherapy in Patients With Advanced Hepatocellular Carcinoma From Asia

Shukui Qin, Yuxian Bai, Ho Yeong Lim, Sumitra Thongprasert, Yee Chao, Jia Fan, Tsai-Shen Yang, Vajarabhongsa Bhudhisawasdi, Won Ki Kang, Yu Zhou, Jee Hyun Lee, and Yan Sun

Partial response rate ~8%

Table 2. Disease Response in ITT Population at Prespecified Final and Follow-Up Analyses

	Final Analysis					Follow-Up Analysis				
	FOLFOX4 (n = 184)		DOX (n = 187)			FOLFOX4 (n = 184)		DOX (n = 187)		
Parameter	No.	%	No.	%	*P**	No.	%	No.	%	*P**
RR†	15	8.15	5	2.67	.02	16	8.70	5	2.67	.01
95% CI	4.63 to 13.09		0.87 to 6.13			5.05 to 13.74		0.36 to 6.13		
DCR‡	96	52.17	59	31.55	< .001	98	53.26	61	32.62	< .001
95% CI	45.78 to 60.64		25.96 to 39.84			45.78 to 60.64		25.96 to 39.84		
CR§	0	0.00	0	0.00		0	0.00	0	0.00	
PR§	15	8.15	5	2.67		16	8.70	5	2.67	
SD§	81	44.02	54	28.88		82	44.57	56	29.95	
PD§	54	29.35	76	40.64		54	29.35	76	40.64	
Not evaluable	34	18.48	52	27.81		32	17.39	50	26.74	

Abbreviations: CR, complete response; DCR, disease control rate; DOX, doxorubicin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.

*Cochran-Mantel-Haenszel test.

†Defined as CR plus PR.

‡Defined post hoc as CR plus PR plus SD.

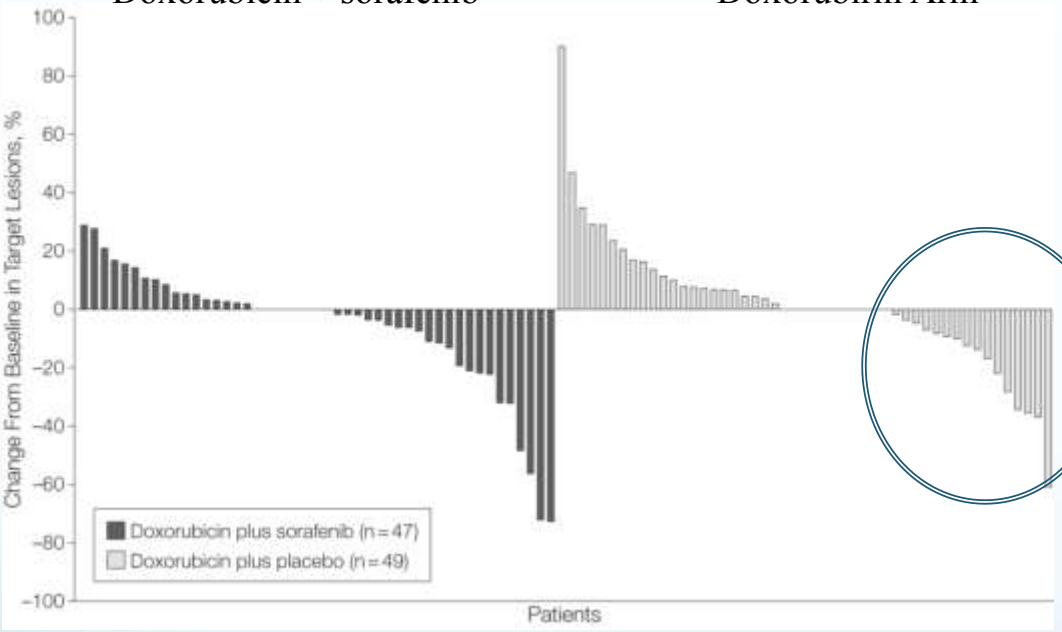
§*P* values not determined for individual parameters.

From: **Doxorubicin Plus Sorafenib vs Doxorubicin Alone in Patients With Advanced Hepatocellular Carcinoma: A Randomized Trial**

JAMA. 2010;304(19):2154-2160. doi:10.1001/jama.2010.1672

Doxorubicin + sorafenib

Doxorubirin Arm



Doxorubicin Arm:
- 4% meets PR criteria (RECIST)
- 29% has shrinkage of tumor

Limitation: Toxicity

Phase III trial FOFLOX 4 vs. DOX

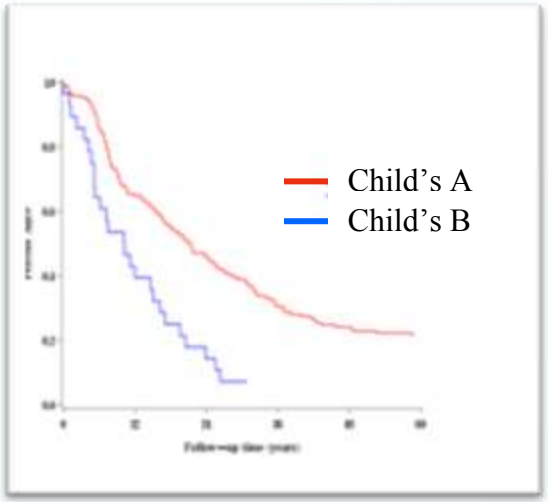
Table 1. Baseline Patient Demographics and Clinical Characteristics in ITT Population

Characteristic	FOLFOX4 (n = 184) No.	%	DOX (n = 187) No.	%
Age, years				
Mean	49.53		49.30	
SD	10.77		10.80	
Sex				
Male	166	90.22	163	87.17
Female	18	9.78	24	12.83
Weight, kg				
Mean	61.45		62.98	
SD	9.24		9.94	
HBV infection	171	92.93	168	89.84
HCV infection	9	4.97	16	8.60
Liver cirrhosis	102	55.74	100	53.48
Duration of disease, years				
Mean	0.66		0.66	
SD	1.57		1.57	
Disease status				
Tumor confined to liver	80	43.48	75	40.11
Metastatic disease	104	56.52	112	59.89
Child-Pugh stage				
A	163	88.59	163	87.17
B	21	11.41	24	12.83

Relatively young (and likely more fit patients)

Qin S et al. J Clini Oncol 2013

Phase III trial PIAF vs. doxorubicin



	Child's A	Child's B	P value
No. of cycle	4	2.5	0.01
G3/4 Hyper-bilirubinemia (%)	11.9	28.6	0.02
GI Bleeding (%)	3.1	17.9	0.001

Yeo W…Chan SL. Contemp Clin Trials 2009

Use of chemotherapy in sorafenib-refractory HCC

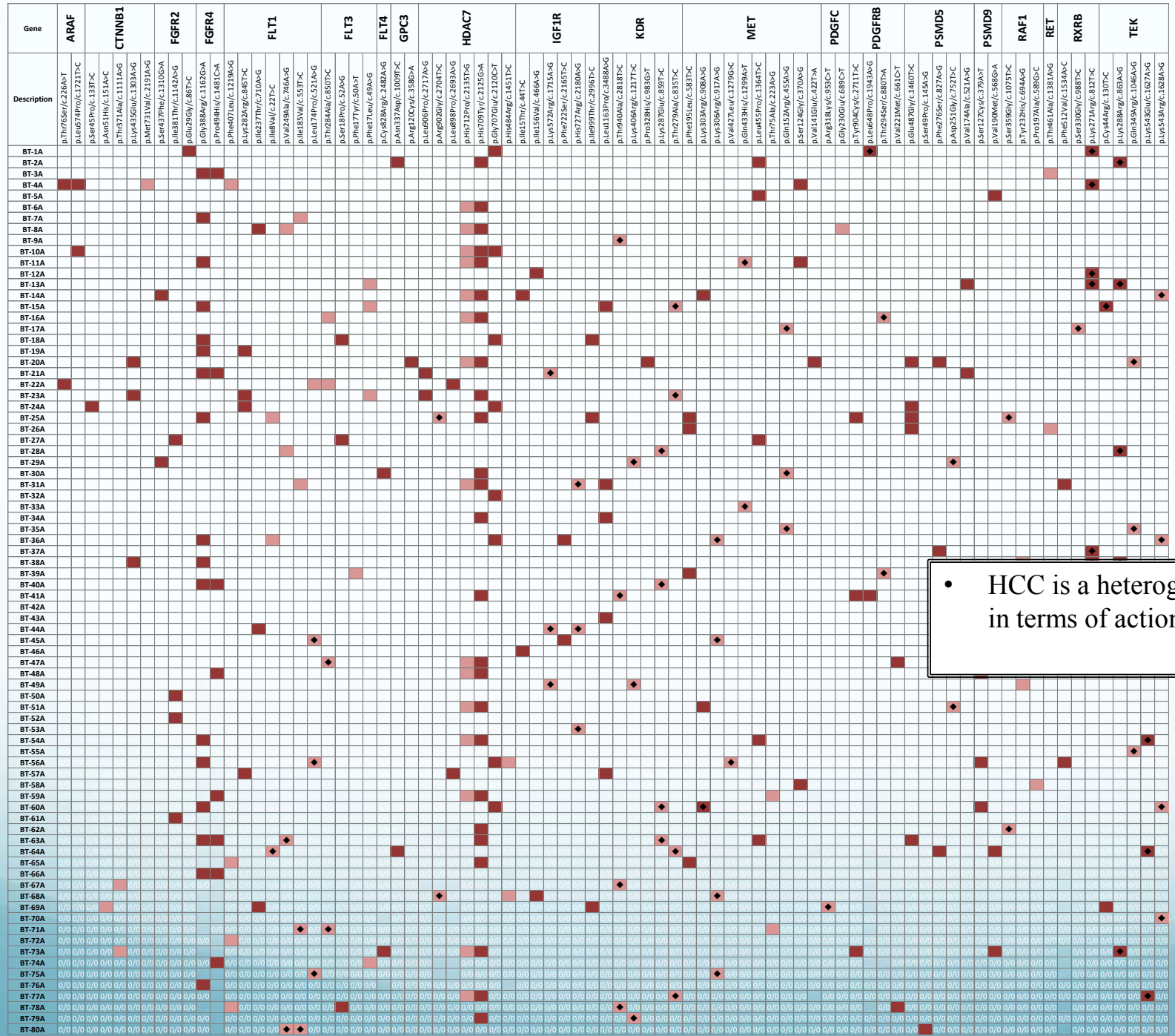
- Clinical data extrapolated from non-sorafenib era/population
- Radiologic response seen in 8-10% of population
- Tolerability; suitable for young patients with good ECOG and Child's A liver function

Molecular targeted agents: Current status

List of Phase III clinical trials on novel agents as the second-line treatment (vs. Placebo)

FGFR: Brivanib	Negative
mTOR: Everolimus	Negative (pending full data)
C-met inhibitor: Tivanitinb	Ongoing
Multi-targeted TKI: • Carbozanitib • Regorafenib	 Ongoing Ongoing
Anti-VEGF Mab: Ramacirumab	Completed
Others: • ADI-PEG20	 Ongoing

MiSeq Data



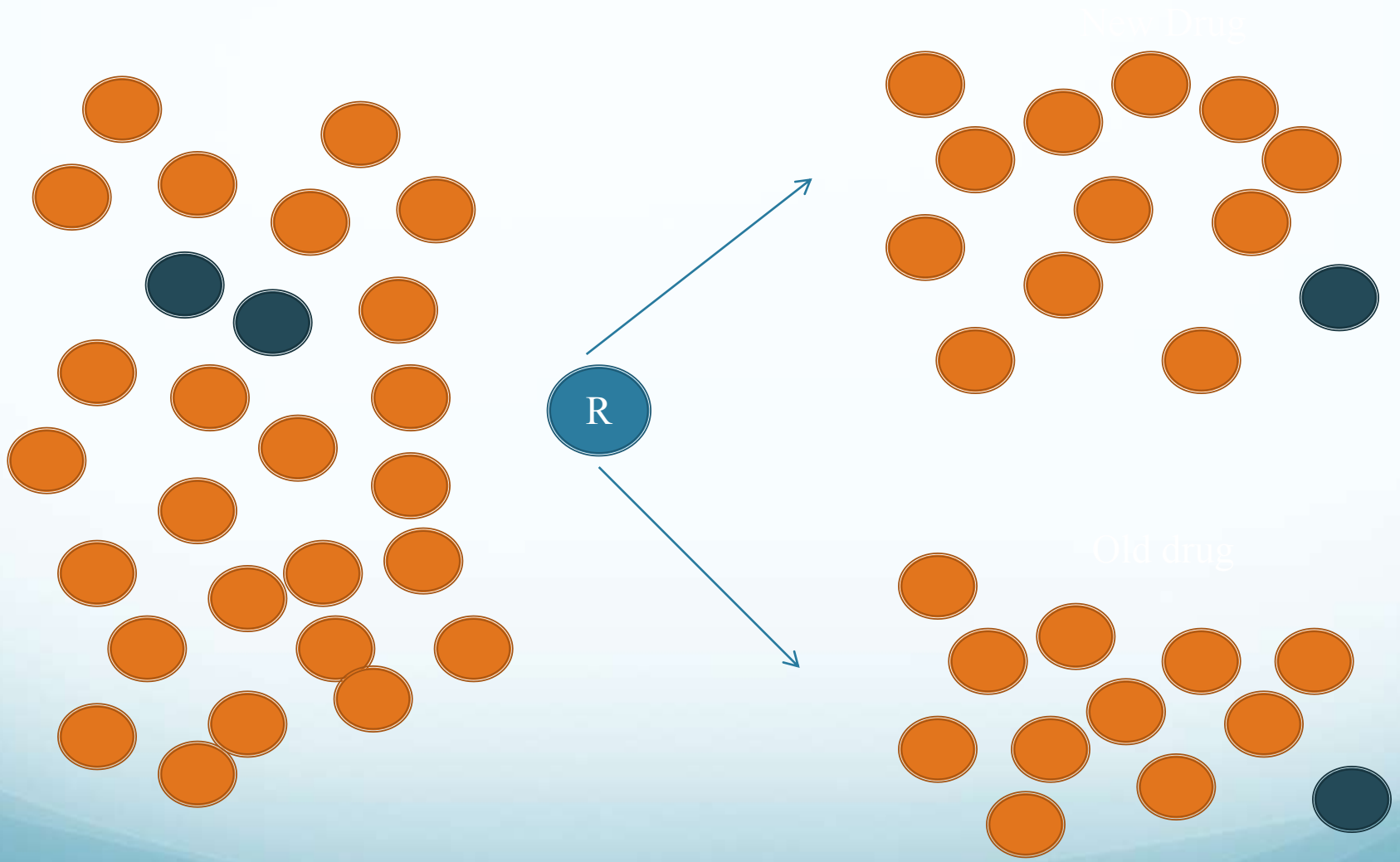
- HCC is a heterogeneous disease in terms of actionable targets.

Tolerated Mutation

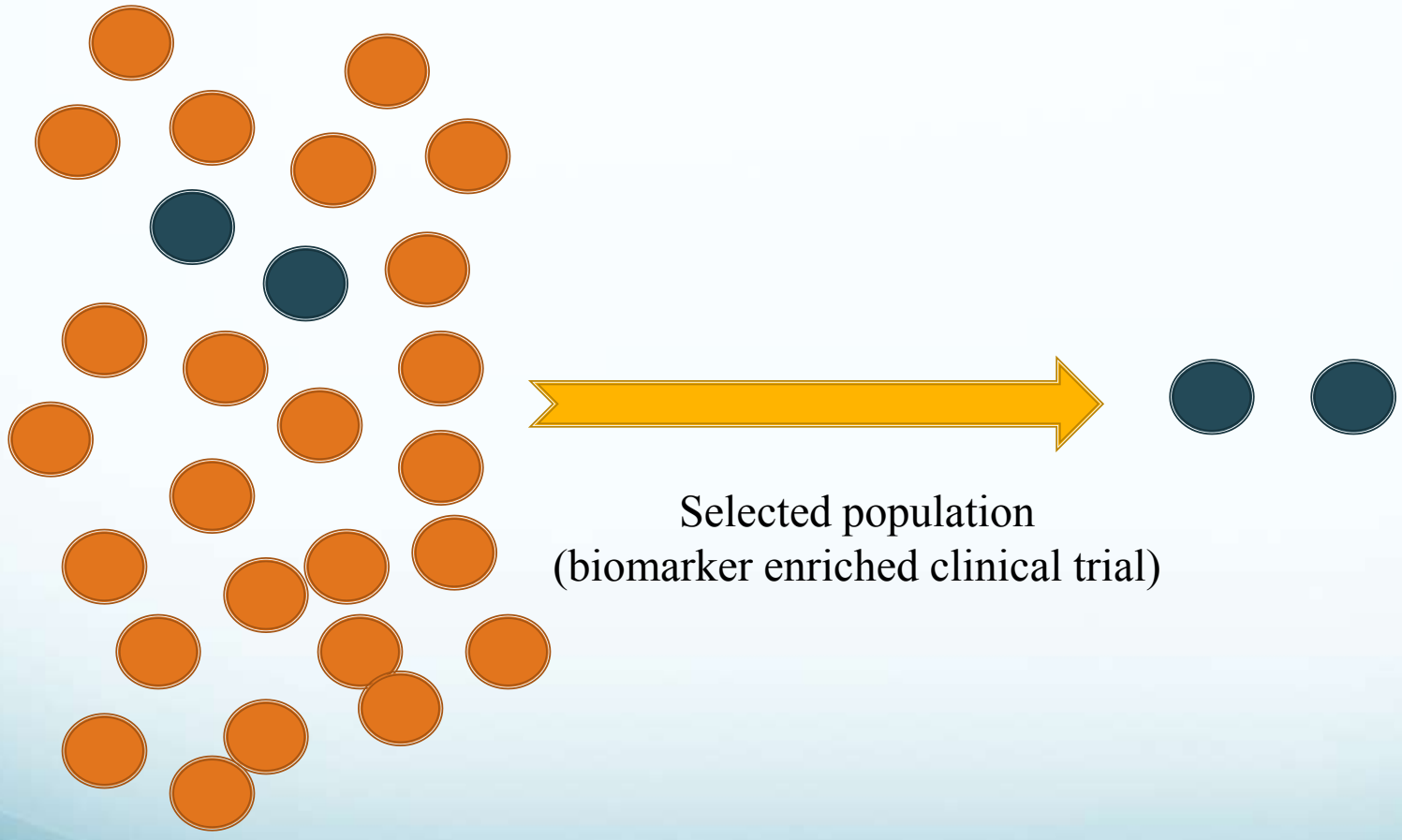
Deleterious Mutation

Mutation Located in Conserved Domain

Hypothesis: Only a small number (few %) of patients respond to the new drug in the clinical trial



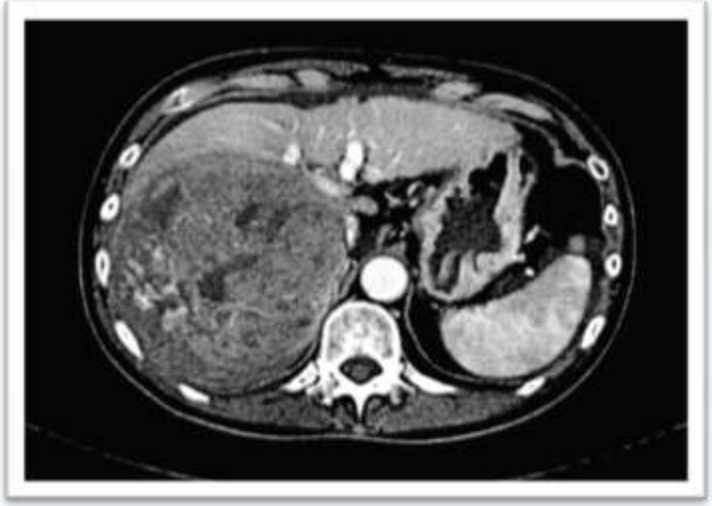
Biomarker enriched trial



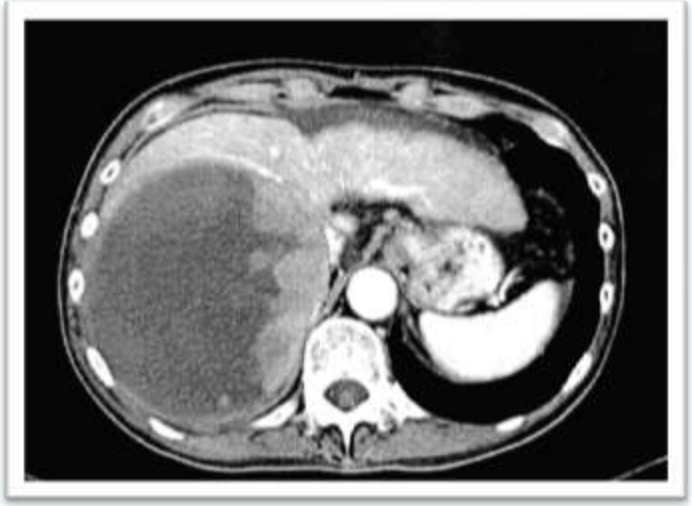
Selected population
(biomarker enriched clinical trial)

Cases of significant response with targeted agent

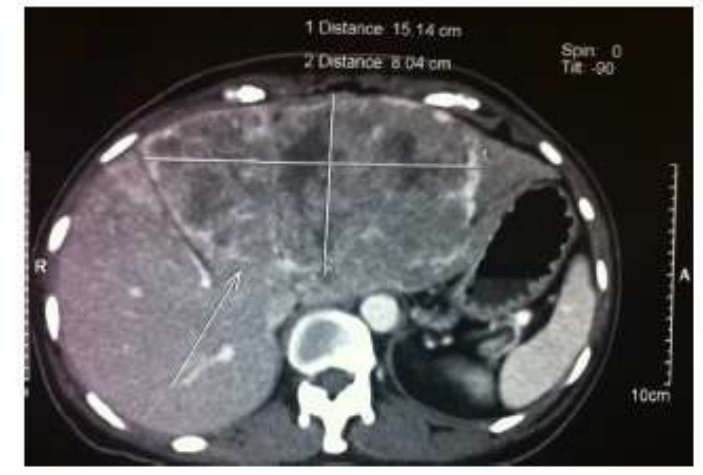
Pre-treatment



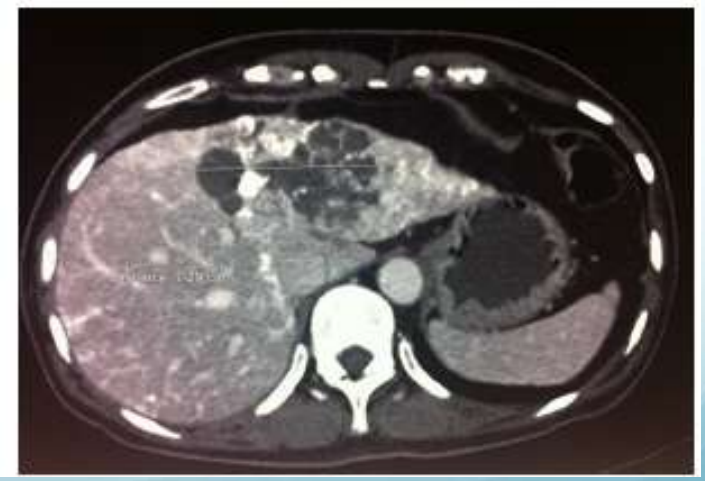
Post-treatment



Pre-treatment

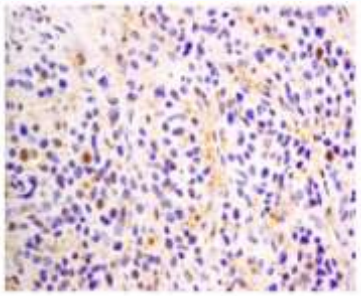


Post-treatment

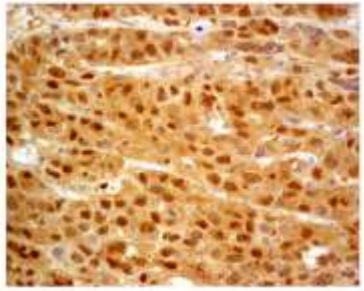


HR23B as predictive biomarker for HDAC inhibitor

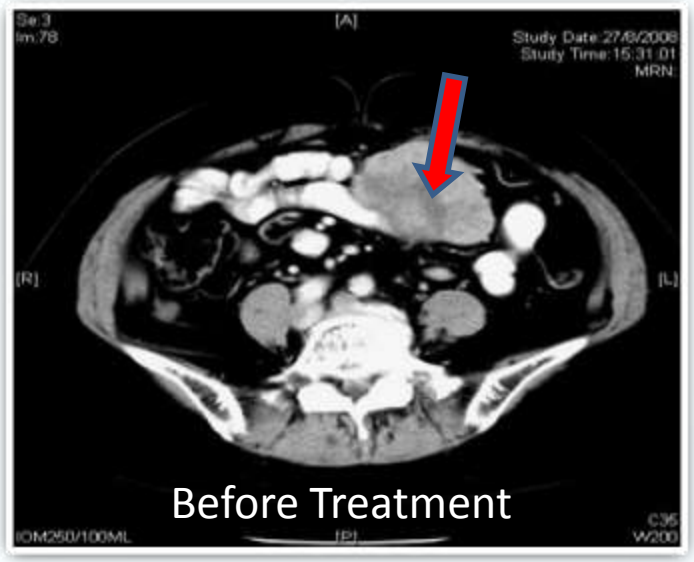
IHC staining (histoscore) of HR23B is associated with disease control rate (CR+PR+SD) ($p<0.05$)

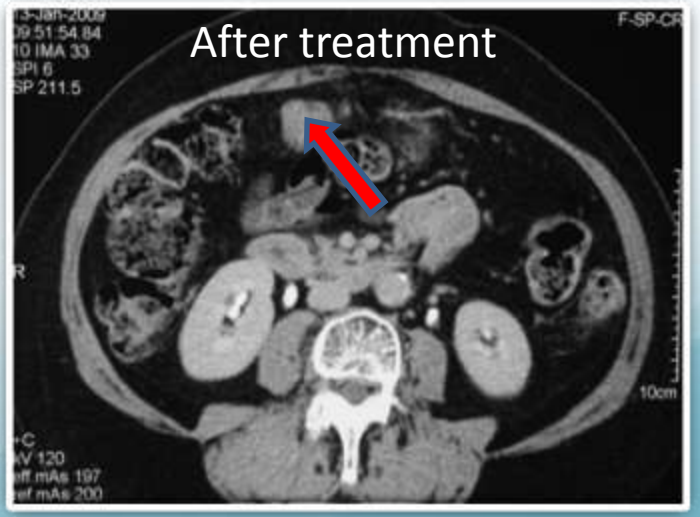


Low
(histoscore 30/300)



High
(histoscore 255/300)



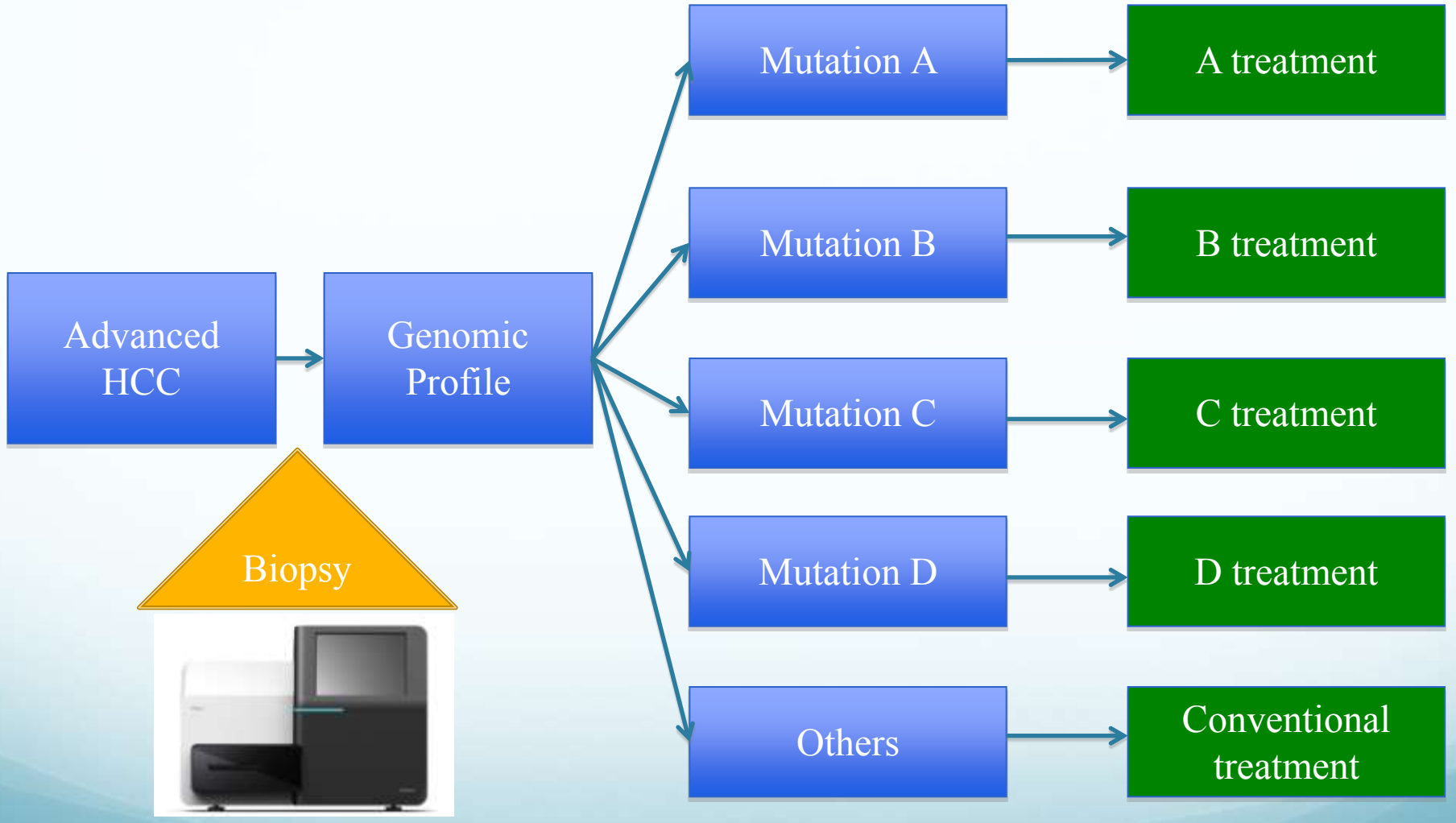


Yeo W et al. J Clin Oncol 2012

Biomarker driven drug testing

- c-met FISH/IHC for c-met inhibitor: under clinical testing in phase II setting
- HR23B for HDAC inhibitor: Phase II data
- More to come….

Genomic profile of druggable targets for HCC



Note on second line targeted therapy for HCC

- No standard second-line agent of proven benefit at present
- Phase III clinical trial results are awaited
- Predictive biomarker may be important for drug development.
- Tissue biopsy is indicated (not for diagnosis but for genomic profiling of tumor)


Thank you