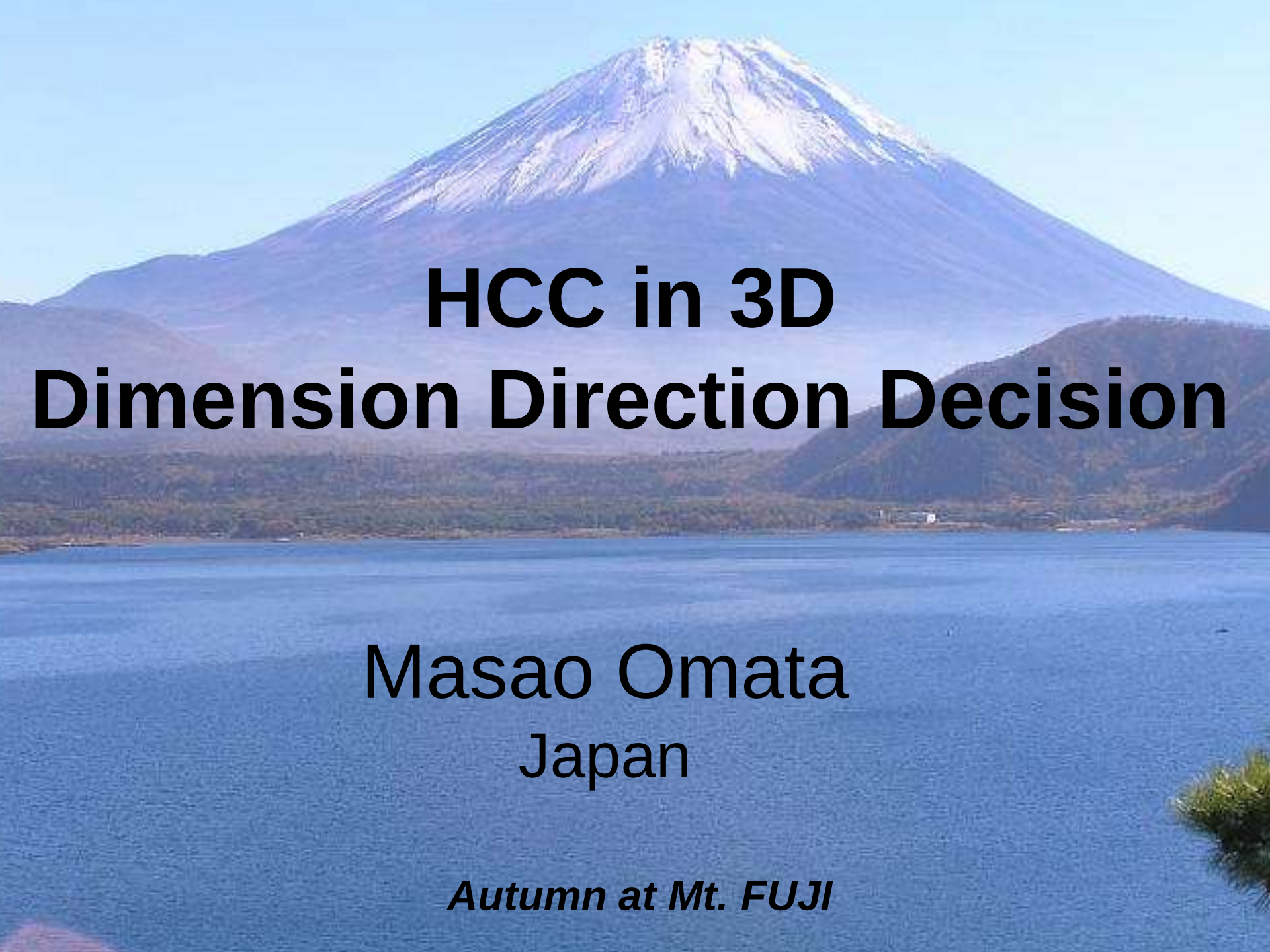


HCC in 3D
Dimension Direction Decision

Masao Omata
Japan

Autumn at Mt. FUJI

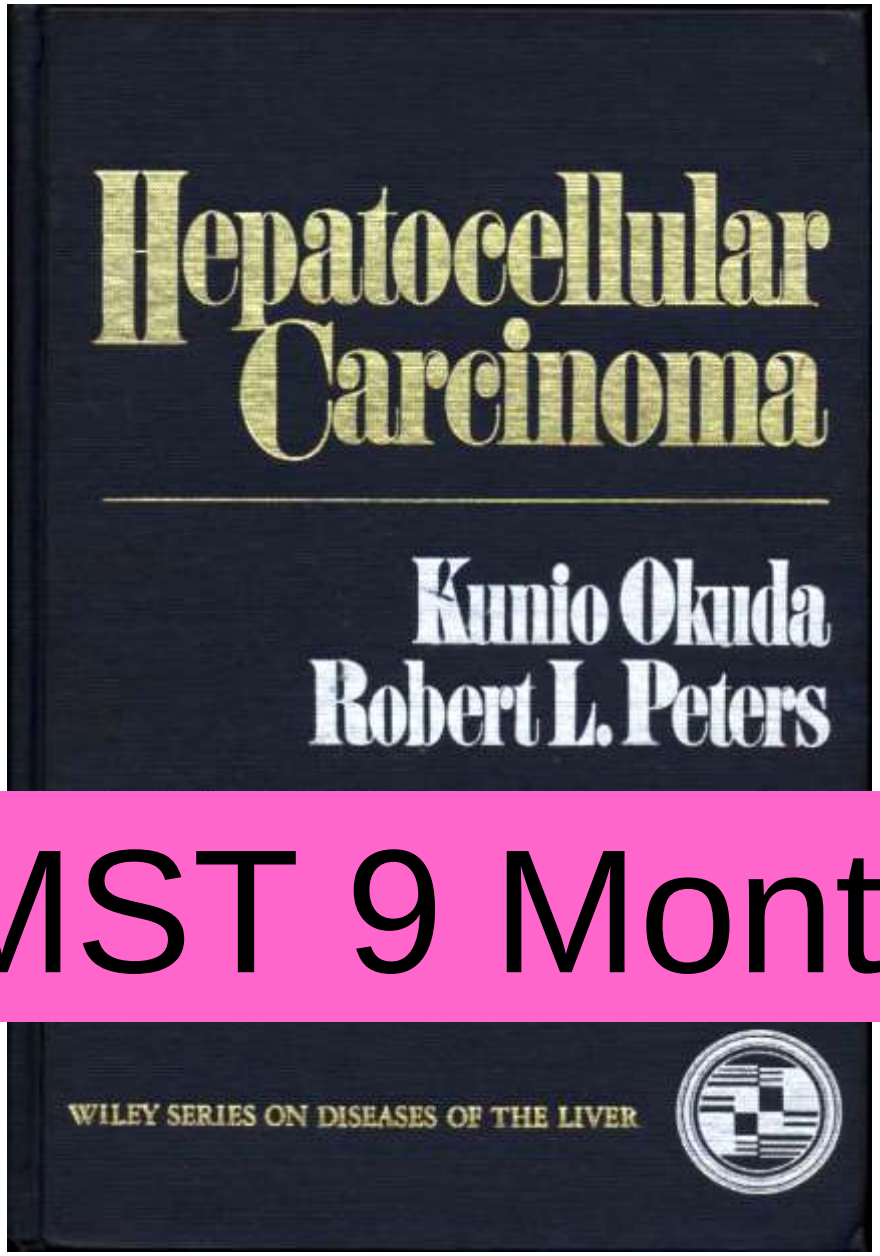
Japan

What were remarkable in the filed of HCC ?

HCV-induced HCC

the Majority !

80%



MST 9 Months

1976

Hepatocellular Carcinoma

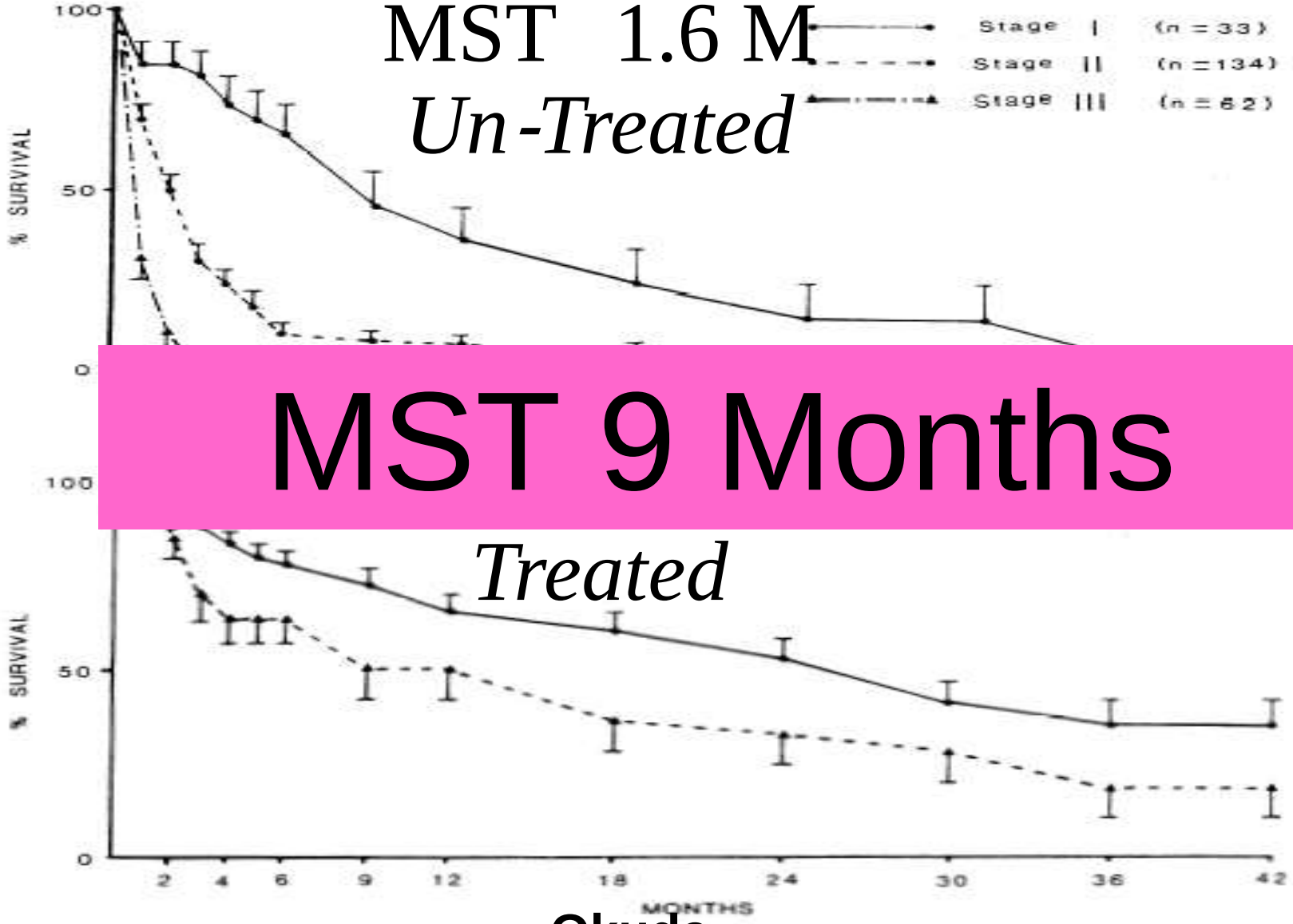
Kunio Okuda
Robert L. Peters

WILEY SERIES ON DISEASES OF THE LIVER

1976

MST 1.6 M

Un-Treated



MST 9 Months

Treated

Okuda

Natural History of HCC ; 850 Cases Cancer 1985:56:918-

Now

MST (Median Survival Time)

90 Months by RFA

40 Months by TAE

By Shiina S

By Obi S

However,
Results
mainly obtained
from Patients
with Small(Early) HCCs

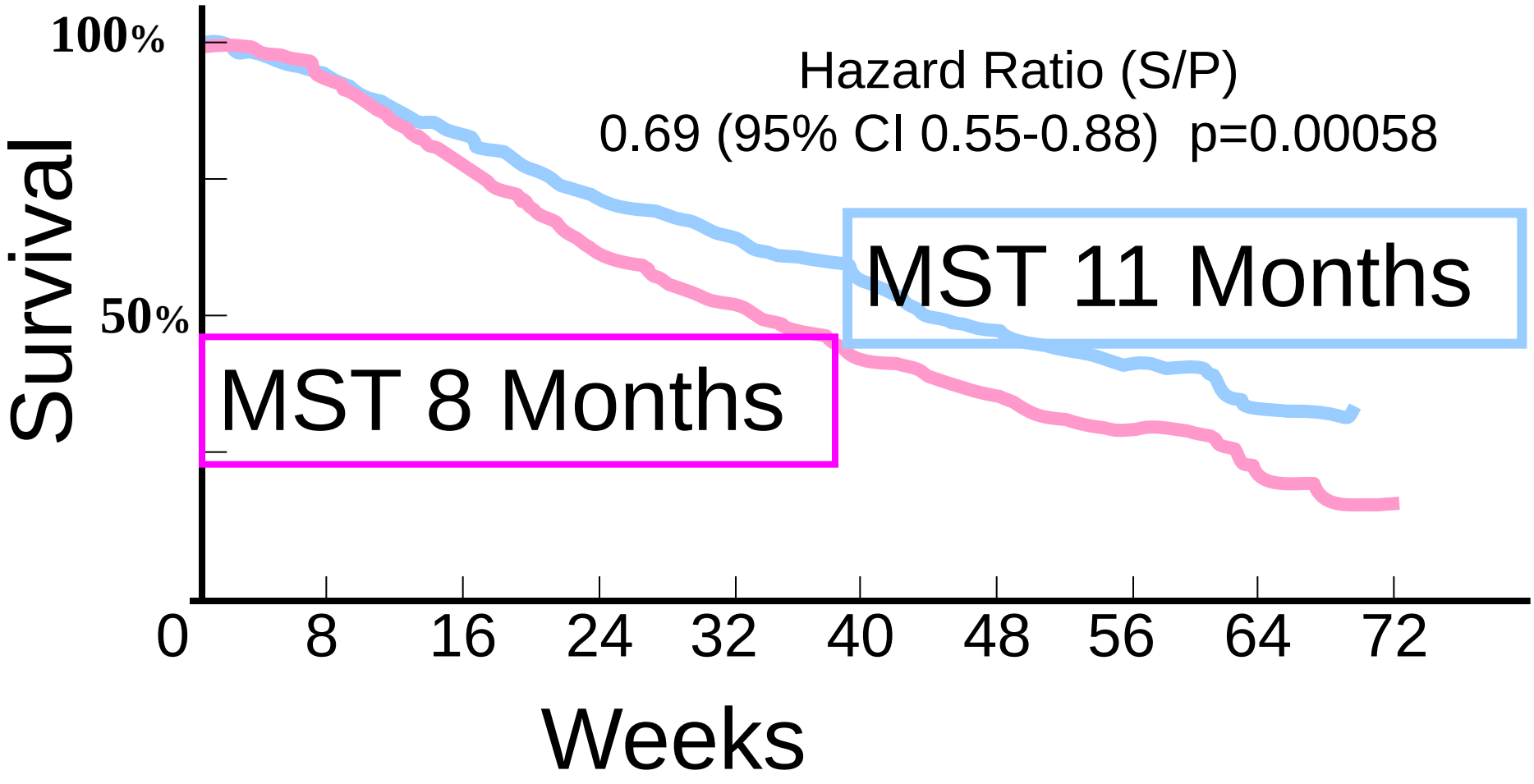
Any Progress in the Advanced ?

The answer

Molecular Targetting Drugs

??

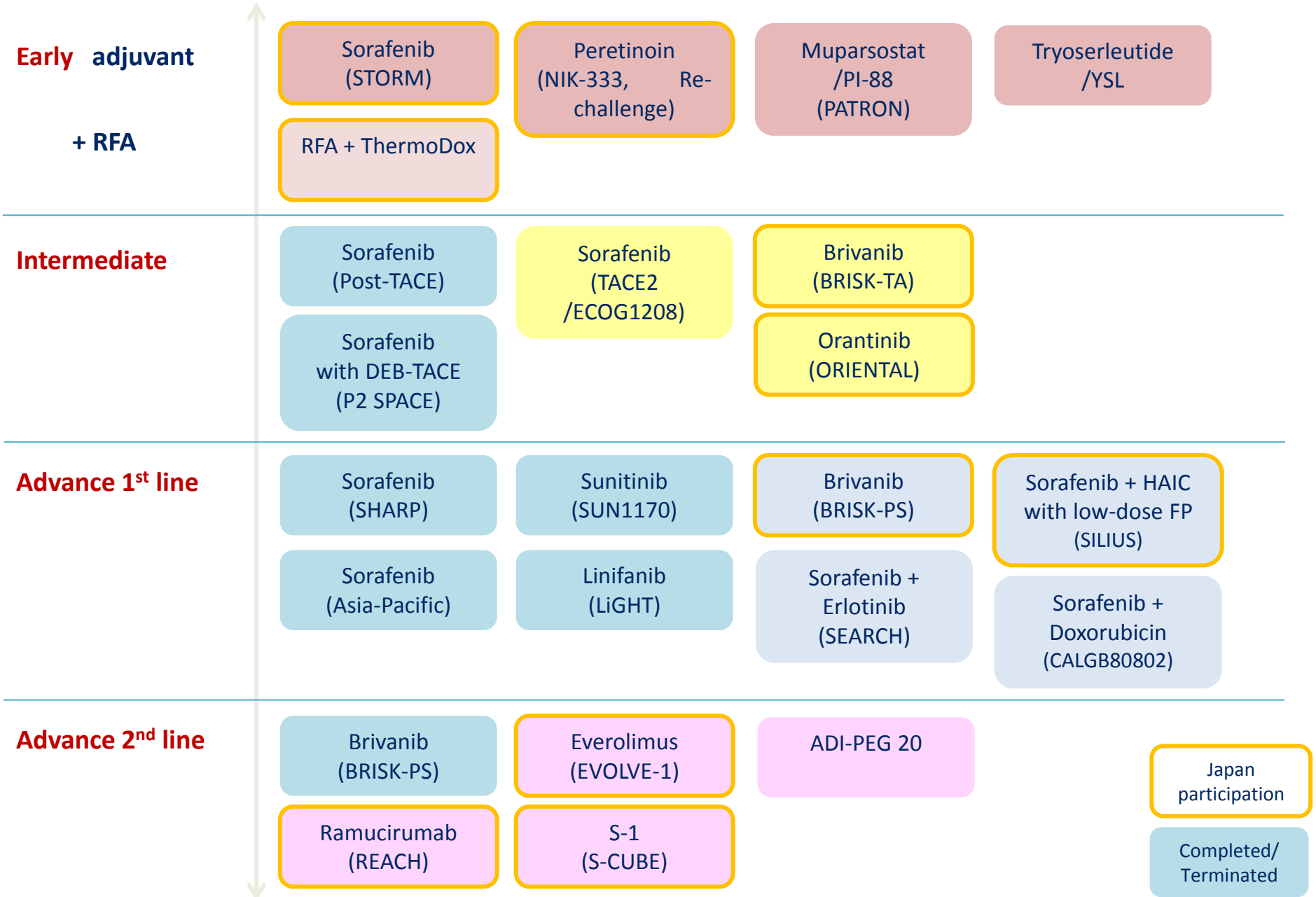
SHARP TRIAL **SORAFENIB**



This field has become

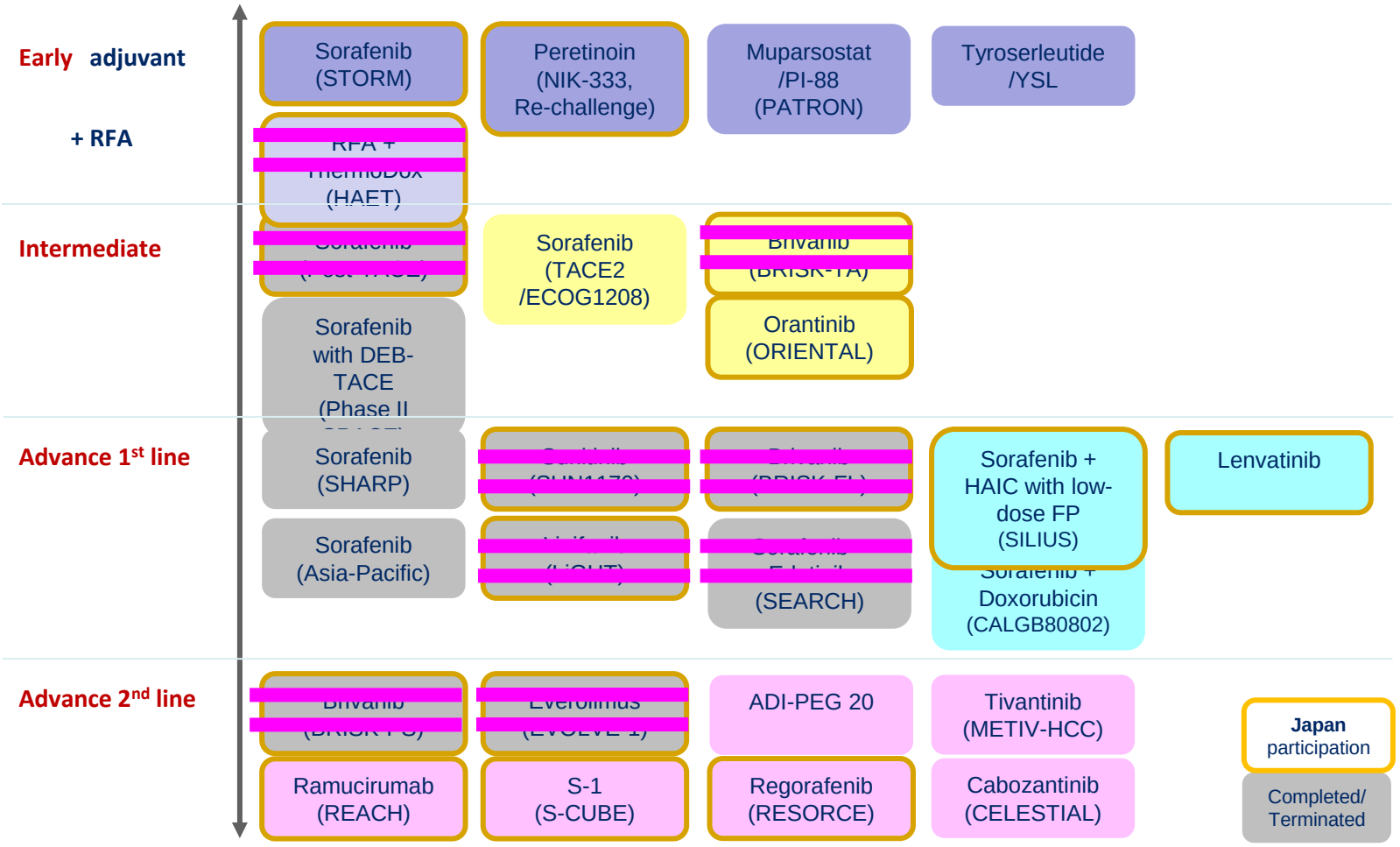
As competitive as that of HCV drugs

Molecular Rxs for HCC in Phase III



Reality？

Molecular Rxs for HCC in Phase III



We are all stuck !

Why
and
How to go beyond ?

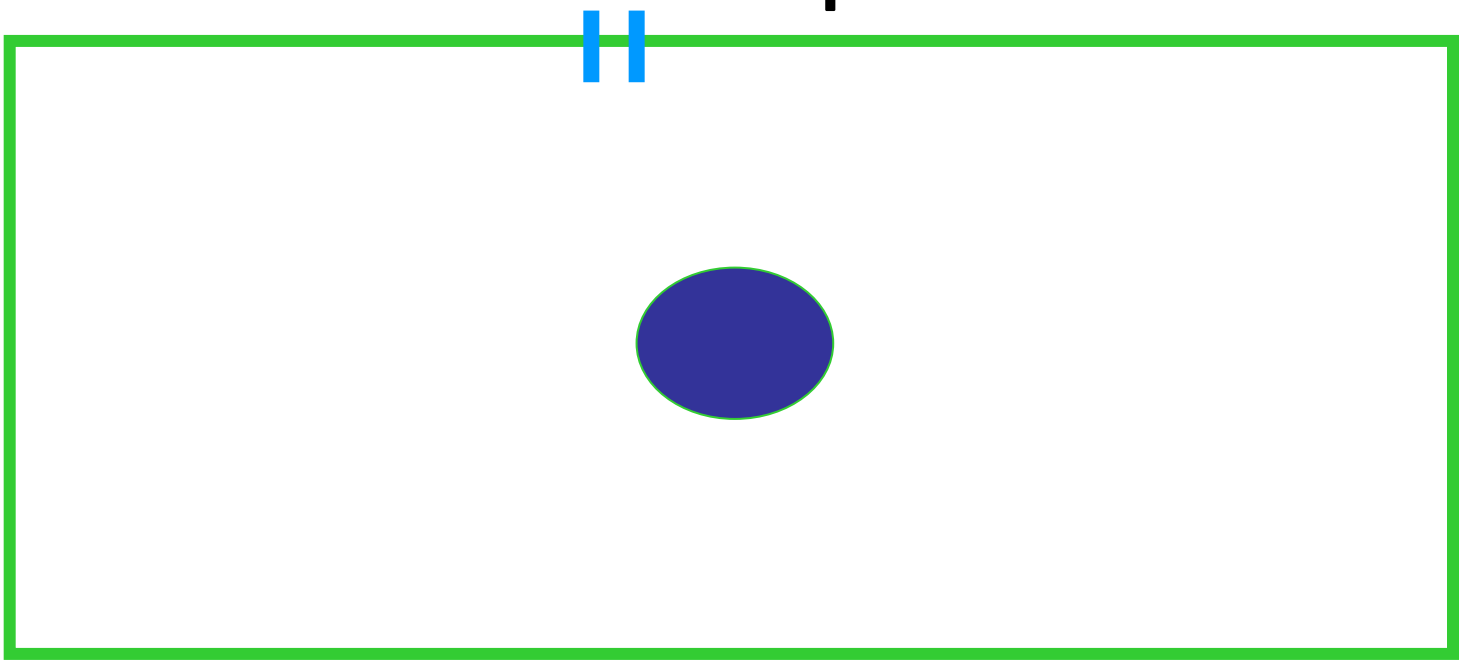
Cell

A Quiescent Town
with **23K Inhabitants**

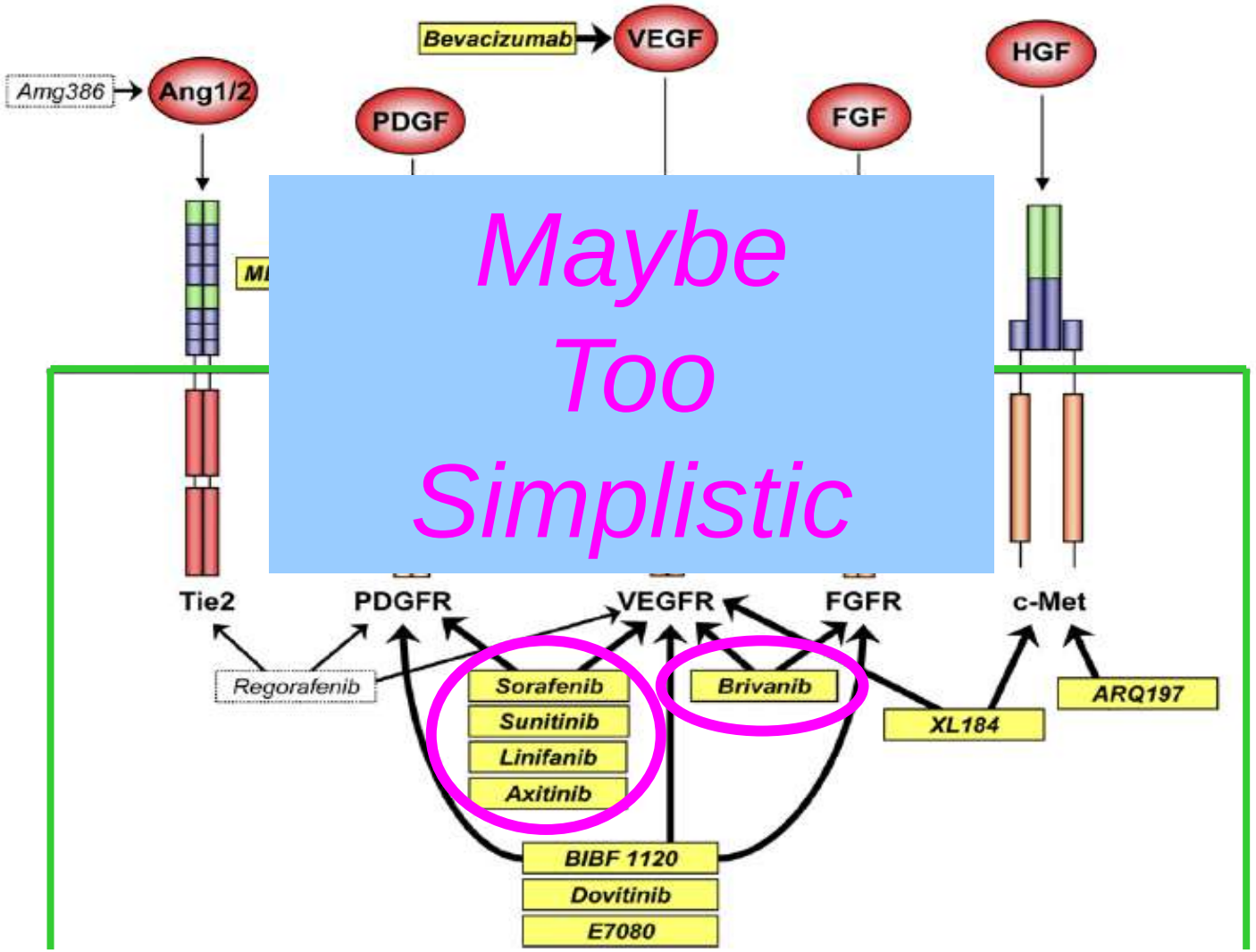
23K Proteins

become Chaos/Turmoil

~~VEGF-Receptor~~



All are *In and Around* the Cell Membrane



S Tanaka, et al. Seminars in oncology 2012;39: 486-492

Do We Understand *Inside*

Enough ?

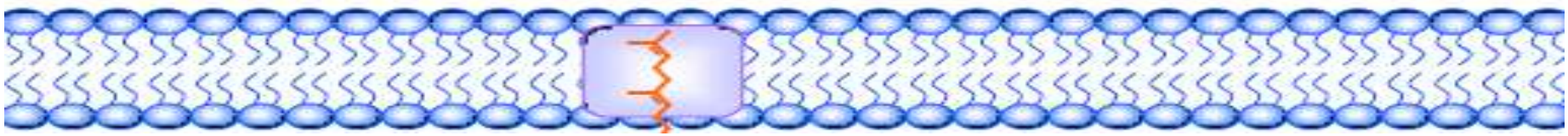
We better learn from

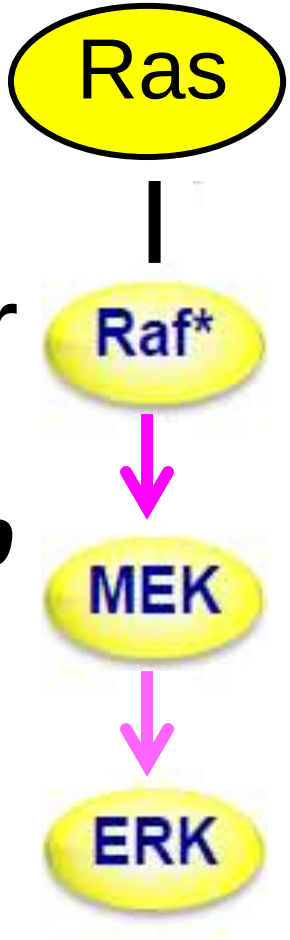
Other Oncologic Areas

Topics !

Melanoma

Inside the Melanoma(Cell)





Melanoma

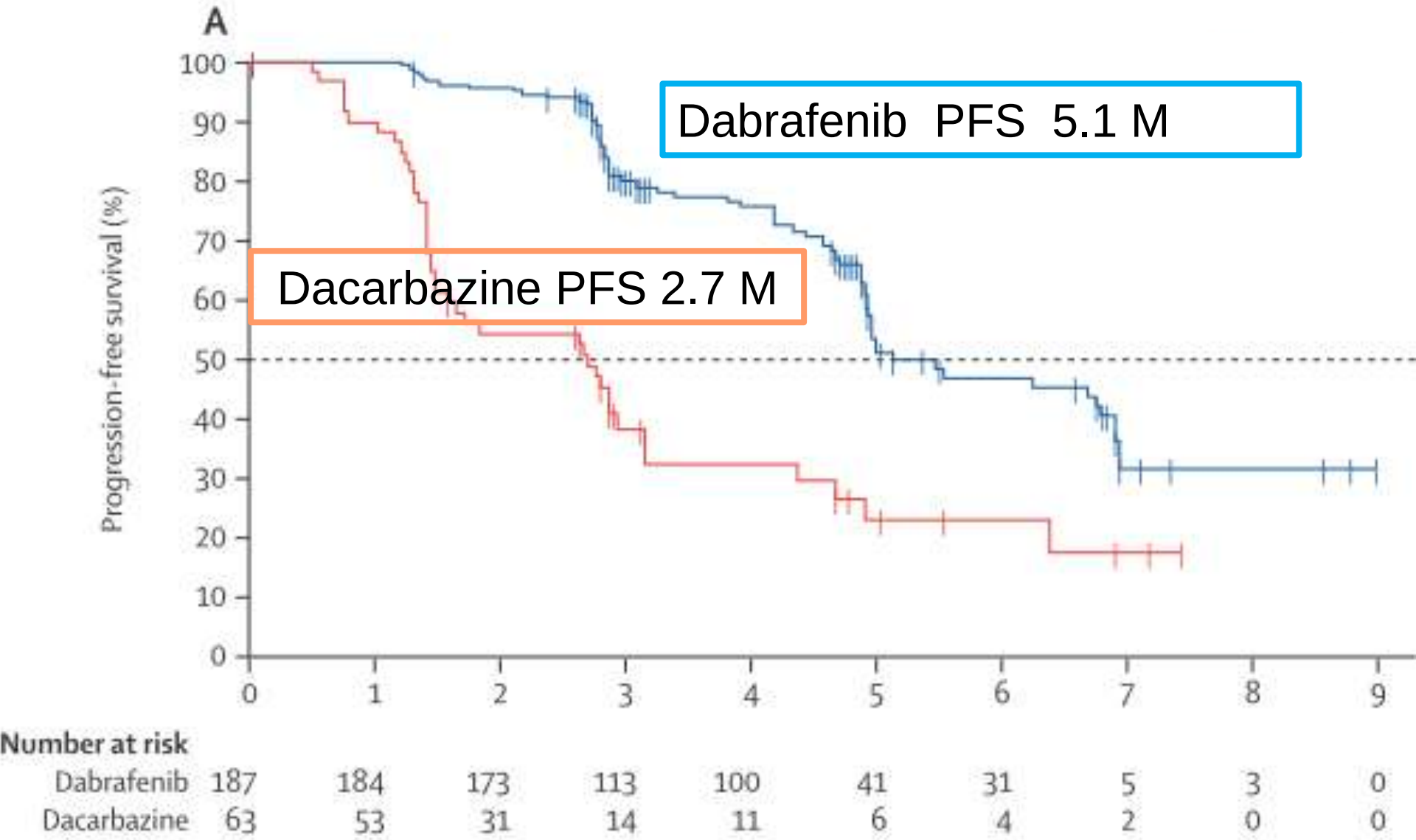
Raf Mutation V600E

RAF Inhibitor

Dabrafenib

Vemurafenib

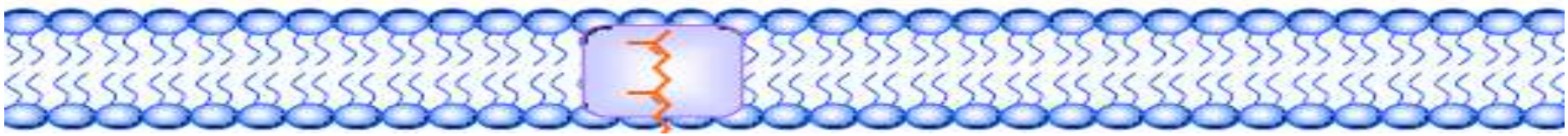
Progression Free Survival

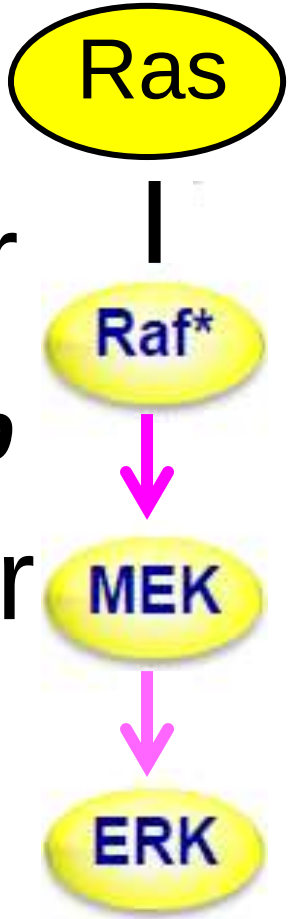


Hauschild A Lancet 380;358-365

However,
Melanoma become resistant to
Dabra/Vemurafenib
and recur

Inside the Cell





RAF Inhibitor
Dabrafenib
Vemurafenib

MEK Inhibitor
Trametinib

Melanoma

Raf Mutation V600E

Doubling Blocking of ***One*** Signal Pathway

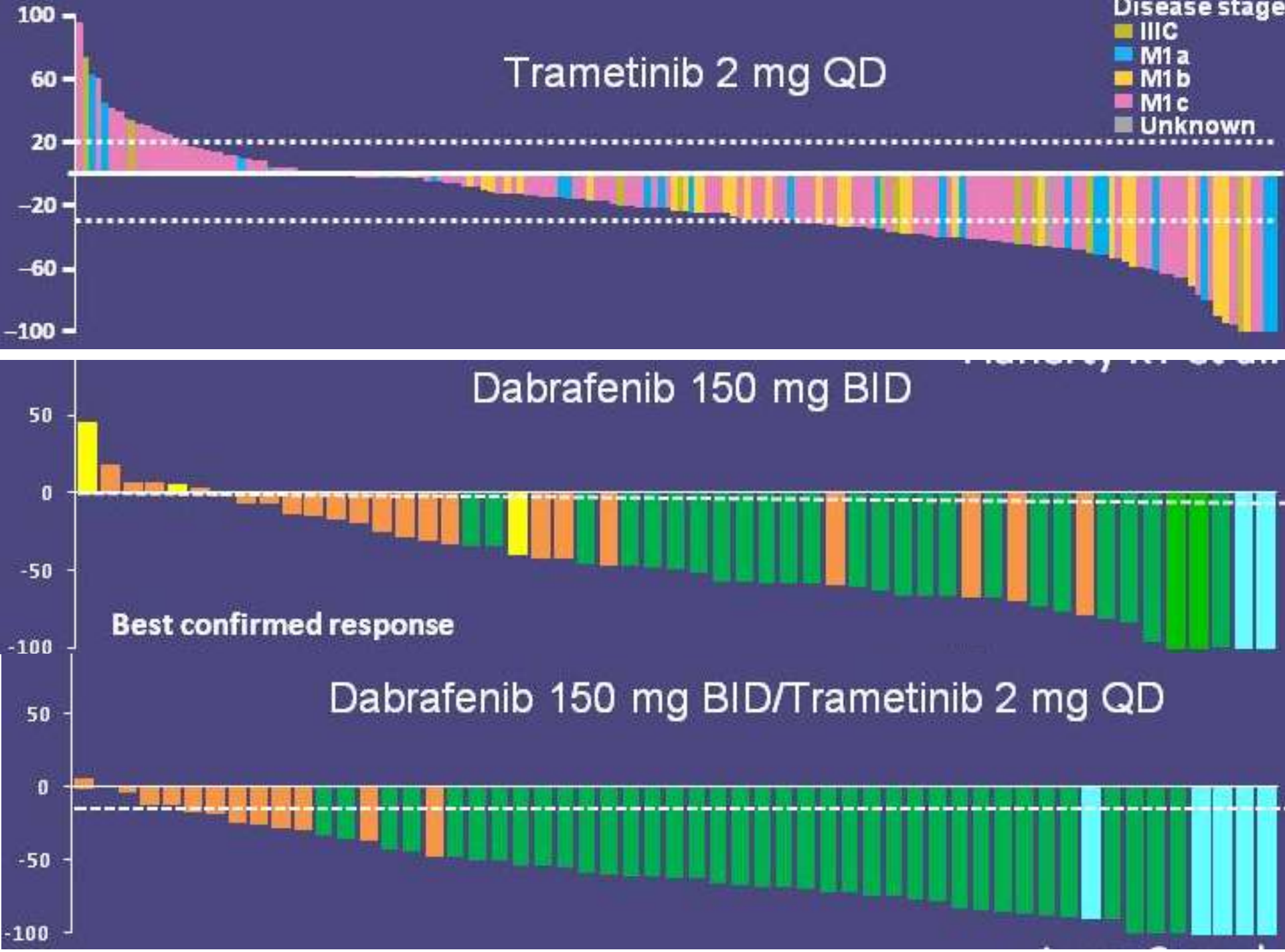
Switch Dabra/Vemura First then to Trametinib

Add-on Dabra/Vemura First then with Trametinib

Dual Dabra/Vemura start with Trametinib

How the Tumor Shrinks

Waterfall Plot


Trametinib 2 mg QD
Disease stage
IIIC
M1a
M1b
M1c
Unknown
100
60
20
-20
-60
-100
Dabrafenib 150 mg BID
50
0
-50
-100
Best confirmed response
Dabrafenib 150 mg BID/Trametinib 2 mg QD
50
0
-50
-100

A bit similar to that we saw in ***Lamivudine*** & ***Adefovir***

Switch *Lam* first then Switch to *Adefo*

Add-on *Lam* first then Add-on to *Adefo*

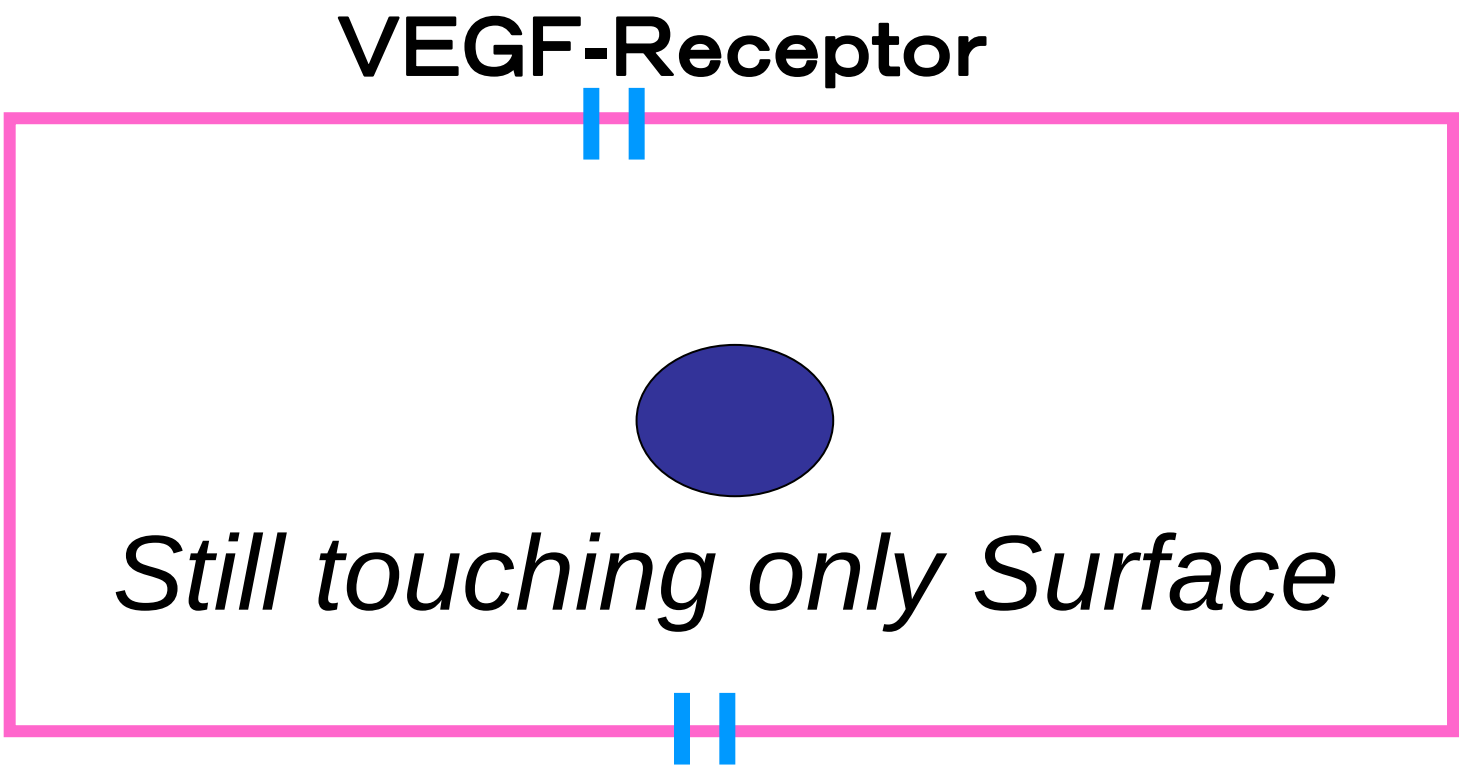
Dual from the Start

How about HCC ?

Are we deep inside ?

2012 ASCO One *Oral* Presentation

2013 ASCO No *Oral* Presentation



Tivantinib **c-Met** *Cabozantinib*

Change Paradigm

Signaling Pathway Blockers

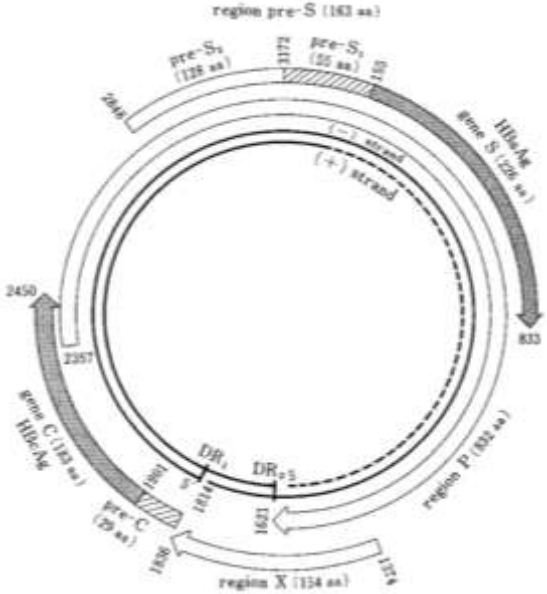
Any significant pathway worthwhile to be blocked In HCC ?

Genomics in HCC
a big step forward

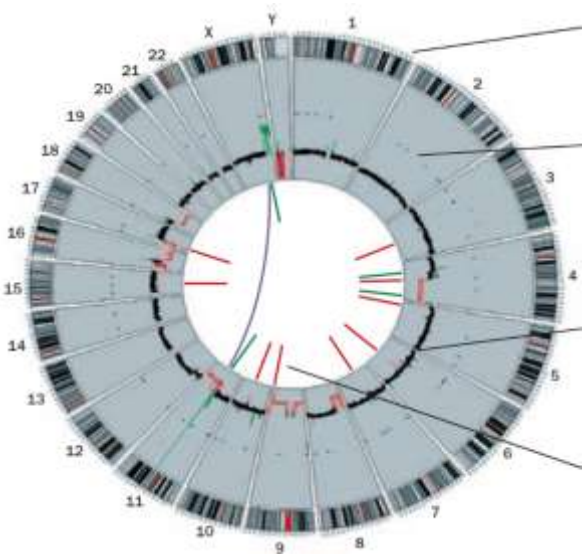
Tateishi R & Omata M ***Nature Rev GastroHepatol*** 2012;9:69-70

Whole Genome/Exon Sequencing

1979



2012

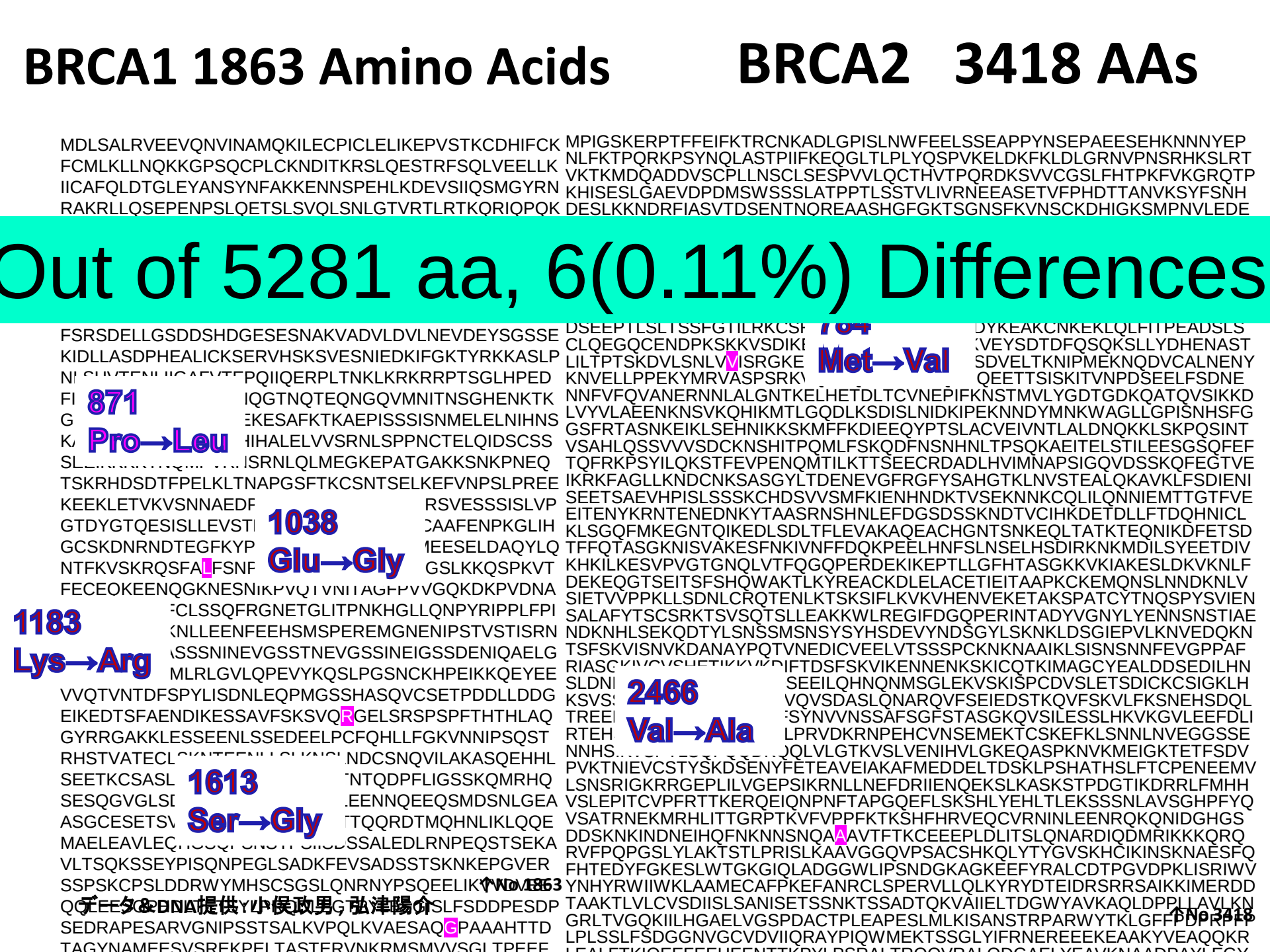


Ion Proton

3000*nt*

3,000,000,000nt

You can get
3 billion AGCT
In a day


BRCA1 1863 Amino Acids
BRCA2 3418 AAs
Out of 5281 aa, 6(0.11%) Differences
871
Pro→Leu
1038
Glu→Gly
1183
Lys→Arg
1613
Ser→Gly
2466
Val→Ala
784
Met→Val
↑No.1863
↑No.3418
データ&DNA提供：小俣政男，弘津陽介

Chimpanzee's BRCA Sequence

BRCA1 1863

MDLSALRVEEVQNVINAMQKILECPICLELIKEPVSTKCDHIFCK
FCMLKLLNQKKGPSQCPLCKNDITKRSLQESTRFSQLVEELLKII
CAFQLDTGLEYANSYNFAKKENNSPEHLKDEVSIIQSMGYRNR
AKRLLQSEPENPSLQETSLSVQLSNLGTVRTLRTKQRIQPQKT

PLCERKEWNKQKLPCSENPRDTEDVPWITLNSSIQKVNEWFS
RSDELLGSDDSHDGGSESNAKVADVLDVLNEVDEYSGSSKKI
DLLASDPHEALICKSERVHSKSVESNTEDKIFGKTYRRKASLPN
LSHVTENLIIGAFVTEPQIIQERPLTNKLKRKRRATSGLHPEDFIK
KADLAVQKTPEMINQGTNQMEQNGQVMNITNSGHENKTKGD
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IKKKKYNQMPVRHSRNLQLMEDKEPATGVKKSNKPNEQTSKR
HDSDTFPELKLTNAPGSFTNCSNTSELKEFVNPSLPREEKEEK
LETVKVSNNAEDPKDLMLSGERVLQTERSVESSSISLVPGTDY
GTQESISLLEVSTLGKAKTEPNKCVSQCAAFENPKGLIHGCSK
DTRNDTEGFKYPLGHEVNHSRETSIEMEESELDAQYLQNTFKV
SKRQSFALFSNPGNPEEECATFSAHCRSLKKQSPKVTFEREQ
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GSRFCLSSQFRGNETGLITPNKHGLLQNPYHIPPLFPIKSFVKT
KCKKNLLEENFEEHSMSPEREMGNENIPSTVSTISRNNIRENVF
KEASSSNINEVGSSTNEVGSSINEVGSSDENIQAELGRNRGPK
LNAMLRLGVLQPEVYKQSLPGSNCKHPEIKKQEYEEVVQTVNT
DFSPCLISDNLEQPMGSSHASQVCSETPDDLLDDGEIKEDTSF
AENDIKESSAVFSKSVQRGELSRSPSPFTHTHLAQGYRRGAKK
LESSEENLSSEDEELPCFQHLLFGKVSNIPSQSTRHSTVATECL
SKNTEENLLSLKNSLNDCSNQVILAKASQEHHLSEETKCSASLF
SSQCSELEDLTANTNTQDPFLIGSSKQMRHQSESQGVGLSDK
ELVSDDEERGTGLEENNQEEQSMDSNLGEAASGCESETSVSE
DCSGLSSQSDILTTQQRDTMQDNLIKLQQEMAELEAVLEQHGS
QPSNSYPSIISDSSALEDLQNPEQSTSEKAVLTSQKSSEYPISQ
NPEGLSADKFEVSADSSTSKNKEPGVERSSPSKCPSLDDRWY
MHSCSGSLQNRNYPSQEELIKVVDVEEQQLEESGPHDLTETS
YLPRQDLEGTPYLESGISLFSDDPESDPSEDKAPESAHVGNIPS
STSALKVPQLKVAESAQSPAAAHTTNTAGYNAMEESVSREKPE

BRCA2 3418

MPIGSKERPTFFEIFKTRCNKADLGPISLNWFEELSSEAPPYNSEPAEESEHKNNNYEPNLFKTP
QRKPSYNQLASTPIIFKEQGLTLPLYQSPVKELDKFKLDLGRNVPNSRHKSLCTVKTKMDQADDV
SCPLLNSCLSESPVVLQCTHVTPQRDKSVVCGSLFHTPKFVKGRQTPKHISESLGAEVDPDMSW
SSSLATPPTLSSTVLIVRNEEASETVFPHDTTANVKSYFSNHDESLKKNDRFIASVTDSENTNQRE

TNKHYAIHDETSYKGKKIPKDQKSELINCSAQFEANAFEAPLTFANADSGLLHSSVKRSCSQNDS
EEPTLSLTSSFGTILRKCSRNETCSNNTVISQDLDYKEAKCNKEKLQLFITPEADSLSCLQEGQCE
NDPKSKKVSDIKEEVLAAACHPVQHSKVEYSDTDFQSQKSLLYDHENASTLILTPTSKDVLSNLV
MISRGKESYKMSDKLKGNNYESDVELTKNIPMEKNQDVCALNENYKNVELLPPEKYMRVASPSR
KVQFNQNTNLRVIQNNQEETTSISKITVNPDSEELFSDNENNFVFQVANERNNLALGNTKELHET
DLTCVNEPIFKNSTMVLYGDTGDKQATQVSIKKDLVYVLAEENKNSVKQHIKMTLGQDLKSDISLN
IDKIPDKNNDYMDKWAGLLGPISNHSFGGSFRTASNKEIKLSEHNIKKSKMFFKDIEEQYPTSLAC
VEIVNTLALDNQKKLSKPQSINTVSAHLQSSVVVSDCKNSHITPQMLFSKQDFNSNHNLTPSQKA
EITELSTILEESGSQFEFTQFRKPSYILQKSTFEVPENQMTILKTISEECRDADLHVIMNAPSIGQVD
SSKQFEGTVEIKRKFAGLLKNDCNKSASGYLTDENEVGFRGFYSAHGTKLNVSTEALQKAVKLFS
DIENISEETSAEVHPISLSSSKCHDSVVSMFKIENHNDKTVSEKNNKCQLILQNNIEMTTGTSVEEI
TENYKRNTENEDNKYTASSRNSHNLEFDGSDSSKNDTVCIHKDETDLLFTDQHNICLKLSGQFM
KEGNTQIKEDLSDLTFLEVVKAQEACHGNTSNKEQLTATKTEQNIKDFETSDTFFQTASGKNISVA
KESFNKIVNFFDQKPEELHNFSLNSELHSDIRKNKMDILSYEETDIVKHKILKESVPVGTGNQLVTF
QGQPERDEKIKEPTLLGFHTASGKKVKIAKESLDKVKNLFDEKEQGTSEITSFSHQWAKTLKYRE
ACKDLELACETIEITTAPKCKEMQNSLNNDKNLVSIETVVPPKLLSDNLCRQTENLKTSKSIFLKVK
VHENVEKETAKSPATCYTNQSPYSVIENSALAFYTSCSRKTSVSQTSLLEAKKWLREGIFDGQPE
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LDSGIEPVLKNVEDQKNTSFSKVISNVKDANAYPQTINEDICVEELVTSSSPCKNKNAAIKLSISNS
NNFEVGPPAFRIASGKIVCVSHETIKKVKDIFTDSFSKVIKENNENKSKICQTKIMAGCYEALDDSE
DILHNSLDNDECSTHSHKVFADIQSEEILQHNQNMSGLEKVSKISPCDVSLETSDICKCSIGKLHKS
VSSTNTCGIFSTASGKSVQVSDASLQNARQVFSEIEDSTKQVFSKVLFKSNEHSDQLTREENTAI
RTPEHLISQKGFSYNVVNSSAFSGFSTASGKQVSILESSLHKVKGVLEEFDLIRTEHSLHYSPTSR
QNVSKILPRVDKRNPEHCVNSEMEKTCSKEFKLSNNLNVEGGSSENNHSIKVSPYLSQFQQDKQ
QLVLGTKVSLVENIHVLGKEQASPENVKMEIGKTETFSDVPVKTNIEVCSTYSKDSENYFETEAVE
IAKAFMEDDELTDSELPSHATHSLFTCPENEEMVLSNSRIGKRRGEPLILVGEPSIKRNLLNEFDRI
IENQEKSLKASKSTPDGTIKDRRLFMHHVSLEPITCVPFRTTKERQEIQNPNFTAPGQEFLSKSHL
YEHLTLEKSSSNLAVSGHPFYQVSATRNEKMRHLVTTGRPTKVFVPPFKTKSHFHRVEQCVRNI
NLEENRQKQNIDGHGSDDSKNKINDNEIHQFNKNNSNQAAAVTFTKCEEEPLDLITSLQNARDIQ
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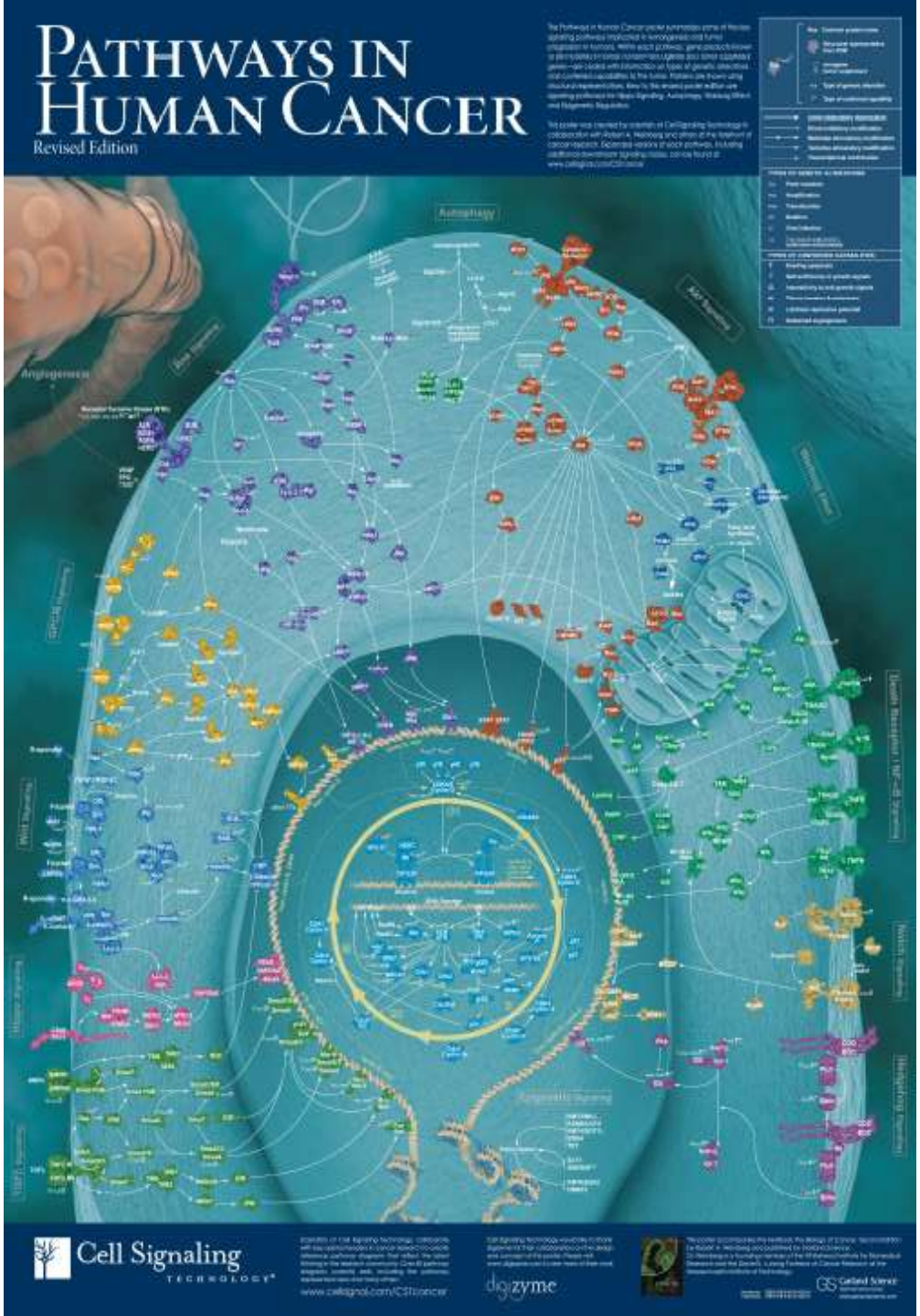
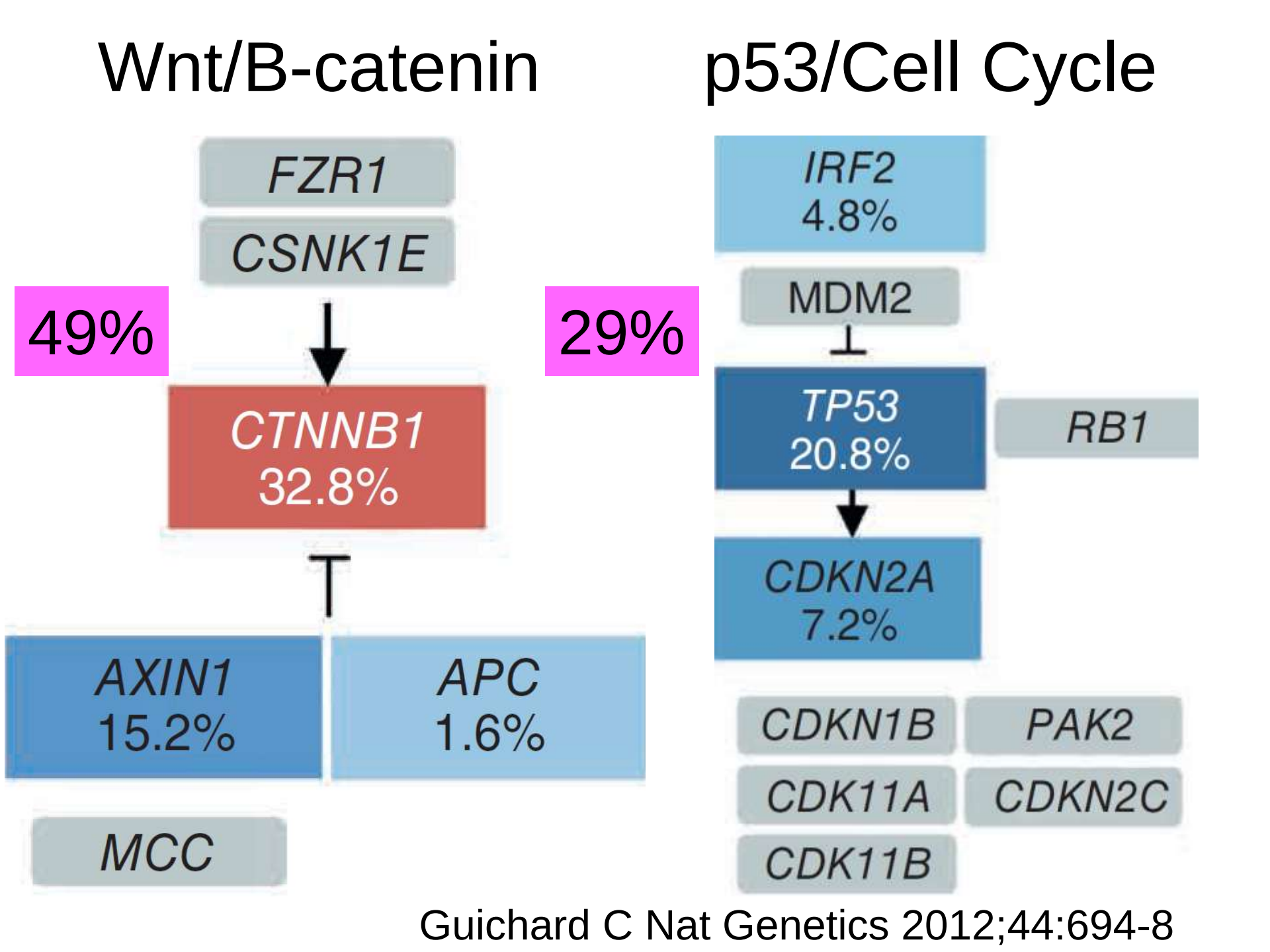
AESFQFHTEDYFGKESLWTGKGIQLADGGWLIPSNDGKAGKEEFYRALCDTPGVDPKLISRIWV
YNHYRWIIWKLAAMECAFPKEFANRCLSPERVLLQLKYRYDMEIDRSRRSAIKKIMERDDTAAKTL
VLCVSDIISLSANISETSSNKTSSADTQKVAIIELTDGWYAVKAQLDPPLLAVLKNGRLTVGQKIILH
GAELVGSPDACTPLEAPESLMLKISANSTRPARWYTKLGFFPDPRPFPLPLSSLFSDGGNVGCV



What to be disclosed ?

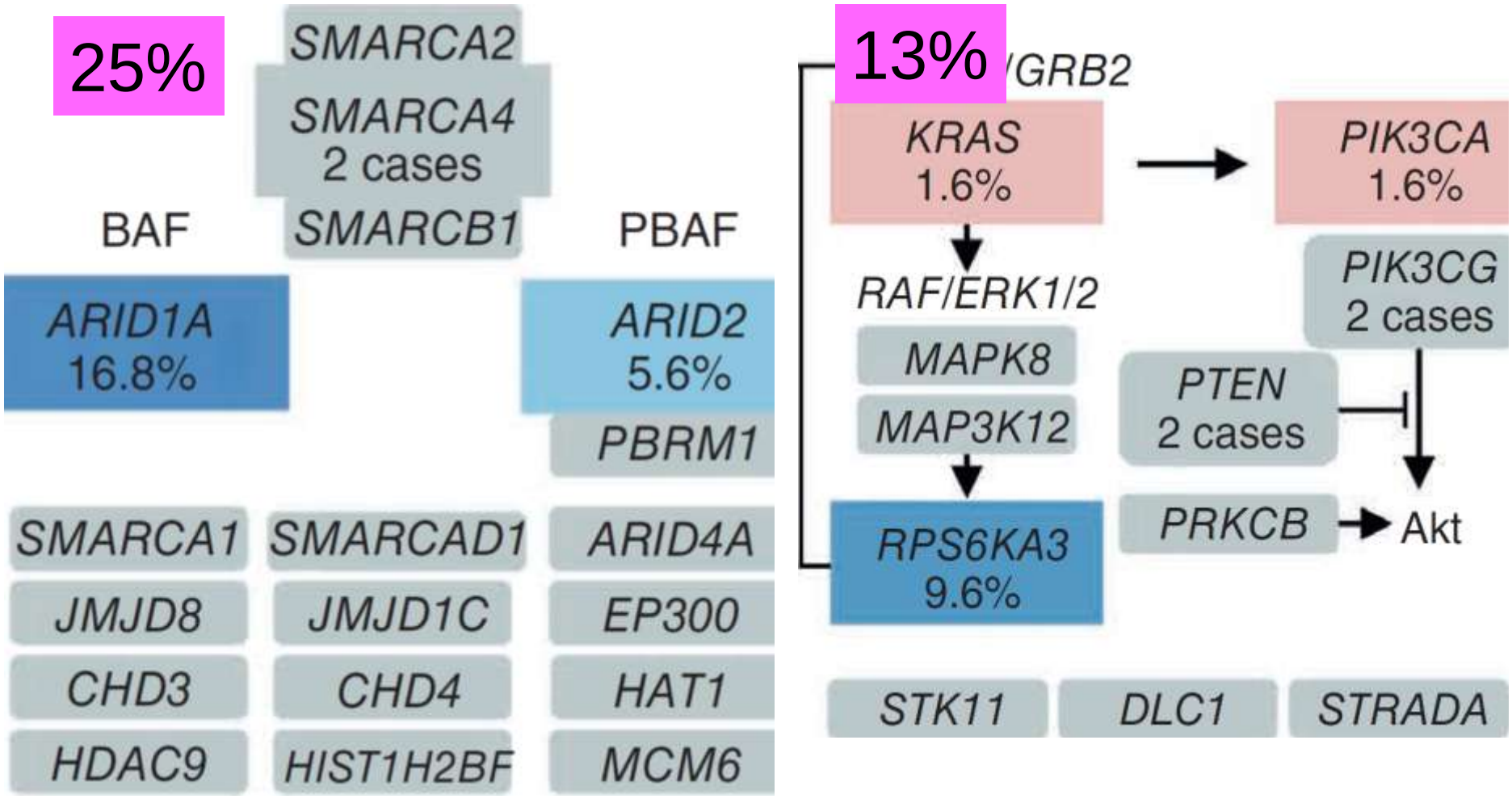
Roughly, ***12*** different, but major Pathways present



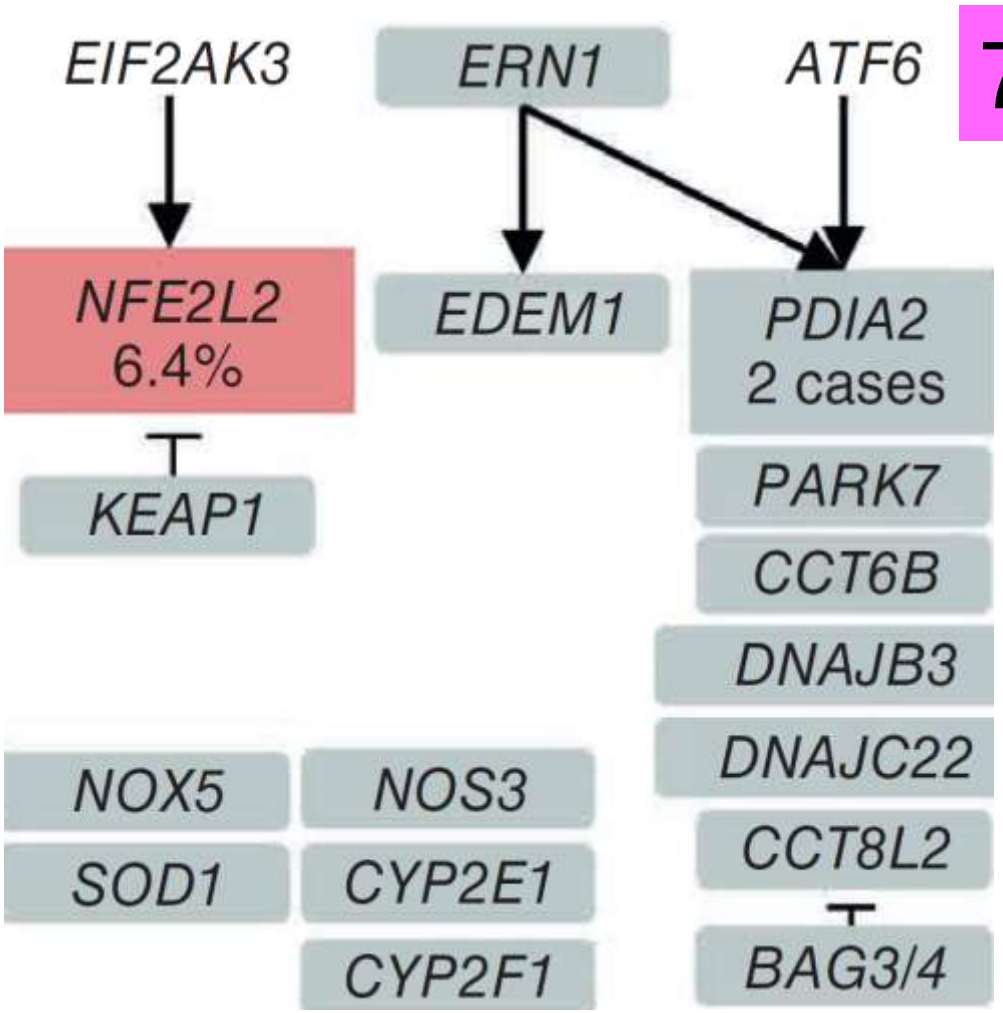
Guichard C Nat Genetics 2012;44:694-8

Chromatin Remodel

PI3K/Ras



Oxidative & ER Stress



We are now checking the ***Signature*** Mutations In everyday samples

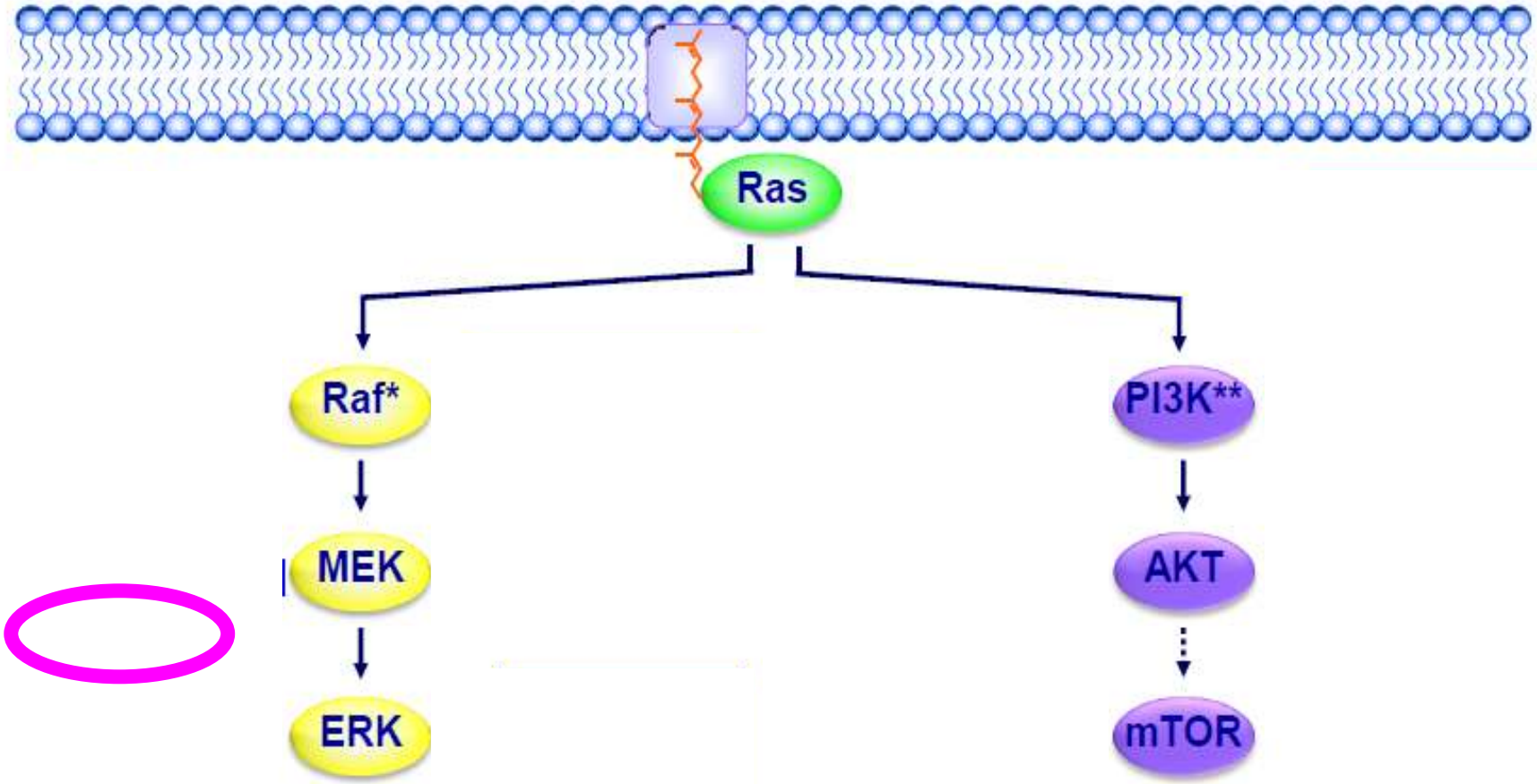
"Druggable" Mutations

P2

Sorafenib
&
MEK Inhibitor(RDEA119)

70 Asian Patients

Inhibitors of Ras effector signaling under clinical evaluation



P2

Sorafenib
&
MEK Inhibitor(RDEA119)

70 Asian Patients

Time to Progression	4.0 Months
Overall Survival	9.5 Months

3 Long-lasting Partial Responders

Ras Mutations

Higher Hopes !

However, patients dying every day

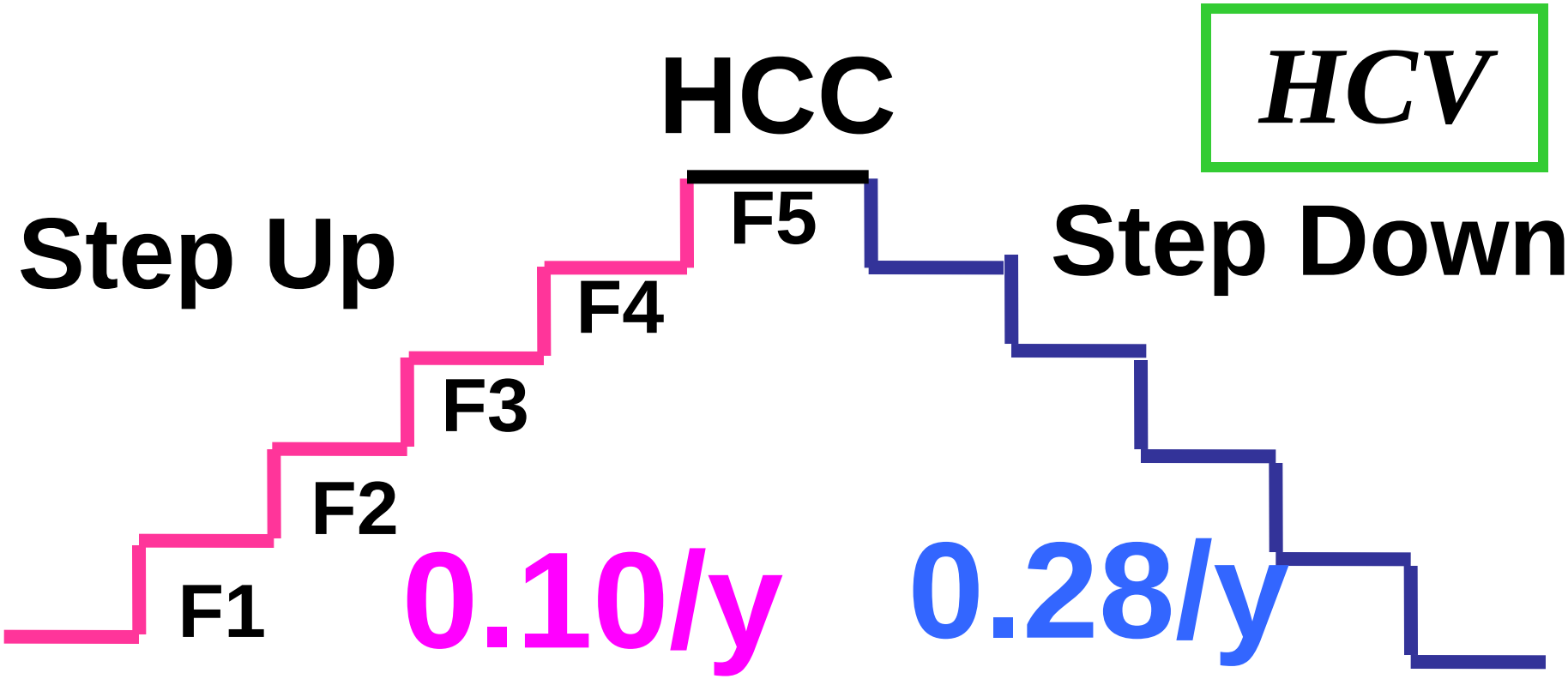
For the time being

Eradication of Virus

May even be a short cut

Because

If the virus eradciated ……



Fibrosis Progression Rate

Fibrosis Regression Rate

Annl Int Med 1999;131:174-181 *Annl Int Med 2000;132:517-524*

IHIT Study

Since 1994

Resolution in “Eradicated”

from	F4	(n=24)	- 0.283
from	F3	(n=45)	- 0.374
from	F2	(n=69)	- 0.284
from	F1	(n=42)	- 0.152

Ann Intern Med 1999 ; 131 : 174-181

Ann Intern Med 2000; 132 : 517-524

Gastroenterology 2002 ; 123 : 483-491

Ann Intern Med 2003; 138 : 299-306

Ann Intern Med 2005; 142 : 105-114

Even Advanced Fibrosis Could Be Resolved

Dose this resolution of fibrosis really prevent recurrence ?

The answer is

Yes

and

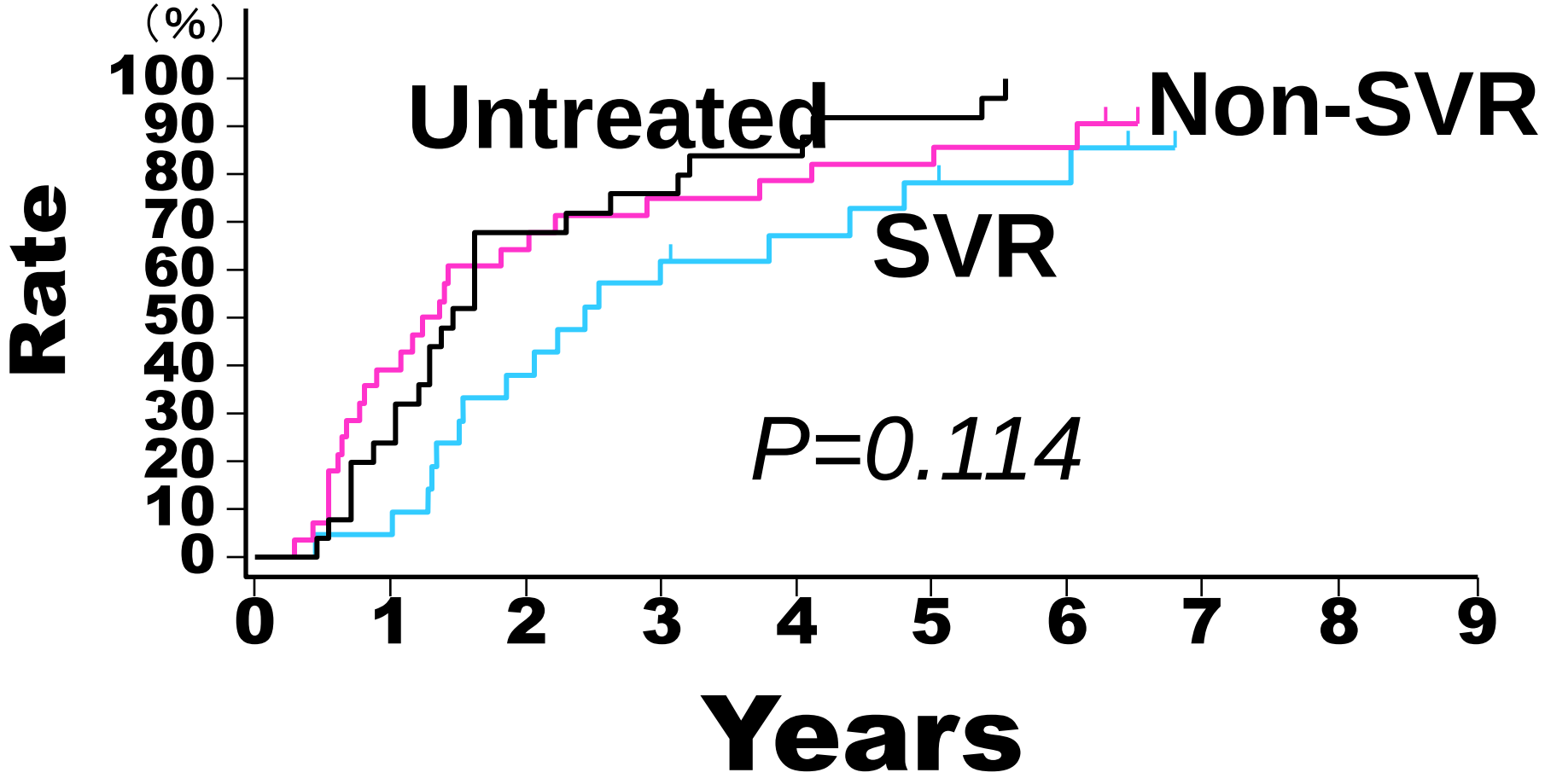
No

SVR

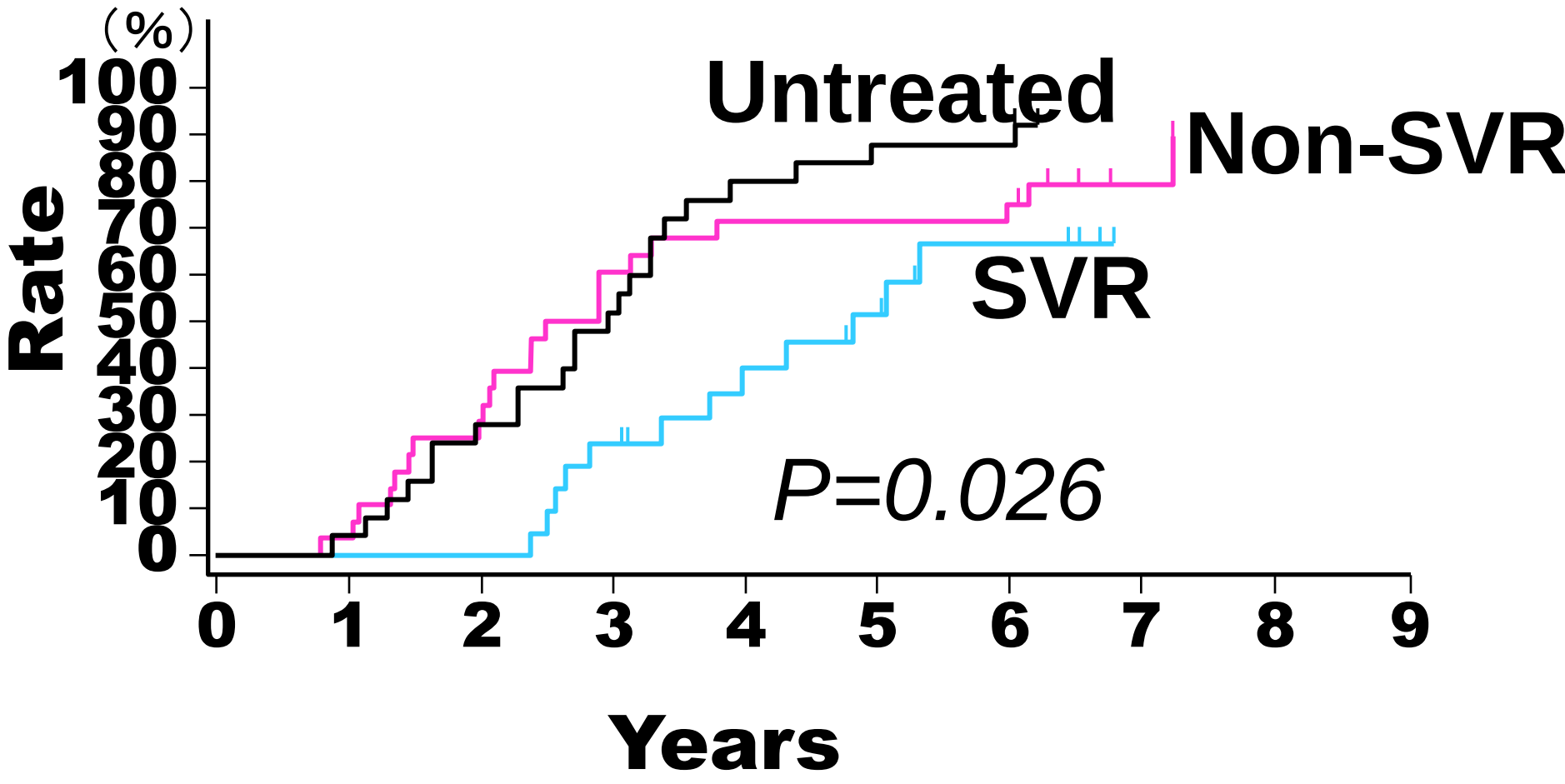
Sustained Virologica Response

Eradication

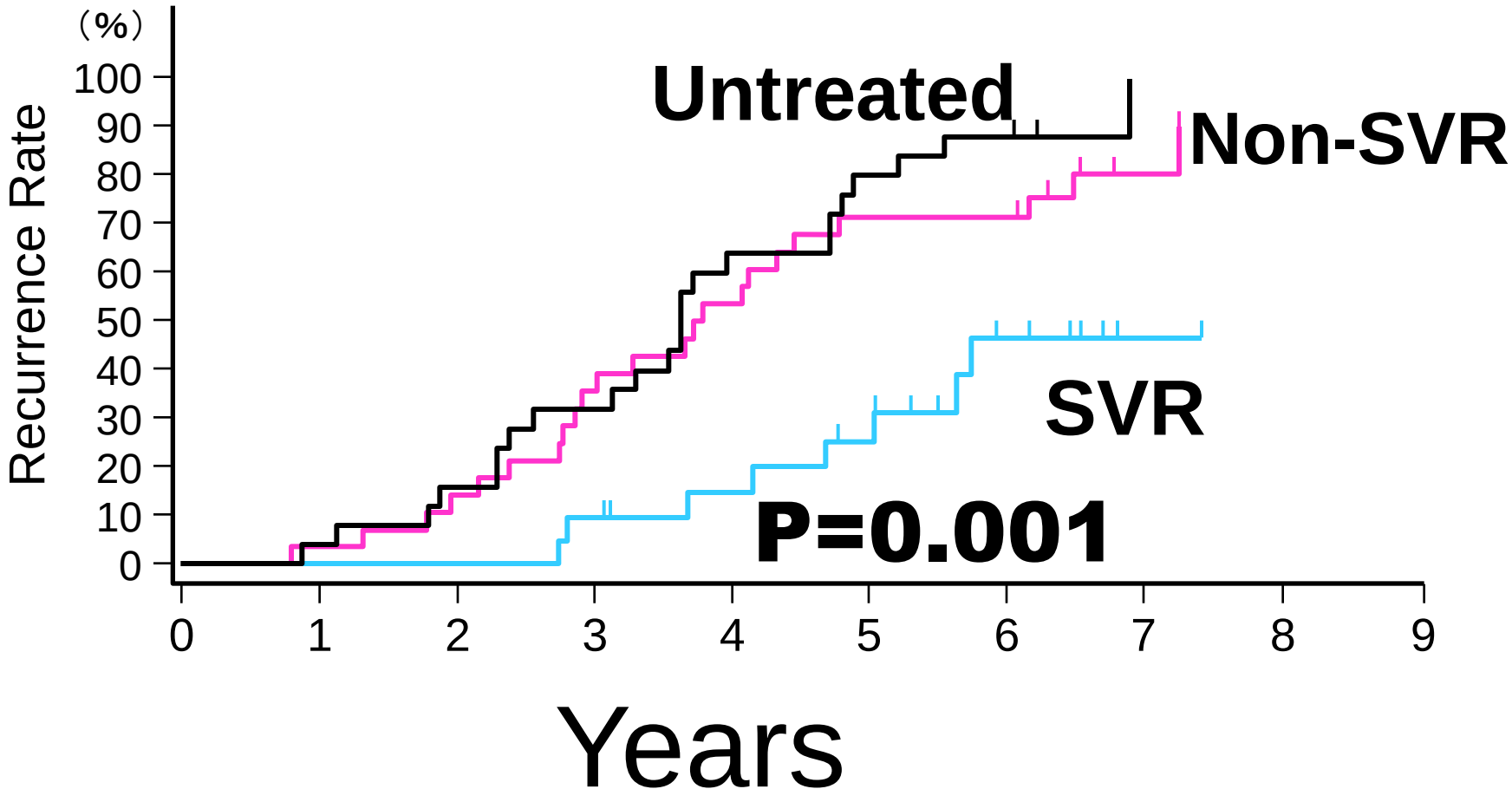
1st Recurrence

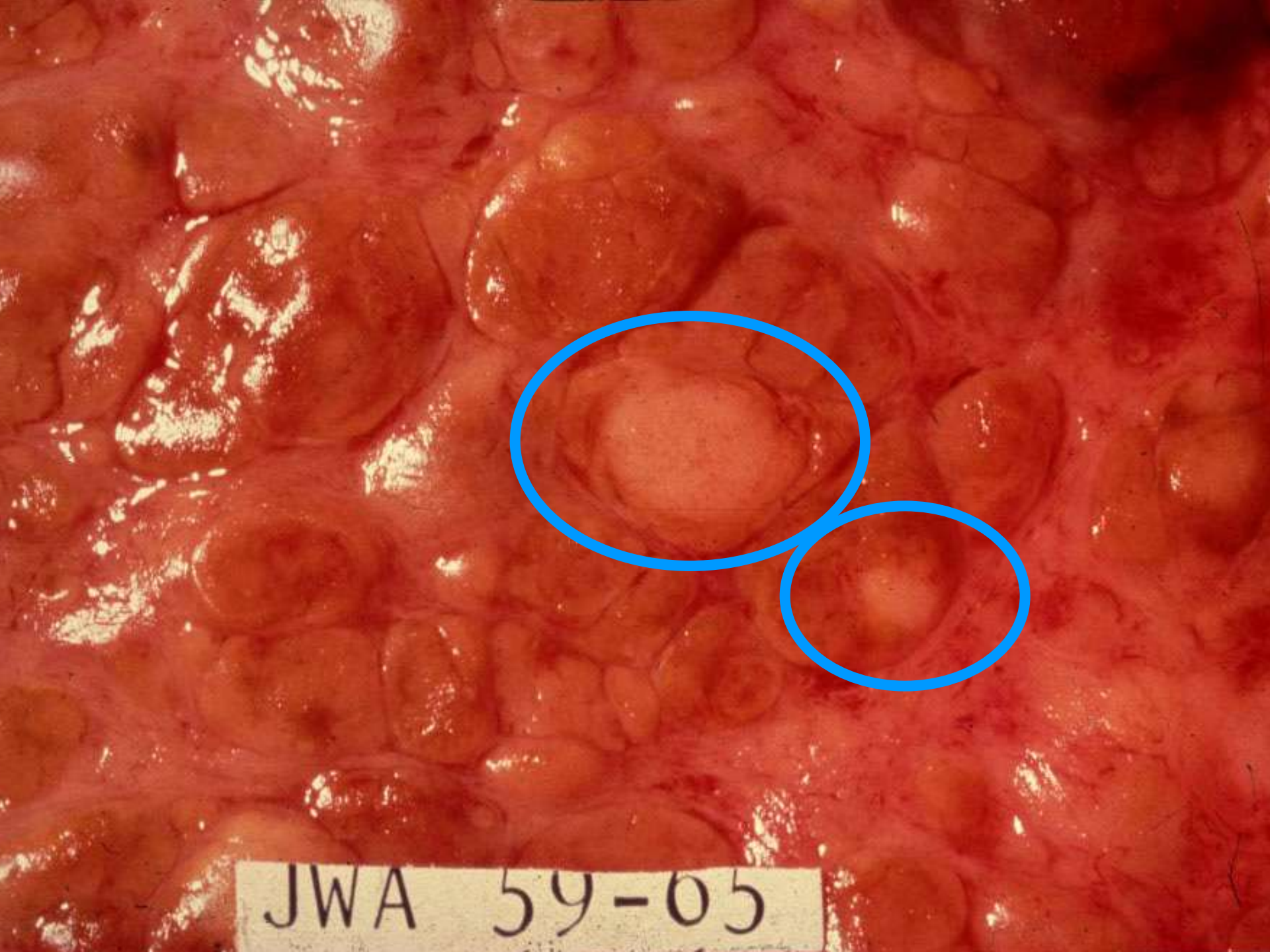


2nd Recurrence



3rd Recurrence




JWA 59-65

Eradication of HCV gradually Resolves Background Fibrosis and Decrease Multicentric Recurrence

5-year Survival (RFA/IFN)

21 SVRs	**83%**
22 n-SVRs	**50%**
31 Untreated	**45%**

5.3 yrs follow-up

Ann Int Med 2003;138:299-306

In Reality

From 1992 to 2006

We treated 1514 cases by RFA
But **only 112 (7.3%)** were treated by IFN/Riv
And 42 (2.8%) achieved SVR
The 42 case showed **5-year survival of 86%**

Limitations of Interferons

Paradigm
Changing
or
Changed

The Business of Antiviral Agents: Paying for Performance
Moderators: ADL Rosa, Pharmasset, USA
David Witzke, PioneerPath Capital, USA

Adam Cutler, Credit Suisse, USA
Rachel McMinn, Bank of America Merrill Lynch, USA
Geoffrey Meacham, JP Morgan Securities, Inc., USA
Vivek Ramaswamy, QVT Financial LP, USA
Katherine Xu, William Blair & Company, LLC, USA

PSI-7977 400 mg with PEG/RBV provides 93% SVR across HCV GT 1, 2, 3
Eric Lawitz, Alamo Medical Research, USA

Mark Sulkowski *(Johns Hopkins Univer*

Co-infections, Therapeutic Modalities
Marion Peters *(University of California,*
Jürgen Rockstroh *(University of Bonn,*
Ken Sherman *(University of Cincinnati*

Immunological Approaches, Vaccines
Frank Chisari *(The Scripps Research In*
T. Jake Liang *(NIDDK, National Institute*
Glenn Randall *(The University of Chica*

Liver Damage: Decompensation, Fi
Diagnostics
Ira Jacobson *(Weill Cornell Medical Co*
Brent Korba *(Georgetown University, U*
Masao Omata *(University of Tokyo, Yam*
Thierry Poynard *(Groupe Hospitalier Pi*

The Business of Antiviral Agents: Pay
Abel De La Rosa *(Moderator, Pharmass*
David Witzke *(Co-moderator, PioneerPa*
Rachel McMinn *(Bank of America Merr*
Geoffrey Meacham *(JP Morgan Securit*
Vivek Ramaswamy *(QVT Financial LP*

HEP DART™ 2011

frontiers in drug development for viral hepatitis

DECEMBER 4-8, 2011

GRAND HYATT KAUAI, KOLOA, HAWAII, USA

The New York Times

MERGERS & ACQUISITIONS | NOVEMBER 21, 2011, 8:05 AM | 2 Comments

Gilead to Buy Pharmasset for $11 Billion

一兆円

BY ANDREW POLLACK AND MICHAEL J. DE LA MERCED

2011/11/21

9:44 p.m. | Updated

Gilead Sciences made a bold move on Monday to capture the lead in developing the next generation of hepatitis C drugs, agreeing to pay $11 billion in cash for Pharmasset.

The treatment of hepatitis C has undergone a revolution this year, with new pills from Vertex Pharmaceuticals and Merck sharply increasing the cure rates and also often cutting the required duration of treatment. But those new drugs still must be used with alpha interferon, a type of drug injected once a week that can cause severe flulike symptoms and other side effects.

David Paul Morris/Bloomberg News

Test samples in a Gilead Sciences laboratory in Foster City, Calif.

Chain Terminator

NS 5b Inhibitor

Modified “Material” as a Drug

to Stop RNA *Elongation*

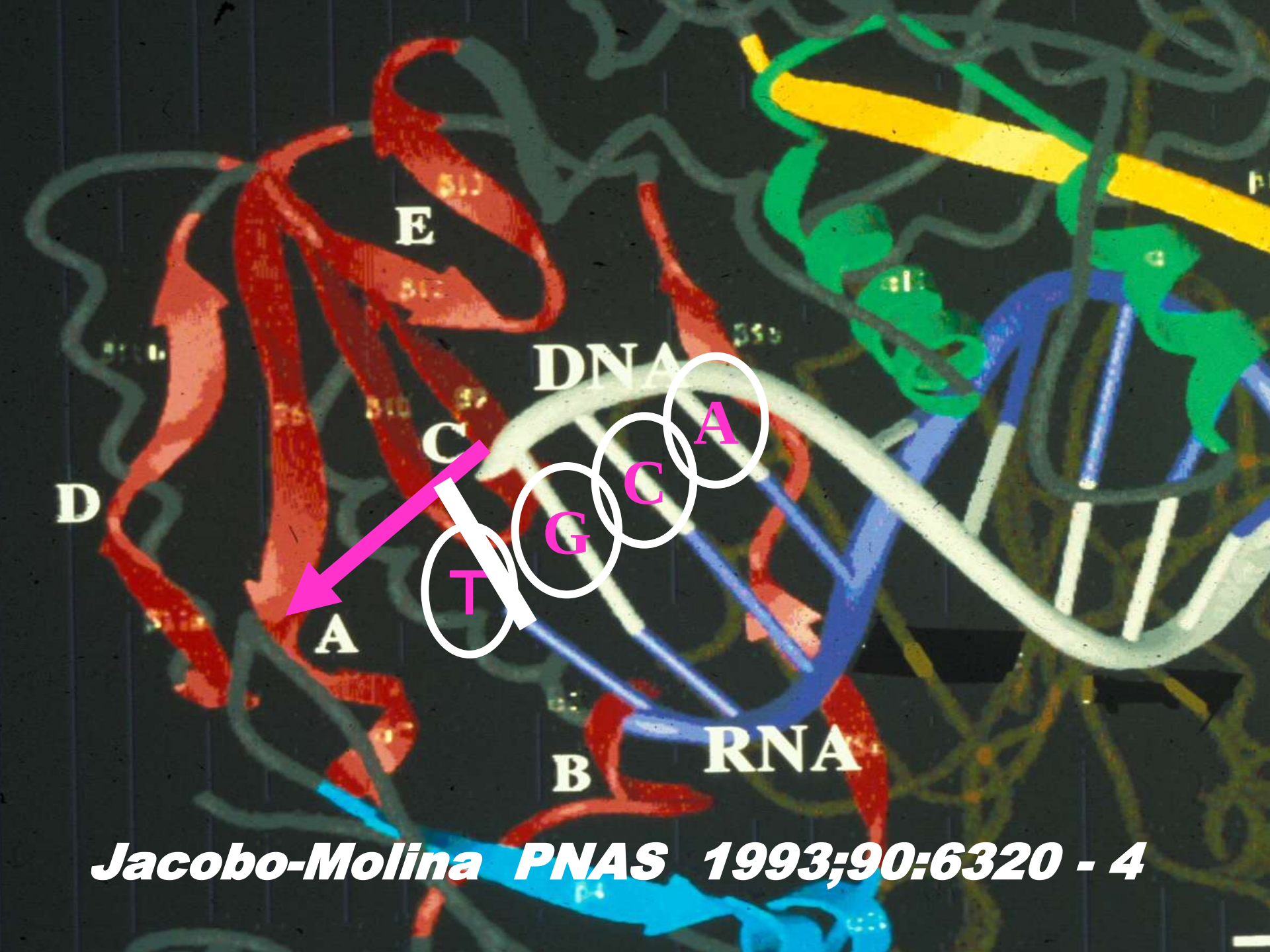
A Adenine

G Guanine

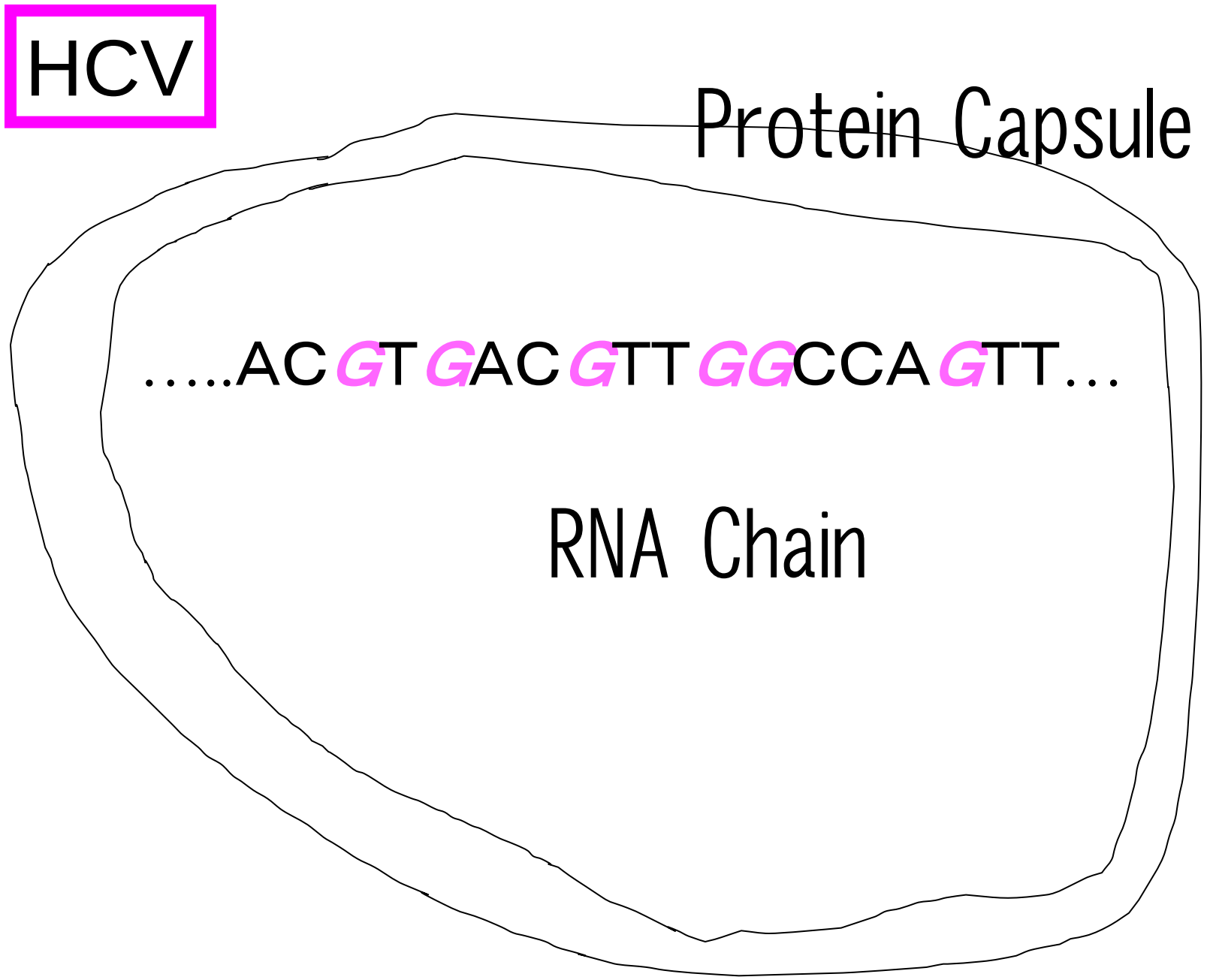
C Cytosine

U Uracil → **GS-7977**

Sofosbuvir SOF



Jacobo-Molina PNAS 1993;90:6320 - 4


HCV
Protein Capsule
.....ACGTGACGTTGGCCAGTTT...
RNA Chain

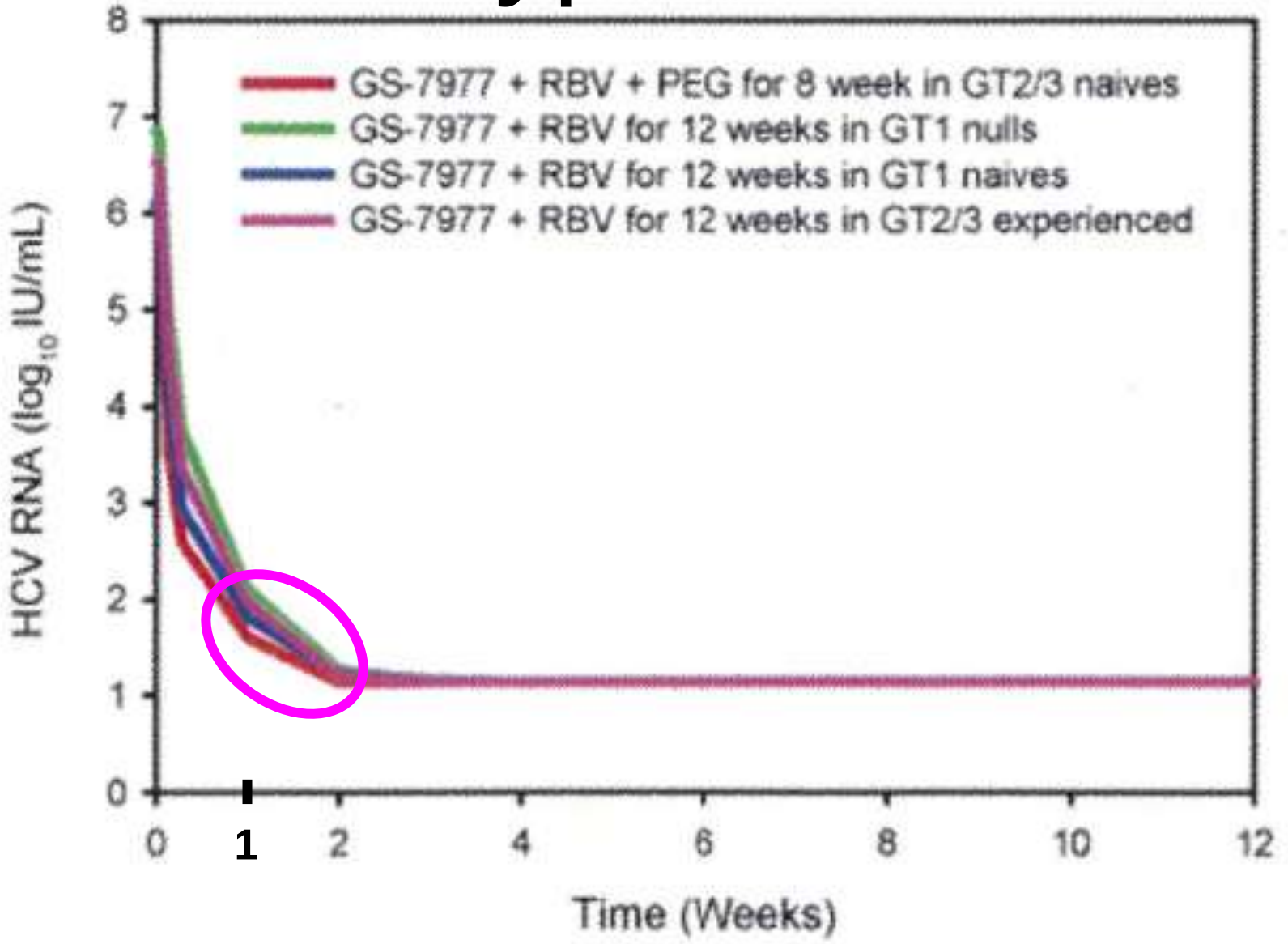
Other Drugs
Interaction to Protein Component

“Steric Hindrance”

‘Leaky’

Electron Study

Genotypes 1 - 3



How about my clinic ?

My Patients (n=300)

Age

Average	Median	Range
64	65	30-85

Over 65	Over 70	Over 75
50%	33%	14%

Sex (Ratio) M 123 (1.00) F 177 (1.44)

Genotypes

GT 1a	3	GT1b	198
GT 2	77	GT 3	0

SOF Update on GTs 2/3

GT 2/3 Studies

SOF+RBV

Press Release	G2	G3
2012/11/27		
POSITRON-12w(Unable, n=207)	**93%**	**61%**
2013/2/4		
FISSION-12w (TN, n=263)	**97%**	**56%**
2013/2/19		
FUSION-12w (TE, n=100)	**86%**	**30%**
2013/2/19日		
FUSION-16w(TE, n=95)	**94%**	**62%**

Japanese Trial

For GT-2 (TN,TE)

Phase III Sarted in Japan

No Age Limitation

Cirrhosis Included

For GT-1 (TN,TE)

Phase III Sarted in Japan

No Age Limitation

Cirrhosis Included

All Orals in Japan

Eradication in All ?

Viral Genotypes

GT 2	***SOF***
GT 1	***?***

“All Orals for GT 1”

	NS3	NS5a	NS5b (Non-Nuc)	NS5b (Nuc)
BMS	Asunaprevir	Daclatasvir		
Gilead			Ledipasvir	Sofosbuvir
BI	Faldaprevir		Deleobuvir	

Steric Hindrance Type

Chain Terminator Type

Mutation

RAV

(Resistant Associated Mutations)

Present in *Nature*

Y93H/Others **in NS5A**

NS5A Sequencing

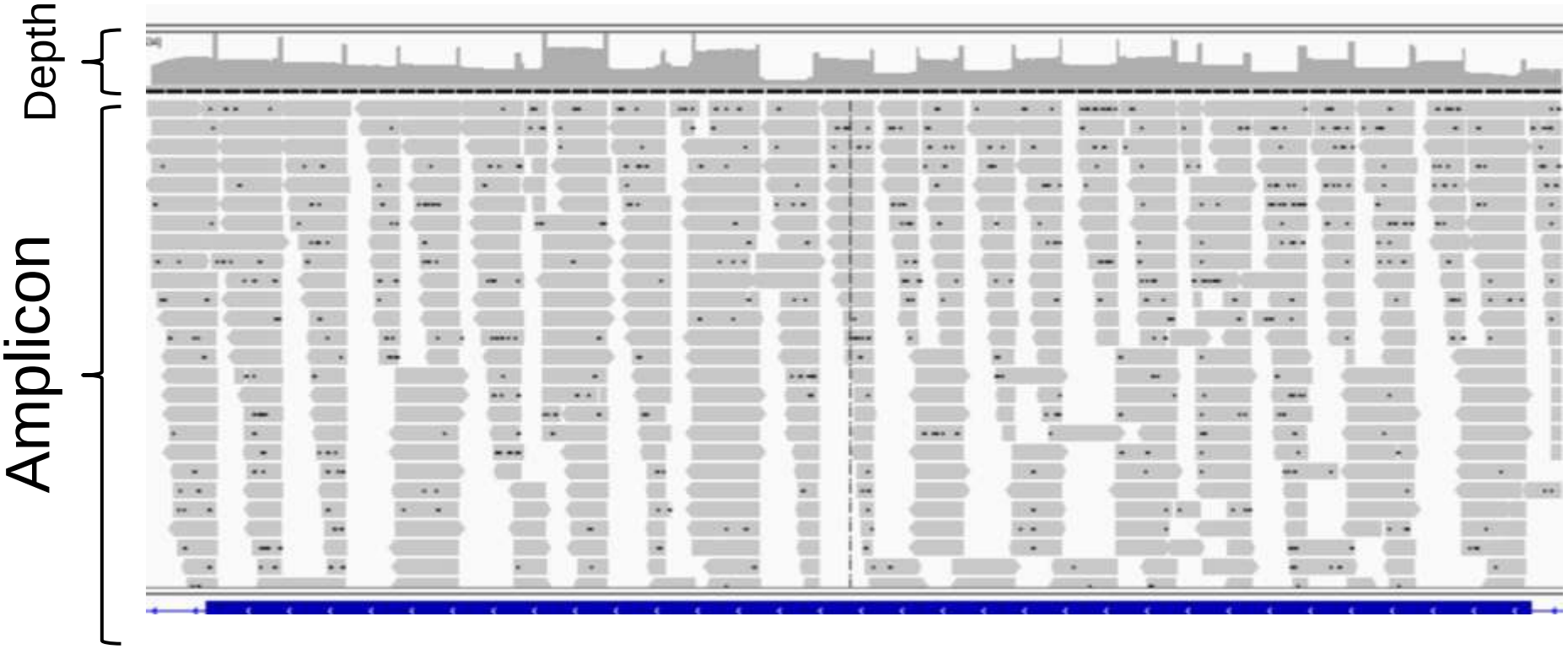
Sanger Method

NGS (Next Generation Seq)

200-3000 *Coverage*

NGS

Amplicon and Depth



NS5A RAVs in my 29 Japanese Patients (GT1b)

	Sanger Sequence	NGS
L28M	2/29 (6.9%)	3/29 (10.3%)
L28V	1/29 (3.4%)	1/29 (3.4%)
R30M	1/29 (3.4%)	1/29 (3.4%)
R30Q	1/29 (3.4%)	3/29 (10.3%)
R30E	0/29 (0%)	1/29 (3.4%)
R30H	0/29 (0%)	1/29 (3.4%)
R30H	0/29 (0%)	1/29 (3.4%)
R30L	0/29 (0%)	1/29 (3.4%)
R30P	0/29 (0%)	1/29 (3.4%)
L31V	0/29 (0%)	14/29 (48.3%)
L31W	0/29 (0%)	1/29 (3.4%)
L31F	0/29 (0%)	4/29 (13.8%)
P58S	1/29 (3.4%)	3/29 (10.3%)
P58R	0/29 (0%)	3/29 (10.3%)
P58Q	0/29 (0%)	4/29 (13.8%)
Y93H	3/29 (10.3%)	5/29 (17.2%)

“All Orals for GT 1”

	NS3	NS5a	NS5b (Non-Nuc)	NS5b (Nuc)
BMS	Asunaprevir	Daclatasvir		
Gilead		Ledipasvir		Sofosbuvir
BI	Faldaprevir		Deleobuvir	

Steric Hindrance Type

Chain Terminator Type

Partner's Ability may

enhance RAV replication

or

eradicate

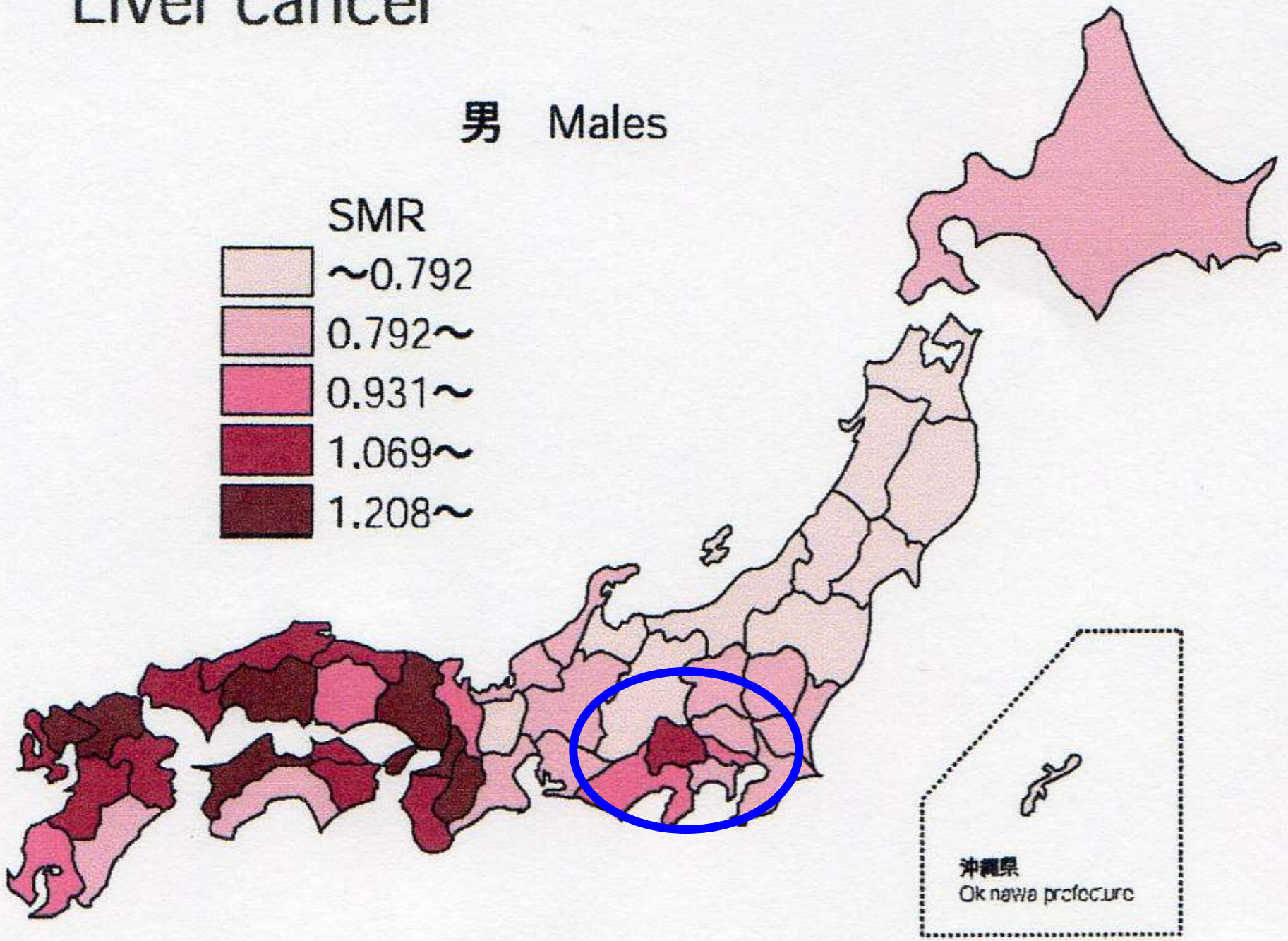
NS5A RAVs

Summary

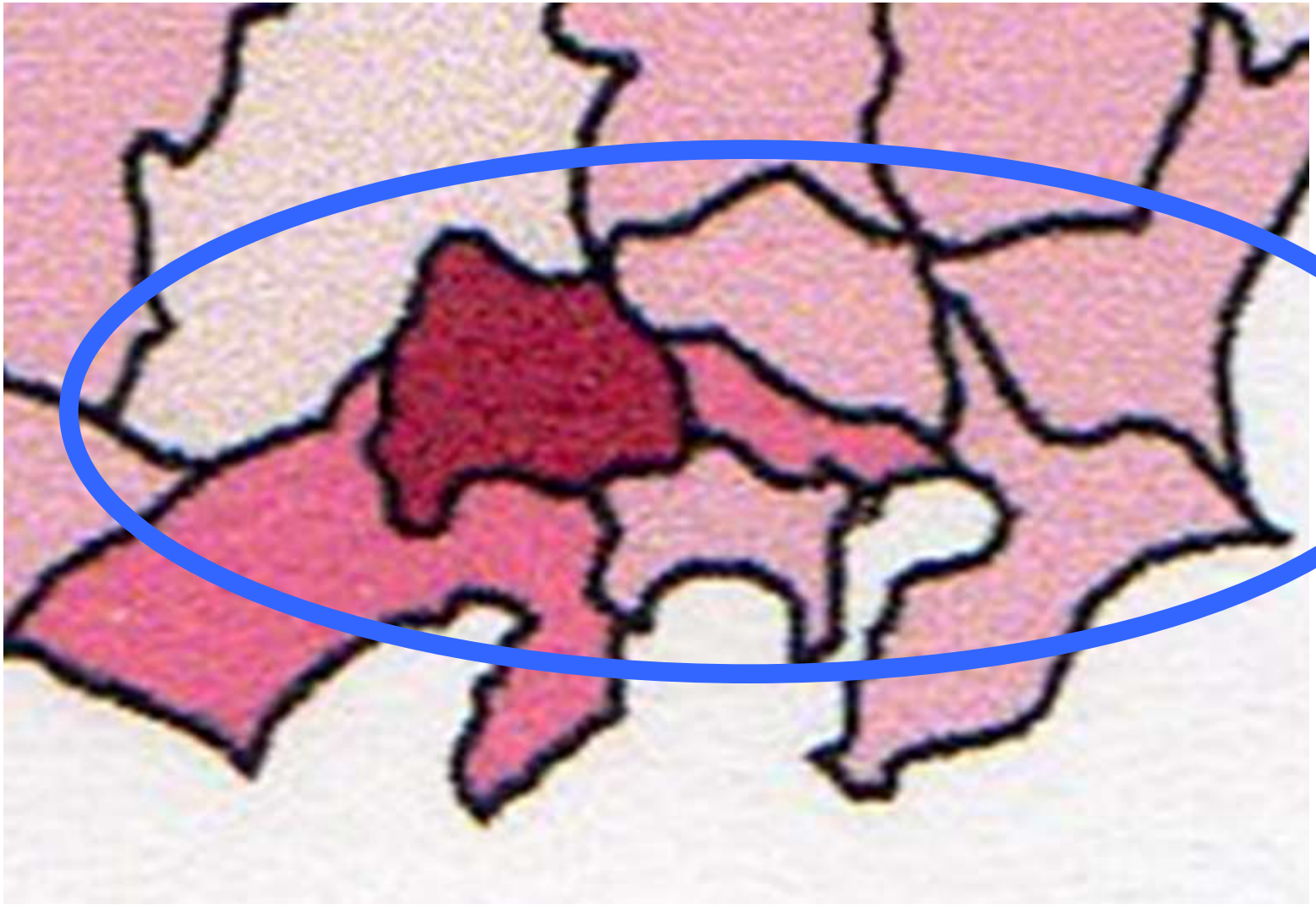
In HCV/HCC country

We have come so close to
5 yr survival of 80%
or
MST of 120 months

Liver cancer

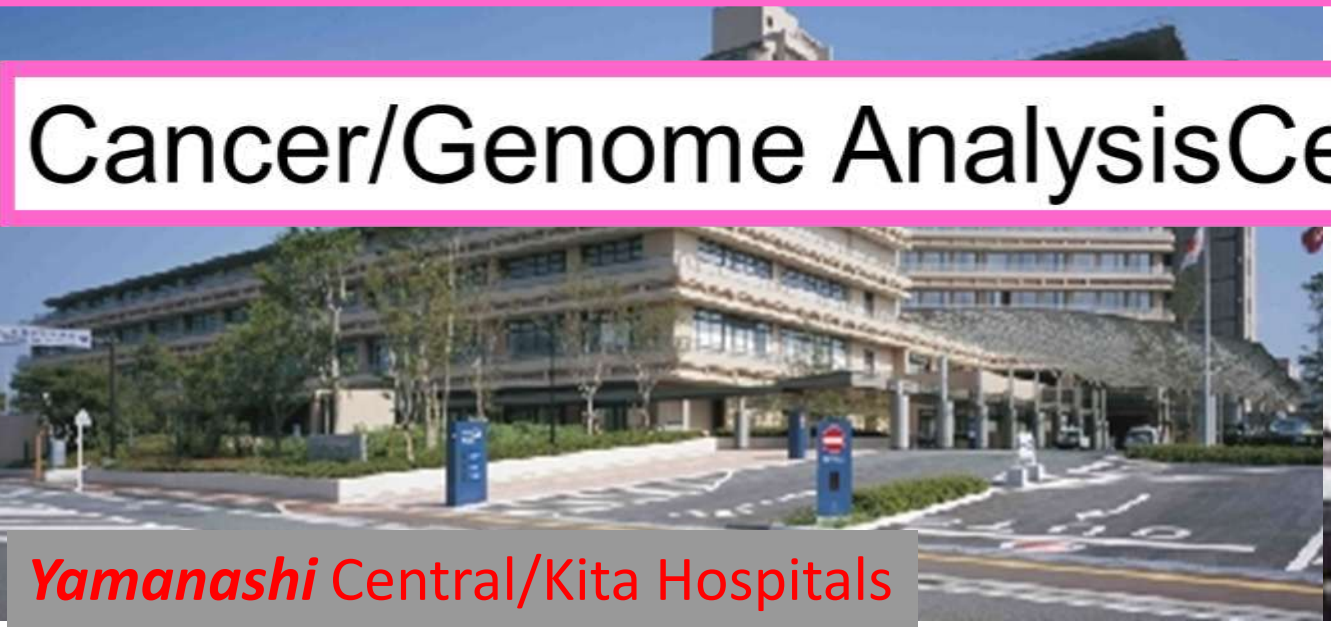


Kofu Tokyo Chiba



Cancer Center

Medical Center (Liver Unit)



Cancer/Genome AnalysisCenter

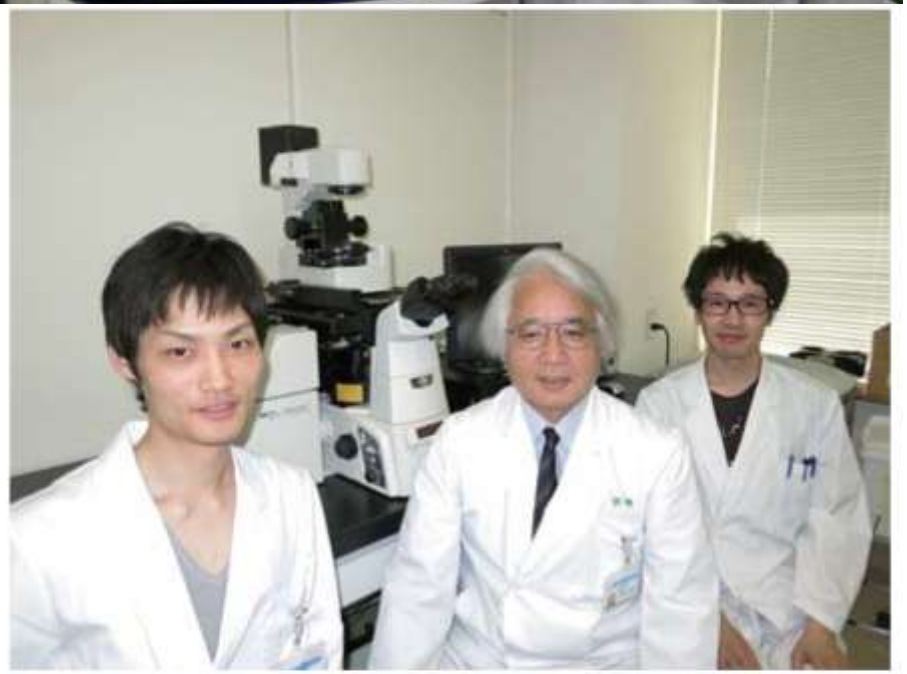
Yamanashi Central/Kita Hospitals

ArcturusXT Laser Capture Microdissection System

ViiA7 Realtime PCR System

BioAnalyzer 2000 (Agilent)

Ion OneTouch 2 S



山梨県立中央病院の
Applied Biosystems® Arcturus XT™ LCM システムの前で

Our Chopper for Flying Doctor

4月から山梨県内全域での運航が始まるドクターヘリ。県立中央病院のヘリポートから医師を乗せて現場へ駆け付ける

山梨日日新聞　2012年（平成24年）10月7日　日曜日

ドクターヘリ救命率97.7%

政府の比援助隊

医療団長に井上氏（県立中央病院医師）

「活動通し勇気与えたい」

台風30号で甚大な被害を受けたフィリピンで救援活動する日本の国際緊急援助隊医療チーム第2次隊の団長に、山梨県立中央病院の井上潤一医師(48)が選ばれ、20日、成田空港から現地に出発した。

日本の国際緊急援助隊医療チーム第2次隊の結団式であいさつする井上潤一医師（写真中央）＝成田空港（JICA提供）

井上医師は今年4月から同病院救命救急センターの主任医長、集中治療室科長として勤務している。チームを派遣する国際協力機構（JICA）によると、井上医師はこれまで国際緊急援助隊メンバーとして2003年のアルジェリア地震をはじめ、04年のスマトラ沖地震など3回の派遣に参加。国際的な災害援助について十分な経験と知識を持つことなどから、団長に選ばれたという。

2次隊は医師や看護師ら29人で構成。1次隊から業務を引き継ぎ、レイテ島タクロバンで医療活動を行うほか、西サマール州の病院の巡回も行う。約2週間活動し、12月3日に帰国する。

成田空港で行われた結団式で、井上医師は「私たちの活動が被災された方々を少しでも勇気づけ、前に進むための助けになればと思う。彼らが笑顔を取り戻せるよう努力したい」と意気込みを語った。

〈桑原久美子〉

Nov 21, 2013

Direct detection of *Mycobacterium tuberculosis* using polymerase chain reaction assay among patients with hepatic granuloma

J of Hepatology 1997;27:620-627

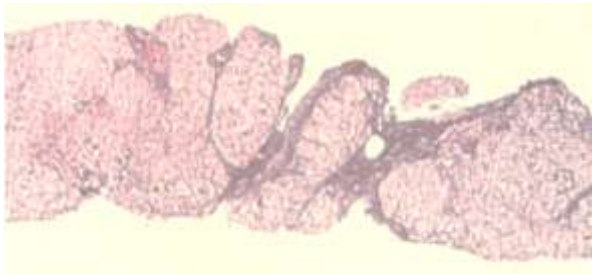
Diana E. Alcantara-Payawal, Masayuki Matsumura, Yasushi Shiratori, Takehito Okudaira, Roy Gonzalez, Roland A. Lopez, Jose D. Sollano, Masao Omata

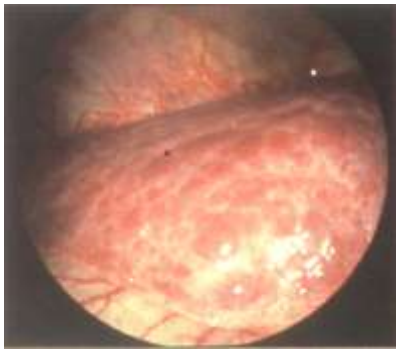
Correspondence: Diana Alcantara-Payawal, MD, D of Internal Medicine (II), University of Tokyo, 7-3-1 Hongo, Bungkyo-ku, Tokyo, Japan, 113.
Section of Gastroenterology, D of Medicine, University of Santo Tomas, Espana St., Manila, Philippines

Freed from Disease

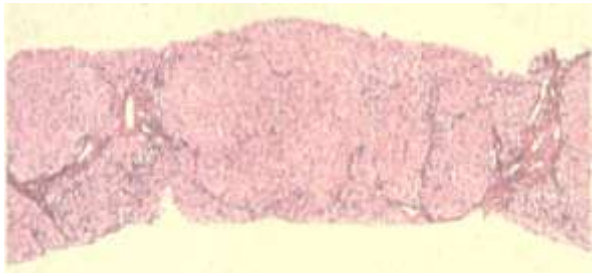
Time from Eradication

0 year





2nd year



4th year

When I graduated medical school 43 years ago, liver disease was the one impossible to treat, but now able to envision to how to cure all.

Congratulation !!!

Wonderful and Successful APASL the 3rd HCC and the 12th STC