I NUOVI TRATTAMENTI PER L'EPATITE C NELL'ANZIANO: PROSPETTIVE E SOSTENIBILITA'

SIGG, Napoli 2015

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And
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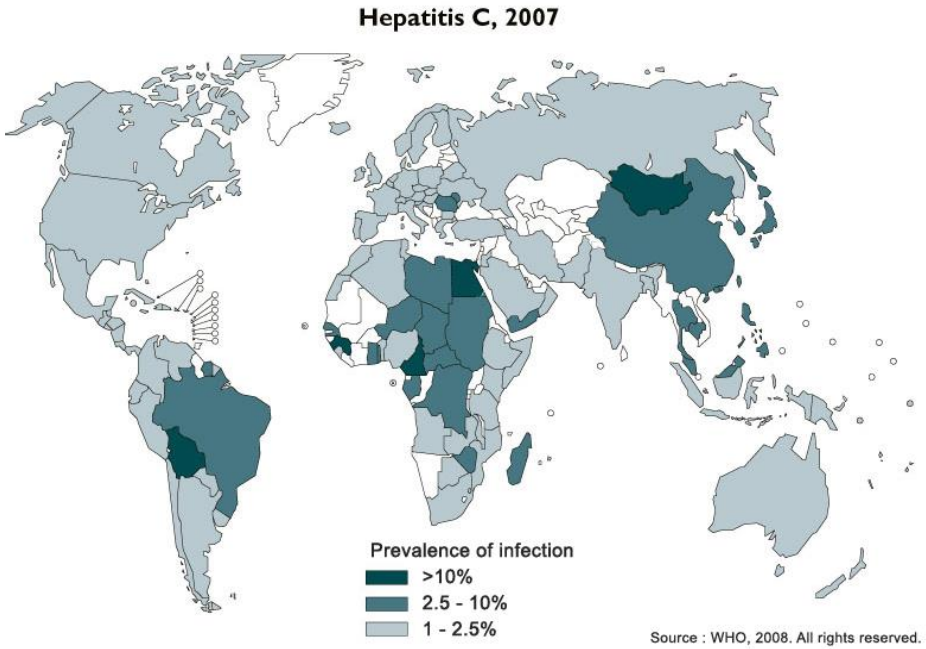
Hepatitis C in the Elderly: Facts

1. Chronic Hepatitis C is a higly frequent progressive disease leading to HCC and ESLD

Hepatitis C: the global burden

About **170M infected** world-wide



Incidence is decreasing in Western Countries

<u>But</u>

Prevalence of advanced disease is becoming higher!

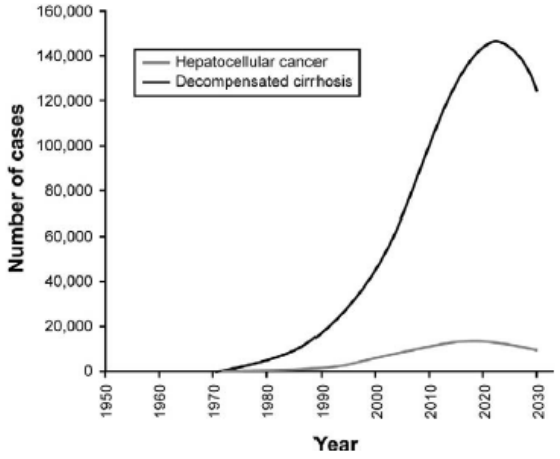
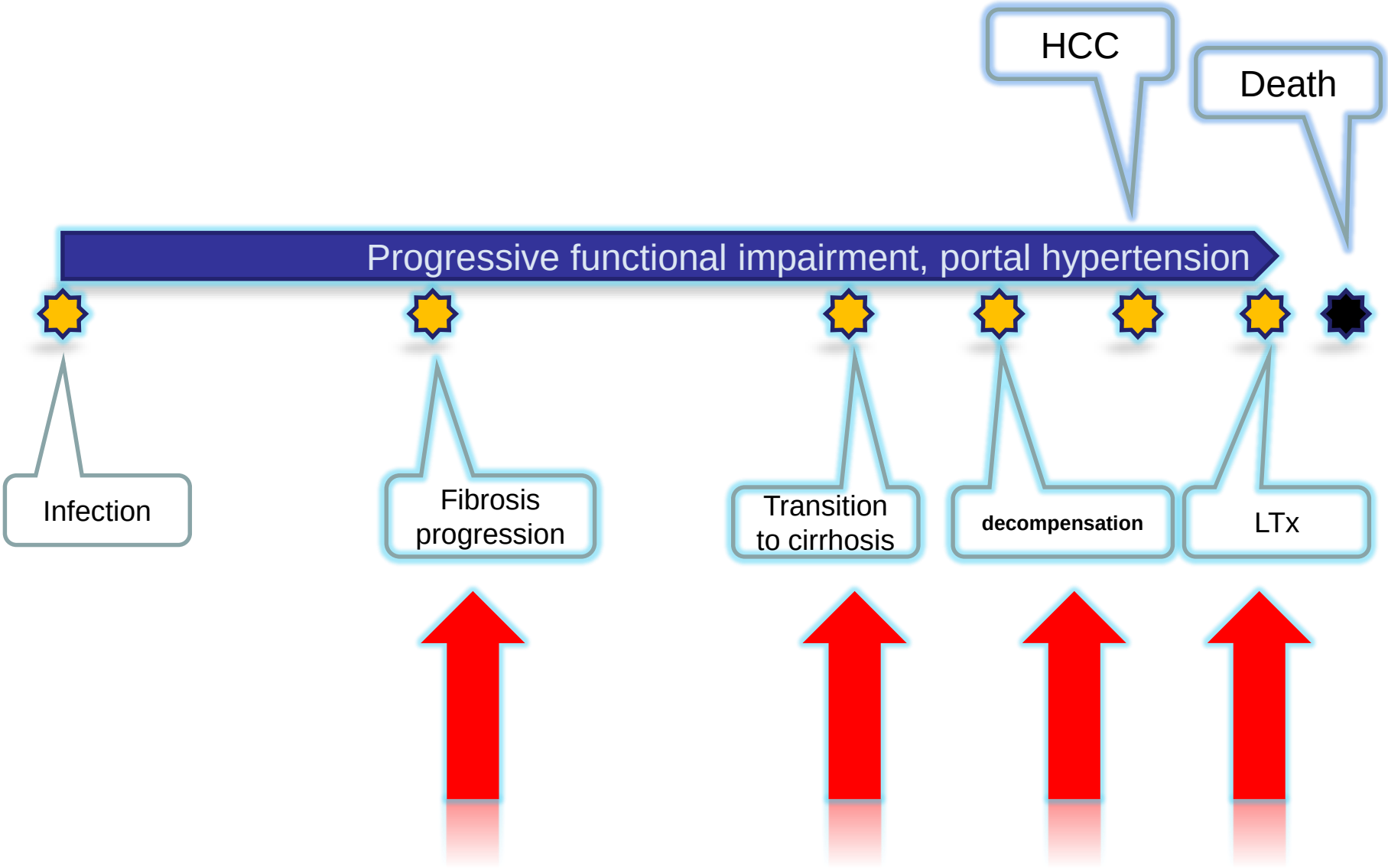


Figure 4. Projected number of cases by year of decompensated cirrhosis (*black*) and hepatocellular carcinoma (*gray*). The model assumes a first year mortality of 80% to 85%, so in contrast to the decompensated cirrhosis projection, the number of cases of hepatocellular carcinoma the prevalence demonstrated here closely resembles annual incidence of liver cancer.

1.Chronic Hepatitis C is a progressive disease leading to HCC and ESLD



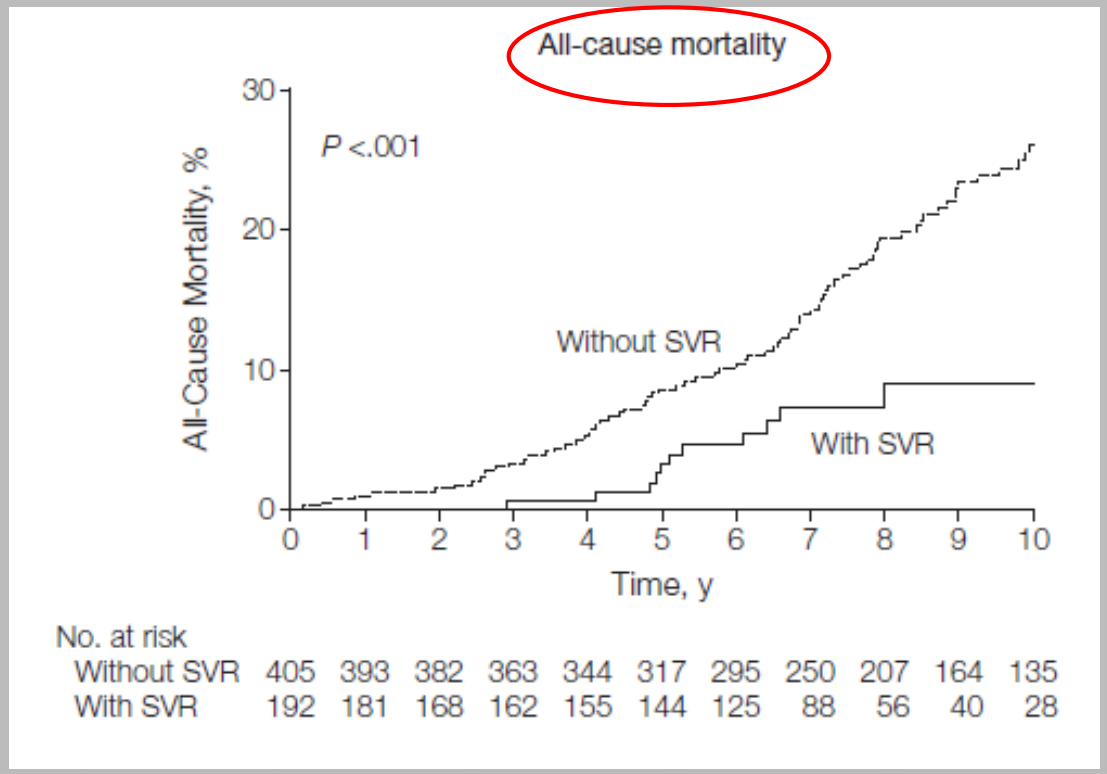
Goals of Antiviral Therapy

Changes according to Stage

Hepatitis with fibrosis →	**avoid fibrosis progression**
Advanced fibrosis →	**avoid progression to cirrhosis**
Cirrhosis →	**avoid complications, failure, HCC**
Decompensated cirrhosis →	**reduce mortality and need for LTX**
Wait list patients →	**reduce post-LTx recurrence**
Transplanted →	**avoid post-LTx HCV-related disease, incl. Re-LTx and severe cholestatic form**

Is viral eradication effective?

Multicenter EU and Canada Study: Outcome of Interferon Therapy in Patients with Advanced HCV



Van der Meer JAMA 2012;308:2584-93

Hepatitis C in the Elderly: Facts

1.Chronic Hepatitis C is a progressive disease leading to HCC and ESLD

2.Prevalence of HCV infection is higher in elderly population

Baldo V, Gerontology 2000;

Monica F, J Viral Hepat 1998;

Sawabe M, Liver 1999;

Mazzeo C, Gut 2003

Hepatitis C in the Elderly

2.Prevalence of HCV infection is higher in elderly population

This is certainly true for Italy, Spain, France, Taiwan and Japan (population studies available)

- Mean prevalence in Italy general population **<2%**
- Prevalence in people >65 years old: **2% - 25%**

Guadagnino, Hepatology 1997
Baldo V, Gerontology 2000;
Monica F, J Viral Hepat 1998;
Mazzeo C, Gut 2003

In EU no mandatory screening in baby boomers

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   Thabut D, Am J Gastroenterol 2006

Hepatitis C in the Elderly

3.Prevalence of HCV infection is higher in elderly population

Characteristics	<65 years (n = 386)	≥65 years (n = 174)	P
HCV awareness (%)	279 (72)	96 (55)	<0.0001
Diagnosis			
Chronic hepatitis (%)	284 (74)	86 (49)	0.000
Liver cirrhosis (%)	84 (22)	67 (39)	0.000
Hepatocellular carcinoma (%)	18 (5)	21 (12)	0.000
Mode of diagnosis			
Histological (%)	137 (35)	34 (20)	0.000
Clinical (%)	249 (65)	140 (80)	
Normal ALT (%)	133 (34)	58 (33)	ns
Asymptomatic patients (%)	362 (94)	149 (86)	0.002
Complication as initial manifestation (%)	6 (2)	9 (5)	0.02
Presence of comorbid conditions (%)	267 (69)	148 (85)	<0.0001
Main comorbid conditions			
Cardiovascular diseases (%)	27 (7)	30 (17)	0.0002
Chronic pulmonary diseases (%)	8 (2)	20 (11)	<0.0001
Hypertension (%)	88 (23)	87 (50)	<0.0001
Diabetes (%)	76 (20)	47 (27)	0.05
Cancer other than HCC (%)	8 (2)	12 (7)	0.004
Chronic renal failure (%)	3 (1)	2 (1)	ns
Cerebrovascular diseases (%)	1 (0.3)	7 (4)	0.002
Psychiatric disorders (%)	42 (11)	10 (6)	0.05
Metabolic syndrome (%)	56 (14)	33 (19)	ns
Hematologic diseases (%)	29 (8)	22 (13)	0.05

Gramenzi A, JVH 2010

Hepatitis C in the Elderly

4.Aging of Population of HCV infected and growing number of elderly patients with more advanced disease

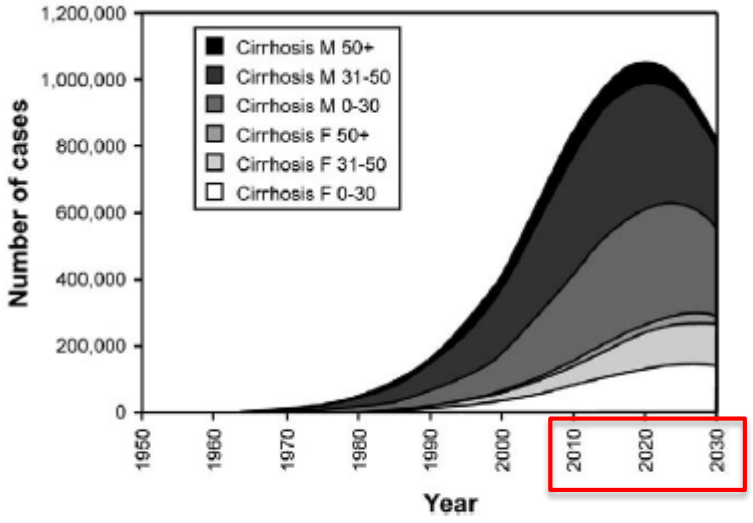
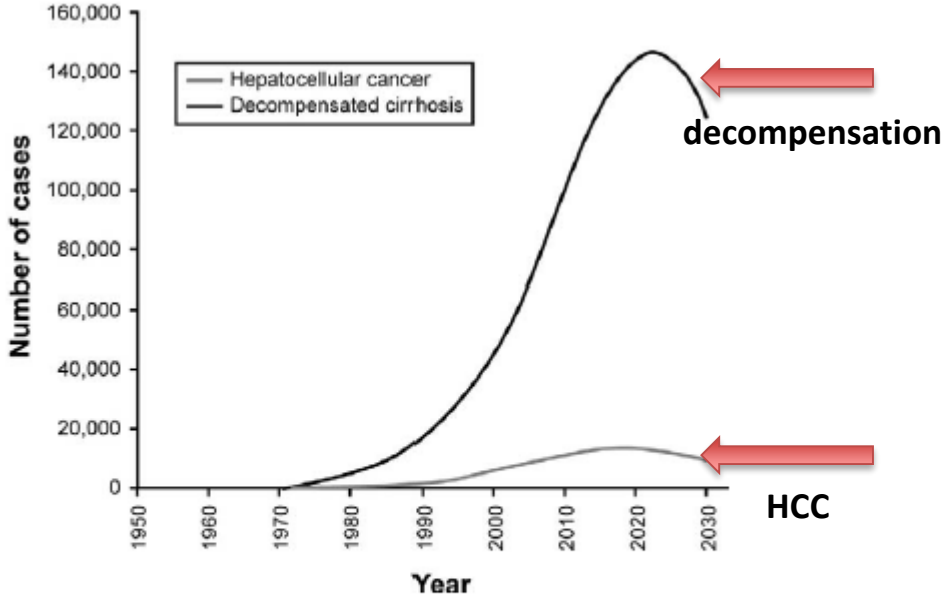


Figure 3. Stacked prevalence curves showing number of cases by year with cirrhosis according to gender and age at time of initial hepatitis C virus infection.



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4. HCV-infected population is aging and a growing number of elderly patients have more advanced disease

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5. **Elderly CHC historically considered poor candidates to IFN-based treatments → very low treatment rate**

   Wright T, Dig Dis Sci 2008
   Floreani A, Dig Dis 2007

Hepatitis C in the Elderly

5. Elderly CHC historically considered poor candidates to IFN-based treatments → very low treatment rate

Multiple barriers to care in the Interferon Era:

- ❑ contraindications more likely in the older patients
- ❑ Higher prevalence of heart disease
- ❑ Higher prevalence of anemia or cytopenia
- ❑ Supposed higher incidence of side effects during therapy
- ❑ Compliance issues
- ❑ Unwilling to adhere to treatment and monitoring schedule

[even after adjusting for known variables that controindicates treatment] we found that older age was independently associated with a ***lower likelihood of being considered a treatment candidate*** → ***CULTURAL ISSUE AMONG HEALTH PROFESSIONALS***

In addition: elderly patients usually excluded from trials.

Wright T, Dig Dis Sci 2008
Floreani A, Dig Dis 2007

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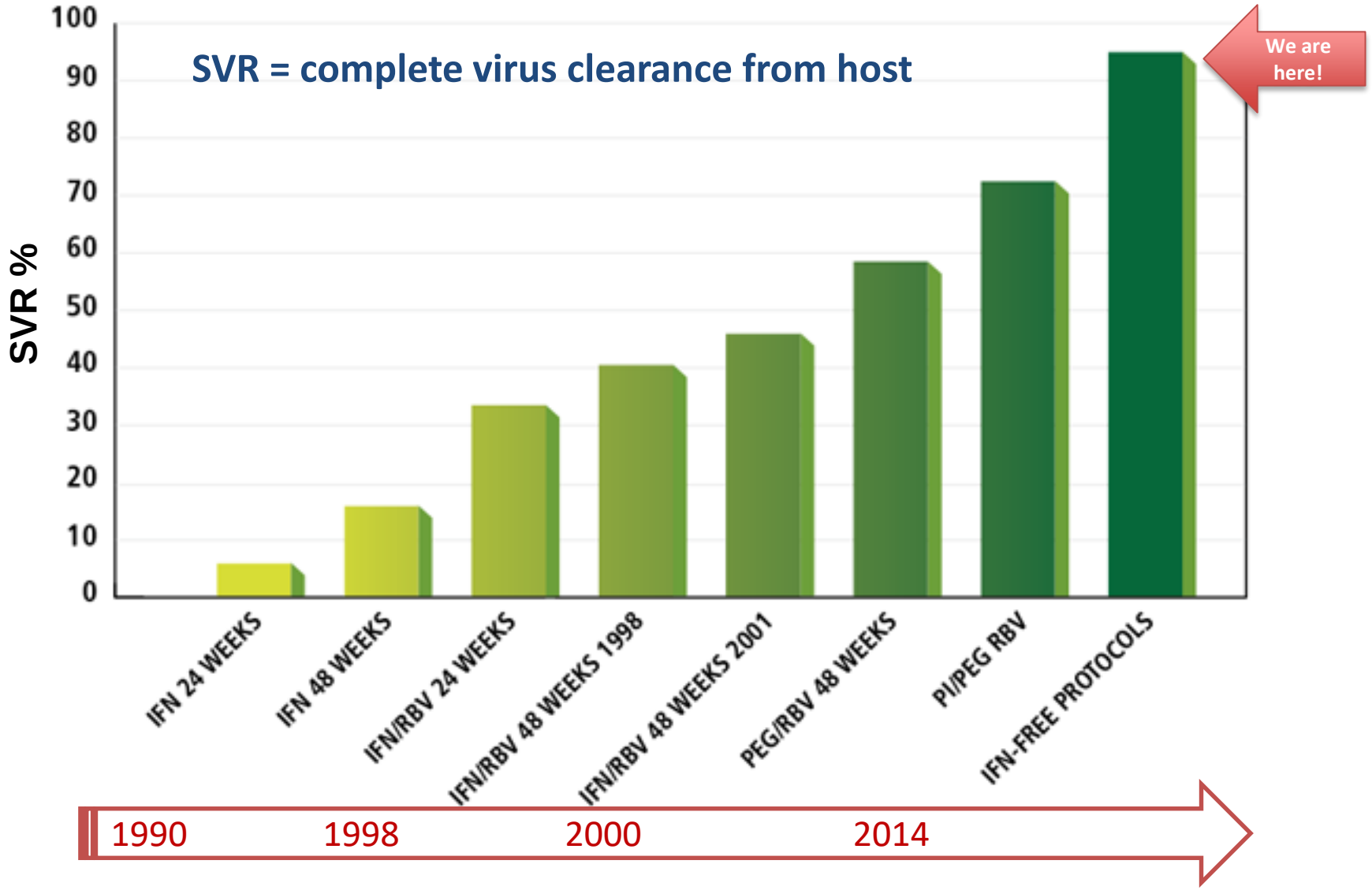
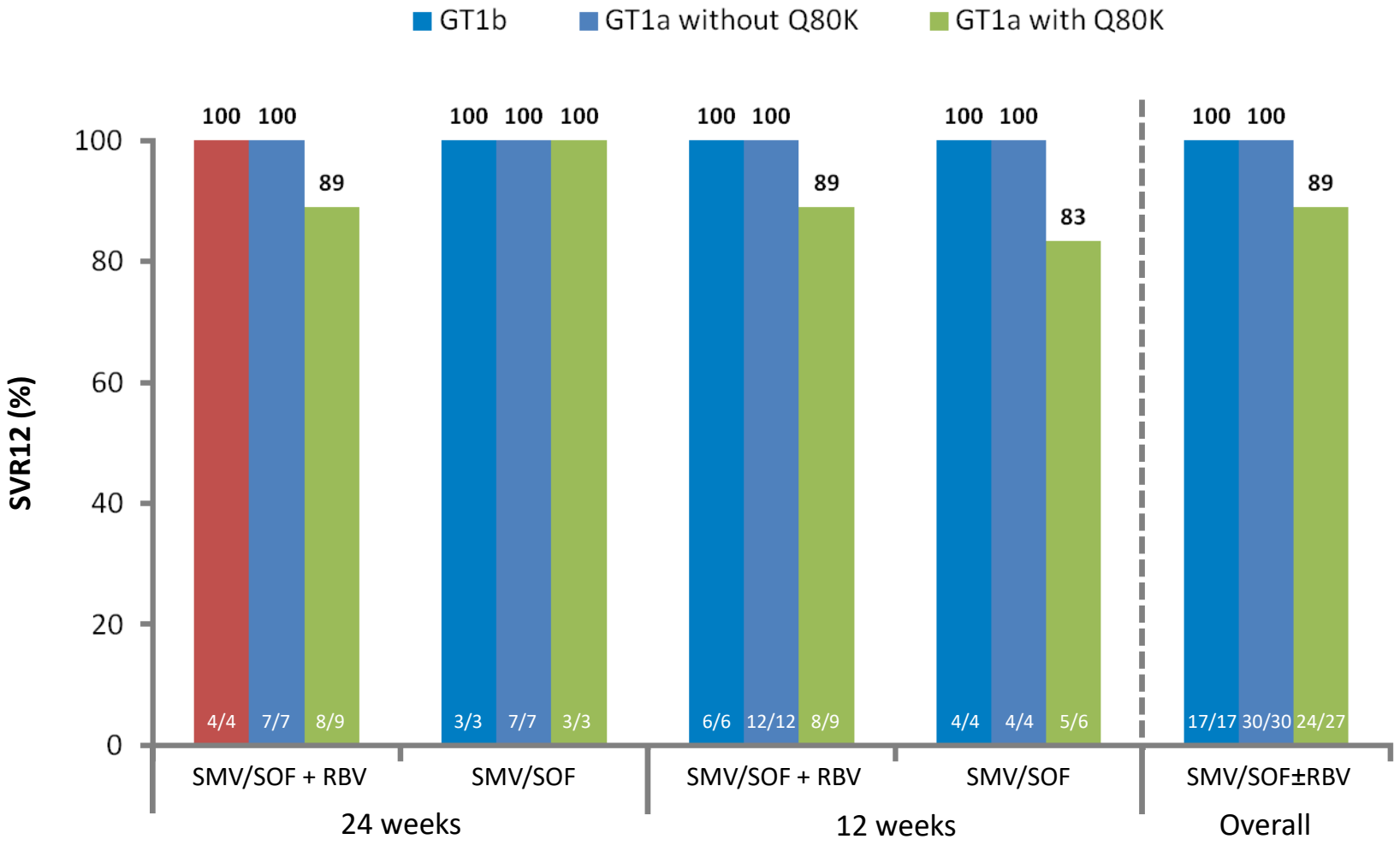
6. Recent availability of effective and safe drug combination, ... but at a price…

From poor response to almost-universal cure



COSMOS Cohort 1: the first IFN-free study ever. SOF + SMV

Proof of best efficacy when **two antivirals with different targets** are given in combination



*Excluding patients who discontinued for non-virologic reasons

PSI 7977

7202 *J. Med. Chem.* **2010,** *53,* 7202–7218
DOI: 10.1021/jm100863x

Journal of Medicinal Chemistry Article

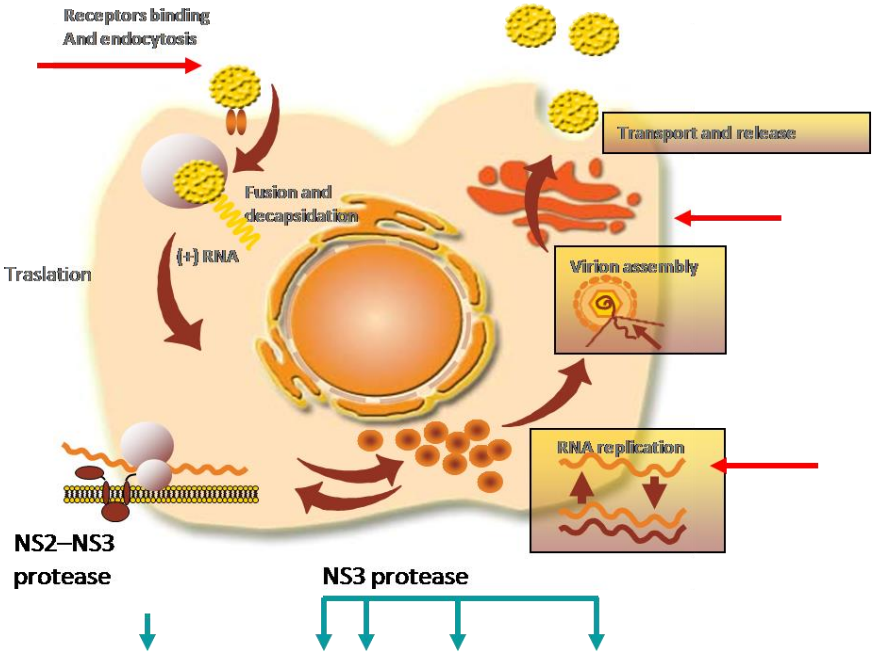
Discovery of a β-D-2′-Deoxy-2′-α-fluoro-2′-β-*C*-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus

Michael J. Sofia,* Donghui Bao, Wonsuk Chang, Jinfa Du, Dhanapalan Nagarathnam, Suguna Rachakonda, P. Ganapati Reddy, Bruce S. Ross, Peiyuan Wang, Hai-Ren Zhang, Shalini Bansal, Christine Espiritu, Meg Keilman, Angela M. Lam, Holly M. Micolochick Steuer, Congrong Niu, Michael J. Otto, and Phillip A. Furman

Pharmasset, Inc., 303A College Road East, Princeton, New Jersey 08540

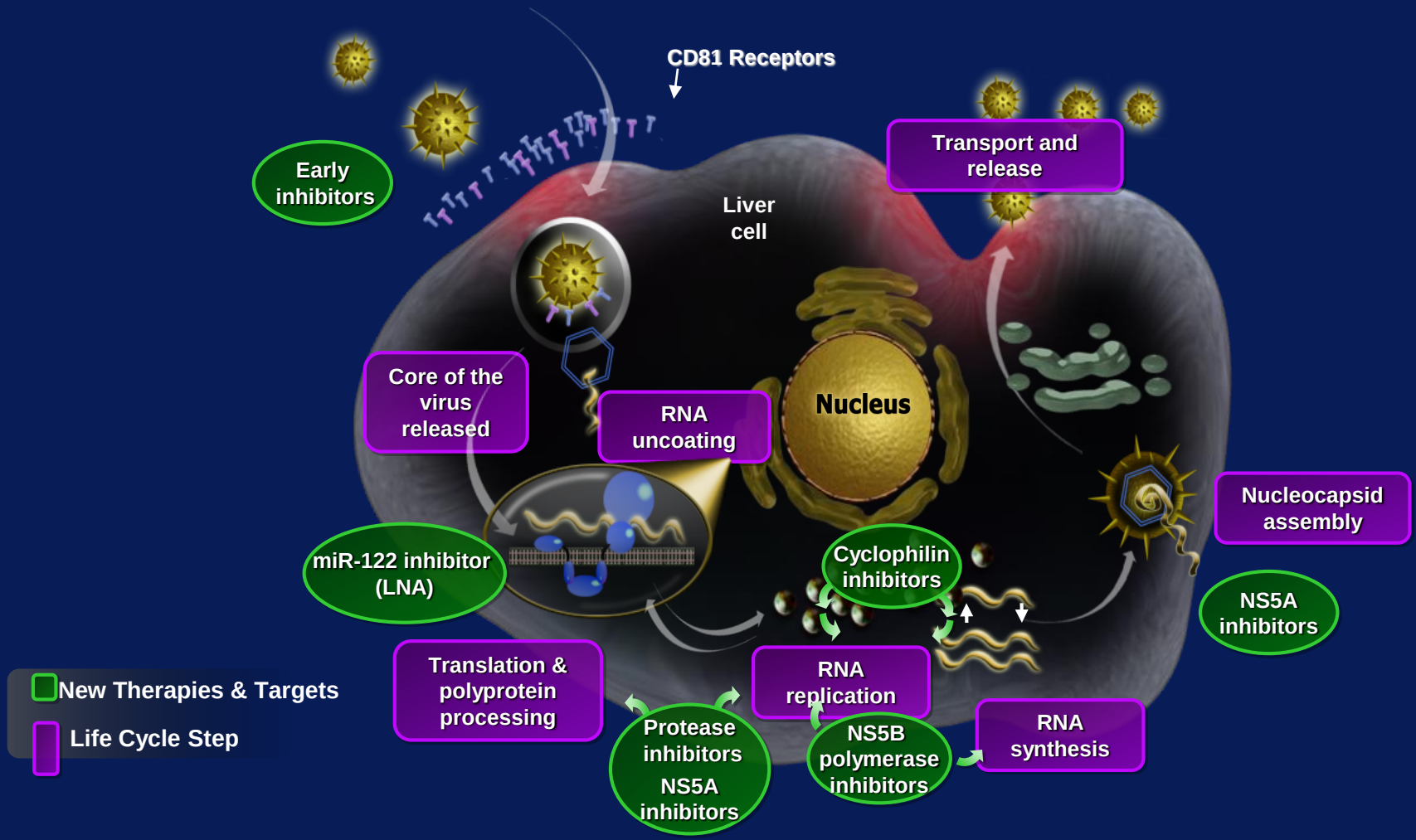
DAAs

Direct Acting Antivirals



- Small molecules
- Interagiscono con target virali molto precisi
- Bloccano il ciclo replicativo virale impedendo ingresso, trascrizione, duplicazione, taglio della poliproteina, assemblaggio dei virioni…

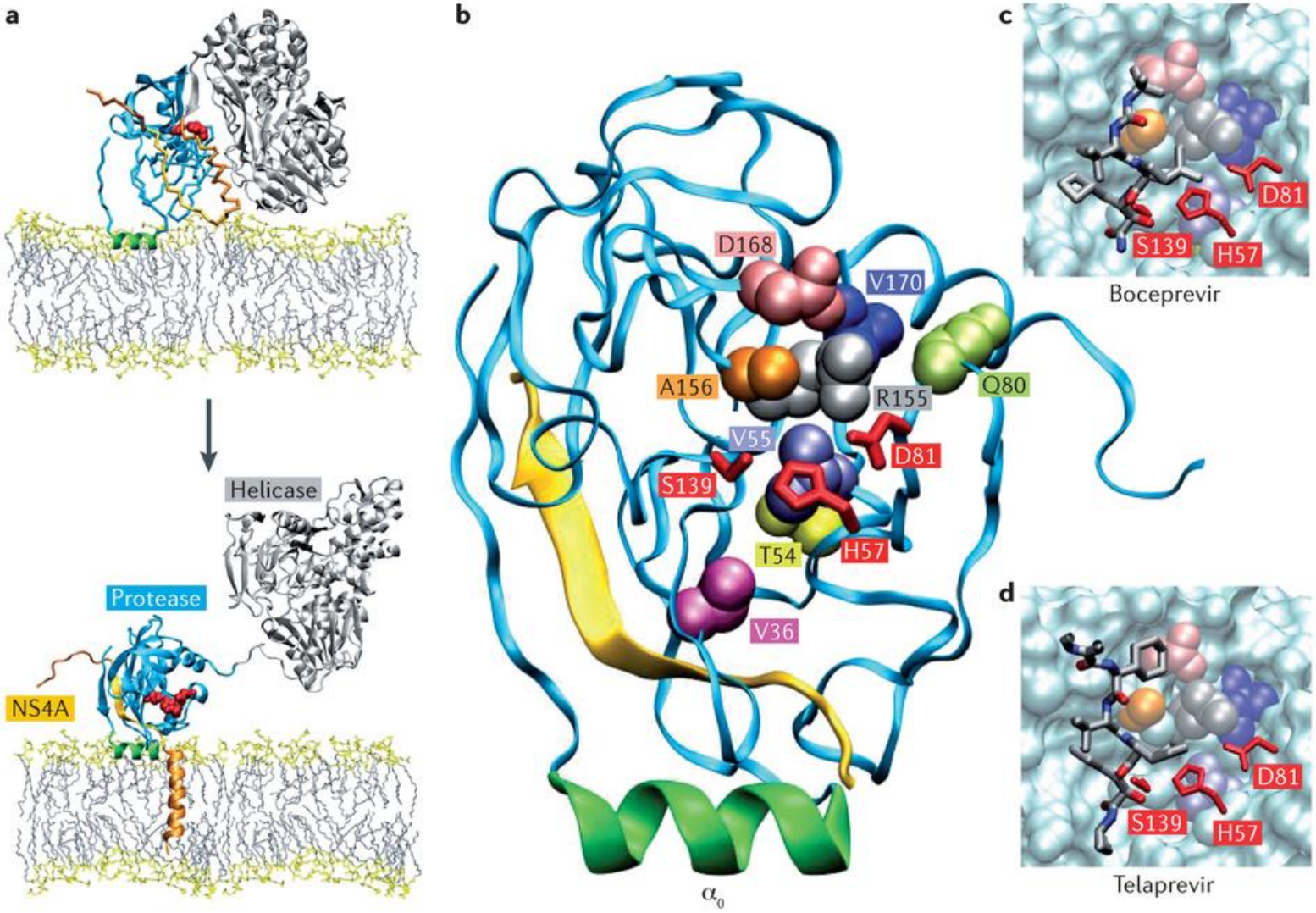
New Antiviral Therapy Targets and Treatments



Courtesy of Prof. Massimo Colombo

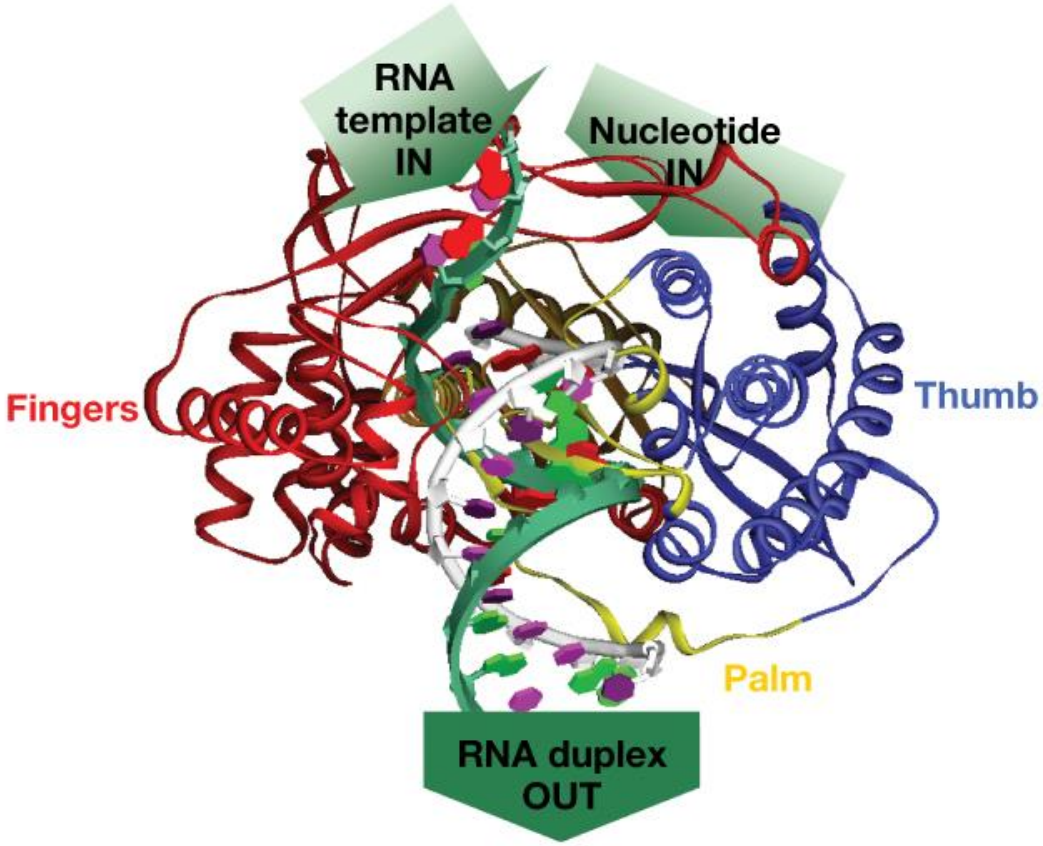
Protease Inhibitors (-PREVIR)

1st generation: telaprevir, boceprevir
2nd generation: Simeprevir



Nature Reviews | Microbiology

HCV Polymerase Inhibitors (-BUVIR)



Nucleos(t)ide inhibitors (NI)
- Mericitabine
- Sofosbuvir

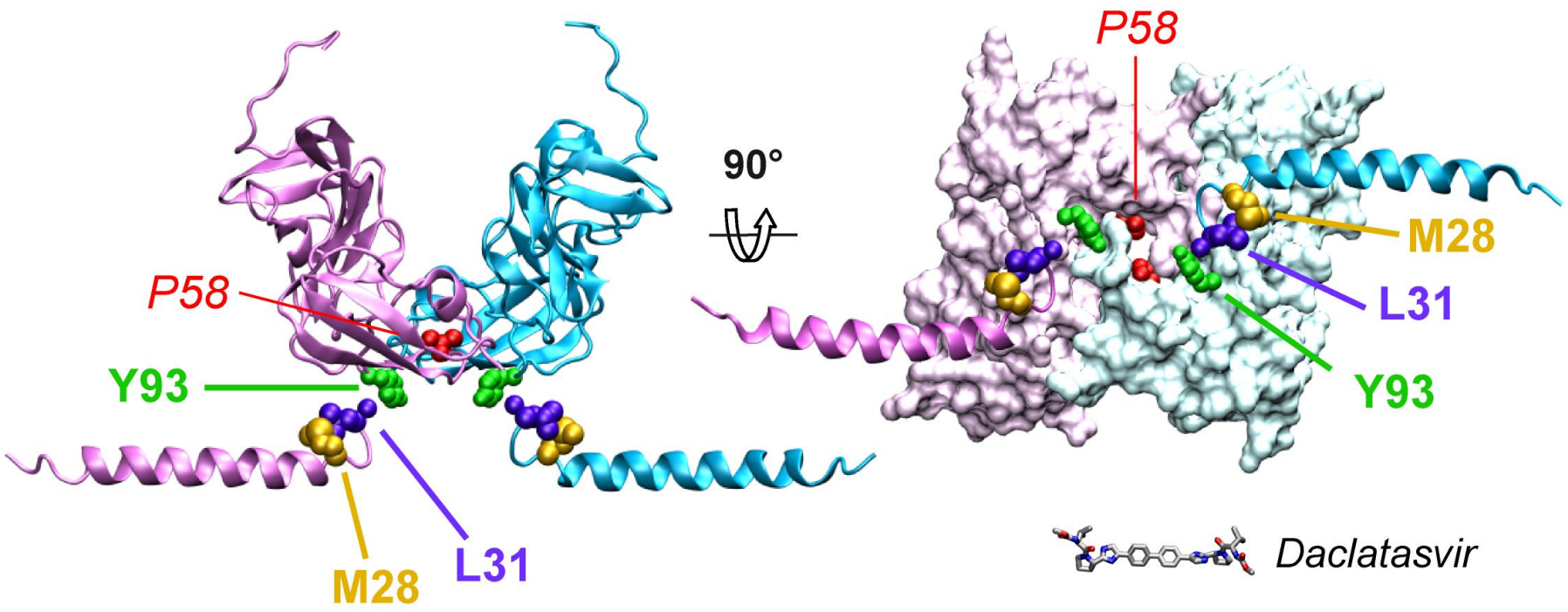
Non-nucleoside inhibitors (NNI) = allosteric inhibitors

- **A** **Thumb I**
  e.g. deleobuvir
- **B** **Thumb II**
  e.g. lomibuvir, filibuvir
- **C** **Palm I**
  e.g. dasabuvir setrobuvir
- **D, E** **Palm II**
  e.g. nesbuvir, tegobuvir

Bartenschlager R *et al*. Nat Rev Microbiol 2013;11:482-496.

See also Scheel TK and Rice CM. Nat Med 2013;19:837-849.

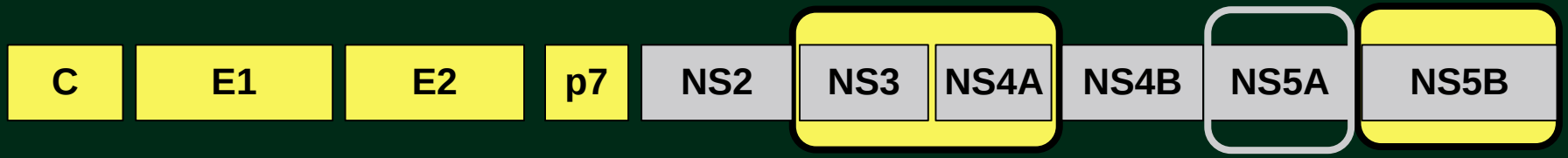
HCV NS5A Inhibitors (-ASVIR)



Prototype: daclatasvir
Other examples: Ombitasvir, ACH2928, ACH3102, AZD7295, BMS824393, GS5816, GSK2336805, ledipasvir, MK8742, PPI668, samatasvir …

Gao M *et al*. Nature 2010;465:96-100.
Reviewed in Bartenschlager R *et al*. Nat Rev Microbiol 2013;11:482-496, Pawlotsky JM. J Hepatol 2013;59:375-382, and Gao M. Curr Opin Virol 2013;3:1-7.

Direct-Acting Antiviral Agents: Key Characteristics



NS3/4A Protease Inhibitors (PI)

- High potency
- Limited genotypic coverage
- Low barrier to resistance

SIM
ABT450
ASV
MK5172

NS5B Nucleos(t)ide Inhibitors (NI)

- Intermediate potency
- Pangenotypic coverage
- High barrier to resistance

SOF
VX135

NS5A Inhibitors

- High potency
- Multigenotypic coverage
- Low barrier to resistance

DCV
LDV
ABT267
MK8742

NS5B Nonnucleoside Inhibitors (NNI)

- Intermediate potency
- Limited genotypic coverage
- Low barrier to resistance

ABT333
Deleobuvir

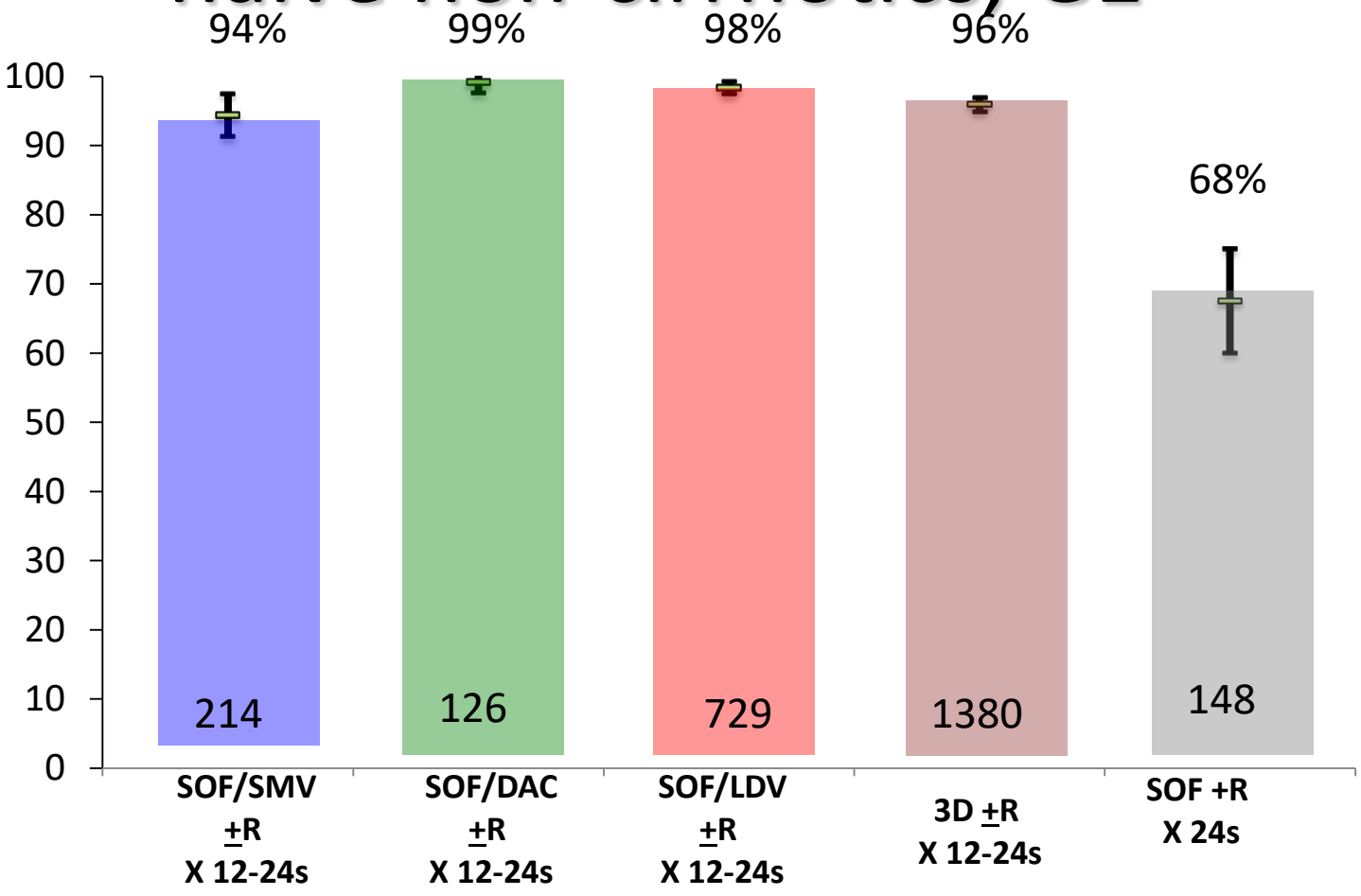
Farmaci disponibili in Italia per il trattamento dell'epatite C, 2015

- ✓ SOVALDI (sofosbuvir)
- ✓ OLYSIO (simeprevir)
- ✓ HARVONI (sofosbuvir + ledipasvir)
- ✓ DAKLINZA (daclatasvir)
- ✓ VIEKIRAK (ombitasvir + paritaprevir + ritonavir)
- ✓ EXVIERA (dasabuvir)

3D

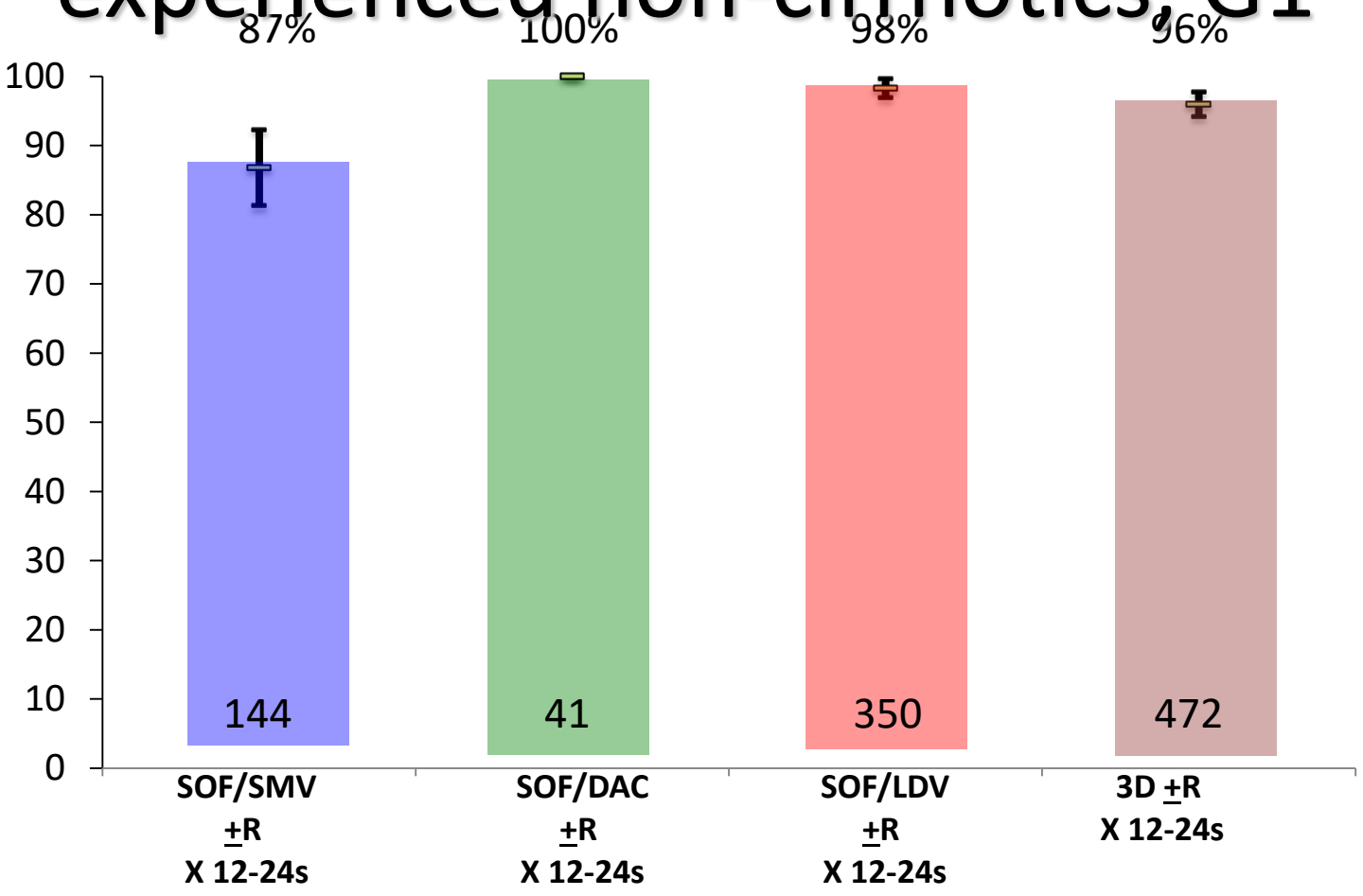
- ✓ Ribavirina

Efficacy of IFN-free regimens in naive non-cirrhotics, G1



SIM/SOF study Cosmos, cohorts: TRIO, TARGET
SOF/LED studies ION-1 ION-3
3D: studies PEARL SAPPHIRE
SOFO + R: SPC Sovaldi

Efficacy of IFN-free regimens in experienced non-cirrhotics, G1



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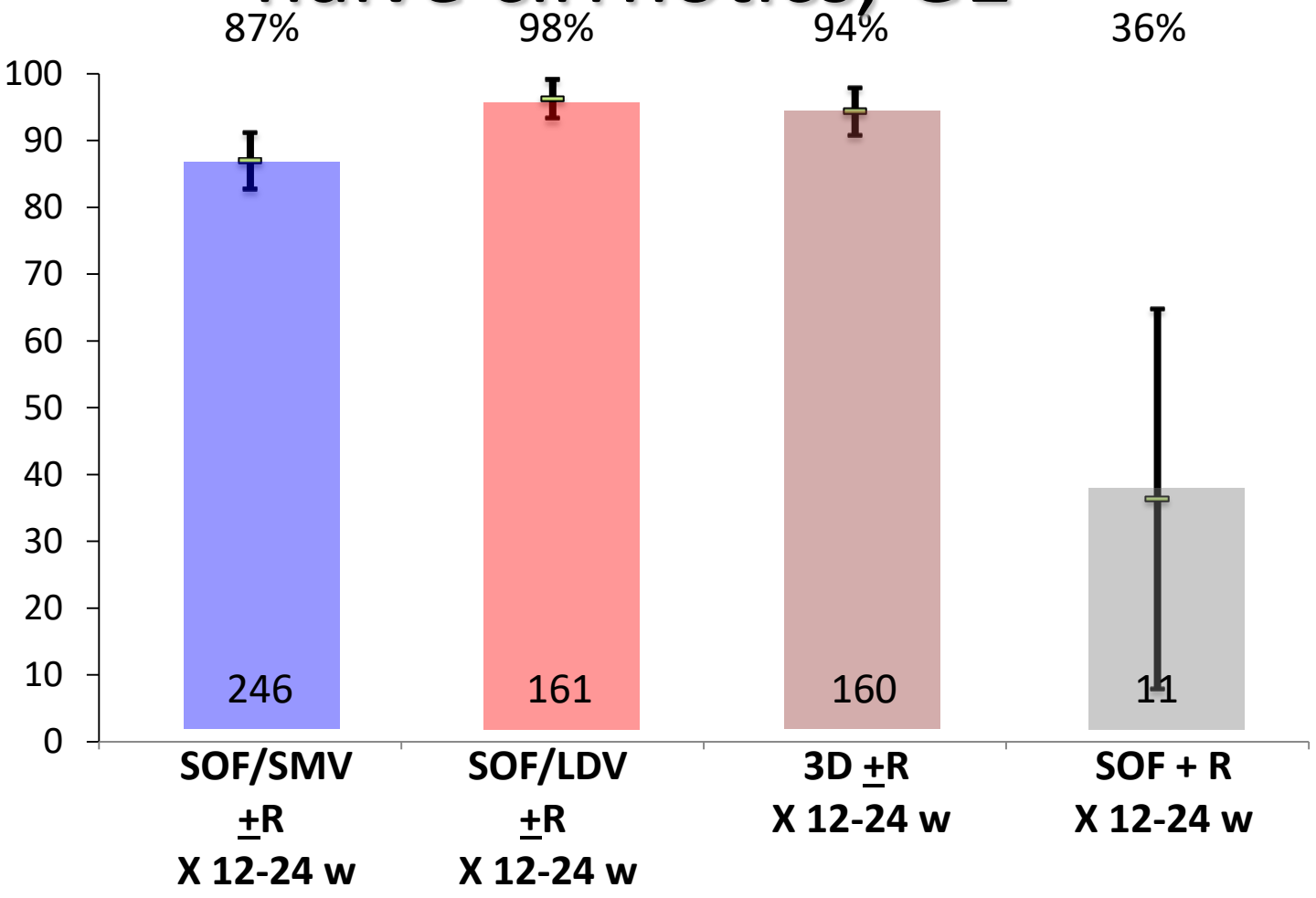

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SOF/LED study meta analysis AASLD 2014
3D: studies Turquoise II

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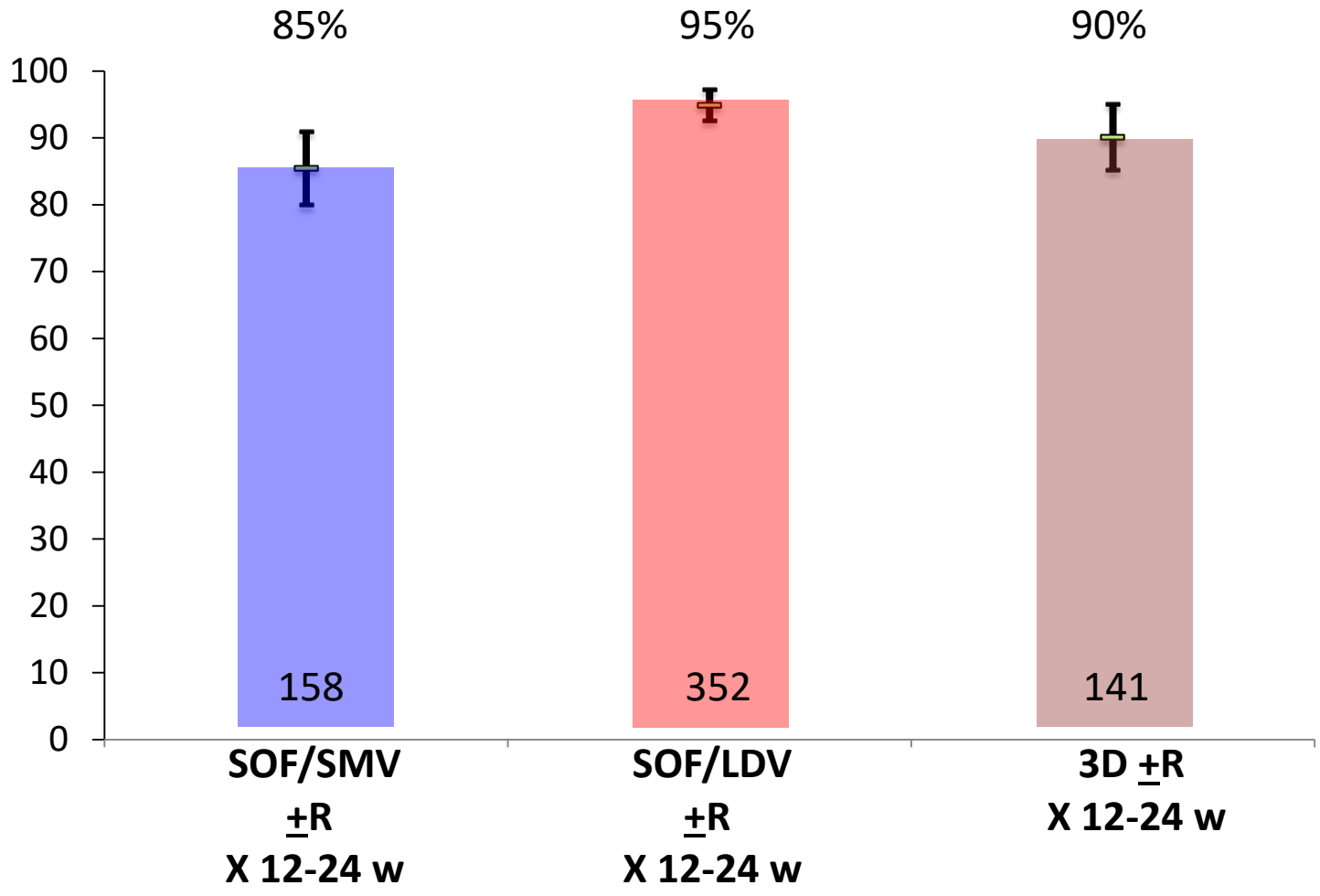

SIM/SOF study Cosmos, cohorts: TRIO, TARGET
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3D: studies Turquoise II

THE NEW CHALLENGE IS THE ACCESS TO CURE

What is the impact of DAAs treaments for HCV hepatitis in the geriatric population?

Question & Answer

A chance for a HCV therapy in the Elderly is now offered by new IFN-free regimens

BUT

Is HCV therapy cost-effective in elderly patients?

Assess the cost-effectiveness of a sofosbuvir-based, IFN-free treatment in 65 years old or older patients with G1 chronic hepatitis C

Special considerations

Elderly CHC patients are not all equal! The benefit of HCV clearance depends on

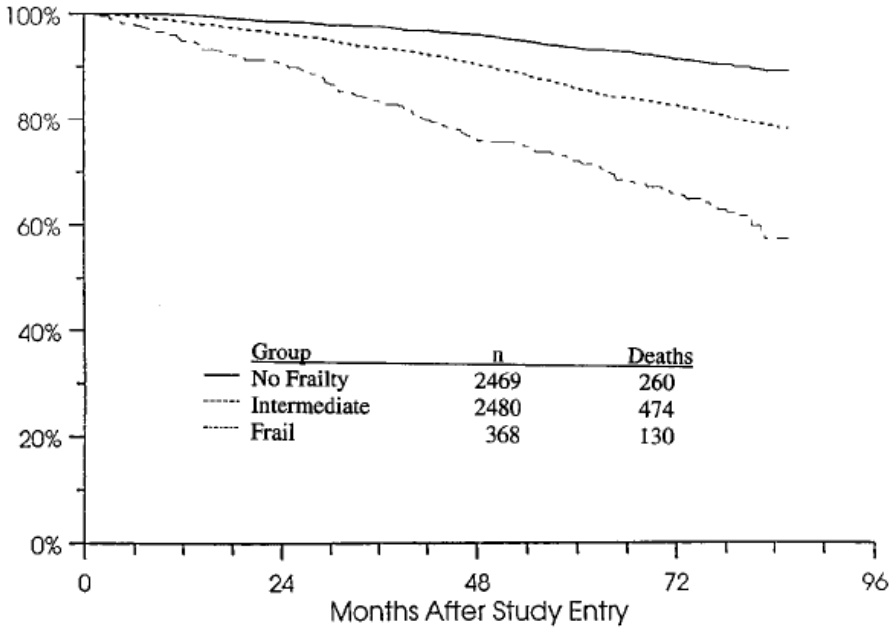
1. The extent of liver disease (mild or advanced fibrosis)
2. Age of patients
3. **General conditions and performance, comorbidity, disability, frailty.**

Frailty: A brief Introduction

Frailty: a biologic **syndrome of decreased reserve and resistance to stressors**, resulting from cumulative declines across multiple physiologic systems, and **causing vulnerability to adverse outcomes.**

Fried's Frailty Phenotype (Fried L, et al. J Gerontol 2001)

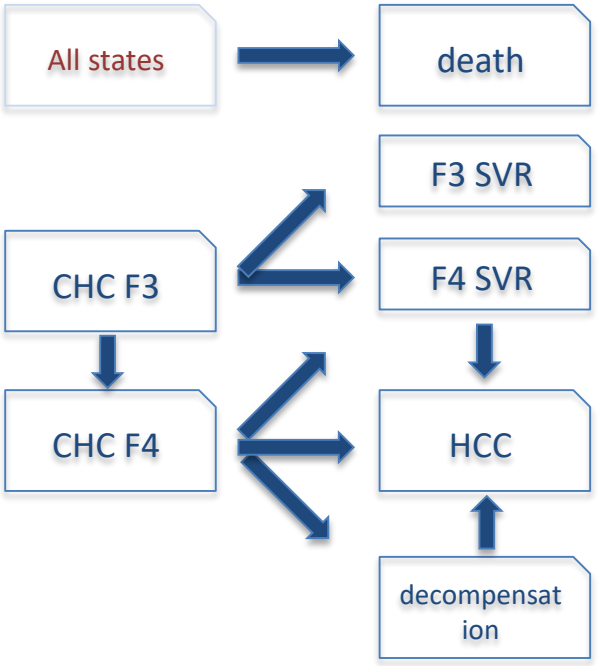
Components
Exhaustion
Weight loss
Low activity
Slow walk
Grip strenght



Number of criteria met	
0	Not frail
1-2	Pre-frail
≥3	Frail

Methods

- A decision-analytic Markov Model of CHC Natural history and treatment was built



State-to-state transitions according to available literature data and to our VBMH cohort study

Study population: CHC G1 patients >65 years,
Stratification:
- Liver fibrosis (METAVIR F3 and F4),
- age (65 to 90 years old, 5-years groups) and
- Fried's frailty phenotype (not frail, pre-frail and frail)

generating 30 simulated cohorts.

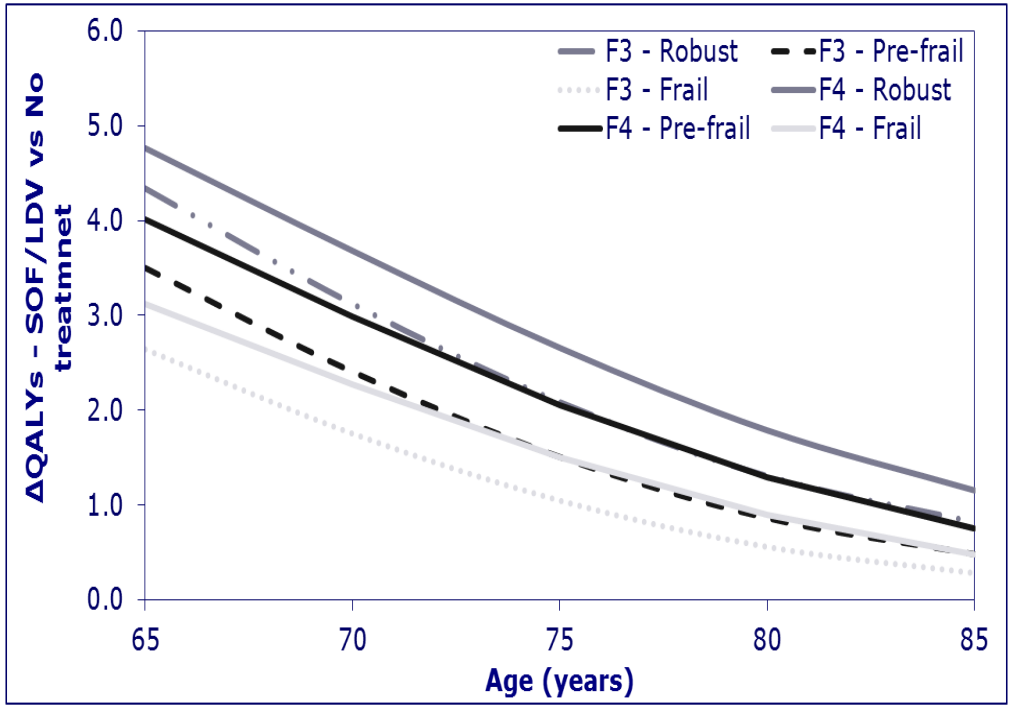
Treatment with sofosbuvir plus ledipasvir (SOF/LDV) versus no treatment was assessed for each cohort.

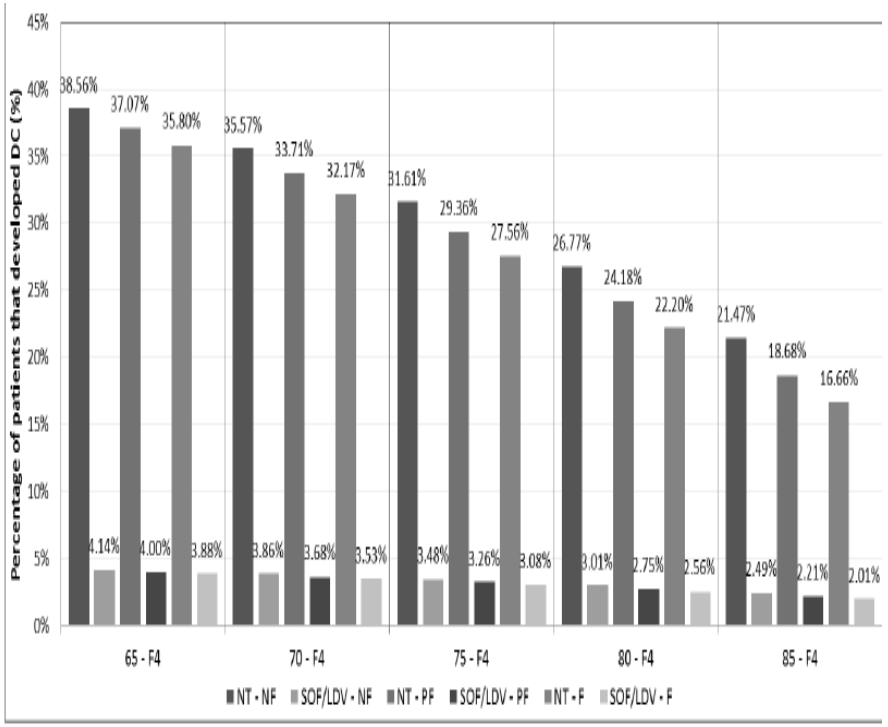
Time horizon: lifetime
Perspective: Public Health System.
Outcome: costs, Life Years and Quality Adjusted Life Years (QALY), ICERs
Cost-effectiveness defined as an ICER under the 40,000€/QALY threshold.

Results: QALYs

The model estimated that the cost-effectiveness of SOF/LDV treatment regimen in HCV elderly patients declined with decreasing fibrosis and with increasing age and level of frailty

Differences in QALYs (QALYs gained) among treated and untreated ranged from 4.76 to 0.28, respectively in 65yo, F4, robust and 85yo, F3, frail patients.

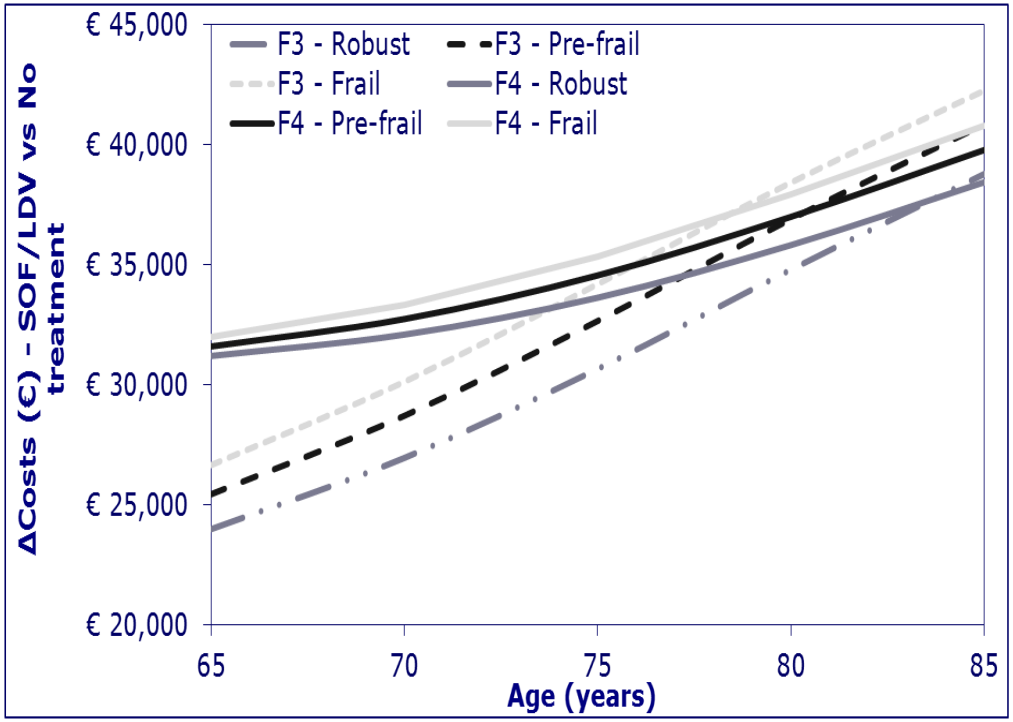




Results: Costs

As expected, costs were much higher in treated patients than in untreated ones, regardless of their age, fibrosis stage and frailty status, with a result that is mostly due to the drug price.

The difference in costs (Δ costs) among treated and untreated patients was lowest in 65yo, F3, and robust (23,992 €), and highest in 85yo, F3, and frail patients, consistent with an increasing cost as an effect of age, frailty status, and fibrosis stage.

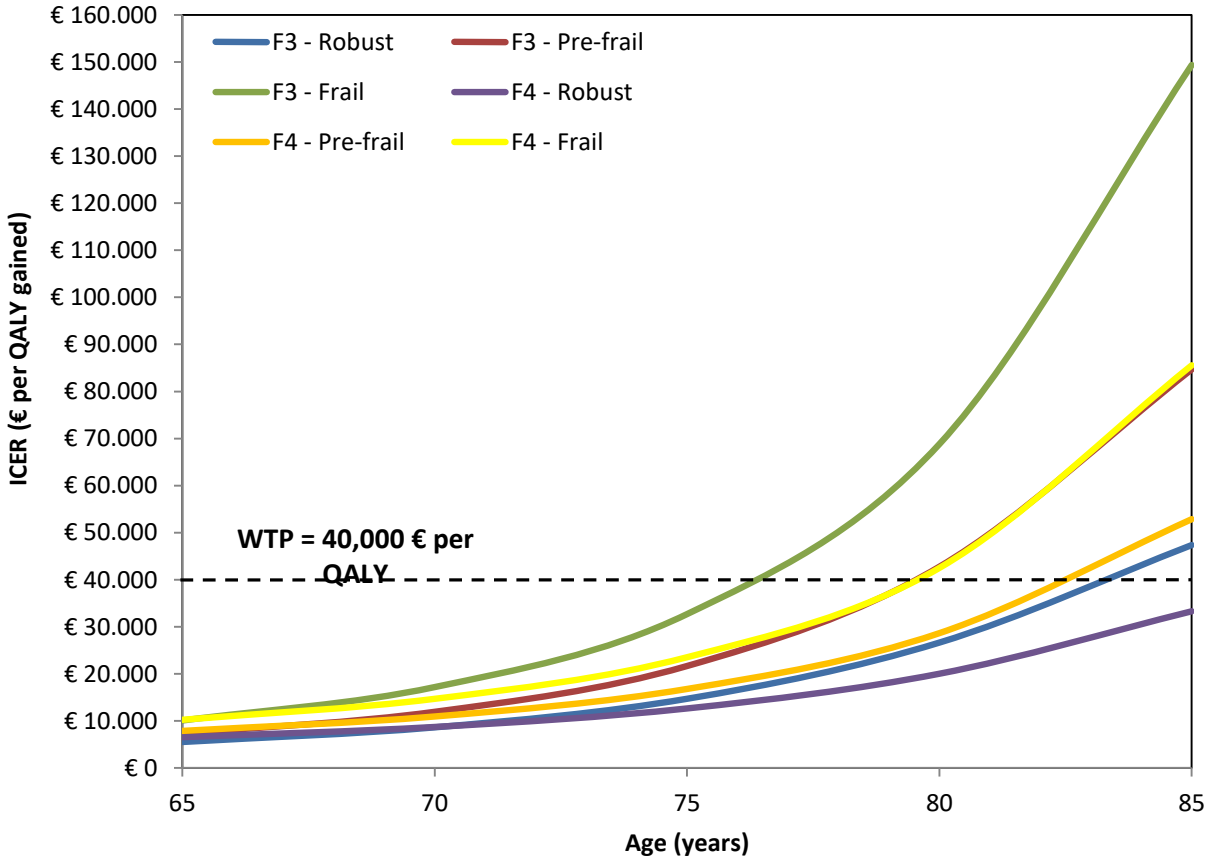


Results: ICERs

$$ICER = \frac{(C_1 - C_0)}{(E_1 - E_0)}$$

ICER= Incremental cost-effectiveness ratio

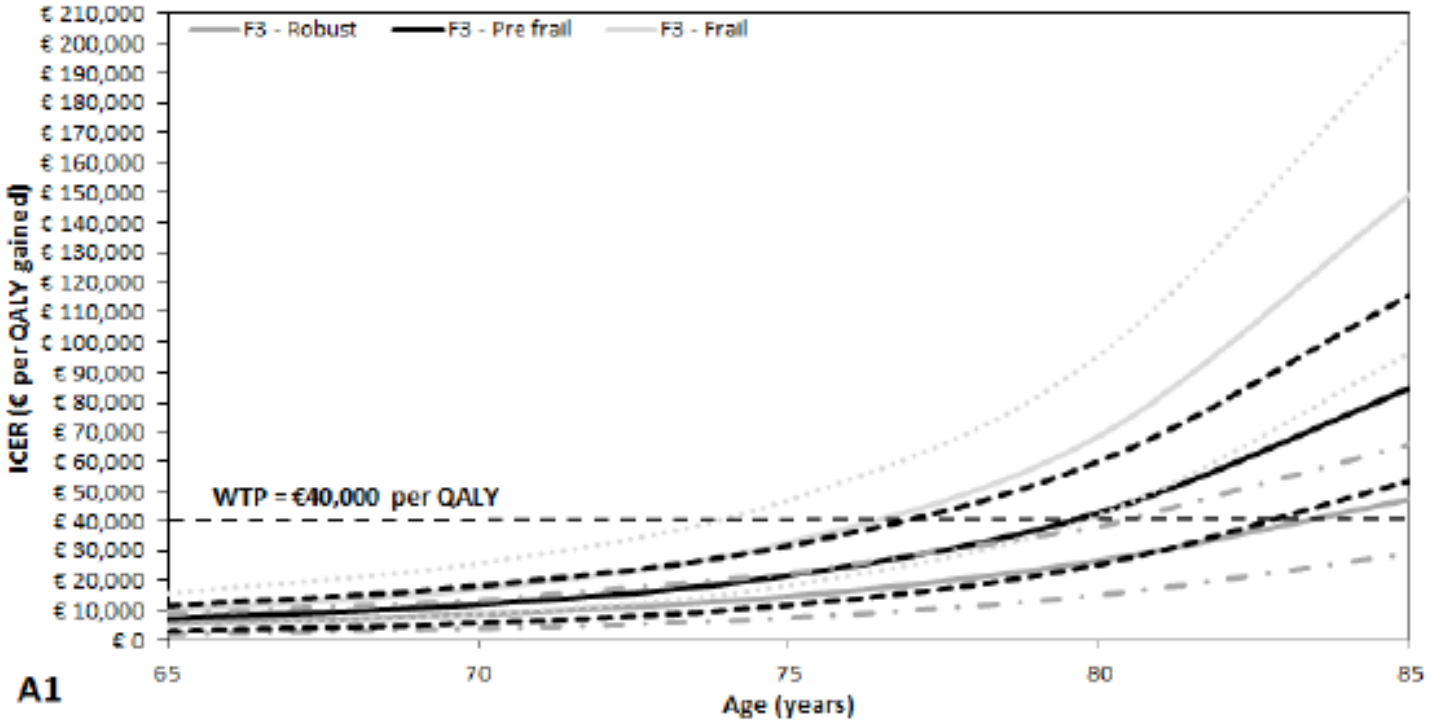
It is defined by the difference in cost between two possible interventions, divided by the difference in their effect.
It is expressed as EUR/QALY gained



Results: sensitivity analysis

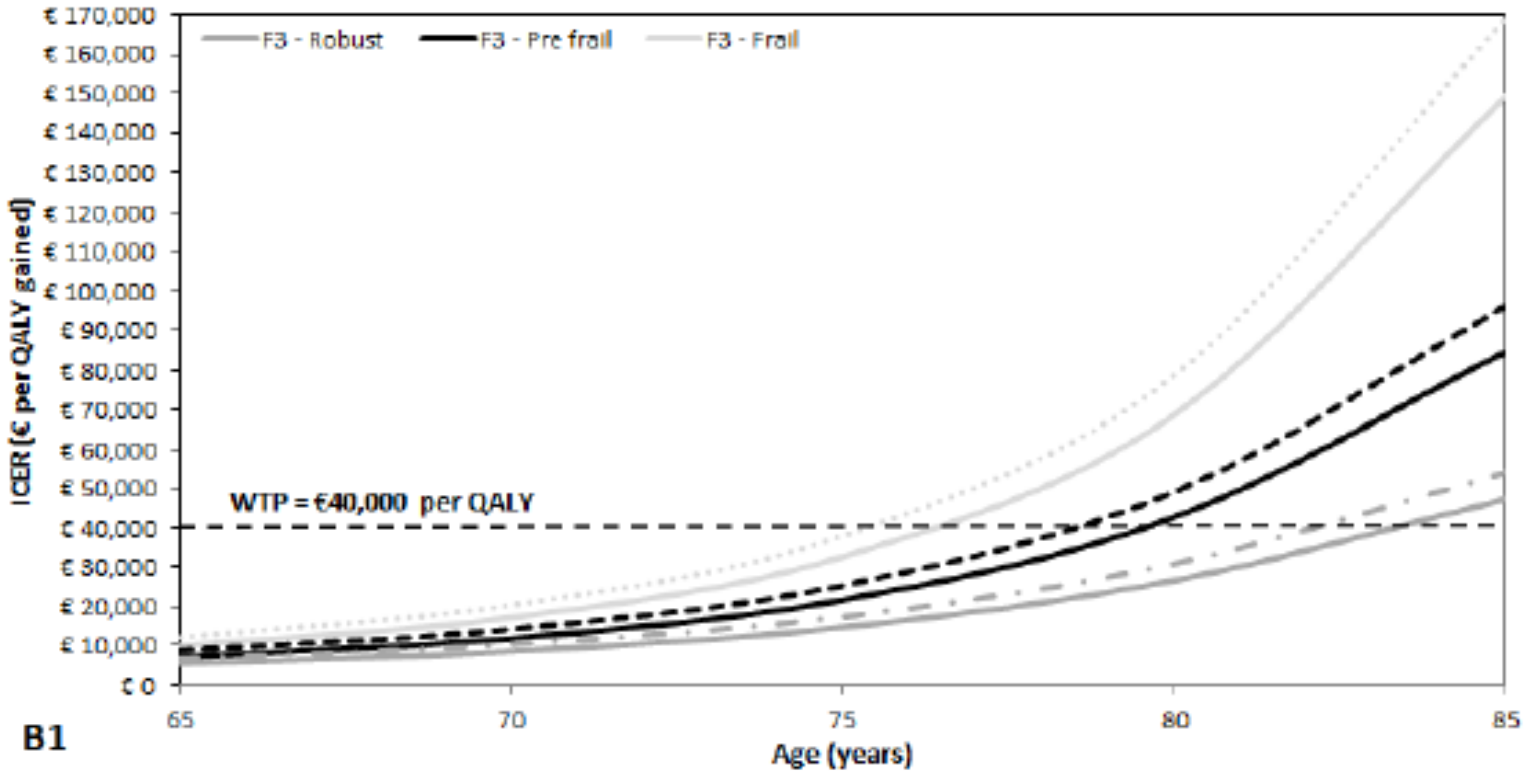
Considering a drug price variation:

Main line = 50.000 Euros
Lower Dotted = 35.000 Euros
Upper Dotted = 65.000 Euros



Results: sensitivity analysis

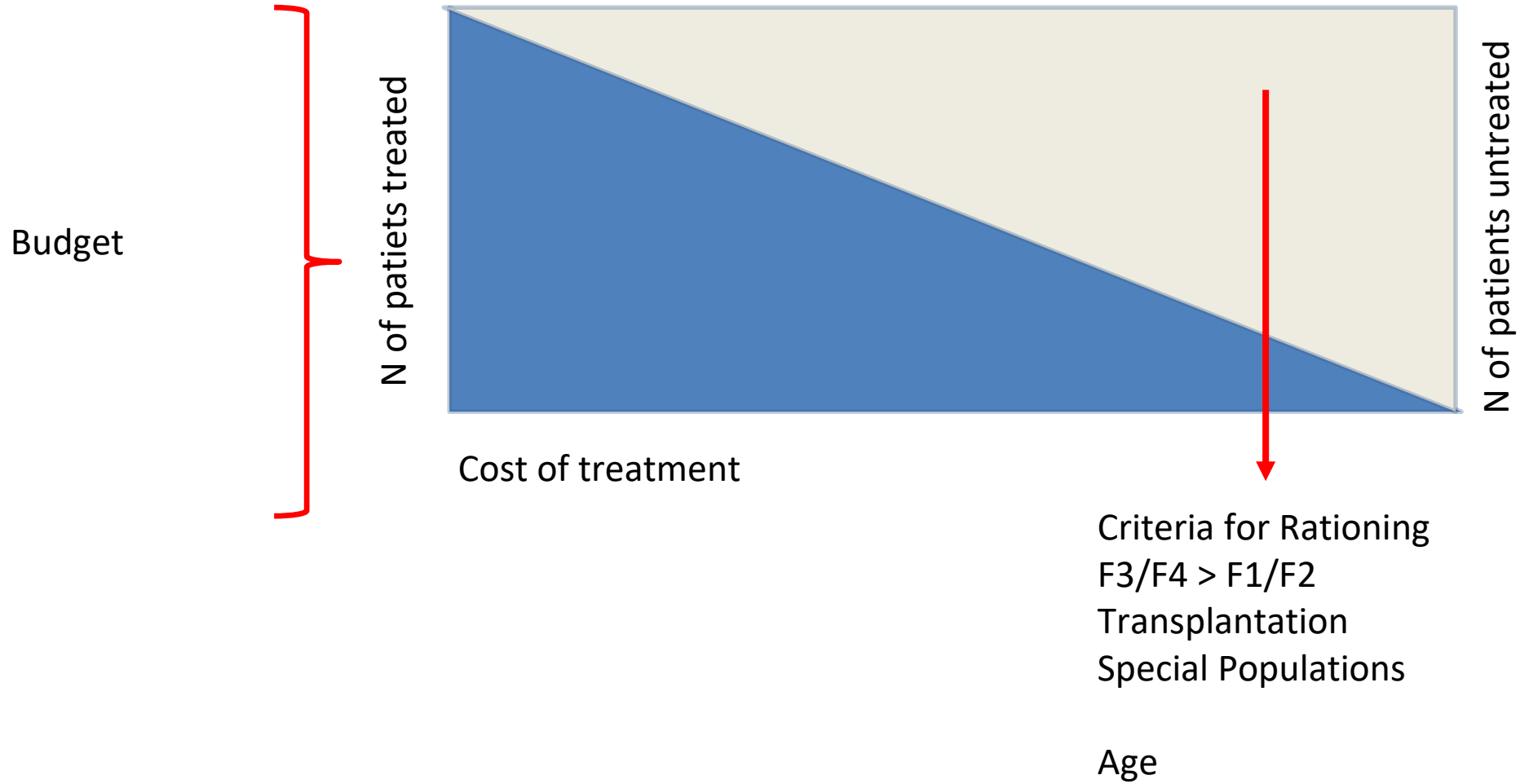
Considering a drug efficacy variation as low as 10% (dotted lines):



Summary of Cost-effectiveness

Age	Fibrosis	Frailty	LYs gained	QALYs gained	Δcost € x 1000	ICER €x1000/ QALY gained
65	F3	Robust	7.71	4.34	24	5.5
65	F4	Pre-frail	6.7	4.01	31.6	7.8
70	F3	Robust	5.18	3.12	27	12
70	F4	Pre-frail	4.70	2.99	32.7	10.9
75	F3	Robust	3.24	2.08	30.6	14.7
75	F4	Pre-frail	3.0	2.06	34.5	16.8
80	F4	Frail	1.37	0.89	38	42.0
85	F3	Frail	0.38	0.28	42.3	149

From Finding a Cure to Providing Access



Conclusions

- The benefit in terms of life years gained ranges from about 2 years for thre worst patient category to about 9 years for the best case
- A benefit is also evident when survival gain is expressed as QALYs
- For each age group, frailty phenotype affects life expectancy
- When a WTP threshold of 40.000 EUR is considered, treatment results cost-effective in most categories
- cost-effectiveness depends on age but
- **For each given age group cost-effectiveness depends on frailty status**

- Limits: model-based, efficacy/safety of SOF/LDV to be assessed in clinical setting.
- Not possible to estabilish wich effect played by co-morbidity

(in our model we assumed co-morbidity to be captured by frailty)

Conclusions

In conclusion: SOF/LDV treatment is cost-effective in most CHC patients with advanced fibrosis older than 65 years, however a careful assessment of the patient geriatric status is mandatory. This cost-effectiveness analysis should promote a prospective clinical study to verify efficacy and side effects in elderly HCV patients.

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