FEGATO ED EPATOCARCINOMA

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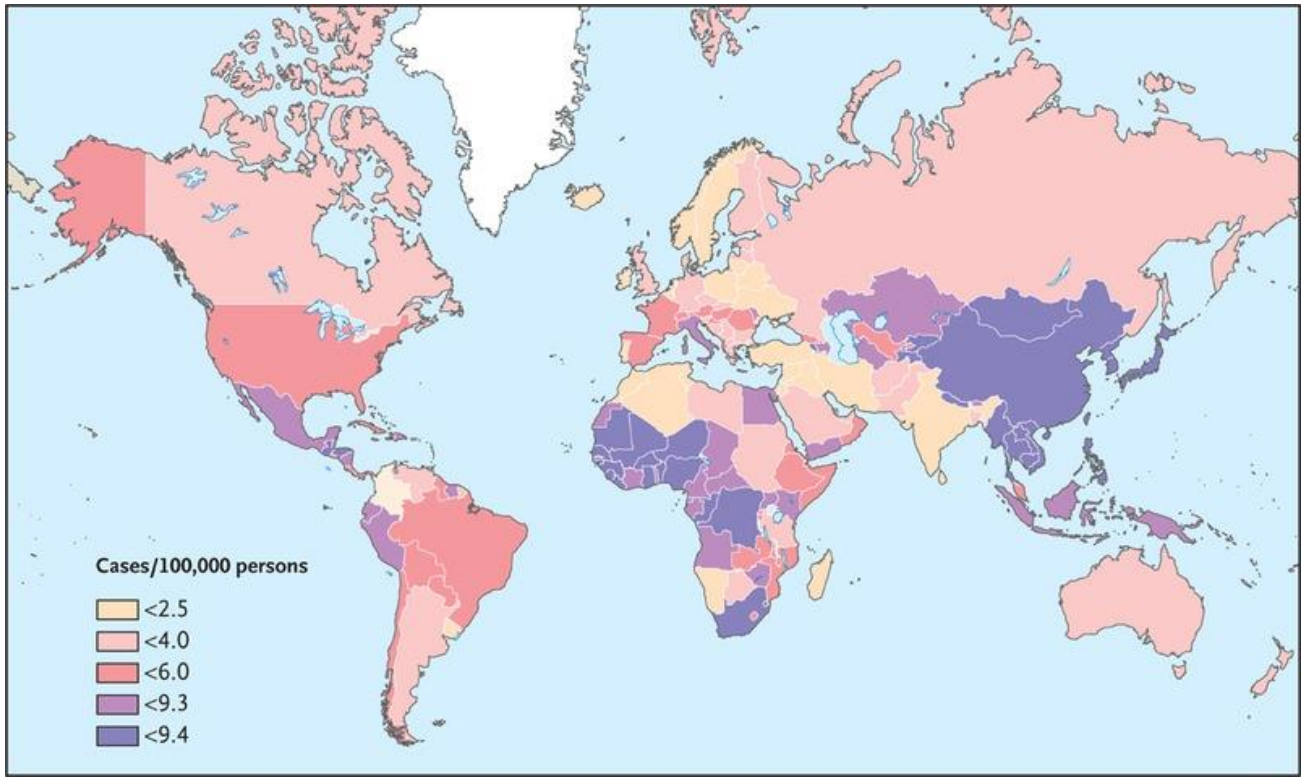
DISCLOSURES

- Viiv Healthcare
- Gilead Sciences

EPIDEMIOLOGIA

- Increasing incidence of HCC (Europe and worldwide)
- >600,000 people worldwide
- 5th most common cancer
- 2nd cause of cancer-related death
- Incidence increases with age
- Geographical imbalance of incidence rates



INCIDENCE RATES (NUMBERS OF CASES PER 100, 000 PERSONS)
NEJM, REVIEW 2011

EPIDEMIOLOGIA

Associazione Italiana Registri Tumori

Rango	Maschi	Femmine	Tutta la popolazione
1°	Prostata (18%)	Mammella (29%)	Mammella (14%)
2°	Colon-retto (15%)	Colon-retto (13%)	Colon-retto (14%)
3°	Polmone (14%)	Polmone (8%)	Polmone (11%)
4°	Vescica* (11%)	Tiroide (6%)	Prostata (9%)
5°	Fegato (5%)	Utero corpo (5%)	Vescica* (7%)

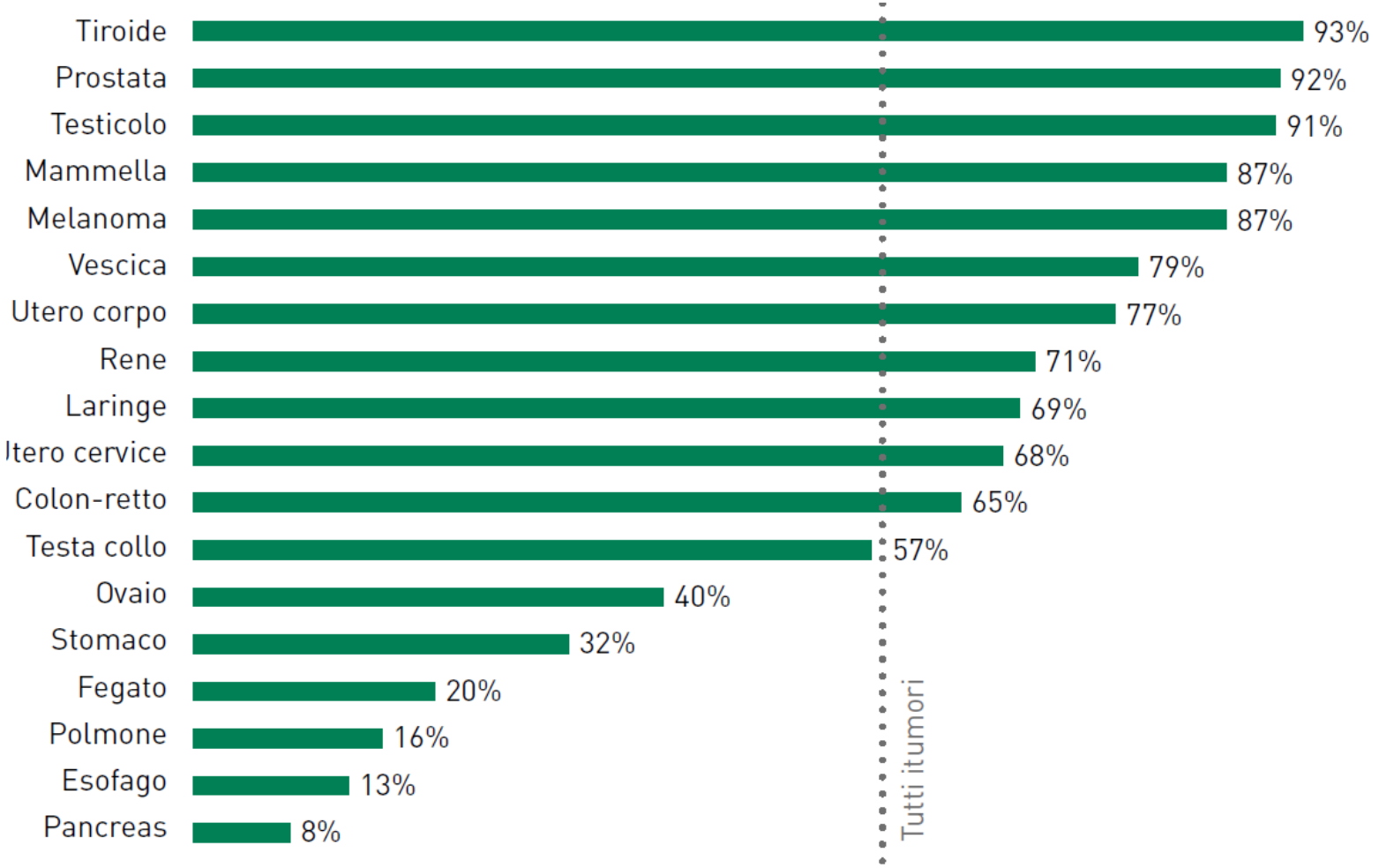
Stime dei primi 5 tumori diagnosticati nel 2018

Rango	Maschi	Femmine	Tutta la popolazione
1°	Polmone (26%)	Mammella (17%)	Polmone (19%)
2°	Colon-retto (11%)	Colon-retto (12%)	Colon-retto (11%)
3°	Prostata (8%)	Polmone (11%)	Mammella (7%)
4°	Fegato (7%)	Pancreas (8%)	Pancreas (6%)
5°	Stomaco (6%)	Stomaco (6%)	Fegato(6%)

Prime 5 cause di morte oncologica (2010-2014)

EPIDEMIOLOGIA

Associazione Italiana Registri Tumori

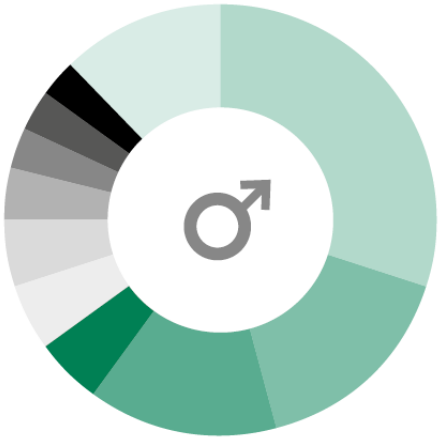


Sopravvivenza a 5 anni dalla diagnosi (standardizzata per età), per il periodo di incidenza 2005-2009 (M+F)

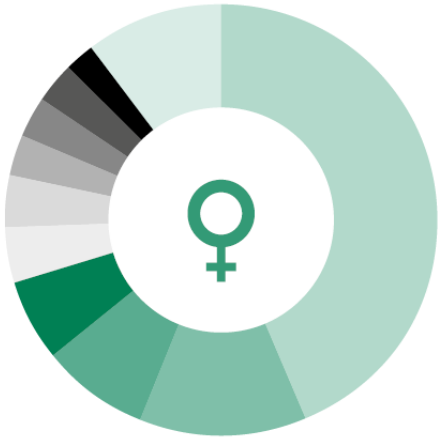
- ✓ Sopravvivenza a 5 anni dalla diagnosi in progressivo aumento dal 1990
- ✓ Sopravvivenza tende a diminuire con l'età
- ✓ Sopravvivenza dopo 10 anni dalla diagnosi è pari al 10 %

EPIDEMIOLOGIA

Associazione Italiana Registri Tumori



Tumore	N.	%
Prostata	457902	30
Colon-retto-ano	244046	16
Vescica	212326	14
Rene, vie urinarie	81603	5
Linfoma n. H.	73570	5
Cute (melanomi)	73076	5
Polmone	67405	4
Testicolo	51062	3
Leucemie	45198	3
Tiroide	44582	3
Altri	180388	12



Tumore	N.	%
Mammella	799196	43
Colon-retto-ano	226652	12
Tiroide	155995	6
Utero corpo	114485	5
Cute (melanomi)	82066	4
Linfoma n. H.	67681	4
Vescica	57196	3
Utero cervice	56063	3
Ovaio	50032	3
Rene, vie urinarie	43858	2
Altri	184185	10

HCC non rientra tra i tumori a maggiore prevalenza in Italia (2018)

- ✓ Risiedono in Italia 33,000 persone con pregressa diagnosi di HCC.
- ✓ Diversa distribuzione geografica:
- 49/100,000 Nord-Ovest
- 45/100,000 Nord-Est
- 37/100,000 Sud
- 29/100,000 Centro

EPIDEMIOLOGIA

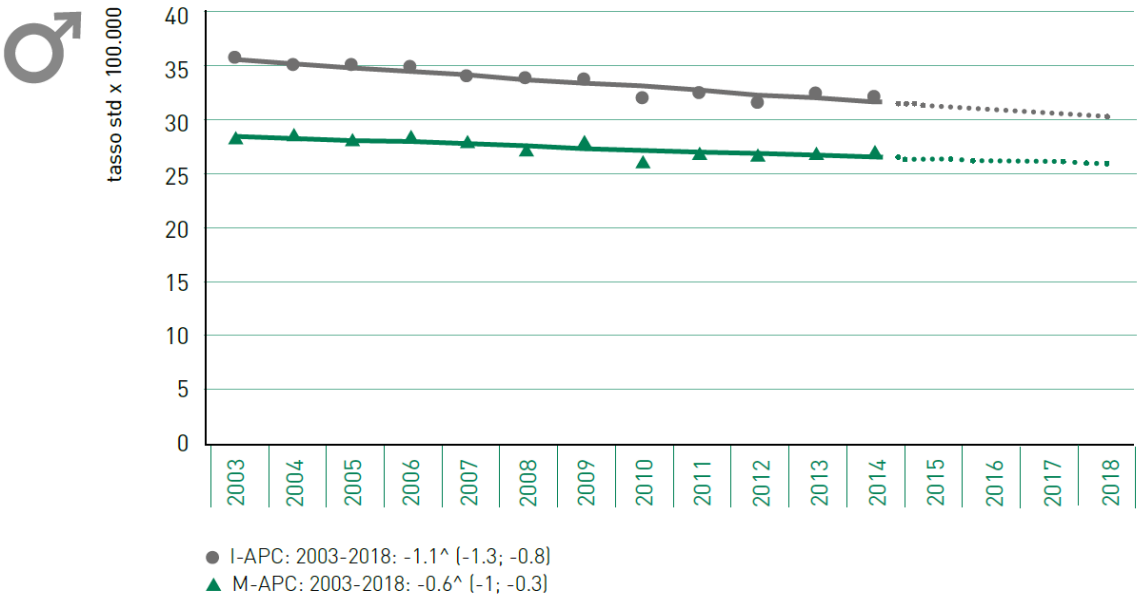
Associazione Italiana Registri Tumori

Sede tumorale	INCIDENZA		MORTALITÀ	
	Maschi	Femmine	Maschi	Femmine
Vie aerodigestive superiori*	↓	↓	↔	↑
Esofago	↓	↓	↓	↓
Stomaco	↓	↓	↓	↓
Colon-retto	↓	↓	↓	↓
Colon	↓	↓	↓	↓
Retto	↓	↓	↓	↓
Fegato	↓	↓	↓	↓
Vie biliari	↔	↓	↔	↓

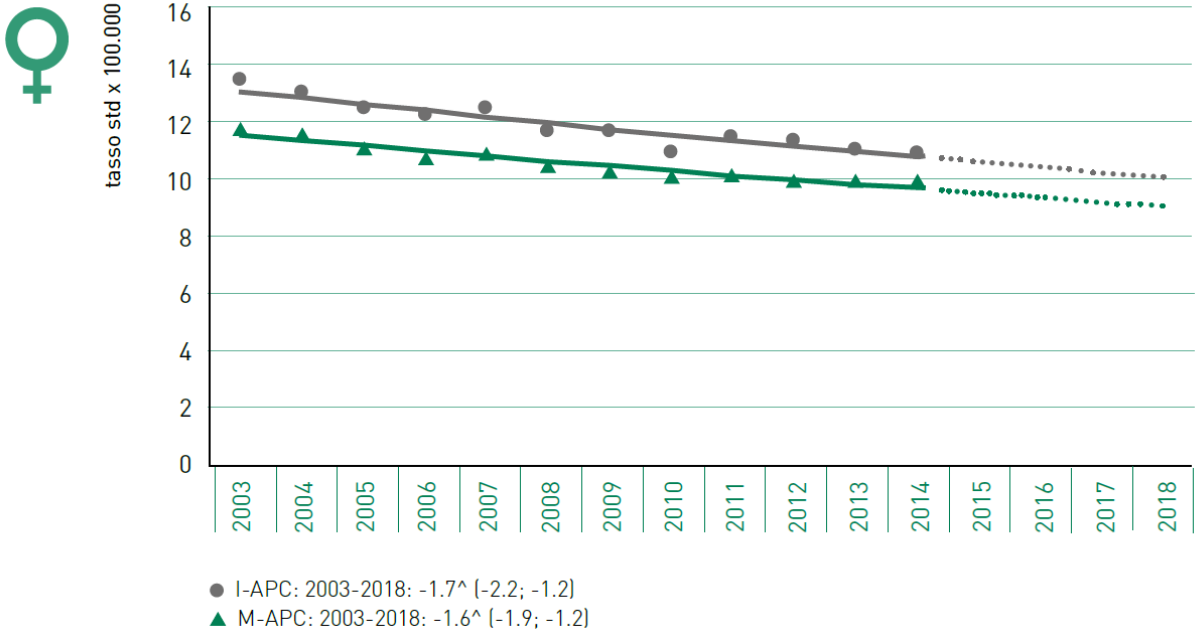
INCIDENZA: 12,800 nuovi casi attesi nel 2018 (3% di tutti i nuovi casi di tumore), rapporto 2:1 M/F
MORTALITA': 9,675 decessi per tumore al fegato nel 2015 (dati ISTAT)

EPIDEMIOLOGIA

Tumore del fegato



Trend di incidenza e mortalità



FATTORI DI RISCHIO PER EPATOCARCINOMA

- **HCV (31%, 170 milioni HCV+)**
- **HBV (54%, 400 milioni HBV+)**
- HDV/HBV (15-20 milioni HDV+)
- **Alcol**
- Aftlatossine (+ HBV)
- Disordini ereditari (e.g. emocromatosi)
- Obesità (+ DM)
- **NAFLD/NASH (con o senza infezione virale)**
- Tabacco

Table 2. Geographical distribution of main risk factors for primary liver cancer world-wide.

	Alcohol (%)	HBV (%)	HCV (%)	Others (%)
Europe				
Western	32	13	44	10
Central	46	15	29	10
Eastern	53	15	24	8
North America	37	9	31	23
Andean Latin America	23	45	12	20
Asia				
East Asia	32	41	9	18
Asia-Pacific	18	22	55	6
South-East Asia	31	26	22	21
Africa				
North Africa, Middle East	13	27	44	16
Southern (sub-Saharan)	40	29	20	11
Western (sub-Saharan)	29	45	11	15

CIRROSI (80-90% dei casi)

EPATOCARCINOMA NEL PAZIENTE HIV +

NON AIDS-DEFINING CANCERS

Tumore	Popolazione target per screening
LINFOMA DI HODGKIN	----
TUMORI ANO-GENITALI ASSOCIATI AD HPV (CARCINOMA DELL'ANO)	MSM; Tutti con storia di condilomi ano- genitali; Donne con istologia genitale patologica
EPATOCARCINOMA	**HCV coinfetti con cirrosi; Tutti HBV con viremia rilevabile; Tutti HBV/HCV aviremici se con cirrosi; Tutti HCV aviremici (post-DAAs) con pregresso epatocarcinoma**.
CARCINOMA POLMONE	Fumatori con storia di > 30 pacchi di sigarette/anno; se ex-fumatori entro 15 anni dalla cessazione; Età> 40 aa
CARCINOMI CUTANEI NON MELANOMA	Pelle chiara; Razza bianca non-ispanica

Linee Guida Italiane, 2017

EPATOCARCINOMA IN PAZIENTI CON INFEZIONE DA HIV

- Incidenza di HCC:

  - Rischio maggiore (3-6 volte) rispetto alla popolazione generale: 10-36/100,000 PY [Shiels MS et al 2009, Engels 2006, Franceschi 2010]
  - Incidenza maggiore nei coinfetti HIV/HCV rispetto ai monoinfetti HCV **solo se** aggiustata per età [Kramer 2015, Lo 2014]
  - The incidence of HCC is higher among patients with HIV infection than controls in the general population, and HIV appears to be an additive co-factor, increasing the risk of HCC in patients with chronic viral hepatitis.[53]

[EASL Clinical Practice Guidelines, 2018]

- EPATOCARCINOMA HCV- RELATO
- EPATOCARCINOMA HBV- RELATO (E HDV/HBD- RELATO)
- EPATOCARCINOMA NAFLD/NASH- RELATO

- **EPATOCARCINOMA HCV- RELATO**
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EPATOCARCINOMA HCV-relato

- Rischio è stimato 3-8% per anno in pz cirrotici HCV+
- Fattori di rischio: età, M, HIV+, HBV+, DM, obesità.
- SVR post-IFN hanno mostrato riduzione del 70% nella incidenza di HCC
- Il rischio è ridotto ma non eliminato (1,5%) → sorveglianza pz cirrotici (F3-F4)

- Risultati contrastanti sull'insorgenza di HCC nei pazienti mono-infetti cirrotici trattati con i **nuovi regimi IFN-free** per epatite cronica C

De novo HCC risk after DAA therapy

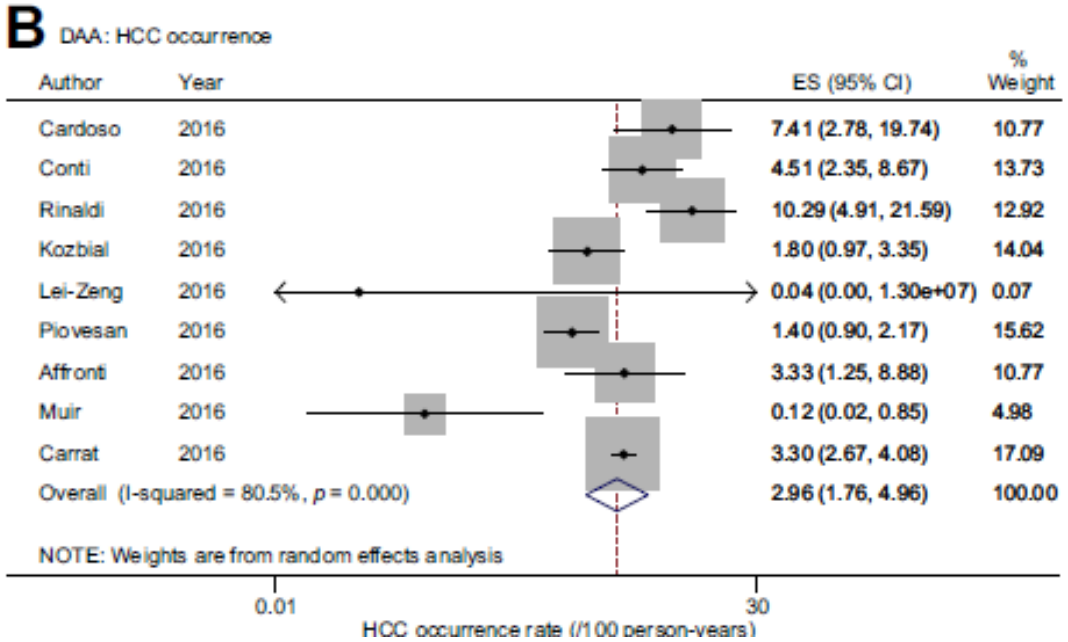


TABLE 1 Studies evaluating risk of de novo HCC after DAA therapy

Authors (reference)	Type of study	n	Cirrhosis (%)	Follow-up (Median)	HCC incidence (%)
Cardoso[23]	Retrospective	54	100	12 mo after SVR	7.4%
Kozbial[17]	Retrospective	195	NA	13 mo after DAA cessation	6.6%
Ravi[19]	Retrospective	66	100	6 mo after DAA cessation	9.1%
Foster[24]	Prospective	467	77.5	6 mo after DAA initiation	5.4%
Conti[15]	Retrospective	285	100	6 mo after DAA cessation	3.16%
Cheung[25]	Prospective	406	100	15 mo after DAA initiation	4% at 6 mo (same as in 261 patients not receiving DAA) 6.7% at 1 y
Calleja[26]	Retrospective	3233	52	18 mo after DAA initiation	0.9%
Kobayashi[27]	Retrospective	77	NA	4 y	2.6%
Toyoda[28]	NA	413	NA	NA	Annual incidence: 0.62%-0.85%
Kanwal[22]	Retrospective	22 500	39	22 963 person-years after DAA cessation	SVR: 0.9 per 100 patient-years Non-SVR: 3.45 per 100 patient-years
Ioannou[21]	Retrospective	21 948	24	6.1 y	1.32 per 100 patient-years

DAA, direct acting antivirals; NA, not available; SVR, sustained virological response; HCC, hepatocellular carcinoma.

HCC recurrence risk after DAA therapy

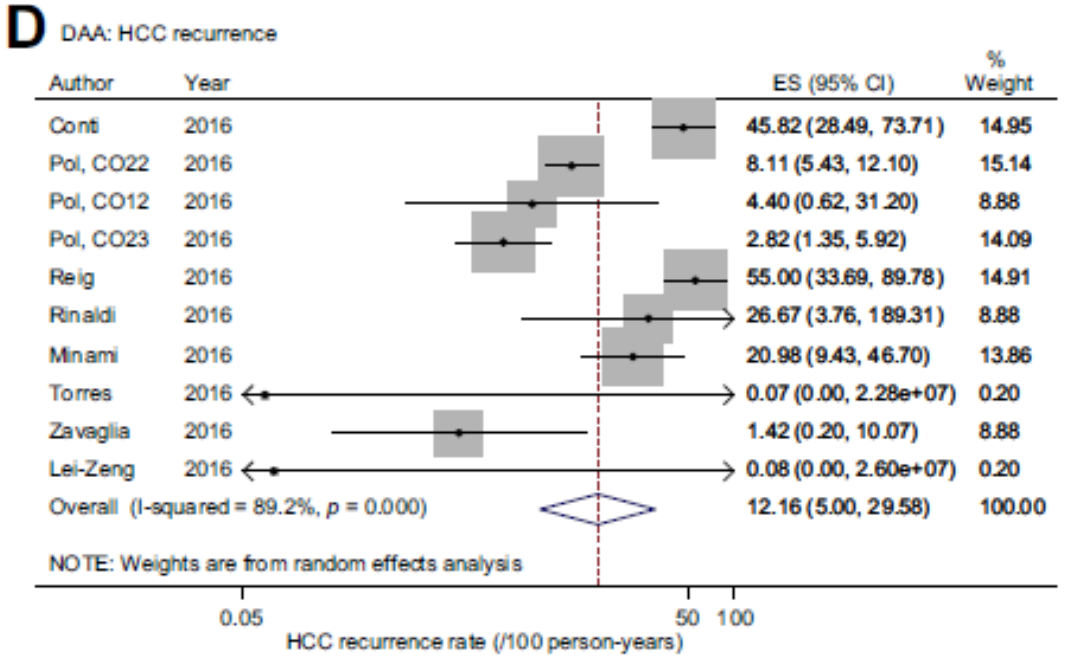


TABLE 2 Studies evaluating risk of HCC recurrence after DAA therapy

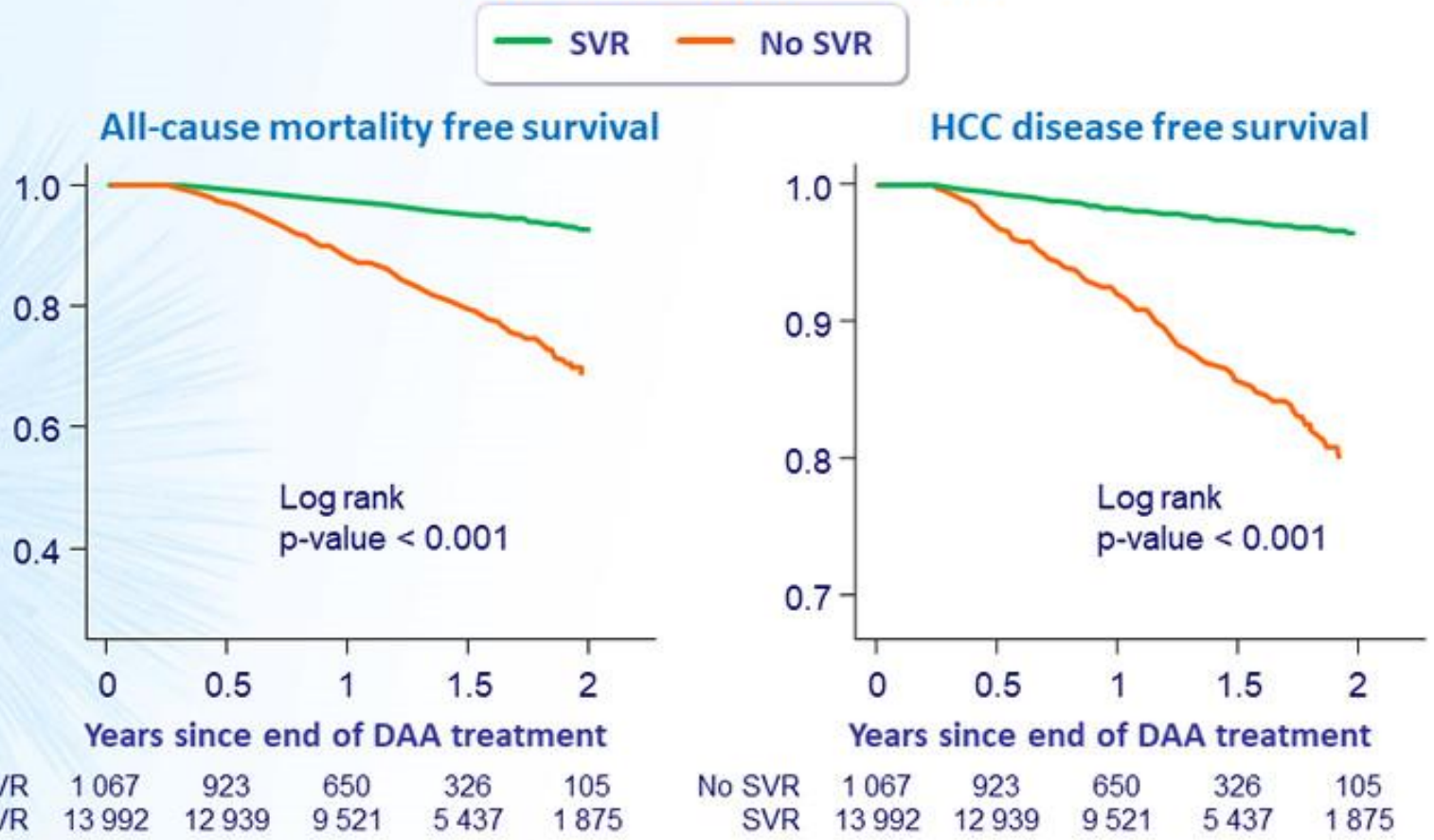
Authors (reference)	Type of study	n	Treatment for previous HCC	Follow-up (Median)	HCC recurrence (%)
Reig[16]	Retrospective	58	Resection, ablation, TACE	6 mo from DAA initiation	27.6% Median 3.5 mo from DAA initiation to HCC recurrence
Conti[15]	Retrospective	59	Resection, ablation, TACE	12 mo from HCC treatment to DAA initiation	28.8% Within 24 wk of DAA completion
ANRS[32]	Prospective	HEPATHER: 189/267 (71%) received DAA	Resection, ablation, LT	DAA-treated: 20 mo from DAA initiation DAA untreated: 26 mo from SVR	DAA-treated: 13% 0.73 per 100 person-months DAA untreated: 21% 0.66 per 100 person-months
		CirVir: 13/76 (17%) received DAA	Resection, ablation	21 mo from SVR	DAA-treated: 1.11 per 100 person-months DAA untreated: 1.73 per 100 person-months
		CUPILT: 314	LT	67 mo (mean) from LT to DAA initiation	2.2%; 7 mo (mean) from DAA initiation to HCC recurrence
Cabibbo[30]	Prospective	143	Resection, ablation, TACE	2 mo (mean) from HCC treatment to DAA initiation Follow-up 9 mo after DAA initiation	12% within 6 mo of DAA initiation 26.6% within 12 mo of DAA initiation
Calleja[26]	Retrospective	70	NA	20 mo (mean) from HCC treatment	12.9% within 6 mo of DAA initiation 30% within 12 mo of DAA initiation
Minami[31]	NA	27/926 (3%)	Ablation	16 mo from DAA initiation	29.8% within 12 mo of DAA initiation (vs 31% in untreated patients)

DAA, direct-acting antivirals; NA, not available; SVR, sustained virological response; HCC, hepatocellular carcinoma; TACE, chemoembolization; LT, liver transplantation.

Clinical outcome after SVR: Veterans Affairs

HCV-trials.com

Survival curves for patients with advanced liver disease with and without SVR



Veterans Affairs

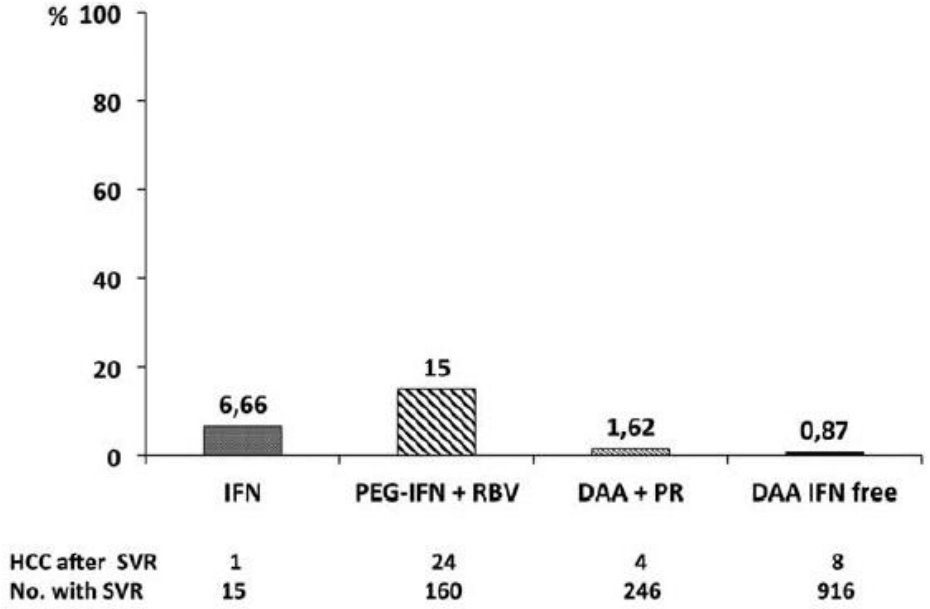
Backus L, AASLD 2017, Abs. 78

Paziente co-infetto HIV/HCV

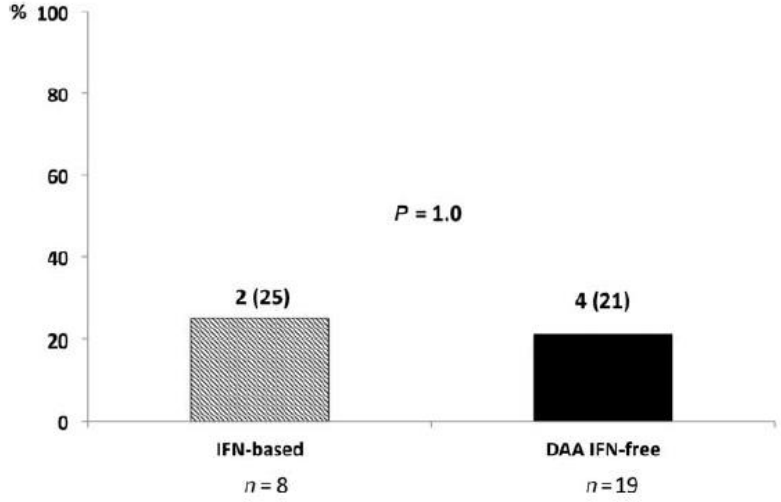
- Pochi dati al momento

- Coorte GEHEP-002 multicentric cohort da 32 centri in Spagna (dal 1999).
- 322 casi di HCC diagnosticati in **pazienti HIV/HCV** .

HCC frequency after SVR in HIV/HCV + with cirrhosis



HCC recurrence frequency after SVR in HIV/HCV + with cirrhosis



Merchante et al, AIDS 2018

- Drop in HCC after SVR with DAA-IFN-free regimens (0,87%).
- Not increased recurrence of HCC associated with DAA regimens.
- Not increased or earlier presentation of *de novo* HCC associated with DAA regimens (0,4-2% annual incidence).

PROGETTO REC-HIV: insorgenza di epatocarcinoma nei pazienti cirrotici con coinfezione da HIV e HCV trattati con antivirali diretti.

- Studio multicentrico per determinare il rischio di HCC dopo SVR post-terapia con regimi DAAs per HCV, nei pazienti con infezione da HIV

CENTRI PARTECIPANTI
UO Malattie Infettive, Policlinico S.Orsola Malpighi, Bologna (centro coordinatore)
UO Malattie Infettive, Policlinico di Modena
UO Malattie Infettive, Arcispedale S.Anna, Ferrara
UO Malattie Infettive, Azienda Ospedaliera Universitaria di Parma
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UO Malattie Infettive, Ospedale Infermi, Rimini
UO Malattie Infettive, Ospedale S. Maria delle Croci, Ravenna
UO Malattie Infettive, Ospedale Niguarda, Milano
UO Malattie Infettive, Ospedale S. Matteo, Pavia

140 pazienti HIV+ HCV+ trattati con DAAs (fino a Gennaio 2017)

134 pazienti con SVR 12

14 diagnosi di HCC post SVR (10,4%)

Caratteristiche pazienti	N (%)
F4 sec. Metavir	71 (78%)
HBsAg +	6 (6,6%)
CDC C	20 (23%)
HIV RNA n.d.	125(93,2%)
CD4+ T-cells	597/mmc
C-P score ≥7	27 (30%)
Passato HCC	5 (3,7%)

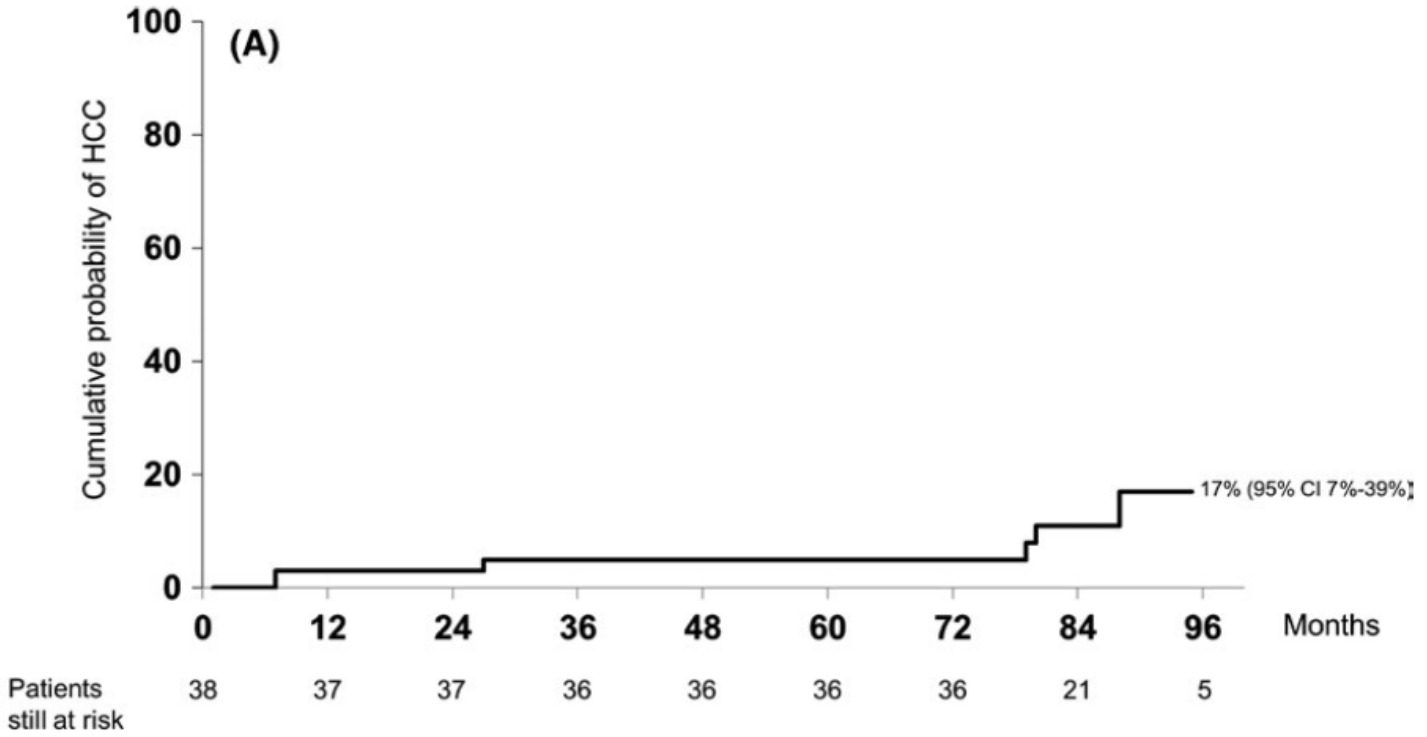
Caratteristiche HCC	N (%)
Nuova insorgenza	12/14 (86%)
Recidiva	2/14 (14 %)
Noduli multipli	2/14 (14%)
Metastatico	0

Unpublished data

Persistence of hepatocellular carcinoma risk in hepatitis C patients with a response to IFN and cirrhosis regression

TABLE 1 Baseline demographic and clinical features of the patients according to fibrosis stage (F4 vs <F4)

Features	Overall (n = 38)	Non-Regressors (F4) (n = 15)	Regressors (<F4) (n = 23)	P value
Age, years[a]	66 (46-75)			
Males, n	24 (65%)			
BMI, Kg/m^2[a]	24.5 (19.9-34			
Anti-HBc, n[a]	17 (48.5%)			
Diabetes, n	4 (10.5%)			
Disease duration, months[a]	186 (60-633			
METAVIR F0/F1/F2/F3/F4, n	0/2/7/14/15			
TE value, kPa[a]	9.8 (4.4-34.			
PLT, 10^3/mm^3[a]	202 (85-401			
ALT, U/L[a]	21 (9-53)			
Normal ALT, n	27 (71%)			
γGT, U/L[a]	28 (11-109)			
Albumin, mg/dL[a]	4.6 (3.7-5.3			
INR[a]	1.01 (0.86-1.			
Bilirubin, mg/dL[a]	0.5 (0.4-2.4			
Cholesterol, mg/dL[a]	210 (154-26			
Cholesterol > 200 mg/dL, n	21 (55%)			
HDL < 60 mg/dL, n	23 (61%)			
Triglycerides, mg/dL[a]	112 (13-211			
Triglycerides > 150 mg/dL, n	5 (13%)			
Glucose, mg/dL[a]	89 (71-297			



The 8-years cumulative probability of HCC was 17%, with an annual estimated incidence rate of 1,2%.

D'Ambrosio, Liv Inter 2018

- EPATOCARCINOMA HCV- RELATO
- **EPATOCARCINOMA HBV- RELATO (E HDV/HBD- RELATO)**
- EPATOCARCINOMA NAFLD/NASH- RELATO

EPATOCARCINOMA HBV-relato

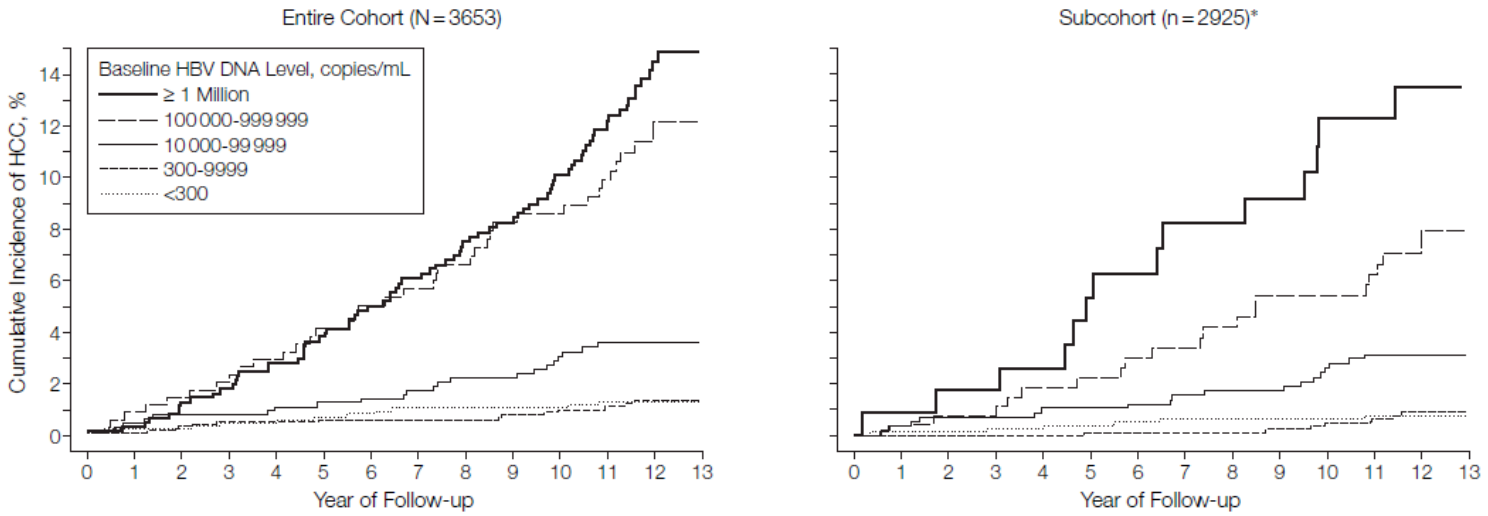
- Rischio 2% per anno in pazienti cirrotici HBV+
- 54% degli HCC, paesi a basso-medio reddito
- HBV DNA, Genotipo C, HBsAg, HBeAg+
- Fattori dell'ospite (età, M, familiarità, aflatossine, NASH/NAFLD)
- Altri fattori virali (coinfezioni)
- Meccanismi molecolari di induzione di HCC:
  - Infiammazione immuno-mediata
  - Integrazione di HBV
  - Proteina HBx
  - HBsAg

Ming Wang et al. Hepatol Int (2017)

Risk of Hepatocellular Carcinoma Across a Biological Gradient of Serum Hepatitis B Virus DNA Level

REVEAL-HBV study

Figure 2. Cumulative Incidence of Hepatocellular Carcinoma by Serum HBV DNA Level at Study Entry



No. at Risk

Baseline HBV DNA Level, copies/mL														
≥1 Million	627	621	611	604	593	582	571	561	550	541	528	513	499	414
100 000-999 999	349	346	342	338	333	327	321	317	310	304	302	294	288	228
10 000-99 999	643	637	633	633	627	625	622	615	609	606	597	588	586	490
300-9999	1161	1155	1146	1139	1137	1131	1129	1123	1119	1113	1102	1091	1082	879
<300	873	865	862	854	850	845	836	826	823	819	814	807	802	720

Subcohort (n = 2925)*														
≥1 Million	116	115	113	113	111	108	105	101	101	100	95	94	92	78
100 000-999 999	271	271	269	268	265	262	259	256	250	246	246	241	237	186
10 000-99 999	595	590	586	586	581	580	578	572	568	566	557	548	546	454
300-9999	1104	1099	1095	1090	1088	1082	1080	1074	1070	1065	1055	1044	1036	847
<300	839	832	830	823	819	815	806	797	794	790	786	780	775	697

All participants were seropositive for the hepatitis B surface antigen (HBsAg) and seronegative for antibodies against the hepatitis C virus. Asterisk indicates these participants were seronegative for the hepatitis B e antigen and had a normal level of serum alanine aminotransferase and did not have liver cirrhosis at study entry. HBV indicates hepatitis B virus; HCC, hepatocellular carcinoma.

JAMA, January 4, 2006—Vol 295, No. 1

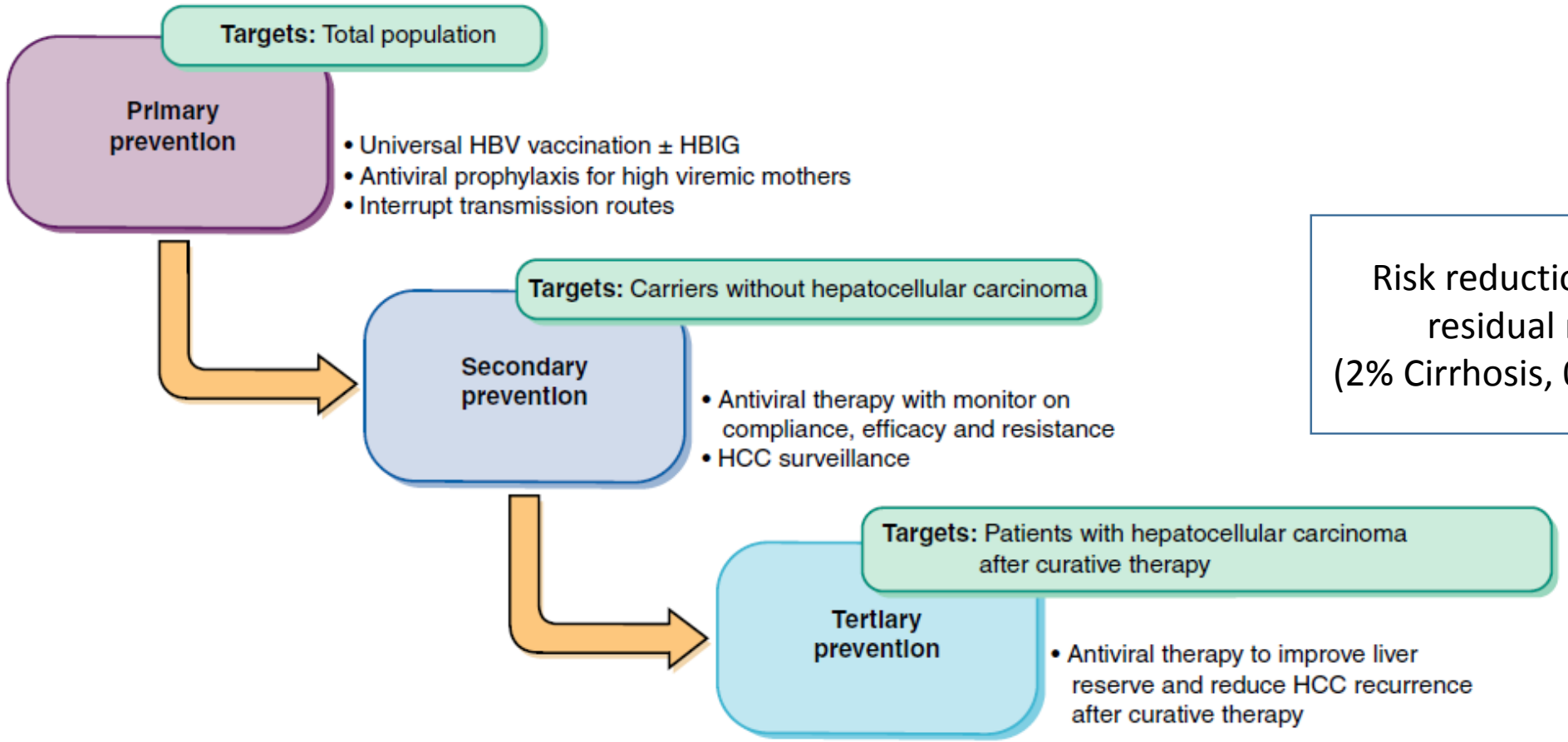
Systematic review of risk factors of hepatocellular carcinoma after hepatitis B surface antigen seroclearance

- 28 studies
- More than 100,000 patients.
- Rate of HBsAg seroclearance was 6,77 %
- Incidence of HCC was significantly lower in those who experienced HBsAg seroclearance (1,86 % vs 6,56 %, p< 0,001)
- Risk factors: cirrhosis, male, age older than 50 years old.
- Scarce evidence to support surveillance in this group.

X-J Kuang, J Viral Hepat 2018

Review article: the prevention of hepatitis B-related hepatocellular carcinoma

Lin and Kao, 2018



Risk reduction with NA, but residual risk remains
(2% Cirrhosis, 0,4% no Cirrhosis)

EPATOCARCINOMA HBV/HDV-relato

Table 1. The epidemiological studies on the role of hepatitis D virus infection in increasing the risk of hepatocellular carcinoma

Fattovich *et al.* [26]	Estimated risk for HCC 13% for HBV/HDV cirrhotics as compared with 2–4% for HBV cirrhotics
Cross *et al.* [27]	Risk of HCC similar in HDV positive and negative patients
Uzunalim [28]	
Değertek	
Toukan e	
Romeo e	l 2.8%
Buti *et al.*	d HCC
Ji *et al.* [	ng risk
Romeo e	ciated
Tamura *et al.* [35]	1127 patients were followed for at least 3 years. The prevalence was 4.05 per 1000 person years in HDV co-infection patients compared with 2.73 in patients with HBV alone
Huo *et al.* [36]	42 HDV co-infected patients were compared with 255 HBV patients, all with HCC, over a period of 8 years. HDV co-infection does not accelerate HCC development, and the outcomes are the same as HBV mono-infection
Amougou *et al.* [37]	88 consecutive HCC patients and 85 controls without known liver disease were analysed. The analysis of risk factors associated with the development of HCC demonstrated a strong association with the presence of HBV, HCV and HDV markers (OD = 16.3, 9.6 and 29.3)
Béguelin *et al.* [38]	HDV infection appeared strongly associated with overall death (adjusted hazard ratio 2.33), liver-related death (7.71) and HCC occurrence (9.30)

TRATTAMENTO DI HDV

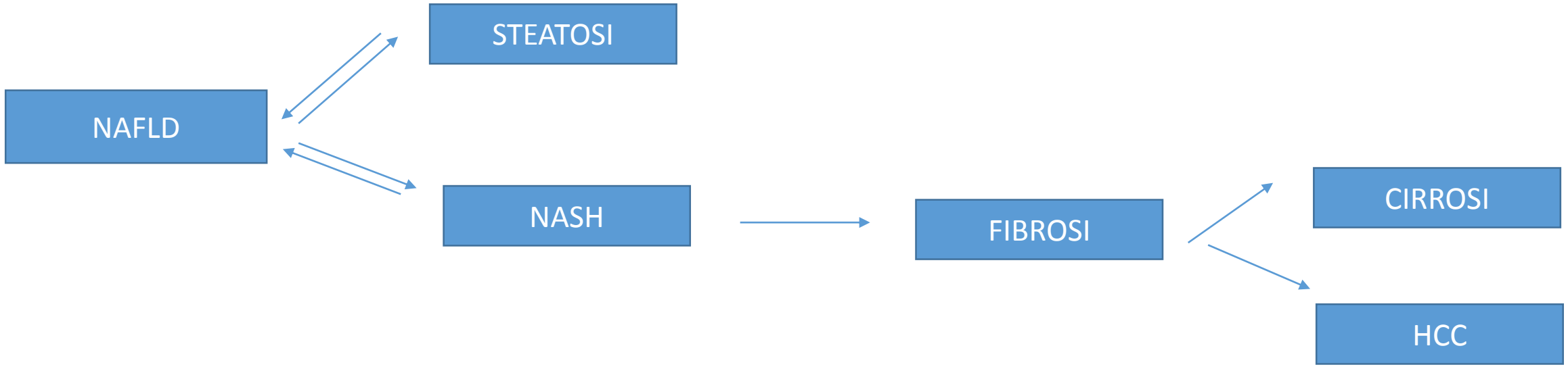
- HBsAg clearance
- Inefficiacia di antivirali da soli
- **Peg-IFN** (HDV RNA n.r. a 6 mesi e basse GGT : predittori di risposta virologica)
- Associazione Peg-IFN + NA
- Myrcludex B

Romeo R et al, Epidemiology and Infection (2018)

- EPATOCARCINOMA HCV- RELATO
- EPATOCARCINOMA HBV- RELATO (E HDV/HBD- RELATO)
- **EPATOCARCINOMA NAFLD/NASH- RELATO**

EPATOCARCINOMA NAFLD/NASH -RELATO

- NAFLD: Non Alcoholic Fatty Liver Disease
- NASH: Non Alcoholic Steato-Hepatitis
- 1 /4 - 1/3 della popolazione mondiale ha NAFLD
- NAFLD causa sempre più frequente di HCC in Italia (Bucci et al Liv Inter 2017)
- HCC 1° causa di morte per NAFLD (Ekstedt et al Hepatol 2015)



APPROCCIO A SOSPETTA NAFLD

- Sindrome metabolica, uso di d-drugs come antiretrovirali (ddC, ddI, d4T)
- Alterazione enzimi epatici in assenza di altre patologie del fegato
- Ecografia compatibile
- Fibroscan con CAP (controlled attenuation parameter) > 250 dB/m
- Biopsia per differenziare steatosi semplice da NASH

SCREENING e PREVENZIONE di HCC

→ PAZIENTI CON INFEZIONE CRONICA DA HBV (+/- HDV) O HCV (+/- HIV), EPATOPATIA ALCOLICA, NASH

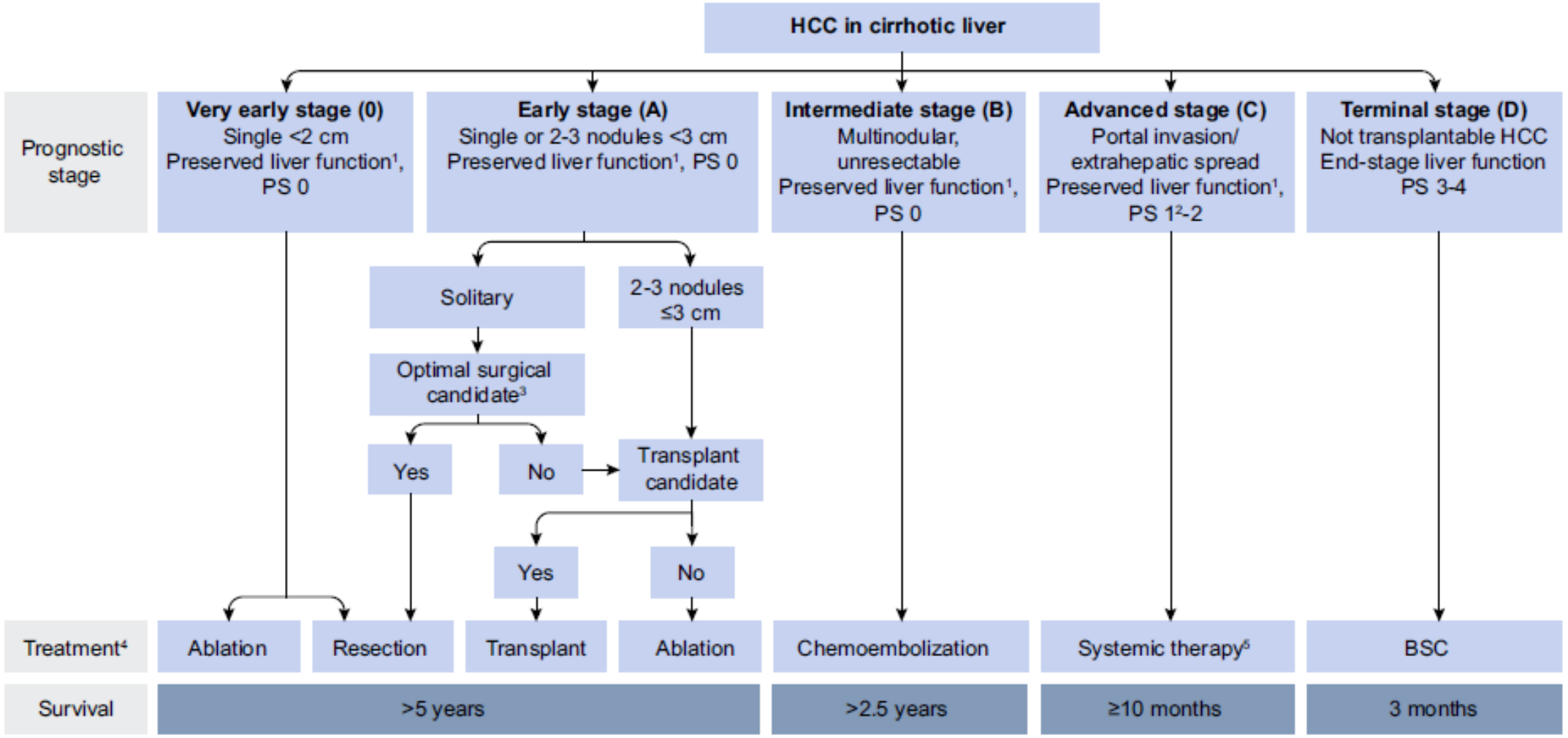
- Terapia della infezione da HCV, da HBV e da HDV
- Inizio precoce della terapia antiretrovirale (coinfezione HIV)
- Ecografia addominale ogni 6-12 mesi nella popolazione a rischio (Linee Guida HIV Italia, AASLD)
- Bassa sensibilità e specificità di Alfafetoproteina come test di screening → mai come unico test di screening
- Migliore sopravvivenza di HCC diagnosticati in esame di screening (candidabili a trattamenti curativi)

APPROCCIO DIAGNOSTICO

- Diagnosis in cirrhotic patients should be based on non-invasive criteria and/or pathology
- Diagnosis in non-cirrhotic patients should be confirmed by pathology
- Non-invasive criteria can be applied to cirrhotic patients for nodules ≥1 cm and are based on imaging techniques obtained by CT, MRI or CEUS.
- APHE plus wash-out on portal venous/delayed phases.
- CT or MRI should be used first
- FDG PET scan is not recommended for early diagnosis of HCC

EASL Clinical Practice Guideline 2018

TRATTAMENTO DELL'EPATOCARCINOMA



Clinical Practice Guidelines-EASL 2018

Trattamenti curativi

- Resezione chirurgica
- Trapianto epatico (OLT)
- Terapie locali ablative (PEI, RFA)

Trattamenti non curativi

- Chemio-embolizzazione
- Terapia sistemica
- BSC

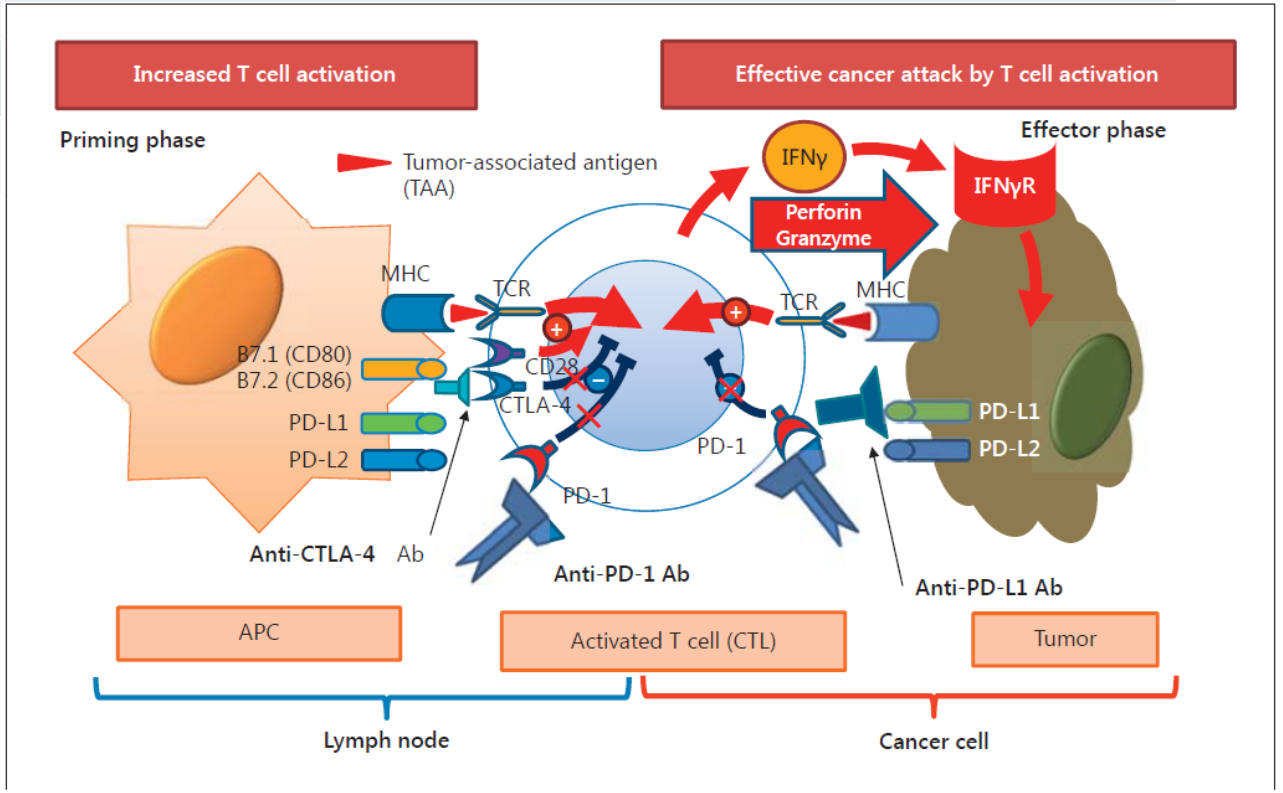
VERLY EARLY/EARLY STAGE

INTERMEDIATE/ ADVANCED/TERMINAL STAGE

TERAPIA SISTEMICA: update

Molecular targeted Agents (TKIs)	Immune Check-points Inhibitors
SORAFENIB (SHARP study 2008)	**Ab monoclonali Vs PD-1**
LENVATINIB (REFLECT trial 2018)	Ab monoclonali Vs PD-L1
BRIVANIB (BRISK-FL study 2013)	Ab monoclonali Vs CTLA-4
REGORAFENIB (RESORCE study 2017)*	
CABOZANTINIB (CELESTIAL trial 2018)*	
TIVANTINIB (METIV-HCC study 2018) *	

* Pazienti pre-trattati con Sorafenib



TERAPIA SISTEMICA: update

Table 1. Immune checkpoint inhibitors in HCC clinical trials

Target cell	Target molecule	Development code	Drug name	Commercial name
T lymphocyte	PD-1	BMS-36558 ONO-4538	Nivolumab	Optivo
	PD-1	MK-4375	Pembrolizumab	Keytruda
Tumor cell	PD-L1	MPDL3280A	Atezolizumab	Not yet approved
	PD-L1	MEDI4736	Durvalumab	Not yet approved
	PD-L1	MSB-0010718C	Avelumab	Not yet approved
T lymphocyte	CTLA-4	BMS-734016	Ipilimumab	Yervoy
	CTLA-4	MEDI1123	Tremelimumab	Not yet approved

Kudo M, Oncology 2017

Table 4. Combination trials of immune checkpoint inhibitors with TKIs in HCC

Phase	Target	Agent
Ib/II	PD-1 + TGF-β receptor I	nivolumab + galunisertib (LY2157299)
I	PD-1 + multikinase	pembrolizumab + lenvatinib
I	PD-1 + multikinase	pembrolizumab + nintedanib
I	PD-1 + multikinase	PDR001 + sorafenib
I/II	PD-1 + c-Met	PDR001 + capmatinib (INC280)
I	PD-L1 + VEGF	durvalumab + ramucirumab
I/II	PD-1 + VEGF	nivolumab + cabozantinib
I/II	PD-1 + CTLA-4 + VEGF	nivolumab + ipilimumab + cabozantinib

Real-life experience with sorafenib for the treatment of hepatocellular carcinoma in HIV-infected patients

AIDS 2017, 31:89–95

Table 1. Features of the study population ($n = 44$).

Parameter	Value
Age (years)[a]	50 (46–52)
Male sex, no. (%)	37 (84)
Cause of HCC[b], no. (%)	
Hepatitis C	29 (66)
Hepatitis B	3 (7)
Hepatitis C and B	3 (7)
Hepatitis C and alcohol	9 (20)
HCV[c] genotype, no. (%)[d]	
1	14 (34)
3	13 (32)
4	10 (24)
Unknown	4 (10)
Previous therapy against HCV[c], no. (%)[d]	22 (54)
Previous sustained virological response, no. (%)[d]	6 (15)
Plasma HIV RNA < 50 copies/ml, no. (%)	41 (93)
$CD4^+$ cell count (cells/μl)[a]	346 (192–621)
CDC[e] C stage, no. (%)[f]	12 (32)
Antiretroviral therapy, no. (%)	44 (100)
Child–Turcotte–Pugh stage, no. (%)	
A	21 (48)
B	19 (43)
C	4 (9)
Barcelona-Clinic Liver Cancer stage, no. (%)	
A	3 (7)
B	6 (14)
C	30 (68)
D	5 (11)

66%→ HCV-related
20% → HCV/alcohol- related
7%→ HBV-related
7% → HCV/HBV-related

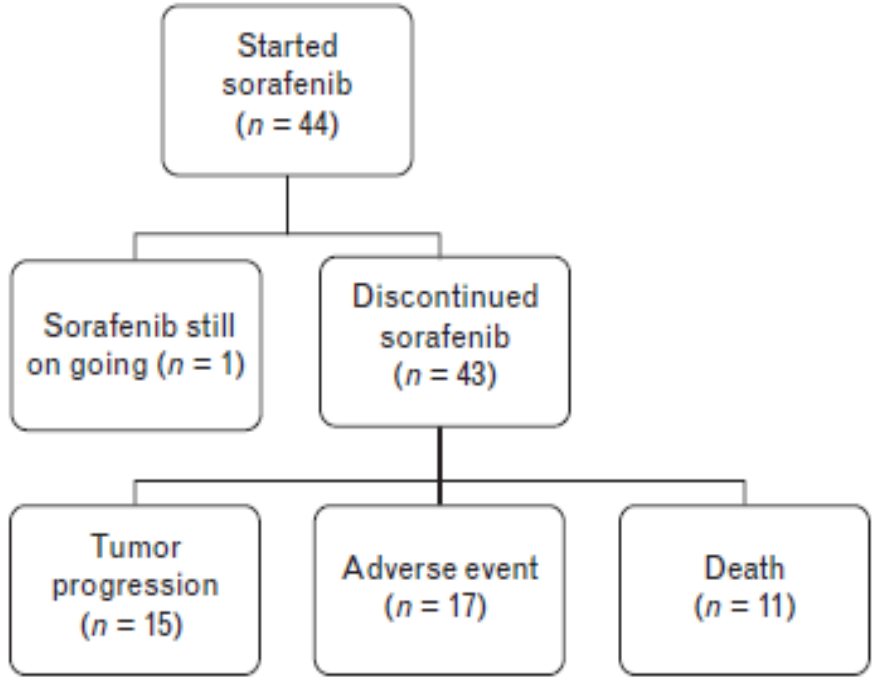


Fig. 1. Patient disposition at the end of the follow-up and reasons for sorafenib discontinuation ($n = 44$).

- **Conclusion**: The *efficacy of sorafenib under real-life conditions in HIV-infected patients seems lower* than that reported in registration clinical trial. On the contrary, *the tolerability of sorafenib appears to be similar* to what seen in patients without HIV. Sorafenib does not seem to modify the efficacy of ART.

Safety of raltegravir-based antiretroviral therapy in HIV-infected patients receiving multi-kinase inhibitors

Table 1 Patients characteristics and oncological outcomes

Characteristic	Observation
Gender: male / female: n (%)	7/5 (58/42)
Age, years: median (range)	55 (41–68)
Primary tumor: n (%)	
GIST	4 (33)
Soft tissue sarcoma	3 (25)
Hepatocellular carcinoma	3 (25)
Neuro-endocrine tumor	1 (8.5)
NSCLC	1 (8.5)
MKI received: n(%)	
Imatinib	3 (25)
Sorafenib	3 (25)
Pazopanib	3 (25)
Sunitinib	2 (16.5)
Erlotinib	1 (8.5)
Duration of MKI treatment, months: median (range)	4 (1–20+)
Worse MKI-related toxicities (grade 2): n	
Hypertension	3
Hand-foot skin reaction	2
Diarrhea	2
Skin rash	2
Hypothyroidism	1
Anemia	1
Thrombocytopenia	1
Hypophosphatemia	1
Worse MKI-related toxicities (grade 3): n	
Hypertension	2
Hand-foot skin reaction	2
Diarrhea	1

- ✓ **No Grade 4 or 5 toxicity observed**
- ✓ **No MKI reduction required**
- ✓ **No virological failure**
- ✓ **No RAL discontinuation**

TERAPIA ANTIVIRALE DOPO DIAGNOSI DI HCC

- **HIV** → inizio/continuazione di HAART è fortemente raccomandato (DDIs!)
- **HCC HBV-relati** → Analoghi Nucleos(t)idici

1. per sopprimere la replicazione HBV e stabilizzare l'epatopatia HBV-relata
2. per ridurre il rischio di recidiva di HCC
3. **HCC HCV-relati** → Direct-Acting Antivirals

1. Pazienti con HCC in lista OLT

- In patients with HCC awaiting liver transplantation with an HCV infection, liver transplantation must be considered as the main therapeutic goal and the antiviral treatment decision must be made on a case-by-case basis through a multidisciplinary discussion (**A1**).
- Antiviral treatment can be initiated before liver transplantation to prevent recurrence of infection and post-transplant complications, provided that it does not interfere with the management of the patient on the waiting list (**A2**).
- Antiviral treatment can be delayed until after transplantation, with a high likelihood of SVR (**A2**).

2. Pazienti con HCC NON in lista OLT

- Patients with decompensated (Child-Pugh B and Child-Pugh C up to 12 points) cirrhosis not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival should be treated urgently (**A1**).
- Protease inhibitors-containing regimens are contraindicated in patients with Child-Pugh B or C decompensated cirrhosis (**A1**).

Grazie per l'attenzione..