Caso Clinico

La terapia sistemica di 1^ linea

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Storia Epatologica

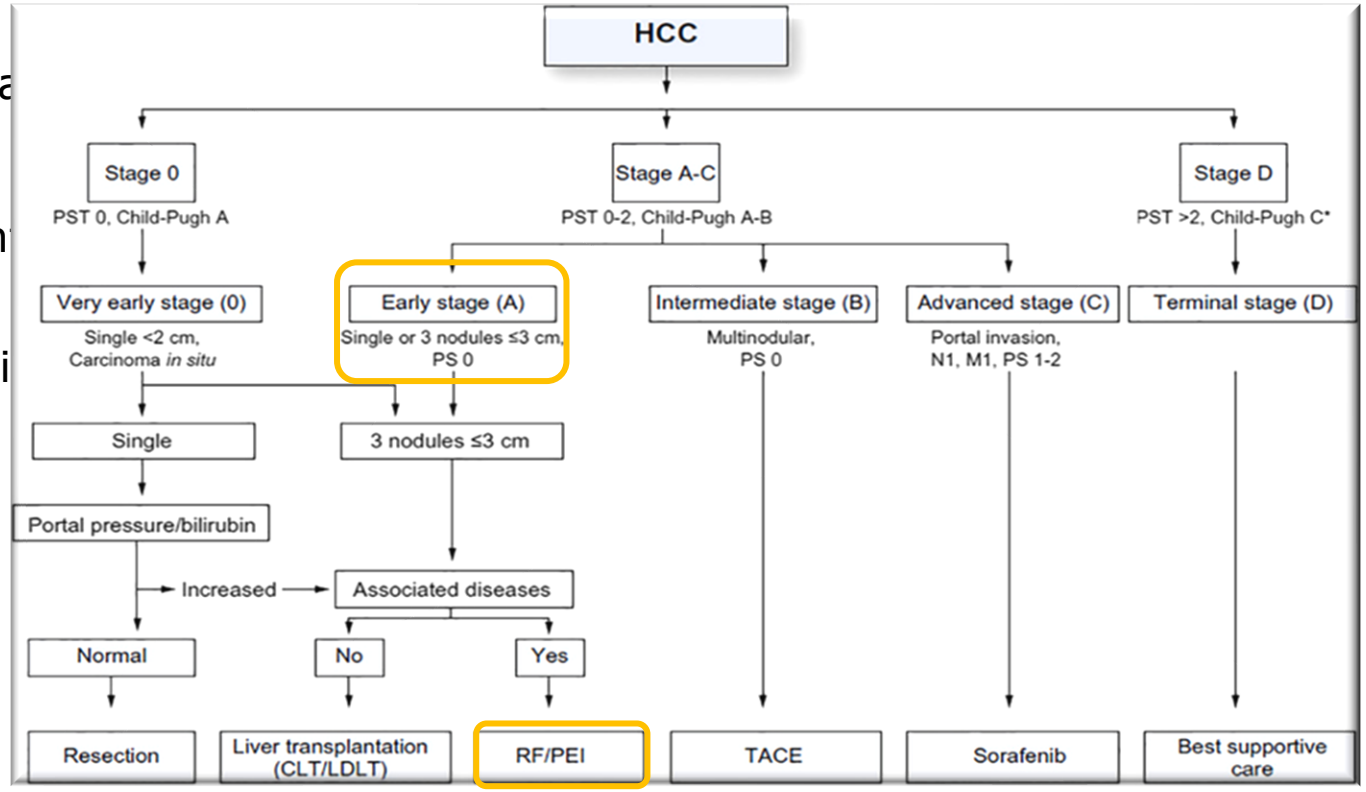
G.A. Maschio di razza caucasica, 74 anni

- 07/2015 riscontro incidentale di rialzo delle tra
- 08/2015 confermato rialzo delle transaminasi
- 09/2015 Eco addome: fegato cirrotico, presen

Avviato a valutazione epatologica con diagnosi di

HCC"

- ECOG PS 0
- AFP negativa
- Child Pugh A
- Lesione singola di 2 cm (stadio BCLC-A)

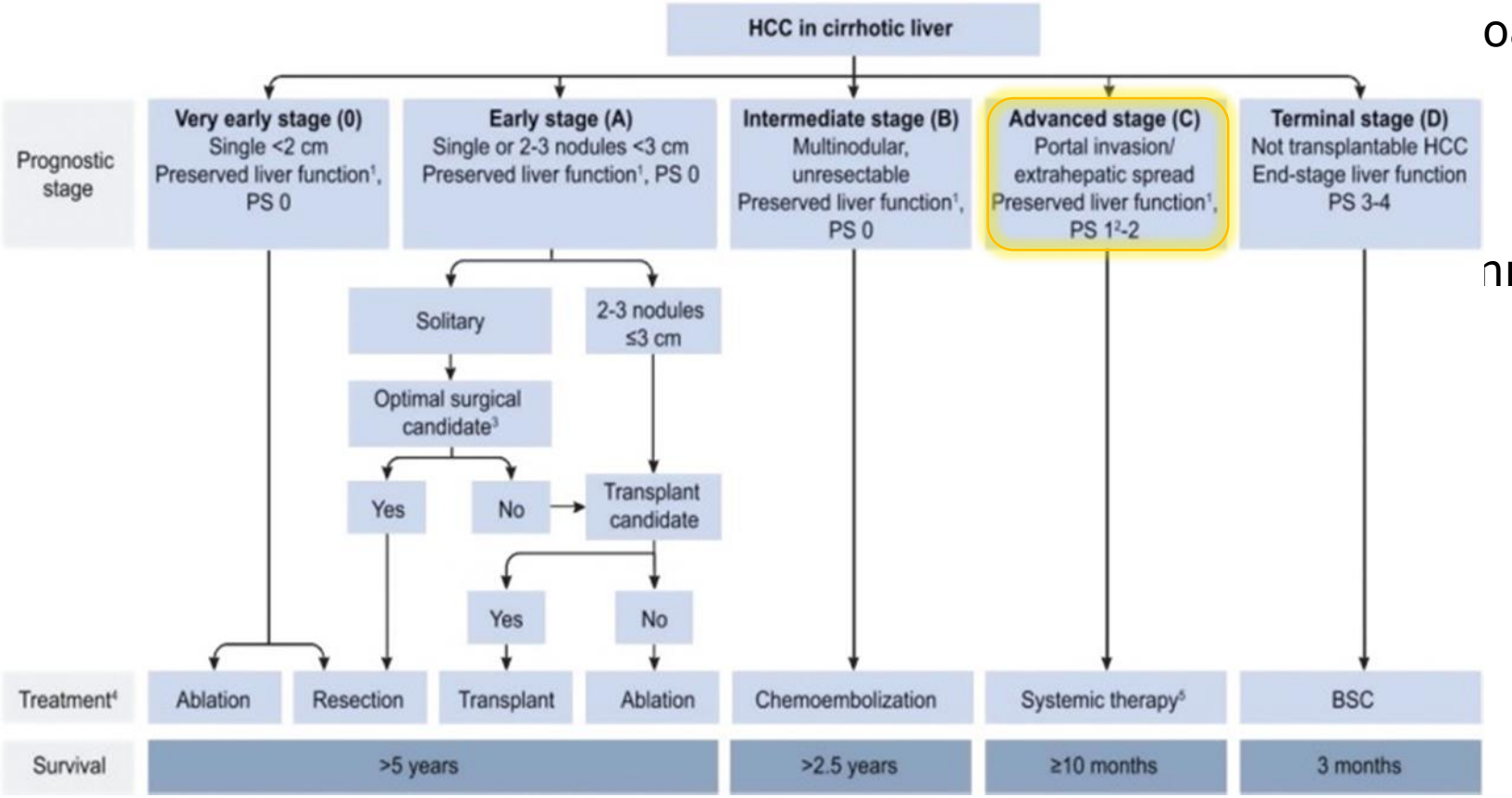


Storia Epatologica

- 12/2015 RFA percutanea S6
- 01/2018 - 03/2018 - 04/2018 TACE
- 25/06/2018 MWA VLS lesioni in S2, S2/S3 e S8
- 02/10/2018 TC: adenopatie retroperitoneali (max 27 x 25 mm), nodulo diaframmatico di 12 mm
- 18/01/2019 PET-TC: positiva a livello delle note adenopatie
- 06/02/2019 *Visita chirurgica*: sconsigliata terapia sistemica per basso carico e la lenta evolutività di malattia e per l'impatto sulla qualità di vita degli effetti collaterali
- 03/04/2019 TC: PD linfonodale addominale (incremento numerico e dimensionale)
- 04/04/2019 Agobiopsia linfonodale in ecoendoscopia --> EI: Epatocarcinoma G2
- 11/04/2019 AFP 14,7

Storia Epatologica

- 17/05/ oadenopatia della v
- 15/06/ nm), PD epatica
- 11/07/



Storia Epatologica

04/07/2019 Discussione GOM Epatobiliare (PD): confermata la ripresa di malattia epatica extraepatica -> stadio BCLC-C

INDICATA VALUTAZIONE ONCOLOGICA PER TERAPIA SISTEMICA

1^ visita Oncologica (30/07/2019)

79 anni, ECOG PS 0

Anamnesi patologica remota

- Ipertensione arteriosa nota dal 1990
- Cirrosi epatica HCV relata nota dal 2015 (trattamento antivirale con DAAs nel 2016 con SVR)
- Remoto tabagismo (20 sigarette/die per 15 anni, sospeso da 45 anni)
- Non storia di potus

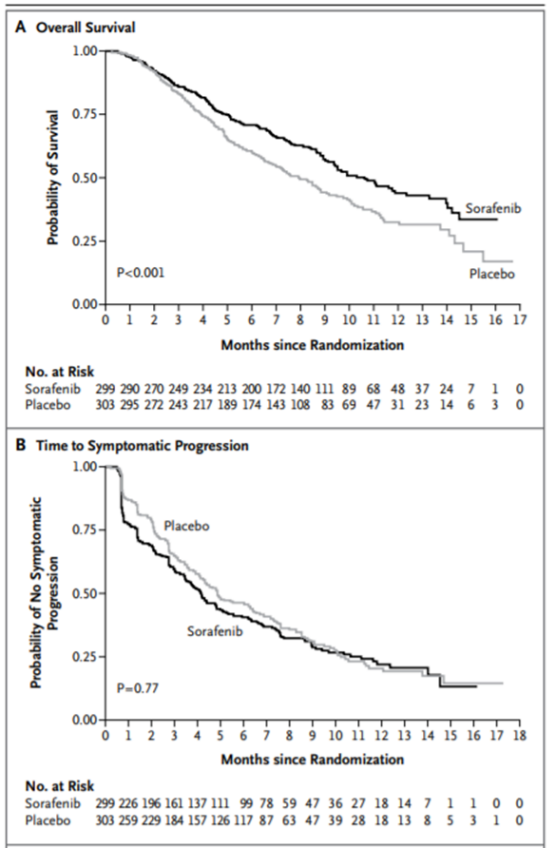
•Terapia farmacologica domiciliare

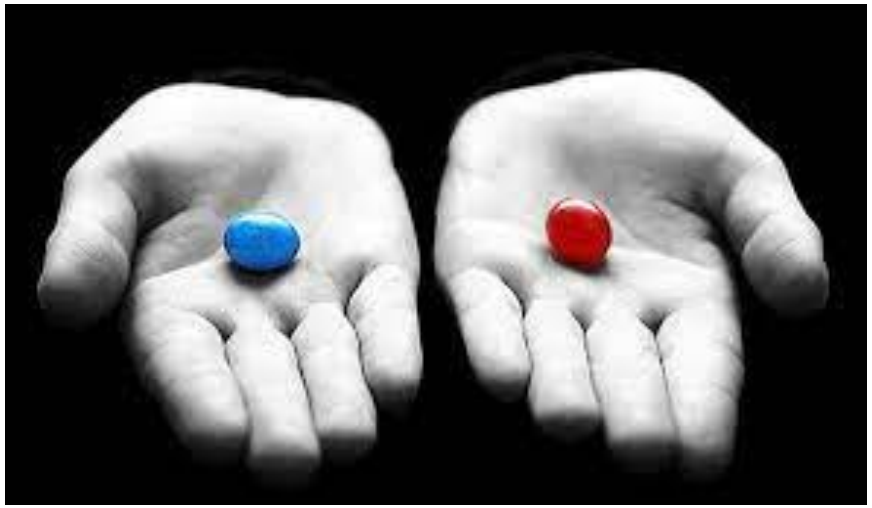
- Zolpidem 10 mg ½ cp
- Losartan 50 mg 1 cp
- Furosemide 25 mg 1 cp

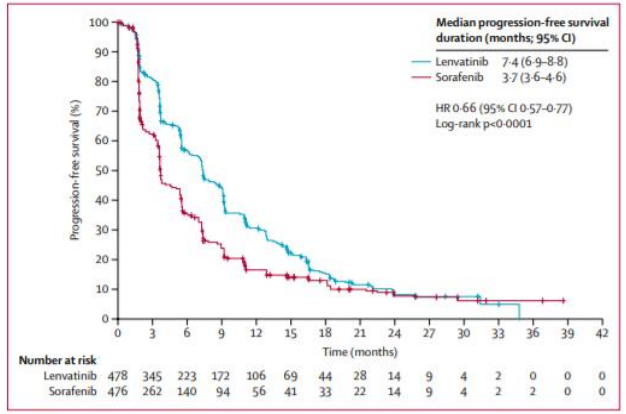
Valutazione Geriatrica Multidimensionale

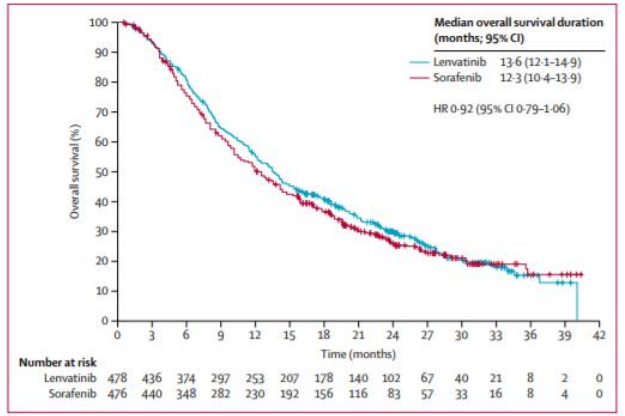
FIT

Opzioni terapeutiche









Llovet J et al NEJM 2008

Kudo M J et al Lancet 2018

Opzioni terapeutiche

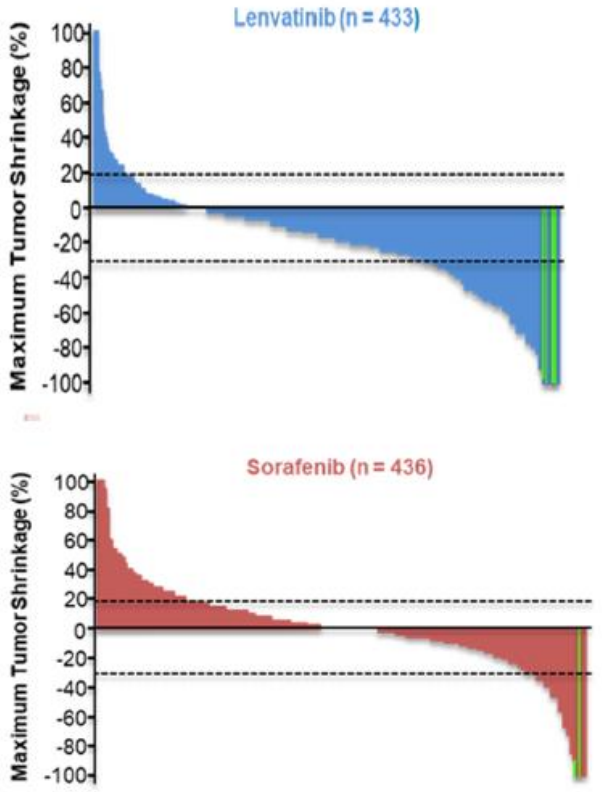
TEAE (≥20% in either arm)	Lenvatinib, % (n = 476)		Sorafenib, % (n = 475)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hypertension	42	23	30	14
Diarrhea	39	4	46	4
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Fatigue	30	4	25	4
Palmar-plantar erythrodysesthesia	27	3	52	11
Proteinuria	25	6	11	2
Dysphonia	24	0	12	0
Nausea	20	1	14	1
Alopecia	3	0	25	0

Cheng A-L, presented at ASCO 2017

Opzioni terapeutiche

Masked independent imaging review according to mRECIST				
Objective response (%, 95% CI)	194 (40·6%, 36·[illegible]–45·0)	59 (12·4%, 9·4–[illegible]·4)	OR 5·01 (3·59–7·01)	<0·0001
Complete response	10 (2%)	4 (1%)	..	..
Partial response	184 (38%)	55 (12%)	..	..
Stable disease	159 (33%)	219 (46%)	..	..
Durable stable disease lasting ≥23 weeks	84 (18%)	90 (19%)	..	..
Progressive disease	79 (17%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	46 (10%)	..	..
Disease control rate (%, 95% CI)	353 (73·8%, 69·9–77·8)	278 (58·4%, 54·0–62·8)	..	..

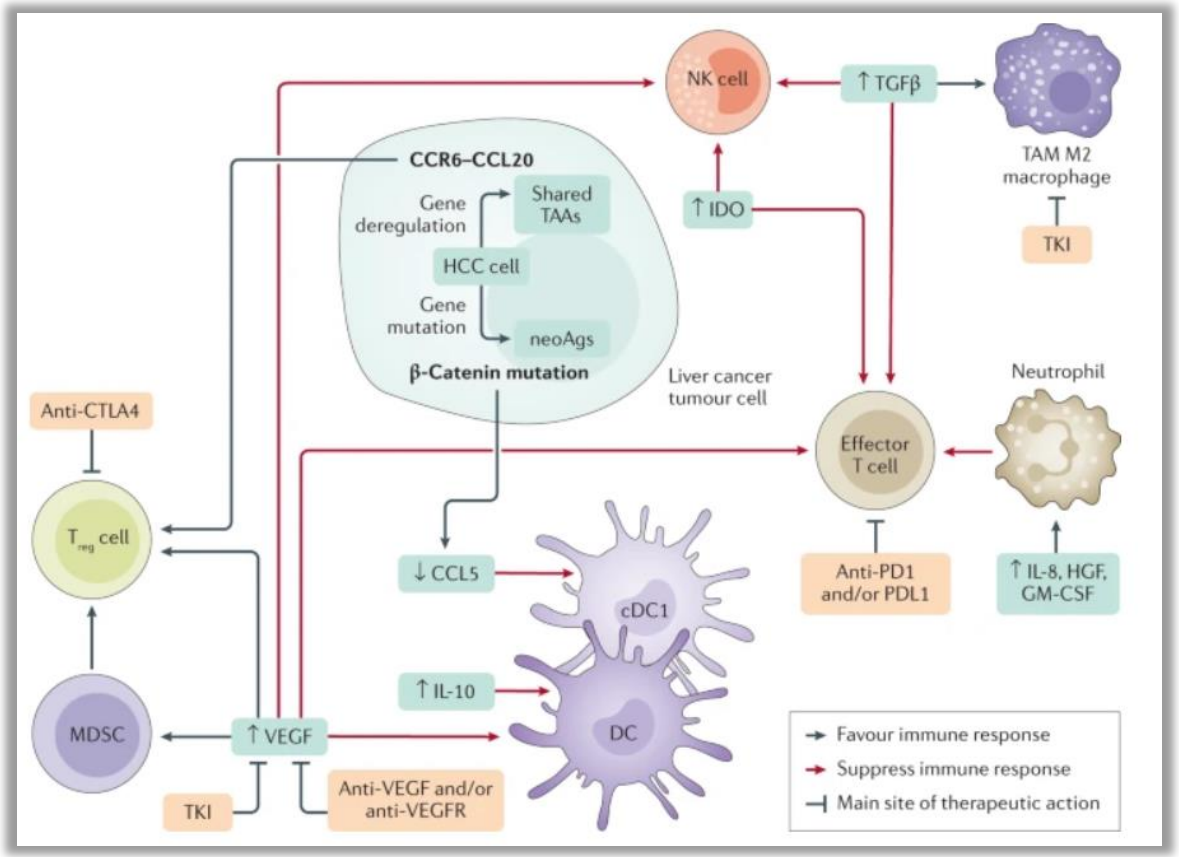
Investigator review according to mRECIST				
Objective response (%, 95% CI)	115 (24·1%, 20·2–27·9)	44 (9·2%, 6·6–11·8)	OR 3·13 (2·15–4·56)	<0·0001
Complete response	6 (1%)	2 (<1%)	..	..
Partial response	109 (23%)	42 (9%)	..	..
Stable disease	246 (51%)	244 (51%)	..	..
Durable stable disease lasting ≥23 weeks	167 (35%)	139 (29%)	..	..
Progressive disease	71 (15%)	147 (31%)	..	..
Unknown or not evaluable	46 (10%)	41 (9%)	..	..
Disease control rate (%, 95% CI)	361 (75·5%, 71·7–79·4)	288 (60·5%, 56·1–64·9)	..	..



Kudo M J et al Lancet 2018

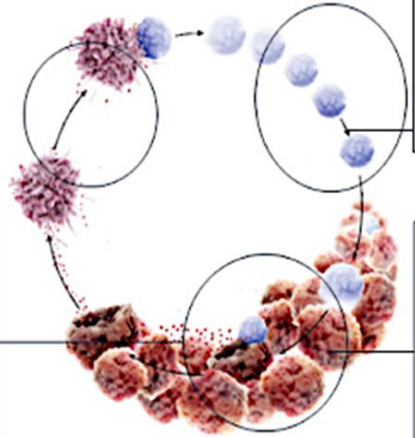
Opzioni terapeutiche

Opzioni terapeutiche



RECOGNISE: Anti-VEGF, by inhibiting VEGF-mediated suppression of dendritic cell maturation, enables efficient priming and activation of T-cell responses against tumour antigens

REPROGRAMME: Anti-VEGF, by decreasing the activity of MDSCs, T_{reg} cells and TAM enables reprogramming of the tumour microenvironment from immune suppressive to immune permissive



RECRUIT: Anti-VEGF normalises the tumour vasculature, resulting in an increased infiltration of T cells into the tumour

RESTORE: IO's ability to restore anticancer immunity, through T-cell mediated cancer cell killing, is further enhanced through Anti-VEGF-mediated immunomodulatory effects

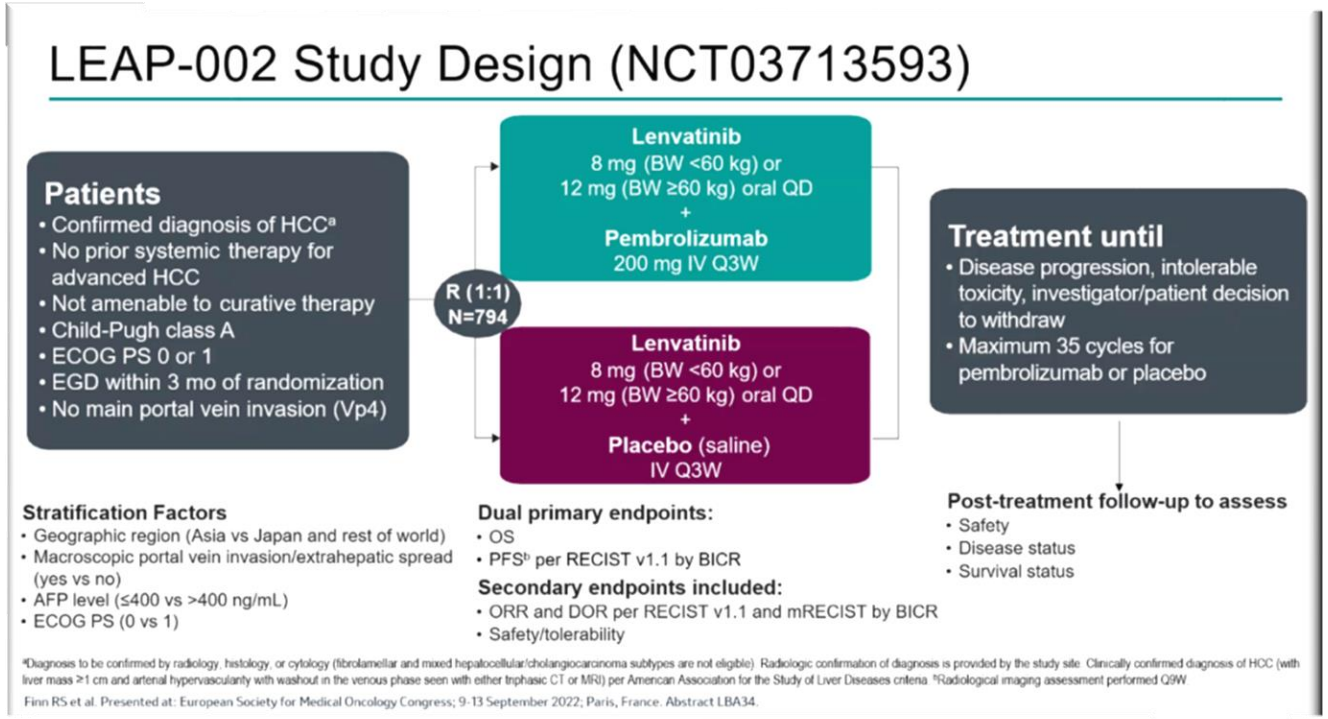
Sangro B. et al Nature Reviews Gastroenterology & Hepatology (2021)
Kudo M. Cancers 2020;12:1089


KEEP CALM
IT'S
Summer
TIME

2^ visita Oncologica (02/09/2019)

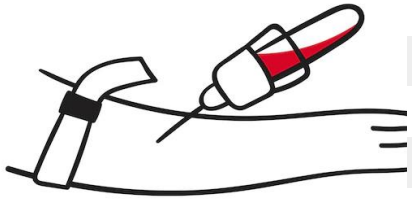
- ECOG PS 0
- Asintomatico
- Accetta avvio di terapia sistemica

Proposta la partecipazione allo studio **MK7902-002**



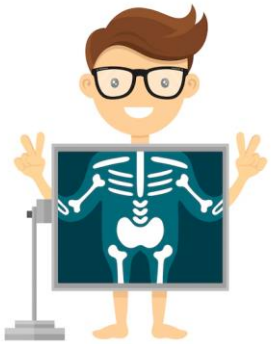
Esami di screening

17/09

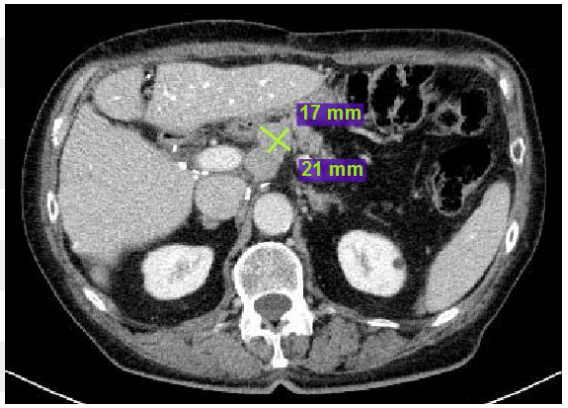


17/09

13/09



13/09



Inizio terapia (24/09/2019)

- ECOG PS 0, peso 68 kg
- Child Pugh A5
- AFP basale 6,8

→ Lenvatinib 4 mg 3 cp/die + Pembrolizumab/Placebo q3w

Iter terapeutico

24/01/2019

01ª 02 03 04

Comparsa di FA G2

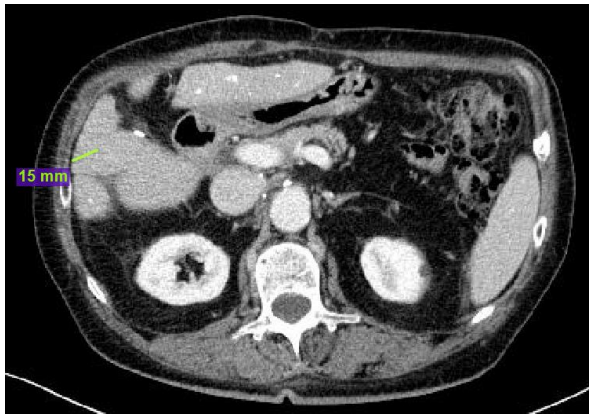
Inizia EBPM profilattica e B-bloccante

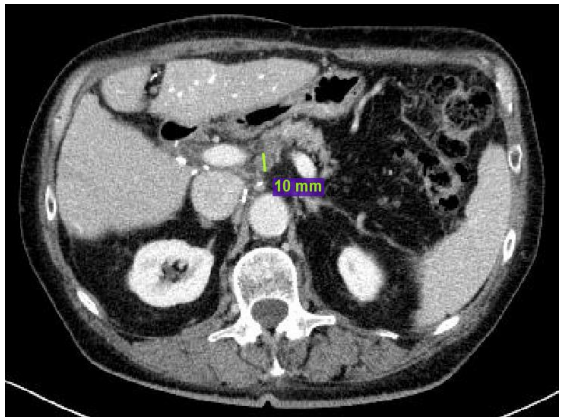
Ipertiroidismo G1

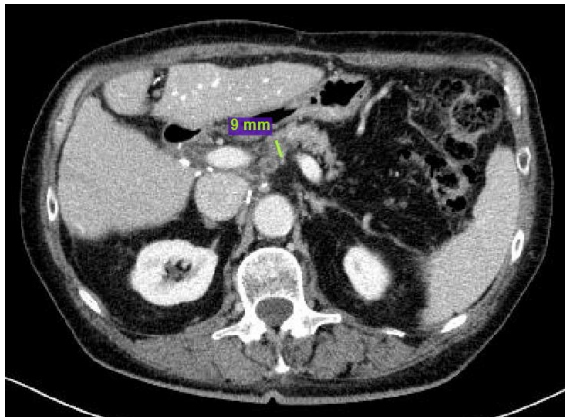
Iter terapeutico

24/01/2019

01a 02 03 04







03/12/2019

Somma lesioni target TC basale: 52 mm

Somma lesioni target TC 1aRiv: 34 mm (- 34.6%)

Iter terapeutico

24/01/2019

01 a

02

03

FA G2

04

Ipertiroidismo G1

05

Ipotiroidismo G1

06

Ipotiroidismo G1
Ipertensione G2

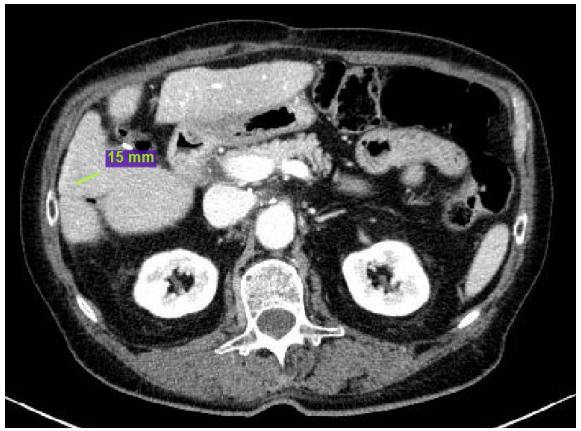
Avvia Lecarnidipina 4 mg
e Levotiroxina

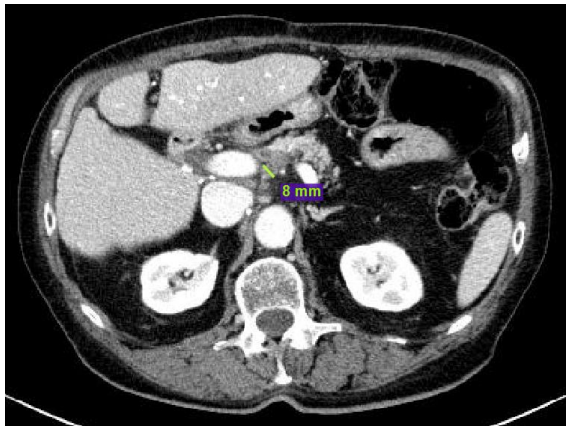
Iter terapeutico

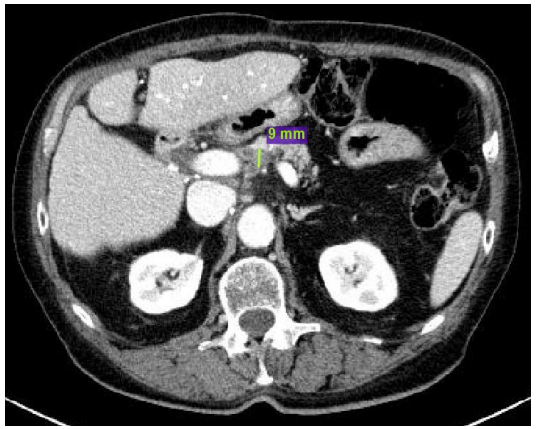
07 08 09 10

Ipotiroidismo G2

Aumento del QTc G1







30/03/2019

Somma lesioni target TC basale: 52 mm

Somma lesioni target TC 1aRiv: 34 mm (- 34.6%) PR

Somma lesioni target TC 2aRiv: 32 mm (- 38.5%) PR

Somma lesioni target TC 3aRiv: 19 mm (- 63.5%) PR

Iter terapeutico

16	17	18	19	20
	HFS G2 Stop Lenva	*Lenvatinib* 8 mg/die		*HFS G1*

21	22	23	24	25
HFS G1	*HFS G1*			*Diarrea G1*

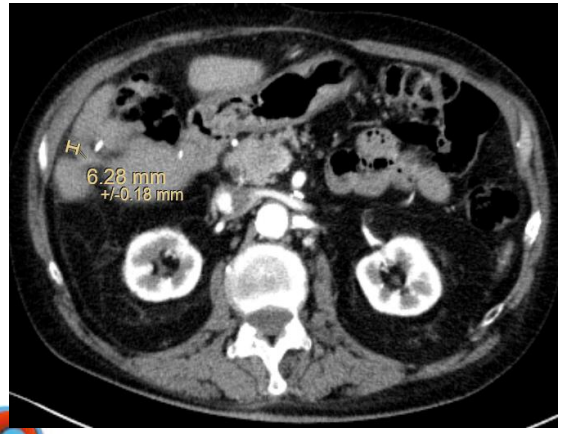
Iter terapeutico

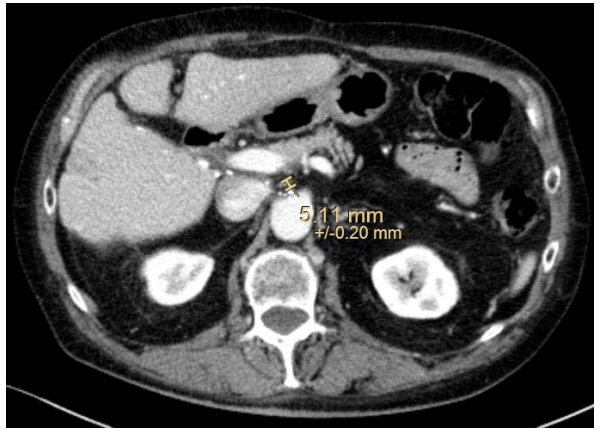
06/09/2021

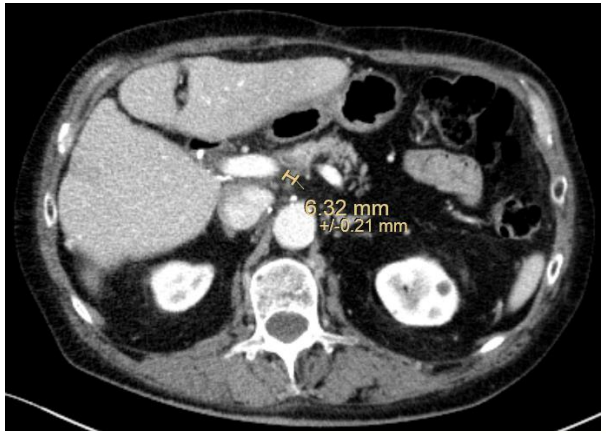
31 | 32 | 33 | 34 | 35

Astenia G1

Astenia G1
Diarrea G1







Iter terapeutico

- Conclusi i cicli previsti da protocollo
- ECOG PS 1
- Ottimo stato di compenso epatico (Child Pugh A)
- Buona tolleranza alla terapia
- Esclusa eventuale chirurgia

Proposta di proseguire terapia con Lenvatinib

Iter terapeutico

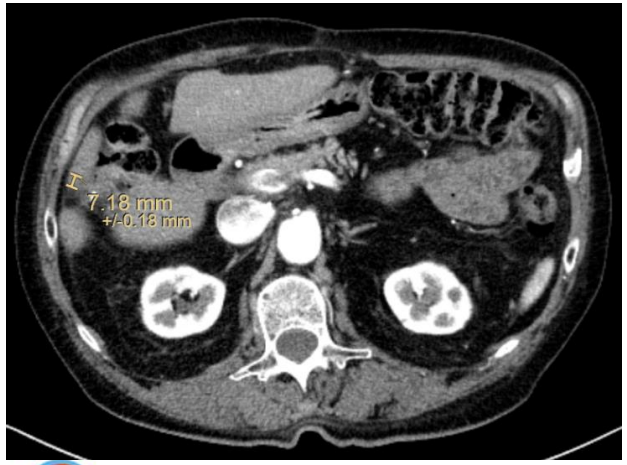
27/09/2021

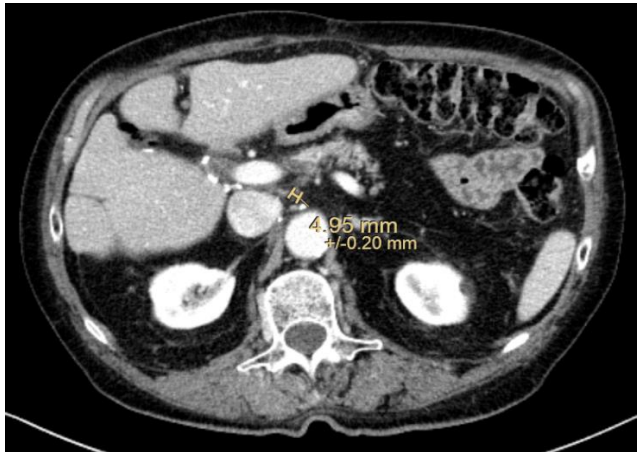
36 — 37 — 38 — 39 — 40

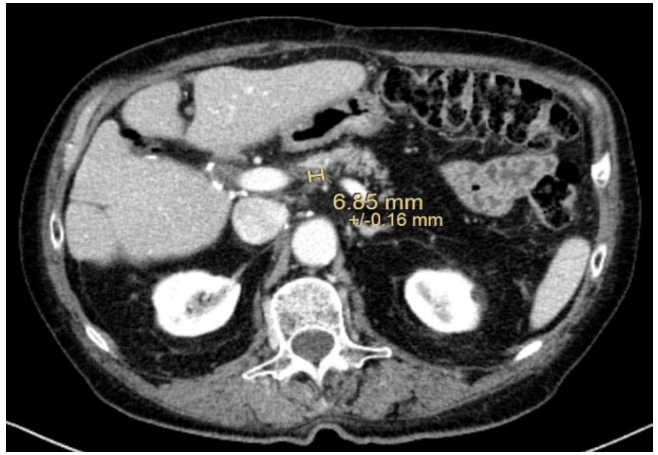
Lenvatinib
8 mg/die

HFS G1

HFS G1







Iter terapeutico

21/03/2022

41 — *Astenia G1*
HFS G1

42 — *HFS G1*
Diarrea G1

43 — *Astenia G1*
HFS G1

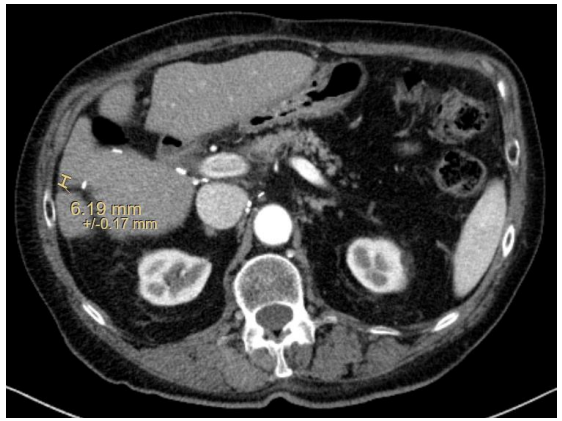
44

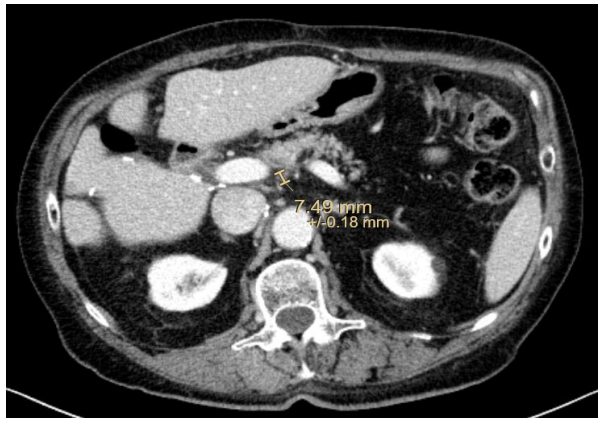
- 29/03/2022 Accesso in PS per episodio di amnesia G2
  - TC Encefalo: negativa
  - Esami ematochimici (compresa ammoniemia) nella norma
  - Visita neurologica: "..episodio di amnesia globale transitoria"
  - Quadro risoltosi in meno di 24 ore spontaneamente

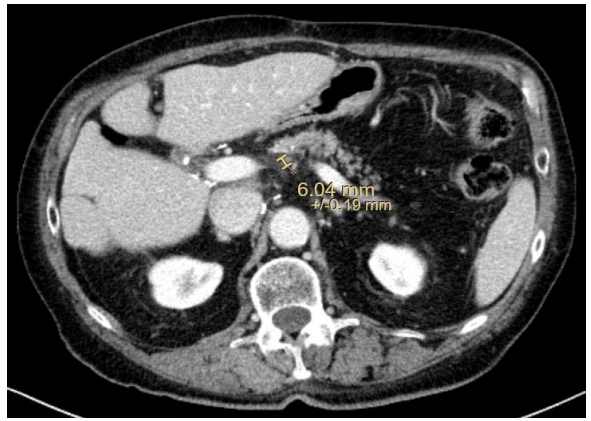
Iter terapeutico

22/04/2022

- 83 anni, ECOG PS 1
- Ulteriore episodio di amnesia G2
- Eseguiti complessivamente 44 cicli di terapia
- 19/04/2022 TC: mantenimento della risposta

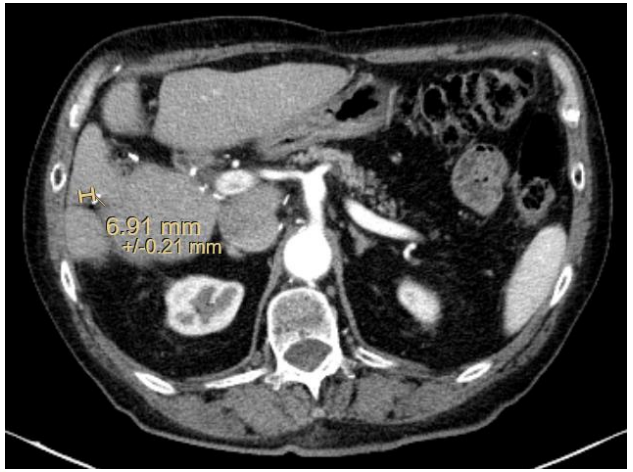


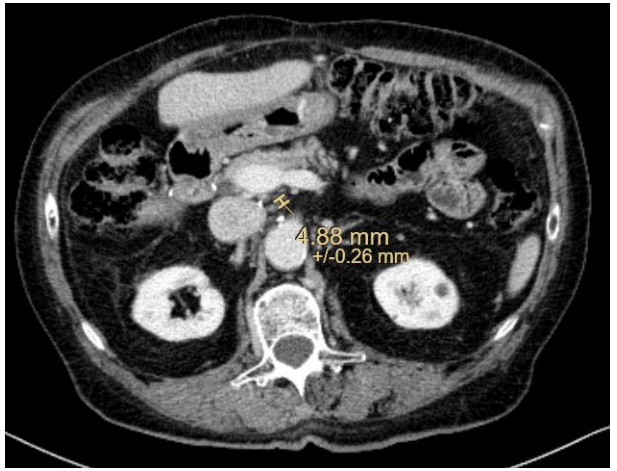


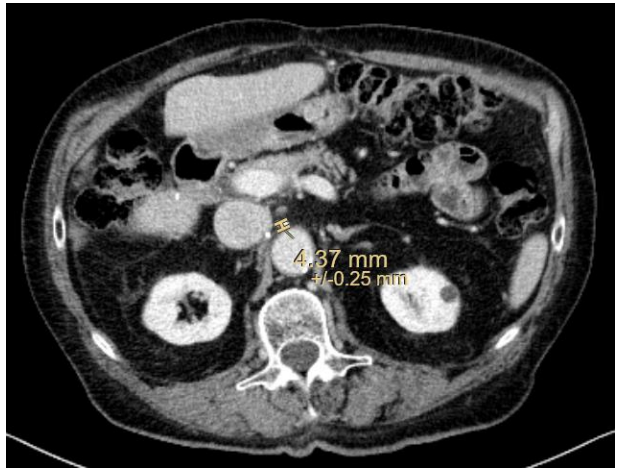


Ultimo follow up (22/12/2023)

- 84 anni, ECOG PS 1
- Esami ematochimici nella norma (Child Pugh A)
- 21 mesi dall'ultimo ciclo di terapia
- 18/12/2023 TC: mantenimento della risposta parziale

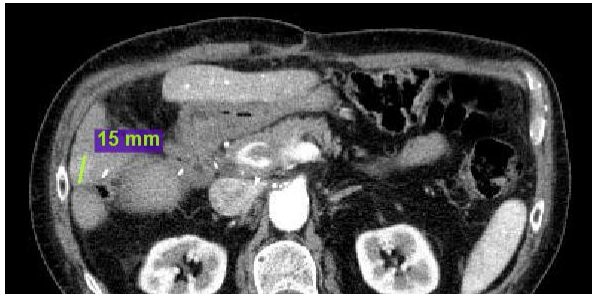


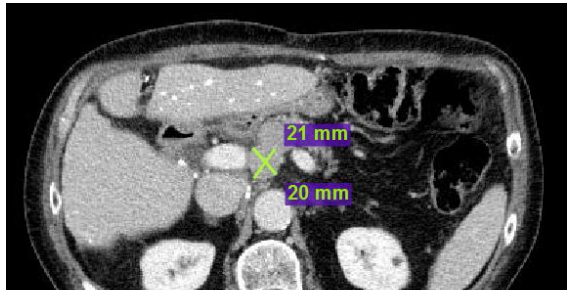


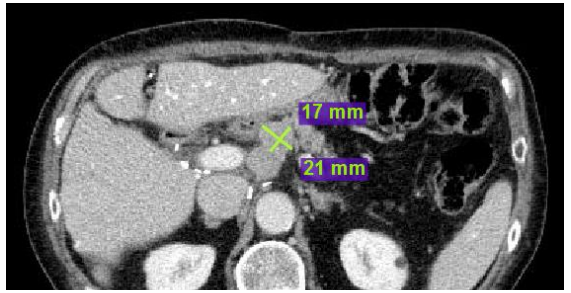


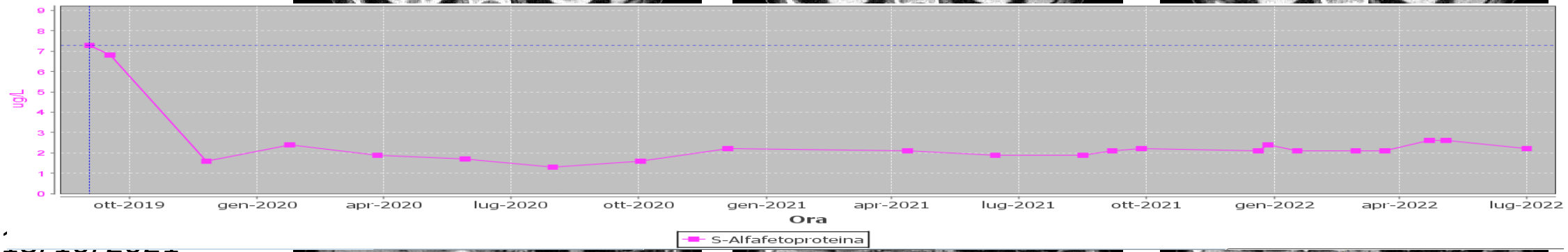
Risposta radiologica

13/09/2019
Basale

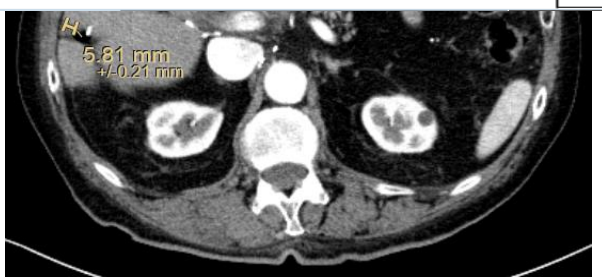


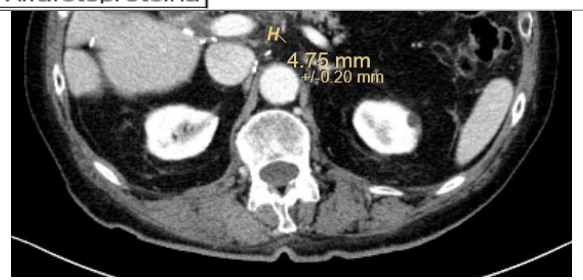


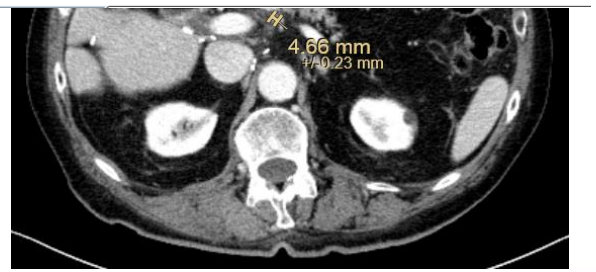




Nadir di risposta
(-69,2%)

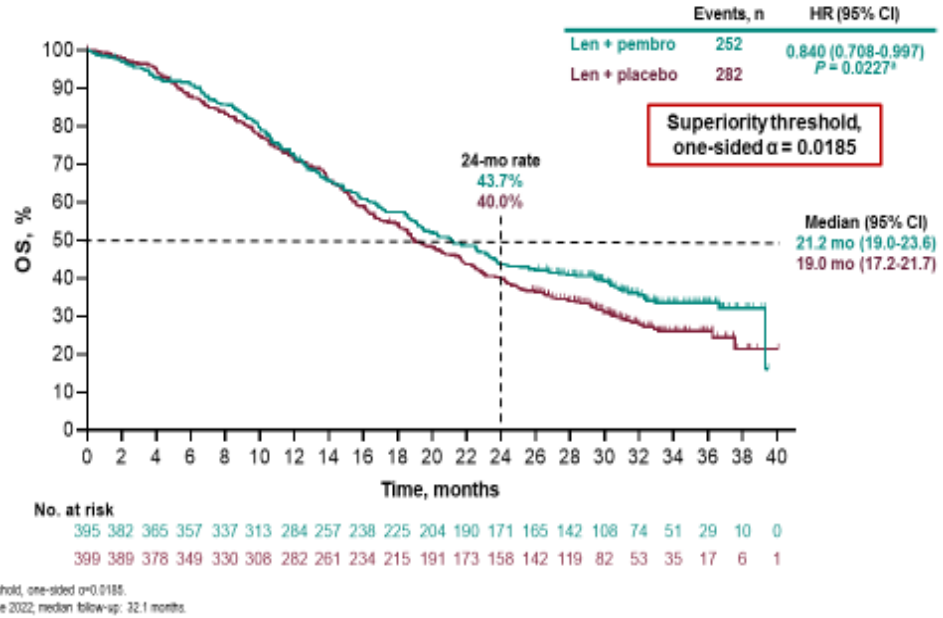






Leap-002: Overall Survival, ITT, FA

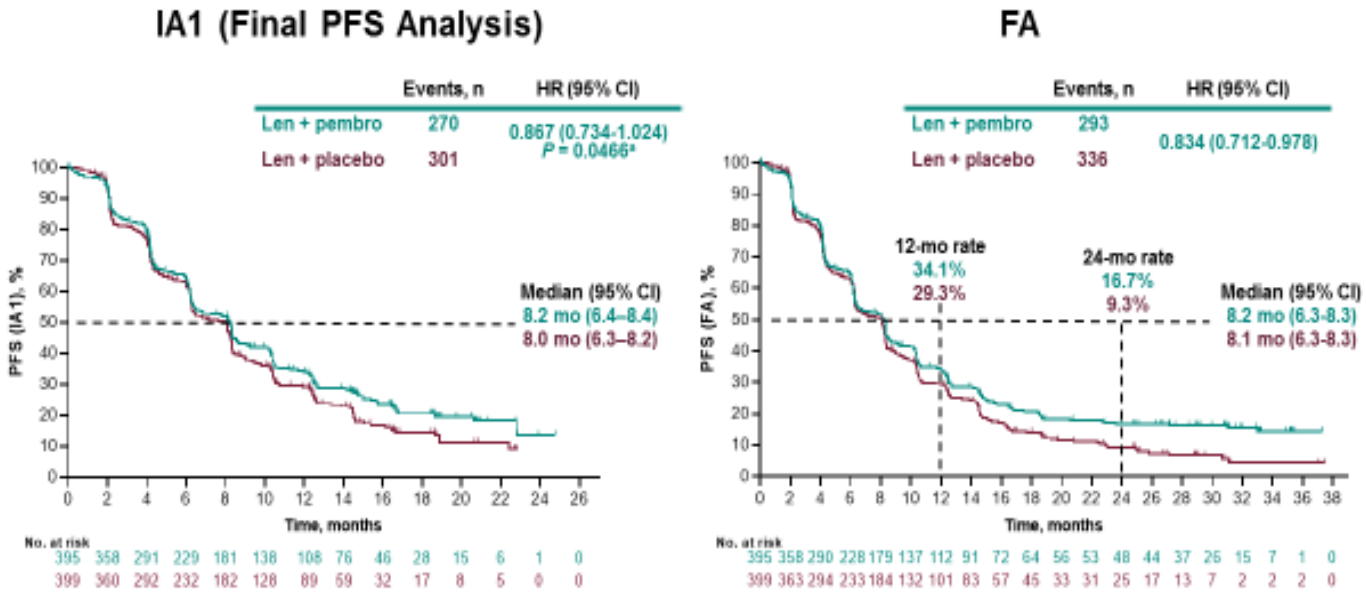
n (%)	Len + pembro N = 395	Len + placebo N = 399
Age, median (range), years	66.0 (19-88)	66.0 (20-88)
≥65 years, n (%)	209 (52.9)	215 (53.9)
Male	317 (80.3)	327 (82.0)
Region		
Asia without Japan	121 (30.6)	123 (30.8)
Western regions and Japan	274 (69.4)	276 (69.2)
ECOG PS 1	127 (32.2)	126 (31.6)
Etiology		
Viral etiology[a]	247 (62.5)	237 (59.4)
HBV+	192 (48.6)	193 (48.4)
HCV+	94 (23.8)	87 (21.8)
Alcohol etiology	118 (29.9)	133 (33.3)
AFP >400 ng/mL	119 (30.1)	132 (33.1)
Child Pugh class A	393 (99.5)	397 (99.5)
Macroscopic portal vein invasion or extrahepatic disease	268 (67.8)	262 (65.7)
Extrahepatic disease	249 (63.0)	243 (60.9)
Macrovascular invasion	71 (18.0)	62 (15.5)
BCLC stage		
B	85 (21.5)	95 (23.8)
C	310 (78.5)	302 (75.7)
Liver cirrhosis	263 (66.6)	275 (68.9)
Locoregional therapy	193 (48.9)	204 (51.1)



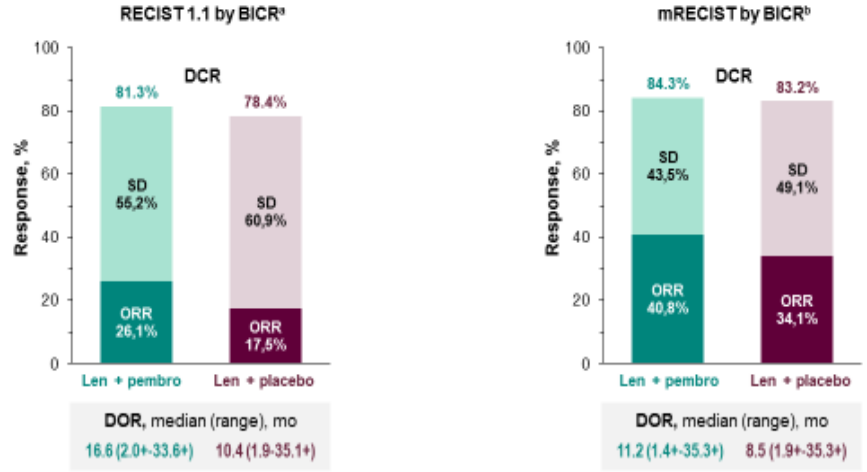
[a]Did not reach superiority threshold, one-sided α=0.0185.
Data cutoff date for FA: 21 June 2022; median follow-up: 32.1 months.

Finn RS, ESMO 2022

Leap-002: PFS e ORR



aDid not reach superiority threshold (one-sided α= 0.002) at IA1 (there was no statistical testing of PFS at FA).
Data cutoff date for IA1: 5 April 2021; Data cutoff date for FA: 21 June 2022.



aCR=1.5% in both arms; PD=12.2% for len + pembro and 15.0% for len + placebo.
bCR=9.4% for len + pembro and 9.5% with len + placebo; PD=9.4% for len + pembro and 10.3% for len + placebo.
Data cutoff date for FA: 21 June 2022.

Finn RS, ESMO 2022

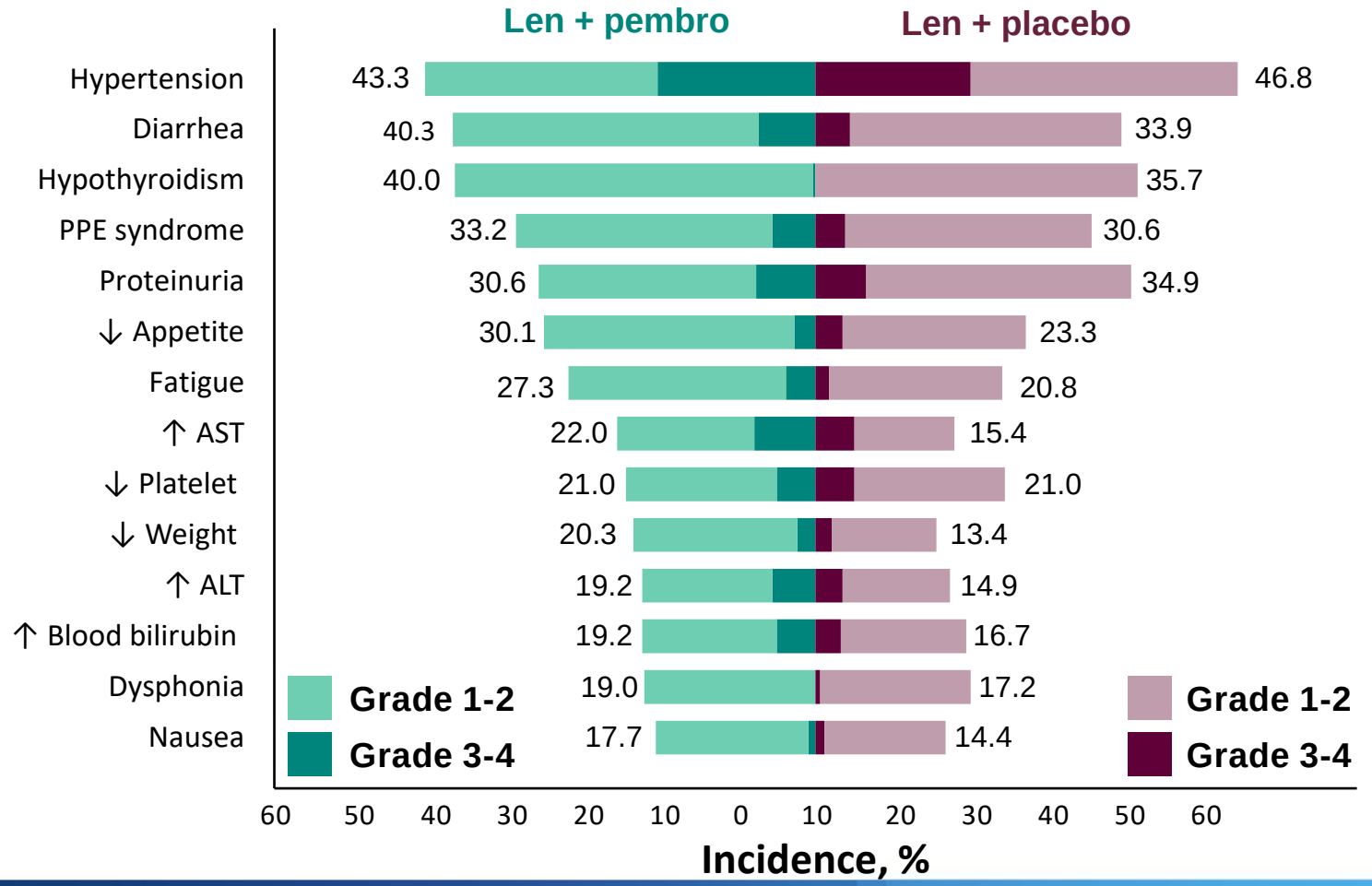
Leap-002: Treatment-related Adverse Events

Treatment Exposure

Median (range), mo	Len + pembro N = 395	Len + placebo N = 395
Duration on therapy	8.6 (0.1-39.3)	9.5 (0-38.9)

TRAEs

n (%)	Len + pembro N = 395	Len + placebo N = 395
Any grade	381 (96.5)	378 (95.7)
Grade 3-4[a]	243 (61.5)	224 (56.7)
Grade 5[b]	4 (1.0)	3 (0.8)
Led to discontinuation, any treatment	71 (18.0)	42 (10.6)
Led to discontinuation, both treatments	22 (5.6)	18 (4.6)

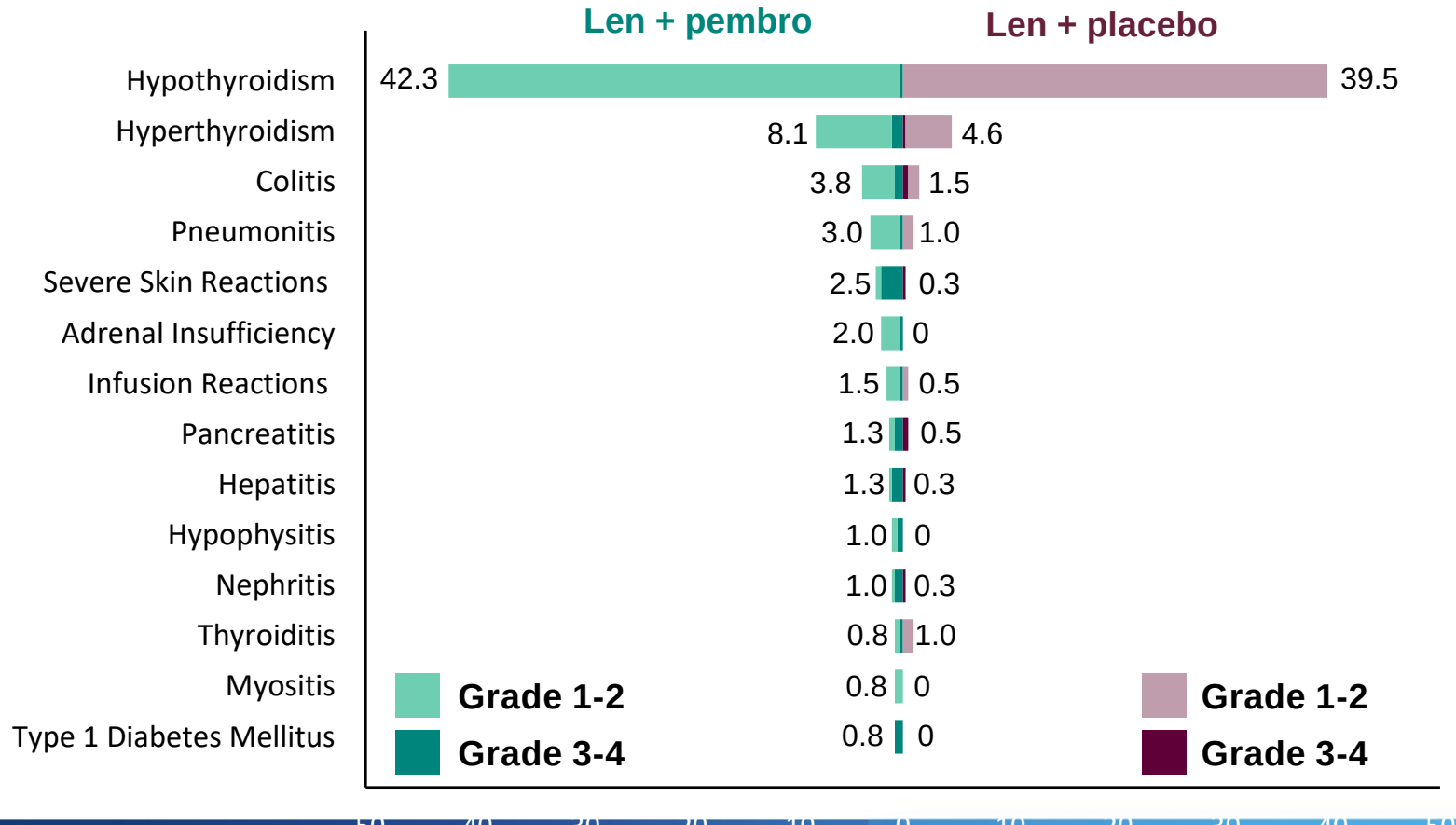


Finn RS, ESMO 2022

Leap-002: Immune-Mediated AEs and Infusion Reactions

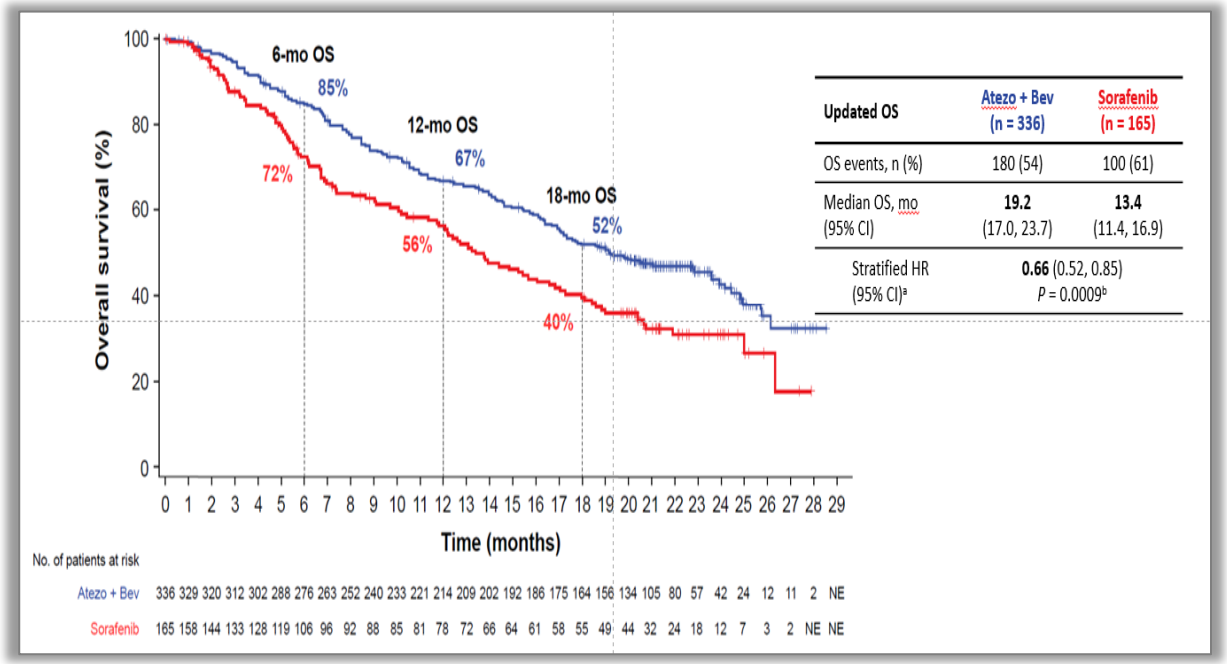
Immune-Mediated AEs and Infusion Reactions

n (%)	Len + pembro N = 395	Len + placebo N = 395
Any grade	208 (52.7)	180 (45.6)
Grade 3-4	35 (8.9)	9 (2.3)
Grade 5	0	0
Led to discontinuation, any treatment	14 (3.5)	3 (0.8)
Led to discontinuation, both treatments	2 (0.5)	1 (0.3)
Systemic corticosteroids	38 (9.6)	7 (1.8)



Finn RS, ESMO 2022

Imbrave 150: Atezolizumab/bevacizumab



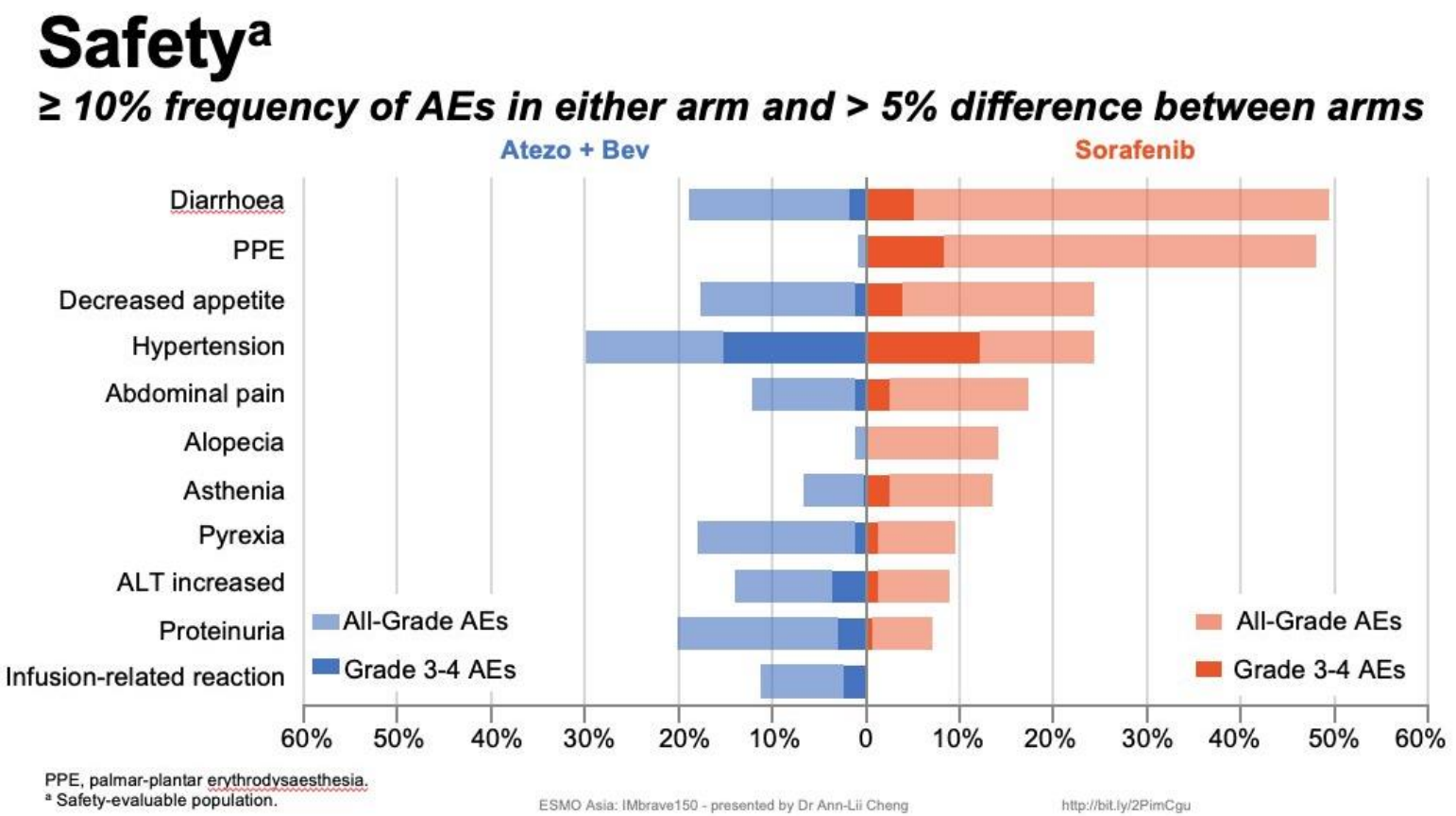
Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

	Updated analysis[a]			
	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. DCR, disease control rate.
[a] Only patients with measurable disease at baseline were included in the analysis of ORR.
[b] Only confirmed responders were included in the analysis of ORR and DOR.

Finn RS, ASCO GI 2021

Imbrave 150: Atezolizumab/bevacizumab



Cheng AL et al. Presented at ESMO Asia 2019

Himalaya Trial: Durvalumab/tremelimumab

Study population
- Patients aged ≥18 years with uHCC
- BCLC stage B (not eligible for locoregional therapy) and stage C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

R N=1324

STRIDE (n=393): Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

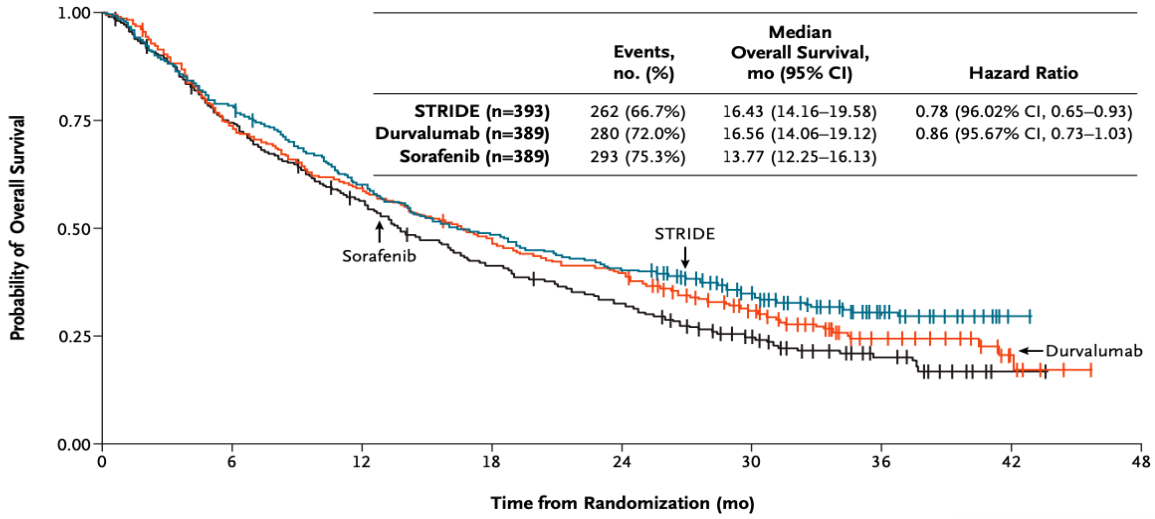
Durvalumab (n=389): Durvalumab monotherapy 1500 mg Q4W*

Sorafenib (n=389): Sorafenib 400 mg BID*

T75+D (n=153): *arm closed*† Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

Stratification factors
- Macrovascular invasion: yes vs no
- Etiology of liver disease: HBV vs HCV vs others
- Performance status: ECOG 0 vs 1

	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* %	20.1	17.0	5.1
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months 25th percentile 75th percentile	22.34 8.54 NR	16.82 7.43 NR	18.43 6.51 25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ % 6 months 12 moths	 82.3 65.8	 81.8 57.8	 78.9 63.2

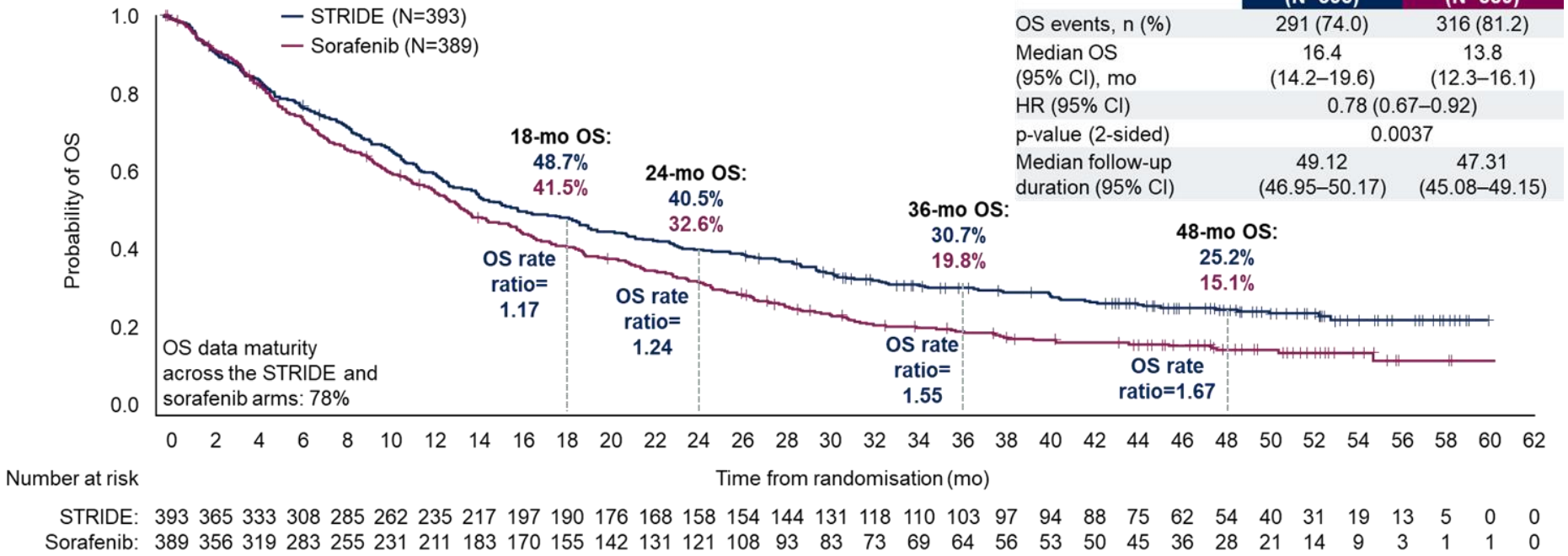


	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

Abou-Alfa GK et al. N Engl J Med 2022

Himalaya Trial: Durvalumab/tremelimumab

4-year OS Update

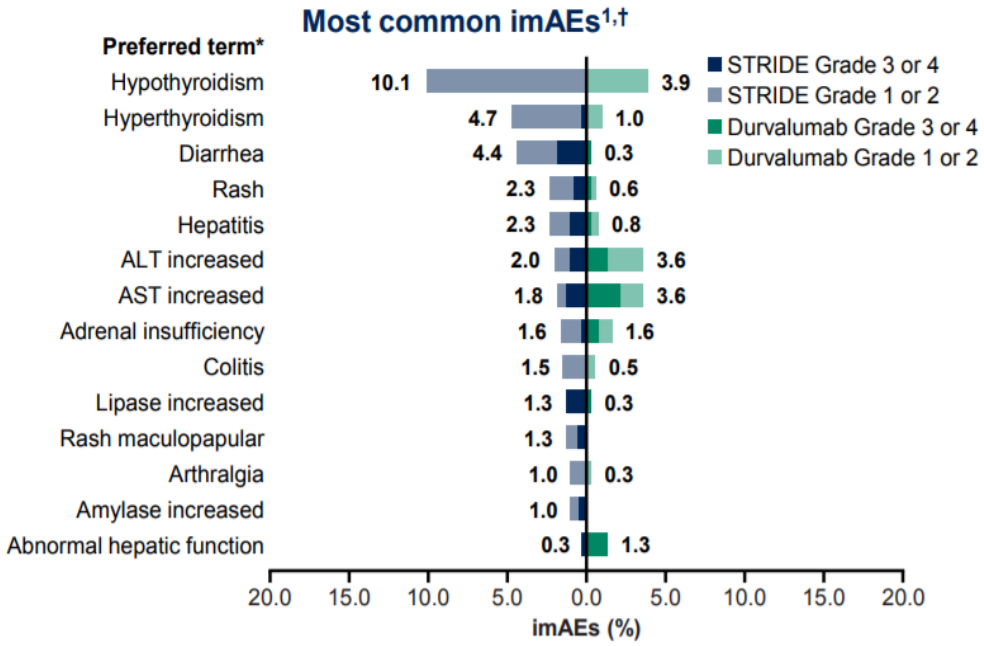


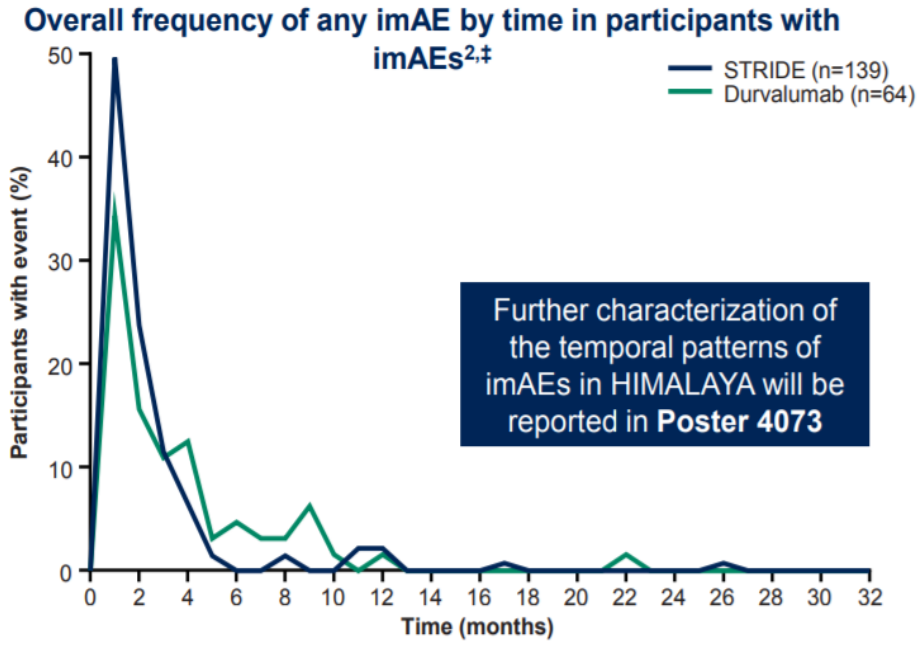
	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), mo	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (95% CI)	0.78 (0.67–0.92)	
p-value (2-sided)	0.0037	
Median follow-up duration (95% CI)	49.12 (46.95–50.17)	47.31 (45.08–49.15)

ESMO-WCGIC 2023

Himalaya Trial: Durvalumab/tremelimumab

Most imAEs with STRIDE or durvalumab were low grade, and most occurred within the first 3 months of treatment[1,2]



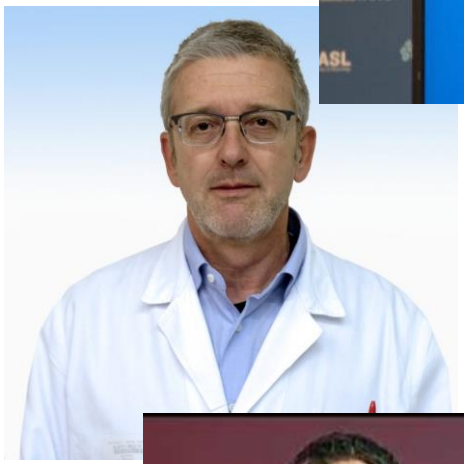


*Preferred term was as reported by the investigator. †imAEs that occurred in ≥1% of participants in the in the STRIDE or durvalumab treatment arms are included. ‡The percentage of participants with an event is the number of participants who experienced ≥1 imAE event at each time interval divided by the number of participants who experienced ≥1 imAE event at any time; includes first imAE only, regardless of grade.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; imAE, immune-mediated adverse event.
1. Sangro B, et al. Presented at: ILCA 2022 16th Annual Conference; September 1–4, 2022; Madrid, Spain. Oral presentation O-28. 2. Lau G, et al. Poster presented at: ASCO Annual Meeting 2023; June 2–6, 2023; Chicago, IL. Poster 4073.

Presented by George Lau at ASCO Meeting 2023

Conclusioni

- Scenario terapeutico in rapido cambiamento (opzioni terapeutiche e modalità di approccio)
- Mandatoria la gestione multidisciplinare
- Non precludere le opzioni terapeutiche solo sulla base dell'età anagrafica
- Gestione degli effetti collaterali fondamentale per il percorso di cura
- Precoce integrazione delle cure simultanee
- Anche nei pazienti con malattia avanzata considerare la ridiscussione collegiale



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Patient Journey

Approccio personalizzato al paziente e esperienze a confronto:
Epatocarcinoma e Colangiocarcinoma

*Nessun Collega
è stato maltrattato
per queste foto

01 Febbraio 2024
VERONA