Systemic Therapy Including ICI to Downstage to Transplant in HCC Patients

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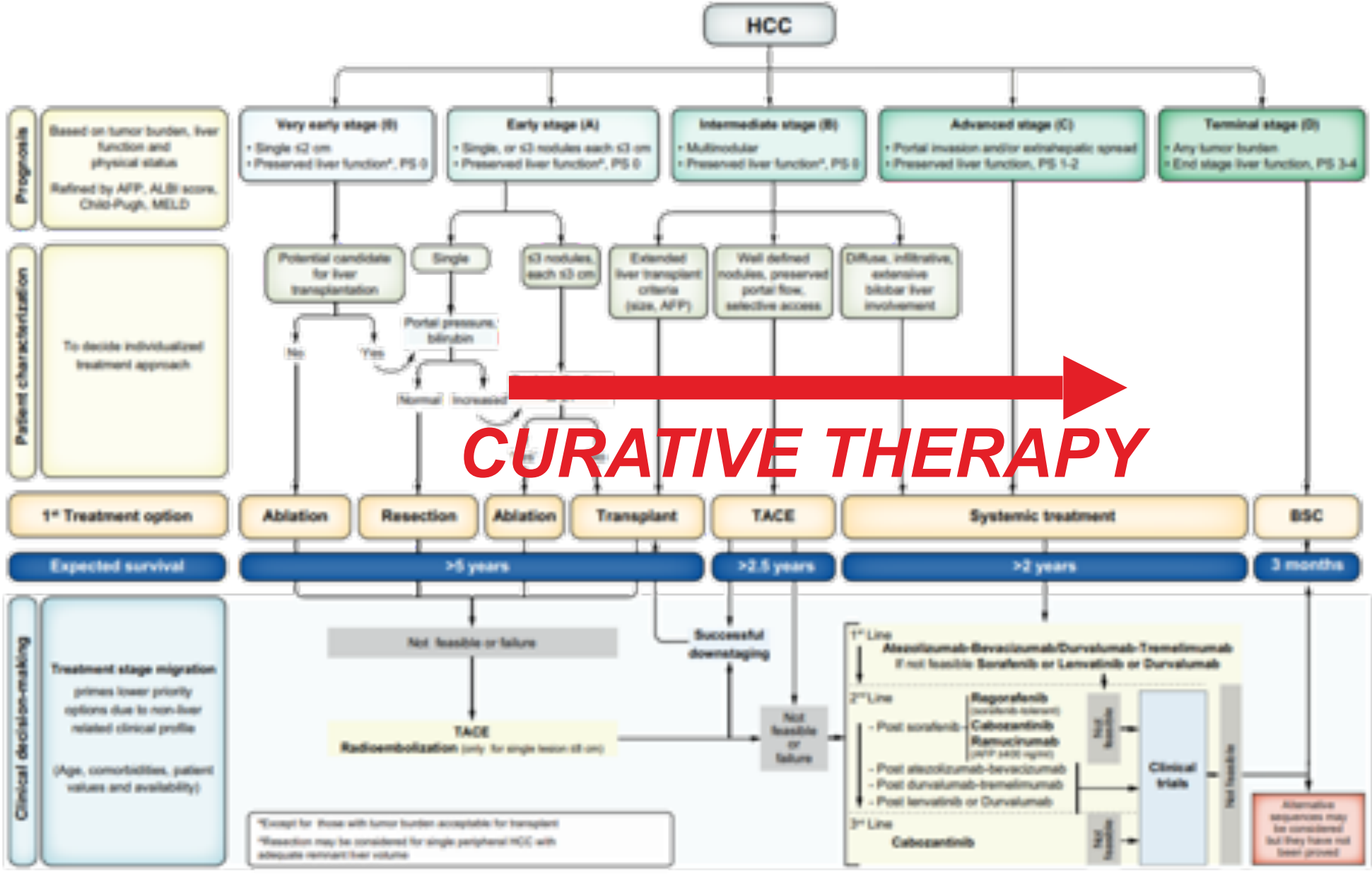
The Liver Transplant Symposium 2023

Disclosures

- Bayer
- Boston Scientific
- AstraZeneca

WHY ?



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Reig et al, Journal of Hepatology 2022

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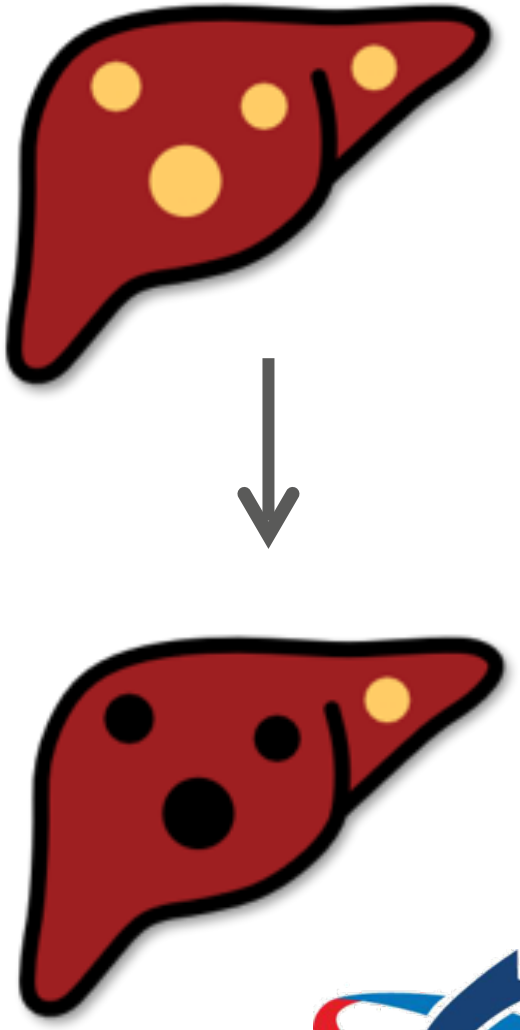
Downstaging outcomes

Inclusion Criteria:

HCC exceeding UNOS T2 criteria but meeting one of the following:

- Single lesion ≤ 8 cm
- 2 or 3 lesions each ≤ 5 cm with the sum of the largest tumor diameters ≤ 8 cm
- 4 or 5 lesions each ≤ 3 cm with the sum of the largest tumor diameters ≤ 8 cm



No vascular invasion

Successful downstaging → Residual tumor(s) within MC

Downstaging failure → Progression of tumor(s) beyond MC

→ Vascular invasion, extrahepatic disease

Minimum observation period of 3 months before LT

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Yao et al. Hepatology 2015
Tabrizian et al. JAMA surg 2022

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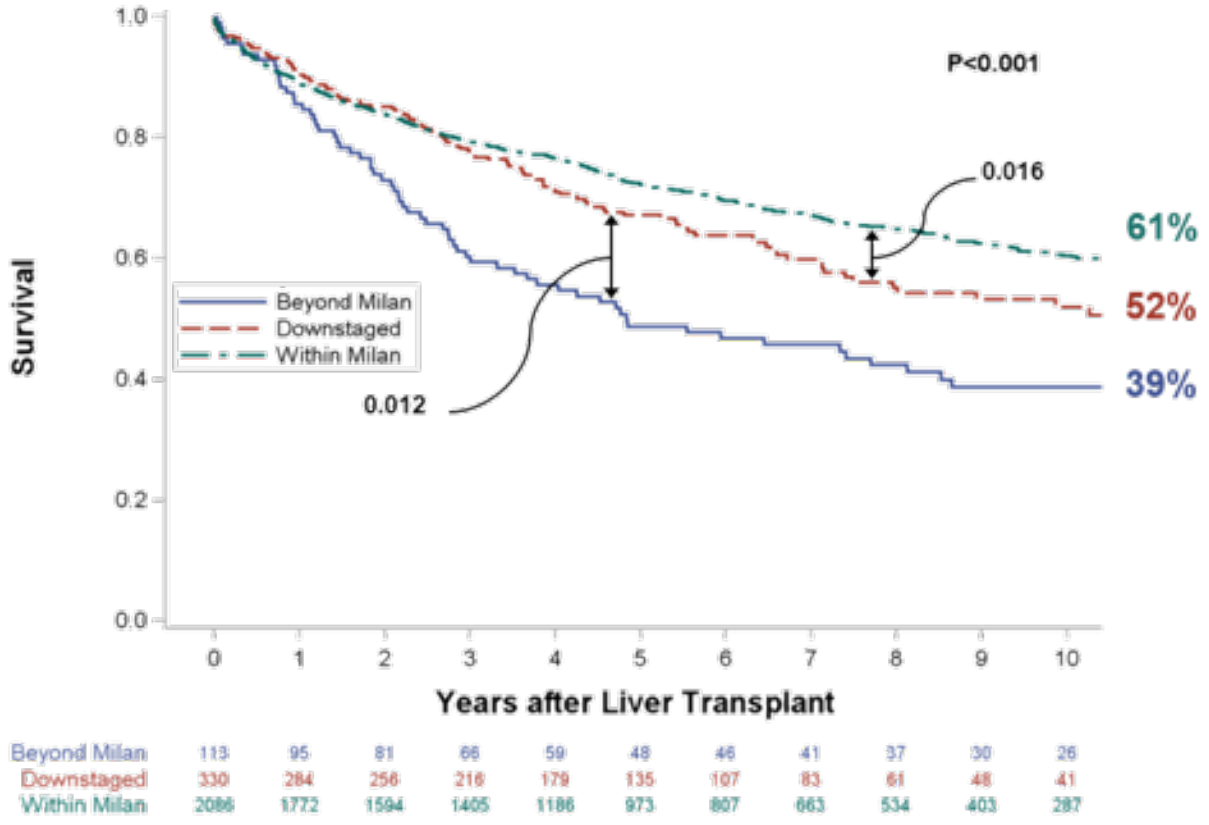
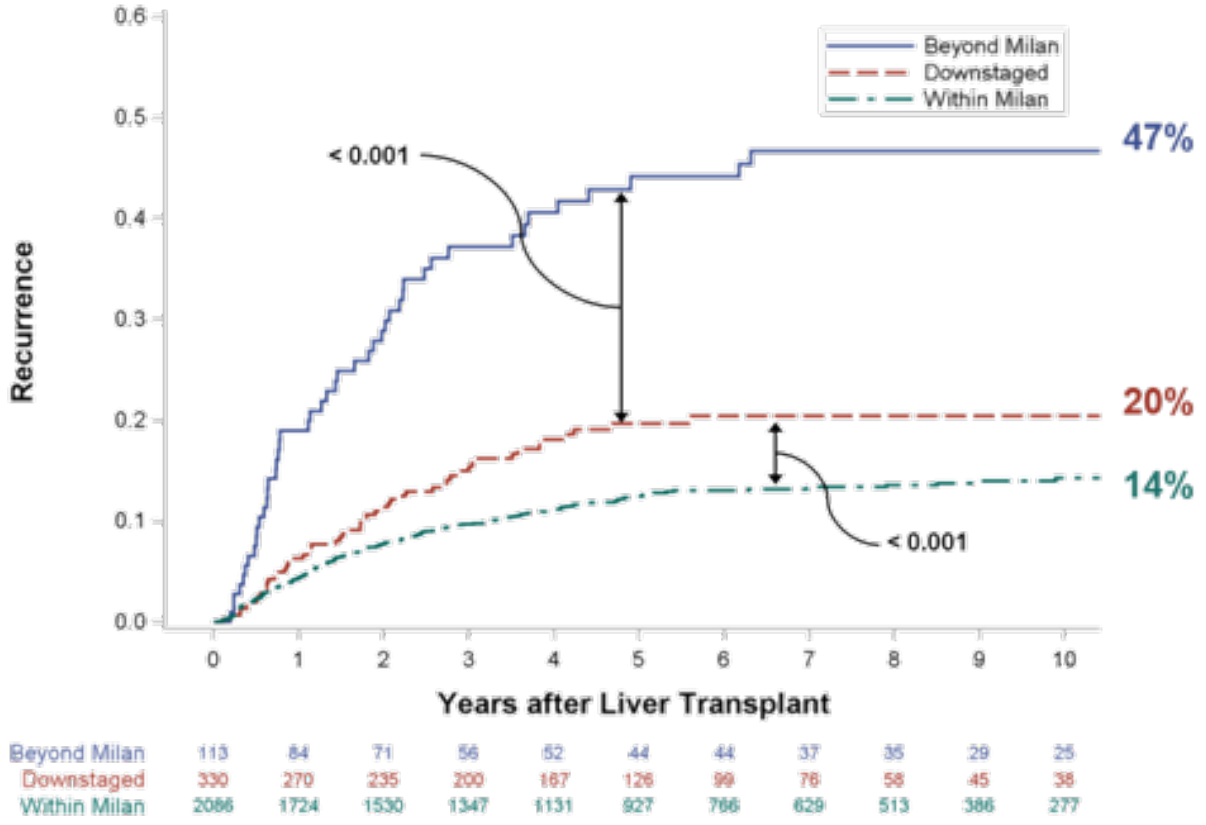
Downstaging outcomes





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Tabrizian et al. JAMA surg 2022

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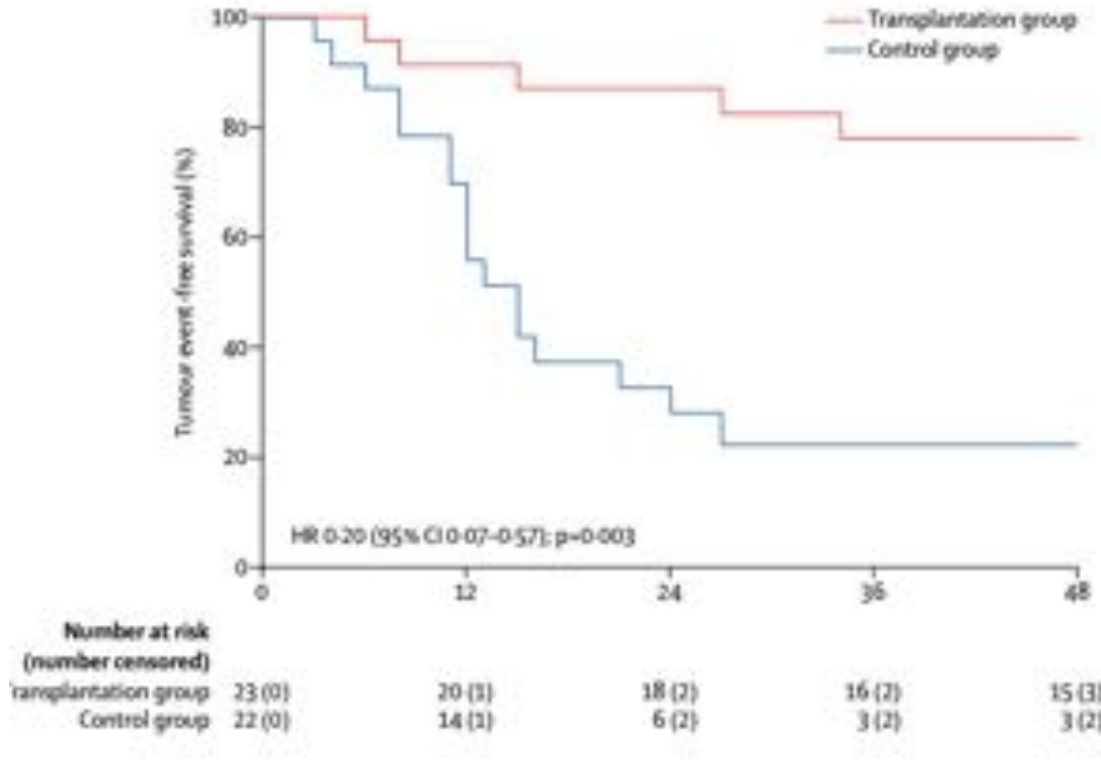
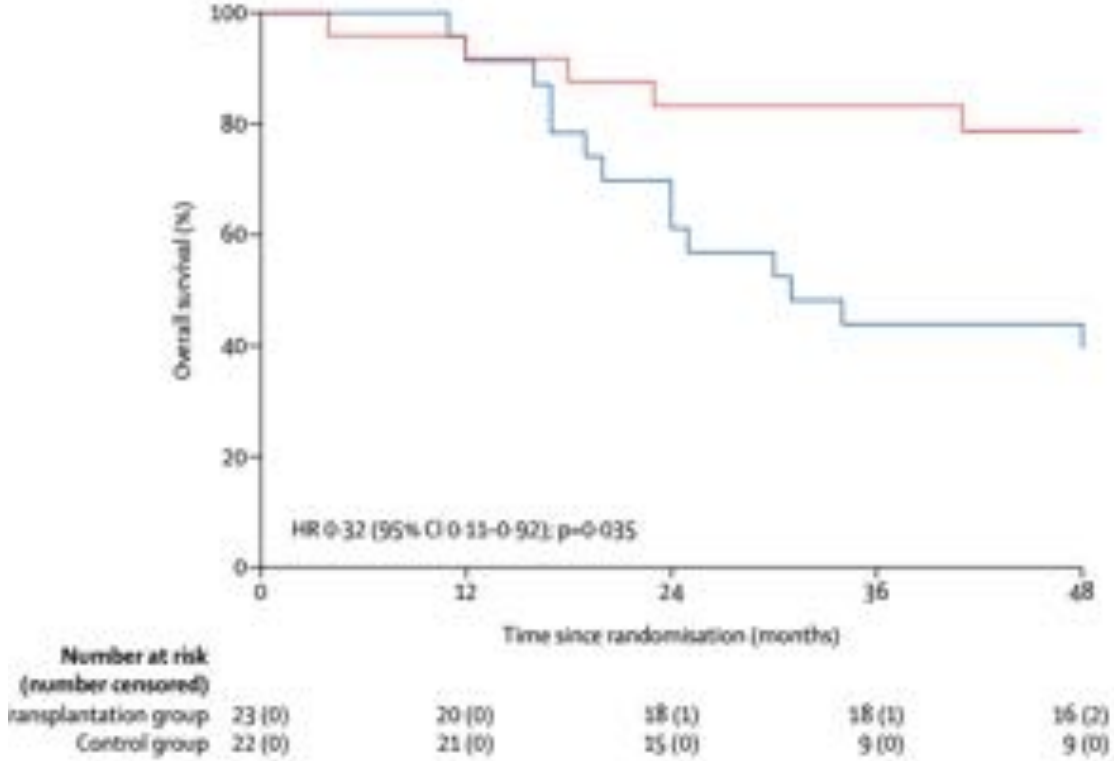
RTC downstaging





5-year OS 77% vs 31%

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Mazzaferro et al. Lancet Oncol 2020

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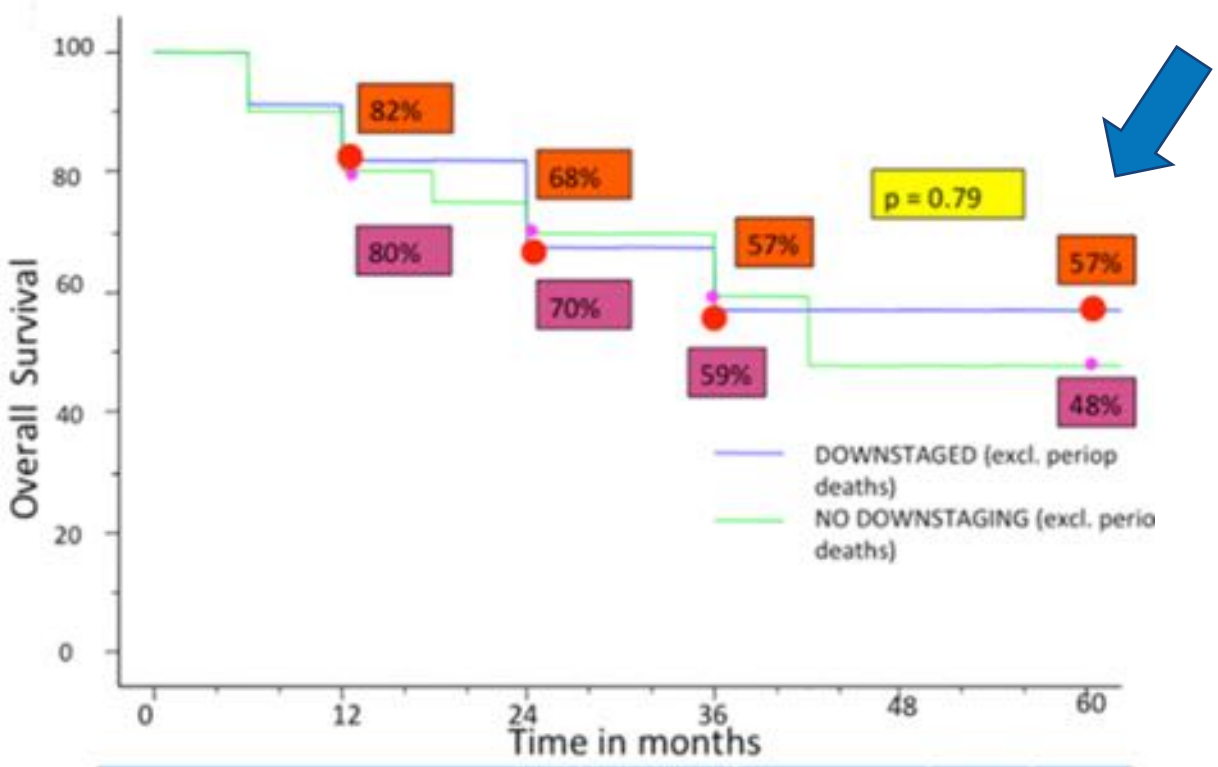
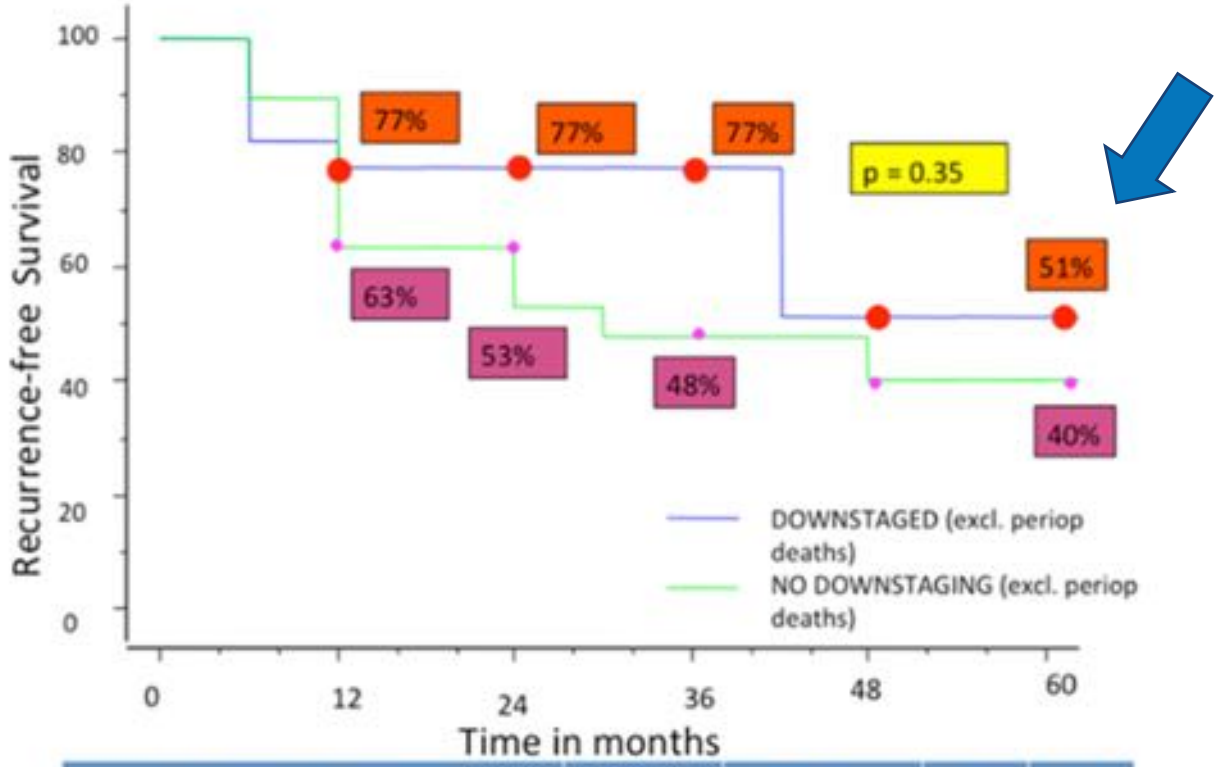
LDLT-PVT-Downstaging



No. of patients exposed	1 yr	2 yrs	3 yrs	4 yrs
Downstaged patients (23)	15	8	4	2
No downstaging (20)	16	14	11	5



No. of patients exposed	1 yr	2 yrs	3 yrs	5 yrs
Downstaged patients (23)	13	7	4	1
No downstaging (20)	12	10	8	4

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Soin et al. Transplantation 2020

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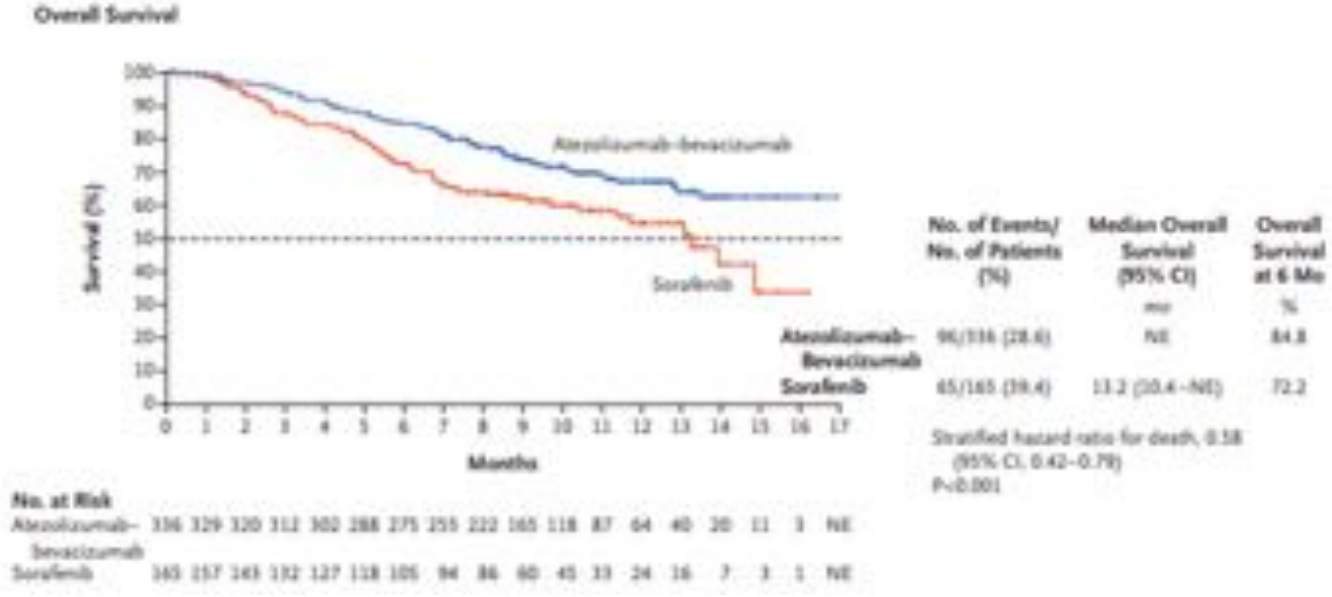
IMbrave150 trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D., Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D., Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D., Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D., Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D., Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D., for the IMbrave150 Investigators*



Finn et al. NEJM 2020

Safety

Table 1. Patient Characteristics at Baseline.*

Variable	Atezolizumab–Bevacizumab (N = 336)	Sorafenib (N = 165)
Median age (IQR) — yr	64 (56–71)	66 (59–71)
Male sex — no. (%)	277 (82)	137 (83)
Geographic region — no. (%)		
Asia, excluding Japan	133 (40)	68 (41)
Rest of the world†	203 (60)	97 (59)
ECOG performance status score — no. (%)‡		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child–Pugh classification — no./total no. (%)§		
A5	239/333 (72)	121/165 (73)
A6	94/333 (28)	44/165 (27)
Barcelona Clinic liver cancer stage — no. (%)¶		
A	8 (2)	6 (4)
B	52 (15)	26 (16)
C	276 (82)	133 (81)

Table 4. Adverse Events with an Incidence of More Than 20% in Either Group.

Event	Atezolizumab–Bevacizumab (N = 329)		Sorafenib (N = 156)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Hypertension	98 (29.8)	50 (15.2)	38 (24.4)	19 (12.2)
Fatigue	67 (20.4)	8 (2.4)	29 (18.6)	5 (3.2)
Proteinuria	66 (20.1)	10 (3.0)	11 (7.1)	1 (0.6)
Aspartate aminotransferase increase	64 (19.5)	23 (7.0)	26 (16.7)	8 (5.1)
Pruritus	64 (19.5)	0	15 (9.6)	0
Diarrhea	62 (18.8)	6 (1.8)	77 (49.4)	8 (5.1)
Decreased appetite	58 (17.6)	4 (1.2)	38 (24.4)	6 (3.8)
Pyrexia	59 (17.9)	4 (1.2)	15 (9.6)	2 (1.3)
Alanine aminotransferase increase	46 (14.0)	12 (3.6)	14 (9.0)	2 (1.3)
Constipation	44 (13.4)	0	22 (14.1)	0
Blood bilirubin increase	43 (13.1)	8 (2.4)	22 (14.1)	10 (6.4)
Rash	41 (12.5)	0	27 (17.3)	4 (2.6)
Abdominal pain	40 (12.2)	4 (1.2)	27 (17.3)	4 (2.6)
Nausea	40 (12.2)	1 (0.3)	25 (16.0)	1 (0.6)
Cough	39 (11.9)	0	15 (9.6)	1 (0.6)
Infusion-related reaction	37 (11.2)	8 (2.4)	0	0
Weight decrease	37 (11.2)	0	15 (9.6)	1 (0.6)
Platelet count decrease	35 (10.6)	11 (3.3)	18 (11.5)	2 (1.3)
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Asthenia	22 (6.7)	1 (0.3)	21 (13.5)	4 (2.6)
Alopecia	4 (1.2)	0	22 (14.1)	0
Palmar-plantar erythrodysesthesia syndrome	3 (0.9)	0	75 (48.1)	13 (8.3)

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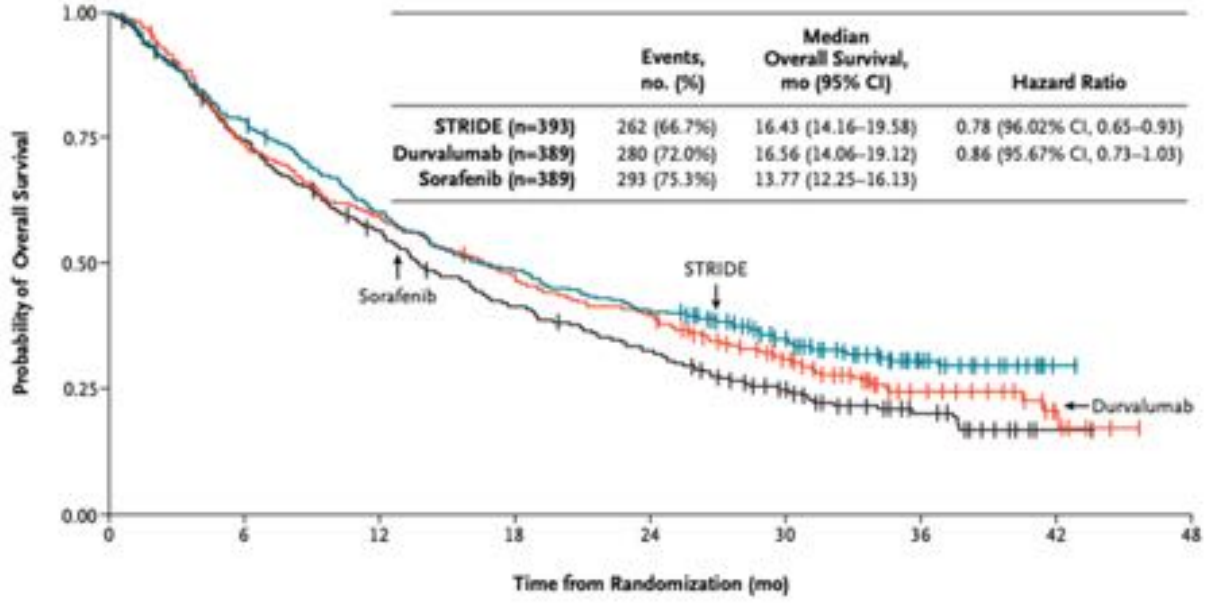
Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma

Ghassan K. Abou-Alfa, M.D., M.B.A.,[1,2] George Lau, M.D., F.R.C.P.,[3] Masatoshi Kudo, M.D., Ph.D.,[4] Stephen L. Chan, M.D.,[5] Robin Kate Kelley, M.D.,[6] Junji Furuse, M.D., Ph.D.,[7] Wattana Sukeepaisarnjaroen, M.D.,[8] Yoon-Koo Kang, M.D., Ph.D.,[9] Tu Van Dao, M.D., Ph.D.,[10] Enrico N. De Toni, M.D., Ph.D.,[11] Lorenza Rimassa, M.D.,[12,13] Valeriy Breder, M.D., Ph.D.,[14] Alexander Vasilyev, M.D.,[15] Alexandra Heurgué, M.D.,[16] Vincent C. Tam, M.D.,[17] Kabir Mody, M.D.,[18] Satheesh Chiradoni Thungappa, M.D.,[19] Yuriy Ostapenko, M.D.,[20] Thomas Yau, M.D.,[21] Sergio Azevedo, M.D.,[22] María Varela, M.D., Ph.D.,[23] Ann-Lii Cheng, M.D., Ph.D.,[24] Shukui Qin, M.D., Ph.D.,[25] Peter R. Galle, M.D., Ph.D.,[26] Sajid Ali, M.D.,[27] Michelle Marcovitz, Ph.D.,[27] Mallory Makowsky, Pharm.D.,[27] Philip He, Ph.D.,[27] John F. Kurland, Ph.D.,[27] Alejandra Negro, Ph.D.,[27] and Bruno Sangro, M.D., Ph.D.,[28] for the HIMALAYA Investigators*



	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)	

No. at Risk									
STRIDE	393	308	235	190	158	98	32	1	0
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

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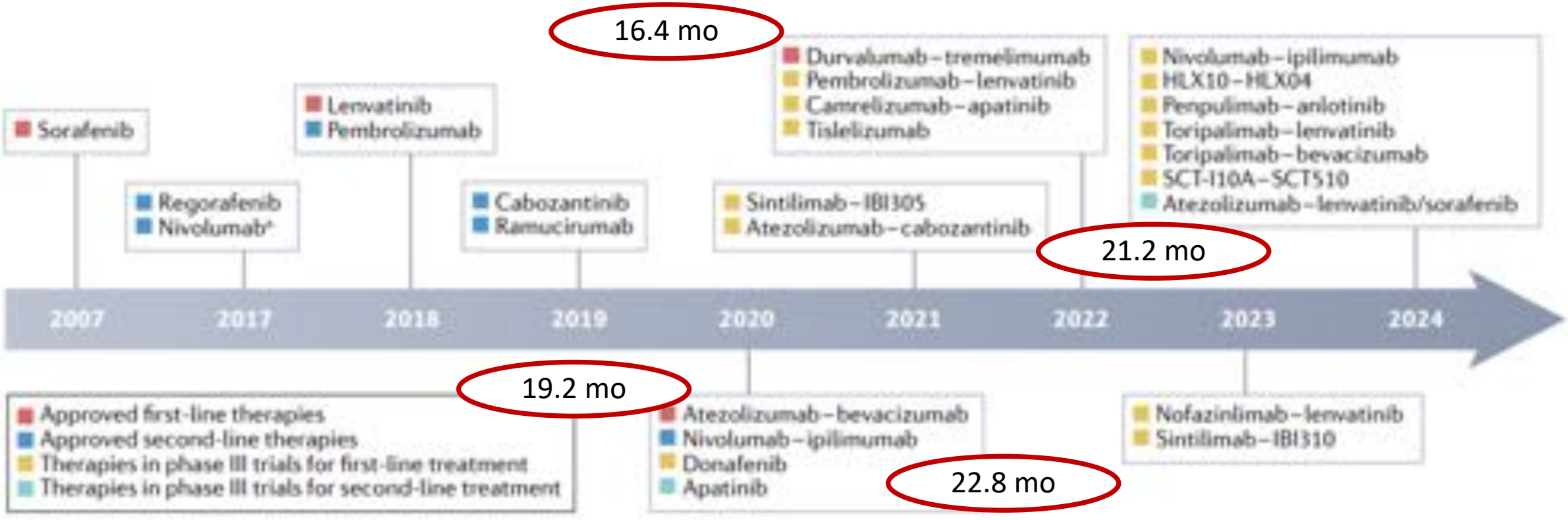
Therapeutic landscape of advanced HCC



Should immunotherapy be incorporated earlier ?

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Yang et al. Nature Reviews Gastroenterology and Hepatology 2022

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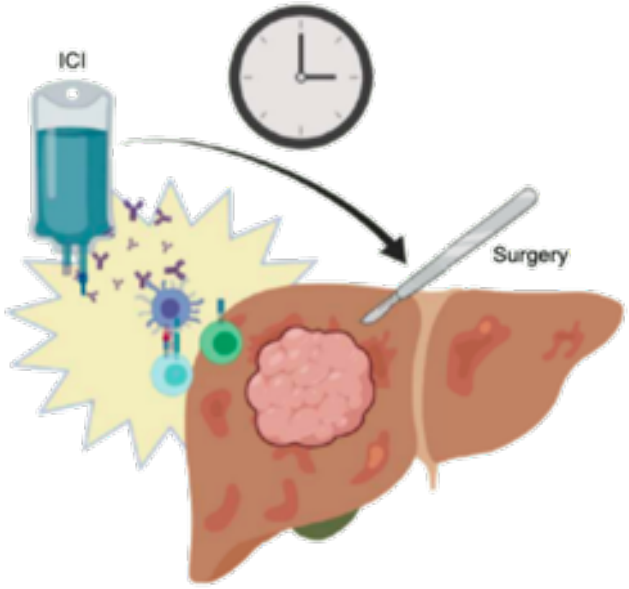
- Improved surgical outcomes
- Early treatment of micrometastases
- *In vivo* sensitivity test
- Paired assessment of biomarkers pre/ post therapy

↑ chances getting to transplant/cure
↑ outcomes in those high-risk pts
↑ downstaging rates



- No measurable responses
- Deferred treatment of micrometastases
- No insight as to mechanism of action

- Histological confirmation
- Deferred primary therapy
- Drop-out risk due to toxicity, tumor progression

Rejection
Toxicity

- Patient selection based on histopathological risk-stratification
- No delay of primary therapy

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Pinato et al. Hepatology 2020

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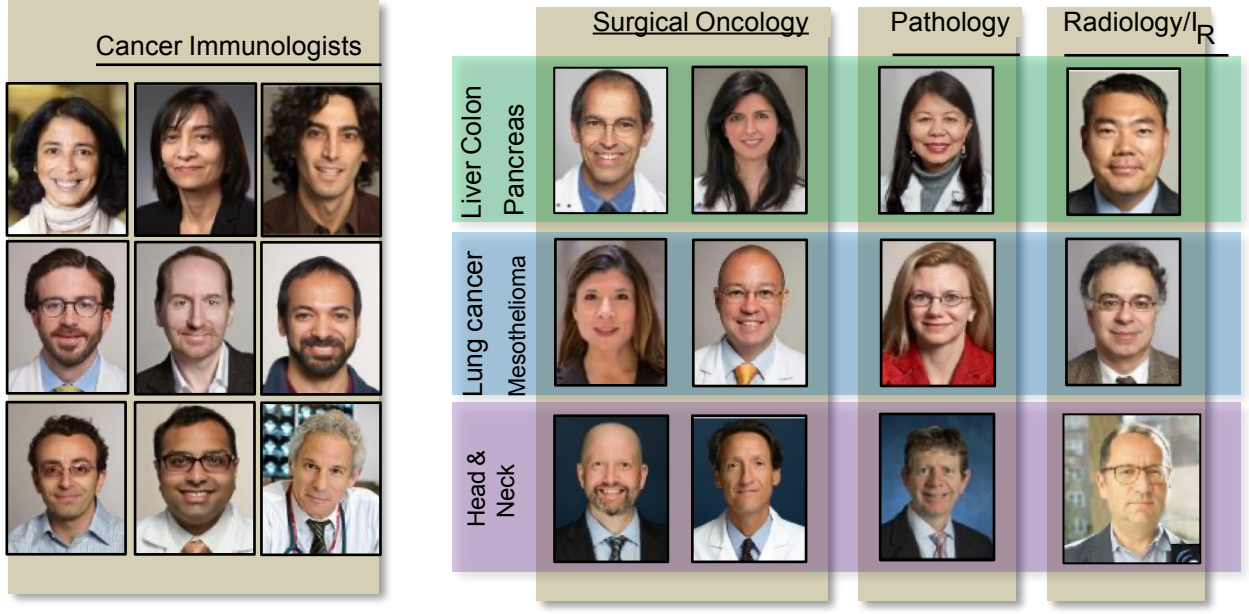
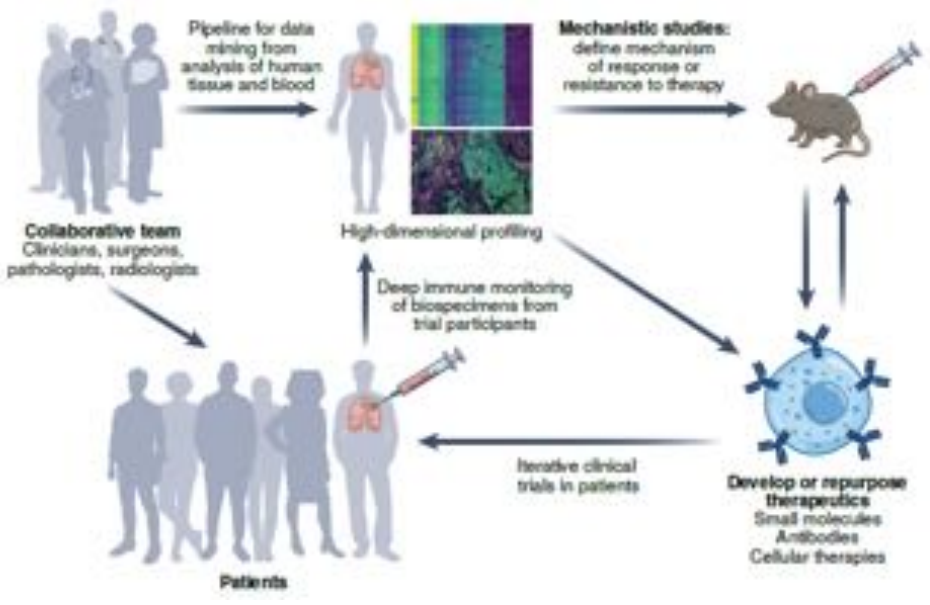
TARGET

The neo-Adjuvant Research Group to Evaluate Therapeutics

Building cancer immune knowledge starting with early treatment naïve surgical cancer lesions
Reduce confounding variables induced by prior therapy, intact immune system





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Marron et al. Nature Medicine 2022

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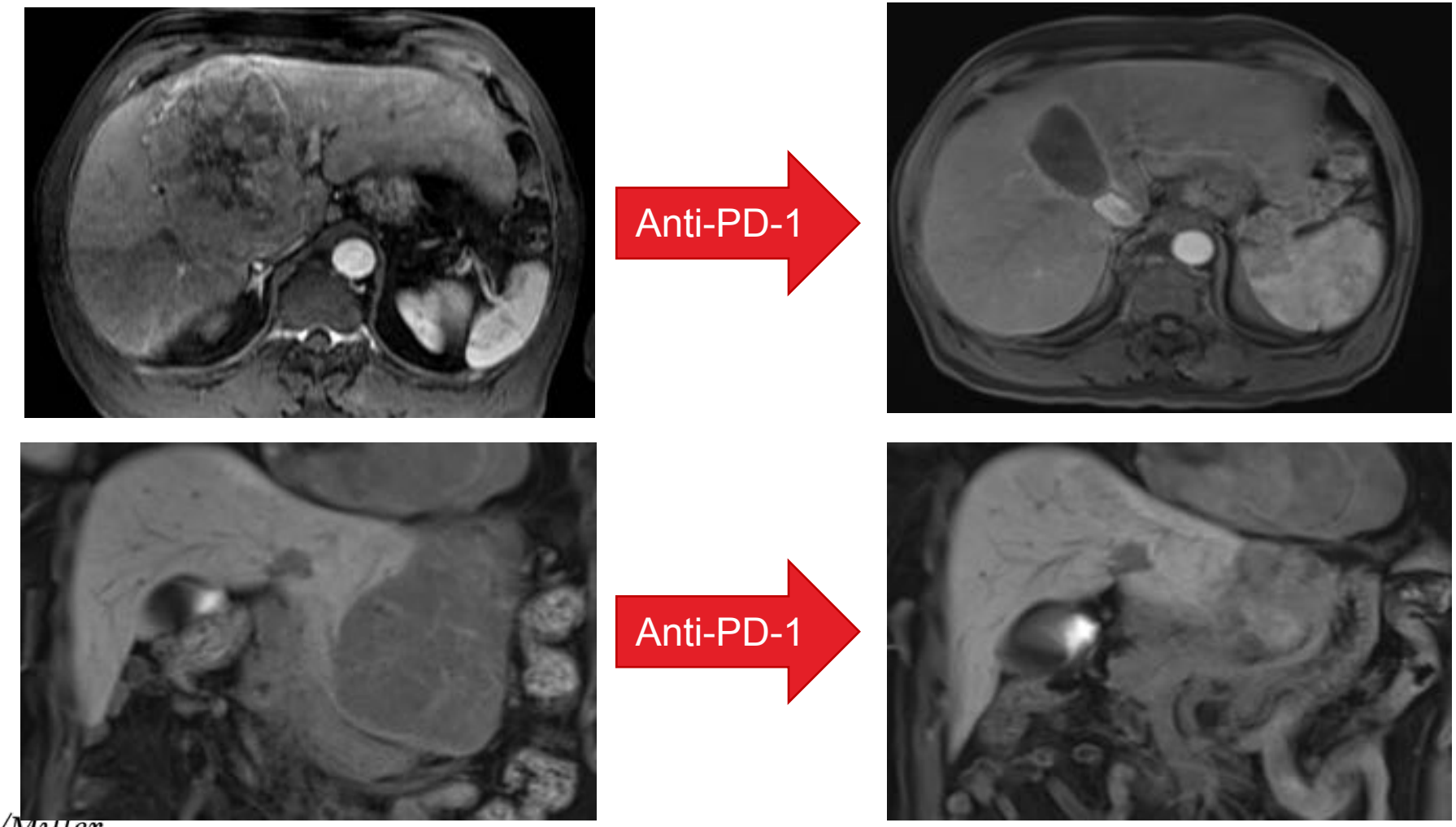
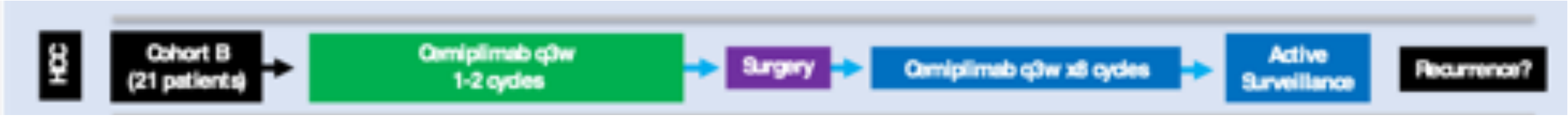
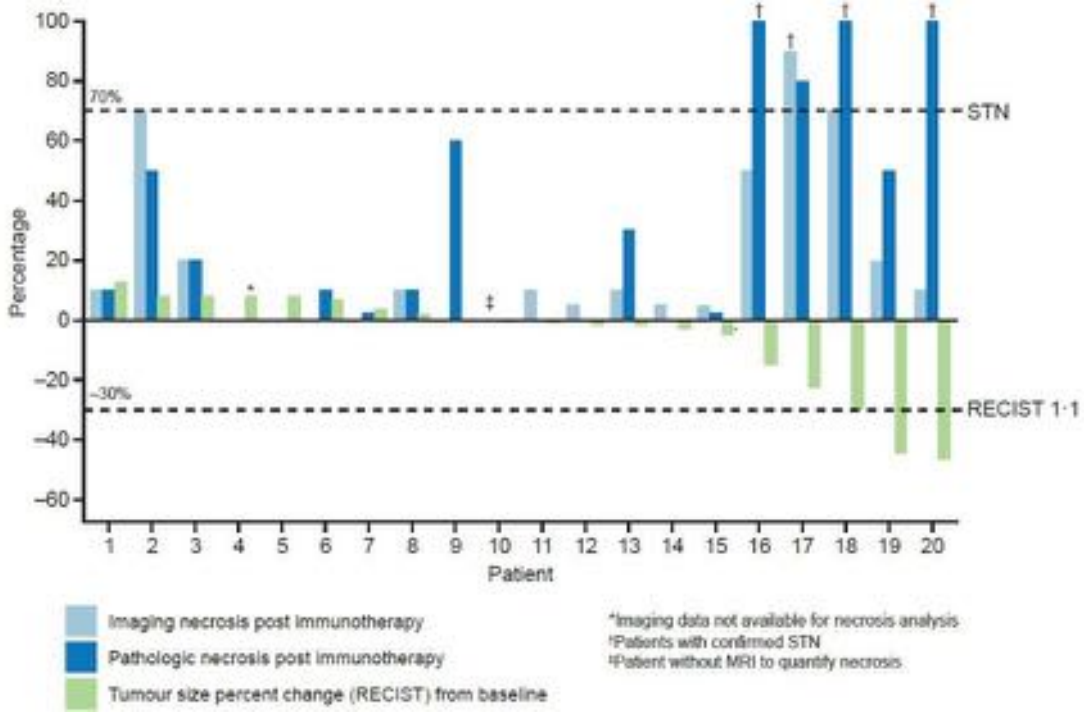
Downstaging- HCC resections



TCI neoadjuvant Cemiplimab trial





Pathologic tumour necrosis	n (%)
STN (>70%)	4 (20)
Complete tumour necrosis (100%)	3 (15)
Tumour necrosis ≥50%	7 (35)
Tumour necrosis <50%	13 (65)

STN=significant tumour necrosis.

No grade 4 or 5 events were observed

N=1 pneumonitis, delay in surgery by 2 weeks

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Marron et al. Lancet Gastroenterology and Hepatology 2021

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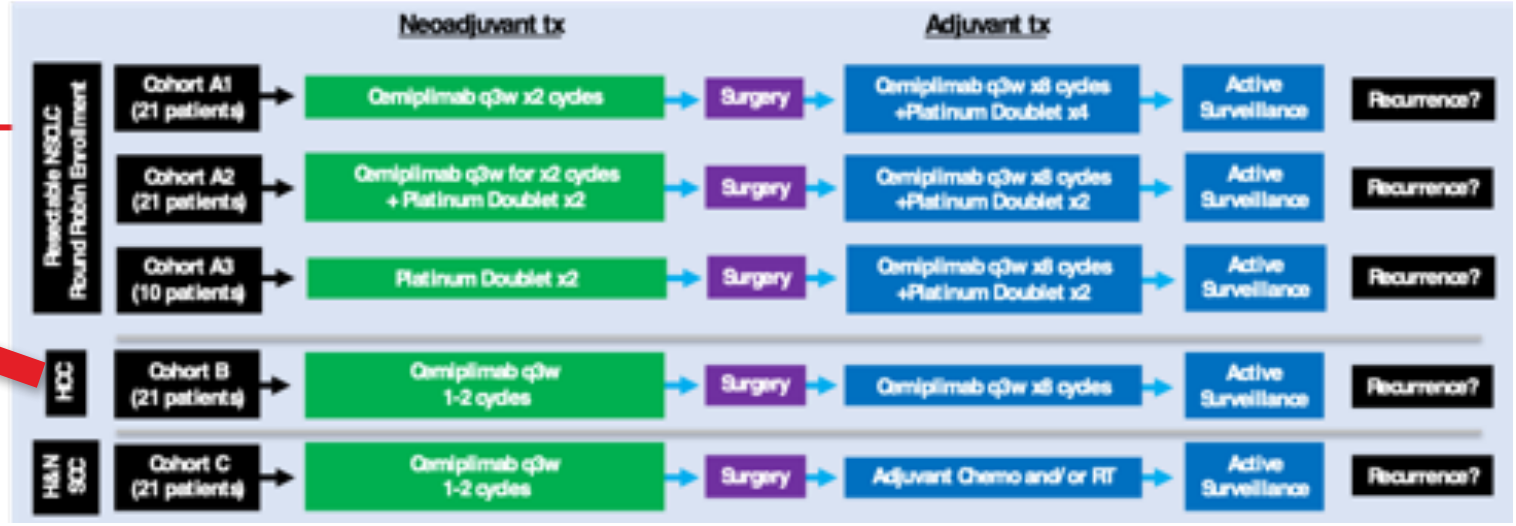
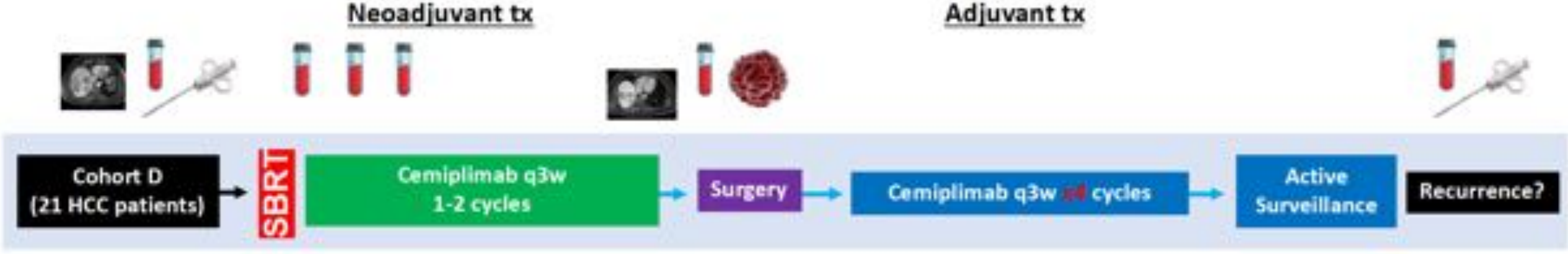
NCT03916627: Amendment



New HCC (using funds already allocated for Cohorts A3 and C): ***first-in-man*** **trial of neoadjuvant PD-1 blockade + RT in HCC**



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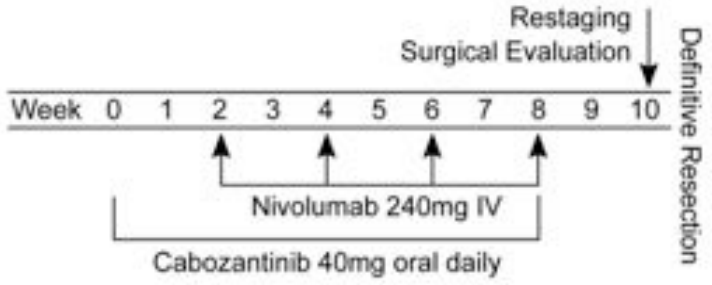
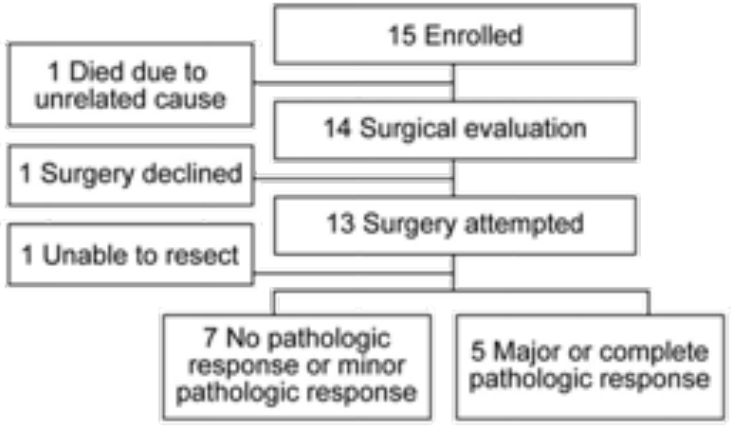
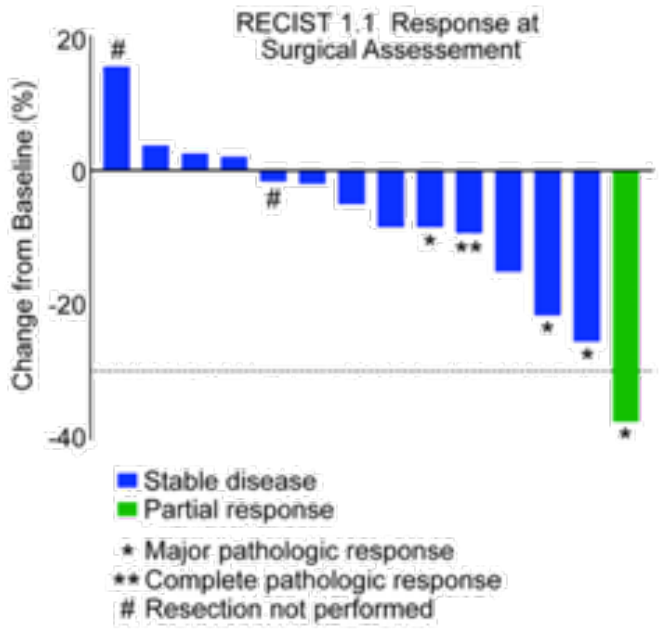
ICI before surgical resection is safe and feasible

Neoadjuvant cabozantinib and nivolumab convert locally advanced hepatocellular carcinoma into resectable disease with enhanced antitumor immunity







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Jin Ho Nature Cancer 2021

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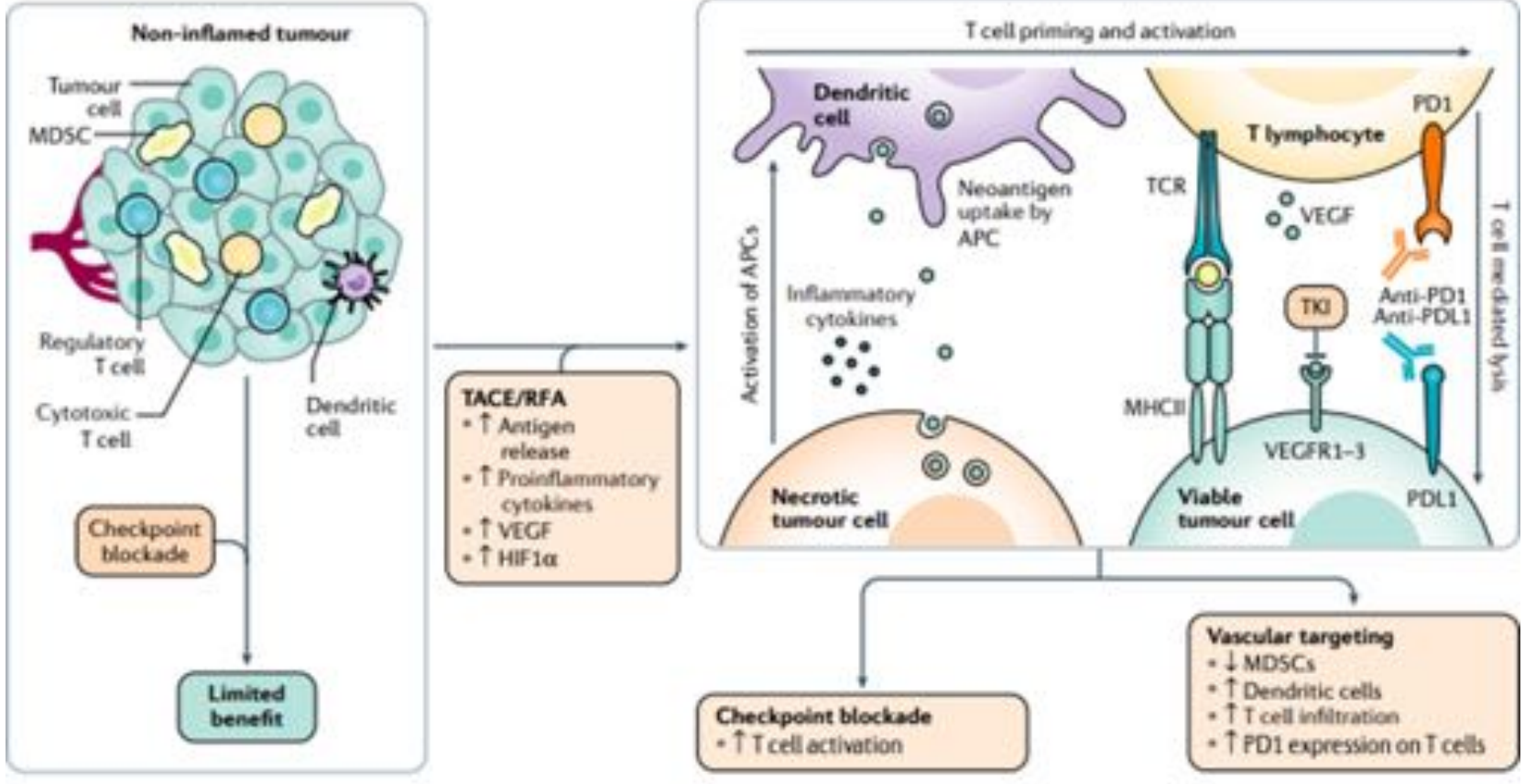
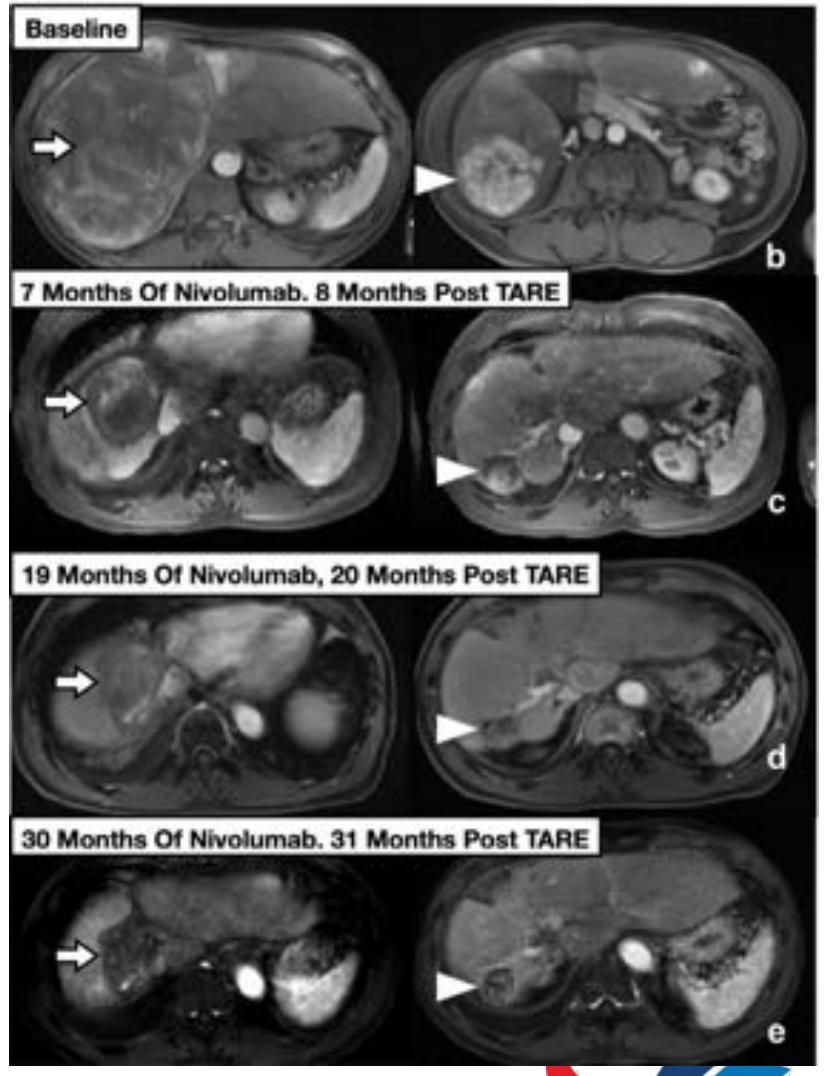
LRT with immunotherapy- Safety ?





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Marinelli et al. J Vasc Interv Radiol 2020
Llovet et al. Nat Rev Gastroenterol Hepatol 2021

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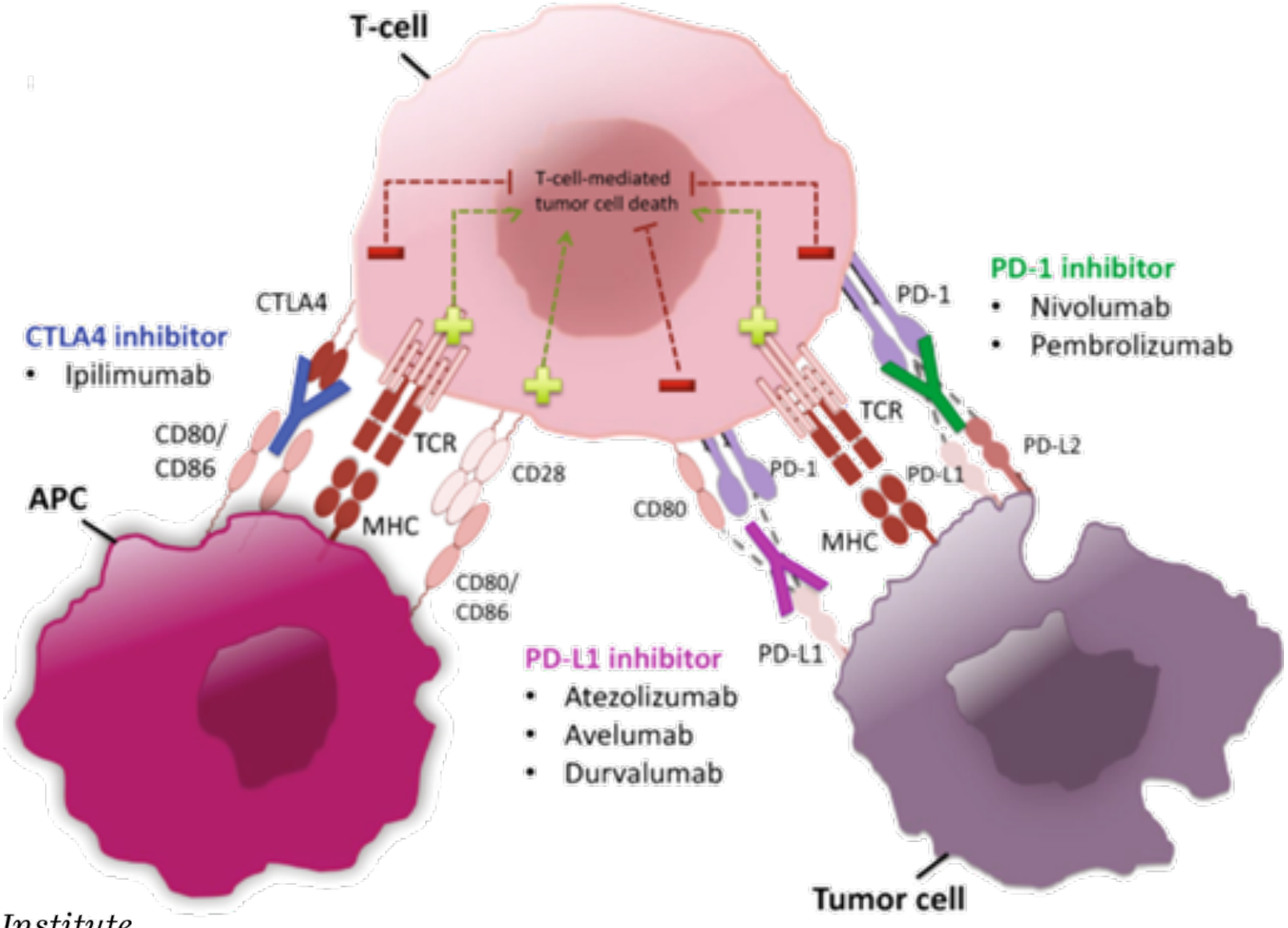
Type of article	Authors	Year	Journal	N	LRT	IT	Safety
Systematic review	Min Ding	2016	PLOS ONE	19 studies	TACE or RFA	IT no ICP	No reported
	He	2016	International Immunopharmacology	4 studies	TACE	DC	patients were more likely to suffer a fever in the TACE- DC-CIK group P = 0.001
Randomized	Zhang	2022	Clinics and Research in Hepatology and Gastroenterology	46/46	TACE	Camrelizumab + TACE.	There was no significant difference of AEs between the two groups ($\chi 2 = 3.419$, P = 0.064).
Non-randomized prospective	Cui	2013	International Journal of Cancer	32/30	RFA	Cellular immunotherapy (CIT) + RFA	there was no toxic effect in the RFA/CIT group.
	Duffy	2016	JHEP	32	RFA + Treme		No DLT was encountered.
	Zhao	2022	Medicine	55/45	TACE	GSMs-TACE followed by combined DC sequential therapy	There were no statistical differences in intervention-related adverse events between the 2 groups
	De la Torre	2022	Journal for ImmunoTherapy of Cancer	42	+ Y90 + nivo		AEs and SAEs grade 3 or higher were observed in 19% and 26% of patients, respectively. No treatment-related deaths were reported.
Non-randomized retrospective	Huang	2013	Journal of Immunotheraphy	89/85	TACE and RFA,	TACE + RFA + CIK	There were no major complications, grade 3–4 liver toxicities or procedure-related deaths in either group afterthe TACE and RFA procedures.
	Alnaggar	2018	Cellular Physiology and Biochemistry	20/20	Electroporation (IRE) or TACE	plus NK cell (IRE-NK)	No severe complications (such as ruptured or hepatic failure, myoglobinuria, or acute renal failure) were reported post-IRE. Several mild adverse effects occurred, but the affected patients eventually recovered with or without symptomatic management
	Zhan	2019	JVIR	26	Checkpoint inhibitor + Y90		There were no early (30-day) mortality or grades 3/4 hepatobiliary or immunotherapy-related toxicities.
	Guo	2022	BMC Cancer	20/51	TACE	TACE + Camrelizumab	No treatment-related deaths occurred in this study.
	Marinelli	2020	JVIR	29	RE + nivolumab		No reported
	Smit	2020	Journal of Radiation Oncology volume	21	RT + Nivo		No reported
	Zhang	2022	Journal of Hepatocellular Carcinoma	34	TACE plus Camrelizumab		There were no deaths associated with the treatment

Immunotherapy and liver transplant



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Early vs late TCMR

- **Early TCMR**
- Early days of LT up to 60 % had TCMR
- Modern series 11% (SRTR) to 25% (A2ALL) < 6 months post LT

- **Late TCMR**
- Variably defined-> 6 months post LT
- Affect 7-23% of recipients

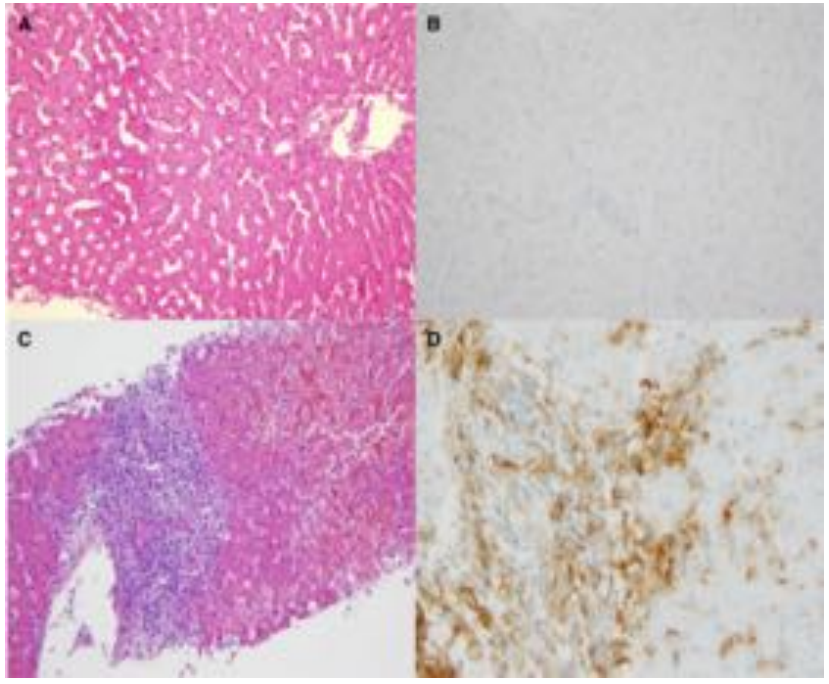
Wiesner et al, Hepatology 1998
Levitsky et al CGH 2016

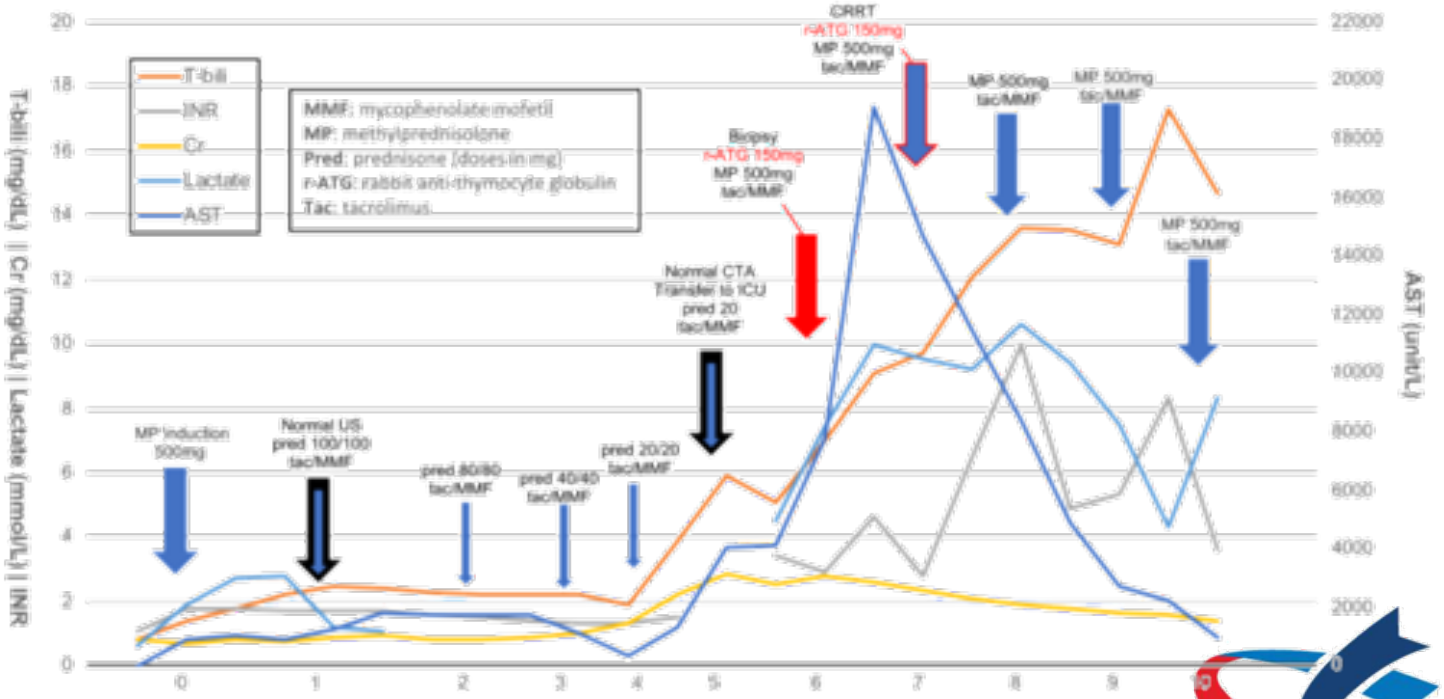
ICI-Bridge to OLT

Fatal hepatic necrosis after nivolumab as a bridge to liver transplant for HCC: Are checkpoint inhibitors safe for the pretransplant patient?

Mina F. Nordness[1] | Stephanie Hamel[2] | Caroline M. Godfrey[1] | Chanjuan Shi[3] | Douglas B. Johnson[4] | Laura W. Goff[4] | Heather O'Dell[1] | Roman E. Perri[5] | Sophoclis P. Alexopoulos[1]

ICI within 8 days from LT





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Nordness et al. AJT 2019

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ICI-Bridge to OLT

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

CLINICAL OBSERVATIONS IN HEPATOLOGY | HEPATOLOGY, VOL. 72, NO. 4, 2020

Immunotherapy as a Downstaging Therapy for Liver Transplantation

Birgit Schwacha-Eipper,[1,2] Iulia Minciuna,[1] Vanessa Banz,[2] and Jean François Dufour[1,2]

Pre LT-ICI

No.	MELD Dx	Milan in/out at diagnosis	Max AFP pre-LT (ng/mL)	LRT (No)	Nivolumab (days pre-LT)	Complication	Rejection	Recurrence
1	6	Milan out within UCSF	3	2	18	None	None	None
2	18	Milan out within UCSF	4.4	2	22	None	None	None
3	7	Milan out within UCSF	9.4	6	1	None	None	None
4	6	Milan in	507	7	2	None	None	None
5	6	Milan in	1493	2	22	None	Mild	None
6	17	Milan in	158	None	13	Bile leak	None	None
7	7	Milan in	479	2	253	None	None	None
8	7	Milan in	820	3	7	None	None	None
9	7	Milan out within UCSF	124	1	30	None	None	None
10	8	Milan out within UCSF	< 2	5	10	None	None	None

Immunotherapy pre-LT

Publication	N	Age (yrs)	Gender	ULD	Milan criteria	Explant / Pathology	ICI type	ICI duration	Last dose pre-LT (days)	Follow up post-LT (days)	AR post-LT
Nordness 2020	1	65	M	HCV	Within	100% necrosis	Nivolumab	2 years	8	10 (died)	Yes
Schwacha-Eipper 2020	1									365	No
Chen 2021	1									3 (died)	Yes
Sogbe 2021	1									730	No
Qiao 2021	7									N/A	1 yes 6 no
Schnickel 2022	5									61–1155 (1 re-LT)	2 yes 3 no
Dehghan 2021	1									548 (re-LT)	Yes
Aby 2022	1									480	Yes
Tabrizian 2021	9									243–700	1 yes 8 no
Wang 2023	16	37–67	14 M / 2 F	14 HBV 2 ALD	Outside	10 MPR 6 CPR	2 nivolumab 7 pembrolizumab 4 sintilimab 2 camrelizumab 1 multiple	1–27 cycles	7–184	352.5 (median)	9 yes 7 no

- Heterogeneous
- Case series/reports
- ICI type and washout period
- Lack of biopsy
- Immunosuppression

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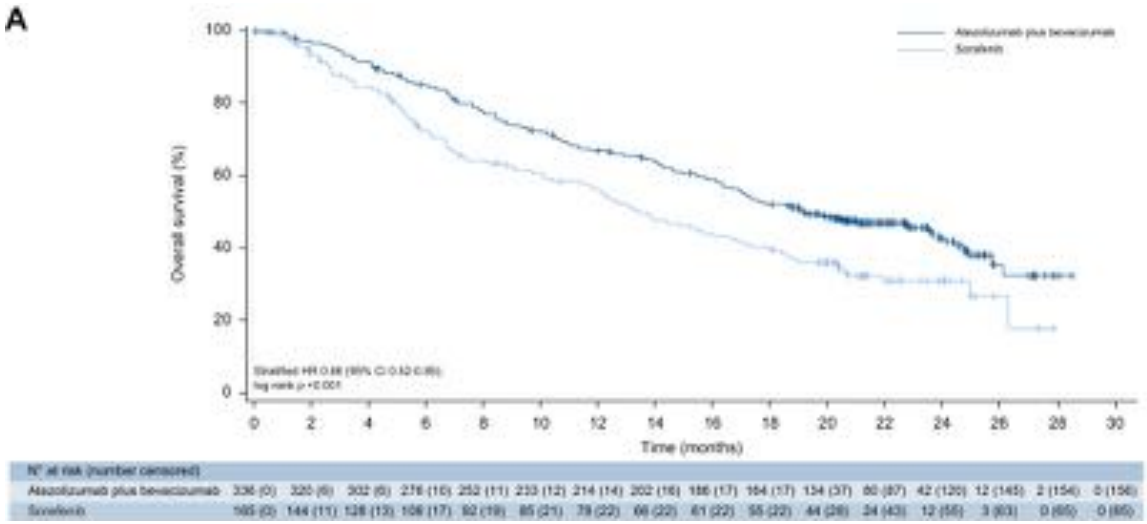
#1: Patient selection

- In advanced HCC, do we know who needs a transplant?
- Lack long-term data on outcomes of patients with excellent responses



- Transplant survival excellent, however some with diminished QOL

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Cheng et al. *J Hep*. 2021

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Decompensated patients?

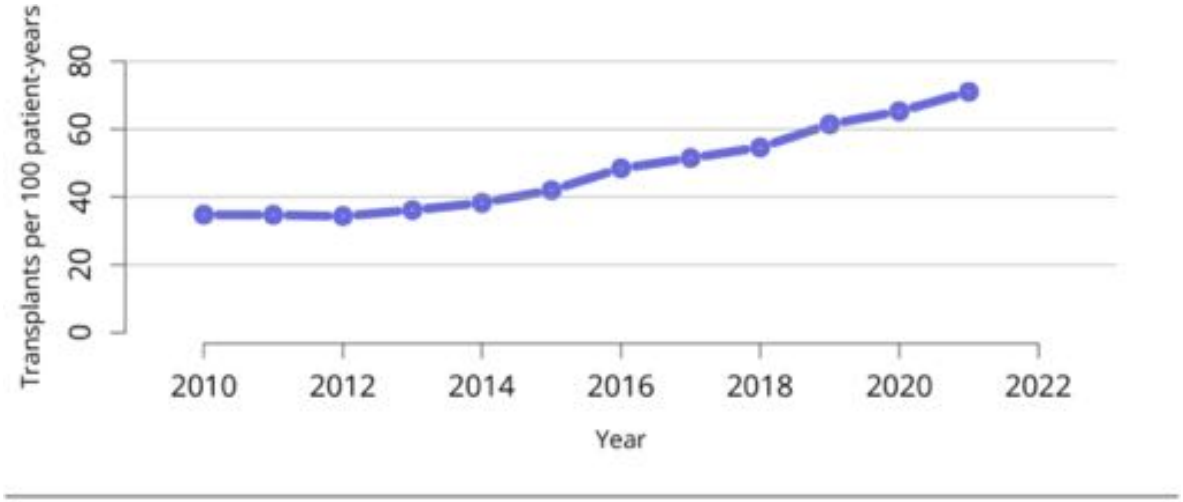
- Imaging sensitivity for HCC staging diminishes with decompensation
  - Presence of ascites
  - Infiltrative tumors
  - Prior treatment

- Bevacizumab may not be as well tolerated in decompensated cirrhosis
  - Diminished efficacy of single agent immunotherapy – 10-15% response rates
  - Even less data on safety of combination immunotherapies

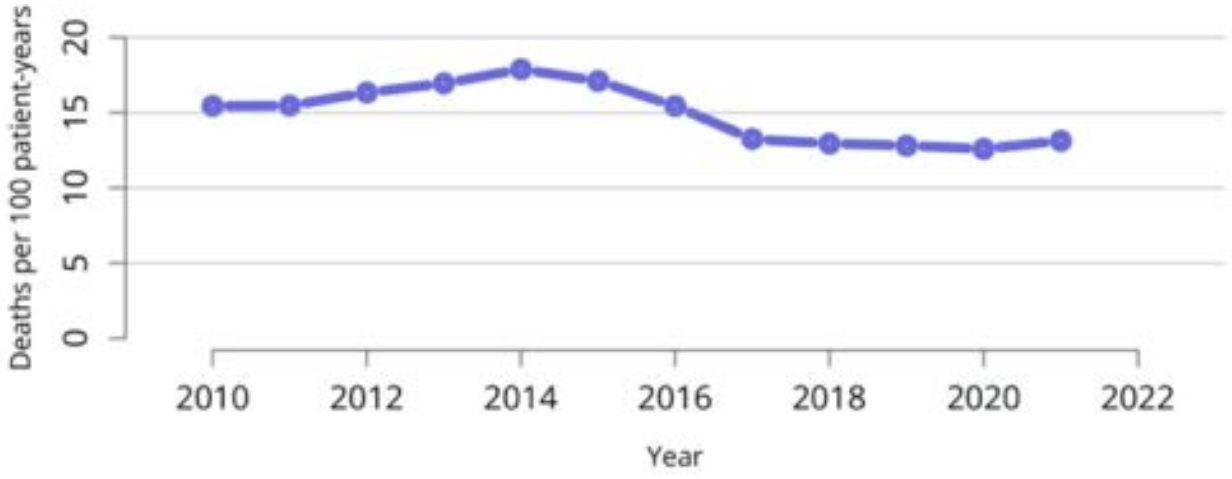
#2: Reporting biases

- Evidence that reporting biases in research are prevalent
- Are the reported results generalizable?
- No capture of immunotherapy exposure in the UNOS database
- Case series and reports may not be representative of actual clinical outcomes

#3: Organ availability vs expansion of LT



OPTN/SRTR 2021 Annual Data Report



OPTN/SRTR 2021 Annual Data Report

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Kwong et al. Am J Transplant. 2023

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Just use a living donor ?

- Ethics of living donation in a high-risk recipient population warrant consideration
- Risk (financial, QOL) to donors should not be discounted

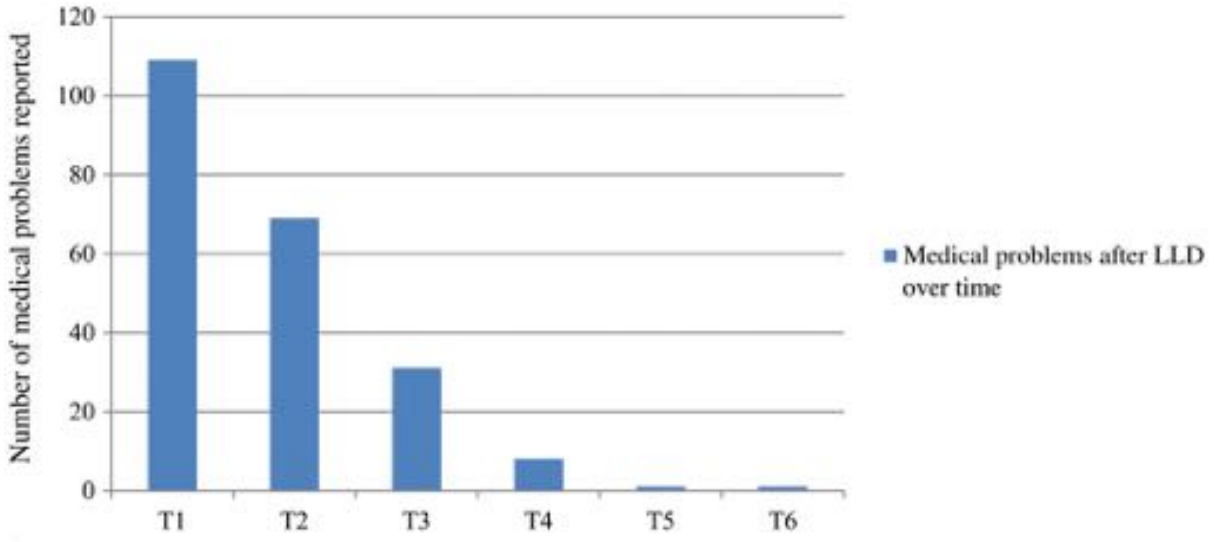


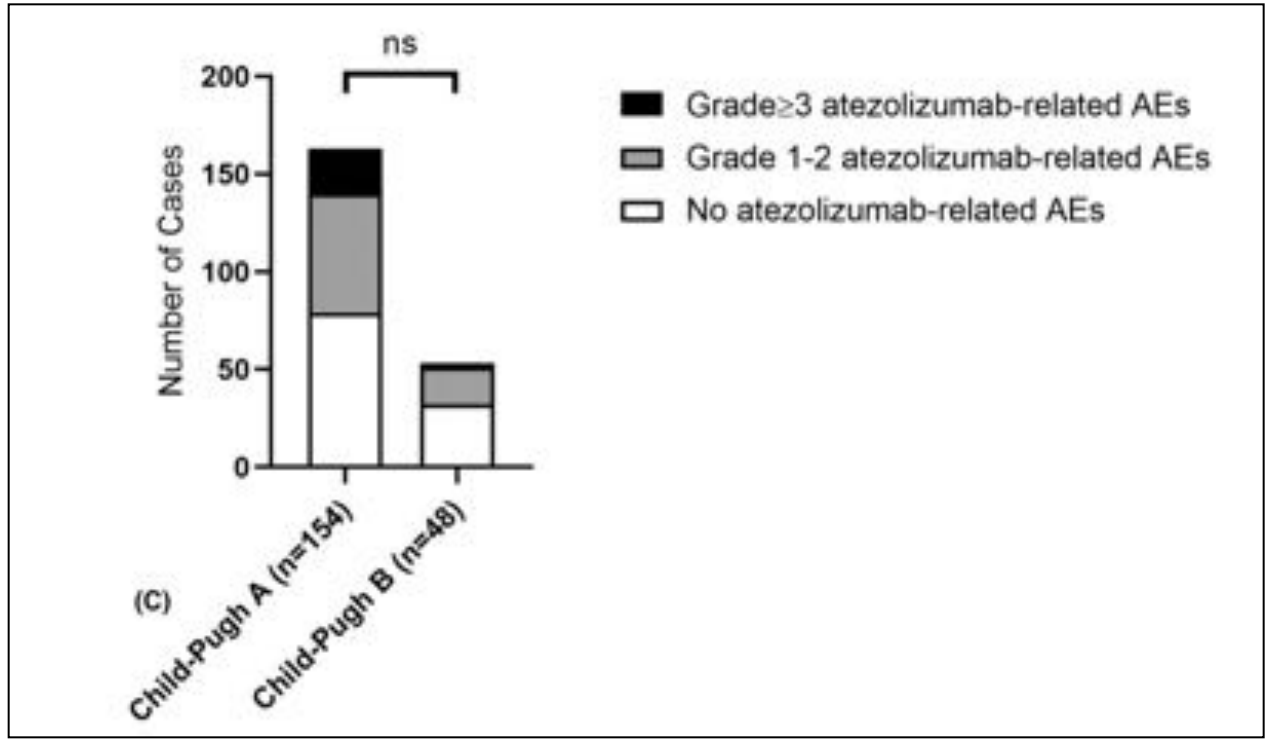
Table 4: Financial outcome characteristics over time

Outcome	3 mo after donation (n = 250)	6 mo after donation (n = 241)	1 year after donation (n = 201)	2 years after donation (n = 139)
Donation costs were a burden[1]	39.6% (99)	28.4% (67)	25.4% (51)	19.4% (27)
Incurred medical costs related to donation[1,2]	26.4% (66)	16.5% (39)	12.4% (25)	9.4% (13)
Incurred nonmedical costs related to donation[1]	73.2% (183)	36.9% (87)	20.4% (41)	13.7% (19)
Costs compared with expectations[2]				
Less than expected	8.1% (20)	13.2% (31)	11.0% (22)	14.4% (20)
About what was expected	75.7% (187)	71.8% (169)	77.5% (156)	73.4% (102)
More than expected	16.2% (40)	15.0% (35)	11.5% (23)	12.2% (17)
Changed jobs or modified work due to donation[4,5]	34.2% (83)	12.6% (22)	2.1% (3)	1.0% (1)
Personal income affected by donation[5,6]				
Decreased	41.1% (76)	8.4% (15)	4.1% (6)	1.0% (1)
No change	58.4% (108)	87.7% (157)	92.5% (135)	98.1% (101)
Increased	0.5% (1)	3.9% (7)	3.4% (5)	1.0% (1)
Problems getting or keeping health insurance[7,8]	2.4% (6)	2.1% (5)	1.0% (2)	3.6% (5)
Problems getting or keeping life insurance[7,8]	1.2% (3)	0.8% (2)	1.0% (2)	1.4% (2)
Currently have no health insurance[6]	7.2% (18)	6.3% (15)	6.5% (13)	2.2% (3)

Rudrow et al. *Liver Transplantation*. 2018
Dimartini et al. *AJT*. 2019.

#4: Waitlist safety

- Bridging paradigm: Risks of routine adjuvant therapy with IS?
- Adjuvant data excluded patients with significant liver dysfunction
- Relying on small reports of safety in this population
  - Any grade AE: 40-50%
  - Grade 3 or greater AE: 15-16%
- Waitlist outcomes a tracked metric



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D'Allesio et al. Hepatology. 2022

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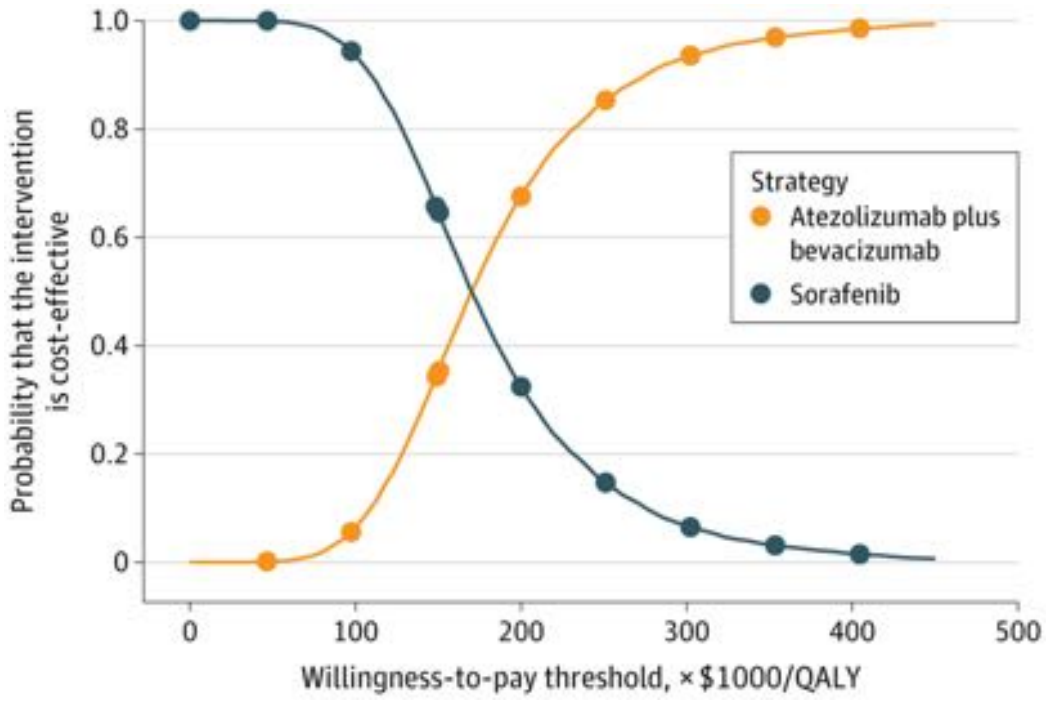
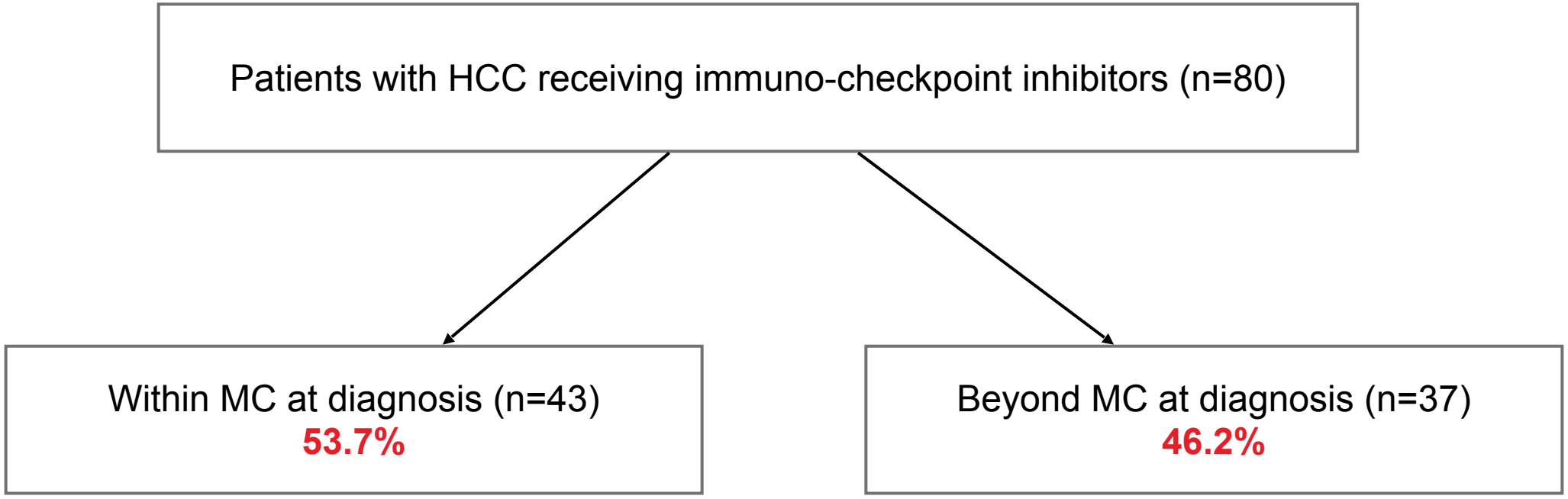
#4 Waitlist Management

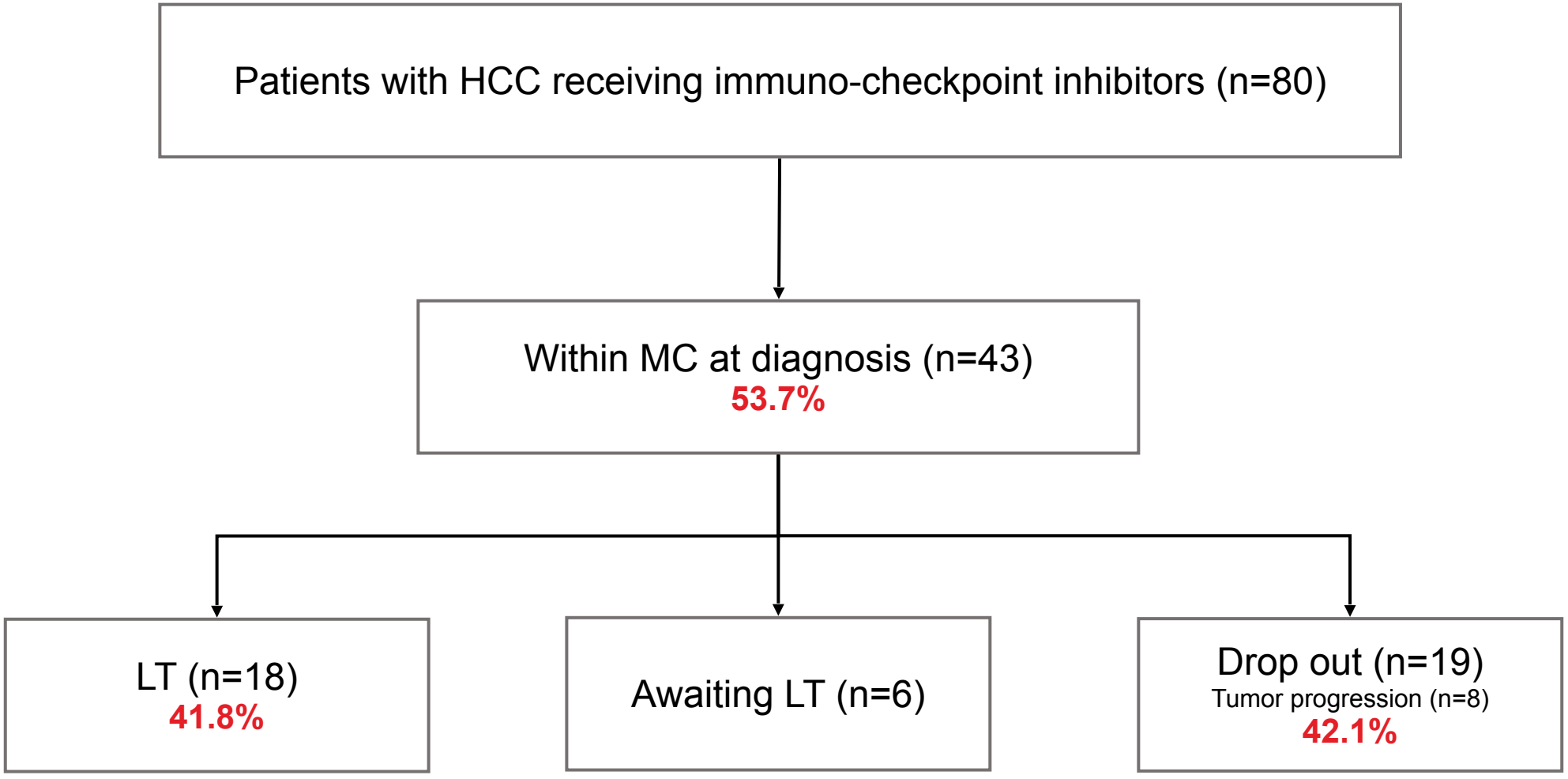
- Timing of stopping immunotherapy (and Bev) for sufficient “washout” period
  - Coordination with oncology
  - Centers with high average MELD
- Management of AEs and when to hold on transplant
- Financial toxicity associated with receipt of therapy every 3-4 weeks
- Exacerbation of disparities in liver transplant receipt



Su et al. JNO. 2021

Immunotherapy while awaiting LT





The 3-year cumulative probability of dropout was 44.8% if within MC

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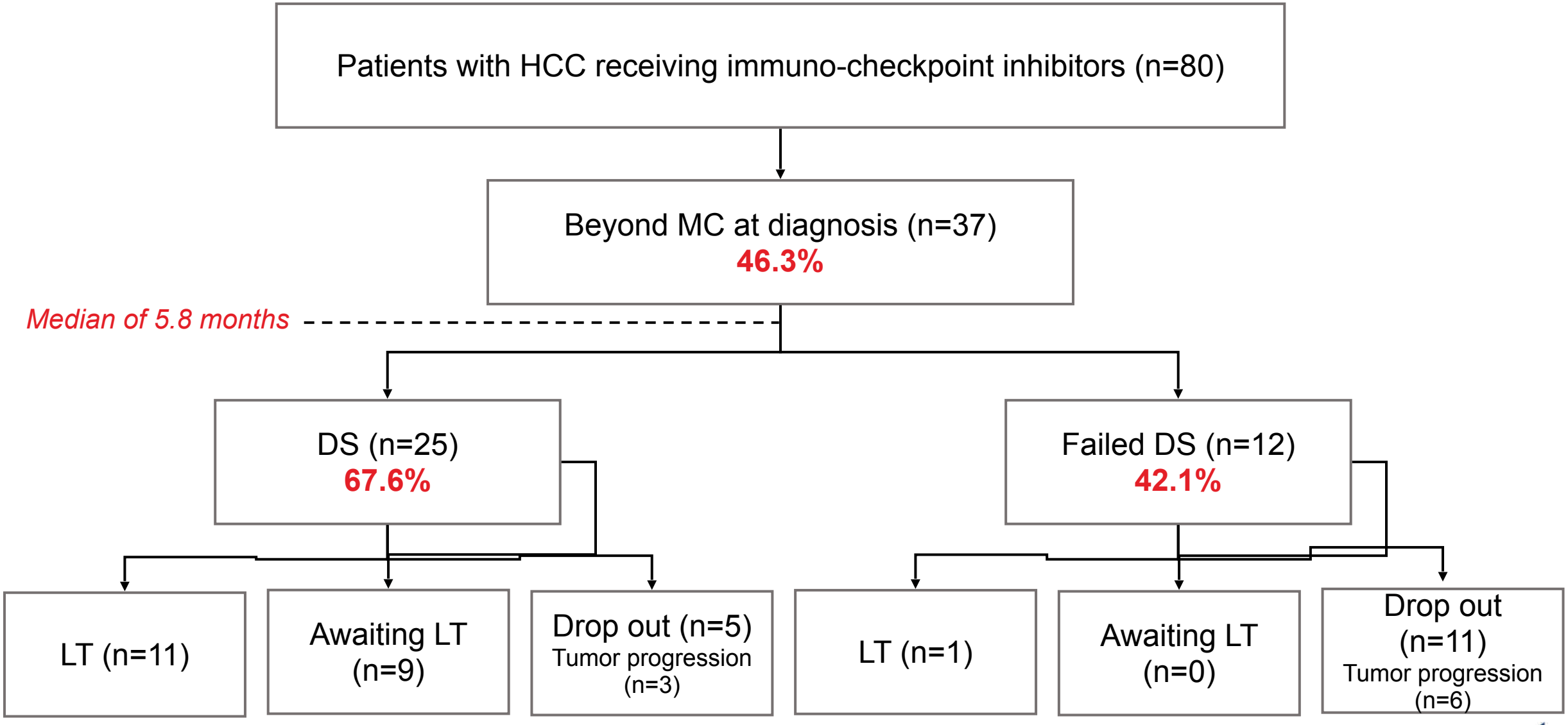

The 3-year cumulative probability of dropout 53.7% beyond MC

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Rejection post-LT

- Post-LT rejection rate was 16.6%

  n=2 severe, 1 graft loss and re-LT

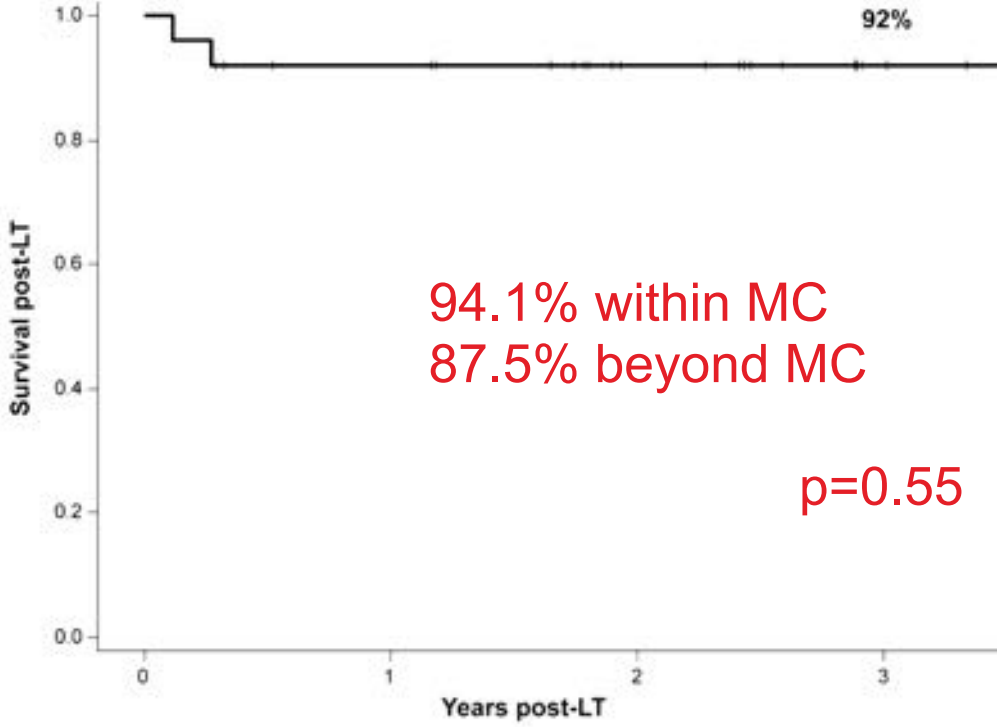
  n=3 mild secondary to low immunosuppression

- ICI dose < 3 months pre-LT was associated with increased rejection (p=0.04)

  → Type, duration, ULD not significant

Overall survival (ITT and post LT)

ITT survival
3-yr 69%



94.1% within MC
87.5% beyond MC

p=0.55

HCC recurrence occurred in 3 cases at a median time of 24 months (18-28) post-LT

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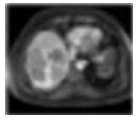
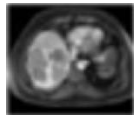
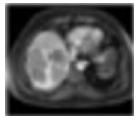
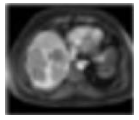
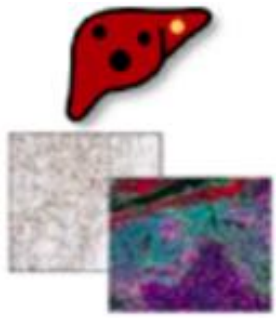
Optimal timing ? Remains unclear but…

Recommend stopping ICI 2-3 half lives (8-12 weeks) prior to LT

	Trade Name	Mechanism	Half Life
Nivolumab	Opdivo	PD1 Inhibitor	26.7 days
Pembrolizumab	Keytruda	PD1 Inhibitor	23 days
Atezolizumab	Tecentriq	PD L1 Inhibitor	27 days
Durvalumab	Imfinzi	PD L1 Inhibitor	18 days
Ipilimumab	Yervoy	CTLA-4 Inhibitor	15.4 days

Diagnosis ← Listing Time → Downstaged → Transplant

Patient selection:

- High risk
- High tumor burden
- AFP
- Number LRT
- Long wait list
- Downstaging/all comers
- Underlying liver disease?

- Choice of IO
- Observation period
- Washout period
- Living donor?

- Choice of Immunosuppression
- Induction therapy?

- Risk of Rejection and management
- Adjuvant use?

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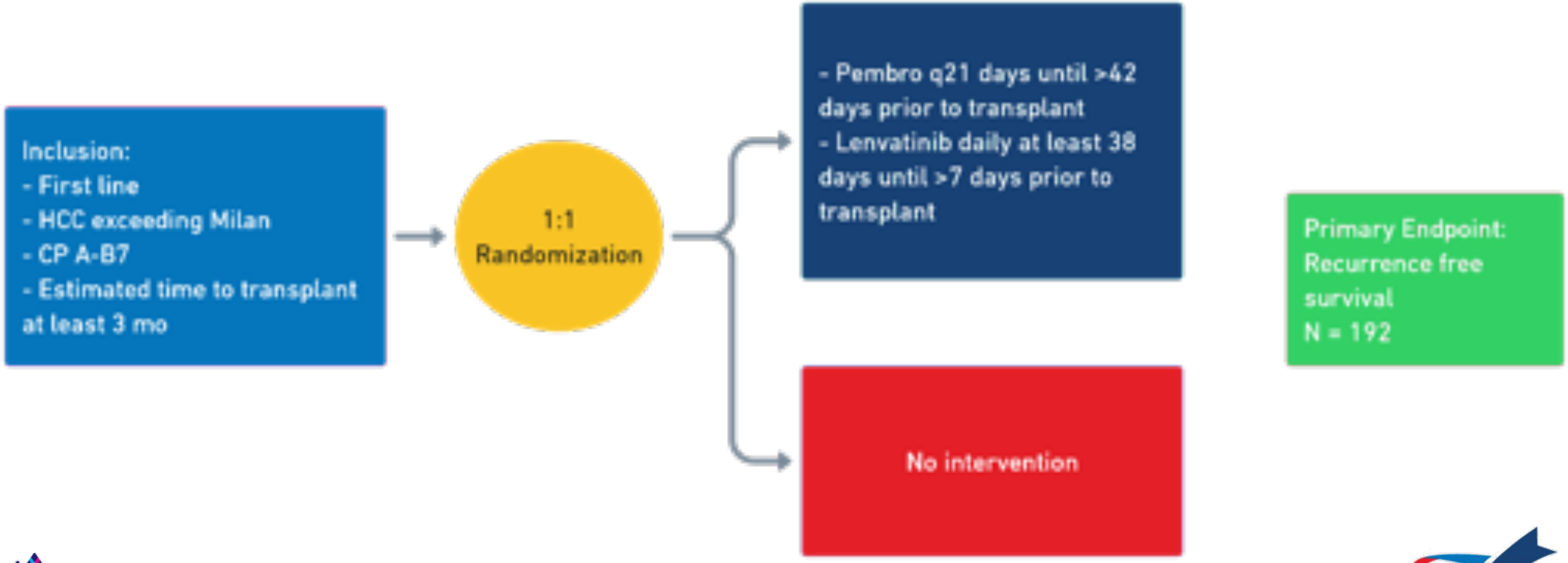
Immunotherapy before Liver Transplantation ClinicalTrials.gov

Trial	NCT	Phase	Treatment arms	Endpoint	Adjuvant	N=
Neoadjuvant pre LT						
PLENTY202001	NCT04425226	Phase 2	Pembro/Len	RFS	No	192
	NCT05185505	Phase 2	Atezo/Bev	Feasibility % rejection	No	24
	NCT05027425	Phase 2	Durva/Tremi	30d rejection rate	No	30
	NCT04443322	NA	Durva/Len	PFS/RFS	No	20

Trial Number	Status	Allocation	Intervention	Region
NCT04035876	Recruiting	Single Arm	Camrelizumab plus Apatinib	China
NCT04443322	Recruiting	Single Arm	Durvalumab plus Lenvatinib	China
NCT05411926	Recruiting	Case-Control	PD-1/PD-L1 inhibitor monotherapy	China
NCT05475613	Not yet recruiting	Single Arm	PD-1/PD-L1 inhibitor plus Lenvatinib plus HAIC	China
NCT05027425	Recruiting	Single Arm	Durvalumab plus Tremelimumab	USA
NCT05339581	Not yet recruiting	Parallel Assignment	PD-1/PD-L1 inhibitor plus Lenvatinib plus IMRT	China

Plenty 202001- Randomized Phase II NCT04425226



Atezo/Bev + TACE (NCT05185505)
Single Arm, Open label, Phase II

Inclusion:
- First line
- HCC exceeding Milan
- CP <A6
- Eligible for TACE
- Life expectancy >6mo
- EGD wo varices

- TACE q 3 mo (max 4 treatments)
- Atezolizumab / bevacizumab up to 6 mo

Primary Endpoint:
Acute allograft rejection within 1 year
N = 24

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Multidisciplinary care

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ANNALS OF SURGERY

Vol. 202 October 1985 No. 4

Role of Liver Transplantation in Cancer Therapy

SHUNZABURO IWATSUKI, M.D., ROBERT D. GORDON, M.D., BYERS W. SHAW, JR., M.D.,
THOMAS E. STARZL, M.D., PH.D.

Moratorium on liver transplantation for HCC

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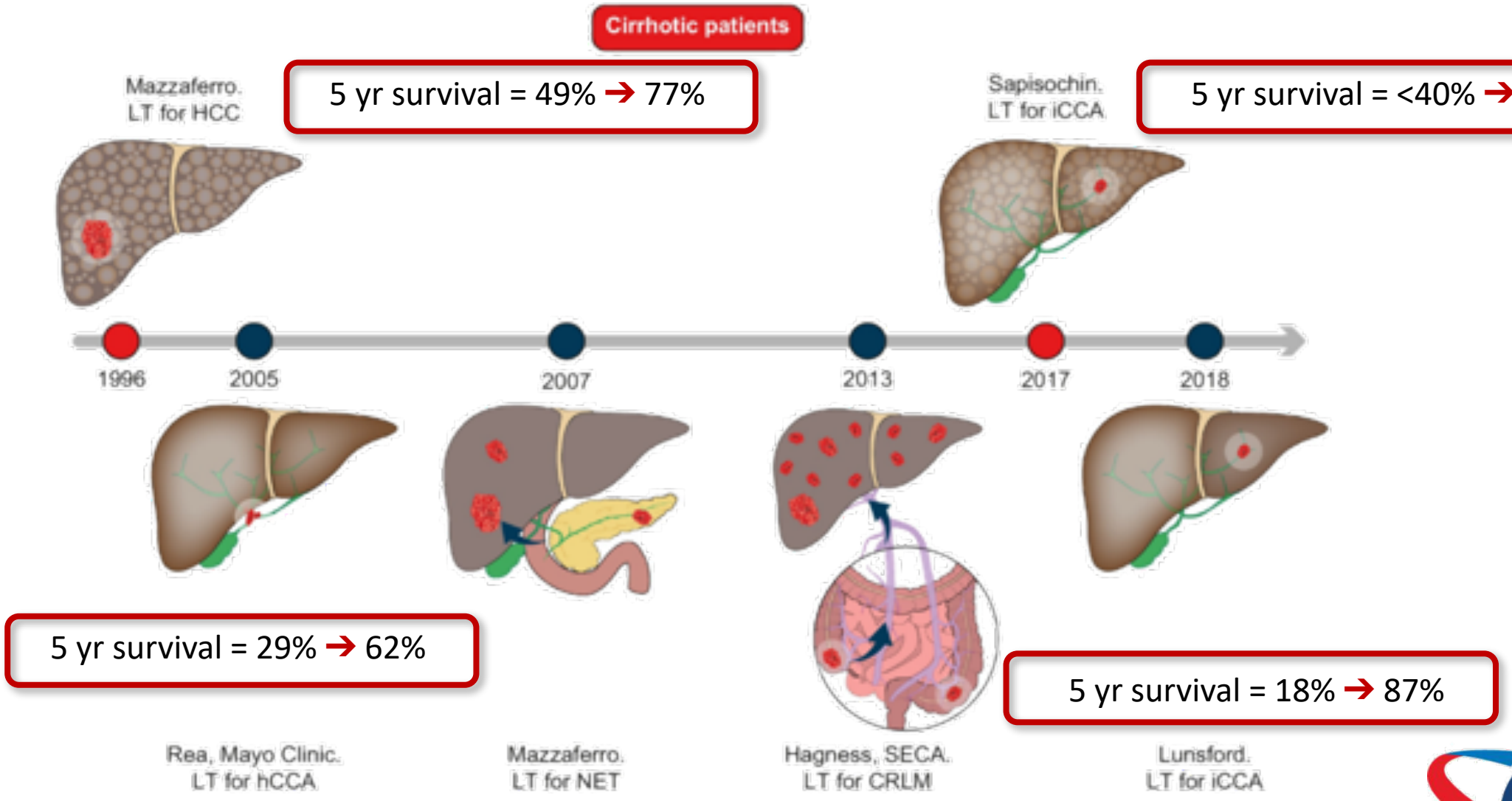
Advances in transplant for cancer



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Thank you