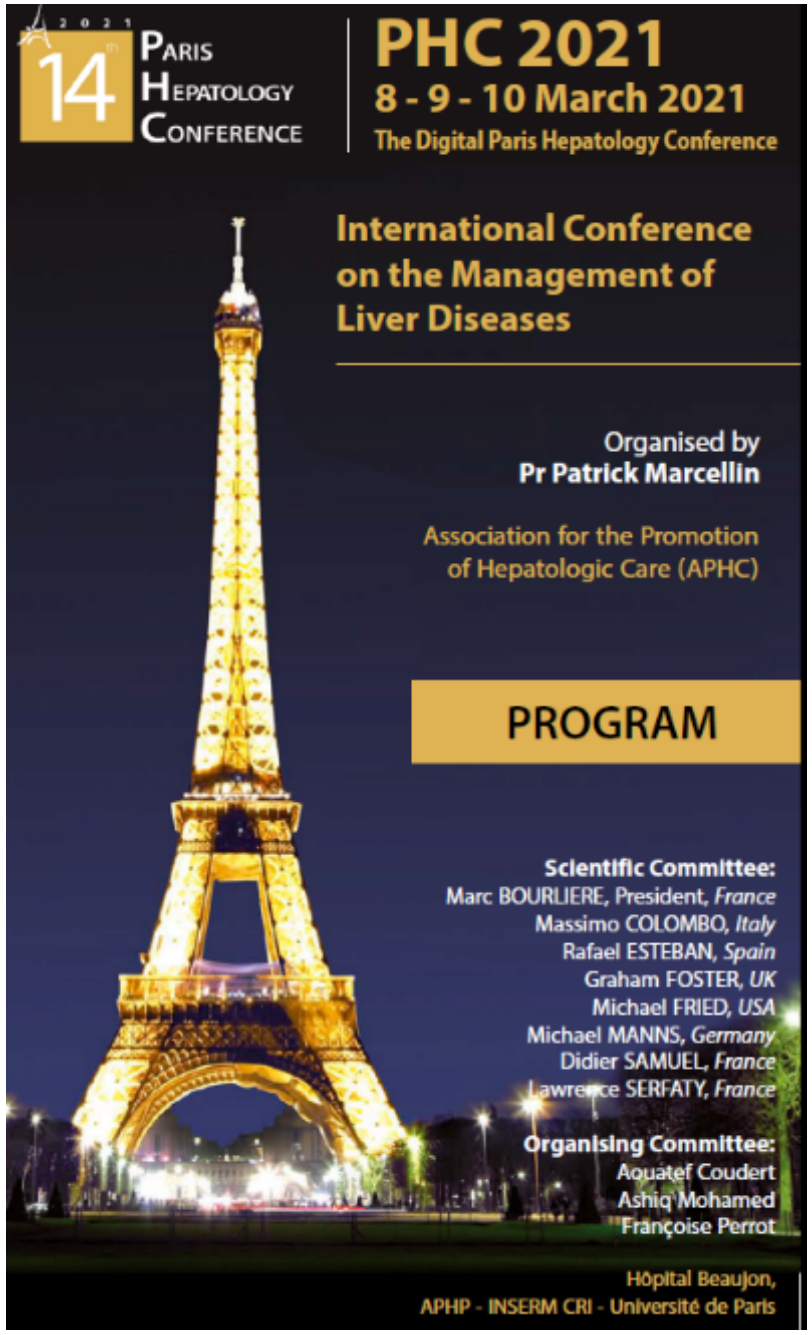


# Evolving concepts for trans-arterial radioembolization (TARE) or selective internal radiation therapy (SIRT) in hepatocellular carcinoma (HCC)

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UNIVERSITÀ DEGLI STUDI DI MILANO

FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

# Safety and technology of $Y^{90}$ radiating microspheres: a 47 year old story

**From safety concern due to limited technology…**

Treatment of Inoperable Primary Pancreatic and Liver Cancer by the Intra-Arterial Administration of Radioactive Isotopes ($Y^{90}$ Radiating Microspheres) *

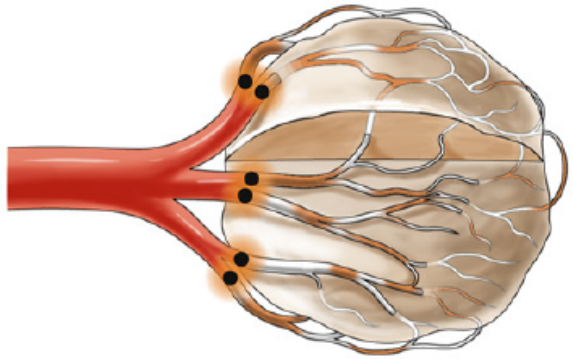
Ariel IM, Ann Surg 1965

**...to phase II experiences demonstrating safety and efficacy**


**Safety and Efficacy of $^{90}Y$ Radiotherapy for Hepatocellular Carcinoma With and Without Portal Vein Thrombosis**

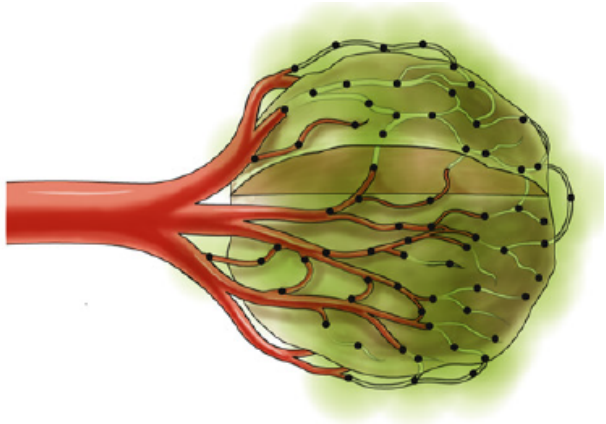
Kulik LM, Hepatology 2008

# TARE has a peculiar non-embolizing mechanism of action



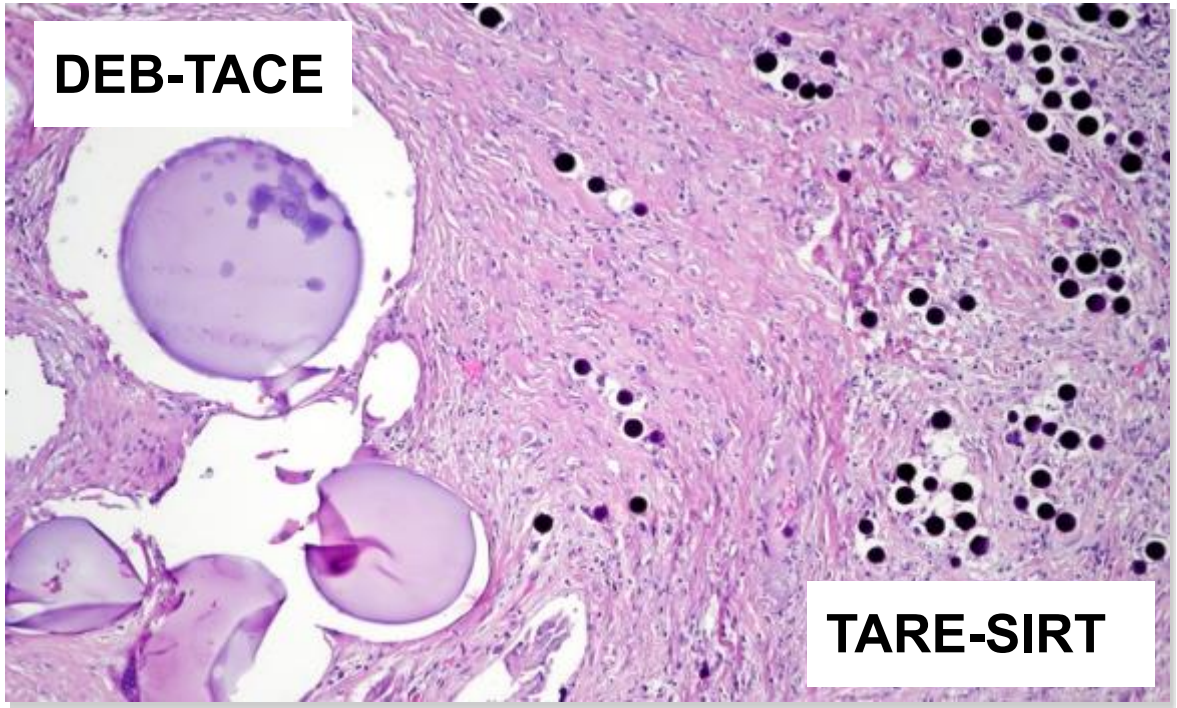
**DRUG-ELUTING BEAD CHEMOEMBOLIZATION**

- **MECHANISM OF ACTION:** Delivery of drug-loaded microspheres that provide local, sustained tumor drug delivery combined with tumor ischemia/hypoxia. The drug distributes up to 0.06 mm from the microspheres (orange).
- **PARTICLE SIZE:** 100–300 μm



**RADIOEMBOLIZATION**

- **MECHANISM OF ACTION:** Delivery of β-emitting microspheres that provide local, high dose tumor radiation. The radiation affects tissues 2.5–11 mm from the delivered microsphere (green).
- **PARTICLE SIZE:** 20–60 μm



# Initial large series of TARE in HCC (phase II)

| | | Intermediate Stage | | Branch PVT | | Main PVT | | Branch or Main PVT | |
|---|---|---|---|---|---|---|---|---|---|
| **Reference** | **Child** | **N** | **OS (95%CI)** | **N** | **OS (95%CI)** | **N** | **OS (95%CI)** | **N** | **OS (95%CI)** |
| Hilgard 2010 (N=108) | A/B | 51 | 16.4 (12.1-n.c.) | | | | | 33 | 10 (6-n.c.) |
| Salem 2010 (N=291) | A | 48 | 17.3 (13.7-32.5) | 19 | 16.6 (8.8-24) | 16 | 7.7 (3.3-13.2) | 35 | 10.4 (7.2-16.6) |
| | B | 35 | 13.5 (6.4-25.4) | 27 | 6.5 (5-8.5) | 30 | 4.5 (2.9-6.6) | 57 | 5.6 (4.5-6.7) |
| Sangro 2011 (N=325) * | A | 82 | 18.4 (13.6-23.2) | 44 | 10.7 (8.3-17.1) | 32 | 9.7 (4.8-11.8) | 76 | 10.2 (7.7-11.8) |
| | B | 5 | 3.6 (2.4-10.8) | | | | | | |
| Mazzaferro 2012 (N=51) | A | 15 | 18(13-38) | 23 | 17(13-21) | 5 | 9 (4-n.c.) | | |
| | B | 2 | -- | 6 | 8(5-10) | 1 | 5 | | |

# First large series of TARE in HCC

| | | Intermediate Stage | | Branch PVT | | Main PVT | | Branch or Main PVT | |
|---|---|---|---|---|---|---|---|---|---|
| **Reference** | **Child** | **N** | **OS (95%CI)** | **N** | **OS (95%CI)** | **N** | **OS (95%CI)** | **N** | **OS (95%CI)** |
| Hilgard 2010 (N=108) | A/B | 51 | 16.4 (12.1-n.c.) | | | | | 33 | 10 (6-n.c.) |
| Salem 2010 (N=291) | A | 48 | 17.3 (13.7-32.5) | 19 | 16.6 (8.8-24) | 16 | 7.7 (3.3-13.2) | 35 | 10.4 (7.2-16.6) |
| | B | 35 | 13.5 (6.4-25.4) | 27 | 6.5 (5-8.5) | 30 | 4.5 (2.9-6.6) | 57 | 5.6 (4.5-6.7) |
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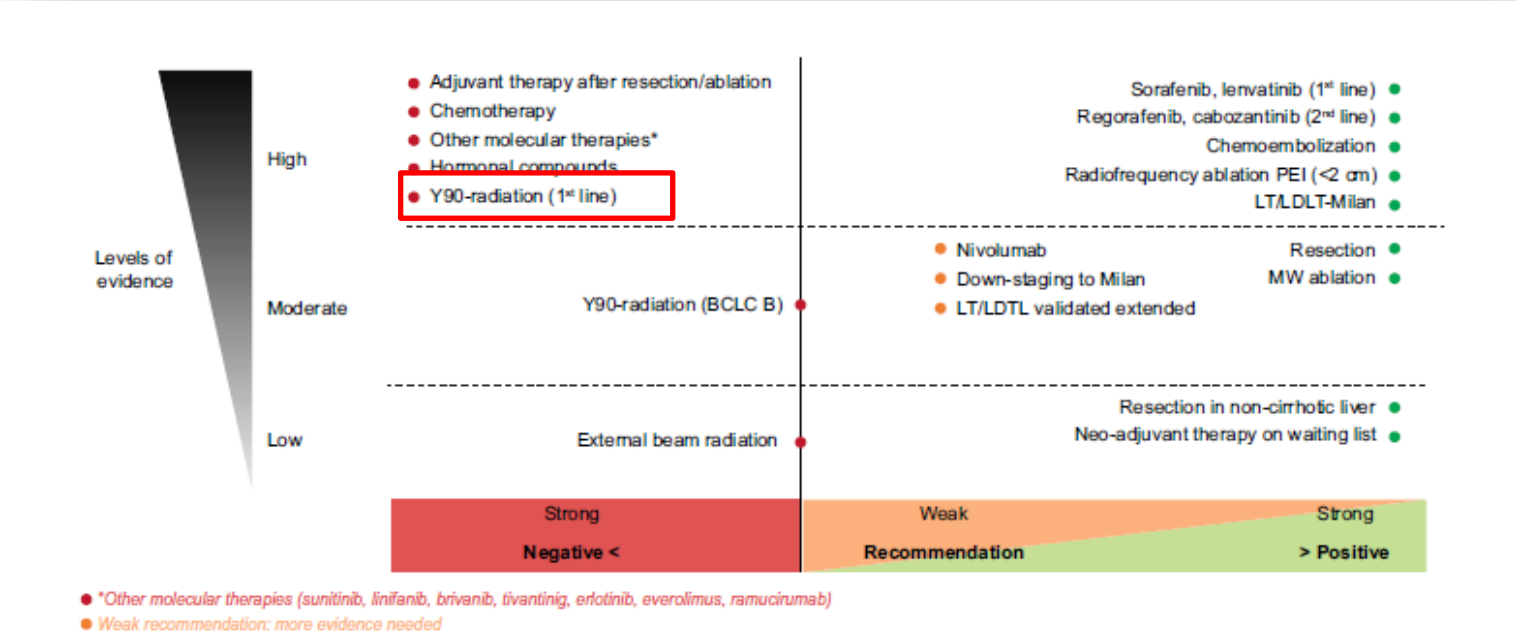
| | B | 5 | 3.6 (2.4-10.8) | | | | | | |
| Mazzaferro 2012 (N=51) | A | 15 | 18(13-38) | 23 | 17(13-21) | 5 | 9 (4-n.c.) | | |
| | B | 2 | -- | 6 | 8(5-10) | 1 | 5 | | |

# The phase III studies from hypothesis generating data failed

| Acronym | NCT ID | Phase | Countries | N | Endpoint | Experimental Arm | Comparator | Estimated Completion Date | Status |
|---|---|---|---|---|---|---|---|---|---|
| PREMIERE | 00956930 | II | USA | 124 | TTP | Y90 | cTACE | Aug 2018 | Halted |
| SIRveNIB | 01135056 | III | Asia-Pacific | 360 | Survival | Y90 | Sorafenib | Jul 2015 | Negative |
| SARAH | 01482442 | III | France | 400 | Survival | Y90 | Sorafenib | Mar 2015 | Negative |
| STOP | 01556490 | III | USA-Europe | 400 | Survival | Y90 + Sorafenib | Sorafenib | Oct 2016 | Halted |
| SORAMIC | 01126645 | III | Europe | 375 | Survival | Y90 + Sorafenib | Sorafenib | Feb 2014 | Negative |
| YES-p | pending | III | Europe, Asia, USA | 328 | Survival | Y90 | Sorafenib | - | Halted |

# EASL HCC GUIDELINES 2018

Representation of EASL recommendations for treatment according to levels of evidence and strength of recommendation
(adaptation of the GRADE system)




**SIRT IN FIRST LINE IN ADVANCED STAGE**

"At present, the survival benefit of RE compared to sorafenib in advanced **HCC is still not proven...**"

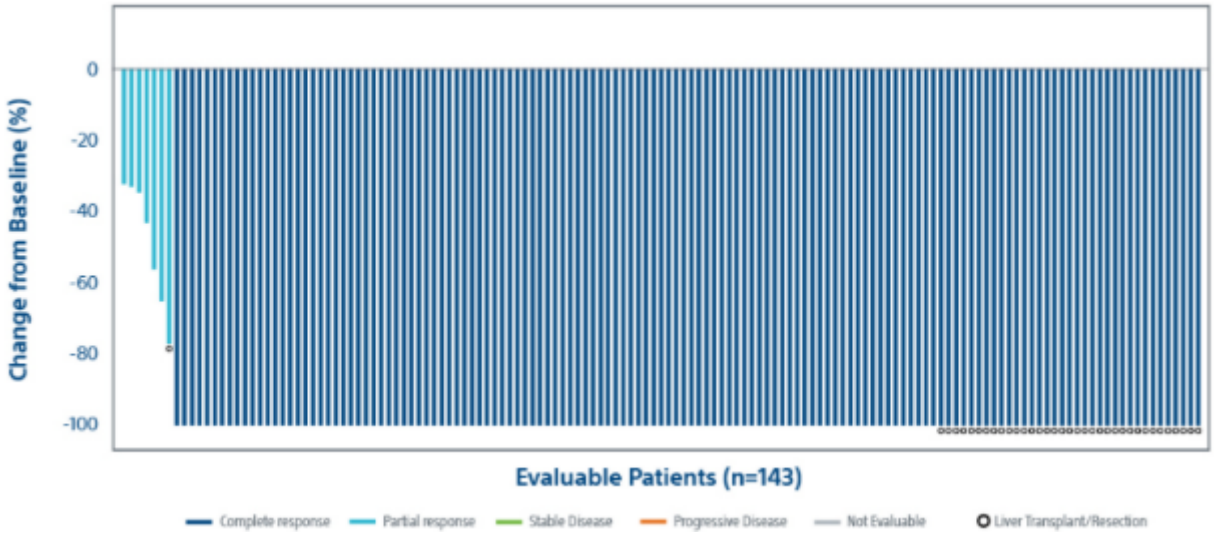
# Yttrium-90 glass microspheres in the treatment of early and advanced solitary HCC: The LEGACY study

Endpoints: Local tumor control (ORR) and duration of response (DoR: CR+PR) in unresectable HCC following TARE as either a neoadjuvant or stand-alone therapy. Eligibility: Child-Pugh A; ECOG score of 0 or 1; BCLC A or C; solitary tumor >2 and ≤8 cm

**162 pts in 3 US Centers** (2014-2017)

- **ORR: 72.2%**
- **3-year OS: 86.6%**
- **DoR >6mo: 76.1%**

- For 45/162 (27.8%) of patients, $Y^{90}$ treatment served as neoadjuvant therapy (resection-transplant): 3-year OS: 92.8%
- For the 117/162 (72.2%) patients who did not go on to surgical treatment: 3-year OS: 83.5%
- Liver function were maintained throughout the study (92.9% for albumin and 85.3% for bilirubin)



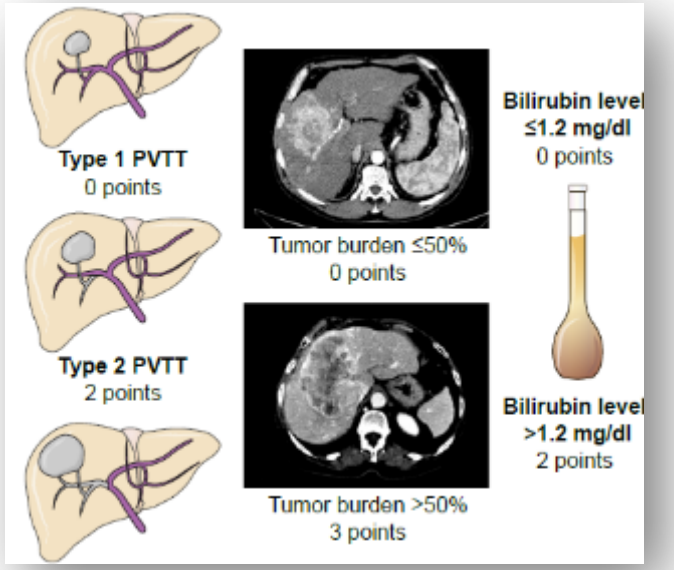

88% demonstrated rate of best response by TheraSphere (i.e. CR, PR) by localized mRECIST.

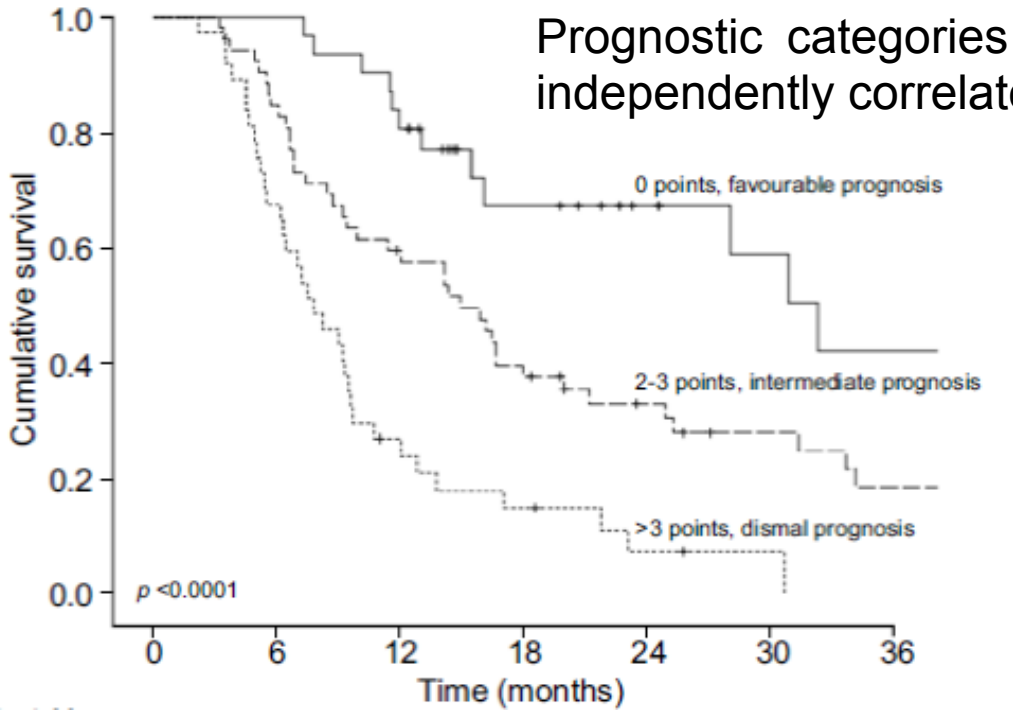
**Radiation treatment with Y90 glass microspheres is an effective means of treating solitary HCC while preserving liver function**

Lewandowski R. et al. ASCO Meeting 2021 Abs. JCO 2021

# TARE and PVT

| Variable | HR (95% CI) | *p* value | β | Points |
|---|---|---|---|---|
| **Bilirubin serum level** | | | | |
| ≤1.2 mg/dl | ref. | 0.037 | | 0 |
| >1.2 mg/dl | 1,636 (1,030-2,597) | | 0.492 | 2 |
| **PVTT extension** | | | | |
| PV1 (segmental) | ref. | <0.0001 | | 0 |
| PV2 (second order) | 1,900 (1,126-3,205) | | 0.642 | 2 |
| PV3 (main right/left) | 3,017 (1,793-5,074) | | 1.104 | 3 |
| **Tumor burden** | | | | |
| ≤50% liver volume | ref. | <0.0001 | | 0 |
| >50% liver volume | 2,642 (1,608-4,342) | | 0.972 | 3 |



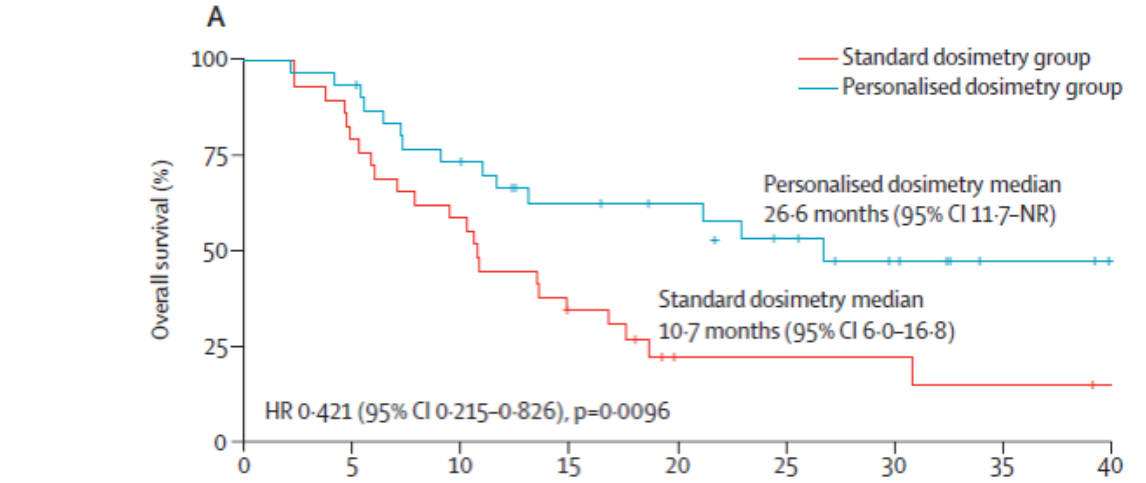




Prognostic categories built on bilirubin, extension of PVT and tumor burden independently correlated with survival

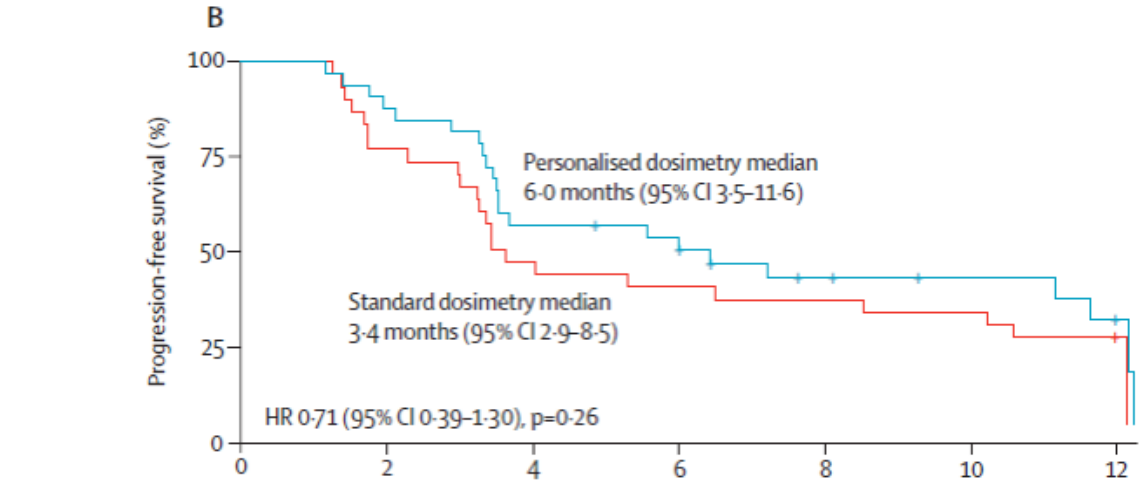
- **Radioembolization with Yttrium$^{90}$ is effective in patients with HCC and PVT.**
- **The prognostic stratification may help to better identify good candidates for the treatment, and those for whom TARE may be futile.**

Spreafico C and Mazzaferro V. J Hep. 2018

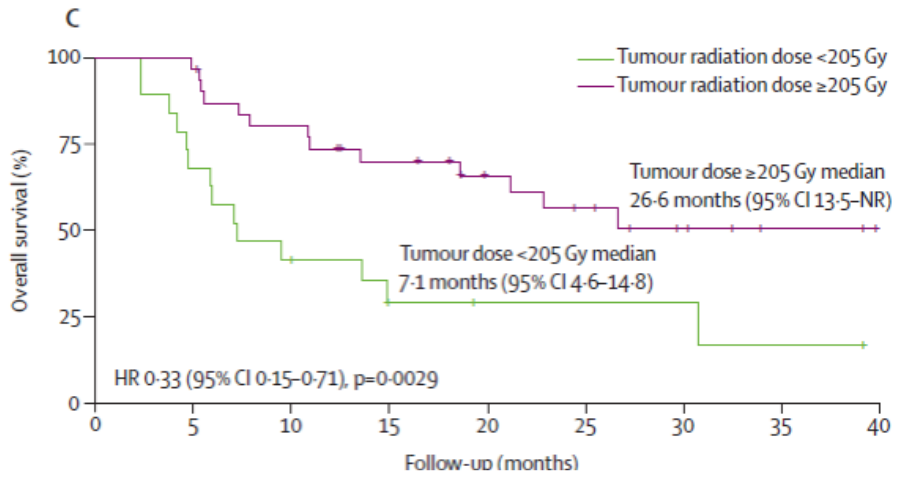
**60 locally advanced HCC** (at least one lesion ≥7cm) randomly assigned to receive either standard dosimetry (120±20 Gy) targeted to the perfused lobe or personalised dosimetry (≥205 Gy targeted to the index lesion)




| Number at risk (number censored) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Standard dosimetry group | 29 (0) | 23 (0) | 17 (0) | 9 (1) | 3 (4) | 3 (4) | 3 (4) | 2 (4) | 1 (5) |
| Personalised dosimetry group | 31 (0) | 29 (0) | 21 (2) | 16 (4) | 14 (6) | 10 (8) | 6 (11) | 2 (15) | 0 (17) |




| Number at risk (number censored) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Standard dosimetry group | 29 (0) | 22 (0) | 13 (0) | 11 (0) | 10 (0) | 9 (0) | 1 (6) |
| Personalised dosimetry group | 31 (0) | 27 (0) | 17 (0) | 15 (1) | 9 (4) | 7 (6) | 2 (9) |




**Personalised dosimetry significantly improves the objective response in patients with locally advanced HCC. Personalised dosimetry is likely to improve outcomes in clinical practice**

Garin E et al. Lancet Gastroenterol Hepatol 2021

# ESMO HCC GUIDELINES 2018

In the phase III studies, SIRT was associated with higher response rates, delayed tumour progression in the liver and fewer adverse events (AEs) compared with sorafenib. Thus, in exceptional circumstances, for patients with liver-confined disease and preserved liver function in whom neither TACE nor systemic therapy is possible, SIRT may be considered.

Vogel A, Ann Oncol 2018

## (ESMO update 2020, accessed March 2021)

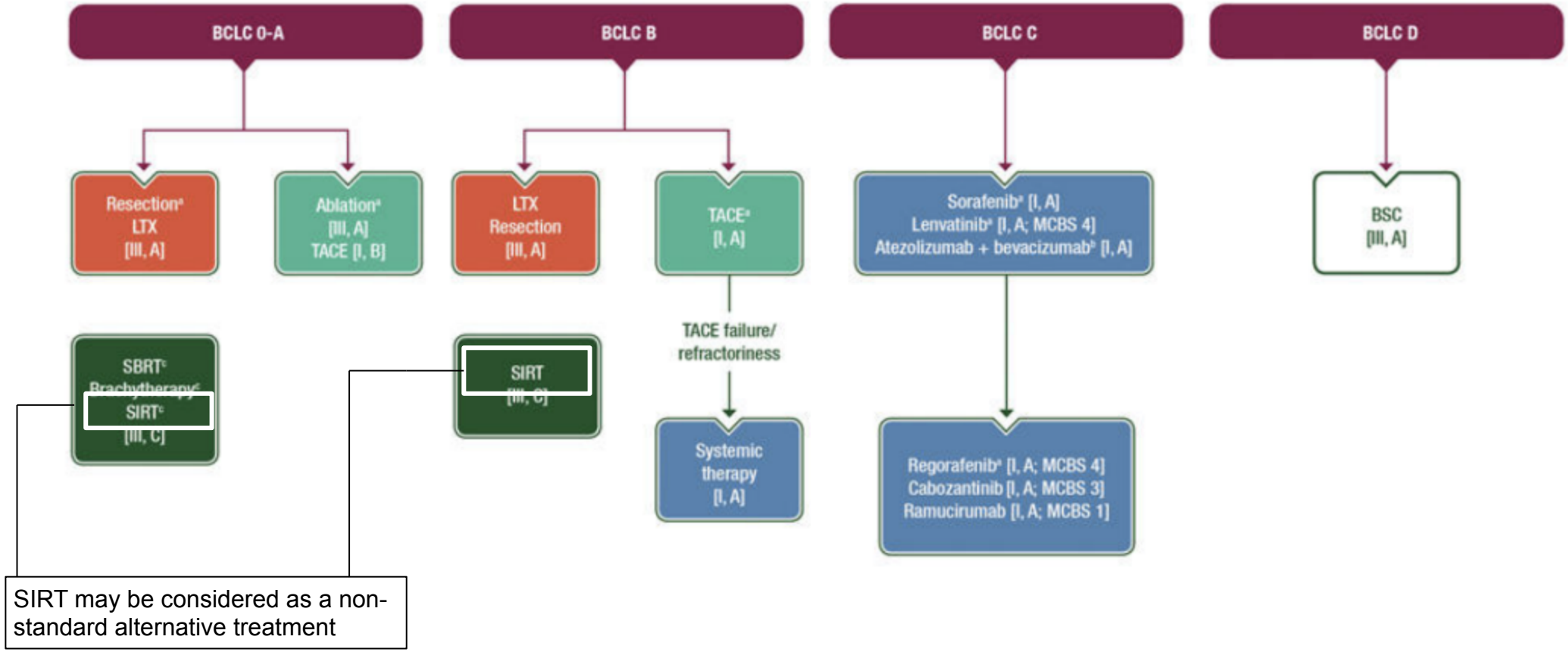


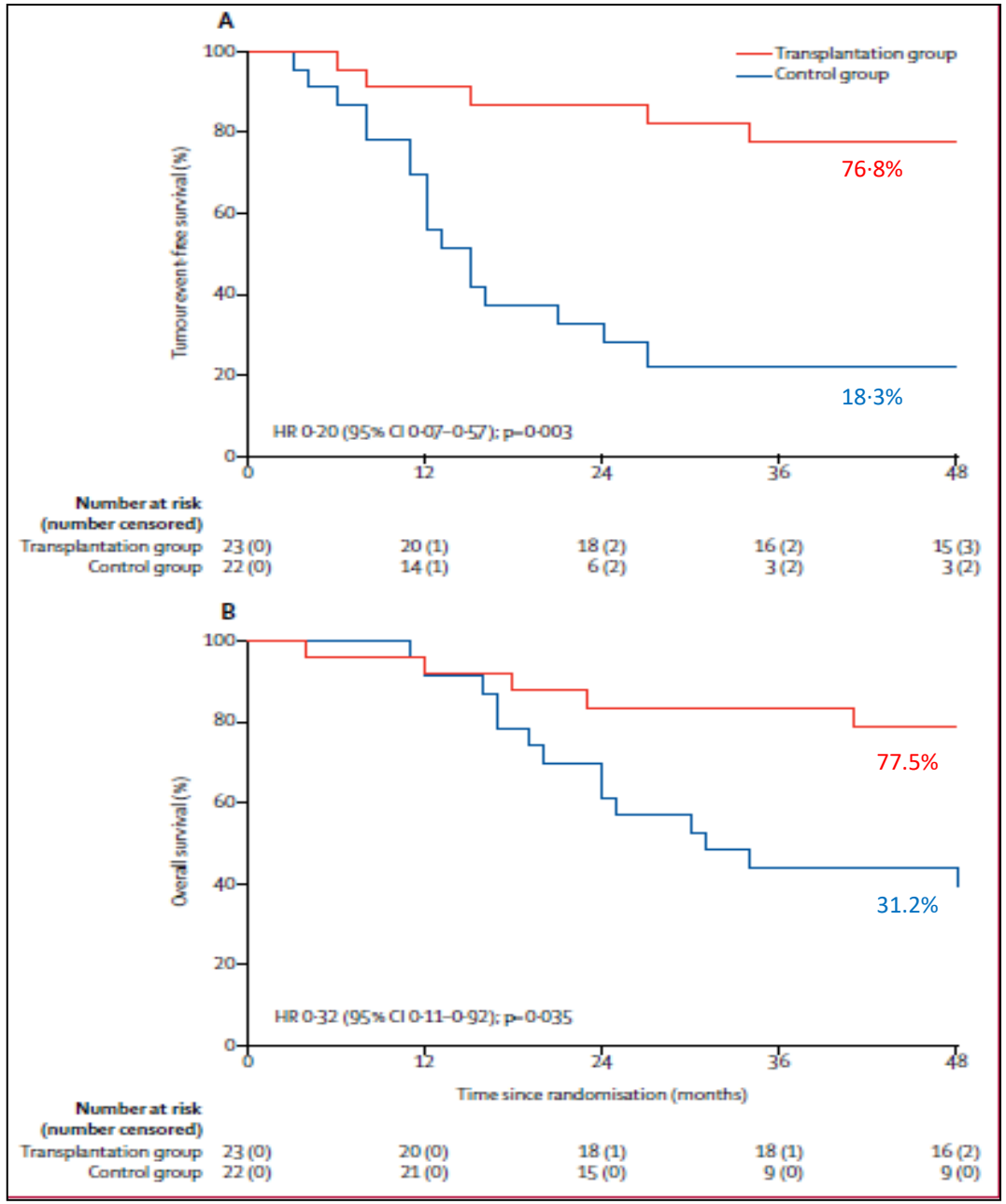
**Table 4. Summary of Asian treatment guidelines according to corresponding BCLC staging**

| BCLC | 0/A<br>Very early/early | B<br>Intermediate HCC | | C<br>Advanced HCC | | D | |
|---|---|---|---|---|---|---|---|
| | Single or ≤3 cm × 2–3 | Multiple nodules | | MVI and/or EHM | | Child-Pugh C | |
| KLCSG[8] | Single/≤2 cm (I)<br>Single/>2 cm (IIa) | Multiple/≤2 cm/MVI− (IIb)<br>Multiple/>2 cm/MVI− (IIIa) | | MVI+ (IIc/IIIb/IVa)<br>Single Multiple | EHM+ IVa (LN)/IVb (others) | | |
| | LR<br>RFA (size ≤3 cm)<br>OLT (≤5 cm) | TACE (SIRT as alternative)<br>RFA (<3 cm & <3 nodules)<br>OLT (within Milan's criteria) | | TACE (SIRT) ±<br>EBRT<br>Sorafenib<br>Lenvatinib | Sorafenib<br>Lenvatinib | | |
| | (TACE/TARE, EBRT) | [LR (≤2), EBRT (≤3) nodules] | | (LR, × 1-3, Vp1-3)<br>(CT, HAIC if MKI failed or not available) | (TACE/EBRT) | | |
| HKLCS[14] | Early (I/IIa)<br>≤5 cm & ≤3 nodules | Intermediate (IIb/IIIa)<br>>5 cm or ≥4 nodules<br>Locally advanced (IIIb)<br>>5 cm & ≥4 nodules | | Intermediate<br>I/IIa + Vp 1–3<br>Locally advanced<br>IIb/IIIa + Vp 1–3 | EVM (IVa/IVb)<br>Vp 4 and/or EHM | Milan's | Others |
| | LR/OLT/ablation | LR (IIb/IIIa, CP A)<br>TACE (IIb/IIIa, CP B or IIIb) | | | Systemic | OLT | BSC |
| China[12] | Milan's criteria (Ia, Ib)<br>Single ≤5 cm (Ia) | >3 cm × 2–3 (IIa) | ≥4 nodules (IIb) | MVI+ (IIIa) | EHM+ (IIIb) | | |
| | LR/ablation<br>TACE (Ib), OLT | LR<br>TACE, OLT (UCSF) | TACE<br>LR, systemic | TACE<br>MKI or FOLFOX, RT | MKI or FOLFOX<br>TACE, RT | BSC | |
| JSH[9] | Single or <3 cm × 2–3 | > 3 cm × 2–3 | ≥4 nodules | MVI+ | EHM+ | Milan's | Others |
| | LR/ablation | LR<br>TACE | TACE<br>HAIC, MKI | TACE/LR/HAIC/<br>MKI | MKI | OLT | BSC |
| TLCA[11] | Single or <3 cm × 2–3 | >3 cm × 2–3 | ≥4 nodules | MVI+ | EHM+ | Milan's | Others |
| | LR/ablation/TACE<br>SIRT (>3 cm × 2–3 nodules)<br>(EBRT) | | LR/TACE/SIRT | LR/MKI<br>TACE + RT<br>SIRT, HAIC | MKI ± (TACE/SIRT/LR)<br>Chemotherapy | OLT | BSC |

BCLC, Barcelona Liver Cancer; BSC, best supportive care; CP A, Child-Pugh score A; CP B, Child-Pugh score B; CT computed tomography; EBRT, external beam radiation therapy; EHM, extrahepatic metastases; EVM, extrahepatic vascular metastasis; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HKLCS, Hong Kong Liver Cancer Staging system; JSH, Japanese Society of Hepatology; KLCSG, Korean Liver Cancer Study Group; LN, lymph node; LR, liver resection; MKI, multi-kinase inhibitor; MVI, macrovascular invasion; OLT, orthotopic liver transplantation; RFA, radiofrequency ablation; RT, radiation therapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolisation; TLCA, Taiwan Liver Cancer Association; Vp 1–3/4 portal vein thrombosis with unilateral 3rd (Vp1), 2nd (Vp2) or 1st branch (Vp3) of portal vein/bilateral 1st branches or main (Vp4) portal vein involvement.

Chen LT, Ann Oncol 2020

# Liver Transplantation after successful HCC downstaging



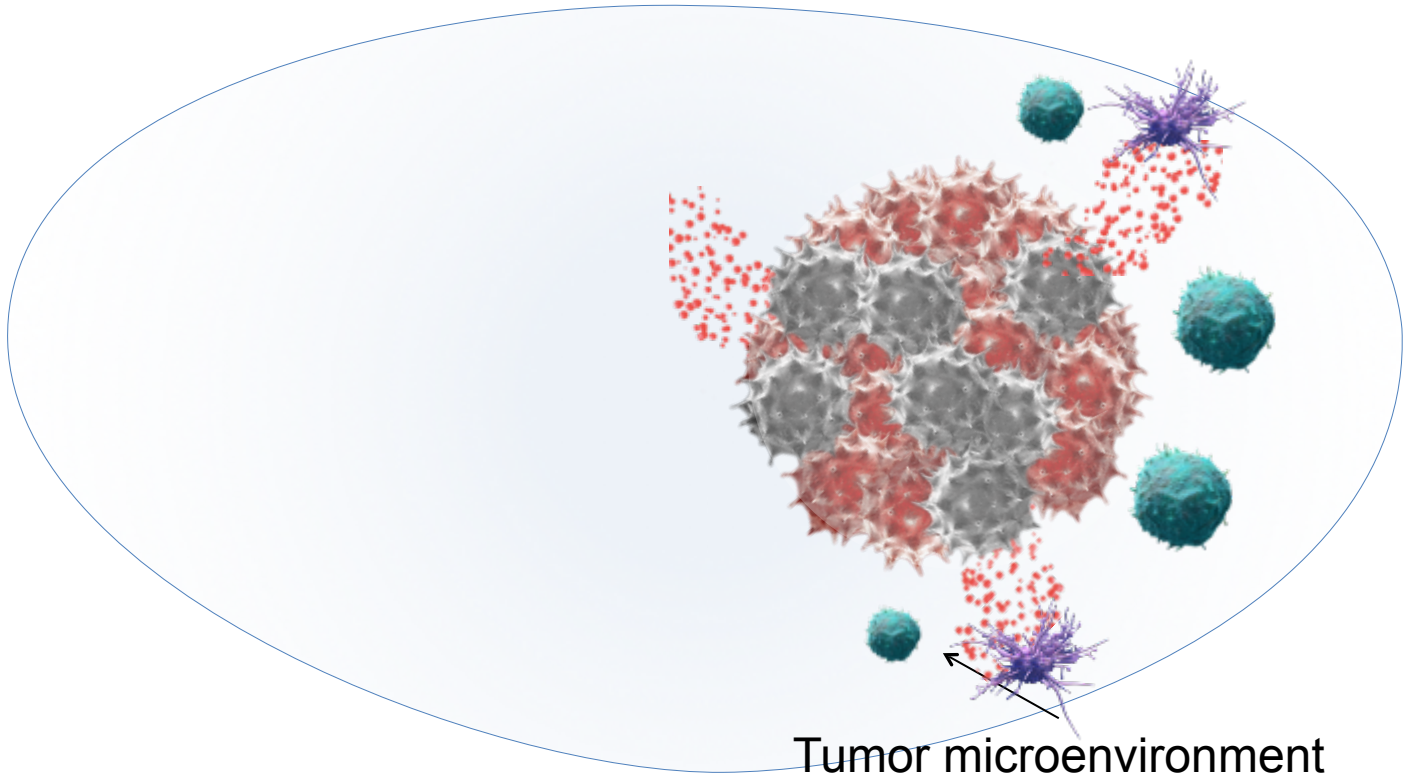

| | | |
|---|---|---|
| Downstaging procedures | | |
| TACE only | 12 (52%) | 10 (45%) |
| RFA, SIRT, or surgery only | 5 (22%) | 3 (14%) |
| RFA | 2 (9%) | 2 (9%) |
| SIRT | 1 (4%) | 0 (0%) |
| Surgery* | 2 (9%) | 1 (5%) |
| Combinations of treatments | 6 (26%) | 9 (41%) |
| At least one of: | | |
| TACE | 17 (74%) | 18 (82%) |
| RFA | 8 (35%) | 9 (41%) |
| SIRT | 1 (4%) | 1 (5%) |
| Surgical resection | 4 (17%) | 3 (14%) |
| Number of treatment sessions | | |
| 1 | 10 (43%) | 8 (36%) |
| 2 | 8 (35%) | 5 (23%) |
| 3 | 4 (17%) | 3 (14%) |
| >3 | 1 (4%) | 6 (27%) |

- **The study shows significantly longer patient survival and fewer tumor events in patients receiving LT after successful tumor downstaging of HCC beyond Milan criteria**
- **Different schemes and combinations of neoadjuvant locoregional therapies might be proposed to patients with HCC beyond MC** who can be transformed into transplant candidates according to the end-treatment tumour response.

Mazzaferro V et al. Lancet Oncology 2020

# Rationale behind immunotherapy +LRT

**Locoregional therapy**
(TACE/TARE/RT/RFA/PEI)




Following physical tumor destruction:

- release of high antigen load and trigger of tumor-specific T-cell response (CD8 and NK)

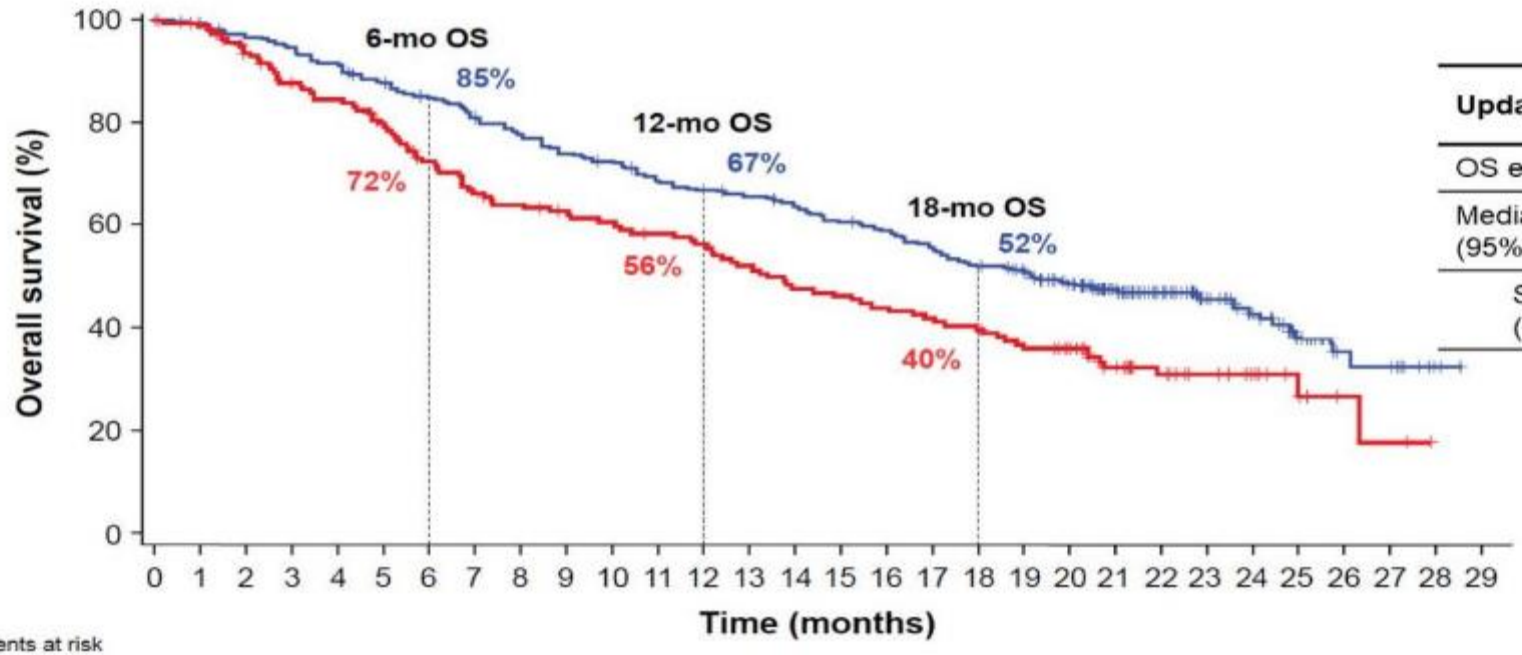
- release of heat shock proteins in the peripheral blood (activation of DC)

- changes in the TME

**All conditions associated to an improved antitumor response and survival**

Greten T, Rev Recent Clin Trial. 2018

# Updated OS




| 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] | |

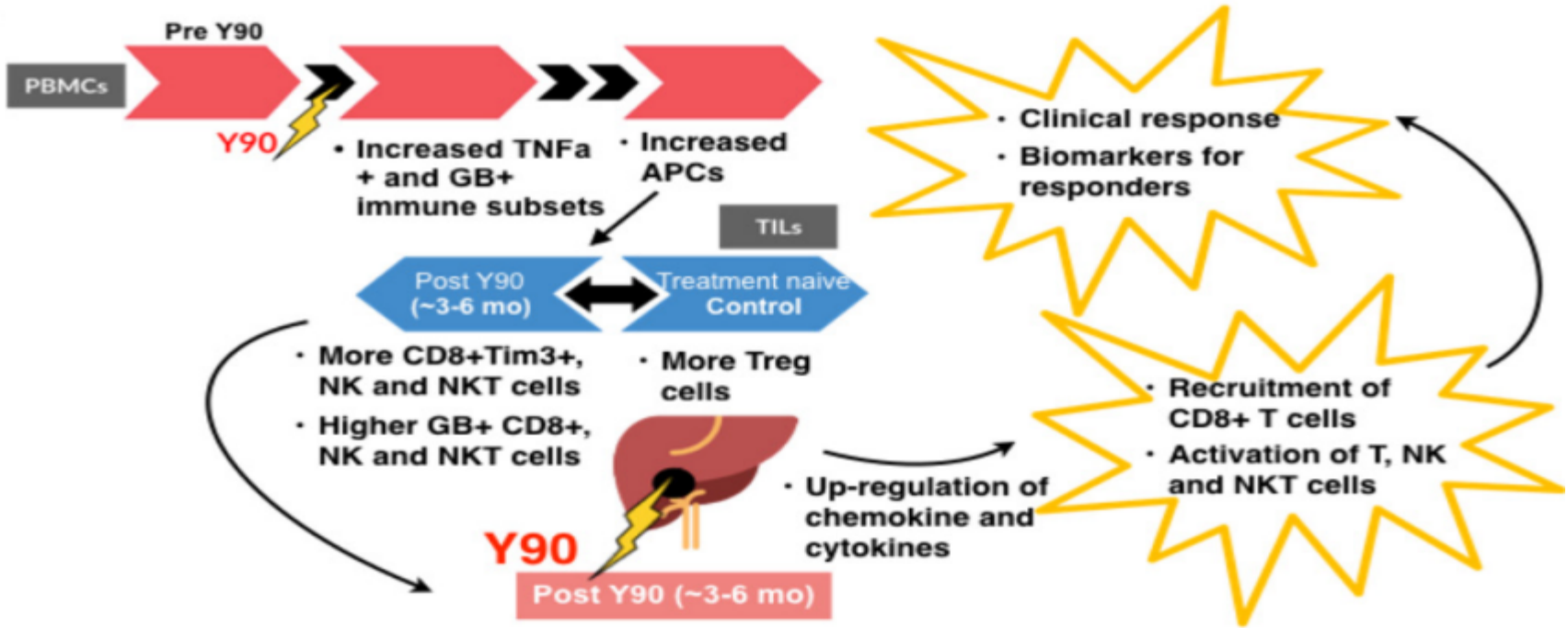
No. of patients at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezo + Bev | 336 | 329 | 320 | 312 | 302 | 288 | 276 | 263 | 252 | 240 | 233 | 221 | 214 | 209 | 202 | 192 | 186 | 175 | 164 | 156 | 134 | 105 | 80 | 57 | 42 | 24 | 12 | 11 | 2 | NE |
| Sorafenib | 165 | 158 | 144 | 133 | 128 | 119 | 106 | 96 | 92 | 88 | 85 | 81 | 78 | 72 | 66 | 64 | 61 | 58 | 55 | 49 | 44 | 32 | 24 | 18 | 12 | 7 | 3 | 2 | NE | NE |

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.
[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

Finn R et al NEJM 2020
Finn R et al. ASCI G.I 2021

# The immunological impact of SIRT with $Y^{90}$




**Analysis of the tumor and systemic immune landscapes at different time points before and after SIRTwith Y90, both in tumor (TIL) and in perioheral blood cells (PBMCs)**

In both TILs (tumor infiltrating lymphocytes) and in peripheral blood cells, increase of:
- infiltration of granzyme B (GB)-expressing CD8
- natural killer (NK) cells
- upregulation of chemokines for TCELL priming

Chew V, Gut 2018

0-27 **NIVOLUMAB AFTER SELECTIVE INTERNAL RADIATION THERAPY (SIRT) USING SIR-SPHERES RESIN MICROSPHERES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: THE NASIR-HCC TRIAL**

Manuel de la Torre-Alaez[1], Ana Matilla[2], Maria Varela[3], Mercedes Iñarrairaegui[4], Maria Reig[5], Jose Luis Lledo[6], Juan Arenas[7], Sara Lorente[8], Milagros Testillano[9], Carlos Gomez-Martin[10], Laura Marquez[2], Leonardo da Fonseca[5], Jose I Bilbao[11], **Bruno Sangro***[4]

[1]Clinica Universidad de Navarra, [2]Hospital Universitario Gregorio Marañón, CIBEREHD, Madrid, [3]Hospital Universitario Central de Asturias, Oviedo, [4]Clinica Universidad de Navarra and CIBEREHD, Pamplona, [5]BCLC group. Hospital Clinic de Barcelona. IDIBAPS. CIBEREHD, Barcelona, [6]Hospital Universitario Ramón y Cajal, Madrid, [7]Hospital Universitario de Donostia, San Sebastian, [8]Hospital Clínico Lozano Blesa, Zarazgoza, [9]Hospital Universitario de Cruces, Baracaldo, [10]Hospital Universitario [12] de Octubre, Madrid, [11]Clinica Universidad de Navarra, Pamplona, Spain

**Introduction**: The success of immunotherapy in advanced hepatocellular carcinoma (HCC) has led to the investigation of its use in earlier stages in combination with intraarterial therapies. Here we report safety, tolerability and efficacy of Nivolumab in this phase 2, single-arm trial testing the combination of SIRT using SIR-Spheres (Y90-loaded resin microspheres) and the anti-PD-1 antibody Nivolumab (NCT03380130).

**Methods**: Enrollment included patients (pts) with unresectable HCC not good candidates to transarterial chemoembolization because of single large tumors > 5 cm; multiple tumors in the BCLC-B2 substage; or predominantly unilobar tumors with segmental or lobar portal vein invasion. Three weeks after SIRT, patients received Nivolumab (240 mg IV Q2W for a maximum of 24 doses, each course consisting of 3 doses of Nivolumab). Safety was the primary objective and toxicity was graded by CTCAE v 4.0. Key secondary endpoints were overall response rate (ORR) and disease control rate (DCR) by investigator evaluation using RECIST v1.1, and time to progression (TTP).

**Results**: Results are presented for 42 patients treated with SIRT, since 1 out of 43 pts was withdrawn from study due to high lung shunt. Lobar extended or whole-liver SIRT was performed in 12 pts (31%) and median injected Y90 activity was 1.3 GBq (range 0.64-3.4 GBq). Median follow-up was 7.8 months (range 2.5-16.3). One patient did not receive Nivolumab due to early liver abscess formation following SIRT. The median number of Nivolumab courses was 3.5 (IQR 2-7). Treatment-related adverse events (TRAE) occurred in 33 patients (79%). TRAE were considered to be related with SIRT in 24 pts (57%) and with Nivolumab in 15 pts (36%). TRAE grade ³3 appeared in 20 pts (48%). TRAE grade ³3 were considered to be related with SIRT in 9 pts (21%) and with Nivolumab in 10 pts (24%). Few pts experienced serious TRAE (n=5, 12%) and TRAEs leading to transient (n=11, 26%) or permanent (n=1, 2.5%) Nivolumab discontinuation. There were no treatment-related deaths. No events of radioembolization-induced liver disease were recorded. Eight patients (19%) experienced immune-mediated AE. ORR was 38% including 11.9% complete responses, while DCR was 81%. TTP was 9.3 months (95%CI 7.84-10.1) and median overall survival was 20.6 months (95%CI 17.3-24.0). Four patients had a liver resection to treat residual tumor (one had a complete pathological response).

**Conclusion**: In this phase 2 trial, HCC pts treated with SIRT and Nivolumab showed a favorable safety profile with no signs of synergistic toxicity. The encouraging efficacy data warrant further exploration in controlled trials.

# Nivolumab after SIRT using SIR-resin spheres in patients with HCC: the NASIR study

Multicenter phase 2 single-arm clinical trial conducted at -academic hospitals in Spain.

Safety, tolerability, and preliminary antitumoral efficacy of SIRT and anti PD-1 in 42 patients with HCC.

**Favorable safety profile with no signs of synergistic toxicity**

ORR of 40% of patients (12.5% with CR and 27.5% with PR)

Future randomized controlled trials are needed to further explore and confirm the efficacy of SIRT treatment followed by nivolumab

de la Torre M, ILCA 2020

ILCA Annual Conference, 2020

# ASCO 2021
# Atezo + Beva + TARE vs. TARE


Open-label, multicenter, randomized phase II study of Y90 TARE and BEV plus ATEZO compared with Y90 TARE alone in pts with unresectable HCC.

The primary study objective is to assess and compare the progression-free survival (PFS) (per mRECIST 1.1) of pts in each arm.

The main secondary objective is to determine the safety and tolerability (CTCAE v5) of TARE combined with ATEZO and BEV in pts with HCC.

# Clinical trials of new combination therapies including SIRT

| Clinical Trial Gov # ID | Study | Country |
|---|---|---|
| NCT04541173 | Study of Atezolizumab and Bevacizumab With Y-90 TARE in Patients With **Unresectable** Hepatocellular Carcinoma (HCC) | Georgetown University Genentech, Inc. |
| NCT04522544 | Durvalumab (MEDI4736) and Tremelimumab in Combination With Either Y-90 SIRT or TACE for **Intermediate** Stage HCC With Pick-the-winner Design | Germany |
| NCT04124991 | Safety and Efficacy Study of Radioembolization in Combination With Durvalumab in **Locally Advanced and Unresectable HCC** (SOLID) | Seoul |
| NCT03812562 | Nivolumab and Yttrium-90 in Treating Patients With Liver Cancer Undergoing Surgical Resection **neoadjuvant** | Northwestern |
| NCT03099564 | Pembrolizumab Plus Y90 Radioembolization in HCC Subjects | MSD and Hoosier Cancer Research Network |
| NCT03033446 | Study of Y90-Radioembolization With Nivolumab in Asians With Hepatocellular Carcinoma | Singapore |
| ROWAN study | Combination therapy of radioembolization and immunotherapy in **early and intermediate** hepatocellular carcinoma (HCC) patients not eligible for curative treatments | Mayo + Georgetown |

# Conclusions

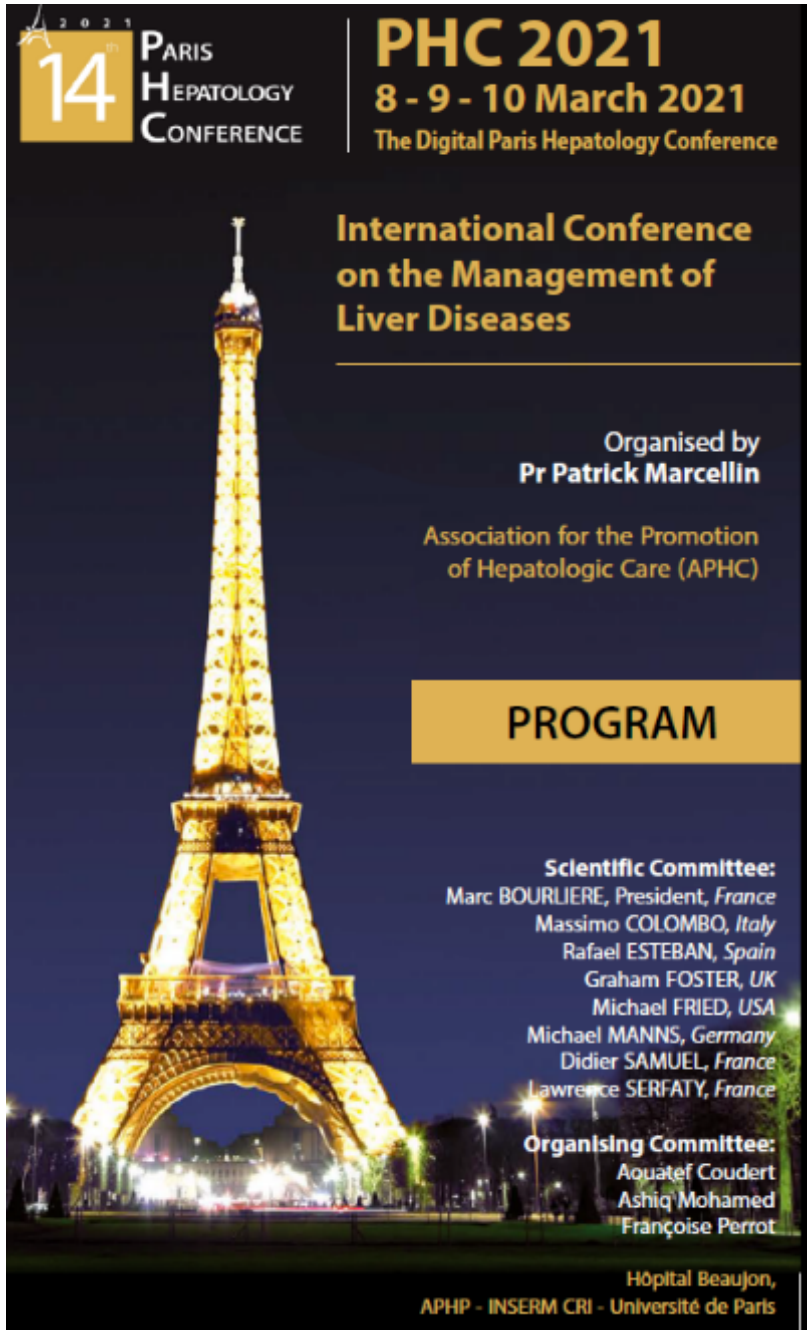
- SIRT has not gained a positive recommendation in the last EASL guidelines but results in retrospective studies have set the basis for its wide use worldwide.

- Refinements to the definition of “ideal candidate” for SIRT should be further investigated.

A biologic/clinical/physical markers is un unmet need. In this respect there is room for work “beyond the genome” thanks to the development of new technologies (metabolomics, epigenetics, non-coding RNA studies, artificial intelligence).

- The use of SIRT is a valuable option for downstaging strategies; if successfull and sustained, downstaging represents a strong selection tool for transplantation and resection in HCC beyond conventional criteria

- Immunotherapy has now a proven activity in advanced HCC. There is a strong rationale for its combination with SIRT in earlier stages of disease, as LRTs increase the tumoral antigenic release and favor immunotherapeutic strategies.




**Thank you very much for your attention !**

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