The game-changing clinical papers in hepatology in 2020

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60
CARAVELLE
OH NO 2020

Liver4Life

A new perfusion machine to keep human livers *ex vivo* alive

nature biotechnology

ARTICLES

https://doi.org/10.1038/s41587-019-0374-x

An integrated perfusion machine preserves injured human livers for 1 week

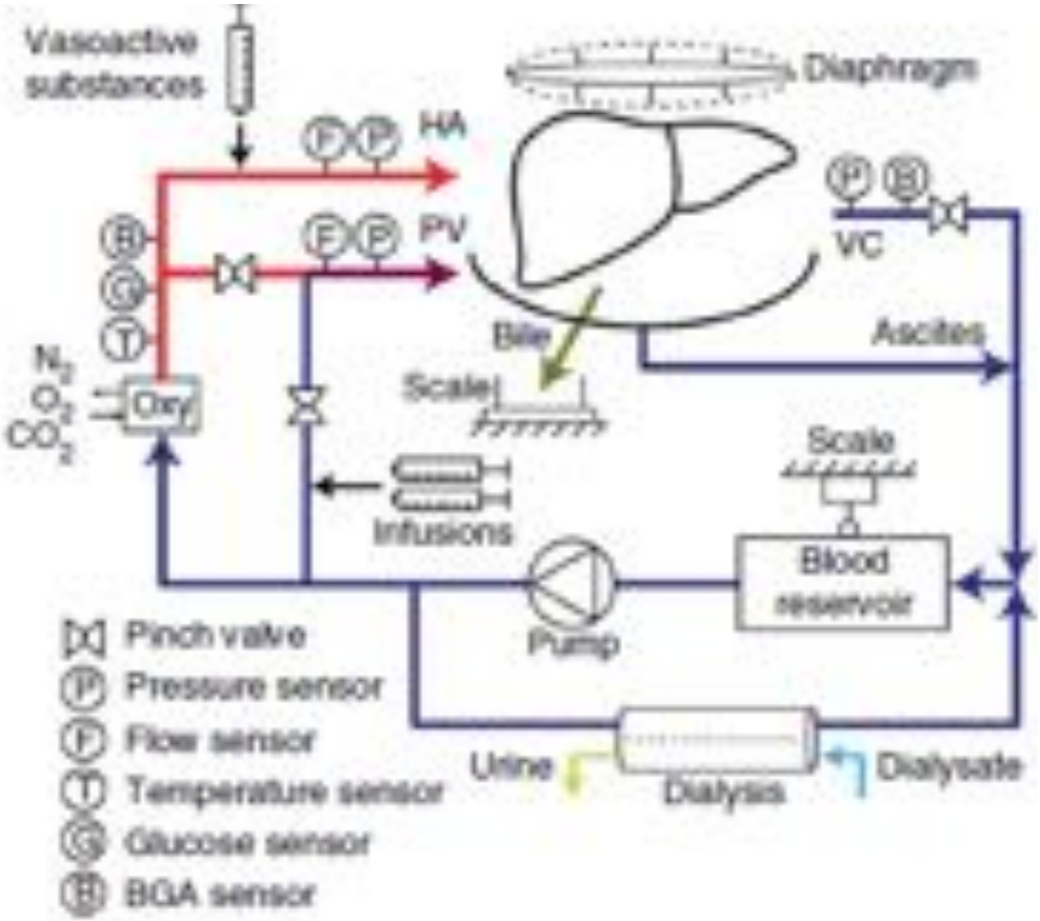
Dilmurodjon Eshmuminov[1,2,6], Dustin Becker[2,3,6], Lucia Bautista Borrego[1,2], Max Hefti[2,3], Martin J. Schuler[2,3], Catherine Hagedorn[1,2], Xavier Muller[1,2], Matteo Mueller[1,2], Christopher Onder[2,4], Rolf Graf[1,2], Achim Weber[5], Philipp Dutkowski[1,2], Philipp Rudolf von Rohr[2,3,7] and Pierre-Alain Clavien[1,2,7*]

Eshmuminov D et al., Nature Biotechnology, 2020

The BIG problem in transplantation: Scarcity of organs

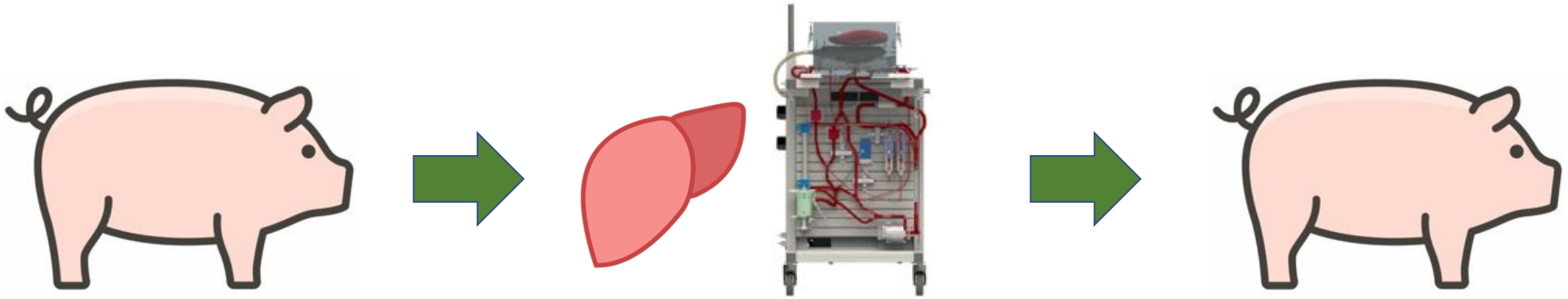
- **Increasing numbers** of patients on **waiting transplant list**
- Deaths on waiting list - 2019: **427** listed/**168** transplanted/**18** died
- **Living donor liver transplantation** not often performed in Switzerland (2019: **2**)
- “Marginal livers” often discarded
- Current approaches for *ex vivo* perfusion can **preserve human livers for only 24 h**
- The ability to preserve metabolically active livers ***ex vivo* for 1 week or more** could allow **repair of poor-quality livers** that would otherwise be declined for transplantation


Hormone infusions replace the pancreas
Donor liver
LIVER 4LIFE
An oxygenator replaces the lungs
Nutrient infusions replace the bowel
A pump replaces the heart
A dialysis unit replaces the kidneys


Vasoactive substances
Diaphragm
HA
PV
VC
Bile
Ascites
Scale
Scale
Infusions
Blood reservoir
Pump
Urine
Dialysis
Dialysate
Pinch valve
Pressure sensor
Flow sensor
Temperature sensor
Glucose sensor
BGA sensor

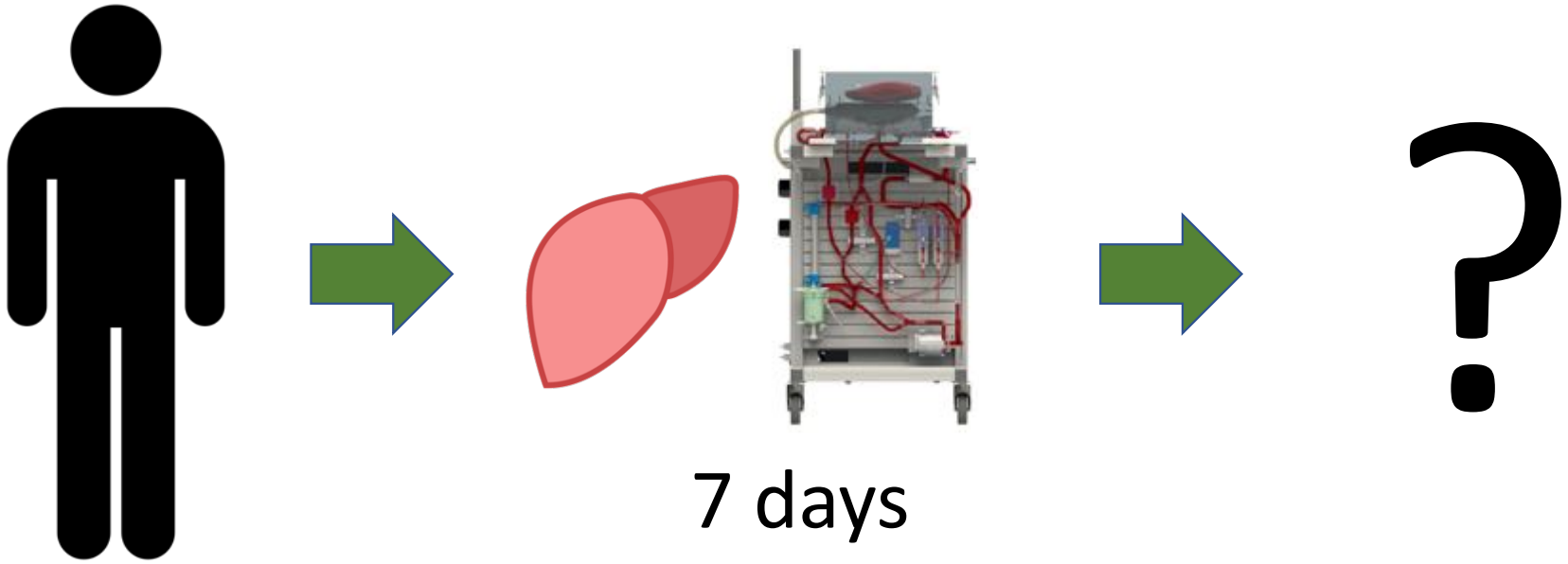

LIVER
4LIFE

- **Pig livers:** Study of multiple ***ex vivo*** parameters (n=70) and early phase reperfusion ***in vivo*** (n=3) demonstrated the **viability of pig livers perfused for 1 week** without the need for additional blood products or perfusate exchange

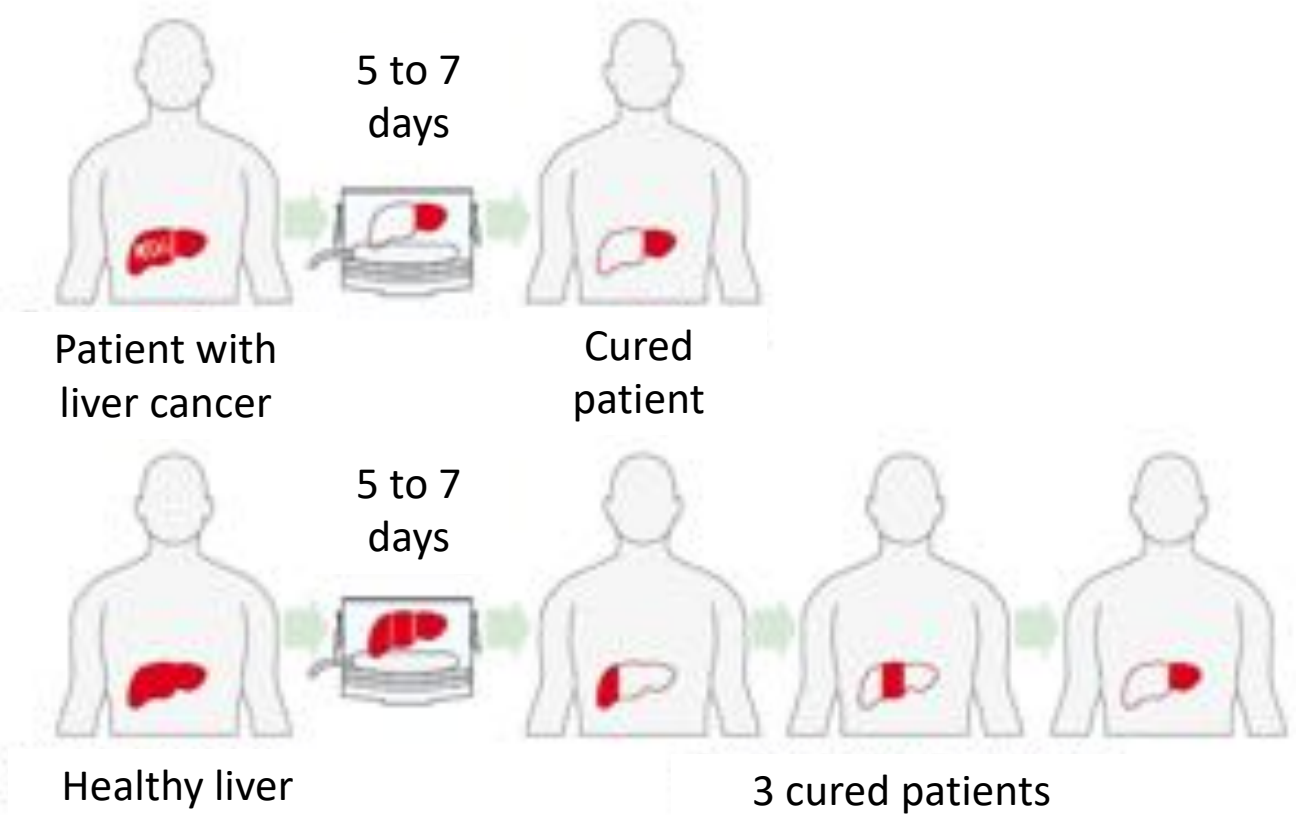


7 days

Human livers: Testing the approach on **10 injured human livers** that had been **declined for transplantation** by all European centers. After a **7-d perfusion**, **6** of the **human livers showed preserved function** as indicated by **bile production**, synthesis of **coagulation factors**, maintained cellular energy (**ATP**) and intact **liver structure**



Perspective: Liver4Life machine perfusion - Opening future possibilities to expand livers *ex vivo*



Atezolizumab/Bevacizumab

New first line treatment in unresectable HCC

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*

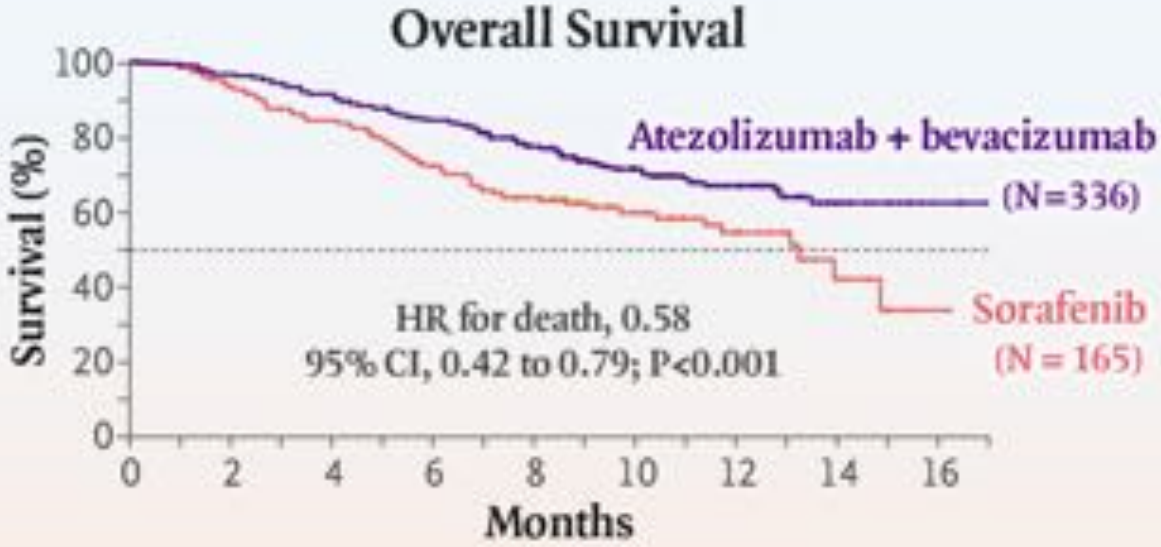
Finn RS et al., N Engl J Med, 2020

Atezolizumab + Bevacizumab for Hepatocellular Carcinoma

PHASE 3, OPEN-LABEL, MULTICENTER, RANDOMIZED TRIAL

501

Patients with locally advanced hepatocellular carcinoma (metastatic, unresectable, or both)



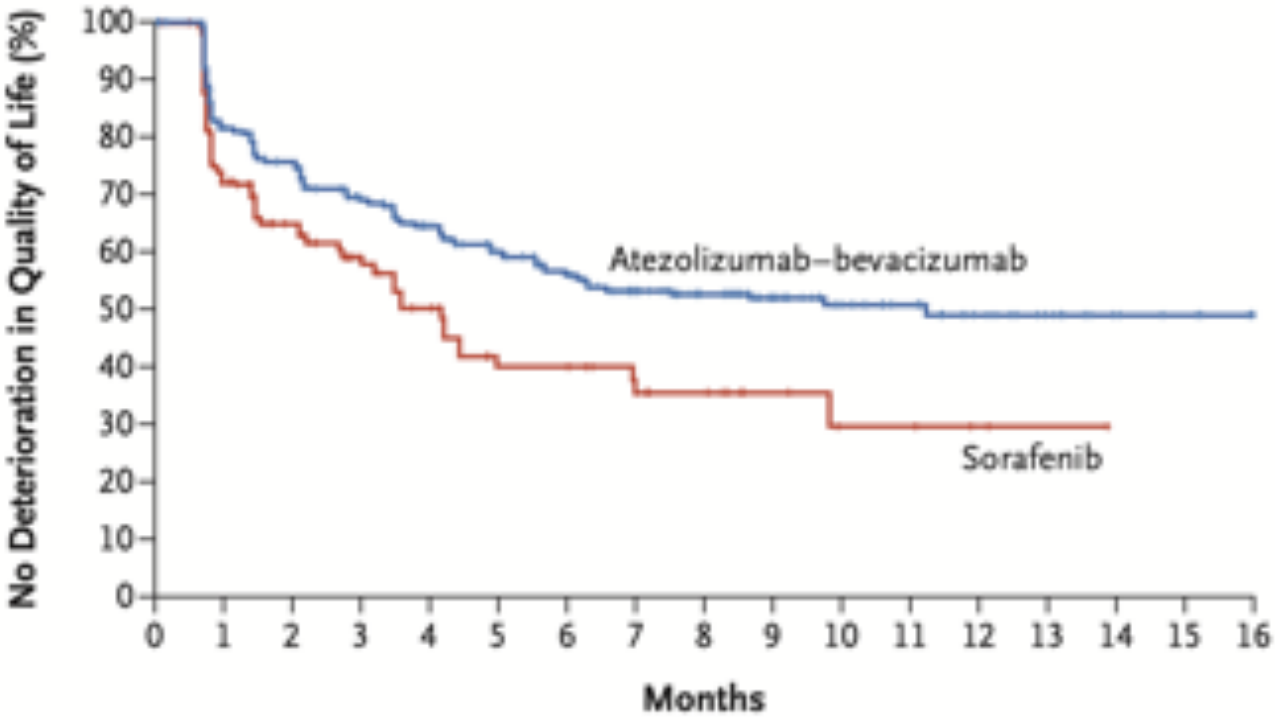
Median progression-free survival

Atezolizumab + bevacizumab	Sorafenib
6.8 Mo	4.3 Mo

HR for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001

R.S. Finn et al. 10.1056/NEJMoa1915745

Time to deterioration of quality of life



	Quality of Life — Median Time to Deterioration (95% CI)
	mo
Atezolizumab–Bevacizumab	11.2 (6.0–NE)
Sorafenib	3.6 (3.0–7.0)

Hazard ratio, 0.63 (95% CI, 0.46–0.85)

No. at Risk

Atezolizumab–bevacizumab	336	239	208	181	157	134	121	99	78	58	40	32	20	14	7	5	NE
Sorafenib	165	93	60	39	31	22	22	14	12	7	4	4	2	1	NE	NE	NE

Adverse events from any cause

Variable	Atezolizumab–Bevacizumab (N=329)	Sorafenib (N=156)
	number (percent)	
Patients with an adverse event from any cause	323 (98.2)	154 (98.7)
Grade 3 or 4 event*	186 (56.5)	86 (55.1)
Grade 5 event†	15 (4.6)	9 (5.8)
Serious adverse event	125 (38.0)	48 (30.8)
Adverse event leading to withdrawal from any trial drug	51 (15.5)	16 (10.3)
Withdrawal from atezolizumab–bevacizumab	23 (7.0)	—
Adverse event leading to dose modification or interruption of any trial drug	163 (49.5)	95 (60.9)
Dose interruption of any trial treatment	163 (49.5)	64 (41.0)
Dose modification of sorafenib	—	58 (37.2)

CLINICAL PRACTICE GUIDELINES

An ESMO Product

Management of toxicities from immunotherapy

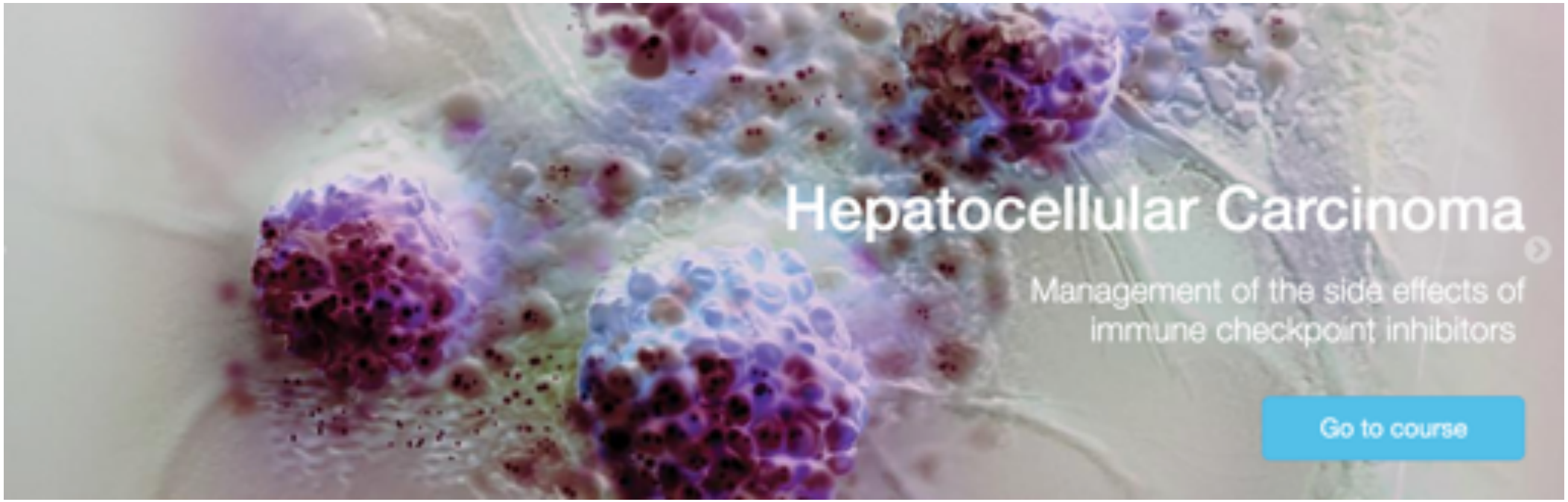
ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan,
on behalf of the ESMO Guidelines Committee

*For details of author affiliations, correspondence and versions, please see the full version at esmo.org/Guidelines/Supportive-and-Palliative-Care

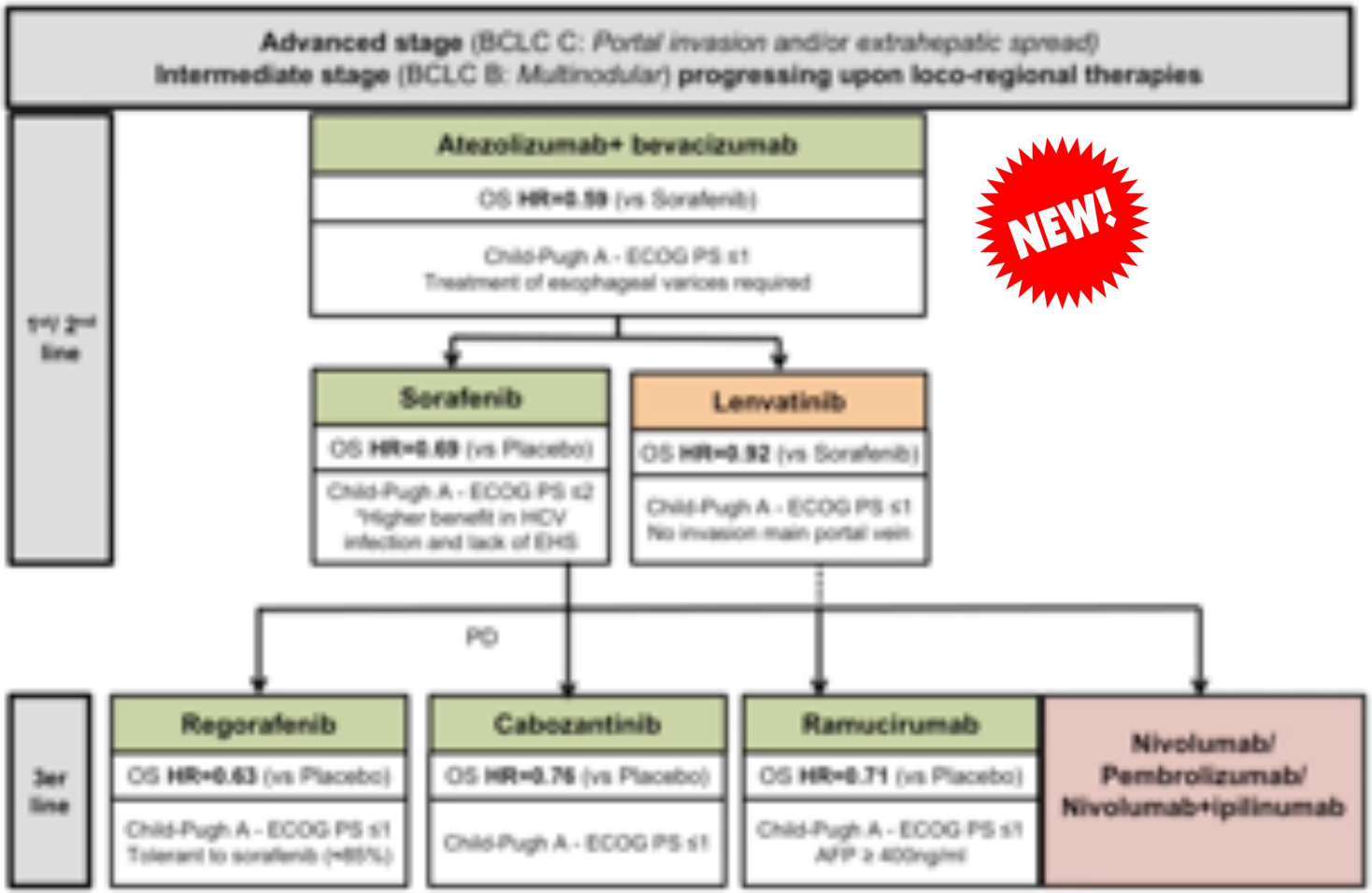
Haanen J et al., Ann Oncol, 2017
https://www.esmo.org/guidelines/supportive-and-palliative-care/toxicities-from-immunotherapy

Management of side effects of immune checkpoint inhibitors



easlcampus.eu

Treatment strategy 2020 for advanced HCC



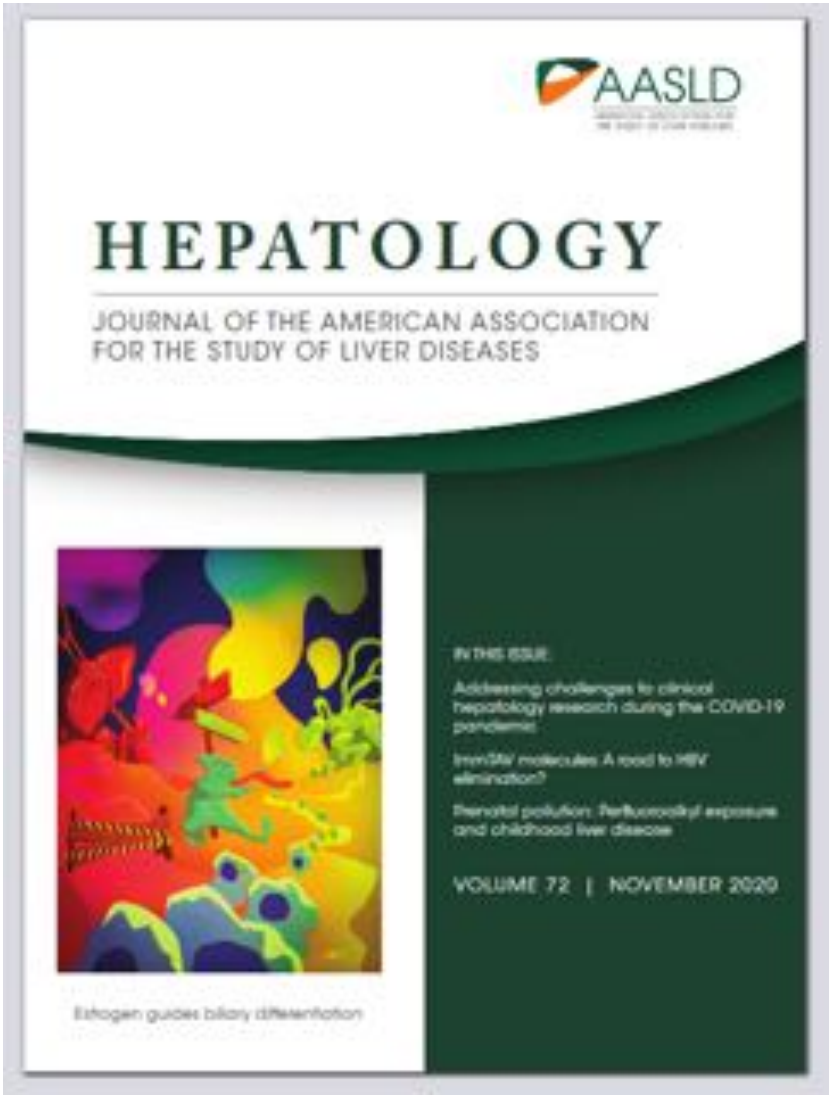
Llovet JM et al., et al., Harrison 21st edition, in press

Perspective Atezolizumab/Bevacizumab in HCC:

- Establishes **immune therapy** as first line treatment in unresectable HCC
- **Approved** by FDA, EMEA and Swissmedic (Nov 10th 2020)
- Changes the **care setting** of HCC patients (i.v. **infusions q3 weeks**)
- Be prepared to manage **different side effects** – exchange your experience in interdisciplinary immune therapy boards!

VOCAL-Penn Score

Refining prediction of post-operative mortality in cirrhotic patients



Original Article

Novel Risk Prediction Models for Post-Operative Mortality in Patients with Cirrhosis

Nadim Mahmud MD MS MPH MSCE,[1,*] Zachary Fricker MD,[1,*] Rebecca A. Hubbard PhD,[2] George N. Ioannou MD MS,[3,4] James D. Lewis MD MSCE,[2] Tamar H. Taddei MD,[5] Kenneth D. Rothstein MD,[6] Marina Serper MD MS,[1,3] David S. Goldberg MD MSCE,[7] David E. Kaplan MD MS[8]

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8. VA Connecticut Healthcare System, West Haven, CT
9. Department of Medicine, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA
10. Division of Digestive Health and Liver Diseases, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL

Mahmud N et al., Hepatology, 2020

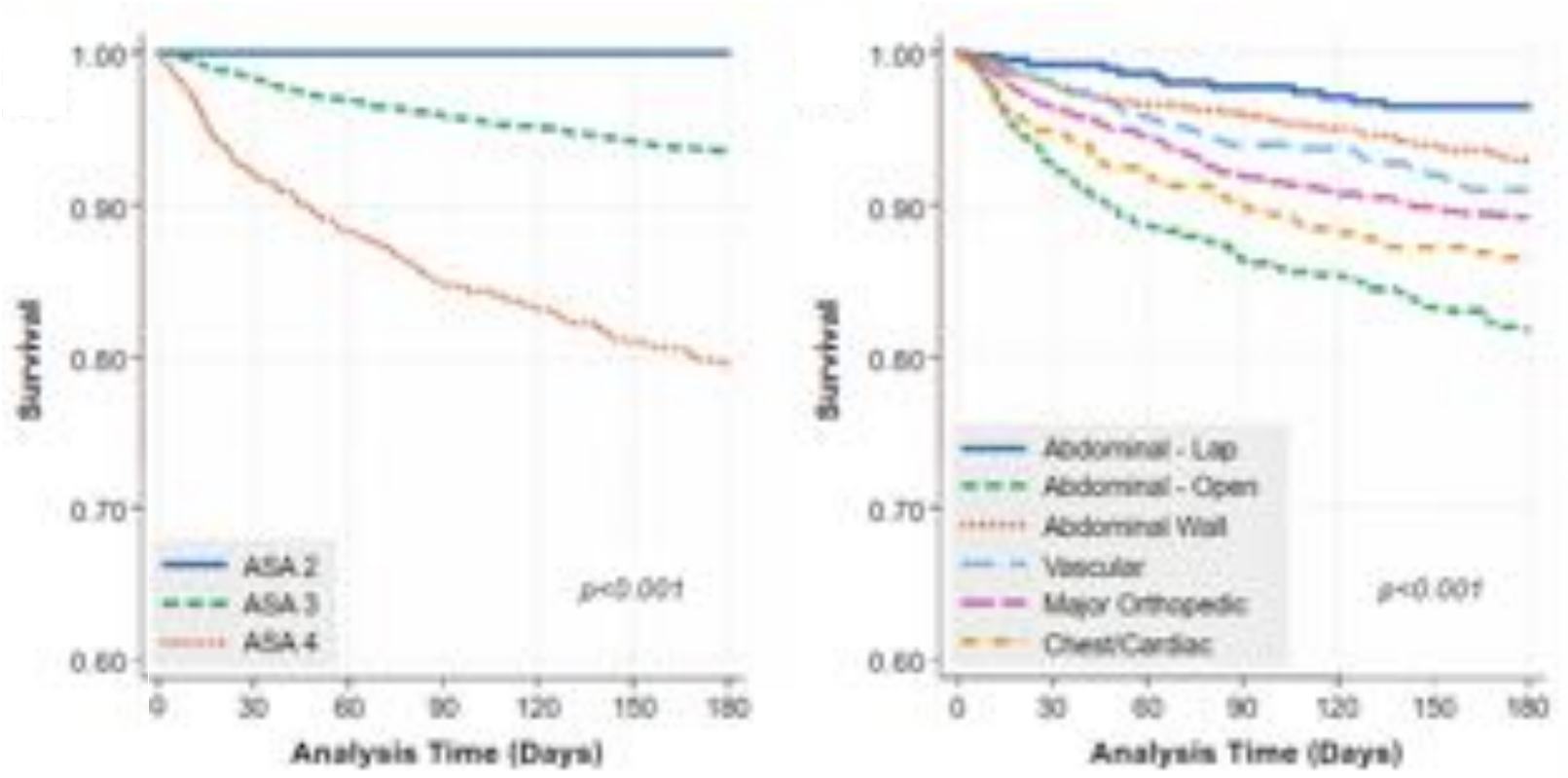
Surgery in patients with liver cirrhosis

- Patients with cirrhosis are at increased **risk of post-operative mortality**
- **Currently available tools** to predict post-operative risk are suboptimally calibrated and **do not account for surgery type**
- The objective was to use **population-level data** to **derive and internally validate** novel cirrhosis surgical risk models

Methods

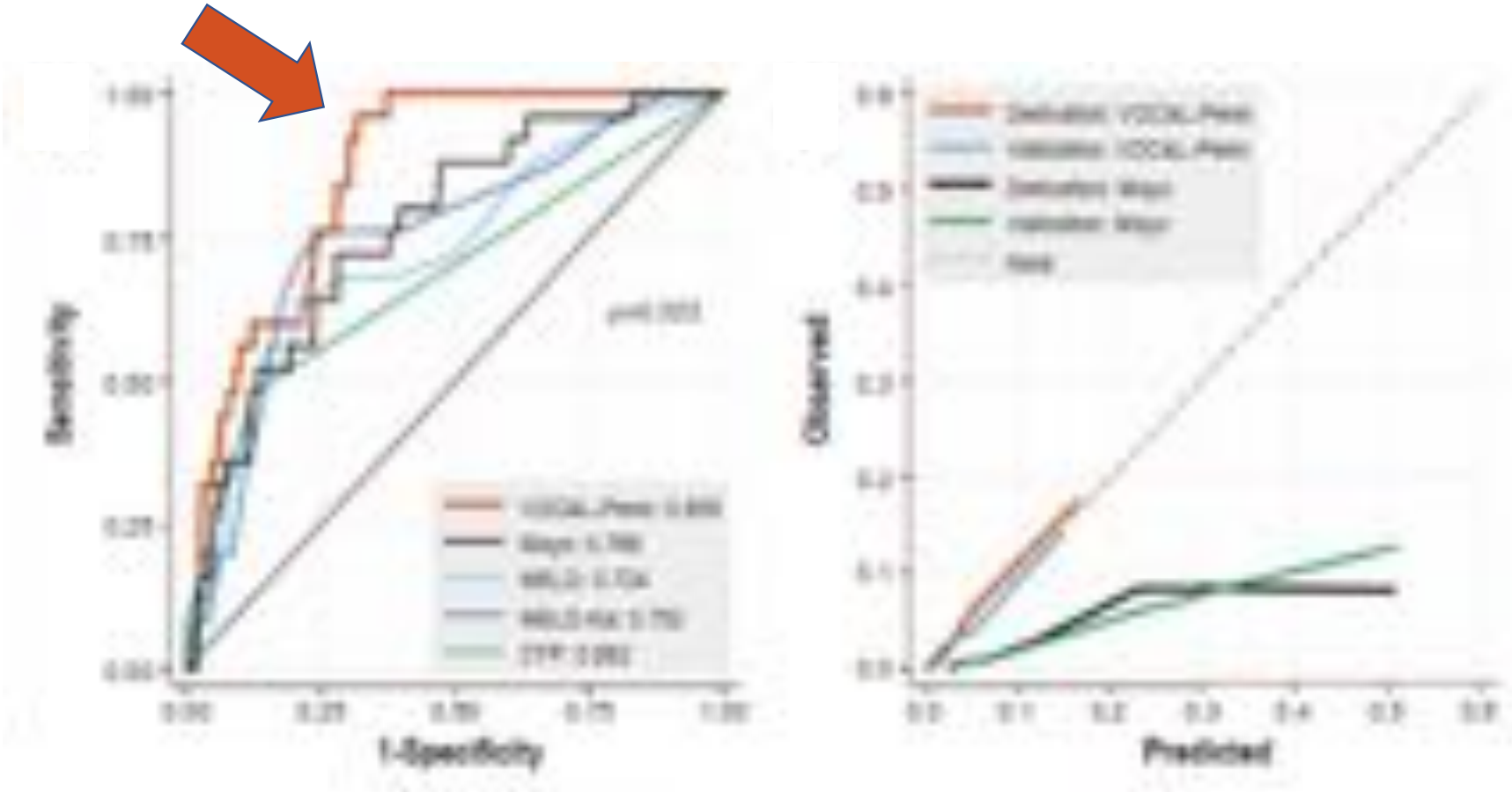
- **Retrospective cohort** study using data from the **Veterans Outcomes** and Costs Associated with Liver Disease (VOCAL)
- **128** United States medical **centers**
- **Categorized surgeries** as abdominal wall, vascular, abdominal, cardiac, chest, or orthopaedic
- **Multivariable logistic regression** to model **30, 90, and 180-day** post-operative mortality (VOCAL-Penn models)
- **Compared to** Mayo risk score (MRS), MELD, MELD-Na, and Child-Turcotte-Pugh (CTP) scores

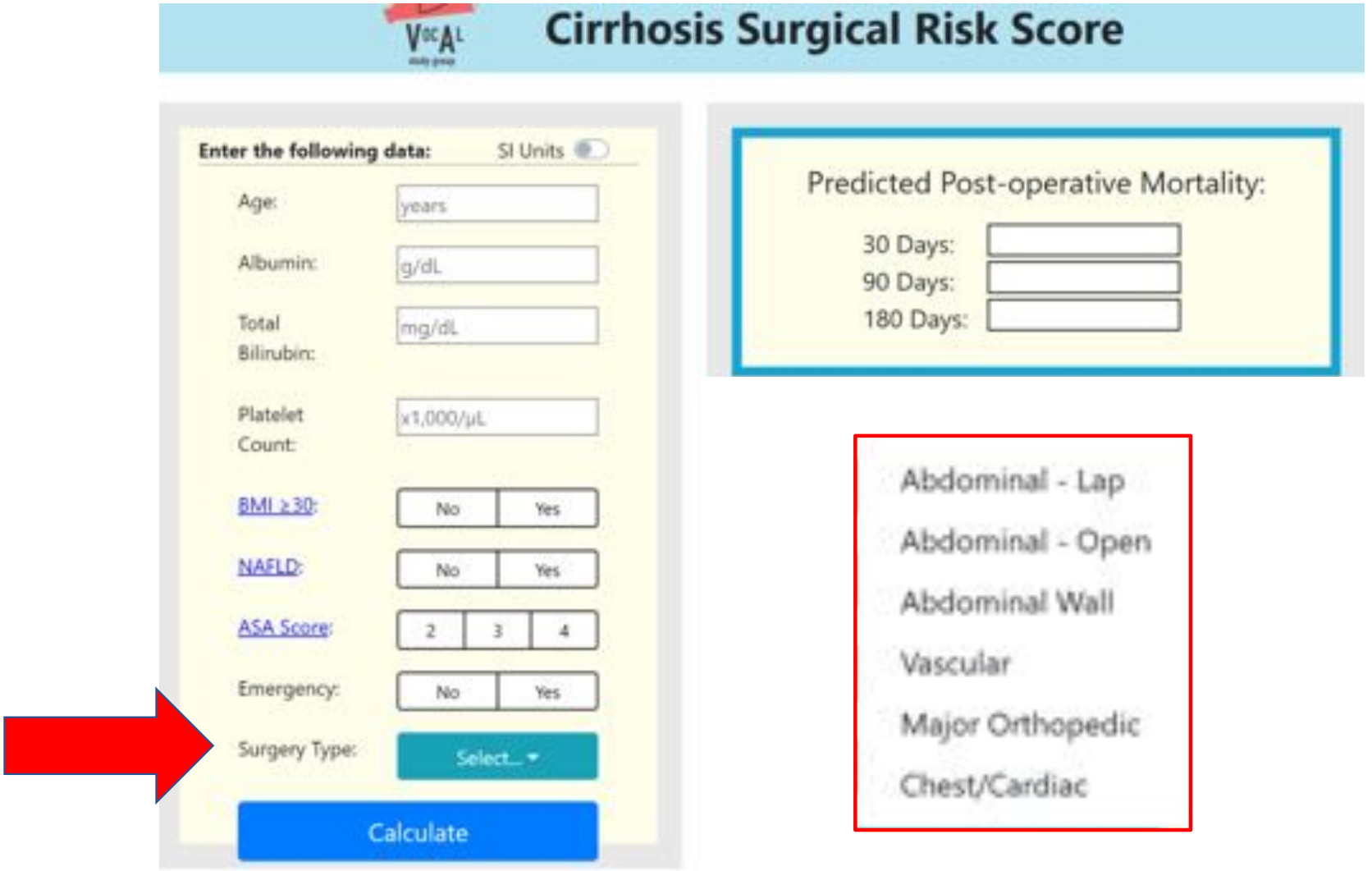
4’712 surgical procedures in 3’785 patients with cirrhosis: **Mortality predictors**



Age, pre-operative albumin, platelet count, bilirubin, surgery category, emergency indication, NAFLD, ASA classification, and obesity

Model performance was superior to MELD, MELD-Na, CTP, and Mayo Risk Score at all timepoints:





www.vocalpennscore.com

Givosiran

First drug for liver disease using RNA interference

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 11, 2020 VOL. 382 NO. 24

Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria

M. Balwani, E. Sardh, P. Ventura, P.A. Peiró, D.C. Rees, U. Stölzel, D.M. Bissell, H.L. Bonkovsky, J. Windyga, K.E. Anderson, C. Parker, S.M. Silver, S.B. Keel, J.-D. Wang, P.E. Stein, P. Harper, D. Vassiliou, B. Wang, J. Phillips, A. Ivanova, J.G. Langendonk, R. Kauppinen, E. Minder, Y. Horie, C. Penz, J. Chen, S. Liu, J.J. Ko, M.T. Sweetser, P. Garg, A. Vaishnaw, J.B. Kim, A.R. Simon, and L. Gouya, for the ENVISION Investigators*

Balwani M et al., N Engl J Med, 2020

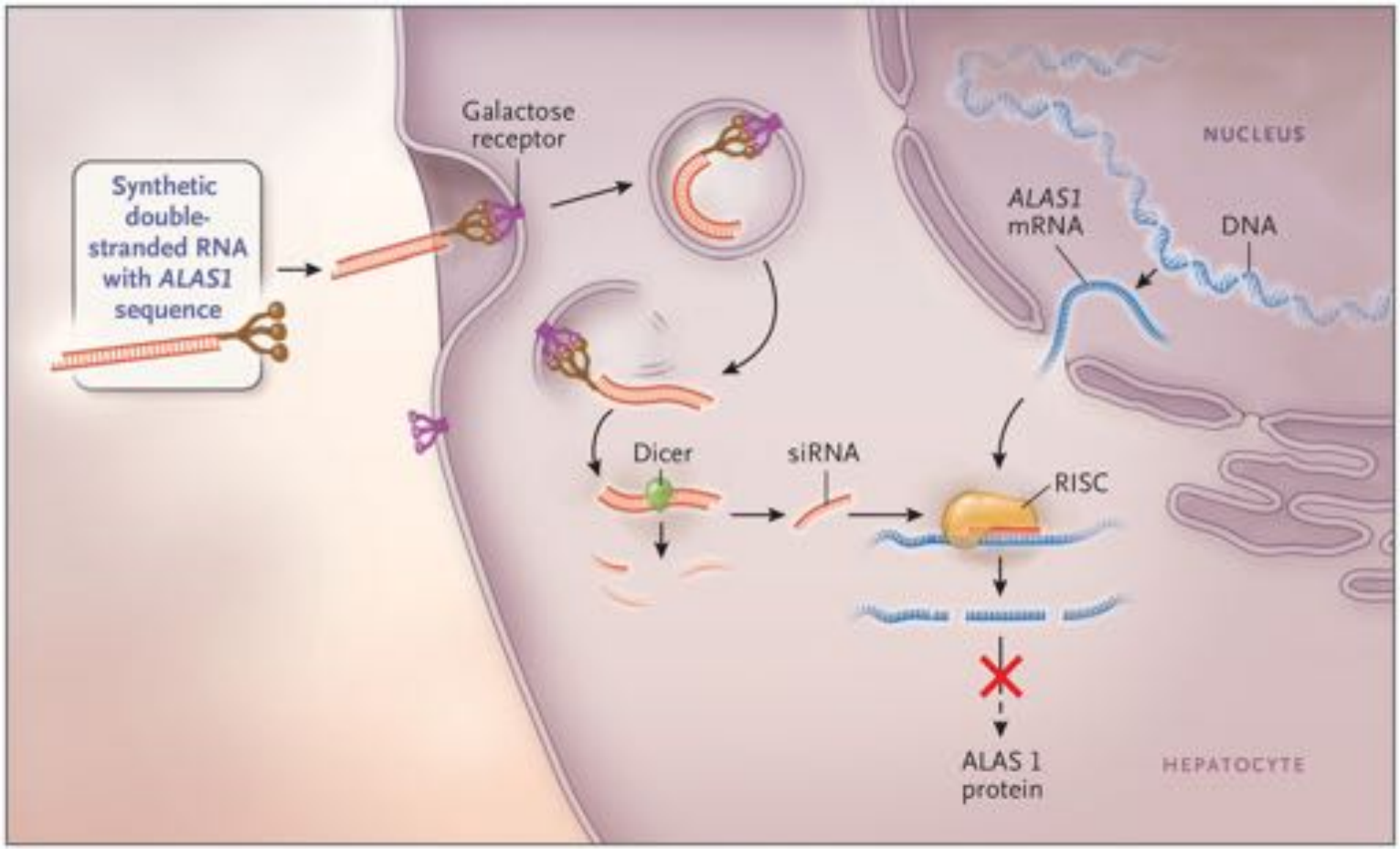
Acute intermittent porphyria (AIP)

- Rare disease, prevalence ca. 1/75’000, in 80% of cases females, typically 20 to 45 years
- Inherited enzyme deficiency in the liver
- Pathophysiology: Up-regulation of hepatic **delta-aminolevulinic acid synthase 1 (ALAS1)**, with resultant **accumulation** of **delta-aminolevulinic acid** (ALA) and **porphobilinogen** leading to acute attacks and chronic symptoms
- Symptoms: **Neuro-visceral attacks** with intense abdominal pain, **neurological** symptoms (muscular weakness, sensory loss or convulsions) and **psychological symptoms** (irritability, anxiety, auditory or visual hallucinations, mental confusion)
- Treatment in acute attack: **Intravenous hemin** (250 mg, Normosang), hydration, opioids

Double-blind, placebo-controlled, phase 3 trial in symptomatic AHP patients (n=98)

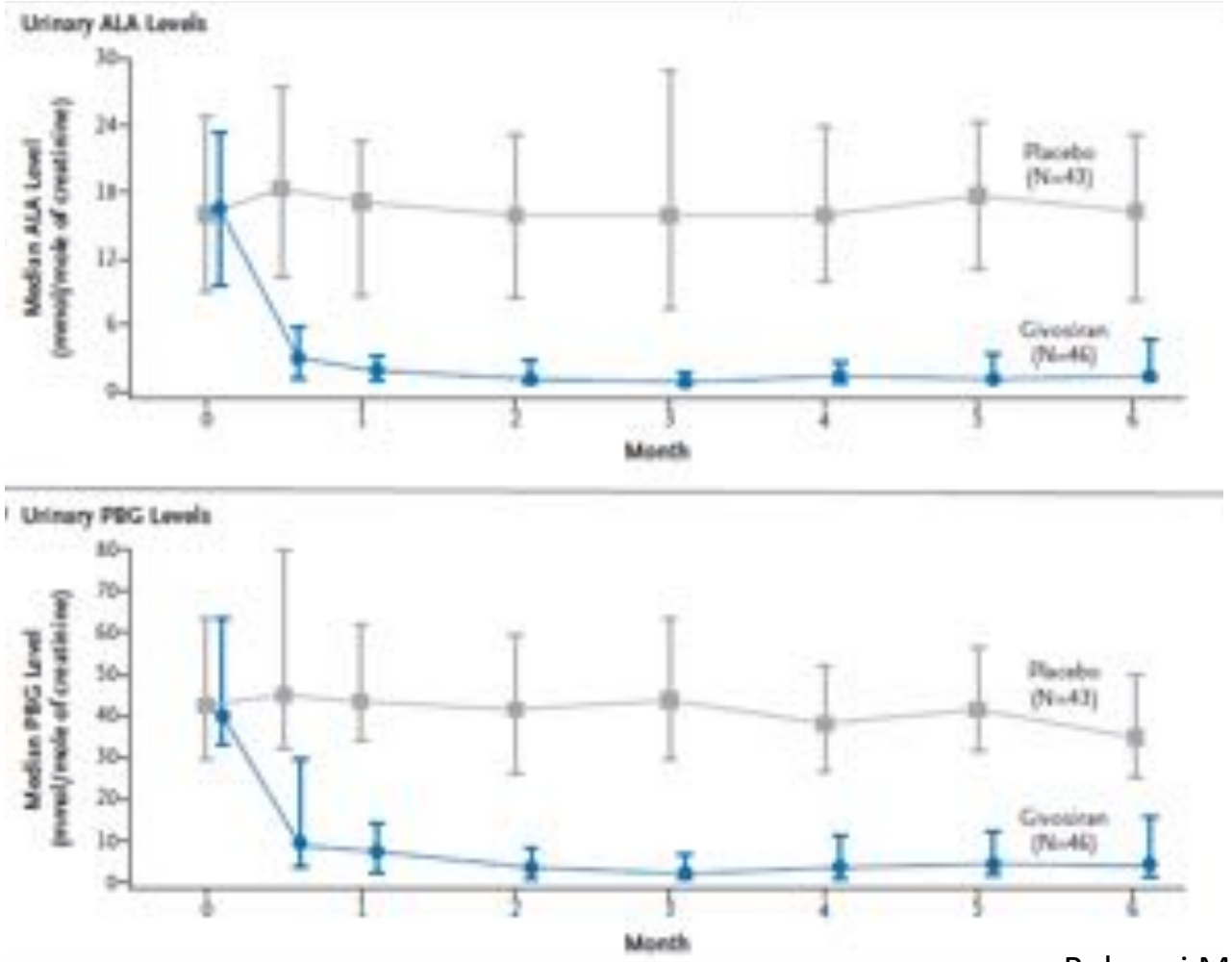
- **Givosiran** (2.5 mg/kg **s.c. once monthly**) vs. **placebo** monthly for **6 months**
- Primary end point: annualized rate of **composite porphyria attacks**
- Composite porphyria attacks: hospitalization, ER visit, or i.v. hemin at home
- Secondary end points: **levels of ALA** and **porphobilinogen** and the annualized attack rate, daily **worst pain scores** in patients

Givosiran, an RNA interference therapy, inhibits ALAS1 expression by hepatocyte-targeted delivery of siRNA via GalNAc–siRNA conjugates



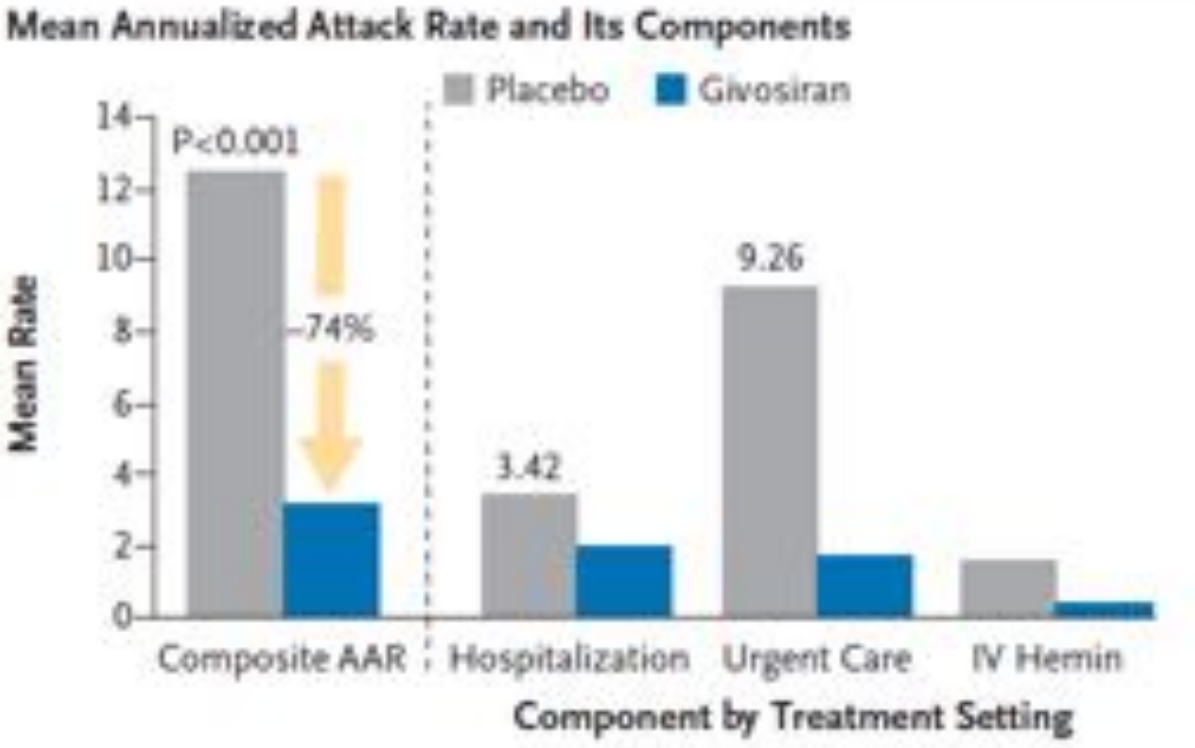
Wang B et al., Hepatol Commun, 2018

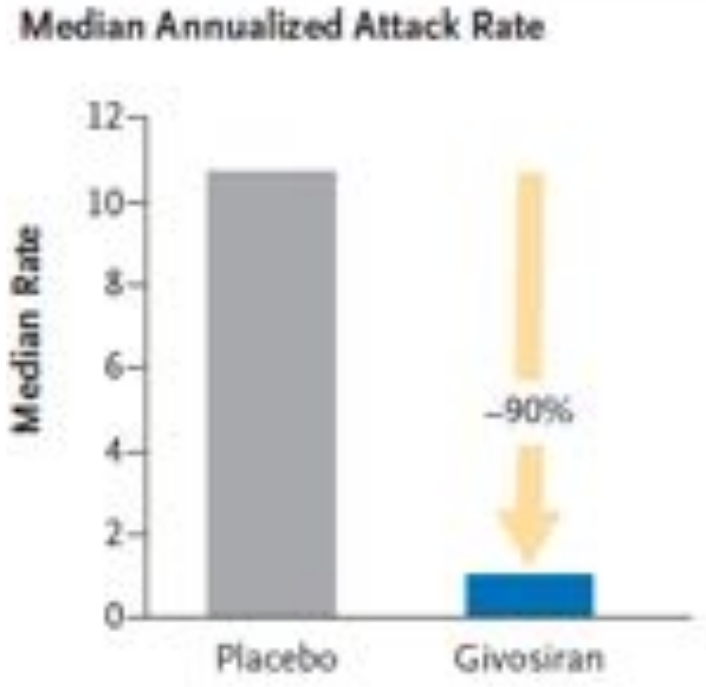
Givosiran leads to lower levels of urinary ALA and porphobilinogen



Balwani M et al., N Engl J Med, 2020

Givosiran significantly reduces annualized attack rates





Balwani M et al., N Engl J Med, 2020

Perspective on Givosiran in AIP

- Givosiran (GIVLAARI™): **Novel and highly effective treatment for AIP** patients
- Potentially **reduced need for liver transplantation**
- **Proof of concept** for RNA interference as specific treatment for human diseases
- Elegant **platform for other liver-targeted treatments** (i.e. amyloid, dyslipidemia, HBV)

Suggested reading:
Therapeutic siRNA: state of the art. Bo Hu et al., Signal Transduction and Targeted Therapy, 2020
https://www.nature.com/articles/s41392-020-0207-x

mRNA vaccines

SARS-CoV-2 vaccine development

ORIGINAL ARTICLE

Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates

Edward E. Walsh, M.D., Robert W. Frenck, Jr., M.D., Ann R. Falsey, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., Kathleen Neuzil, M.D., Mark J. Mulligan, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Ping Li, Ph.D., Kenneth Koury, Ph.D., Warren Kalina, Ph.D., David Cooper, Ph.D., Camila Fontes-Garfias, B.Sc., Pei-Yong Shi, Ph.D., Özlem Türeci, M.D., Kristin R. Tompkins, B.Sc., Kirsten E. Lyke, M.D., Vanessa Raabe, M.D., Philip R. Dormitzer, M.D., Kathrin U. Jansen, Ph.D., Uğur Şahin, M.D., and William C. Gruber, M.D.

Walsh EE et al., N Engl J Med, 2020

- **Placebo-controlled**, observer-blinded, dose-escalation, **phase 1 trial** conducted in the United States

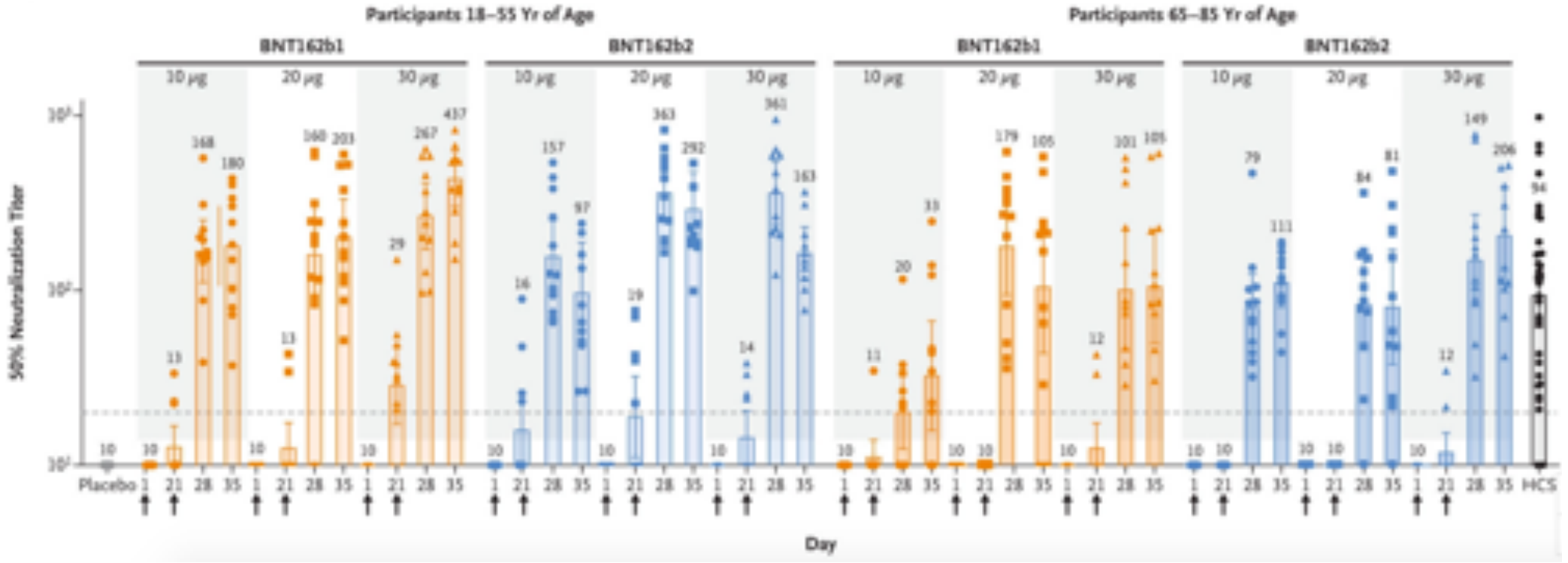
- **195 healthy** adults **18 to 55 years** of age and those 65 to 85 years of age to receive either placebo or a **lipid nanoparticle–formulated**, nucleoside-modified **RNA vaccine** candidate (BNT162b2)

- mRNA encodes a membrane-anchored SARS-CoV-2 full-length **spike protein**, stabilized in the prefusion conformation

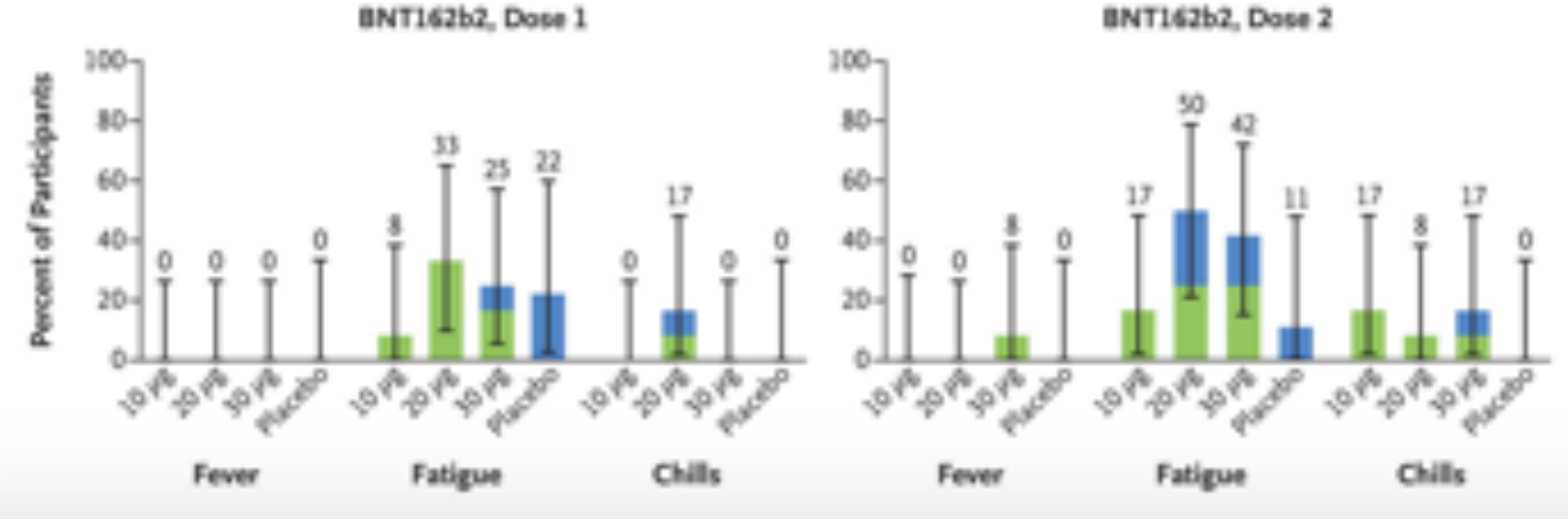
- **Primary outcome:** Safety (local and systemic reactions and adverse events)

- **Secondary outcome**: Immunogenicity

Immunogenicity of BNT162b2



Selected Systemic Events Reported within 7 Days after the Administration of Vaccine or Placebo



Systemic events: Mild Moderate Severe
Fever: 38.0°C–38.4°C >38.4°C–38.9°C >38.9°C–40.0°C

Operation Warp speed

PFIZER AND BIONTECH ANNOUNCE VACCINE CANDIDATE AGAINST COVID-19 ACHIEVED SUCCESS IN FIRST INTERIM ANALYSIS FROM PHASE 3 STUDY

Monday, November 09, 2020 - 06:45am

- *Vaccine candidate was found to be more than 90% effective in preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection in the first interim efficacy analysis*
- *Analysis evaluated 94 confirmed cases of COVID-19 in trial participants*
- *Study enrolled 43,538 participants, with 42% having diverse backgrounds, and no serious safety concerns have been observed; Safety and additional efficacy data continue to be collected*
- *Submission for Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration (FDA) planned for soon after the required safety milestone is achieved, which is currently expected to occur in the third week of November*
- *Clinical trial to continue through to final analysis at 164 confirmed cases in order to collect further data and characterize the vaccine candidate's performance against other study endpoints*

Comparison of advanced COVID-19 vaccines

Company	Type	Doses	How effective*	Storage	Cost per dose
Pfizer-BioNTech	RNA	x2	95%	-70C	£15 ($20)
Moderna	RNA (part of virus genetic code)	x2	95%	-20C up to 6 months	£25 ($33)
Oxford Uni-AstraZeneca	Viral vector (genetically modified virus)	x2	62-90%	Regular fridge temperature	£3 ($4)

* Preliminary phase 3 results, not yet peer reviewed

Sources: World Health Organisation / BBC, press releases

Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination

1. residents in a care home for older adults and their carers
2. all those 80 years of age and over and frontline health and social care workers
3. all those 75 years of age and over
4. all those 70 years of age and over and clinically extremely vulnerable individuals[footnote 1]
5. all those 65 years of age and over
6. all individuals aged 16 years to 64 years with underlying health conditions which put them at higher risk of serious disease and mortality
7. all those 60 years of age and over
8. all those 55 years of age and over
9. all those 50 years of age and over

- i.e. solid organ transplant recipients
- Cancer pts with active cancer treatment

- i.e. chronic liver disease

https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-2-december-2020

Perspective on COVID-19 vaccines

- **UK** starts vaccination program **today** after emergency approval of Pfizer mRNA vaccine
- **EU & USA** expected to approve vaccinations this **12/2020**
- **Switzerland** scheduled for end of **01/2021** pending approval
- **Pre-ordered vaccines in Switzerland** for 400 Mio CHF (3 Mio Pfizer, 4.5 Mio Moderna, 5.3 Mio AstraZeneca)
- **Priority groups (liver disease)** and distribution in Switzerland not known yet