# Targeted Therapies in Advanced Hepatocellular Carcinoma: Optimizing Outcomes with Sequential Treatment

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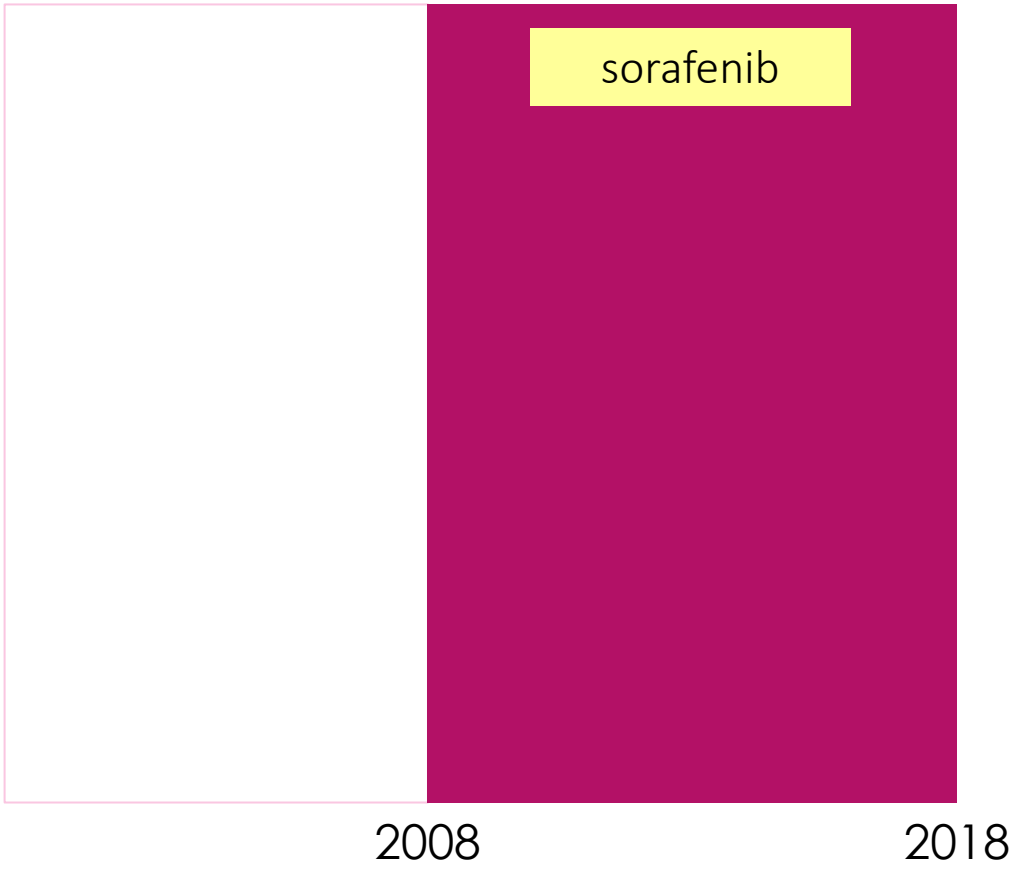
2020 JUL 25

# HCC Systemic Therapy Before 2008



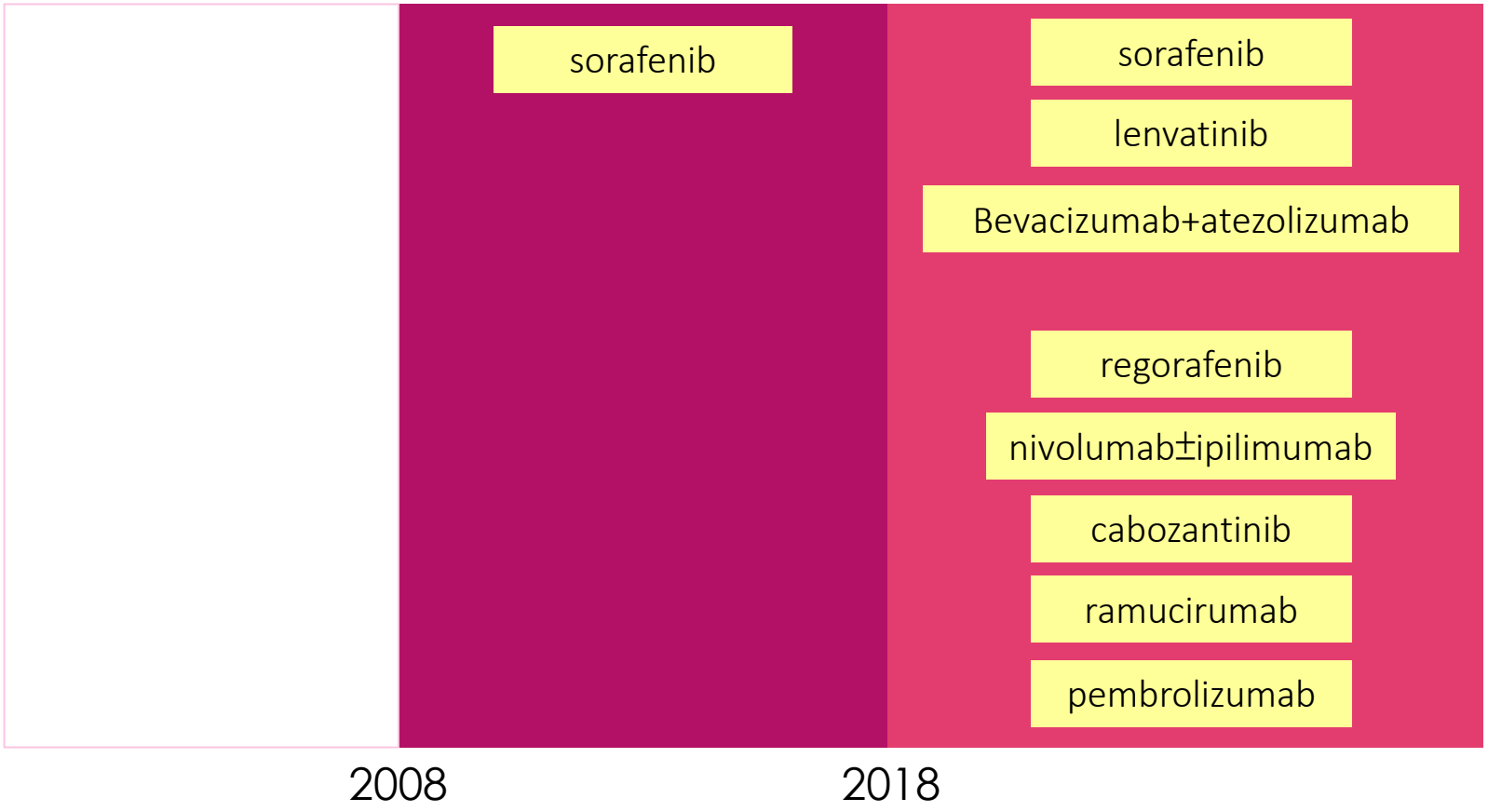
2008

# HCC Systemic Therapy 2008- 2018

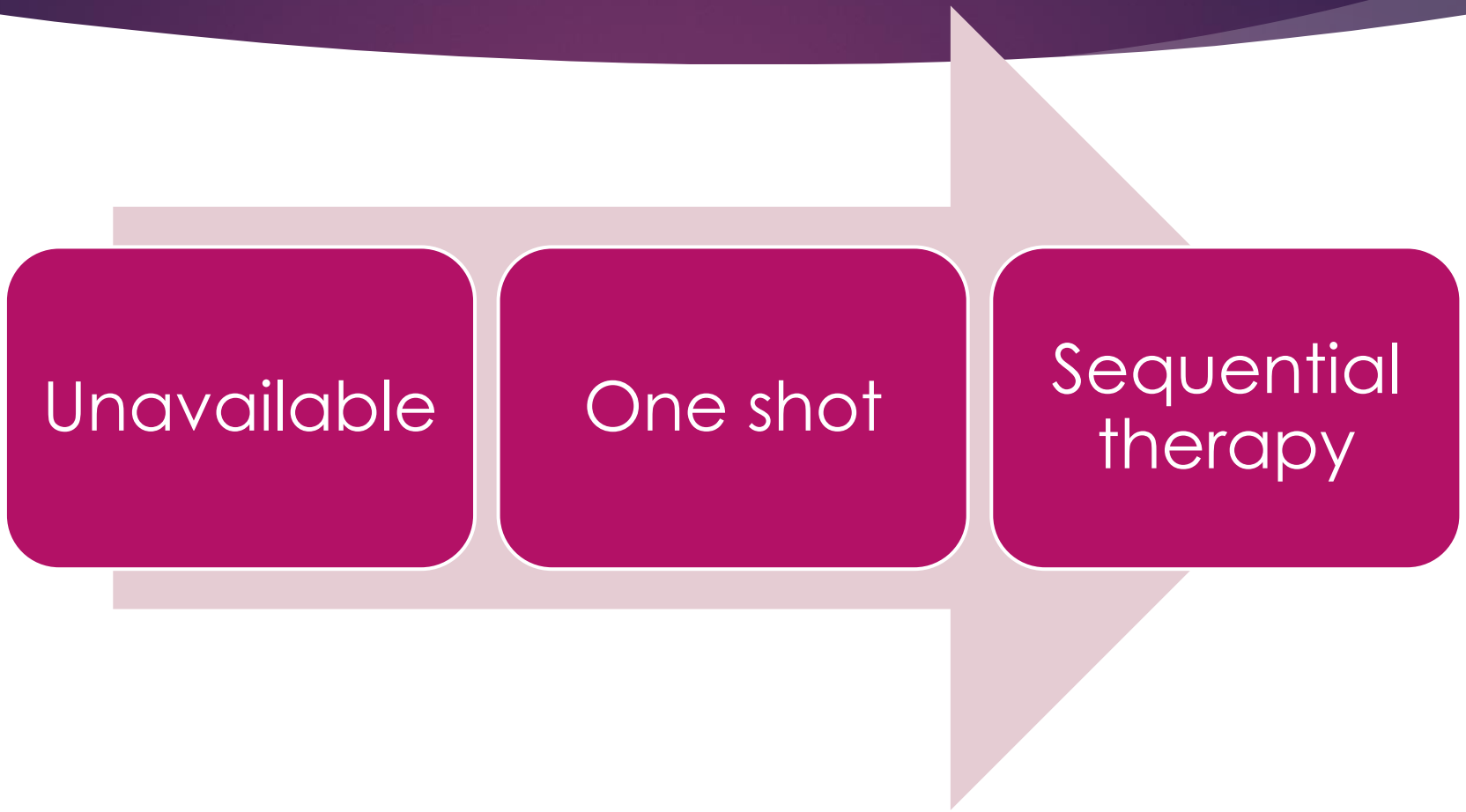



Treatments approved or with phase 3 trial success are listed

# HCC Systemic Therapy After 2018



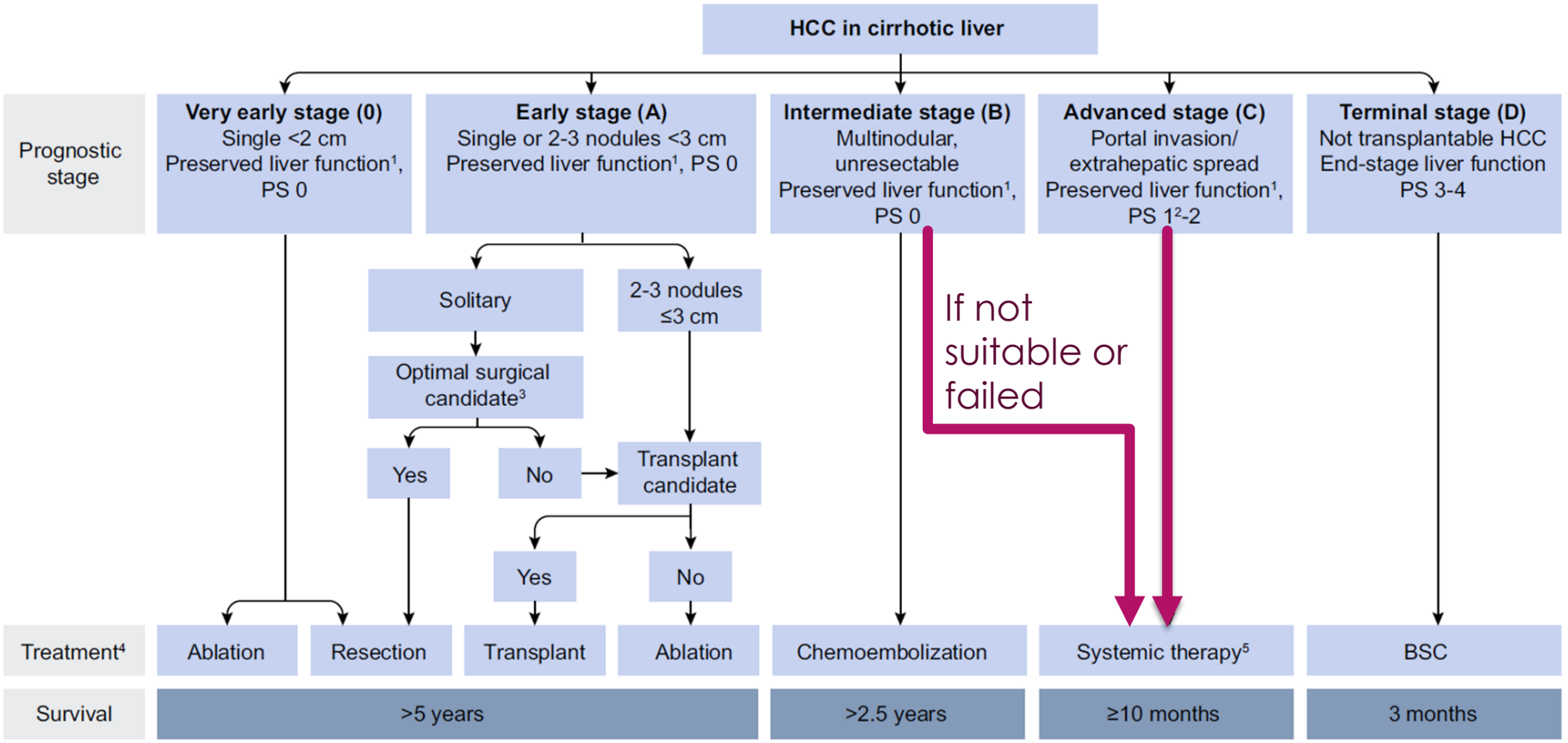
# Advanced HCC Treatment



# Sequential Therapy for Advanced HCC

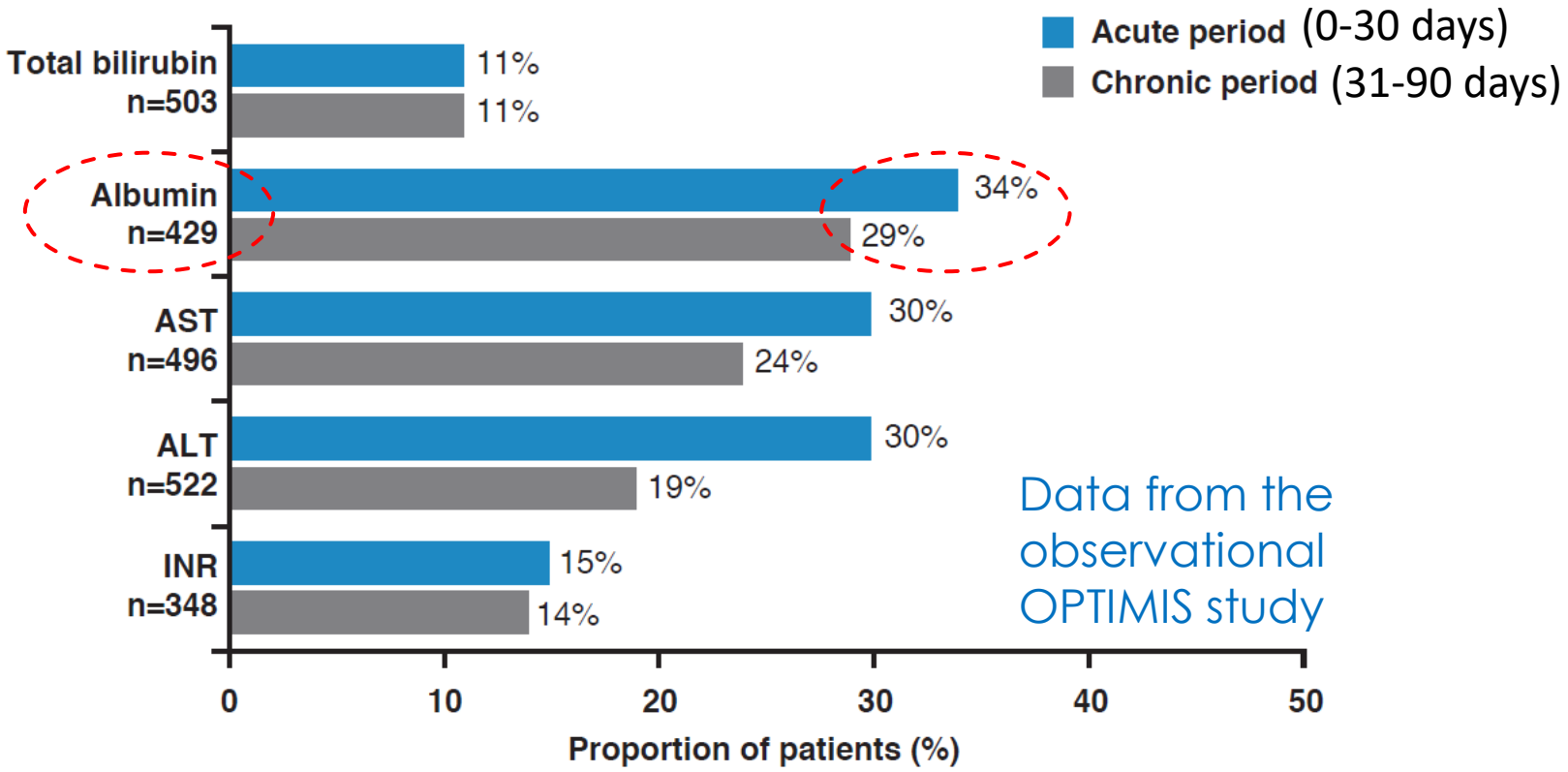
- Start systemic therapy as early as possible
- Availability of sequential therapy
- Regorafenib as salvage therapy
- Potential of kinase inhibitor efficacy after VEGF antibody

# Advanced HCC ≠ BCLC C Disease



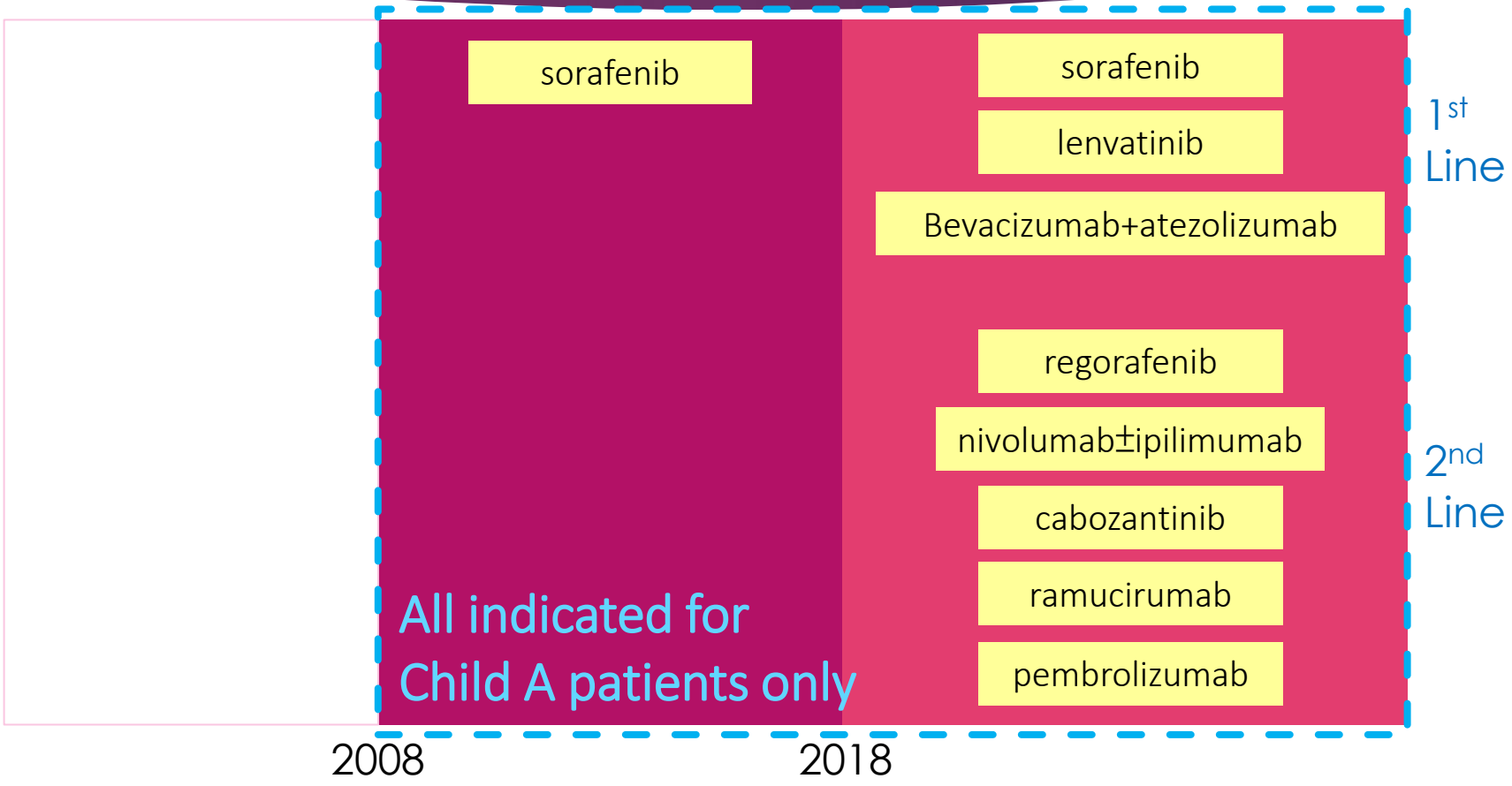

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

# Problems with Repeated TACE: Liver Function Deterioration

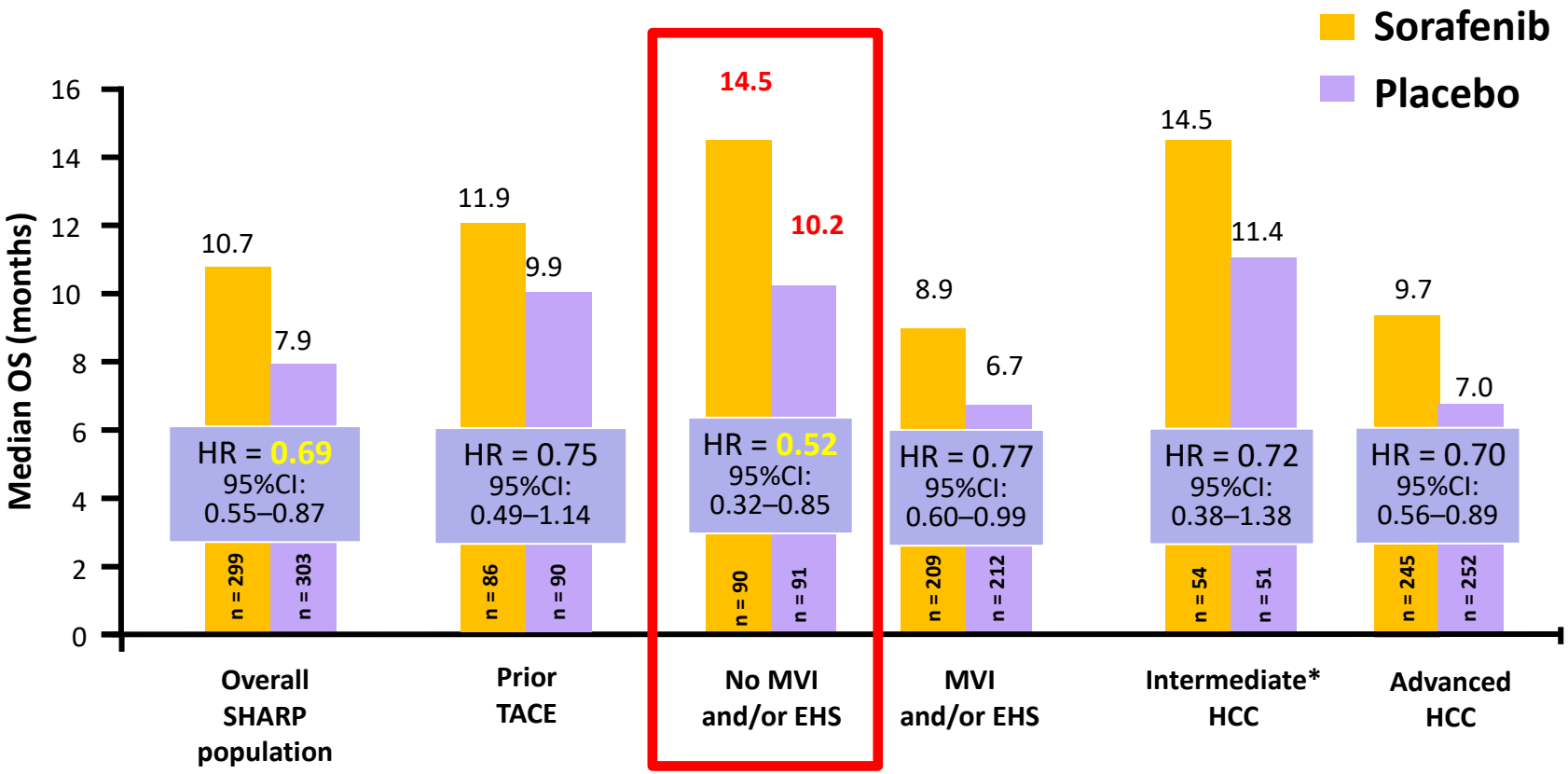



*Peck-Radosavljevic et al. ASCO 2018 abstract 4018; Cheng et al. 2018 APPLE, PE-066; Lee et al, 2018 APPLE, PO-30*

# HCC Systemic Therapy After 2018



# Sorafenib Provides More Survival Benefits for BCLC B Disease




Llovet et al., N Engl J Med 2008;359:378-90

*Intermediate patients = BCLC B patients in SHARP trial.

# HCC Treatments are NOT One-Directional Options

9.34. Sorafenib（如 Nexavar）：
(98/10/1、100/6/1、101/8/1、104/6/1、105/11/1、106/1/1、107/7/1、108/6/1)

1.（略）

2.晚期肝細胞癌部分：(101/8/1、105/11/1、108/6/1)

(1)轉移性或無法手術切除且不適合局部治療或局部治療失敗之 Child-Pugh A class 晚期肝細胞癌成人患者，並符合下列條件之一：

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Ⅲ.經導管動脈化學藥物栓塞治療（Transcatheter arterial chemoembolization, T.A.C.E.）失敗者，需提供患者於 12 個月內 >=3 次局部治療之記錄。

(2)需經事前審查核准後使用，初次申請之療程以 3 個月為限，之後每 2

9.63 Lenvatinib（如 Lenvima）
(107/7/1、109/1/1)

1.用於放射性碘治療無效之局部晚期或轉移性的進行性(progressive)分化型甲狀腺癌(RAI-R DTC)：需經事前審查核准後使用，每次申請之療程以 3 個月為限，送審時需檢送影像資料，每 3 個月評估一次。

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3. Lenvatinib 與 sorafenib 僅得擇一使用，不得互換；且 lenvatinib 治療失敗後，不得申請使用 Stivarga 或 Opdivo。(109/1/1)

# Sequential Therapy for Advanced HCC

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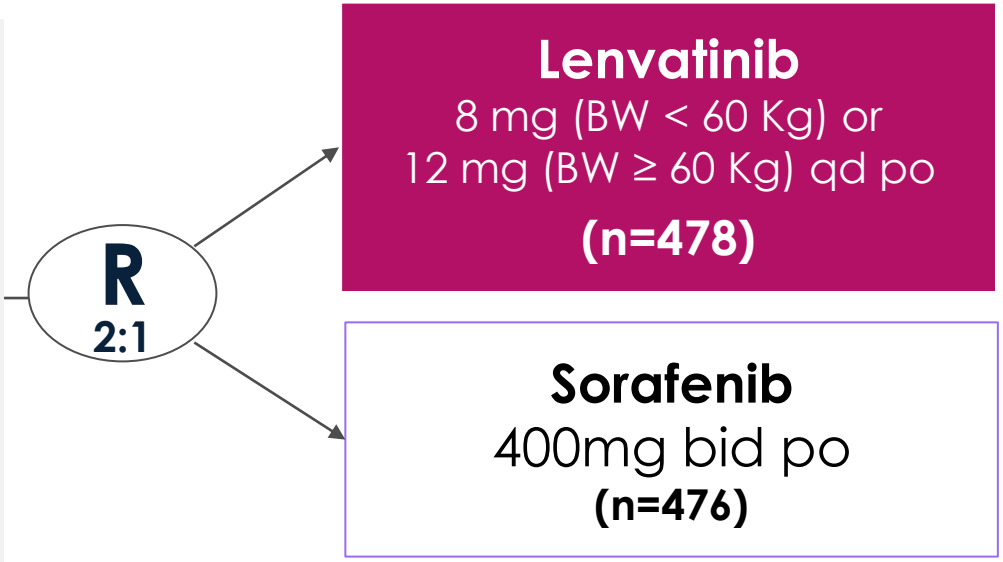
# REFLECT study

A randomized, open-labelled, phase 3, noninferiority trial

**N= 954**

- Patients with unresectable HCC receiving no prior systemic therapy
- Exclude:
  - ECOG ≥ 2
  - **≥ 50% liver involvement**
  - **Clear bile duct invasion**
  - **Main portal vein invasion**




Primary endpoint: overall survival

**Noninferiority margin**: HR 1.08

Tumor assessment every 8 weeks by mRECIST

*Kudo et al. Lancet 2018; 391: 1163–73*

# Best Response by mRECIST

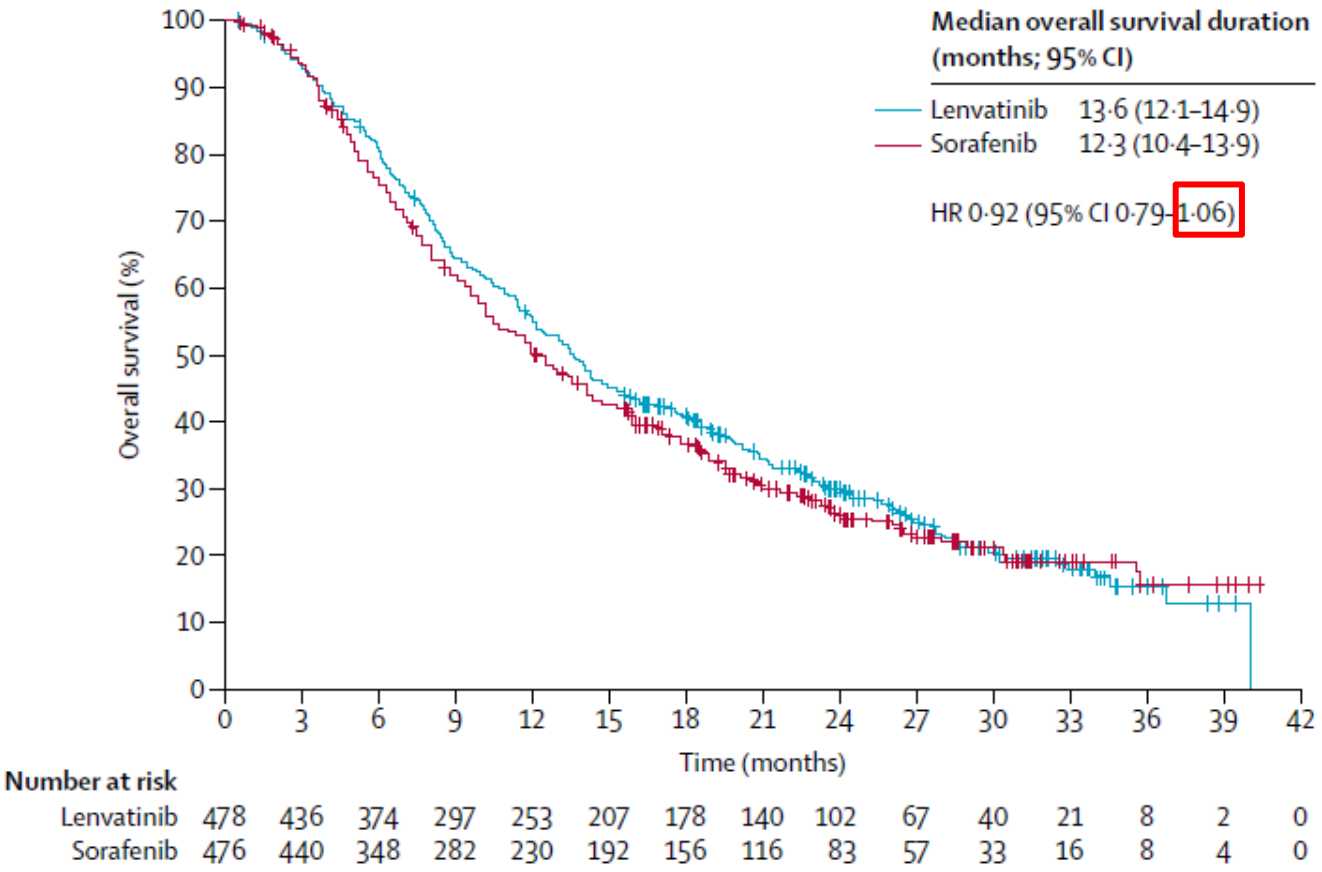
Secondary endpoint

| | Lenvatinib (n=478) | Sorafenib (n=476) |
|---|---|---|
| **Investigator review according to mRECIST** | | |
| Overall survival (months) | 13·6 (12·1–14·9) | 12·3 (10·4–13·9) |
| Progression-free survival (months) | 7·4 (6·9–8·8) | 3·7 (3·6–4·6) |
| Time to progression (months) | 8·9 (7·4–9·2) | 3·7 (3·6–5·4) |
| Objective response (%, 95% CI) | 115 (24·1%, 20·2–27·9) | 44 (9·2%, 6·6–11·8) |
| 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 et al. Lancet 2018*

# Lenvatinib Shows Noninferiority for Overall Survival

Primary endpoint




*Kudo et al. Lancet 2018*

# Subsequent Therapy is NOT the cause of similar OS in REFLECT Study

| | Lenvatinib | | | Sorafenib | | |
|---|---|---|---|---|---|---|
| | Asia-Pacific Subgroup (n = 321) | Western Subgroup (n = 157) | Total (n = 478) | Asia-Pacific Subgroup (n = 319) | Western Subgroup (n = 157) | Total (n = 476) |
| Received any anticancer therapy during survival follow-up— no. (%) | 162 (50.5) | 44 (28.0) | 206 (43.1) | 172 (53.9) | 71 (45.2) | 243 (51.1) |
| Received any anticancer medication (not given for any procedure) during survival follow-up— no. (%) | 115 (35.8) | 41 (26.1) | 156 (32.6) | 123 (38.6) | 61 (38.9) | 184 (38.7) |
| Underwent any anticancer procedure during survival follow-up — no. (%) | 111 (34.6) | 11 (7.0) | 122 (25.5) | 112 (35.1) | 18 (11.5) | 130 (27.3) |

46%

54%

Ongoing 1st line therapy 27 25

*Kudo et al. Lancet 2018*

# Efficacy
## Second-Line Antiangiogenic Therapy for Advanced HCC

| | | RESORCE | | REACH-II (AFP≥ 400 ng/mL) | | CELESTIAL | |
|---|---|---|---|---|---|---|---|
| | | Regorafenib | Placebo | Ramucirumab | Placebo | Cabozantinib | Placebo |
| **OS** | **Median** (m) | 10.6 | | 8.5 | 7.3 | 11.3 | 7.2 |
| | **HR** | **0.63** | | **0.71** | | **0.70** | |
| **PFS** | **Median** (m) | 3.1 | 1.5 | 2.8 | 1.6 | 5.5 | 1.9 |
| | **HR** | **0.46** | | **0.45** | | **0.40** | |
| **RR** (%) using RECIST 1.1 | | 6.6 | 2.6 | 4.6 | 1.1 | 4.7 | 0.5 |
| **DCR** (%) | | 65.7 | 34.5 | 59.9 | 38.9 | 67.0 | 31.1 |

*Sangro et al EASL 2017; Meyer et al. EASL 2018; Bruix J, et al. Lancet. 2017;389:56-66; Abou-Alfa et al. NEJM 2018; Kelley et al. ASCO 2018; Zhu et al. ASCO 2018*

# Sequential Therapy for Advanced HCC

- Start systemic therapy as early as possible
- Availability of sequential therapy
- Regorafenib as salvage therapy
- Potential of kinase inhibitor efficacy after VEGF antibody

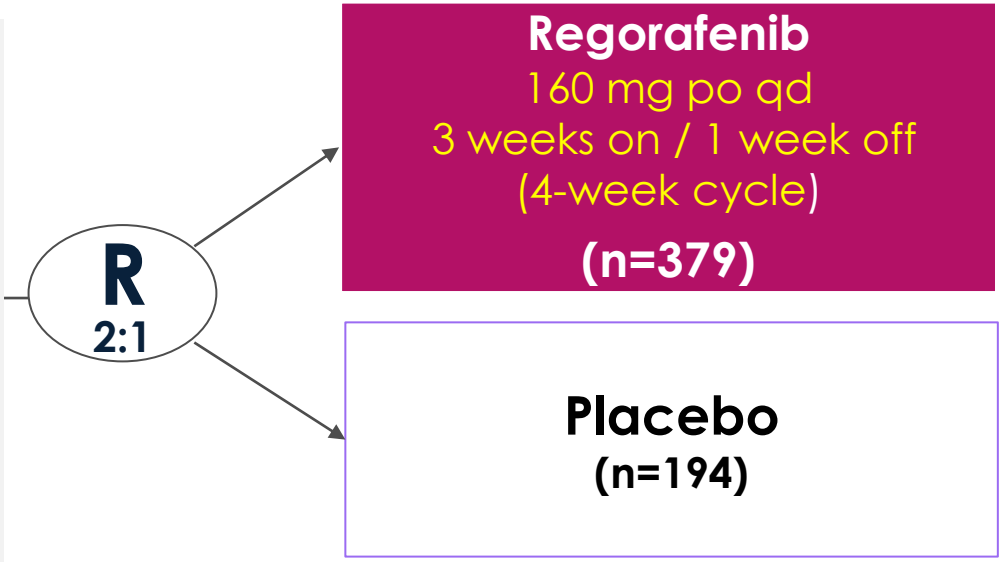
# RESORCE study

A randomized, double-blind, placebo-controlled, phase 3 trial

**N= 573**

- HCC patients with documented radiological progression during sorafenib treatment

- Stratified by:
  - Geographic region (Asia vs others)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (< 400 ng/mL vs ≥ 400 ng/mL)




- 152 centers in 21 countries in North/South America, Europe, Australia, Asia
- Endpoint: Treat until progression, unacceptable toxicity, or withdrawal

*Bruix J, et al. Lancet. 2017;389:56-66*

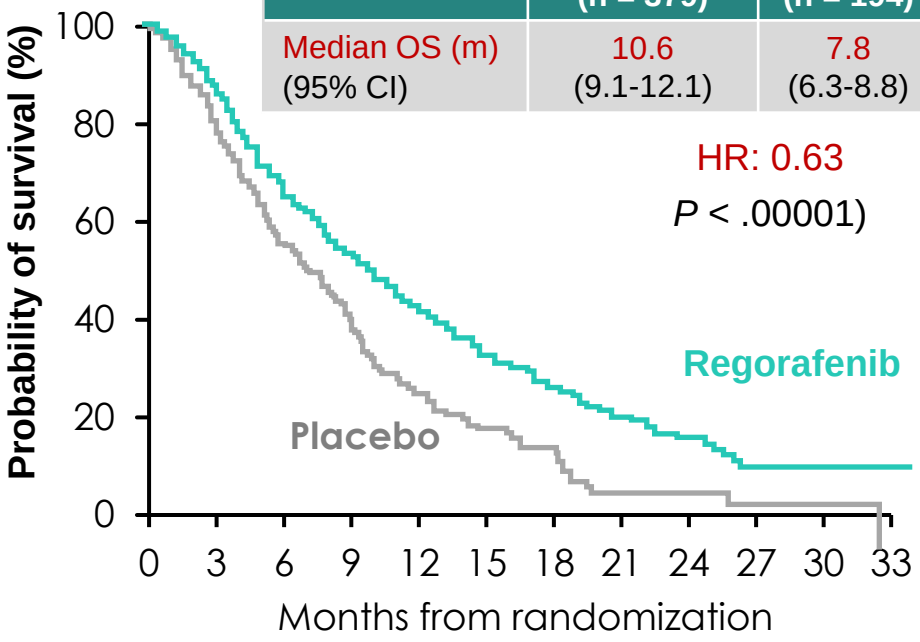
# Phase III RESORCE study
## Key inclusion criteria

- BCLC stage B or C patients who could not benefit from resection, local ablation, or chemoembolization
- **Documented radiological progression during sorafenib**
- **Tolerability of prior sorafenib**, defined as receiving sorafenib **≥400 mg daily for at least 20 of the last 28 days** of treatment
- ECOG PS 0/1
- Child-Pugh A liver function
- Randomization within 10 weeks after the last sorafenib dose

*Bruix J, et al. Lancet. 2017;389:56-66*

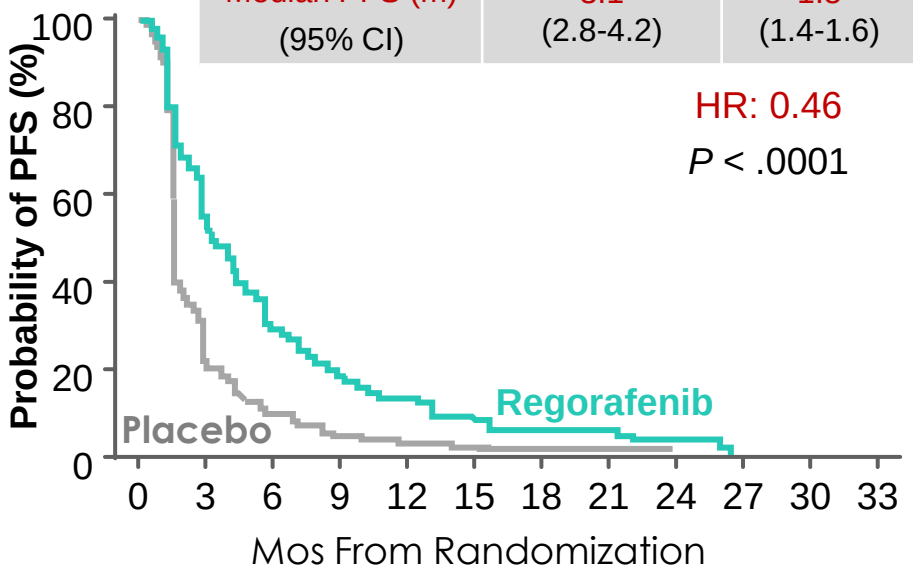
# Regorafenib Significantly Improves Survival

| | Regorafenib (n = 379) | Placebo (n = 194) |
|---|---|---|
| Median OS (m) (95% CI) | 10.6 (9.1-12.1) | 7.8 (6.3-8.8) |




**Primary endpoint: Overall survival**

| | Regorafenib (n = 379) | Placebo (n = 194) |
|---|---|---|
| Median PFS (m) (95% CI) | 3.1 (2.8-4.2) | 1.5 (1.4-1.6) |




**Secondary endpoint: progression-free survival**

*Bruix J, et al. Lancet. 2017 Jan 7;389(10064):56-66*

# 65% Disease Control under Regorafenib Treatment

| Response, % | Regorafenib (n = 379) | Placebo (n = 194) | *P* |
|---|---|---|---|
| **Complete response** | 0 | 0 | |
| **Partial response** | 6.6 | 2.6 | |
| **Stable disease** | 58.8 | 32.0 | |
| **Response rate** | 6.6 | 2.6 | 0.02 |
| **Disease control rate** | 65.7 | 34.5 | < 0.001 |

By RECIST 1.1

*Bruix J, et al. Lancet. 2017;389:56-66*

# Phase III RESORCE study
## Treatment-Emergent AEs in ≥ 5%

| AEs, % | Regorafenib (n = 379) | | | Placebo (n = 194) | | |
|---|---|---|---|---|---|---|
| | Any | Gr 3 | Gr 4 | Any | Gr 3 | Gr 4 |
| **All TEAE** | 100 | 56 | 11 | 93 | 32 | 7 |
| **Drug-Related TEAE** | 93 | 46 | 4 | 52 | 16 | 1 |
| **Hand-foot skin reaction** | **52** | 13 | N/A | 7 | 1 | N/A |
| **Diarrhea** | **33** | 2 | 0 | 9 | 0 | 0 |
| **Fatigue** | **29** | 6 | N/A | 19 | 2 | N/A |
| **Hypertension** | **23** | 13 | < 1 | 5 | 3 | 0 |
| **Bilirubin increased** | 19 | 6 | < 1 | 4 | 2 | 0 |
| AST increased | 13 | 4 | 1 | 8 | 5 | 1 |
| Ascites | 2 | 1 | 0 | 1 | 1 | 0 |
| Anemia | 6 | 1 | < 1 | 1 | 1 | 0 |
| Hypophosphatemia | 6 | 4 | 1 | 1 | 1 | 0 |
| Lipase increased | 5 | 4 | < 1 | 2 | 1 | 0 |

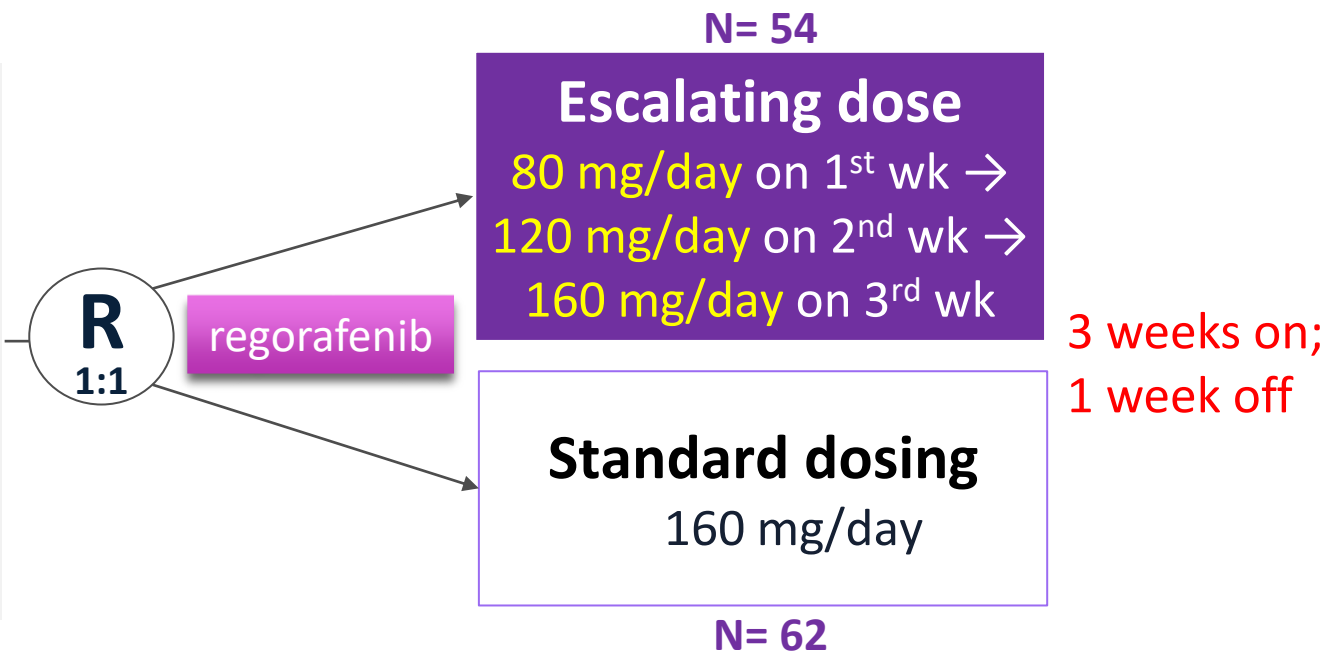
# Adverse Events Management

- Well education
- Prepare symptom-relief medications (urea cream, steroid cream, antibiotic ointment, loperamide…) in advance
- Hold and reduce medications if needed
- Regular physician visits (weekly or biweekly) at the start
- Monitor liver function and blood pressure biweekly to monthly

# ReDOS
## A phase II Study for Regorafenib Dosing

**N= 116**

- Histologically confirmed mCRC
- ECOG ≤1
- Failure of all standard regimens, including appropriate biologics




Primary endpoint: The number of patients finishing cycle 2 at 8 weeks

*Bekaii-Saab TS, et al. J ClinOncol.2018;36(suppl4S): Abstract 611*

# ReDOS
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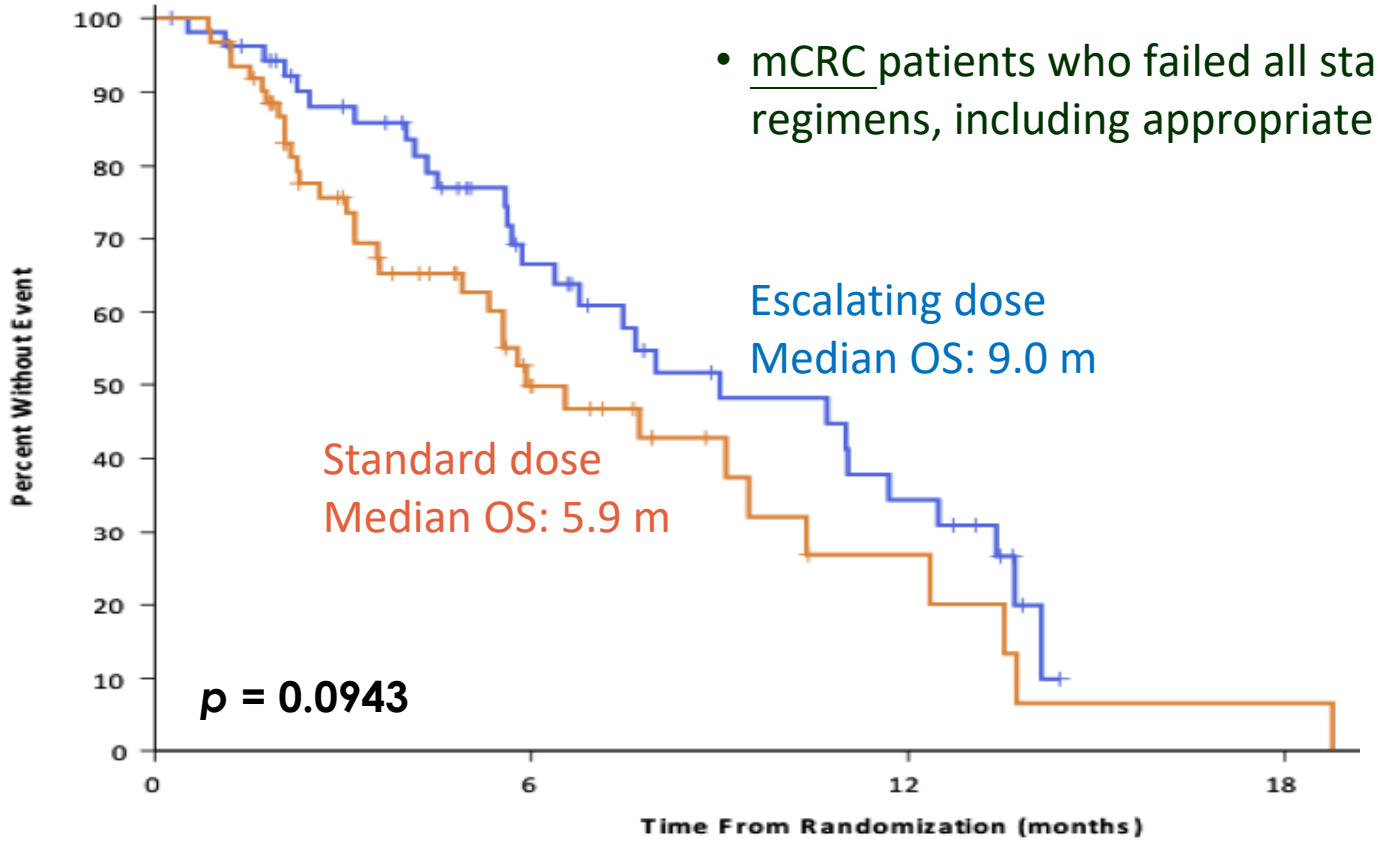
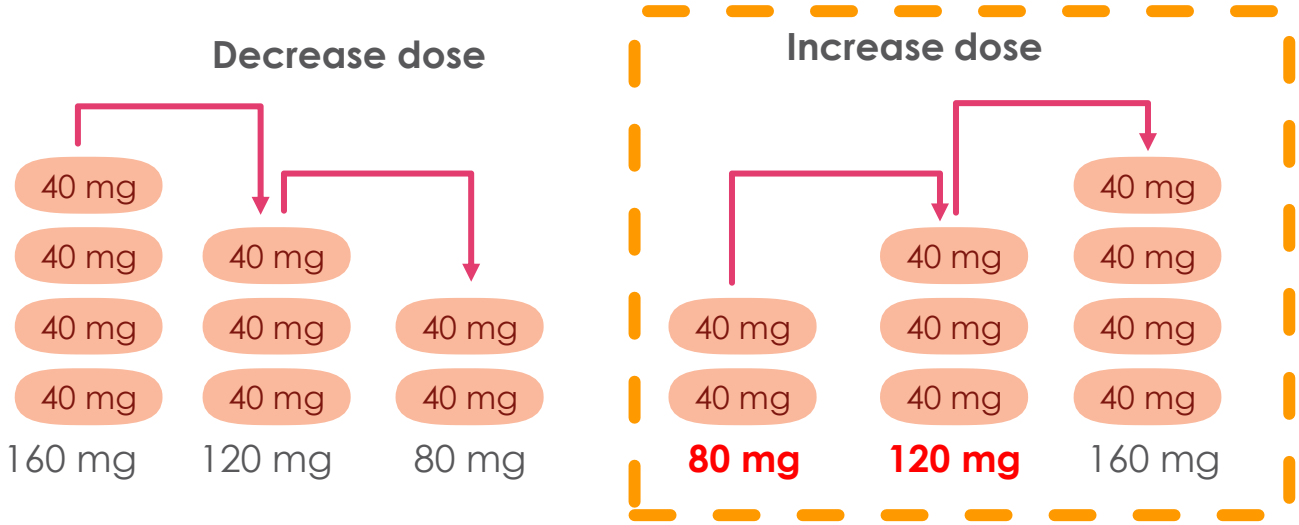



- mCRC patients who failed all standard regimens, including appropriate biologics

*Bekaii-Saab TS, et al. J ClinOncol.2018;36(suppl4S): Abstract 611*

# Stivarga® in Asian Real World


- 3 weeks on, 1 week off
- Standard dose: 160 mg/day
- May start with 120mg or 80mg/day for better tolerance




**Clinical trial** **Real world**

# REFINE:
# An Observational Study

- Patients with unresectable HCC
- Physician's decision to treat with regorafenib
- Global enrollment, N = 1019
- Interim analysis, n= 500

*Lim et al. ASCO 2020*

# Demographics

| N (%) | Regorafenib (N=498) |
|---|---|
| Sex, male, | 419 (84) |
| Age, years | |
| Median (range) | 66 (21–90) |
| Race | |
| Asian | 300 (60) |
| White | 137 (28) |
| Black | 16 (3) |
| Region | |
| Asia | 297 (60) |
| Non-Asia | 201 (40) |
| ECOG PS | |
| 0 | 207 (42) |
| 1 | 201 (40) |
| 2–4 | 26 (5) |
| Child-Pugh class | |
| A | 332 (67) |
| B | 57 (11) |
| C | 4(1) |

| N (%) | Regorafenib (N=498) |
|---|---|
| BCLC stage | |
| 0 (very early) | 1(<1) |
| A (early) | 5 (1) |
| B (intermediate) | 80 (16) |
| C (advanced) | 339 (68) |
| D (end) | 12 (2) |
| Etiology of HCC | |
| Hepatitis B | 186 (37) |
| Alcohol use | 130 (26) |
| Hepatitis C | 113 (23) |
| NASH | 34 (7) |
| Genetic/metabolic | 6 (1) |
| Other | 14 (3) |
| Vascular invasion | |
| Present | 162 (33) |
| Absent | 332 (67) |

*Lim et al. ASCO 2020*

# Treatment Course

| N (%) | Regorafenib (N=498) |
|---|---|
| **Duration of treatment, months*** | |
| **Median (range)** | 3.7 (<1–**19.0**) |
| **Initial daily dose** | |
| **160 mg** | 286 (57) |
| **120 mg** | 63 (13) |
| **80 mg** | 141 (28) |
| **40 mg** | 8 (2) |
| **Any treatment modification** | 267 (54) |
| **Dose reduction** | 203 (41) |
| **Dose escalation** | 95 (19) |
| **Dose interruption** | 138 (28) |
| **Dose restart** | 68 (14) |
| **Treatment modification within the first 4 weeks** | 179 (36) |

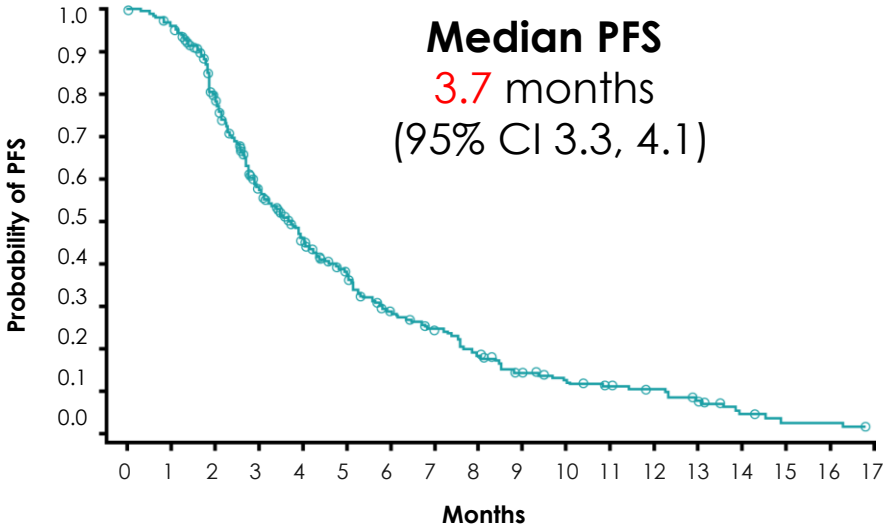
*Lim et al. ASCO 2020*

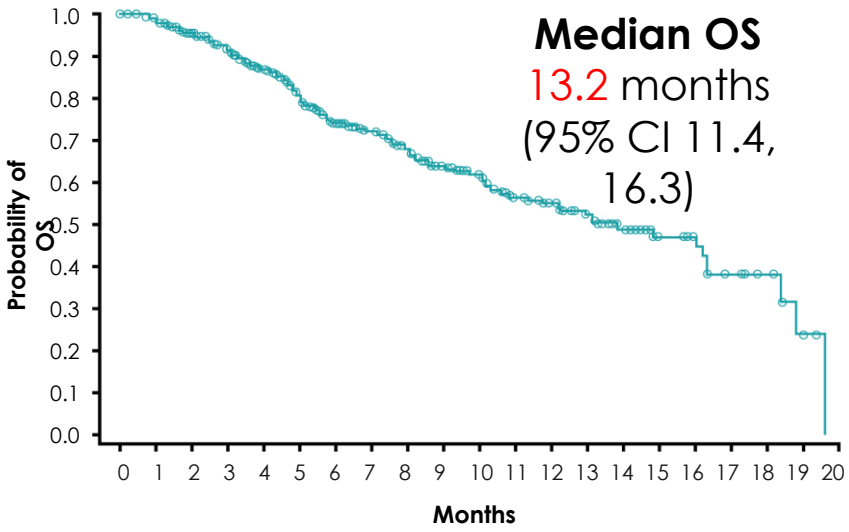
# Adverse Events of Regorafenib Usually Occurred Early

| N (%) | Onset of adverse reactions | | |
|---|---|---|---|
| | ≤56 days | ≤84 days | Any time |
| **Any** | 372 (75) | 399 (80) | 419(84) |
| **Grade 3** | 97 (19) | 121 (24) | 146 (29) |
| **Grade 4** | 7 (1) | 9 (2) | 14 (3) |
| **Grade 5** | 26 (5) | 29 (6) | 55 (11) |
| **Leading to dose reduction** | 111 (22) | 121 (24) | 134 (27) |
| **Leading to dose interruption** | 94 (19) | 105 (21) | 124 (25) |
| **Leading to permanent discontinuation** | 73 (15) | 87 (17) | 123 (25) |

*Lim et al. ASCO 2020*

# Survival Outcomes



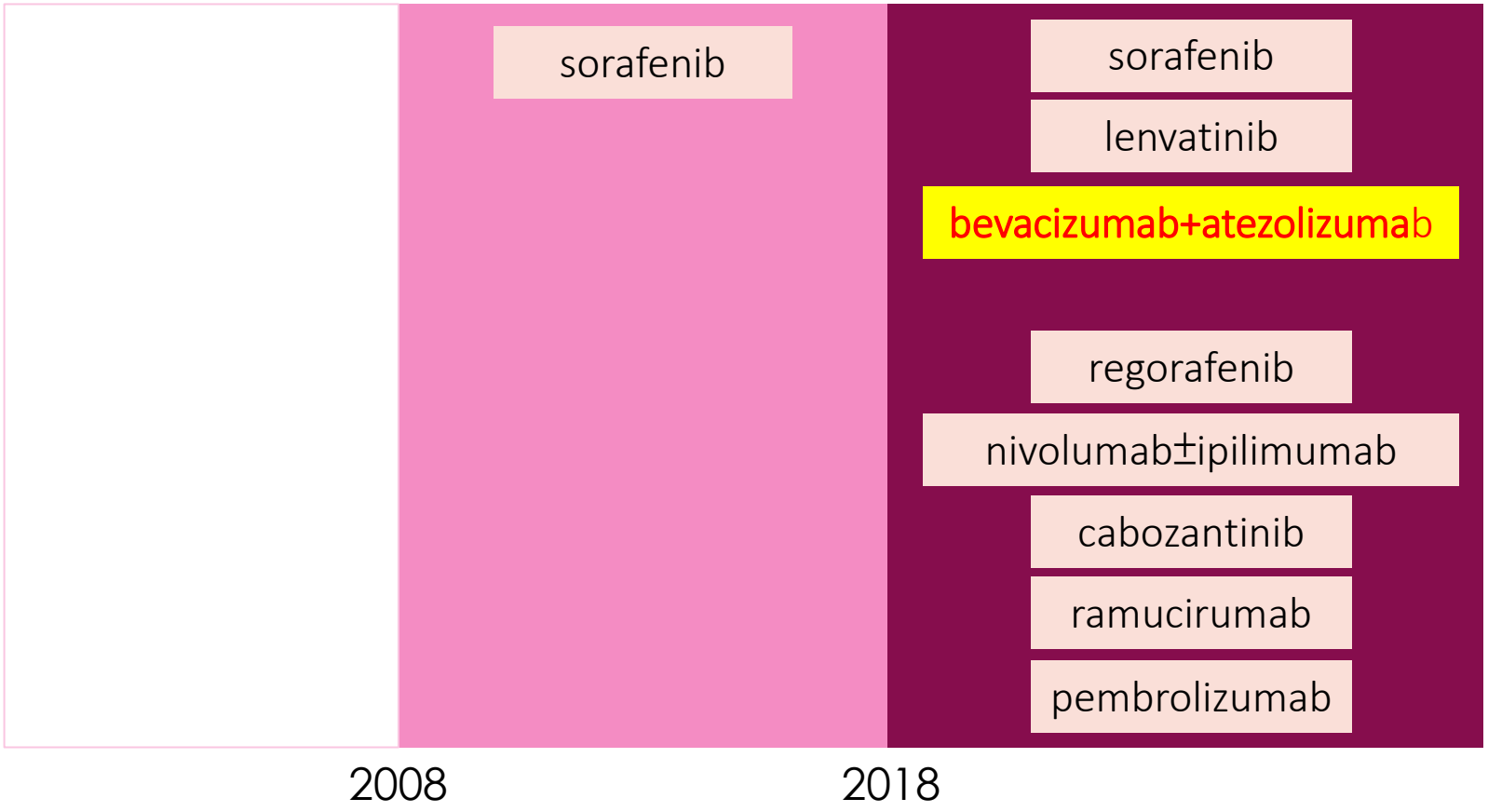

| | Median PFS | Median OS |
|---|---|---|
| RESORCE | 3.2 | 10.6 |
| RESORCE Asia subgroup | 2.8 | 9.1 |

*Lim et al. ASCO 2020*

# Sequential Therapy for Advanced HCC

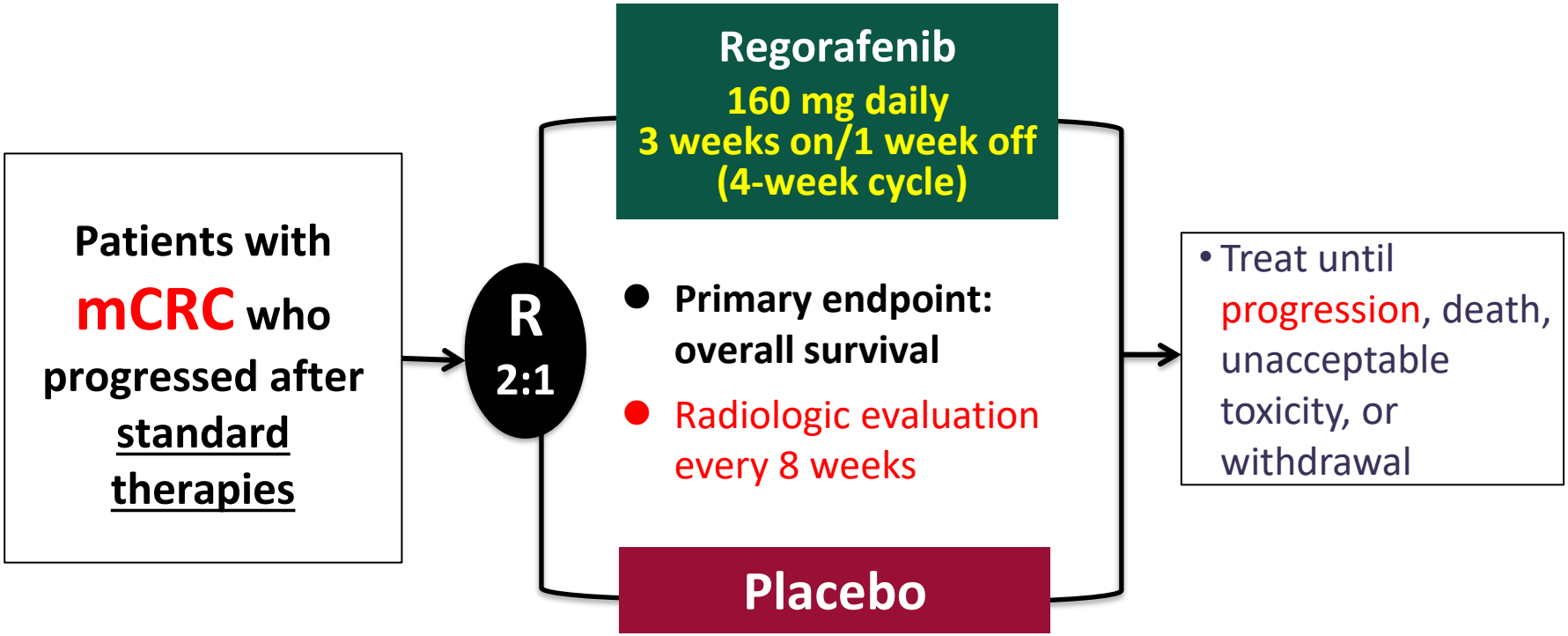
- Start systemic therapy as early as possible
- Availability of sequential therapy
- Regorafenib as salvage therapy
- Potential of kinase inhibitor efficacy after VEGF antibody

# Treatment of Advanced HCC: Since 2018



# Regorafenib for mCRC

## CORRECT




- Secondary endpoints: progression-free survival (PFS), objective response rate (ORR), disease control rates (DCR), and safety
- Tertiary endpoints: duration of response/stable disease, quality of life, pharmacokinetics, biomarkers

*Grothey et al. Lancet 2013*

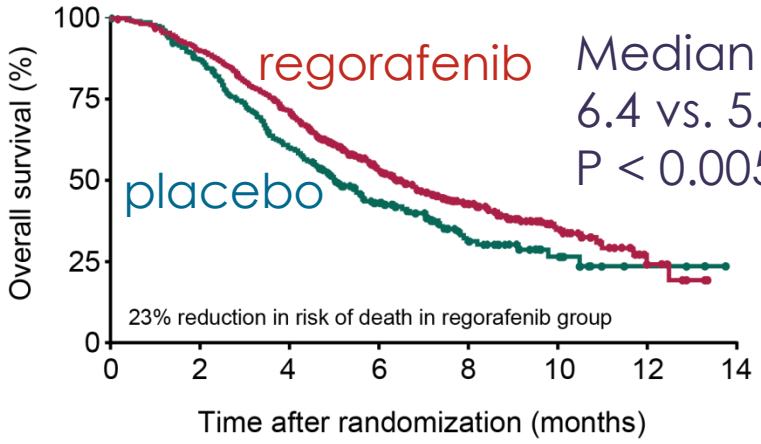
# Regorafenib for mCRC

## CORRECT– Study overview

| | CORRECT |
|---|---|
| No. of patients randomized | 760 |
| Enrollment | 16 countries in Europe, North-America, Asia-Pacific region (~15%), and others |
| Prior targeted therapy: bevacizumab; cetuximab/panitumumab (KRAS wild-type) | Required, 100% |
| Stratification factors for randomization | Previous VEGF-targeting drugs; time from mCRC diagnosis; geographic region |
| ECOG PS | **0-1** |
| Prior lines of mCRC therapy, % | ≥ 3 lines: ~75% |

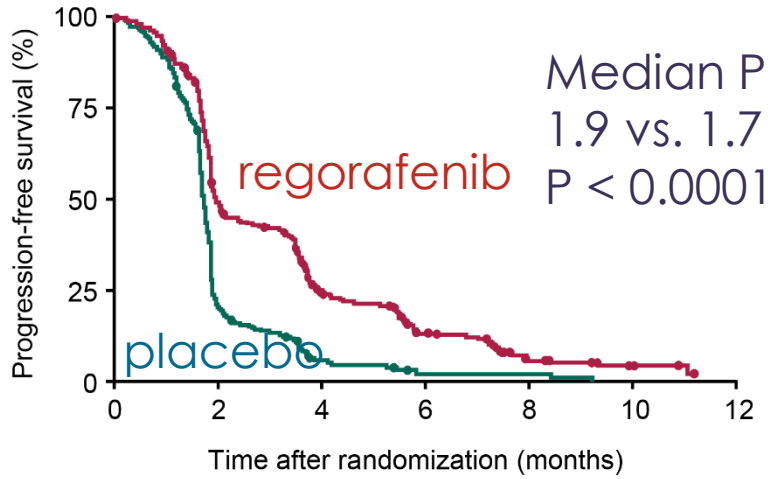
*Grothey et al. Lancet 2013*

# Regorafenib for mCRC
## CORRECT Study




Median OS
6.4 vs. 5.0 months
P < 0.0052

**HR 0.77**




Median PFS
1.9 vs. 1.7 months
P < 0.0001

**HR 0.49**

*Grothey et al. Lancet 2013*

# Conclusion

- Treatment of advanced HCC has evolved from only one line of treatment to sequential therapy
- Sequential therapy is a reality
- Delaying the start of systemic therapy may deprive the patients of sequential therapy possibility
- Under NHI reimbursement, sorafenib-regorafenib sequence is a reasonable choice