2017 NCSCG Post-AASLD Symposium

HEPATOCELLULAR CARCINOMA

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HCC Topics for Review

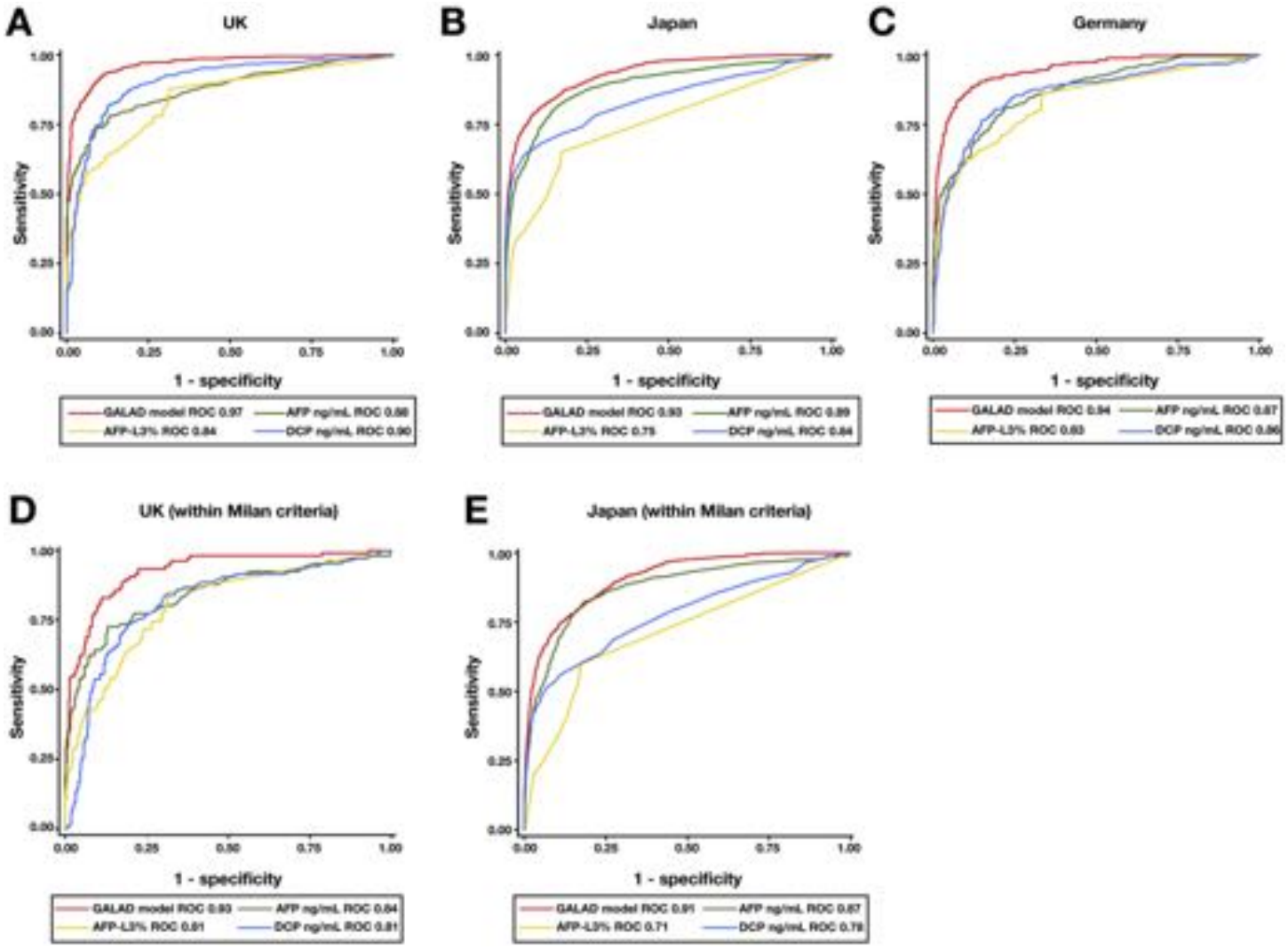
- Biomarkers
  - HCC detection and prognosis
- DAA (HCV) and HCC
  - *De novo* HCC
  - Recurrent HCC post-curative treatment
  - HCC waitlist outcome
- Systemic therapy for advanced HCC
  - What is new beyond sorafenib?

Bio-markers and HCC Detection

- Limitations of HCC screening using alpha-fetoprotein and abdominal ultrasound
- GALAD: Gender, Age, alpha-fetoprotein L3, Alpha-fetoprotein, Des-ɣ-carboxy-prothrombin (DCP) = new serum-based biomarker model found to be superior to individual biomarkers
- Validated to discriminate patients with HCC from patients with chronic liver disease with high AUROC > 0.9 regardless of etiology

Berhane S. et al. Clin Gastroenterol Hepatol 2016;14:875-886

GALAD and HCC Detection



Berhane S. et al. Clin Gastroenterol Hepatol 2016;14:875-886

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Abstract #211 (Oral presentation)

Proposal of GALADUS Score:
Combining Liver Ultrasound with Serum Based Biomarkers for Hepatocellular Carcinoma Surveillance

- Retrospective cohort study
- 111 patients with HCC, 180 controls
- Performance of ultrasound but not GALAD score affected by severity of ascites and CTP score
- 10 patients had false negative ultrasound (9/10 had positive GALAD)
- 37 patients had false positive ultrasound (29/37 had negative GALAD)

Addissie BD et al. AASLD 2017

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Abstract #211 (Oral presentation)

- GALAD performed better than ultrasound in predicting the presence of HCC

Tumor stage	AUC (95% CI)		
	GALAD	Ultrasound	p
Early Stage	0.92 (0.88, 0.96)	0.82 (0.76, 0.87)	<0.01
Non-early Stage	0.99 (0.97, 1.00)	0.80 (0.74, 0.85)	<0.01

Addissie BD et al. AASLD 2017

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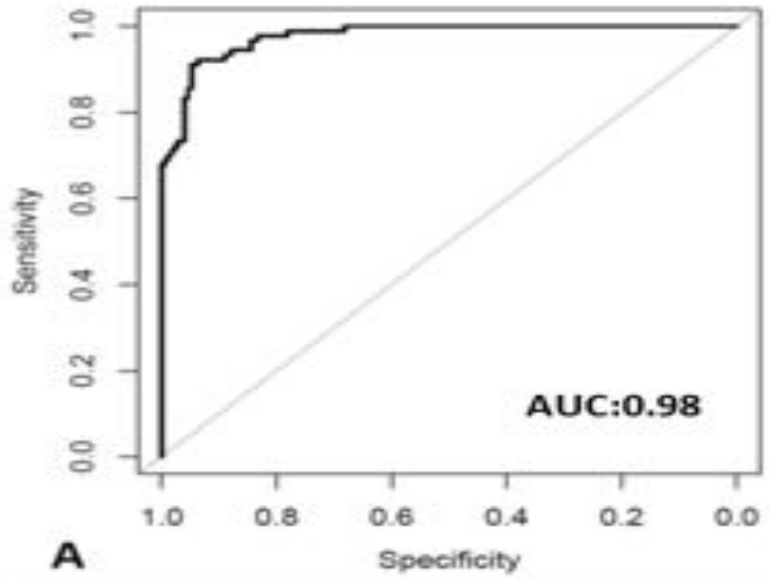
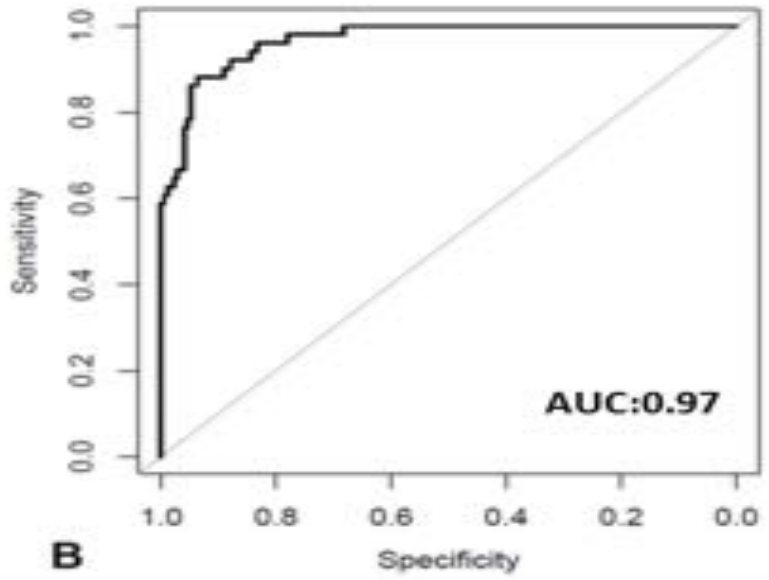
Abstract #211 (Oral presentation)

- GALAD is complementary to ultrasound in detecting HCC
- GALAD-US performed better than ultrasound or GALAD alone

GALAD-US
All patients with HCC



GALAD-US
Early stage HCC



Addissie BD et al. AASLD 2017

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Abstract #1409 (Poster)

- Prospective VA cohort study of a 6-month surveillance program with liver imaging, AFP with collection blood samples retrospectively bio-assayed for AFP, AFP-L3 and DCP
- 26 HCC cases and 543 controls for analysis

	HCC within 12 months	
	Sensitivity	False Positive Rate
AFP > 20 ng/mL	31%	5%
AFP-L3% > 10%	42%	5%
DCP > 2 ng/mL	42%	11%
Either AFP > 20 ng/mL, AFP-L3% > 10%, or DCP > 2 ng/mL	69%	19%
GALAD > -0.63	85%	27%

El-Serag HB et al. AASLD 2017

Biomarkers for HCC Screening

Summary

- GALAD and GALAD-US are promising tools to improve HCC detection
- Potential bias in retrospectively evaluating performance of these tests in patients diagnosed with HCC by CT or MRI – overestimation of test performance
- Prospective studies applying these tests to patients at risk for HCC are needed
- Define optimum cutoff value in GALAD

Biomarkers and Liver Transplant

- Alpha-fetoprotein (AFP) predicts prognosis after liver transplant [1,2]
- High AFP is associated with worse outcome after liver transplant, especially if > 1000[1,2]
- At UCSF, patients with alpha-fetoprotein AFP > 1000 ng/mL are required to show decrease in AFP to < 500 with local regional therapy prior to liver transplant (Milan or down-staging protocol)[1]

1. *Hameed B et al. Liver Transpl 2014;20:945-951*
2. *Duvoux C et al. Gastroenterology 2012;143:986-94*

Biomarkers and Liver Transplant

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1. *Hameed B. et al. Liver Transpl 2014;20:945-951*
2. *Duvoux C et al. Gastroenterology 2012;143:986-94*

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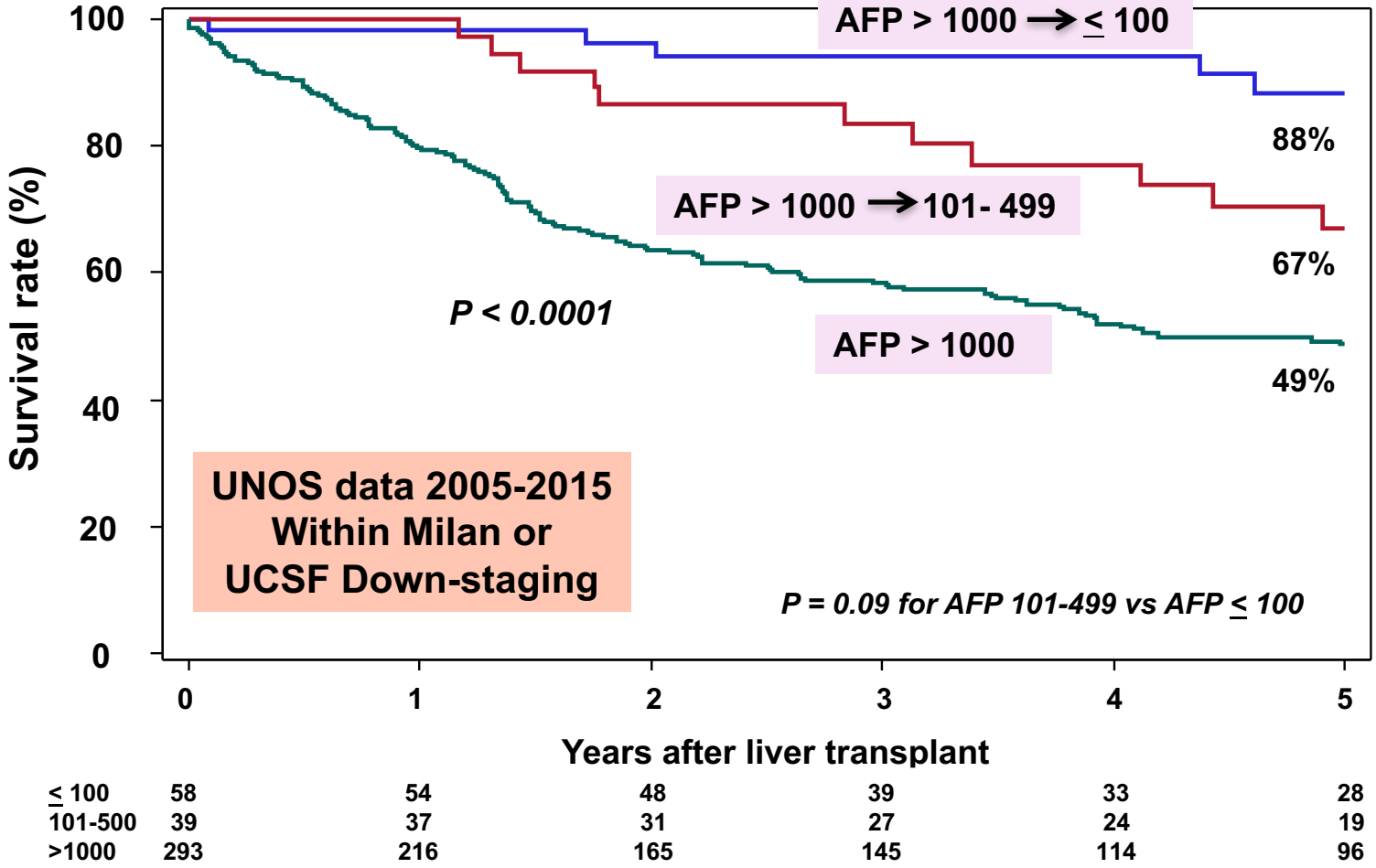
Abstract #139 (Plenary)



≤ 100	58	54	48	39	33	28
101-500	39	37	31	27	24	19
>1000	293	216	165	145	114	96

UCSF Transplant

Yao FY et al. AASLD 2017

DAA and risk of HCC

- Does DAA increase the risk of *de novo* HCC development in patients with cirrhosis?
- Does DAA increase the risk of HCC recurrence after complete response to HCC treatment (resection/ ablation or local regional therapy)?
- Does DAA increase the risk of HCC progression or waitlist dropout before liver transplant?

DAA and de novo HCC

- Three small studies showed *de novo* HCC occurrence rates of 7-9% within 12 months of DAA cessation[1,2,3]

- Potential mechanism?
  - Immunological or molecular changes in the liver microenvironment induced by rapid suppression of HCV replication might boost growth and spread of microscopic HCC foci

1. Cardoso H et al. J Hepatol 2016;65:1070-1071
2. Kozbial K et al. J Hepatol 2016;65:856-858
3. Ravi S et al. Gastroenterology 2017;152:911-912

DAA and *de novo* HCC

- Results from large DAA treatment cohorts have dispelled the notion that DAA promotes *de novo* HCC development

Author	Receiving DAA (n)	Fibrosis/ Cirrhosis (%)	Incidence of *de novo* HCC
Calleja	3,233	18% F3 Fibrosis 52% cirrhosis	0.9% within 18 months of DAA initiation
Cheung	406	73% Child's B 10% Child's C	4% within 6 months of DAA start (same incidence in 261 patients not receiving DAA over 6 month period) 2.5% in months 6-15 from DAA start
Romano	3,075	28% F3 Fibrosis 65% Child's A 7% Child's B	F3 Fibrosis: 0.2 per 100 patient-years Child's A: 1.6 per 100 patient-years Child's B: 2.9 per 100 patients-years
Kanwal	22,500	39% cirrhosis	SVR: 0.90 per 100 patient-years No SVR: 3.45 per 100 patient-years

Calleja JL et al. J Hepatol 2017;66:1138-1148
Cheung MC et al. J Hepatol 2016;65:741-747
Romano A et al. Hepatology 2016;64(Suppl):10A [Abstract]
Kanwal F et al. Gastroenterology 2017;153:996-1005

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Abstract #142 (Plenary)

Eradication of HCV Induced by Direct-Acting Antivirals is Associated with a 79% Reduction in HCC Risk

National VA Healthcare System (167 centers)
Started antiviral therapy 1999-2015
N=62,354

IFN-only	DAA+IFN	DAA-only
N=35,871	N=4535	N=21,948
58%	7%	35%

Range of follow-up = 2-18 years
Mean follow-up = 6.1 years
Incident HCCs = 3271

Ioannou GN et al. AASLD 2017

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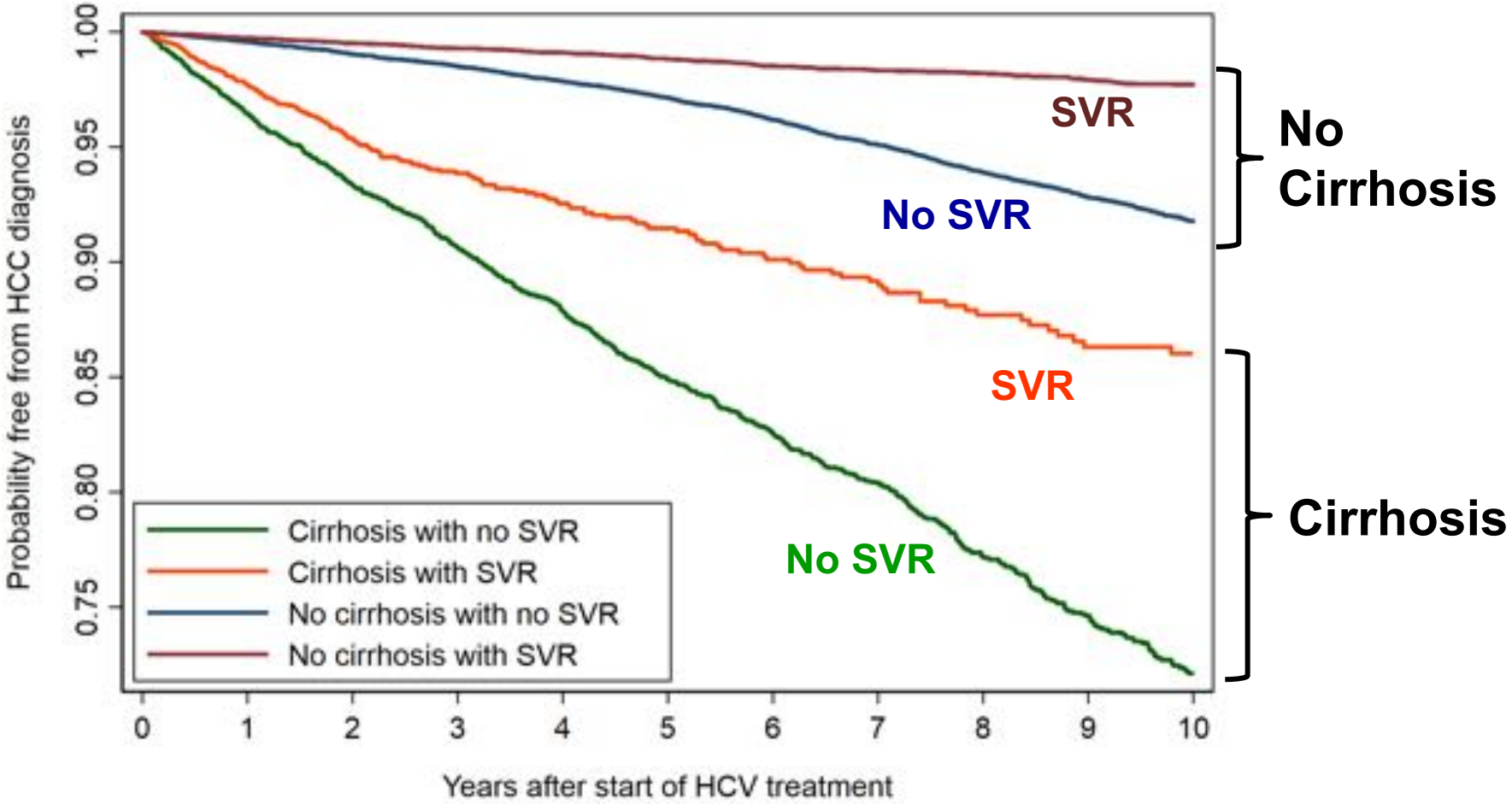
Abstract #142 (Plenary)

- Patients with SVR had lower HCC incidence irrespective of regimen



Ioannou GN et al. AASLD 2017

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Abstract #142 (Plenary)

- DAA-induced SVR is associated with a 71% reduction in HCC risk

	SVR	Patients	HCC	HCC per 100 patient-years	Crude Hazard Ratio	Adjusted* Hazard Ratio	Risk Reduction %
IFN only	No	23,883	2348	1.07	1	1	
	Yes	11,988	303	0.28	0.25	0.32	68%
DAA+IFN	No	1772	116	1.73	1	1	
	Yes	2763	59	0.6	0.34	0.48	52%
DAA only	No	2039	165	5.2	1	1	
	Yes	19,909	280	0.92	0.18	0.29	71%

***Adjusted for 22 confounders:** cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index , HCV genotype, HCV viral load, HIV co-infection, HBV co-infection, type 2 diabetes mellitus, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, serum AST/ALT ratio, INR and hemoglobin.

Ioannou GN et al. AASLD 2017

DAA and risk of HCC

- Does DAA increase the risk of *de novo* HCC development in patients with cirrhosis?

  No, but patients with cirrhosis who achieve SVR after DAA remain at risk for HCC, and require continued HCC surveillance

- Does DAA increase the risk of HCC recurrence after complete response to HCC treatment (resection/ ablation or local regional therapy)?
- Does DAA increase the risk of HCC progression or waitlist dropout before liver transplant?

DAA and risk of HCC

- Does DAA increase the risk of *de novo* HCC development in patients with cirrhosis?

  No

- Does DAA increase the risk of HCC recurrence after complete response to HCC treatment (resection/ ablation or local regional therapy)?
- Does DAA increase the risk of HCC progression or waitlist dropout before liver transplant?

DAA and risk of HCC recurrence

- Two recent studies using historical controls have suggested a higher than expected risk for HCC recurrence after resection/ ablation[1,2]

Author	N	DAA Timing	Severity of Cirrhosis/ HCC stage	HCC Therapy	HCC Recurrence
Conti (Italy)	59	Median 1 year post-HCC treatment	Child's A/B 56/59 < Milan	Resection, RFA, TACE, PEI and combination	29% 24 weeks post-DAA therapy
Reig (Spain)	58	Median 11 months post-HCC treatment	Child's A/B All < Milan	Resection (35%) RFA (55%) TACE (10%)	28% Median 3.5 months after DAA therapy

Modified from *Mehta N and Yao F. Liver Transpl 2017;23:1596-1600*

1. Conti, F et al. J Hepatol 2016;65:727-733
2. Reig M et al. J Hepatol 2016;65:719-726

DAA and risk of HCC recurrence

- Other studies did not show substantially different rates of HCC recurrence than expected

Author	N	N (%) Receiving DAA	HCC Recurrence Rate
Cabibbo	143	143 (100%)	20% overall; 12% within 6 months of DAA initiation 27% within 12 months of DAA initiation
Calleja	70	70 (100%)	13% within 6 months of DAA initiation 30% within 12 months of DAA initiation
Minami	926	27 (3%)	21% within 1 year of DAA initiation (vs 31% in HCV-untreated patients)

Modified from *Mehta N and Yao F. Liver Transpl 2017;23:1596-1600*

Cabibbo G et al. Aliment Pharmacol Ther 2017;46:688-695
Calleja JL et al. J Hepatol 2017;66:1138-1148
Minami T el al. J Hepatol 2016;65:1272-1273

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Abstract #1361 (Poster)

- Retrospective multicenter study (10 US health systems) of patients with HCV-related HCC who achieved complete response to HCC therapy (resection, ablation, locoregional therapy, or multimodal therapy)
- Median follow-up 21 months

	DAA-treated (n=207)	DAA-naïve (n=127)	p-value
HCC Recurrence	**46%**	**50%**	**0.42**
Median time to HCC recurrence	**13.4 months**	**8 months**	**<0.001**

Singal A et al. AASLD 2017

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Abstract #1421 (Poster)

- Retrospective study from Japan of 163 patients treated with DAAs (92% SVR) after HCC diagnosis and treatment (90% radiofrequency ablation)
- Cumulative HCC recurrence rates at 1 and 2 years were 38% and 55% (median follow-up 14.5 months).

Risk factors for Recurrence	Hazard Ratio	p-value
AFP-L3 > 15% before DAA	3.08	0.0004
DCP > 40	2.0	0.057
> 3 HCC treatments	2.25	0.005
Interval between last HCC treatment and DAA > 2 years	0.34	0.009

Minami T et al. AASLD 2017

DAA and risk of HCC

- Does DAA increase the risk of *de novo* HCC development in patients with cirrhosis?

  No

- Does DAA increase the risk of HCC recurrence after complete response to HCC treatment (resection/ ablation or local regional therapy)?

  Probably not

- Does DAA increase the risk of HCC progression or waitlist dropout before liver transplant?

DAA and risk of HCC

- Does DAA increase the risk of *de novo* HCC development in patients with cirrhosis?

  No

- Does DAA increase the risk of HCC recurrence after complete response to HCC treatment (resection/ ablation or local regional therapy)?

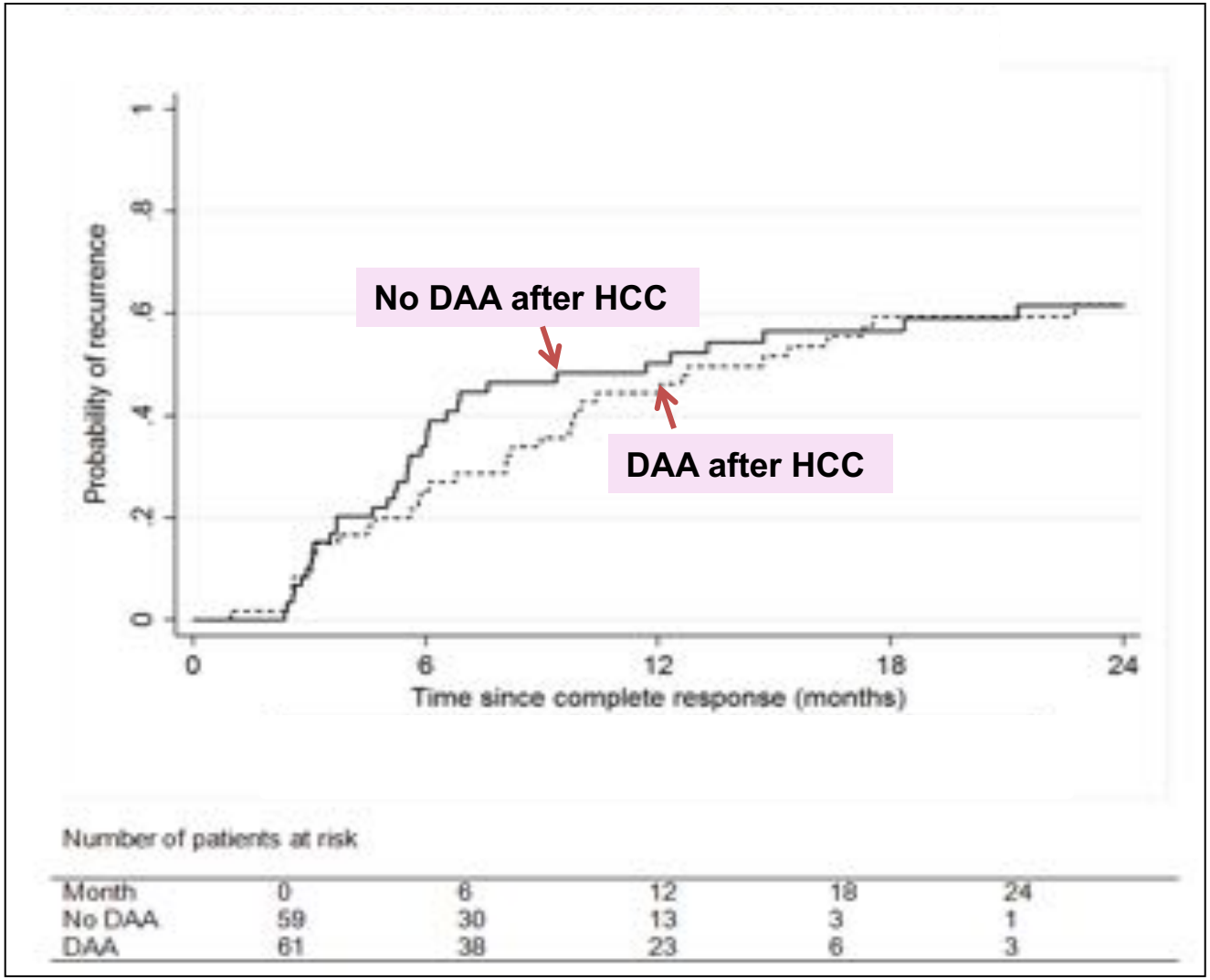
  Probably not

- Does DAA increase the risk of HCC progression or waitlist dropout before liver transplant?

DAA and Waitlist Outcome for HCC

	Pre-transplant DAA and HCC Waitlist outcome			
Study	**N**	**Control**	**SVR%**	**DAA associated with waitlist dropout**
Alberta	13	70	100%	No
Mayo Clinic	18	63	50%	No
Padua	23	23	100%	No
UCSF	62	87	75%	**Decreased**

Cumulative Incidence of HCC Recurrence After Complete Response



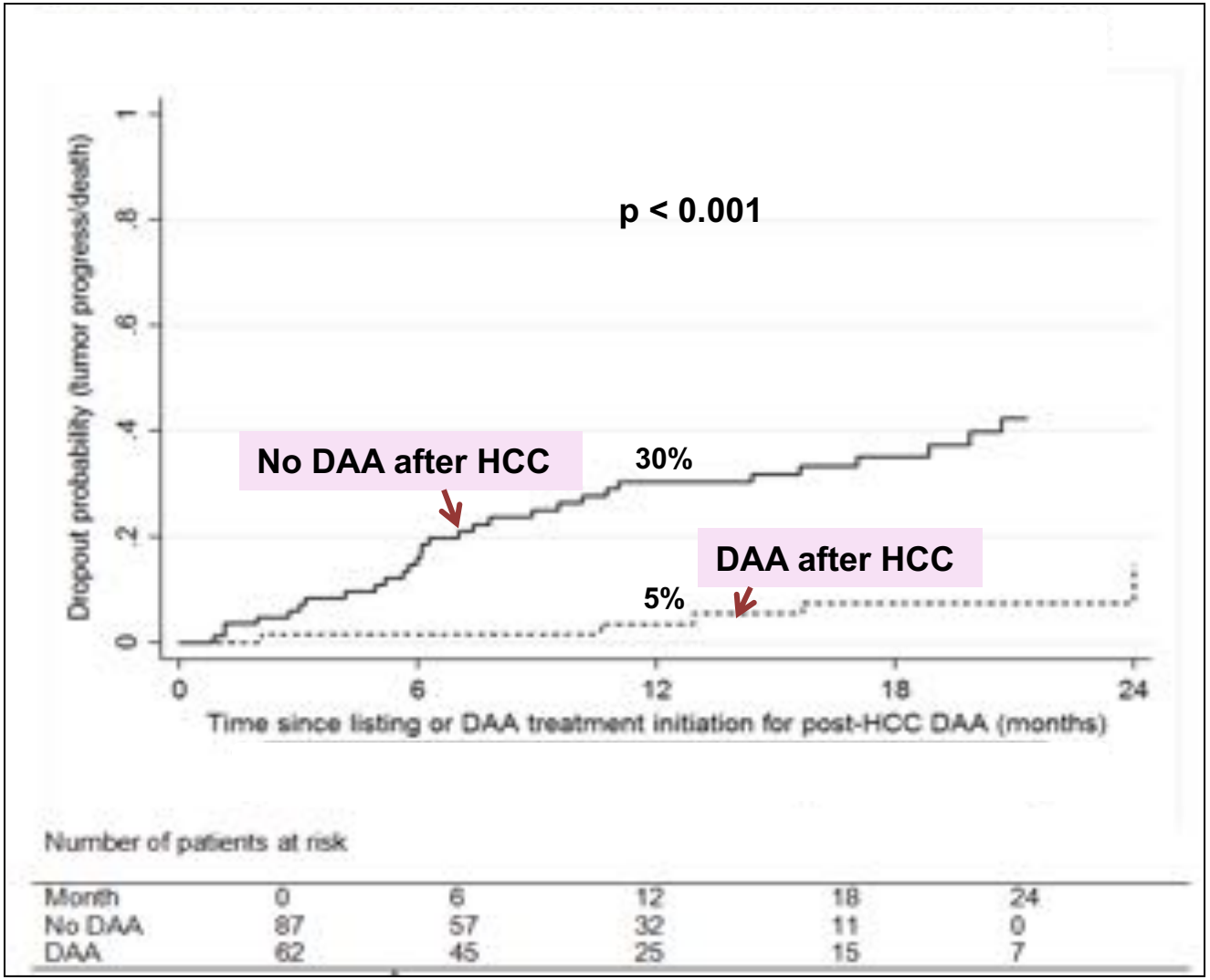
Number of patients at risk

Month	0	6	12	18	24
No DAA	59	30	13	3	1
DAA	61	38	23	6	3

Huang A et al. EASL 2017

UCSF Transplant

Cumulative Incidence of Waitlist Dropout (HCC Progression/Death)



Number of patients at risk

Month	0	6	12	18	24
No DAA	87	57	32	11	0
DAA	62	45	25	15	7

Huang A et al. EASL 2017

UCSF Transplant

DAA and risk of HCC

- Does DAA increase the risk of *de novo* HCC development in patients with cirrhosis?

  No

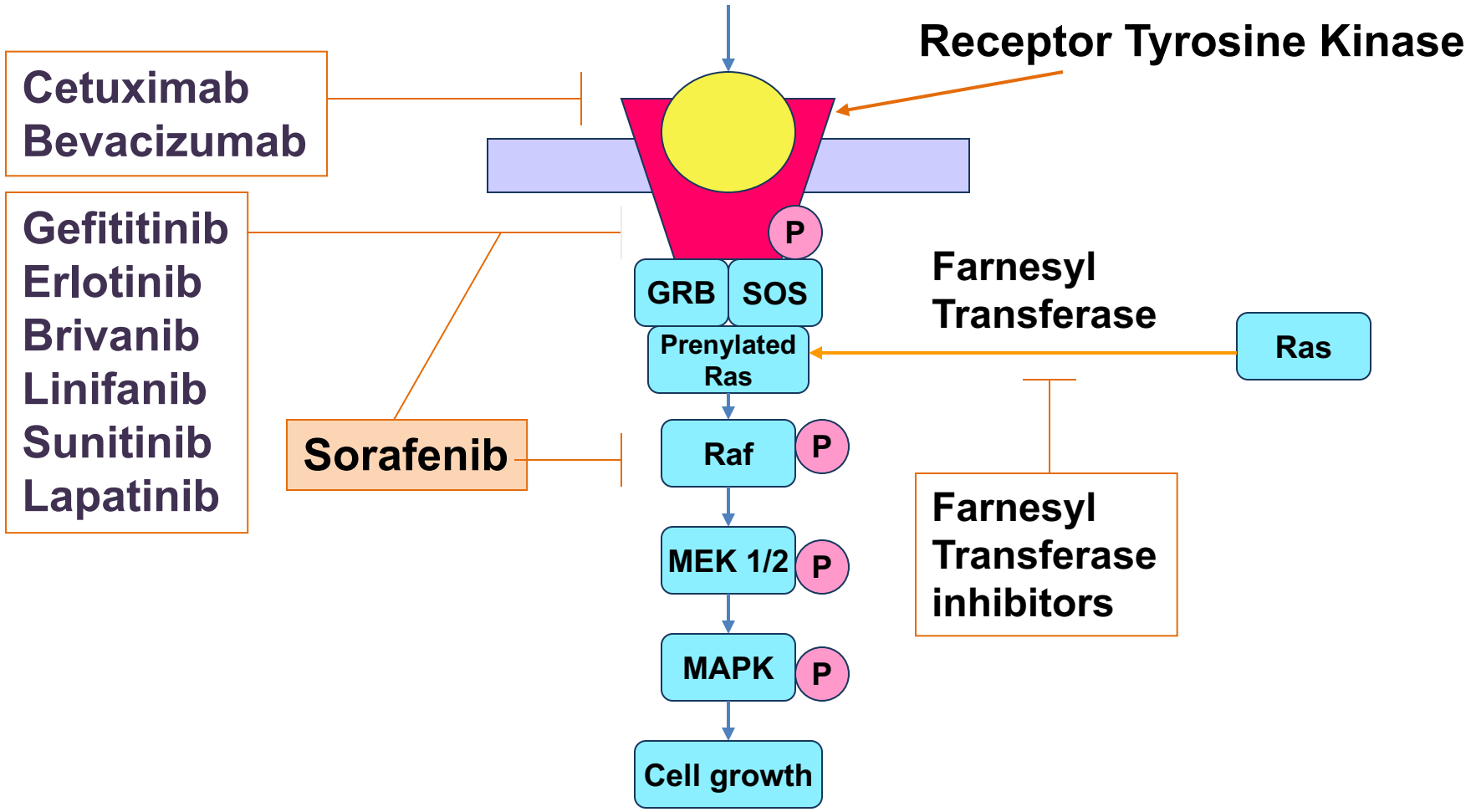
- Does DAA increase the risk of HCC recurrence after complete response to HCC treatment (resection/ ablation or local regional therapy)?

  Probably not

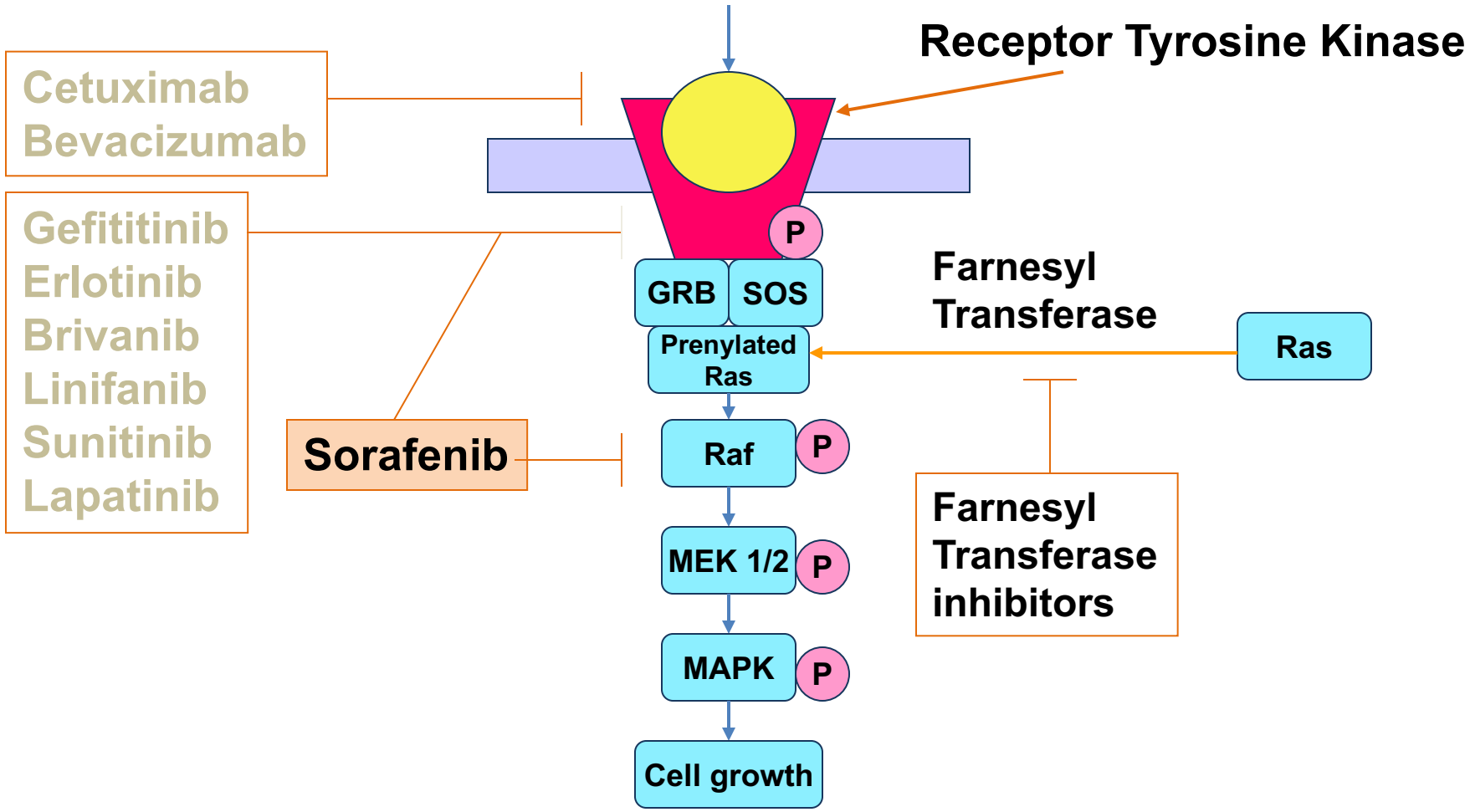
- Does DAA increase the risk of HCC progression or waitlist dropout before liver transplant?

  No

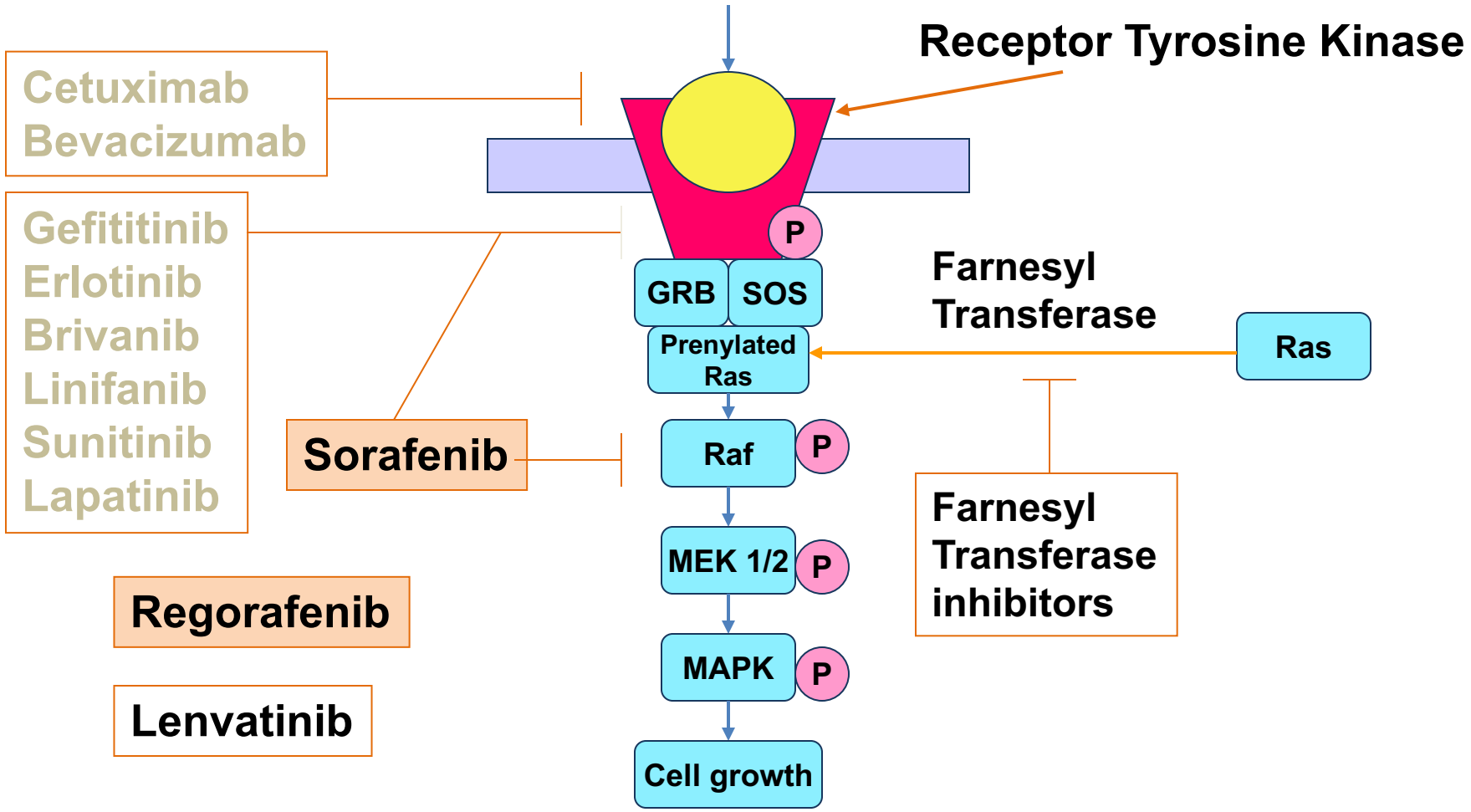
Targeted Therapy for HCC



Targeted Therapy for HCC



Targeted Therapy for HCC



Targeted Therapy for HCC
Sorafenib

- The Sorafenib HCC Assessment Randomized Controlled Protocol (**SHARP**) trial and Asia Pacific study established sorafenib as the standard therapy for advanced unresectable HCC[1,2]
- In the SHARP trial[1], 602 patients with advanced HCC (1/2 with vascular invasion or metastases) randomized to oral sorafenib 400 mg bid versus placebo, showing a significant survival benefit with sorafenib - median survival 3 months longer.

1. Llovet JM et al. NEJM 2008; 359:378-390
2. Cheng AL et al. Lancet Oncol 2009;10:25-34

Systemic Therapy for HCC

- **Regorafenib** in the phase III **RESOURCE** trial[1] for patients who progressed on Sorafenib showed a median overall survival of 10.6 months compared to 7.8 months for placebo (HR 0.63, p< 0.001) and also longer time to progression, disease control rate, and objective response rate.[1]
- **Sorafenib-Regorafenib** sequential therapy option now available.

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

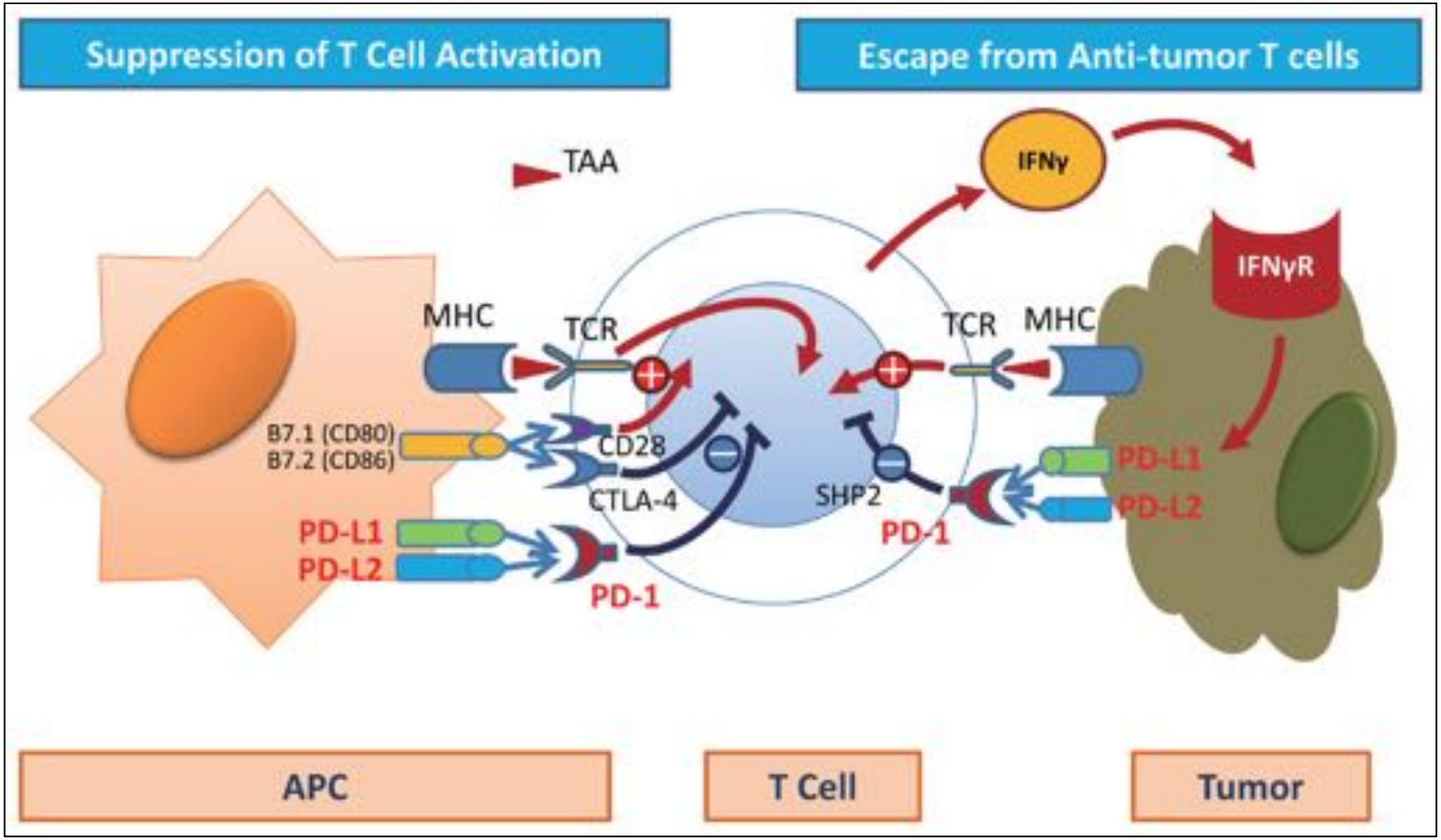
Systemic Therapy for HCC

- **Lenvatinib** in a phase II study[1] showed an objective response rate of 37%, and a disease control rate of 78% by mRECIST criteria.
- in the phase III **REFLECT** trial, Lenvatinib achieved primary end-point of non-inferiority to sorafenib in overall survival. The secondary end-points of progression-free survival, time to progression, and objective response rate were superior to sorafenib.

1. *Ikeda K et al. J Gastroenterology 2017;52:512-519*

Immune Checkpoint Blockade in HCC

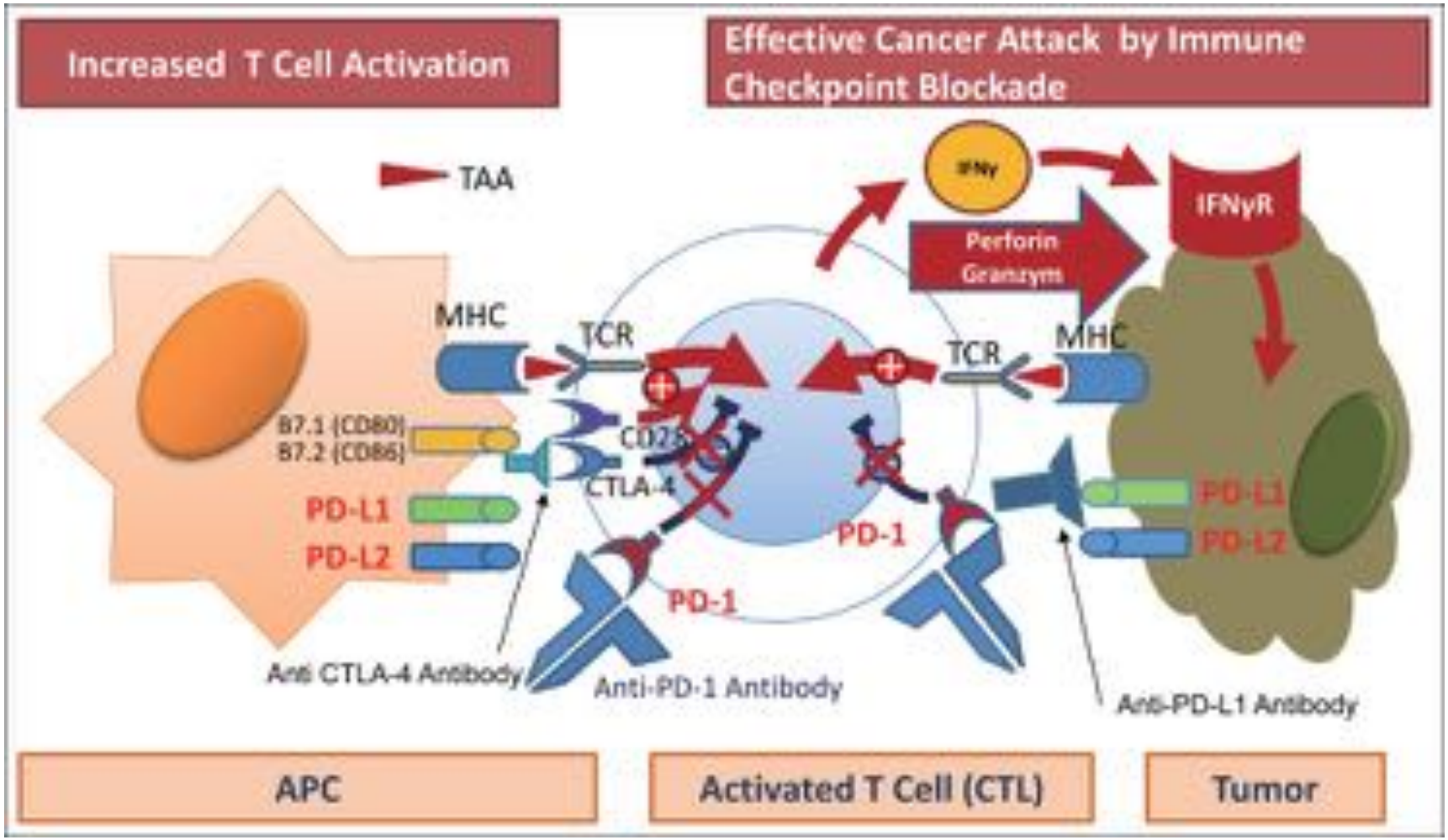
- "Immune escape" of tumor cells from activated CD8(+) T-cells
  Expression of PD-L1/PD-L2 that binds to PD-1



Kudo M. Liver Cancer 2015;6:1-12

Immune Checkpoint Blockade in HCC

- Immune checkpoint blockade: anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies restore cytotoxic T-cell activity



Kudo M. Liver Cancer 2015;6:1-12

Immunotherapy for HCC

- Immunotherapy: PD-1 inhibitor Nivolumab in the phase I/II **Check-Mate 040 study**
- Dose escalation phase (0.1-10 mg/kg every 2 weeks) to evaluate safety and tolerability
- Dose expansion phase (3 mg/kg every 2 weeks) to study an objective response rate.
- Manageable safety profile and acceptable tolerability; adverse events not dose-related.
- Objective response of 20% in dose expansion phase and 15% in dose escalation phase.

El-Khoueiry et al. Lancet 2017;389:2492-2502

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Abstract #141 (Plenary)

Nivolumab in Sorafenib-naïve and -experienced Patients with Advanced Hepatocellular Carcinoma:

Survival, hepatic safety, and biomarker assessment in CheckMate 040

- Updated survival, safety and biomarker analysis with extended follow-up after treatment with PD-1 inhibitor Nivolumab in **Check-Mate 040 study**
- Patients (n= 262) had median follow-up of 14-16 months, 98% had Child-Pugh scores of 5-6 and 68% had extrahepatic disease
- Overall objective response rate 14-20%, and a median duration of response 16.6-19.4 months

Sangro B et al. AASLD 2017

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Abstract #141 (Plenary)

Nivolumab in Sorafenib-naïve and -experienced Patients with Advanced Hepatocellular Carcinoma:

Survival, hepatic safety, and biomarker assessment in CheckMate 040

	Sorafenib-Naïve	Sorafenib-Experienced	
Overall Survival	N= 80	Dose escalation N= 37	Expansion N= 145
Median survival	28.6 months	15 months	15.6 months
12-month survival	73%	58%	60%
18-month survival	57%	46%	44%

Sangro B et al. AASLD 2017

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Abstract #141 (Plenary)

Nivolumab in Sorafenib-naïve and -experienced Patients with Advanced Hepatocellular Carcinoma:

Survival, hepatic safety, and biomarker assessment in CheckMate 040

- Alpha-fetoprotein levels at baseline were not associated with response, but alpha-fetoprotein levels in responders appeared to decrease on treatment
- AST/ALT elevations were 5%-9% in sorafenib-naïve and 3-4% in sorafenib-experienced patients
- No drug-related deaths due to hepatic adverse events

Sangro B et al. AASLD 2017

Systemic Therapy for HCC

Summary

- Sorafenib, Regorafenib and Nivolumab have been FDA-approved for the treatment of advanced unresectable HCC
- FDA approval for Lenvotinib anticipated (phase III trial to be published)
- Role of these agents need to be defined

  Sorafenib – first line

  Regorafenib – Sorafenib failure

  Nivolumab – Second line