# Management of Advanced Hepatocellular Carcinoma:
*At the Dawn of a New Era?*


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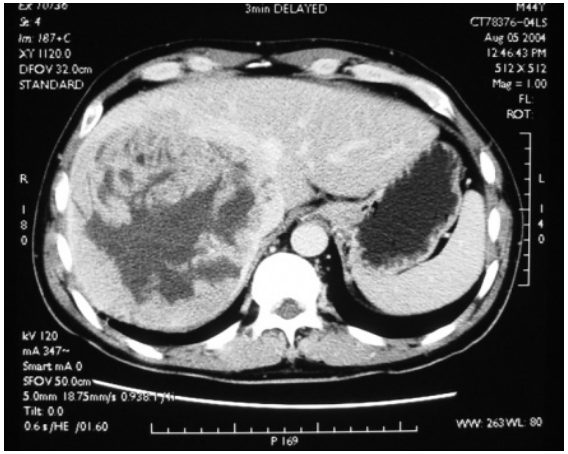
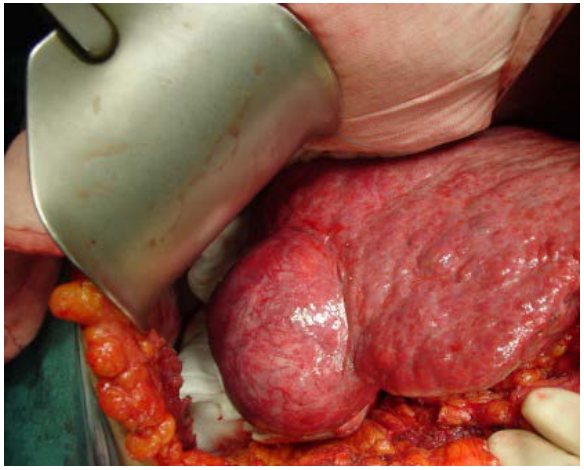
# Challenges in Management of HCC




*One patient with two diseases*

- A highly malignant tumor
  - High propensity for venous invasion
  - Rapid growth (tumor volume doubling time 3 months)
- Associated cirrhosis (80%)
  - Impaired liver function
  - Multicentric hepatocarcinogenesis



# Doxorubicin

## TREATMENT OF HEPATOCELLULAR CARCINOMA WITH ADRIAMYCIN

*Preliminary Communication*

CHARLES L. M. OLWENY, MMED,* TOM TOYA, MD†
EDWARD KATONGOLE-MBIDDE, MB, CHB,‡ JOSUA MUGERWA, MD,‡
SEBASTIAN K. KYALWAZI, FRCS(Ed),‡ AND HERMAN COHEN, PHD**

In a Phase II clinical trial, 14 patients with histologically proven primary hepatocellular carcinoma were treated with adriamycin administered intravenously at a dose of 75 mg/m² every 3 weeks. All 11 evaluable patients responded with 3 exhibiting complete tumor regression after two, three, and five courses of adriamycin respectively. The remission durations for these 3 were 3, 6, and 7 months, and their survivals were 8, 9, and 13 months, respectively. The median survival of the evaluable patients is 8 months (range 1–13 months). The side effects encountered included myelosuppression, anorexia, nausea, vomiting, and alopecia. Adriamycin seems to be an effective agent in hepatocellular carcinoma. Further trials are underway to test its true efficacy both singly and in combination with other drugs in the management of this tumor.

*Cancer* 36:1250–1257, 1975.

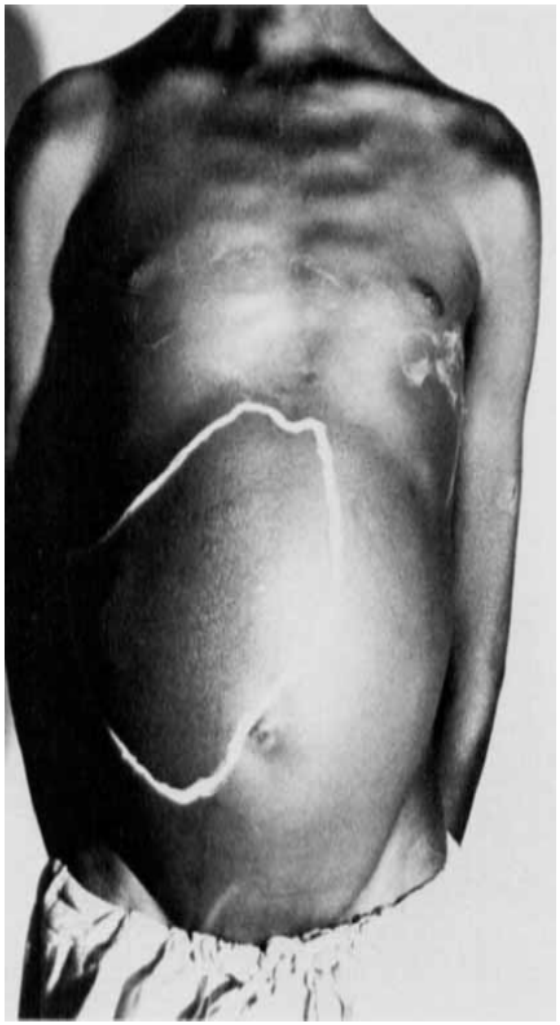


FIG. 1. Patient A.B. on admission. Note the wasting, liver size, and abdominal distention due to ascites.

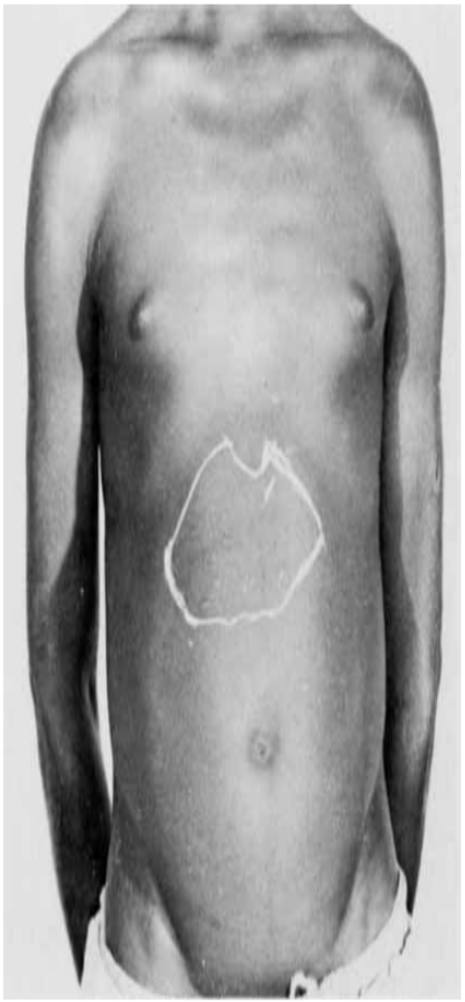
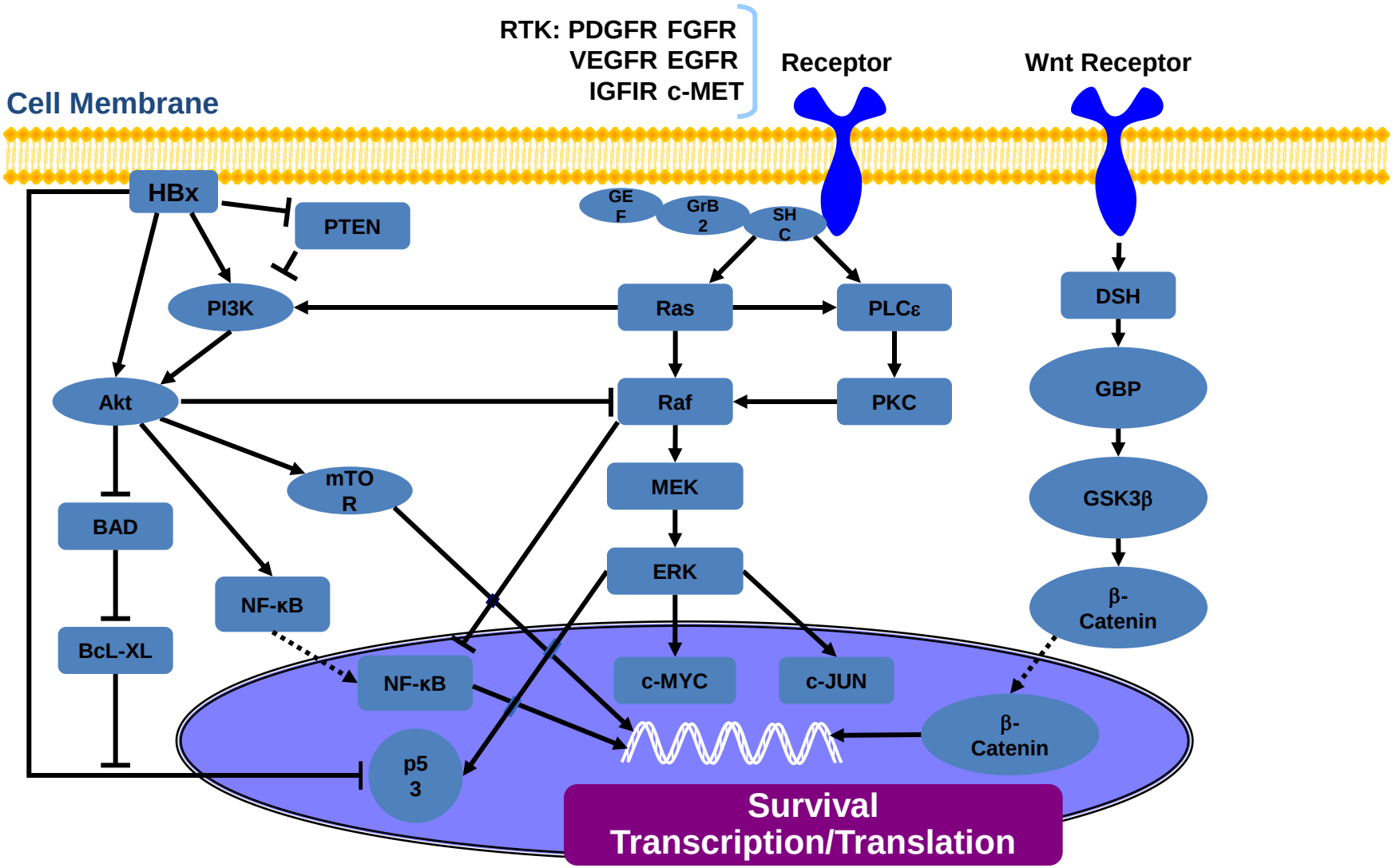


FIG. 3. Patient A.B. a week after first dose of adriamycin. Note the reduction in liver size.

# Systemic Chemotherapy

- Response rate of monotherapy (epirubicin, doxorubicin, cisplatin, 5-FU) < 20%
- Significant toxicity
- No confirmed survival benefit in randomized controlled trials

# Multiple Cellular Signaling Pathways Are Implicated in the Pathogenesis of HCC

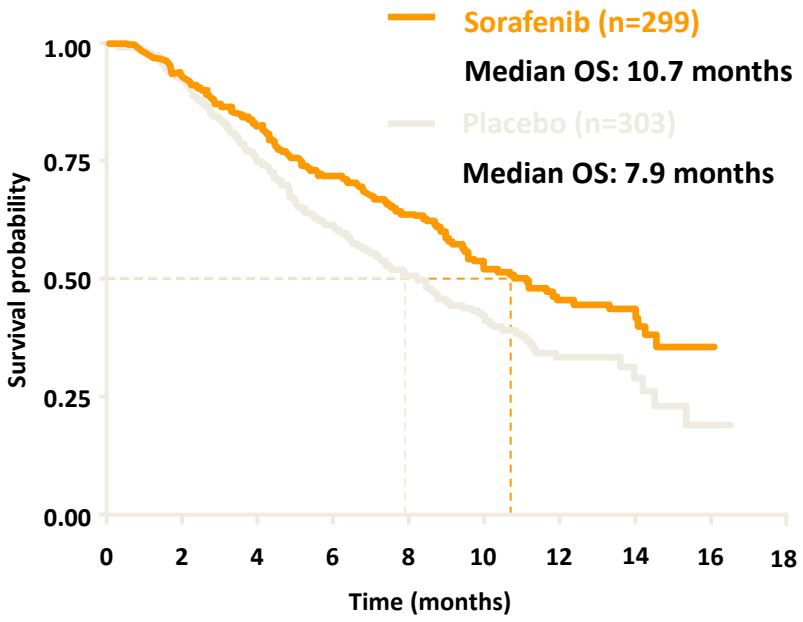



Anzola M. *J Virol Hepat.* 2004;11:383-393; Avila MA, et al. *Oncogene.* 2006;25:3866-3884; Clauss M. *Semin Thromb Hemost.* 2000;26:561-569.

# Phase III SHARP and AP trials

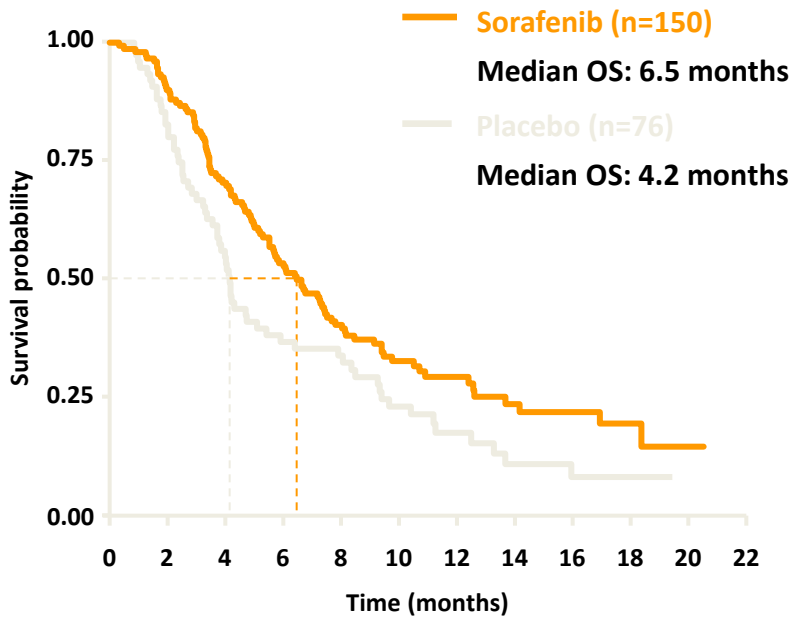
## Sorafenib vs placebo in advanced HCC

### SHARP[1]




**HR=0.69**

### Asia-Pacific[2]




**HR=0.68**

HR, hazard ratio; OS, overall survival; SHARP, Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol.

1. Llovet JM et al. N Engl J Med 2008;359:378–90; 2. Cheng A et al. Lancet Oncol 2009;10:25–34.

# Sorafenib: Indications

-Sorafenib is the first-line treatment of advanced stage patients (portal vein invasion or extrahepatic spread) who are not suitable for locoregional therapy and with Child-Pugh A cirrhosis

,

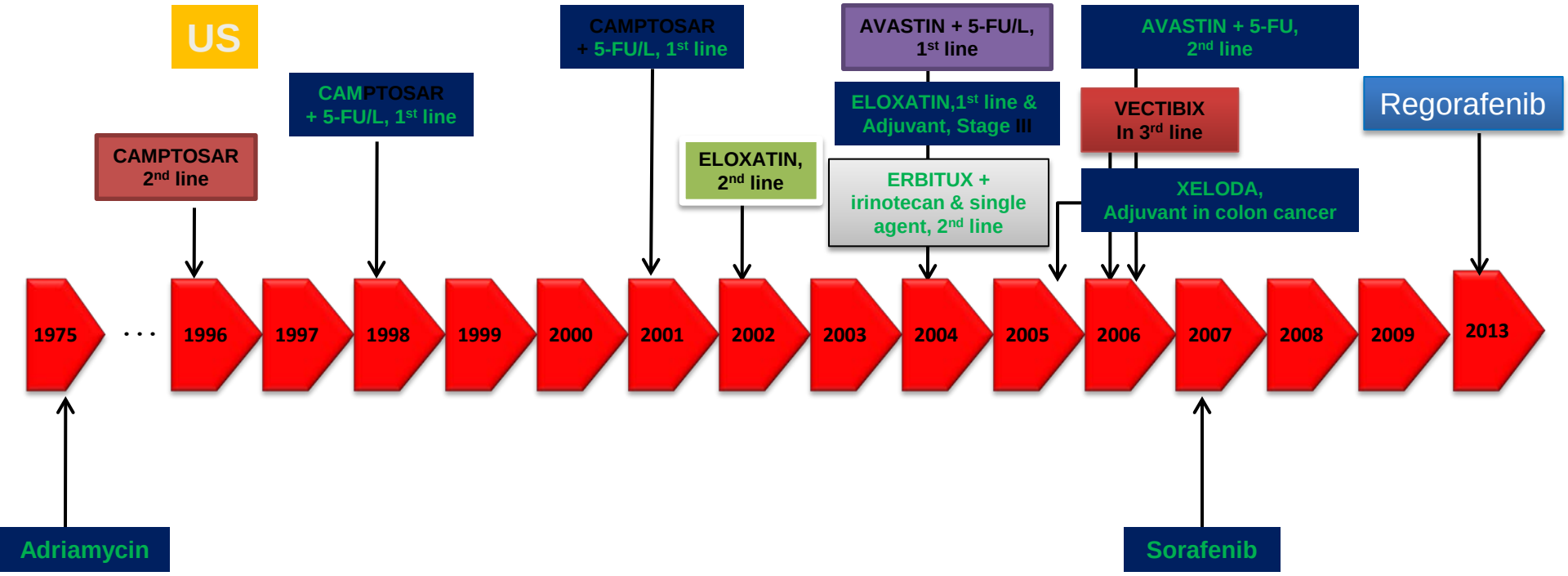
-NCCN(2007)
- APASL (2009)
- JSH (2011)
- BCLC (2012)

Caveats

- Response rate of only 3% and disease control rate of 28%

-Median survival of 5 months in Asian population

## Approval scenario of key marketed drugs in CRC market




## Approval scenario of key marketed drugs in HCC market

# Summary of Failed Phase III Trials for HCC

| Agent | MOA | Patient Population | Trial Design | Results | Comments |
|---|---|---|---|---|---|
| Brivanib[1-3] (BRISK-FL, BRISK-PS, BRISK-TA) | VEGF and FGF inhibitor | • BRISK-FL: 1L unresectable; CP A<br>• BRISK-PS: 2L after sorafenib; CP A/B7<br>• BRISK-TA: adjuvant after 1st TACE; CP A/B | • 1L: briv vs sorafenib (N=1150)<br>• 2L: briv vs BSC(N=395)<br>• Adjuvant: briv vs placebo (N= 870) | • 1L: mOS=9.5 vs 9.9 mo (HR 1.06 [95.8% CI: 0.93–1.22])<br>• 2L: mOS=9.4 vs 8.2 mo (HR 0.89, *P*=0.3307)<br>• Adjuvant: mOS=26.4 vs 26.1 mo (HR 0.9, *P*=0.528) | • Did not improve survival over sorafenib in 1L<br>• Did not meet primary endpoint (OS) in 2L or as adjuvant |
| Linifanib[4] (LIGHT) | VEGFR and PDGFR inhibitor | • 1L unresectable/ metastatic HCC<br>• CP A | Linifanib vs sorafenib (N=1035) | mOS=9.1 vs 9.8 mo (HR 1.046 [95% CI: 0.896–1.221]) | • OS inferior to sorafenib<br>• Safety results favored sorafenib |
| Sunitinib [5,6] (SUN) | VEGFR, PDGFR, FLT3R, KIT, and RET inhibitor | • 1L advanced liver cancer<br>• CP A | Sunitinib vs sorafenib (N=1074) | mOS=7.9 vs 10.2 mo (HR 1.3, one-sided *P*=0.9990) | • OS inferior to sorafenib<br>• Associated with more frequent and severe toxicities |
| Orantinib[7] | VEGFR2, FGFR2, and PDGFR inhibitor | Unresectable HCC | TACE + orantinib vs placebo (N=889) | mOS=NA | • Did not meet primary endpoint (OS) |

**Multiple multikinase inhibitors have failed to show survival benefit akin to sorafenib in HCC pts**

# Failed Phase III Trials for HCC (cont'd)

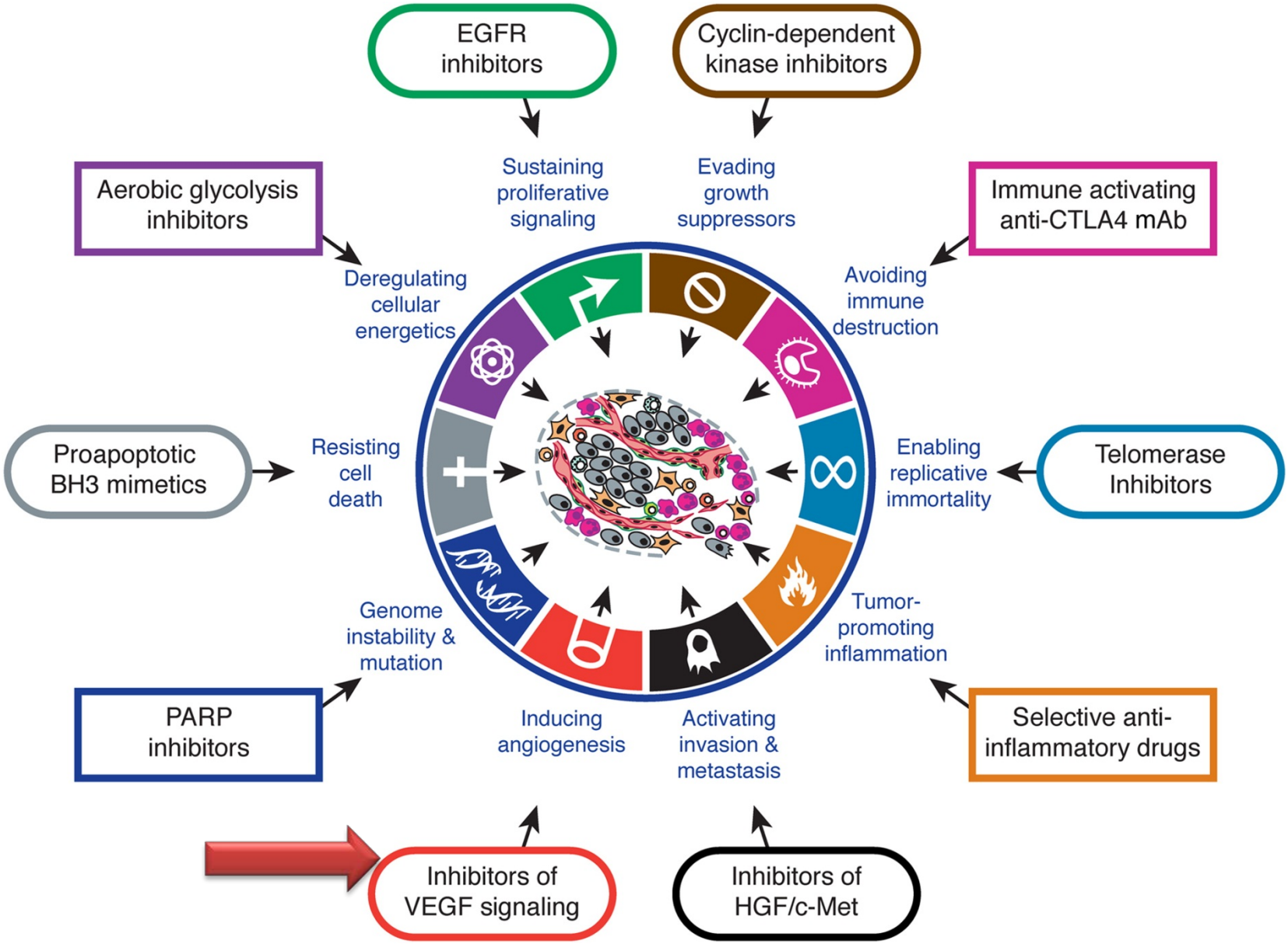
| Agent | MOA | Patient Population | Trial Design | Results | Comments |
|---|---|---|---|---|---|
| Everolimus[1] (EVOLVE-1) | mTOR inhibitor | •Advanced HCC<br>•Sorafenib refractory/ intolerant<br>•CP A | Everolimus + BSC vs placebo + BSC (N=546) | mOS: 7.6 vs 7.3 mo (HR 1.05 [95% CI 0.86–1.27]) | Did not meet primary endpoint (OS) |
| S-1 (TS-1 in Japan)[2] (S-CUBE) | Fluoropyrimidine trio (5-FU prodrug + modulators) | • Advanced HCC<br>• Sorafenib refractory/ intolerant | TS-1 vs placebo (N=334) | mOS: 337.5 days vs 340 days | Did not meet primary endpoint (OS) |
| Peretinoin[3] | Synthetic retinoid; suppresses growth | • HCV-HCC with CR after curative tx<br>• CP class A/B | Peretinoin lower dose and higher dose vs placebo (N=401) | 1-yr RFS: 63.6 vs 71.9 vs 66.0<br><br>3-yr RFS: 24.9 vs 43.7 vs 29.3 | • Did not meet primary endpoint (RFS)<br>• Significant dose-response relationship shown in subgroup analysis |

**No targeted agents other than sorafenib have demonstrated survival benefit in HCC patients[1-4]**

α, transforming growth

factor-alpha;

# Therapeutic Armamentarium

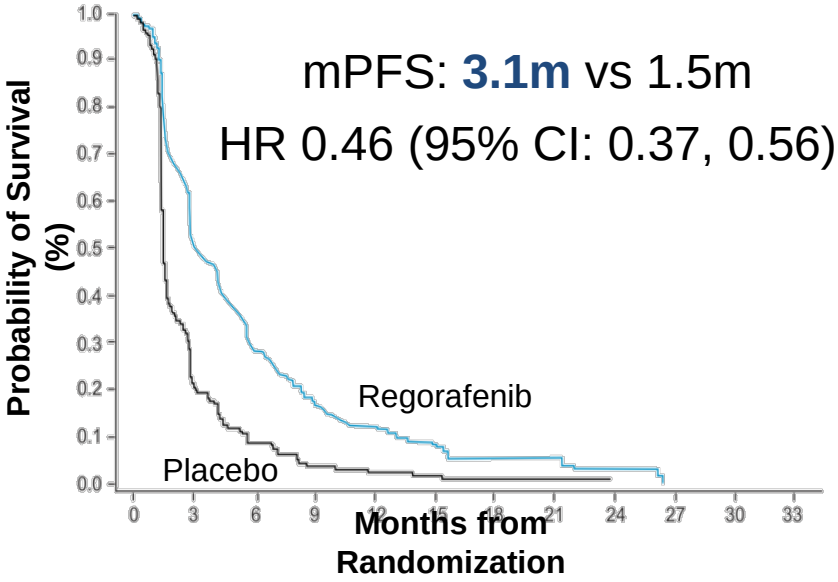


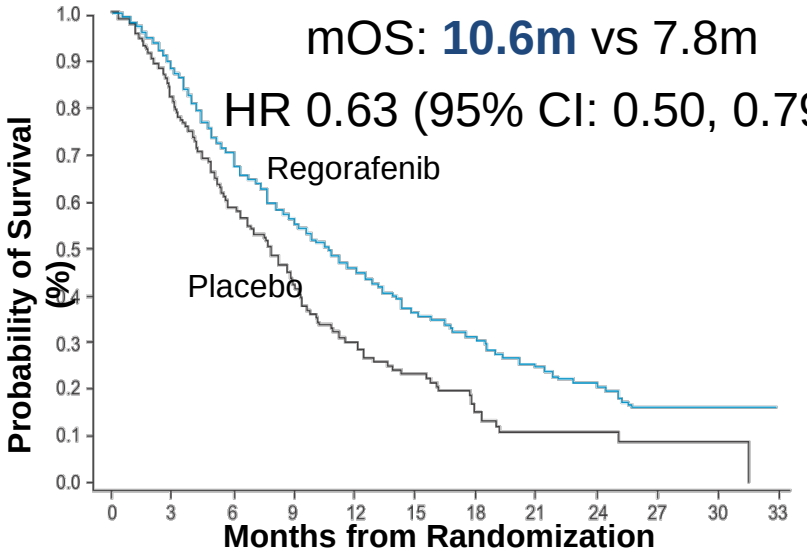

Cell , Volume 144, Issue 5, Pages 646-674

# RESORCE – 2L regorafenib after PD on sorafenib

## Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial

*Jordi Bruix, Shukui Qin, Philippe Merle, Alessandro Granito, Yi-Hsiang Huang, György Bodoky, Marc Pracht, Osamu Yokosuka, Olivier Rosmorduc, Valeriy Breder, René Gerolami, Gianluca Masi, Paul J Ross, Tianqiang Song, Jean-Pierre Bronowicki, Isabelle Ollivier-Hourmand, Masatoshi Kudo, Ann-Lii Cheng, Josep M Llovet, Richard S Finn, Marie-Aude LeBerre, Annette Baumhauer, Gerold Meinhardt, Guohong Han, on behalf of the RESORCE Investigators**




Bruix J et al., Lancet 2017

# 1st line: Update

http://www.onclive.com/web-exclusives/lenvatinib-succeeds-in-phase-iii-frontline-hcc-trial

## Lenvatinib Succeeds in Phase III Frontline HCC Trial

Jason M. Broderick

Lenvatinib non-inferior to sorafenib in OS… improvement in PFS, TTP, ORR

Frontline
noninferi
with unresectable hepatocellular carcinoma (HCC), according to Eisai, the developer of the multikinase inhibitor.

In a phase III trial, known as Study 304, overall survival (OS) outcomes with lenvatinib were noninferior to OS results with sorafenib, meeting the study's primary endpoint. The findings also demonstrated statistically significant improvements with lenvatinib for secondary endpoints, including progression-free survival, time to progression, and objective response rate (ORR). Eisai reported that it intends to present the full data at an upcoming scientific meeting and will also discuss the findings with the FDA and global regulatory authorities.

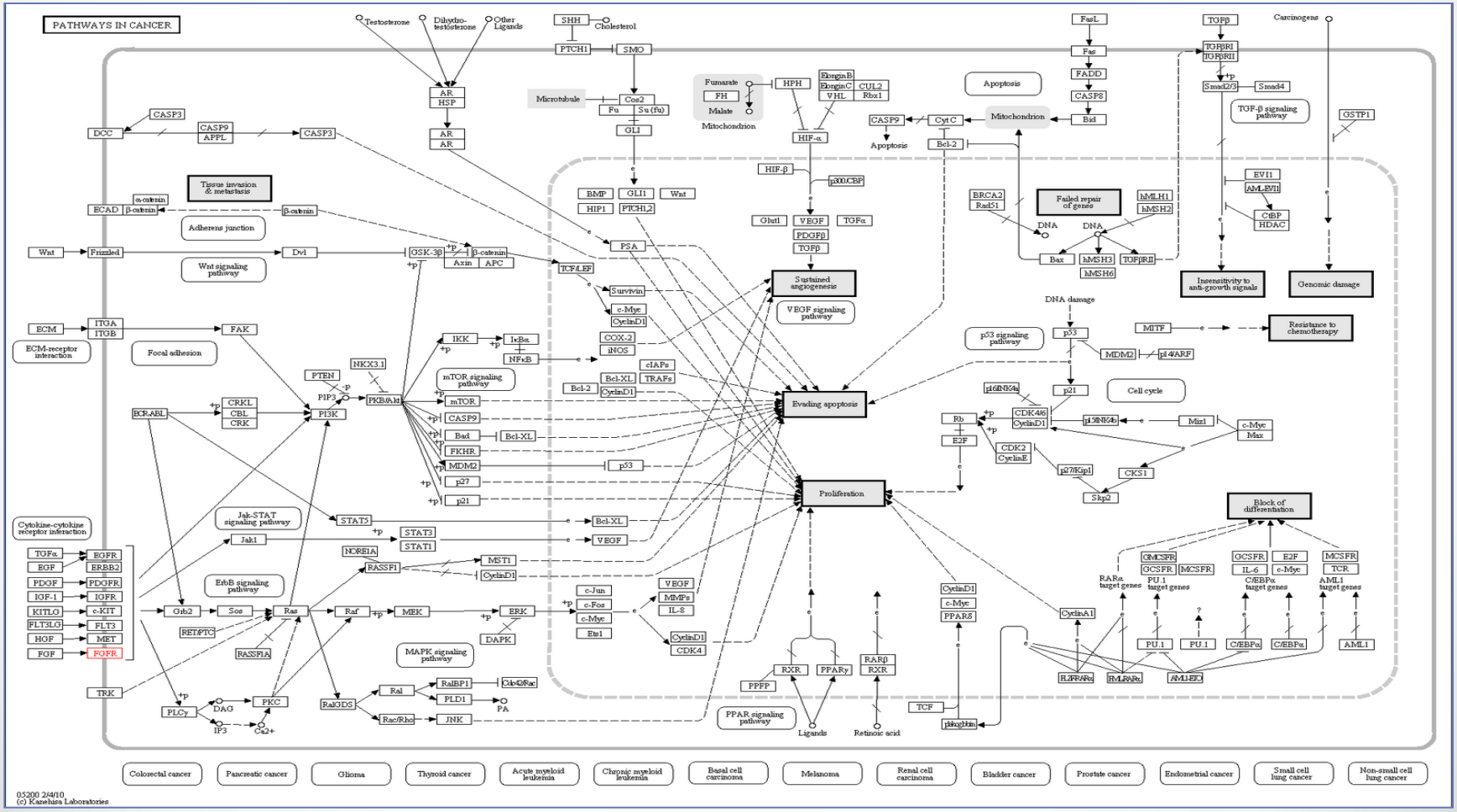
**Results will be presented in ASCO 2017**

medical officer, Oncology Business Group at Eisai, said in a statement. "The findings from this phase III trial represent an important development for previously untreated patients with unresectable hepatocellular carcinoma who unfortunately face a poor prognosis."

The international, multicenter, open-label, noninferiority Study 304 randomized 954 patients with unresectable HCC to frontline treatment with lenvatinib at either 8 mg or 12 mg once per day based on body weight (n = 478) or sorafenib at 400 mg twice daily (n = 476). Patients received treatment until progression or unacceptable toxicity.

# The Future of Cancer Therapy:

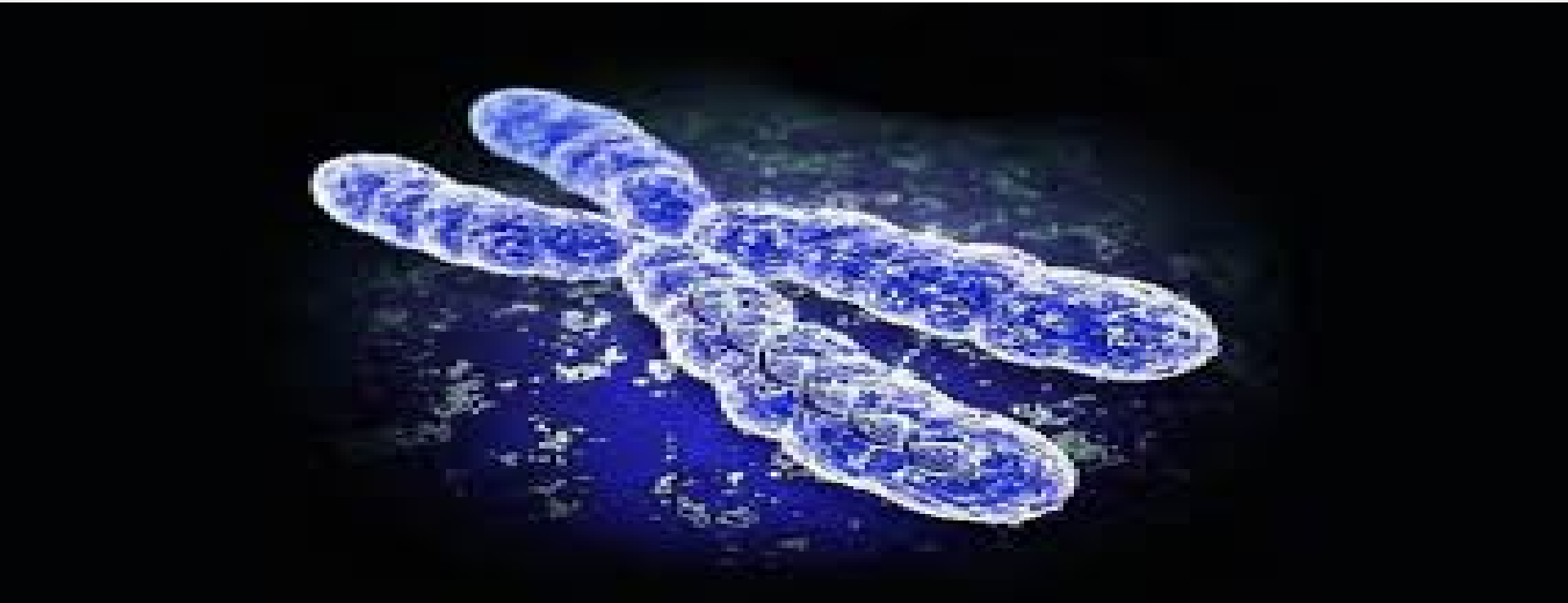
# Targeting Multiple Pathways



Cancer is a genomic disease

Cancers with a driving genetic mutation can be effectively targeted with molecular inhibitors

Identification of such molecular aberrations can enable better matching of drug to patient



# Driver vs Passenger Mutations in Cancer Development

- Somatic mutations found in cancers are either “drivers” or “passengers”

**Driver Mutations** → Causally involved in the neoplastic process and are positively selected for during tumorigenesis (cKIT in GIST)

**Passenger Mutations** → Provide no positive or negative selective advantage to the tumor but are retained by chance during repeated rounds of cell division and clonal expansion (KRAS mutation in mCRC)

Wood LD, et al. *Science*. 2007;318:1108-1113.

# Overview of New Phase III Investigational Therapies for HCC

| Class | Agent | Target/Mechanism of Action |
|---|---|---|
| Targeted Therapies Therapies | Cabozantinib | VEGFR2 and MET TKI[1,2] |
| | Lenvatinib | Multi TKI targeting angiogenesis and oncogenesis (**VEGFR1–3, 3, FGFR1-4, RET, KIT, and PDGFRβ)**[1,3] |
| | Ramucirumab | Anti-VEGFR2 mAb[1,4] |
| | Regorafenib | Multi TKI targeting angiogenesis and oncogenesis (**VEGFR1–3, 3, PDGFRβ, FGFR1, KIT, RET, and BRAF)**[1,5] |
| | Tivantinib | MET TKI[1,6] |
| | ADI-PEG20 | Targets tumor cell growth by degrading arginine[1,7] |
| | Muparfostat | Heparan sulfate mimic targeting angiogenesis (VEGF, FGF1 – 2) and and spread[1,8] |
| Chemotherapy | Doxorubicin TransDrug | Nanoparticle doxorubicin delivered via hepatic artery[1,9] |
| | ThermoDox | Liposomal-encapsulated doxorubicin delivered intravenously[1,10] intravenously[1,10] |

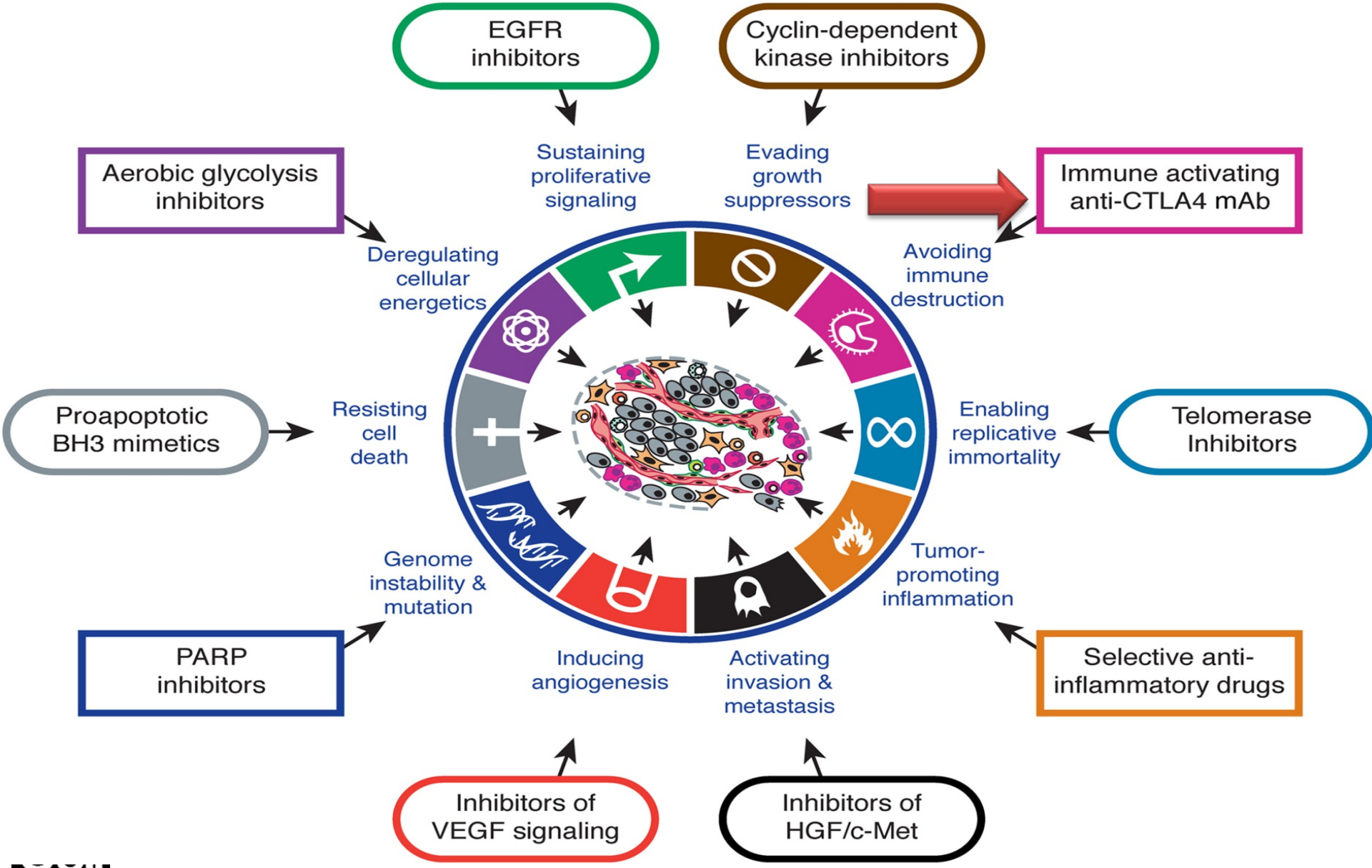
FGFR, fibroblast growth factor receptor; mAb, monoclonal antibody; PDGFR, platelet-derived growth factor receptor; TKI, tyrosine-kinase inhibitor; VEGF, vascular endothelial growth factor.

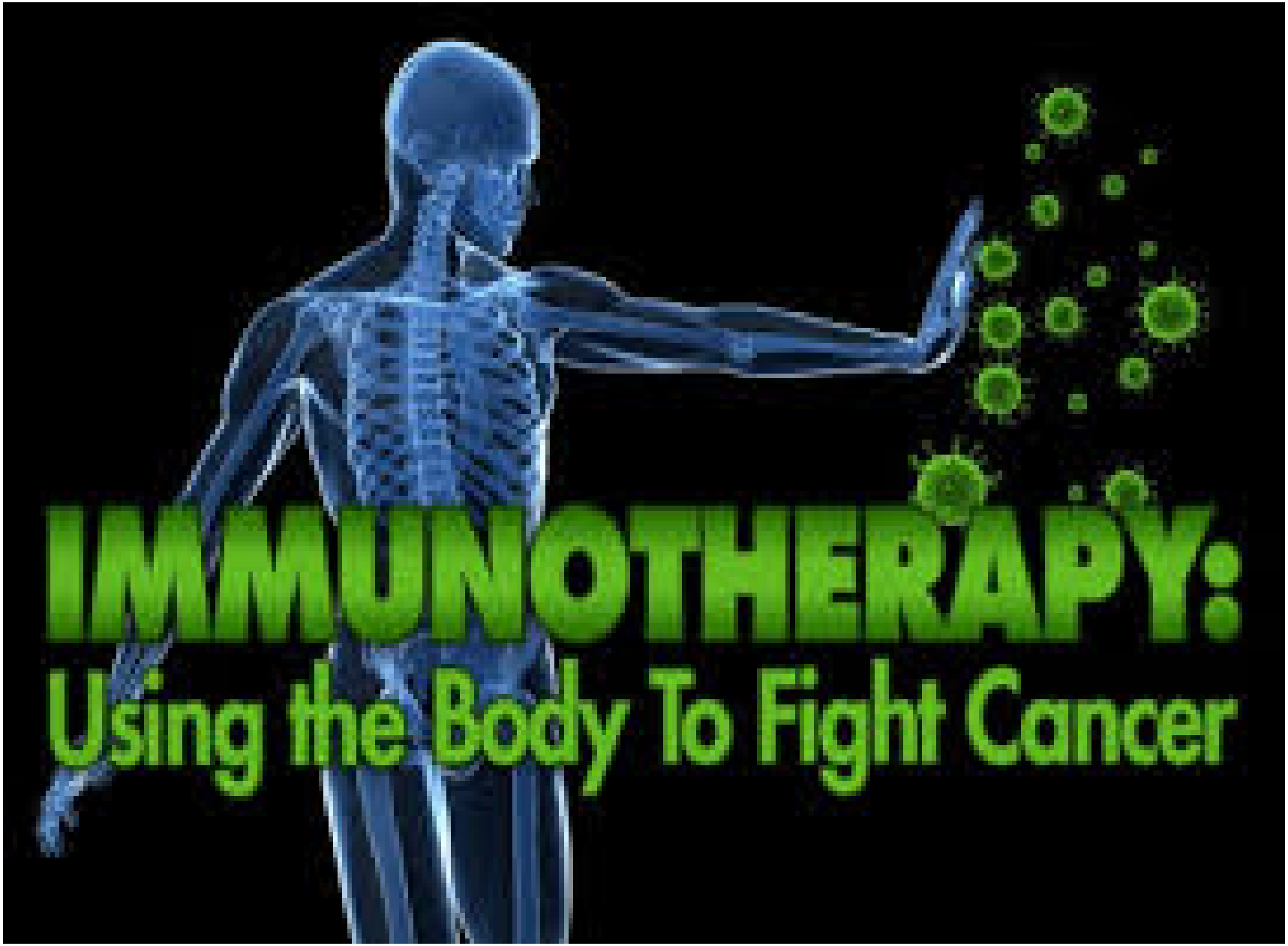

1. Clinicaltrials.gov.
2. Verslype C. Oral presentation at ASCO 2012. 4007.
3. Mitsunaga S et al. ASCO GI Symposium 2013. 231.
4. Zhu AX et al. *Clin Cancer Res.* 2013;19(23):6614-6623
5. Ravi S, Singal AK. *Core Evid.* 2014; 9:81-87.
6. Santoro A et al. *Lancet Oncol.* 2013;14(1):55-63.
7. Polaris Pipeline – ADI-PEG 20. Available at http://www.polarispharma.com/pipeline/adipeg20onc.php. Accessed January 9, 2015.
8. Liu CJ et al. *J Hepatol.* 2009;50(5):958-968.
9. Merle P et al. Oral presentation at ILCA 2011. 0-034.
10. Reuters. Celsion plunges 80 percent as liver cancer therapy fails trial. Available at: http://www.reuters.com/article/2013/01/31/us-celsion-study-thermodox-idUSBRE90U0MI20130131. Accessed January 12, 2015.


FUTURE
PAST

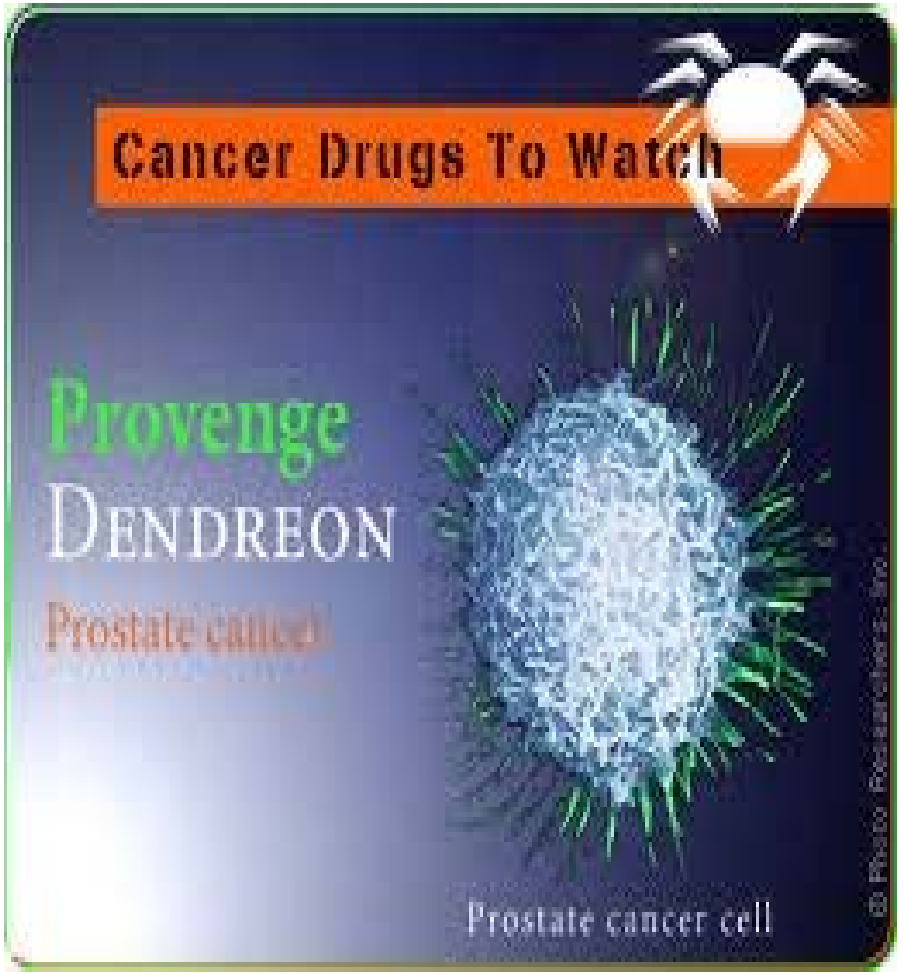

The Future
NEXT EXIT

# Therapeutic Armamentarium



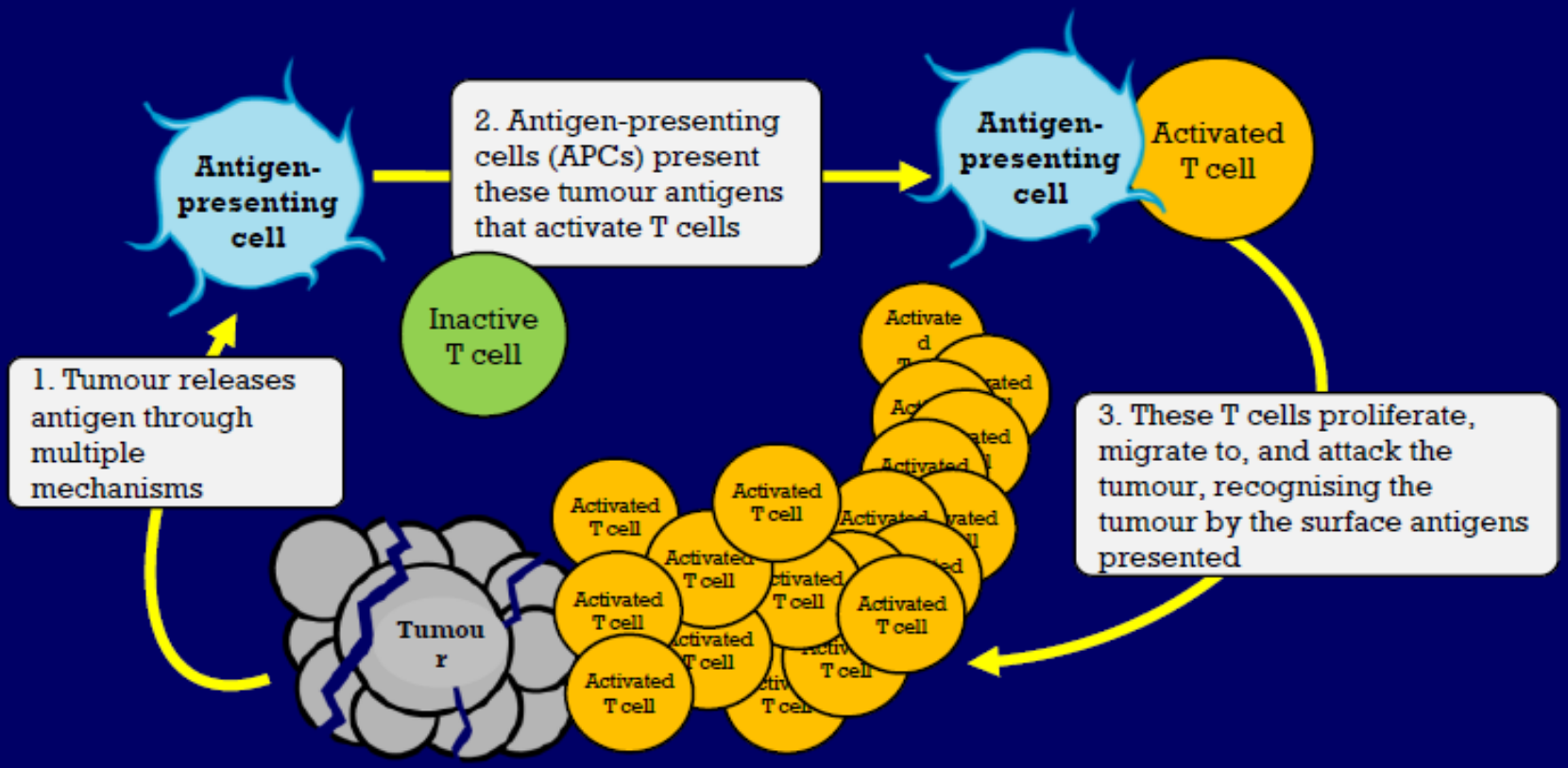

IMMUNOTHERAPY:
Using the Body To Fight Cancer


YERVOY
(ipilimumab)
Injection
200 mg/40 mL
YERVOY
(ipilimumab)
Injection
50 mg/10 mL


Cancer Drugs To Watch
Provenge
DENDREON
Prostate cancer cell

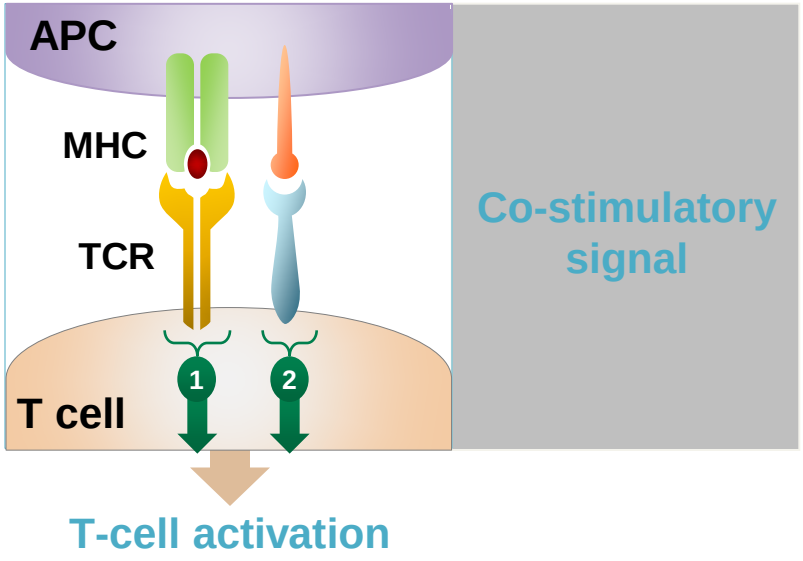
# Normal immune response

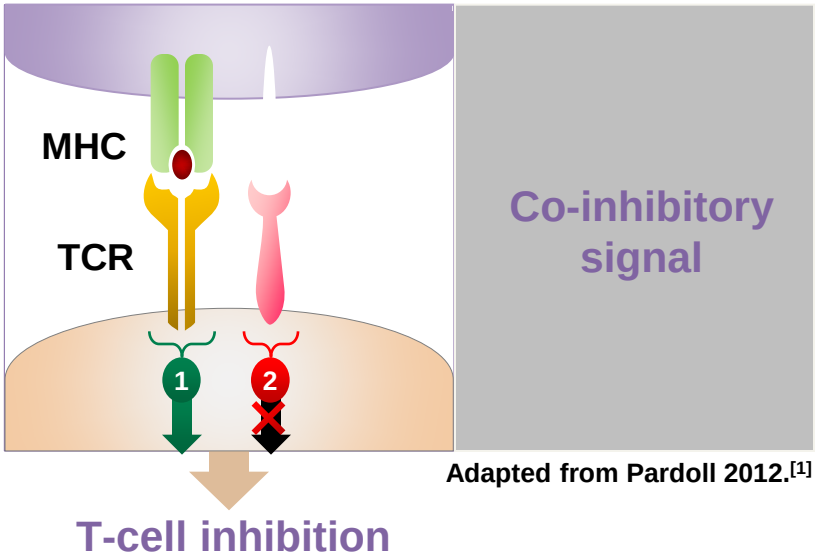
- **Normally, the immune system can recognise many types of cancers and mount an active antitumour response**
  - **Through immunosurveillance, activated T cells remove tumours from the body**



# Function of T Cells in Immune Response

- T-cell responses require 2 signals[1,2]:
  - TCR recognition of MHC-presented antigen
  - Co-signaling interaction, which can be either co-stimulatory or co-inhibitory
- T-cell function is thus regulated by a balance between co-stimulatory and co-inhibitory signals, which are also referred to as "checkpoint" pathways[1,2]:



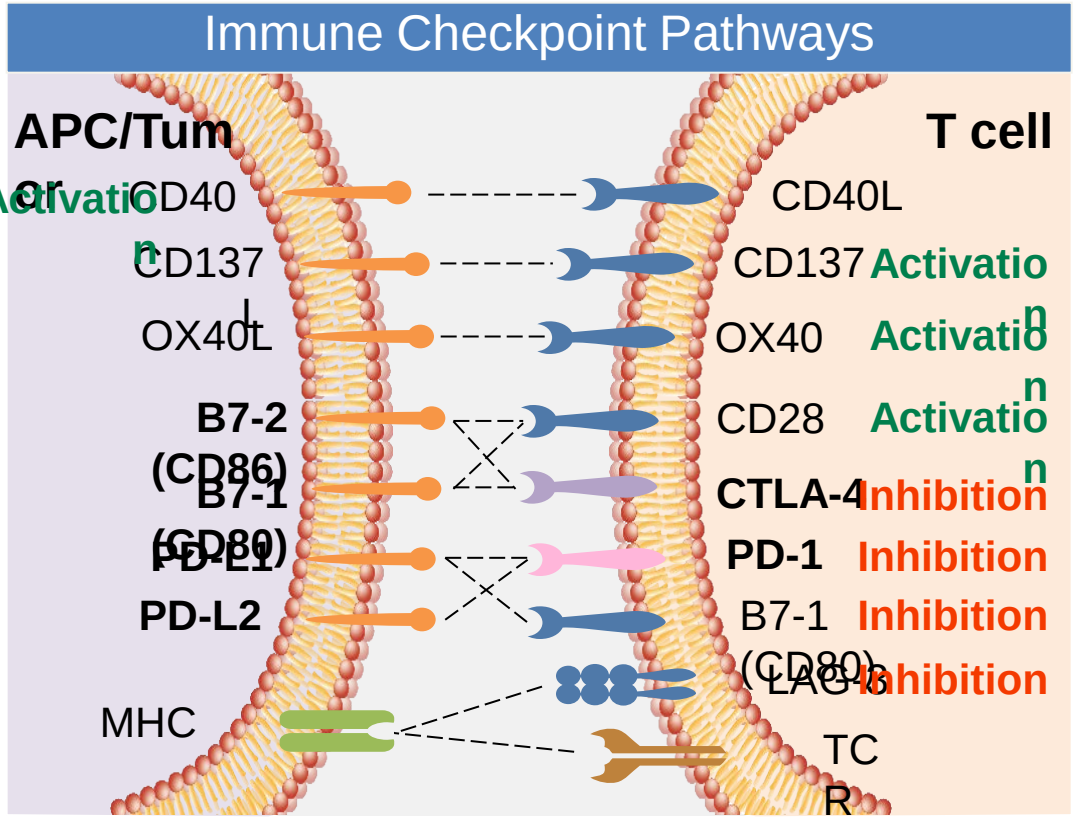

Adapted from Pardoll 2012.[1]

APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.


1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264.
2. Weber J. *Semin Oncol*. 2010;37(5):430-439.

# Immune Checkpoint Pathways Regulate T-Cell Activation

**Various tumors have been found to exploit immune checkpoint pathways to evade**



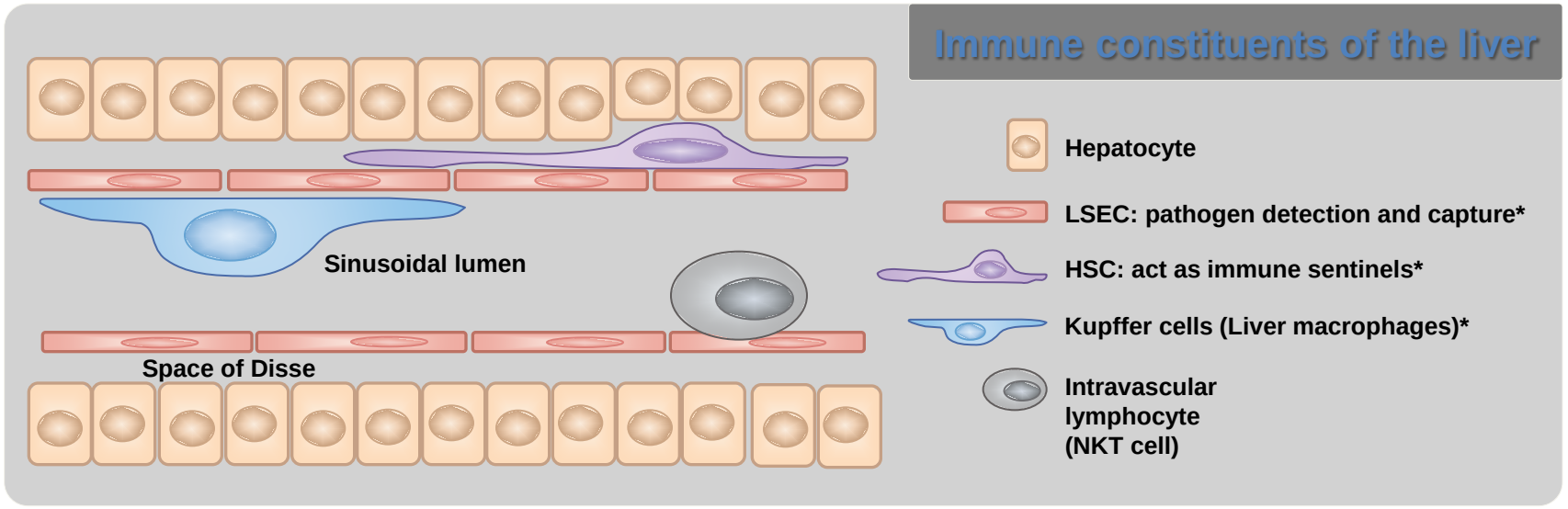

Adapted from Pardoll 2012.[1]

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; LAG-3, lymphocyte activation gene-3; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, PD ligand-1; PD-L2, PD ligand-2; TCR, T-cell receptor.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264; 2. Weber J. *Semin Oncol*. 2010;37(5):430-439.

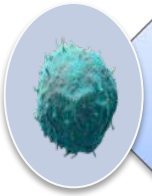
# Immunogenicity of the Liver

- The liver is the frontline immunological organ against gastrointestinal tract antigens as well as systemic antigens[1]
  - Parenchymal cells: hepatocytes (approximately 80% liver cells)[1]
    - Functional cells of the liver
    - Also involved in immune responses
  - Nonparenchymal cells: resident immune cells/constituents (approximately 20% cells)[1]



# Evidence of HCC as an Immunogenic Tumor

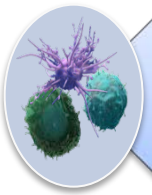
The rate of spontaneous regression is among the highest for solid tumors, and some of them are likely immunologic in nature[1,2]



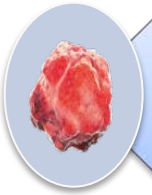
Spontaneous tumor-specific CD8 and CD4 cell responses

have been reported[3,4]

Several immunological features of HCC correlate with outcome[5]



Presence of immune cells in tumor (eg, NK cells, T cells, DCs, macrophages)[3]



HCC expression of TAAs (eg, AFP, GPC3, NY-ESO-1, MAGE-A)[4]

AFP, alpha fetoprotein; CD, cluster of differentiation; DCs, dendritic cells; GPC3, glypican 3; HCC, hepatocellular carcinoma;
MAGE-A, melanoma antigen gene-A; NK, natural killer; TAAs, tumor-associated antigens.

1. Oquiñena S et al. *Eur J Gastroenterol Hepatol*. 2009;21(3):254-257. 2. Huz JI et al. *HPB (Oxford)*. 2012;14(8):500-505. 3. Miamen AG et al. *Liver Cancer*. 2012;1(3-4):226-237. 4. Bertino G et al. *Biomed Res Int*. 2015;2015:731469. doi:10.1155/2015/731469. 5. Pardee AD, Butterfield LH. *OncoImmunology*. 2012;1(1):48-55.

# *The Lancet* 2017 http://dx.doi.org/10.1016

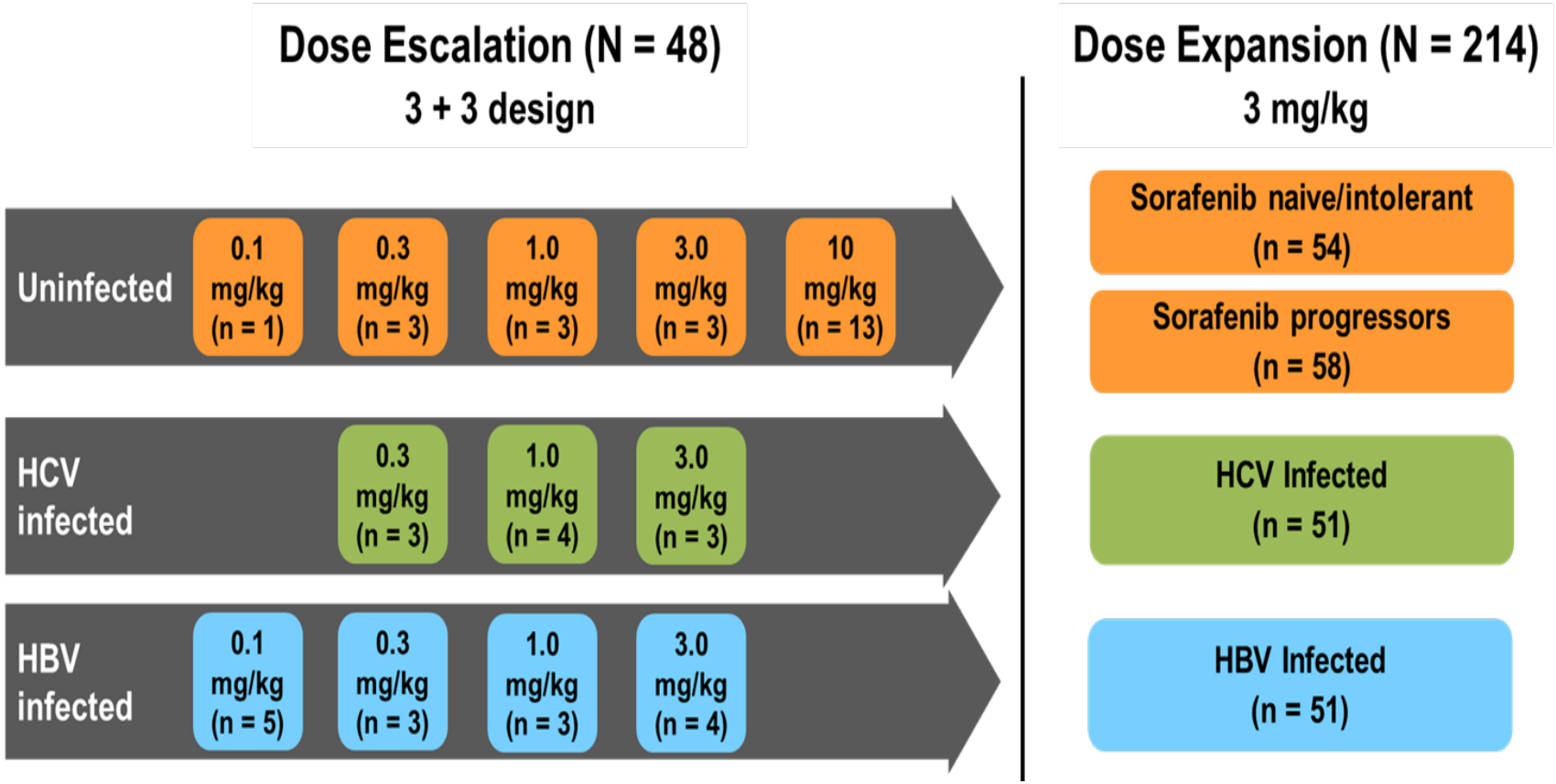
Articles

## Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

Anthony B El-Khoueiry,*Bruno Sangro,*Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero

* Joint First Authors

# CheckMate 040: Phase 1/2 Study of Nivolumab in Patients With Advanced HCC




- Disease assessment imaging (CT or MRI) every 6 weeks
- Interim analysis data cutoff date: March 15, 2016

CT, computed tomography; MRI, magnetic resonance imaging; Q6W, every 6 weeks.

# Key Eligibility Criteria and Study Endpoints

*CheckMate 040 Dose Escalation & Expansion*

## Eligibility criteria

### Inclusion

- Histologically confirmed advanced HCC not amenable to curative resection
- Child-Pugh scores ≤ 7 (escalation) or ≤ 6 (expansion)
- Progression on 1 prior line of systemic therapy, or intolerant of or refused sorafenib
- AST and ALT ≤ 5 × upper limit of normal; bilirubin ≤ 3 mg/dL
- For HBV-infected patients, viral load < 100 IU/mL and concomitant effective antiviral therapy

### Exclusion

- Any history of hepatic encephalopathy
- Prior or current clinically significant ascites
- Active HBV and HCV co-infection

## Study endpoints

### Primary

- Safety and tolerability (escalation)
- Objective response rate[a] (expansion)

### Secondary

- Objective response rate (escalation)
- Disease control rate
- Time to response
- Duration of response
- Overall survival

### Exploratory

- Biomarker assessments

[a] RECIST v1.1 by BICR (blinded independent central review); BICR data are not yet available, and all efficacy assessments are per the local investigator analysis.

# Safety

*CheckMate 040 Dose Escalation & Expansion*

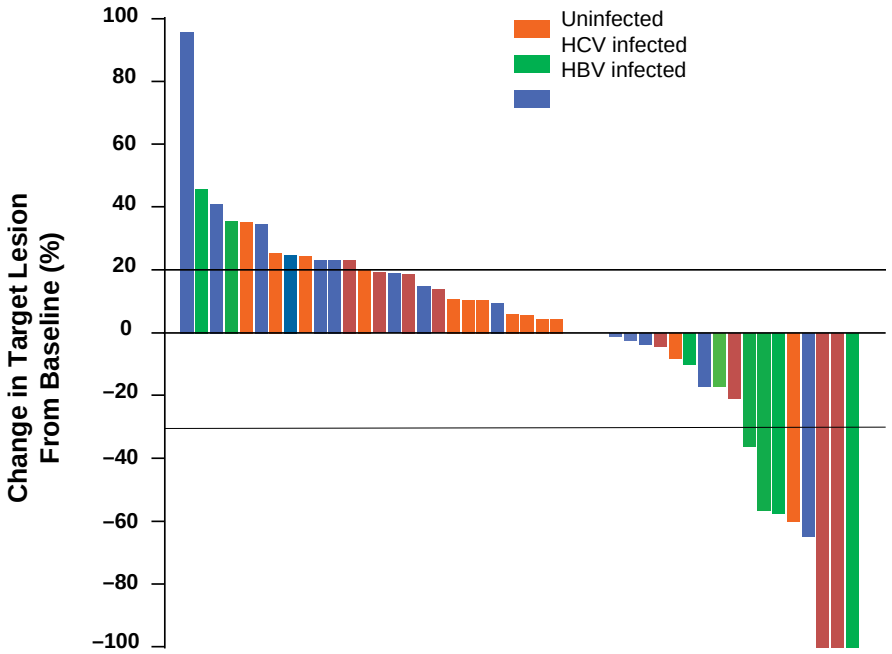
| | Uninfected (n = 135) | | HCV Infected (n = 61) | | HBV Infected (n = 66) | | All Patients (n = 262) | |
|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Patients with any treatment-related AE, n (%) | 91 (67) | 24 (18) | 45 (74) | 21 (34) | 41 (62) | 6 (9) | 177 (68) | 51 (19) |
| Treatment-related AEs reported in ≥ 5% of all patients, n (%) | | | | | | | | |
| Fatigue | 32 (24) | 2 (1) | 7 (11) | 0 | 9 (14) | 1 (2) | 48 (18) | 3 (1) |
| Pruritus | 14 (10) | 0 | 12 (20) | 0 | 14 (21) | 0 | 40 (15) | 0 |
| Rash | 19 (14) | 1 (1) | 9 (15) | 0 | 9 (14) | 0 | 37 (14) | 1 (< 1) |
| Diarrhea | 18 (13) | 2 (1) | 4 (7) | 0 | 2 (3) | 1 (2) | 24 (9) | 3 (1) |
| Nausea | 9 (7) | 0 | 7 (11) | 0 | 0 | 0 | 16 (6) | 0 |
| Decreased appetite | 7 (5) | 0 | 2 (3) | 0 | 4 (6) | 0 | 13 (5) | 0 |
| Laboratory treatment-related AEs reported in ≥ 5% of all patients, n (%) | | | | | | | | |
| AST increase | 13 (10) | 4 (3) | 10 (16) | 10 (16) | 0 | 0 | 23 (9) | 14 (5) |
| ALT increase | 11 (8) | 3 (2) | 9 (15) | 6 (10) | 2 (3) | 0 | 22 (8) | 9 (3) |
| Amylase increase | 10 (7) | 4 (3) | 3 (5) | 1 (2) | 2 (3) | 1 (2) | 15 (6) | 6 (2) |
| Lipase increase | 10 (7) | 7 (5) | 5 (8) | 4 (7) | 2 (3) | 2 (3) | 17 (6) | 13 (5) |

- No treatment-related deaths occurred in either the escalation or expansion cohorts

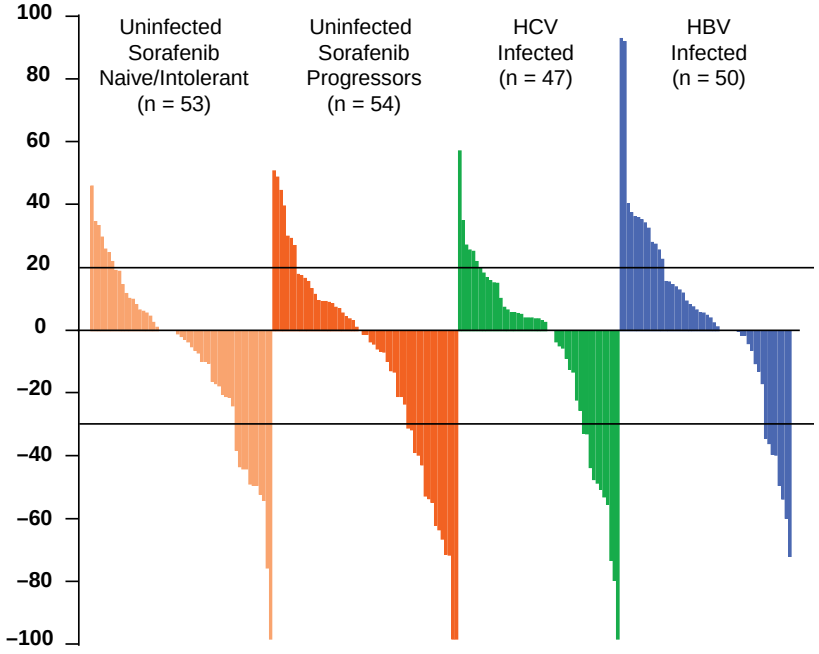
# Best Change in Target Lesions From Baseline

*CheckMate 040 Dose Escalation & Expansion*

## Dose-Escalation Cohort




## Dose-Expansion Cohort




- Objective responses were observed at all dose levels and in all etiologic subtypes

# Overall Survival

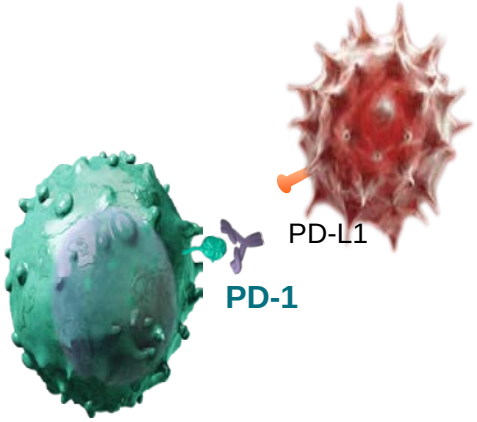
*CheckMate 040 Dose Escalation & Expansion*

| Overall Survival Rate, % (95% CI) | Dose-Escalation Cohort (n = 48) | Dose-Expansion Cohort (n = 214) |
|---|---|---|
| 6 months | 66 (51–78) | 83 (76–88) |
| 9 months | 66 (51–78) | 71 (57–81)[a] |
| 12 months | 59 (44–72) | NC |
| 18 months | 44 (29–58) | NC |
| **Median OS, mo (95% CI)** | 14.3 (9.6–18.9) | NC |

[a] Data cut-off March 15, 2016.

NC, not available/not calculated.

# **CHECKMATE-459:** Phase III trial of Nivolumab vs Sorafenib in 1L Advanced HCC patients




Adapted from Mellman I et al 2011.[2]

**Start Date:** **November 2015**

**Primary Endpoints:**
**TTP, OS**

**Other Endpoints:**
**ORR, PFS, biomarkers**

**Key Eligibility Criteria**

**N=726**

- Advanced HCC not eligible for or progressive after surgical and/or locoregional therapies
- Child-Pugh A

**R**

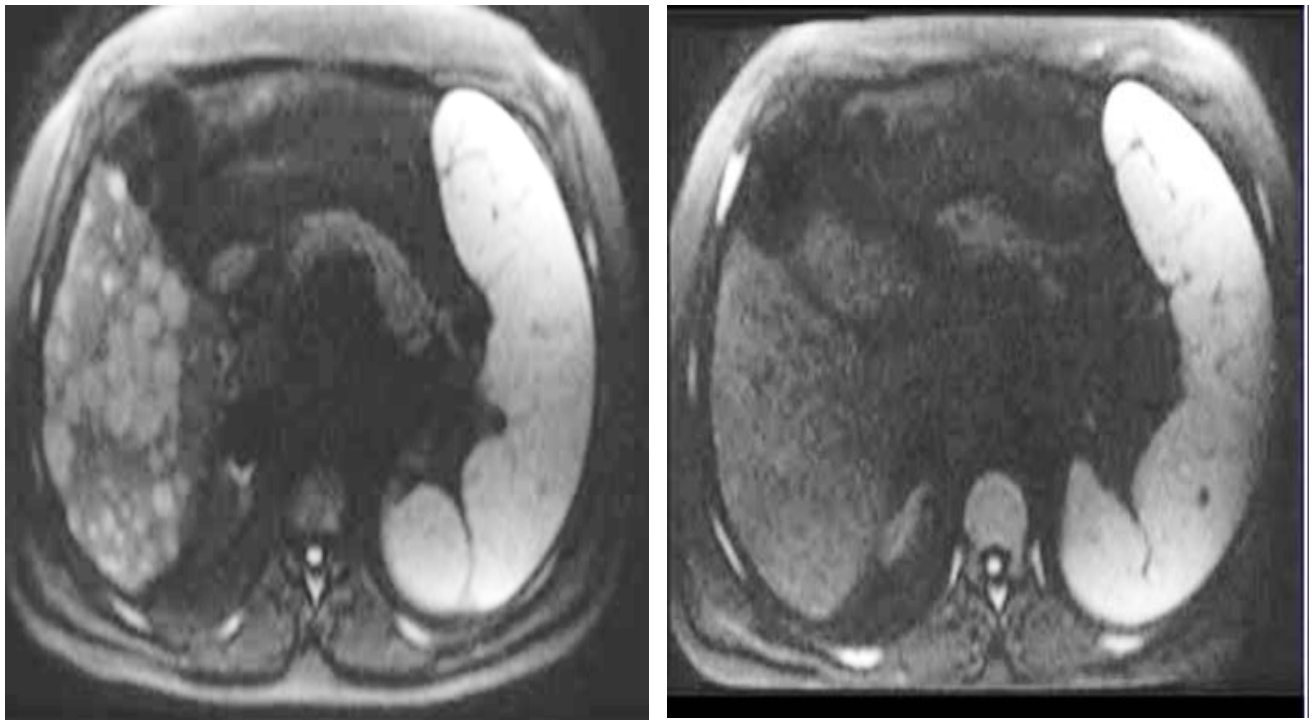
**Nivolumab**

**Sorafenib**

HCC, hepatocellular carcinoma; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; TTP, time to progression.

1. Clinicaltrials.gov. NCT02576509. Accessed July 28, 2016.
2. Mellman I et al. *Nature*. 2011;480(7378):480-489.

# Partial Response to Nivolumab

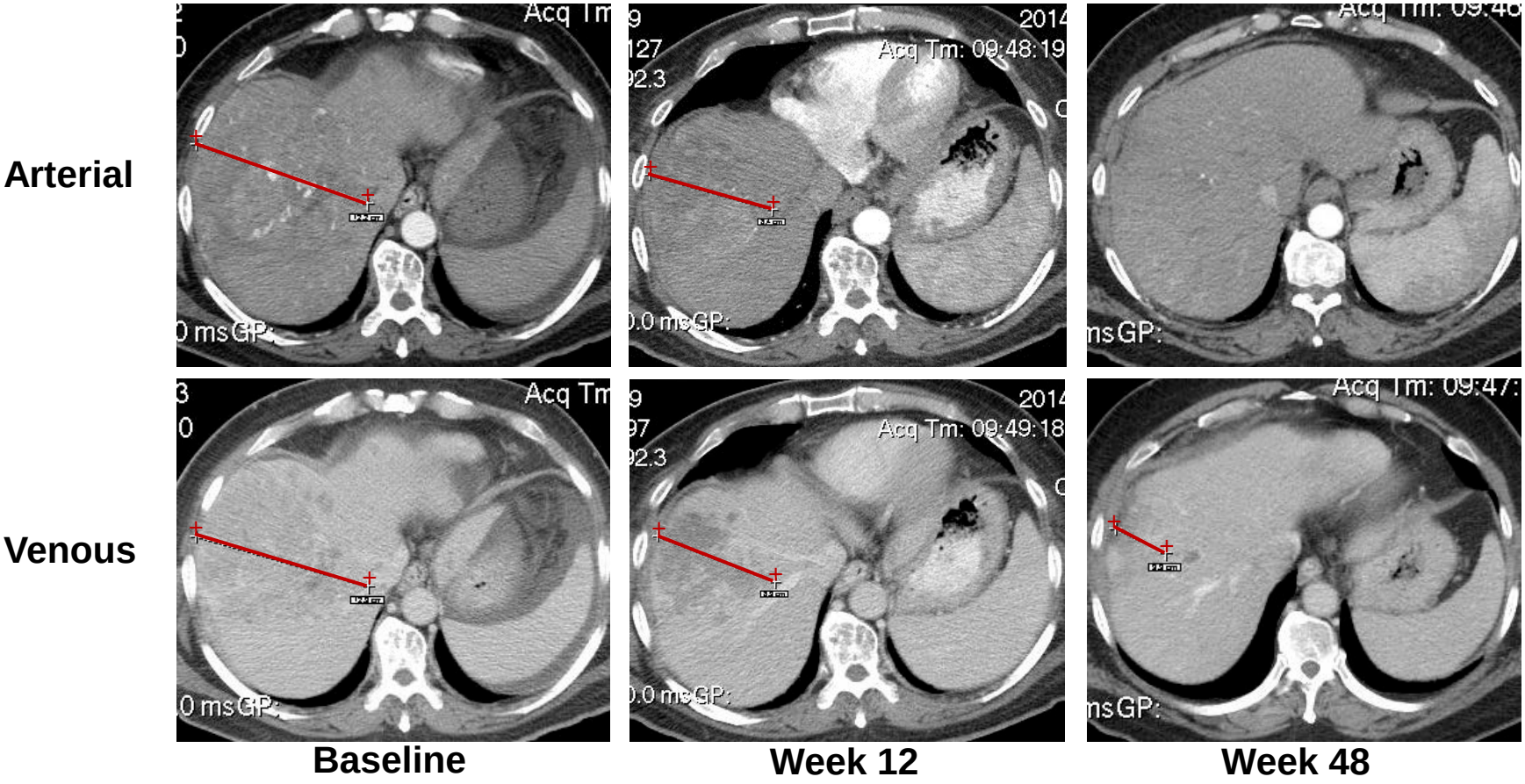


**Baseline**
AFP: 21,000 IU/mL

**Week 6**
AFP: 283 IU/mL

- 63 year-old male, uninfected HCC, Child-Pugh score A5
- No prior sorafenib or other treatment for HCC

# Durable Partial Response to Nivolumab



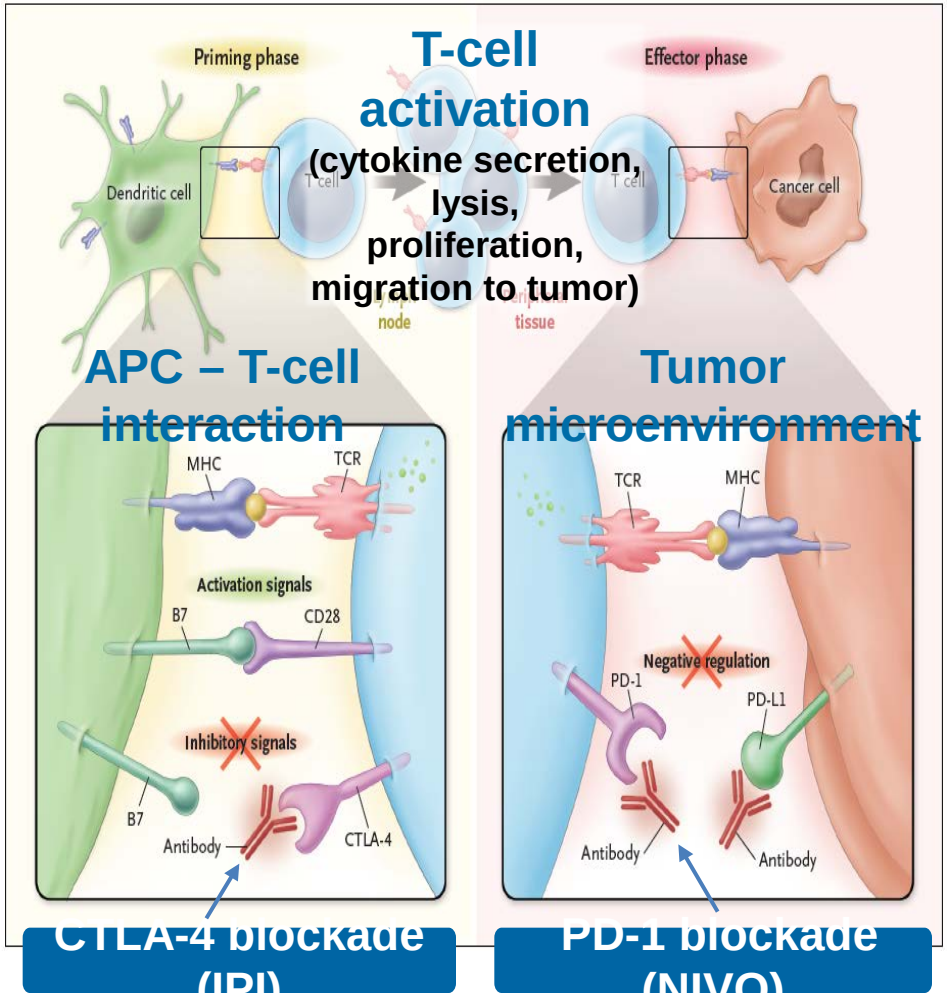

- 58-year-old white male with HCV-infected HCC, ECOG 0, Child-Pugh A5
- Progressed on sorafenib

# Select Investigational Immunotherapies for HCC

| Class | Agent | Target/Mechanism of Action | Ph[1] |
|---|---|---|---|
| Immuno-therapy* | | | |
| | Pexa-Vec (JX-594) | Oncolytic vaccinia virus | II† |
| | Tremelimumab | Checkpoint inhibitor (anti-CTLA4 mAb) | I, II‡ |
| | Durvalumab (MEDI4736) | Checkpoint inhibitor (anti-PD-L1 mAb) | I, I/II§ |
| | MEDI0680 | Checkpoint inhibitor (anti-PD-1 mAb) | I |
| | Pembrolizumab | Checkpoint inhibitor (anti-PD-1 mAb) | I, I/II‖ |
| | MPDL3280A | Checkpoint inhibitor (anti-PD-L1 mAb) | I‖ |
| | Nivolumab | Checkpoint inhibitor (anti-PD-1 mAb) | I |

*

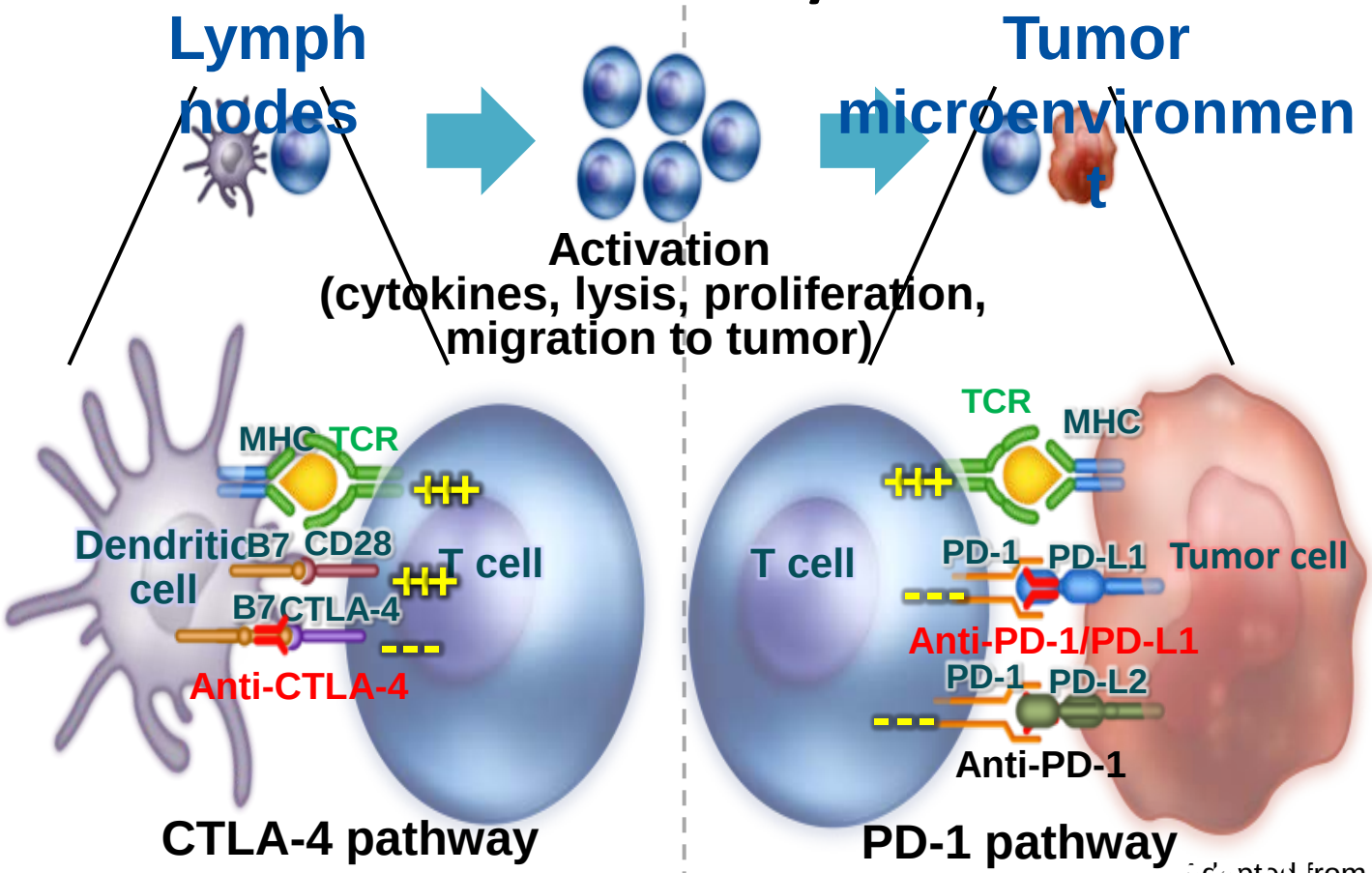
# Investigating Response to Immunotherapy




- PD-1 and CTLA-4 are distinct immune checkpoint proteins with complementary roles in regulating immune responses
- Anti-CTLA-4 agent, ipilimumab (IPI), and anti-PD-1 agent, nivolumab (NIVO) are approved for advanced melanoma alone or in combination (NIVO + IPI)[1,2]
- In CheckMate 067, which compared NIVO and NIVO + IPI vs IPI, numerically higher

Image: Ribas A et al. *N Engl J Med*. 2012;366:2517-2519. MHC = major histocompatibility complex; TCR = T-cell receptor. 1. YERVOY [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2015; 2. OPDIVO [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2017; 3. Larkin J et al. *N Engl J Med*. 2015;373:23-34.

# Therapeutic Targets: CTLA-4 and PD-1 Pathways

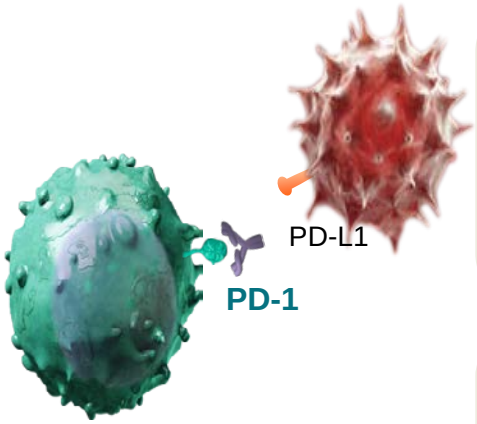



Adapted from Pardoll 2012.[1]

CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; TCR, T-cell receptor.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264.

# **CHECKMATE-040:** Phase I/II trial of Nivolumab ± Ipilimumab in Advanced HCC patients

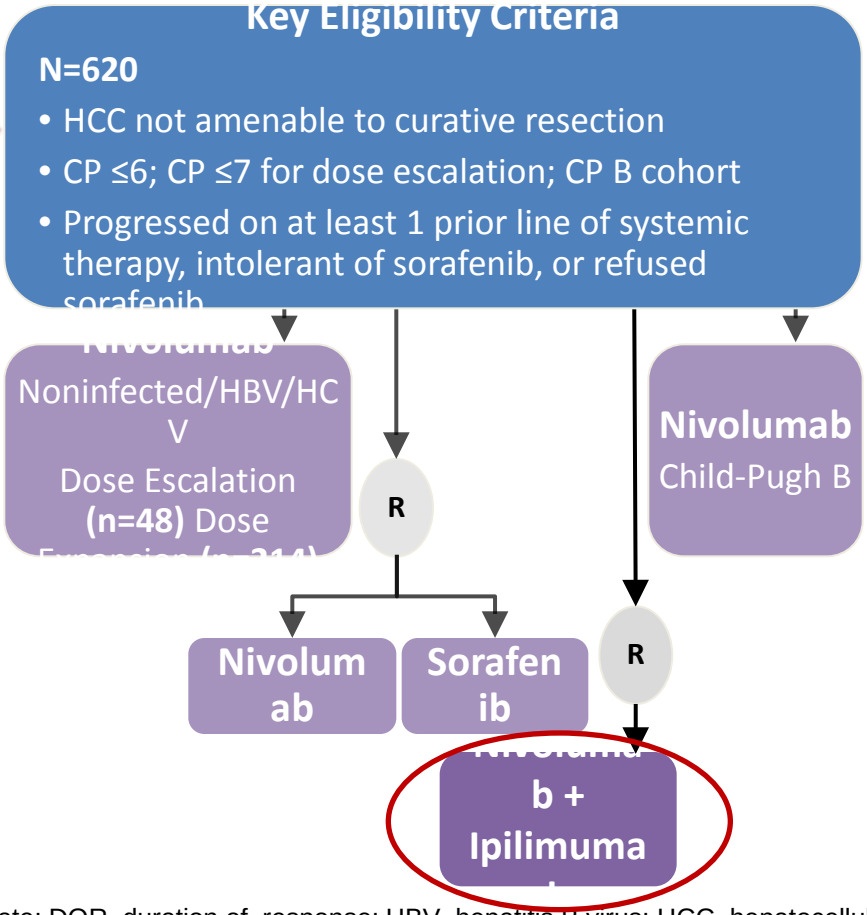



Adapted from Mellman I et al 2011.[3]

**Start Date:** **September 2012**

**Primary Endpoints:** **Safety and tolerability, ORR**

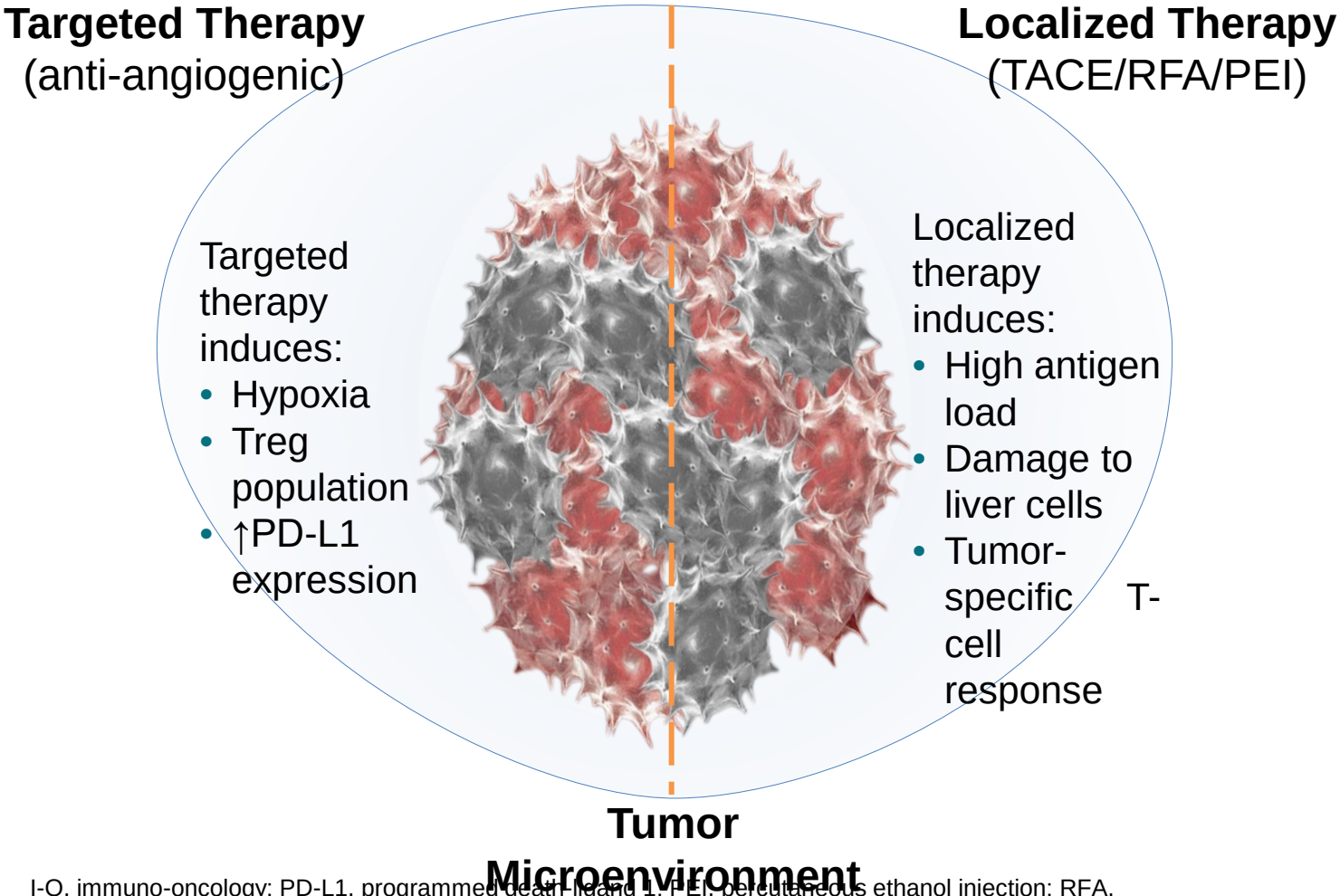
**Other Endpoints:** **CR, DCR, DOR, TTR, TTP, TTP rate, PFS, OS, OS rate, biomarkers, PK**




CR, complete response; CP, Child-Pugh; DCR, disease control rate; DOR, duration of response; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; R, randomize; TTP, time to progression; TTR, time to response.

1. Clinicaltrials.gov. NCT01658878. Accessed July 28, 2016. 2. El-Khoueiry AB et al. Poster presentation at ASCO 2016. 3. Mellman I et al. *Nature*. 2011;480(7378):480-489.

# Rationale Behind I-O + Non–I-O Treatment Modalities[1,2]




I-O, immuno-oncology; PD-L1, programmed death ligand 1; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation;
TACE, transcatheter arterial embolization; Treg, regulatory T cell.


1. Chen Y et al. *Hepatology*. 2015;61(5):1591-1602.
2. Greten et al. *Rev Recent Clin Trial*. 2008;3(1):31-39.

# On-going I-O Combo Treatment Modalities

| Regimen | Phase | Primary Endpoint | Enrollment | Start Date | Completion Date |
|---|---|---|---|---|---|
| Pembrolizumab+ Young TIL+ Aldesleukin | II | Tumor regression rate | 290 | Jul 2010 | Dec 2018 |
| Galunisertib + Nivolumab | Ib/II | Maximum tolerated dose | 100 | Oct 2015 | Apr 2018 |
| Durvalumab+ Tremelimumab | II | SAE, toxicity | 144 | Oct 2015 | Apr 2018 |
| Nivolumab + Ipilimumab | I/II | Safety and tolerability, ORR | 620 | Sep 2012 | Aug 2017 |
| Durvalumab+ Tremelimumab+ TACE/RFA/Cryoablation | I/II | Efficacy | 90 | Jun 2016 | April 2020 |

TIL, tumor-infiltrating lymphocytes; ORR, objective response rate; SAE, serious adverse events; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization

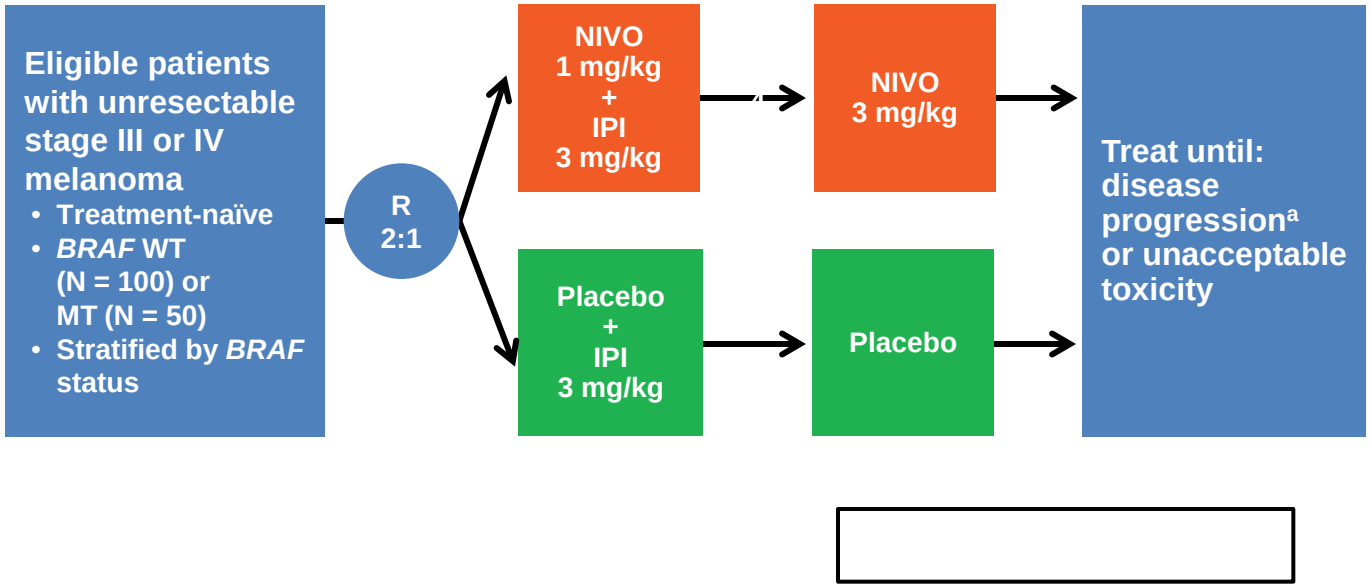
Clinicaltrials.gov. NCT01174121, NCT02423343, NCT01658878, NCT02519348, NCT02821754. Accessed December 13, 2016

# Nivo vs Nivo+Ipi

# NIVOLUMAB– METASTATIC MELANOMA
# 1st LINE COMBINATION WITH IPILIMUMAB

- In combination with ipilimumab, is indicated for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma.

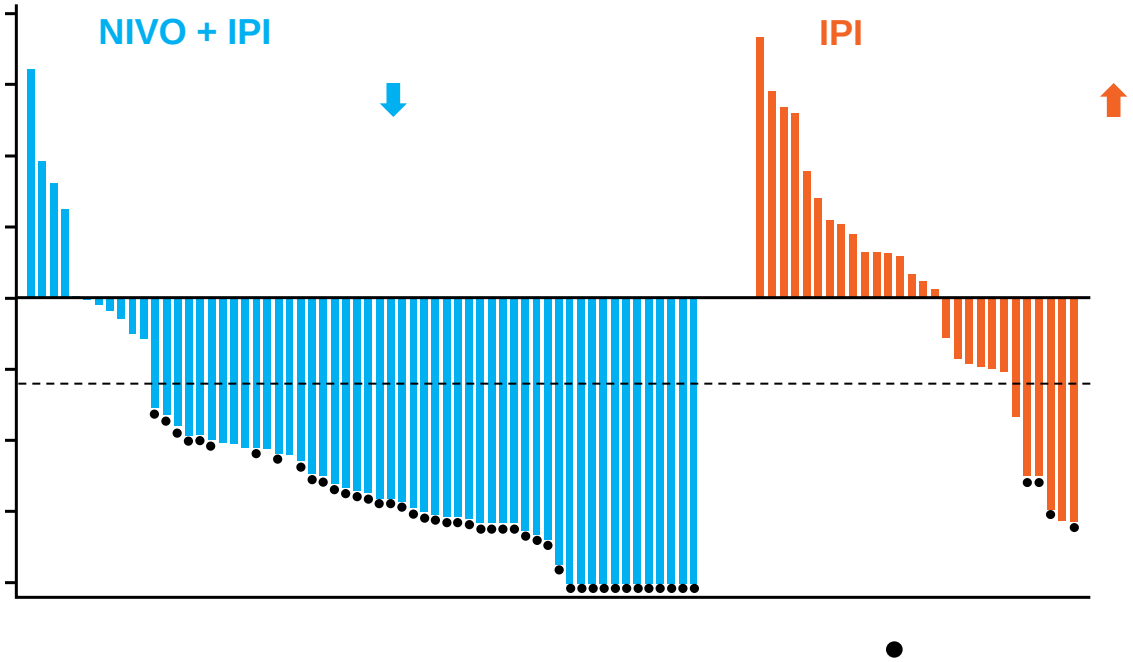
# CA209-069: Study Design



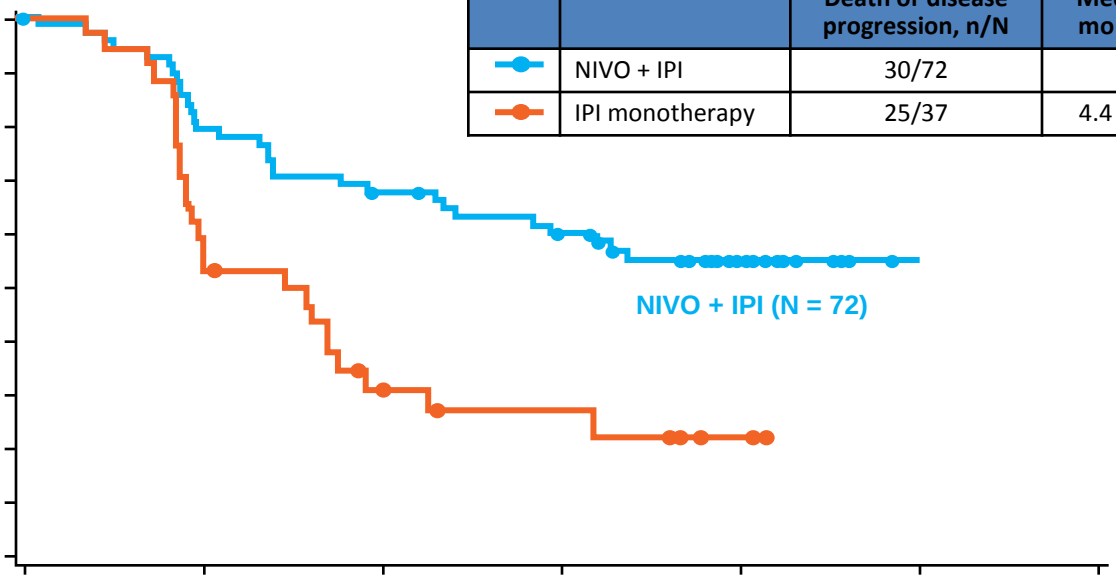
# Baseline Characteristics

| | All randomized patients (N = 142) | |
|---|---|---|
| | **NIVO + IPI (N = 95)** | **IPI (N = 47)** |
| **Age, median (years)** | 64 | 67 |
| **Age ≥65 years, %** | 50 | 57 |
| **Male/female, %** | 66/34 | 68/32 |
| **AJCC stage IV, %** | 89 | 81 |
| **M1c stage, %** | 46 | 45 |
| **ECOG PS of 0, %[a]** | 83 | 79 |
| **Baseline LDH levels, %** | | |
| ≤ULN | 74 | 77 |
| >ULN | 25 | 23 |
| **PD-L1 expression ≥5%[b]** | 25 | 23 |
| ***BRAF* V600 MT, %** | 24 | 21 |

# Tumor Burden Change From Baseline by RECIST v1.1 (*BRAF* WT Patients)



# PFS Among *BRAF* WT Patients




| | | Death or disease progression, n/N | Median PFS, mo (95% CI) |
|---|---|---|---|
| | NIVO + IPI | 30/72 | NR |
| | IPI monotherapy | 25/37 | 4.4 (2.8-5.7) |

# Most Common Treatment-Related Select AEs

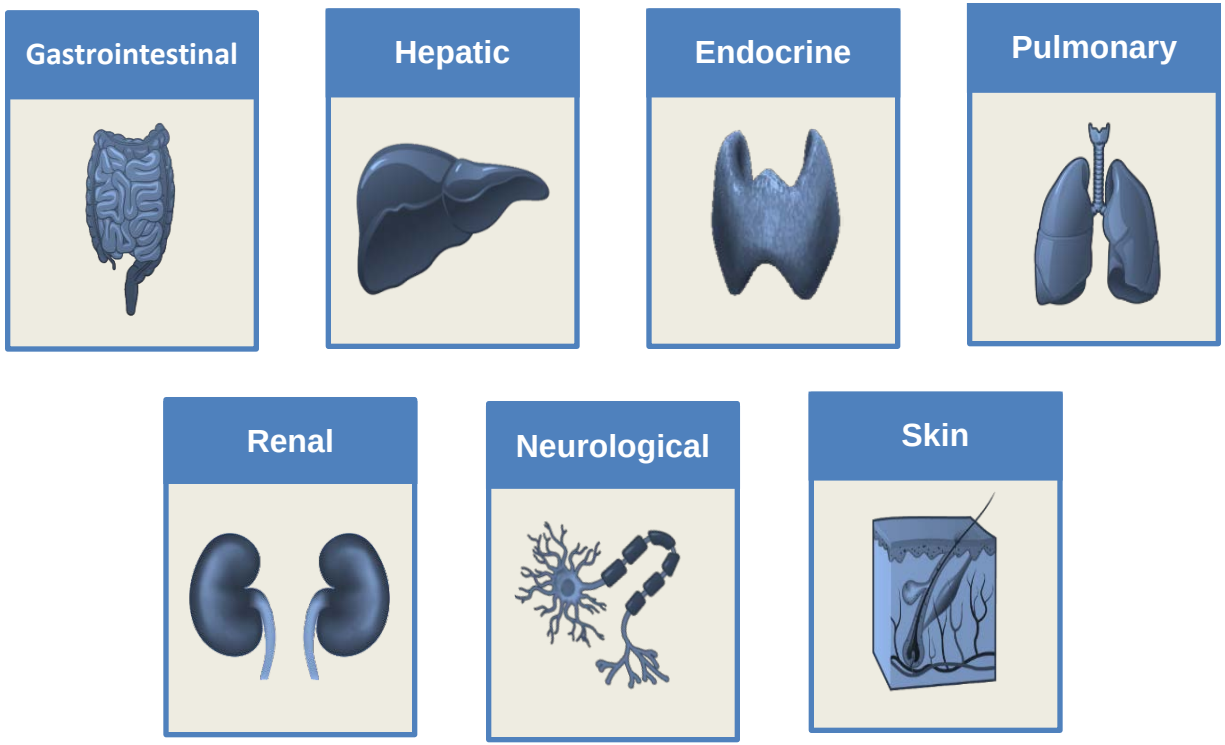
| Patients reporting event, % | NIVO + IPI (n = 94) | | IPI (n = 46) | |
|---|---|---|---|---|
| | Any grade | Grade 3–4 | Any grade | Grade 3–4 |
| **Skin AEs** | 71 | 10 | 59 | 0 |
| Rash | 42 | 5 | 26 | 0 |
| Pruritus | 35 | 1 | 28 | 0 |
| **Gastrointestinal AEs** | 51 | 21 | 37 | 11 |
| Diarrhea | 45 | 11 | 37 | 11 |
| Colitis | 23 | 17 | 13 | 7 |
| **Endocrine AEs** | 34 | 5 | 17 | 4 |
| Thyroid disorder | 23 | 1 | 15 | 0 |
| Hypothyroidism | 16 | 0 | 15 | 0 |
| Hypophysitis | 12 | 2 | 7 | 4 |
| **Hepatic AEs** | 28 | 15 | 4 | 0 |
| ALT increased | 22 | 11 | 4 | 0 |
| AST increased | 21 | 7 | 4 | 0 |
| **Pulmonary AEs** | 12 | 2 | 4 | 2 |
| Pneumonitis | 11 | 2 | 4 | 2 |
| **Renal AEs** | 3 | 1 | 2 | 0 |
| Creatinine increased | 2 | 1 | 0 | 0 |

# Conclusions

- Compared with IPI alone, the NIVO + IPI combination significantly improved ORR and PFS in all randomized patients
  - NIVO + IPI ORR (59%; CR: 22%) versus IPI ORR (11%; CR: 0%)
  - ORR and PFS benefit was observed irrespective of *BRAF* status, tumor PD-L1 status, and presence of poor prognostic factors
- Treatment-related AEs were reported more frequently with NIVO + IPI than with IPI alone
- Patients with poor prognostic factors had a similar safety profile to the entire population
- AEs were generally managed using established guidelines
- The NIVO + IPI regimen provided a favorable benefit-risk profile in treatment-naïve advanced melanoma patients, including those with poor prognostic factors

# Immuno-Oncology Safety and Adverse Event Management

# Organ Types Affected by AEs Are Similar With Anti–PD-1 and Anti–CTLA-4 Alone and in Combination[1-3]




1. Larkin J et al. *N Engl J Med*. 2015;373:23-34.2. Robert C et al. *N Engl J Med*. 2015;372:2521-2532. 3. Long G et al. Presented at ASCO 2016; abstract 9506.

# Safety Monitoring Overview

- Screen patients for AEs
  - Patient education:  Reinforce  to patients the importance of reporting any new or worsening symptom

- Early recognition and early intervention
  - Dose delay/discontinuation
  - Corticosteroids
  - Other immunosuppresants

- Monitor outpatients with ongoing AEs

- For patients admitted to an outside hospital for AEs
  - Frequent contact with admitting physician and subspecialist as appropriate
  - Provide guidance on detection and management of drug-related adverse events

- Select AE's => refer to specific algorithms

# Some Differences Observed….

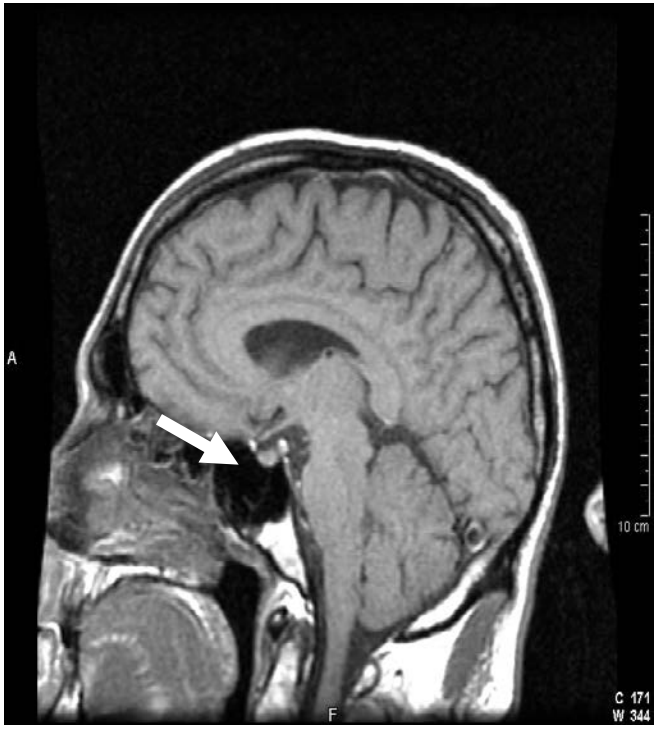
- Single agent anti–PD-1 therapies are better tolerated than single agent IPI
- High-dose IPI 10 mg/kg in the adjuvant melanoma setting has more side effects than IPI 3 mg/kg in the metastatic setting
- Pulmonary AEs seem rare with IPI
- Hepatic AEs appear more frequently with combination than with monotherapy
- Colitis is rare with anti–PD-1 monotherapy, yet occurs more commonly with a regimen containing IPI
- Thyroiditis is more frequent with anti–PD-1-containing regimens than with IPI monotherapy
- Elevations of amylase and/or lipase may occur with the NIVO + IPI regimen, with some patients having symptoms of pancreatitis

IPI = ipilimumab; NIVO = nivolumab.

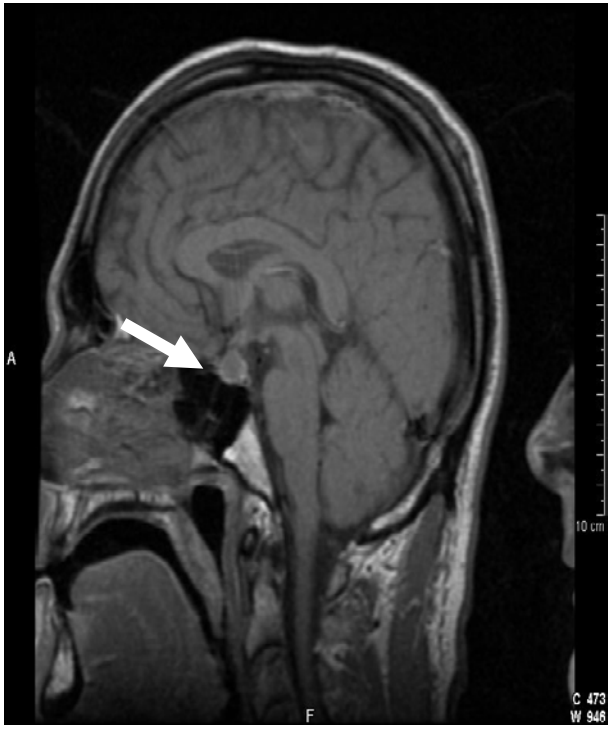
## Endocrinopathy Take-Home Points

- Severe endocrine-related AEs are infrequent
  - Adrenal insufficiency and hypothyroidism < 1%
  - Hyperthyroidism and hypophysitis are rare (<0.1%)
- When encountering non-specific symptoms (fatigue, weakness), think of endocrinopathies
- Consider endocrine consult to interpret lab results and guide management
  - Treatment may be continued once appropriate hormone replacement initiated
- Subjects with endocrinopathy may require replacement dose steroids rather than high-dose steroids

# Radiographic Findings for IPI-Associated Hypophysitis



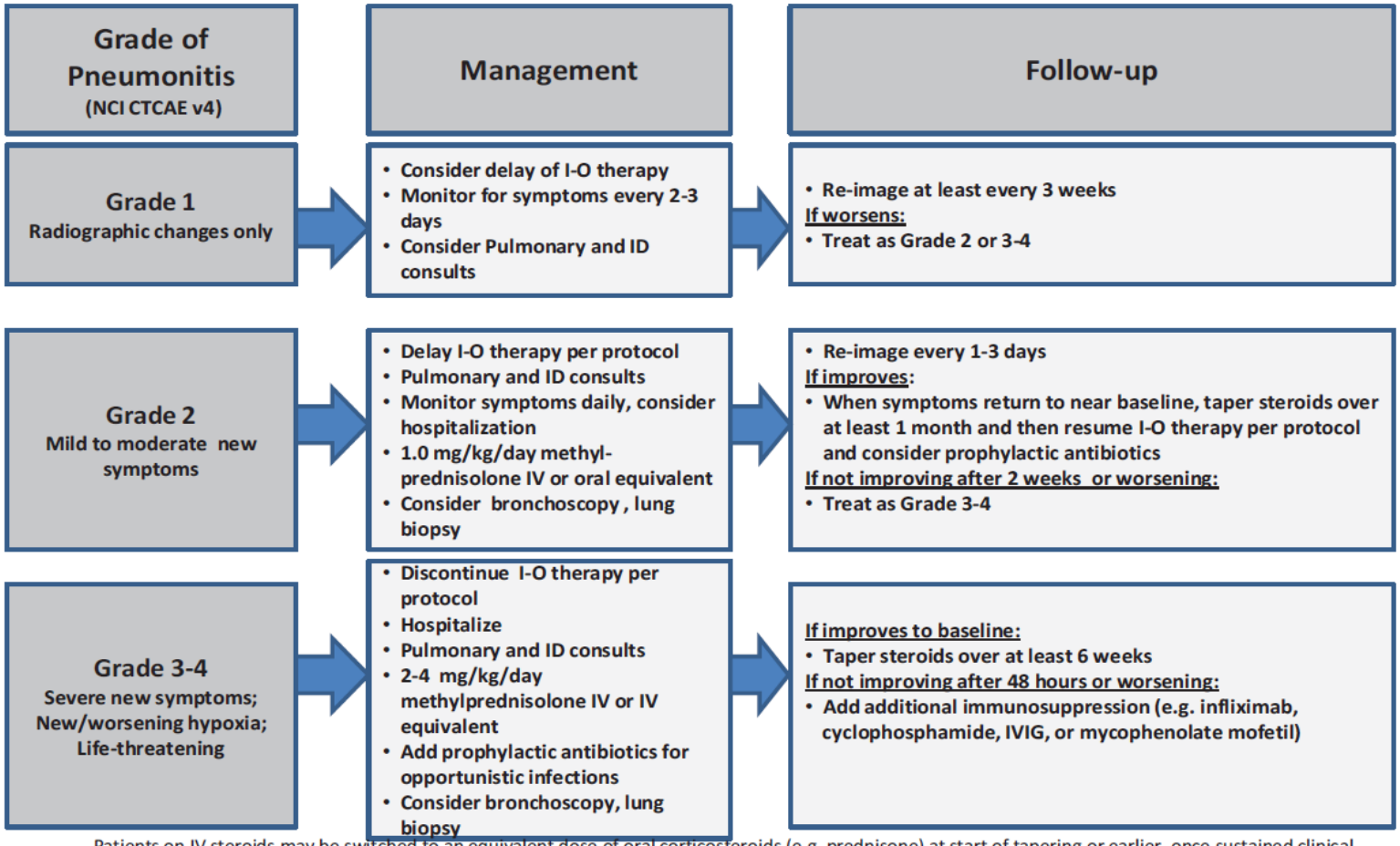

**6/30/04 Baseline (4.5 mm)**




**12/3/04 After 5 doses (10.8 mm) headache/fatigue**

Adapted from Blansfield J, et al. *J Immunother*. 2005;28:593-598.

# Algorithm for Suspected Pulmonary Toxicity




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Pulmonary Toxicity Take-Home Points

- Pulmonary toxicity has been infrequent across the nivolumab program
  - Nivo Monotherapy – Pneumonitis - 3% (all grades), 1% (Grades 3-4)

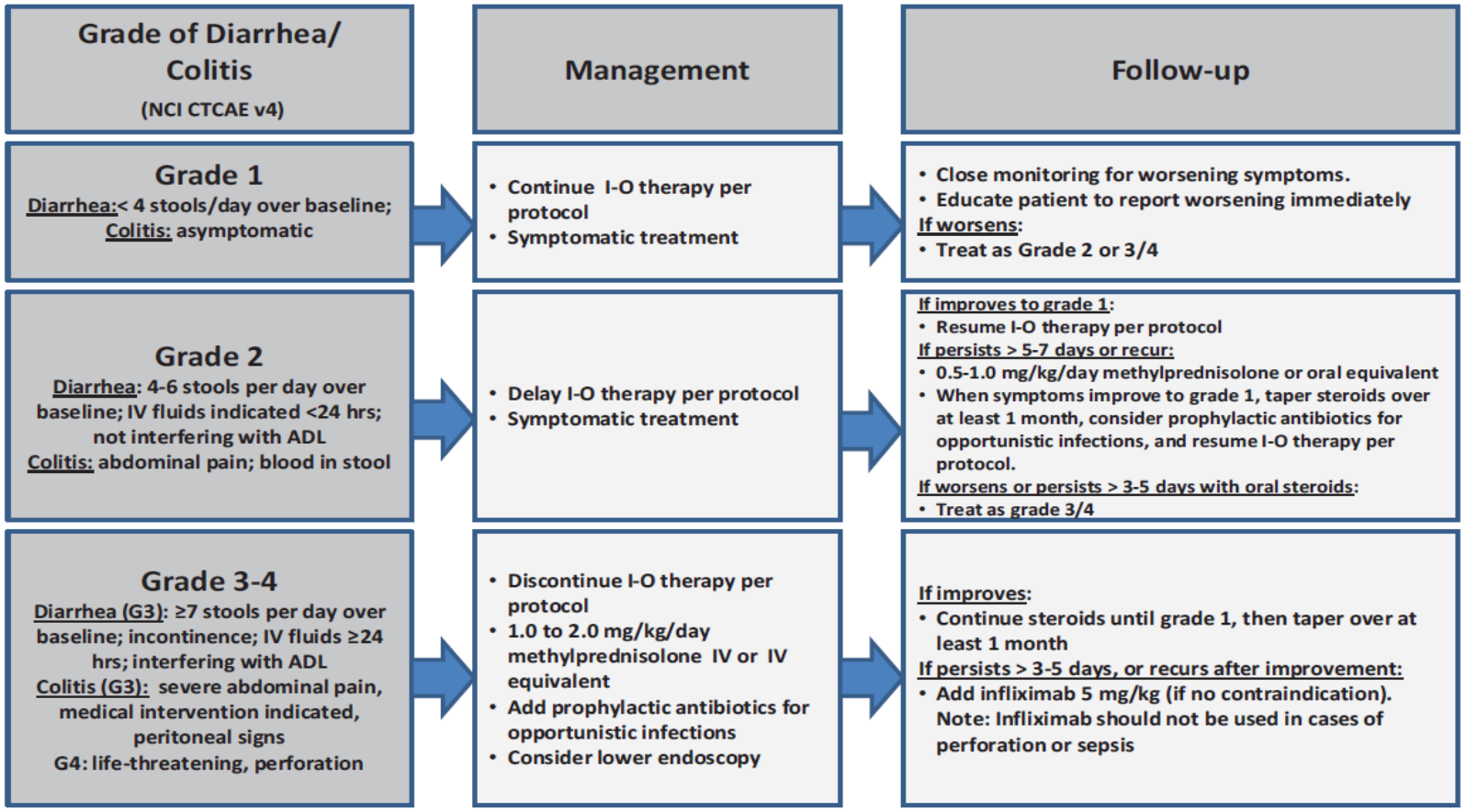
- At presentation: Grades 1-3, the majority are Grades 1-2
-
- Pulmonary toxicity may present with clinical symptoms or may be an incidental finding on scans

- Subjects have been successfully treated with prompt initiation of appropriate doses of corticosteroids

- Subjects with low-grade pulmonary toxicity may be re-challenged with study drug once off steroids

- Consider prophylactic antibiotics for opportunistic infections for those individuals receiving high dose steroids for greater than 4 weeks

# Algorithm for Suspected GI Toxicity




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## GI Toxicity Take-Home Points

- Most cases of diarrhea have been mild (Grade 1)
- Low grade diarrhea may be managed symptomatically ± dose delay
- SAEs of colitis have been uncommon (<1.0%) in the nivolumab program overall
- Use results of diagnostic evaluation to guide management
  - A negative diagnostic evaluation may need to be repeated
- Initiate treatment early
- If steroids are begun, taper slowly
- Consider prophylactic antibiotics for opportunistic infections for those individuals receiving high dose steroids for greater than 4 weeks

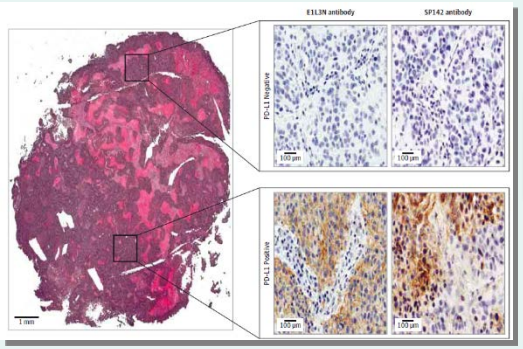
# PD-L1 as a Biomarker: Biological, Technical, and Logistical Complexity

**Challenges Surrounding Biomarker**

**Biology: PD-L1[1-3]**

- Inter and intratumor heterogeneity
- Inducible and dynamic (IFN, post-treatment)
- Cell type (immune cell versus tumor versus both)
- Location (membrane versus cytoplasm)

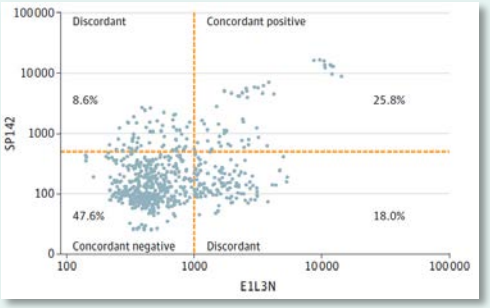
**Expression of PD-L1 is heterogeneous[1]**




**Technical: Assay[1,4,5]**

- Epitope stability
- Distribution (patchy versus diffuse)
- Different antibodies and platforms
- Different thresholds for expression
- Interobserver readability

**Abs are not identical: >25% discordant[1,6,7]**




**Logistics: Tissue[1,8,9]**

- Interval between tissue and treatment (archived versus fresh)
- Primary versus metastatic disease
- Some circumstances not amenable to obtaining any tissue
- Certain biopsy methods result in poor tissue quality/quantity

IFN = interferon; PD-L1 = programmed death ligand 1.

1. McLaughlin J et al. *JAMA Oncol.* 2016;2(1):46-54. 2. Heskamp S et al. *Cancer Res.* 2015;75(14):2928-2936. 3. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264.
4. Wilson BE et al. *J Immunol Methods*. 1991;139:55-64. 5. Phillips T et al. *Appl Immunohistochem Mol Morphol.* 2015;23(8):541-549.
6. Rimm D et al. *Breast Cancer Res Treat.* 2014;147(2):457-458. 7. Velcheti V et al. *Lab Invest*. 2014;94(1):107-116.
8. Check W. *Cap Today*. 2010. 9. Warth A et al. *Recent Results Cancer Res.* 2015;199:71-84.

# Biological Complexity of PD-L1: Dynamic PD-L1 Expression (1 of 1)

| Agent | Cell Type | Effect on PD-L1 Expression |
|---|---|---|
| **Radiation therapy**[1-3] | Colorectal, breast, melanoma‖ | Up-regulated*† |
| **Cisplatin** | Hepatoma[4]<br>HNSCC[5] | Up-regulated*†‡ |
| **Paclitaxel** | Breast[6]<br>Colorectal, hepatocellular carcinoma[7] | Up-regulated*† |
| **Etoposide**[6] | Breast | Up-regulated* |
| **Oxaliplatin**[8] | Plasmacytoid dendritic cells | Up-regulated* |
| **Doxorubicin**[9] | Breast | Down-regulated*†‡ |
| **Gefitinib** | NSCLC | Down-regulated*†‡[10]<br>Up-regulated§[11] |
| **Sunitinib / pazopanib**[12] | Metastatic RCC | Down-regulated§ |

**PD-L1 expression is dynamic, and may change upon treatment with various therapies**[1-12]

*PD-L1 expression determined by flow cytometry. †PD-L1 expression determined by qRT-PCR or transcriptomeic profiling. ‡PD-L1 expression determined by western blots. §PD-L1 expression determined by IHC. ‖ In tumors resistant to radiation + anti-CTLA-4.

HNSCC = head and neck squamous cell carcinoma; IHC = immunohistochemistry; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; RCC = renal cell carcinoma.

1. Dovedi SJ et al. *Cancer Res*. 2014;74(19):5458-5468. 2. Deng L et al. *J Clin Invest*. 2014;124(2):687-695. 3. Twyman-Saint Victor C et al. *Nature*. 2015;520(7547):373-377. 4. Qin X et al. *Cell Mol Biol*. 2010;56 Suppl:OL1366-72. 5. Qiao P et al. Poster presentation at AACR 2014. 3750. 6. Zhang P et al. *Mol Immunol*. 2008;45(5):1470-1476. 7. Gong W et al. *J Chemother*. 2011;23(5):295-299. 8. Tel J et al. *Cancer Immunol Immunother*. 2012;61(7):1101-1111.
9. Ghebeh H et al. *Breast Cancer Res*. 2010;12(4):R48. 10. Lin K et al. *Biochem Biophys Res Commun*. 2015;463(1-2):95-101.
11. Omori S et al. Abstract presented at ASCO 2015 Annual Meeting. e22118. 12. Sharpe K et al. *Clin Cancer Res.* 2013;19(24):6924-6934.

# Overview of PD-L1 Assays

| | BMS* | Merck*[1-3] | Roche*[4-8] | AstraZeneca*[9-11] |
|---|---|---|---|---|
| **Drug** | Nivolumab | Pembrolizumab | Atezolizumab | Durvalumab |
| **Ab clone/epitope** | 28-8 Abcam/ Extracellular domain | 22C3 Dako/ Extracellular domain | SP142 Spring Bioscience/ Intracellular domain | SP263 Spring Bioscience/ Extracellular domain |
| **IVD Class III diagnostic partner** | Dako | Dako | Ventana | Ventana |
| **Sample source** | Archival or fresh tissue | Archival or fresh tissue | Archival or fresh tissue | Archival or fresh tissue |
| **Staining location** | Membrane | Membrane | Membrane | Membrane |
| **Cell type scored** | Tumor cells | Tumor cells | Tumor cells and immune cells | Tumor cells |
| **Scoring method** | % of cells with membrane staining at any intensity | **Tumor Proportion score (TPS):** % of cells with membrane staining at any intensity | **Tumor cell (TC) score:** staining % of tumor cells **Immune cell (IC) score:** staining % of tumor area | % of cells with membrane staining |
| **Current IVD PD-L1 Threshold** | <1% or ≥1% | <50% or ≥50% | N/A | N/A |
| **PD-L1 Thresholds Under Evaluation** | ≥1%, ≥5%, or ≥10% | ≥1%, ≥50% | TC1/2/3 or IC1/2/3 ≥1% | ≥25% |
| **Trial Design** | **057:** All comers **067:** All comers | **KN-001:** PD-L1 ≥1% **KN-010:** PD-L1 ≥1% | **POPLAR:** all comers **FIR:** TC2/3 or IC2/3 | **NCT01693562:** all comers |
| **Testing Requirement** | **Complementary** | Companion | Companion | Companion |

*No head-to-head studies have been conducted and comparisons cannot be made between these assays or antibodies used therein.

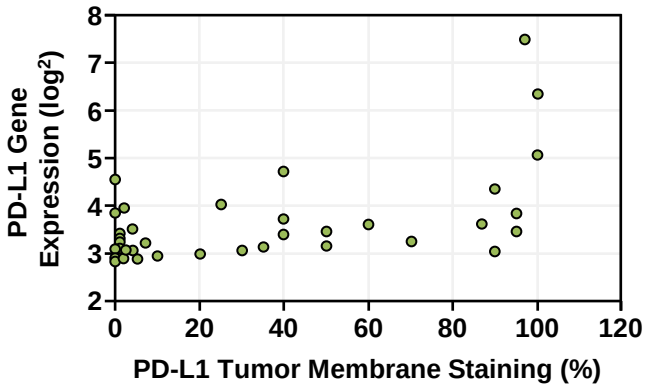
IC = immune cell; IVD = in vitro diagnostic; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; TC = tumor cell; TIIC = tumor-infiltrating IC.

1. Dolled-Filhart M et al. Poster presentation at ASCO 2015. 11065. 2. Rizvi N et al. Poster presentation at ASCO 2015. 8026. 3. Rizvi NA et al. Oral presentation at ASCO 2014. 8007. 4. Spira AI et al. Oral presentation at ASCO 2015. 8010. 5. Spigel DR et al. Poster presentation at ASCO 2015. 8028. 6. Liao Z et al. Poster presentation for Spring Bioscience. 7. ClinicalTrials.gov. NCT01903993. 8. Fehrenbacher L et al. *Lancet.* 2016. doi: 10.1016/S0140-6736(16)00587-0. [Epub ahead of print] 9. Rebelatto MC et al. Poster presentation at ASCO 2015. 8033. 10. ClinicalTrials.gov. NCT01693562. 11. Sholl LM et al. *Arch Pathol Lab Med.* 2016 [Epub ahead of print].

# Alternative Ways to Detect PD-L1

## Gene Expression and Rearrangements

- **RNA:** *CD274** gene expression can be assessed with mRNA levels by microarray. Association with PD-L1 protein levels (detected by IHC) was observed only for samples with greater than 80% staining[1]




- **DNA amplification/translocation:** *CD274** overexpression can occur through gene amplification, or through translocation and fusion of *CD274* with a highly expressed promoter[2,3]

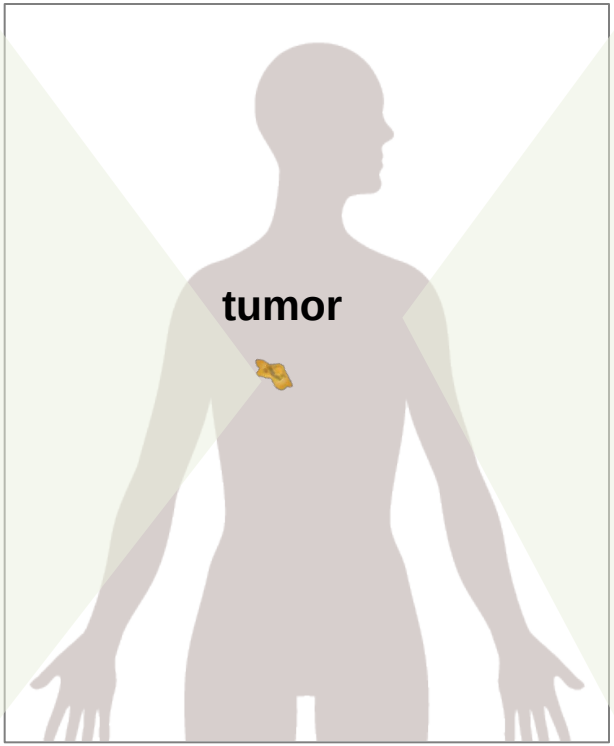
## Protein Expression Levels

- **Soluble PD-L1:** Serum levels of soluble PD-L1 can be assessed by ELISA. Soluble PD-L1 has been detected in patients with autoimmune disease[4]
- **Circulating tumor cells:** Tumor cells extracted from peripheral blood can be assessed for PD-L1 expression[5]
- **Peripheral blood mononuclear cells:** PD-L1 expression can also be assessed in CD4 and CD8 T cells, B cells, plasmacytoid DC, natural killer cells, natural killer T cells, MDSC, monocytic MDSC, granulocytic MDSC, and lineage-negative MDSC[6]

*The CD274 gene encodes for the PD-L1 protein.
DC = dendritic cell; ELISA = enzyme-linked immunosorbent assay; MDSC = myeloid-derived suppressor cell; PD-L1 = programmed death ligand 1.
1. Harbison CT et al. Poster presentation at WCLC 2013. P3.06-040. 2. Green MR et al. *Blood*. 2010;116(17):3268-3277. 3. Steidl C, Gascoyne RD. *Blood.* 2011;118(10):2659-2669. 4. CA209009 Clinical Protocol. 5. Andorsky DJ et al. *Clin Cancer Res*. 2011;17(13):4232-4244.
6. Lepone L et al. *J Immunother Cancer*. 2014;2(suppl 3):P152.

# Other Exploratory Biomarkers

| Tumor biomarkers[1-7] |
| --- |
| TILs/immunoscore (eg, CD4 and CD8 T cells) |
| Gene expression signatures (immune signatures/ inflamed phenotype) |
| Tumor immune marker expression (eg, CTLA-4, PD-L1, PD-L2) |
| Mutational load/burden, neo-antigens |
| TCR sequencing |
| Other known oncogenic driver mutations (eg, EGFR, KRAS, BRAF) |

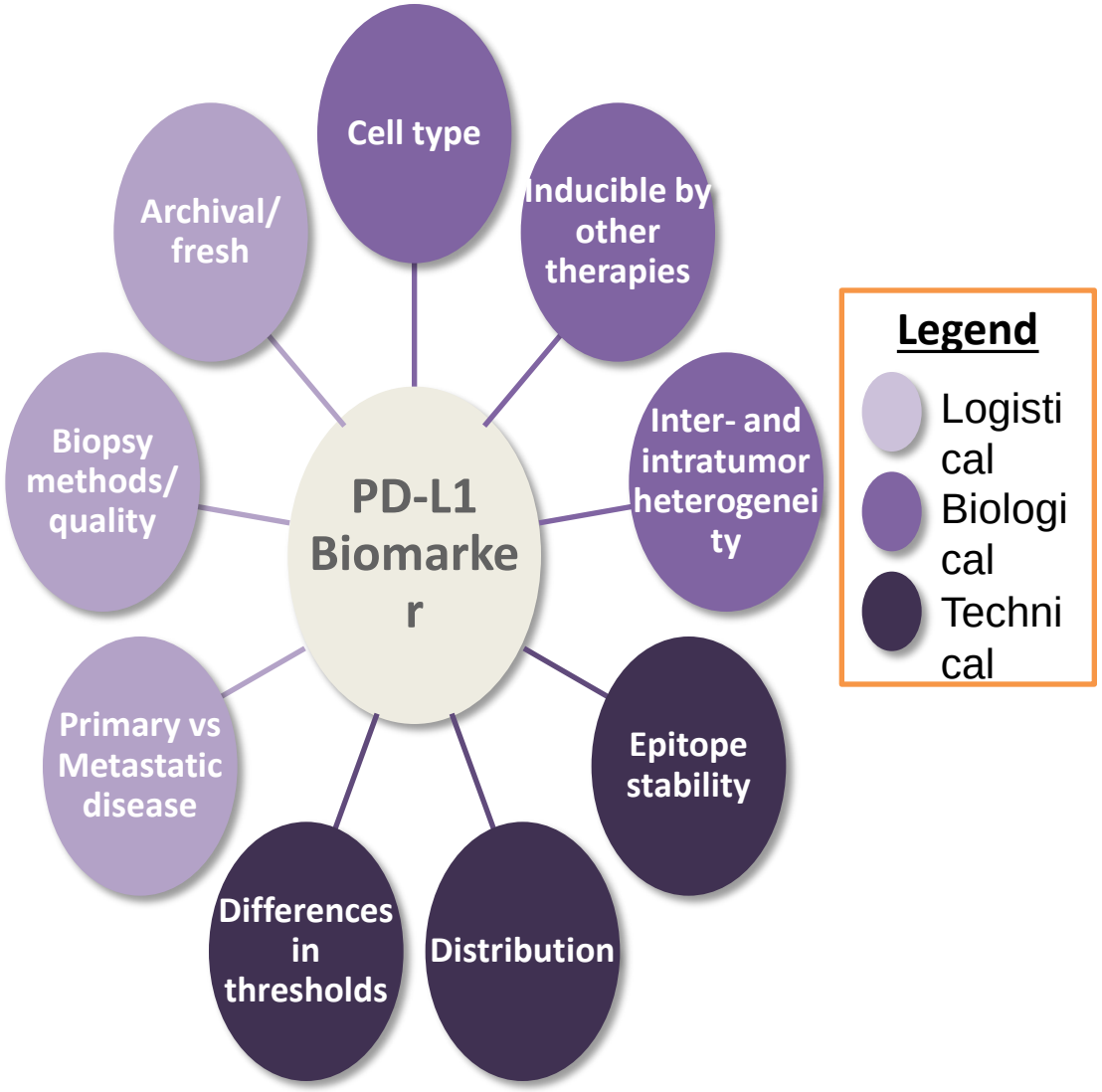



| Peripheral biomarkers[2,3,8-12] |
| --- |
| Immune monitoring: absolute lymphocyte count, circulating T-cell subsets/MDSCs |
| TCR sequencing |
| Gene expression profiling: peripheral blood |
| Serum chemokines/cytokines: interferons, interferon inducible factors, serum soluble factors |
| sPD-L1 |
| Circulating miRNAs |
| Antitumor antibodies |
| SNPs (germline) |

BRAF = serine/threonine-protein kinase B-Raf; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; EGFR = epidermal growth factor receptor; KRAS = Kirsten rat sarcoma viral oncogene homolog; MDSC = myeloid-derived suppressor cells; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; SNP = single nucleotide polymorphism; sPD-L1 = soluble PD-L1; TCR = T-cell receptor; TILs = tumor-infiltrating lymphocytes.

1. Sosman JA et al. Poster presentation at ASCO 2013. TPS3114. 2. Choueiri TK et al. Oral presentation at ASCO 2015. 4500. 3. Clinical Protocol CA209009. 4. Lawrence MS et al. *Nature*. 2013;499(7457):214-218. 5. Antonia SJ et al. Poster presentation at WCLC 2013. P2.11-035. 6. Weber JS et al. *Lancet Oncol*. 2015;16(4):375-384. 7. Brown SD et al. *Genome Res*. 2014;24(5):743-750. 8. Postow MA et al. *J Transl Med*. 2014;12(suppl 1):O8. 9. Komatsu N et al. *Cancer*. 2012;118(12):3208-3221. 10. Wang Z et al. *Med Hypotheses*. 2013;81(1):41-43. 11. Luborsky J et al. *Am J Reprod Immunol*. 2005;54(2):55-62. 12. Schneider BP et al. *Lancet Oncol*. 2012;13(10):e427-e436.

# Challenges for PD-L1 as a Biomarker[1-4]




PD-L1, programmed death-ligand 1.

1. Herbst RS. Presented at ASCO 2015 Annual Meeting. Post-057 discussion.
2. Heskamp S et al. *Cancer Res*. 2015;75(14):2928-36. 3. Atefi M et al. *Clin Cancer Res.* 2014;20(13):3446-3457.
4. Phillips T et al. *Appl Immunohistochem Mol Morphol*. 2015;23(8):541-549.

# Conclusions

- Immunotherapy is a promising modality in the management of advanced HCC
- Nivolumab monotherapy has a manageable safety profile in patients with HCC, including those with HBV or HCV infection
  - The safety profile was similar to that observed in other tumor types
- Durable responses were observed across all dose levels and etiologic cohorts
- These preliminary data support the ongoing clinical development of nivolumab in HCC


Thank You