Systemic ~~Chemo~~therapy: What is Available & What is in the Pipeline?

11th Annual Southwest Liver Disease Symposium: Advances in Hepatology 2017

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DISCLOSURES

- No Relevant Financial Disclosures
- Will Discuss Investigational/Off label compounds

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Objectives

- Understanding current standard of care systemic option(s) for treating HCC
- Understanding new emerging therapies
- Familiarize with potential novel therapies

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The Problem

- Global Issue
  - leading causes of cancer-related death
  - 700,000 new cases/yr with >600,000 deaths are attributed to HCC each year.1
  - US:
    - incidence has tripled over the last three decades
    - >20,000 cases estimated to be diagnosed (2011)

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SHARP Trial

Table 1. Demographic and Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Variable	Sorafenib (N=299)	Placebo (N=303)
Age — yr	64.9±11.2	66.3±10.2
Sex — no. (%)		
Male	260 (87)	264 (87)
Female	39 (13)	39 (13)
Region — no. (%)		
Europe and Australasia	263 (88)	263 (87)
North America	27 (9)	29 (10)
Central and South America	9 (3)	11 (4)
Cause of disease — no. (%)		
Hepatitis C only	87 (29)	82 (27)
Alcohol only	79 (26)	80 (26)
Hepatitis B only	56 (19)	55 (18)
Unknown	49 (16)	56 (19)
Other	28 (9)	29 (10)
ECOG performance status — no. (%)†		
0	161 (54)	164 (54)
1	114 (38)	117 (39)
2	24 (8)	22 (7)
BCLC stage — no. (%)‡		
B (intermediate)	54 (18)	51 (17)
C (advanced)	244 (82)§	252 (83)
Macroscopic vascular invasion — no. (%)	108 (36)	123 (41)
Extrahepatic spread — no. (%)	159 (53)	150 (50)
Lymph nodes	89 (30)	65 (21)
Lung	67 (22)	58 (19)
Macroscopic vascular invasion, extrahepatic spread, or both — no. (%)		
Absent	90 (30)	91 (30)
Present	209 (70)	212 (70)
Child–Pugh class — no. (%)¶		
A	284 (95)	297 (98)
B	14 (5)	6 (2)
Biochemical analysis		
Albumin — g/dl		
Median	3.9	4.0
Range	2.7–5.3	2.5–5.1
Total bilirubin — mg/dl		
Median	0.7	0.7
Range	0.1–16.4	0.2–6.1
Alpha-fetoprotein — ng/ml		
Median	44.3	99.0
Range	0–208×10⁴	0–5×10⁵

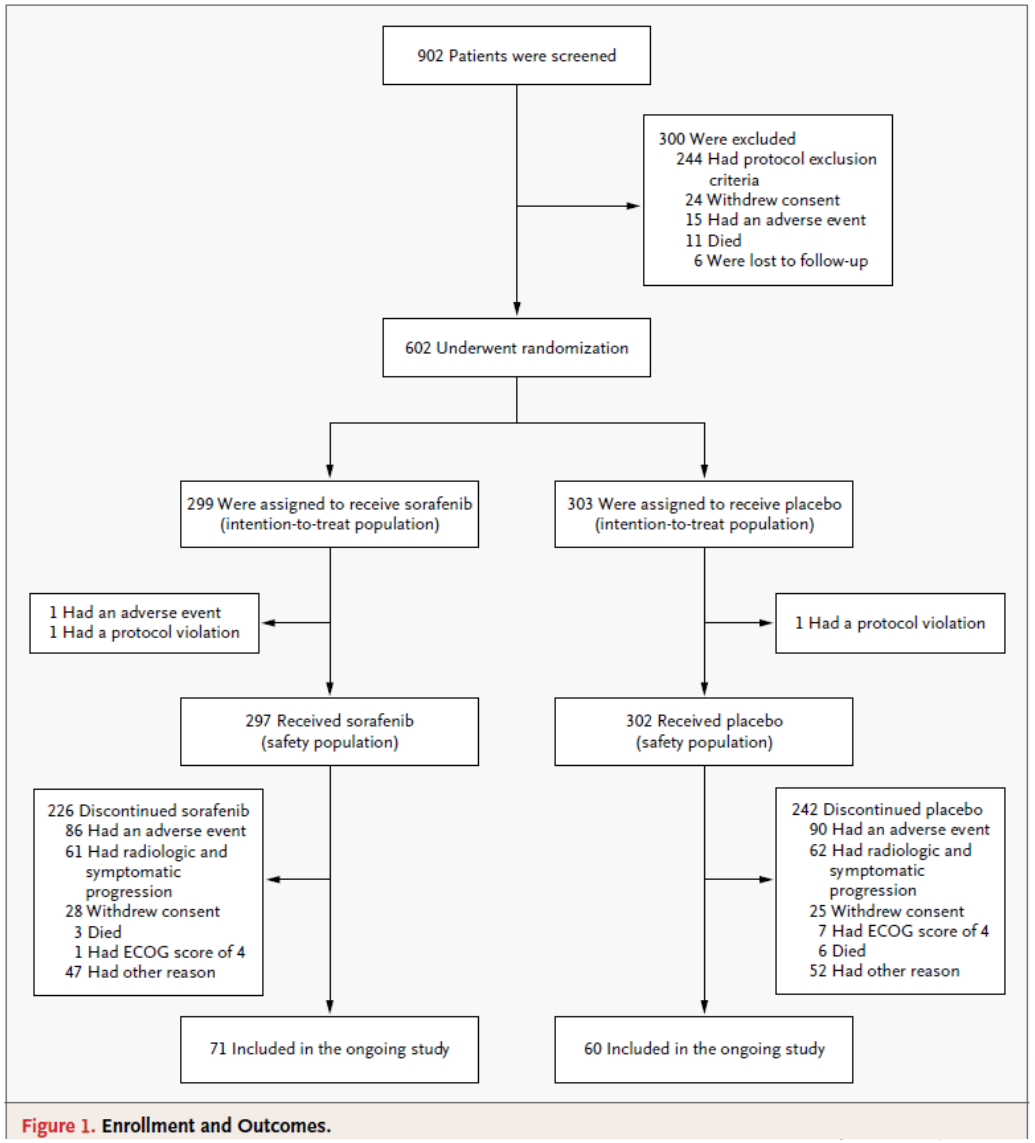

Figure 1. Enrollment and Outcomes.

N Engl J Med 2008;359:378-90.

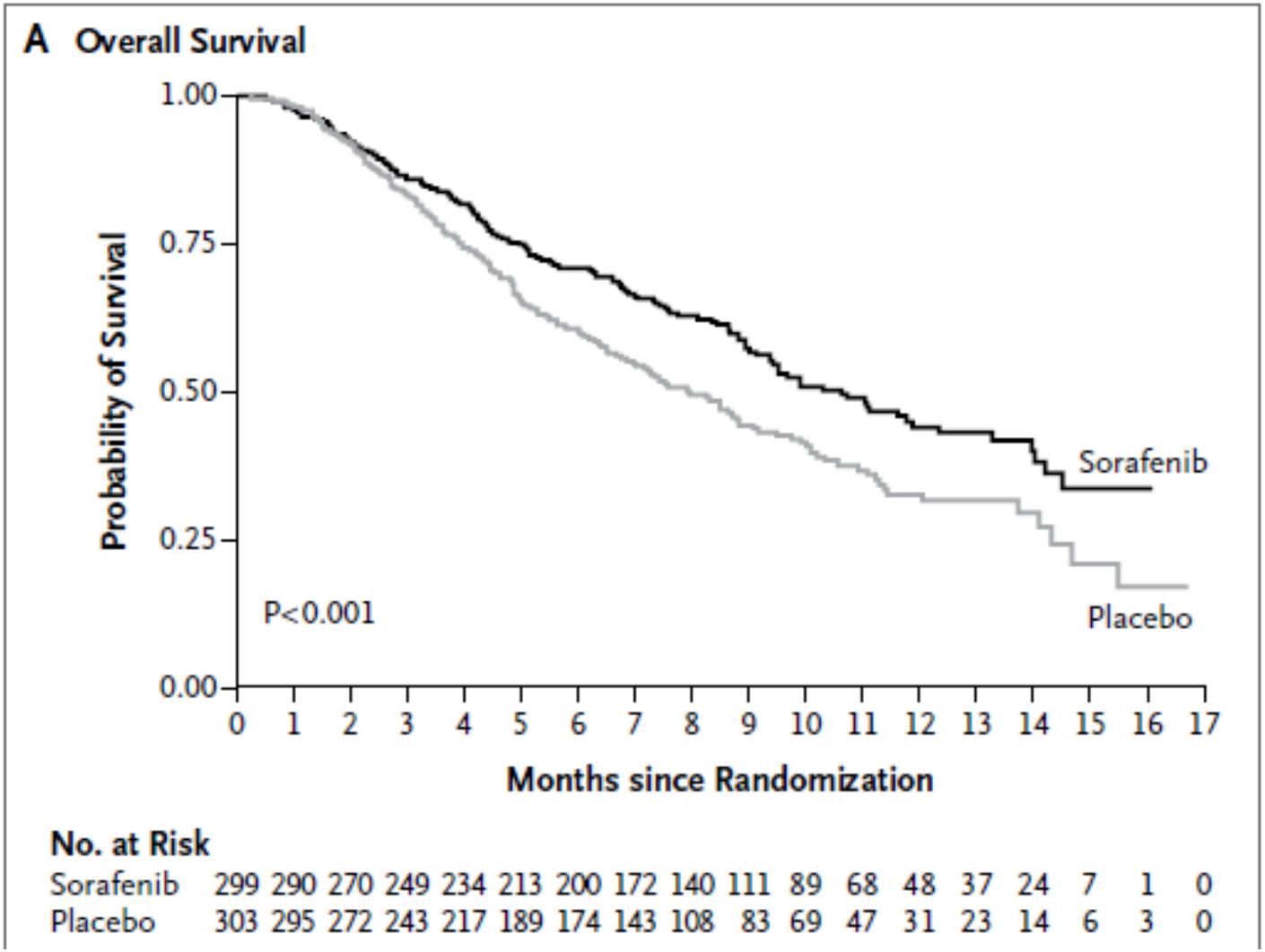

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Table 2. Summary of Efficacy Measures.*

Outcome	Sorafenib (N=299)	Placebo (N=303)	Hazard Ratio (95% CI)	P Value
Overall survival (mo)			0.69 (0.55–0.87)	<0.001
Median	10.7	7.9		
95% CI	9.4–13.3	6.8–9.1		
1-yr survival rate (%)	44	33		0.009
Time to symptomatic progression (mo)†			1.08 (0.88–1.31)	0.77
Median	4.1	4.9		
95% CI	3.5–4.8	4.2–6.3		
Time to radiologic progression (mo)			0.58 (0.45–0.74)	<0.001
Median	5.5	2.8		
95% CI	4.1–6.9	2.7–3.9		
Level of response (%)‡				
Complete	0	0		NA
Partial	2	1		0.05
Stable disease	71	67		0.17
Disease-control rate (%)§	43	32		0.002

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RESORCE

Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib

- oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumor immunity
- randomized, double-blind, placebo-controlled, phase 3 trial
- 152 sites in 21 countries

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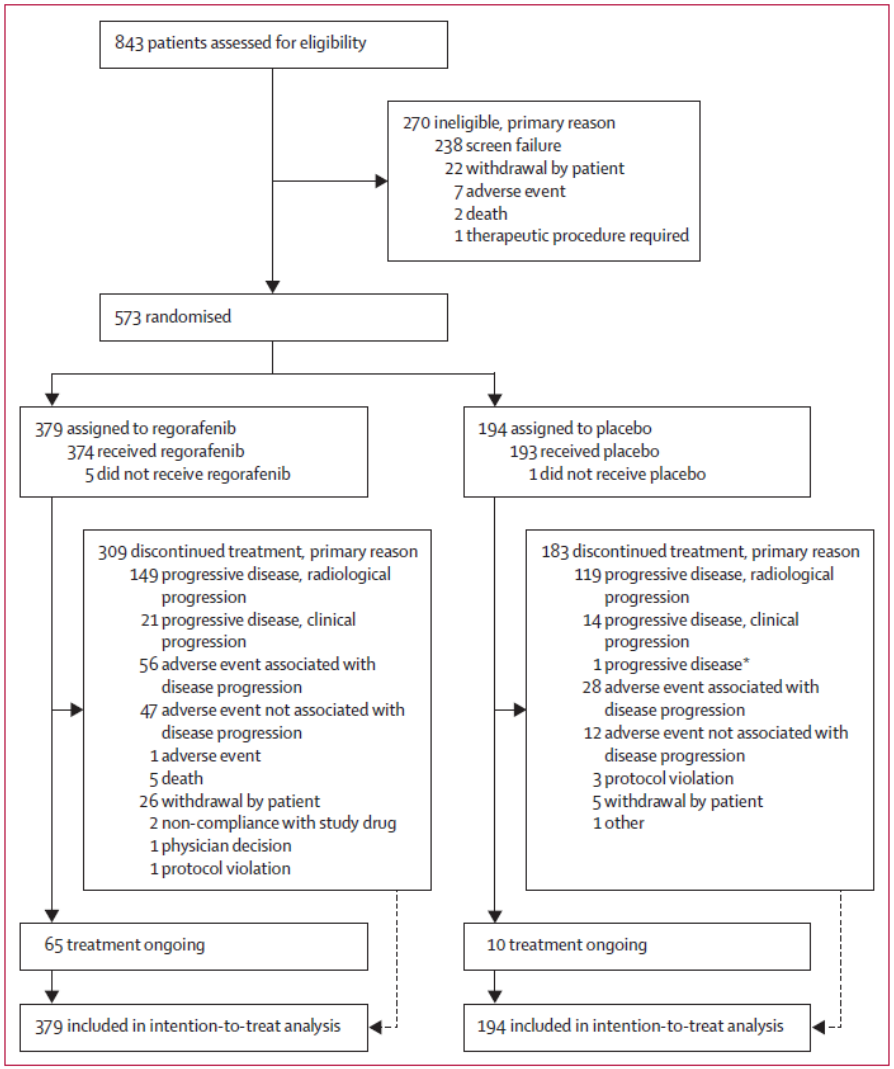
	Regorafenib (n=379)	Placebo (n=194)
Sex		
Male	333 (88%)	171 (88%)
Female	46 (12%)	23 (12%)
Age, years	64 (54–71)	62 (55–68)
Race		
White	138 (36%)	68 (35%)
Asian	156 (41%)	78 (40%)
Black	6 (2%)	2 (1%)
Other/not reported	79 (21%)	46 (24%)
Geographical region		
Rest of world	236 (62%)	121 (62%)
Asia*	143 (38%)	73 (38%)
ECOG performance status		
0	247 (65%)	130 (67%)
1	132 (35%)	64 (33%)
Macrovascular invasion	110 (29%)	54 (28%)
Extrahepatic disease	265 (70%)	147 (76%)
Macrovascular invasion and/or extrahepatic disease	304 (80%)	162 (84%)
Lung, target lesion†	98 (26%)	48 (25%)
Lymph node, target lesion†	58 (15%)	36 (19%)
Lung, non-target lesion†	121 (32%)	57 (29%)
Lymph node, non-target lesion†	61 (16%)	29 (15%)
Pattern of progression on previous sorafenib treatment		
New extrahepatic lesion	153 (40%)	80 (41%)
New intrahepatic lesion	168 (44%)	88 (45%)
Growth of intrahepatic or extrahepatic lesions, or both	307 (81%)	156 (80%)
α-fetoprotein ≥400 ng/mL	162 (43%)	87 (45%)
Child-Pugh class‡		
A	373 (98%)	188 (97%)
B	5 (1%)	6 (3%)
BCLC stage		
A (early)	1 (<1%)	0
B (intermediate)	53 (14%)	22 (11%)
C (advanced)	325 (86%)	172 (89%)

	Regorafenib (n=379)	Placebo (n=194)
(Continued from previous column)		
Liver cirrhosis (investigator assessed)	285 (75%)	144 (74%)
Aetiology of HCC§		
Hepatitis B	143 (38%)	73 (38%)
Alcohol use	90 (24%)	55 (28%)
Hepatitis C	78 (21%)	41 (21%)
Unknown	66 (17%)	32 (16%)
Non-alcoholic steatohepatitis	25 (7%)	13 (7%)
Other	28 (7%)	10 (5%)
Number of target lesions (mRECIST)¶		
1	67 (18%)	31 (16%)
2	175 (46%)	88 (45%)
3	68 (18%)	37 (19%)
4	43 (11%)	26 (13%)
5	19 (5%)	12 (6%)
Time from initial HCC diagnosis to start of study treatment, months		
Median (IQR)	21 (11–38)	20 (12–32)
Mean (SD)	29 (28)	27 (22)
Duration of sorafenib treatment, months	7·8 (4·2–14·5)	7·8 (4·4–14·7)
Time from progression on sorafenib to start of study treatment, months	1·4 (0·9–2·3)	1·4 (0·9–2·2)
Time from discontinuation of sorafenib to start of study treatment, months	0·9 (0·7–1·3)	0·9 (0·7–1·3)

Data are n (%) or median (IQR), unless otherwise specified. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group. HCC=hepatocellular carcinoma. mRECIST=modified RECIST for HCC. *Includes patients from China, Japan, South Korea, Singapore, and Taiwan. †RECIST version 1.1. ‡The Child-Pugh system describes liver disease severity: patients are divided into classes from A to C, with class C representing the worst prognosis. Child-Pugh class was missing in one patient in the regorafenib group. Those patients who progressed to Child-Pugh B after screening and before randomisation were included. §Patients could have more than one aetiology of HCC. ¶n=372 in the regorafenib group.

Table 1: **Baseline characteristics (efficacy population)**



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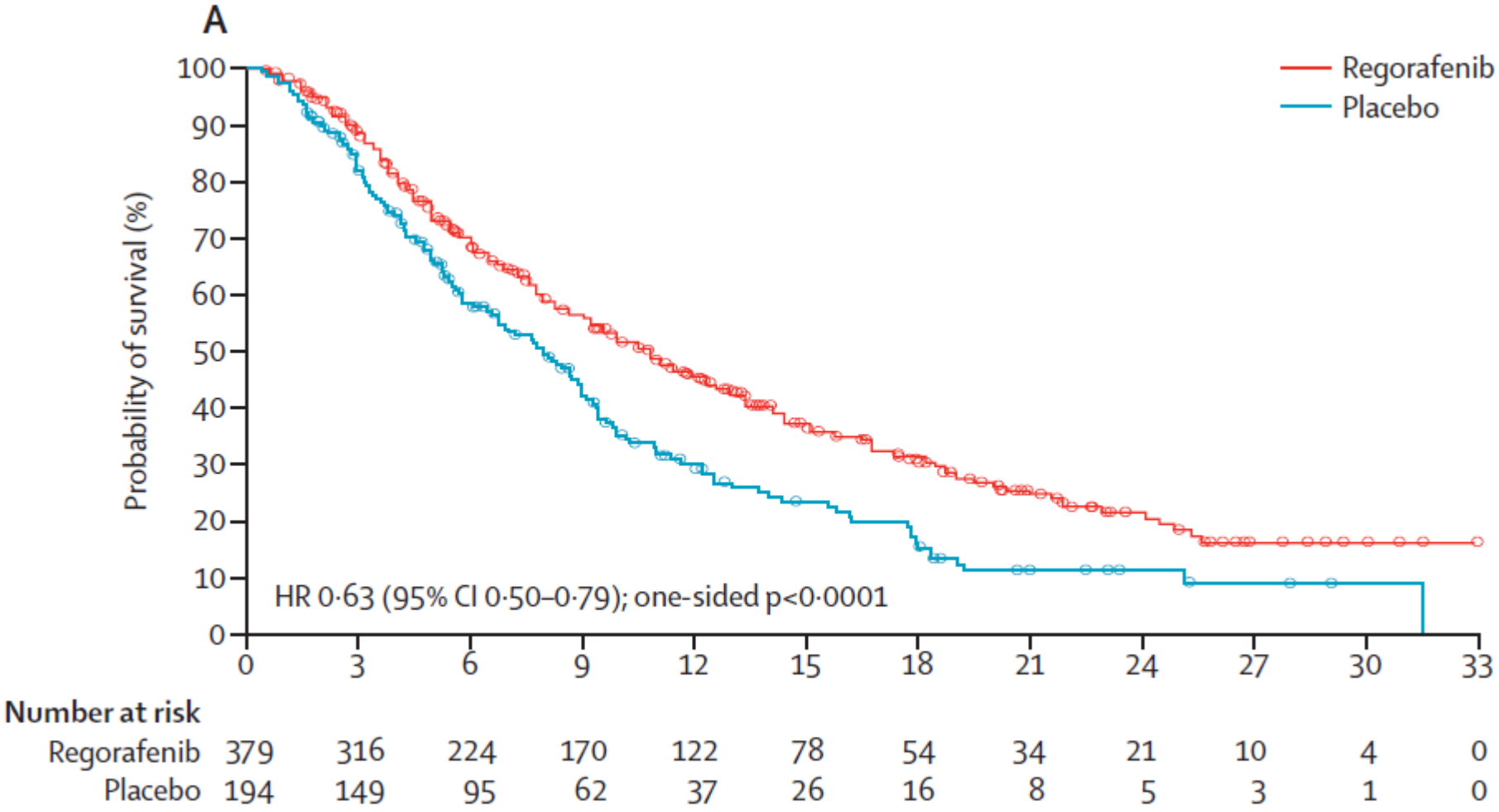
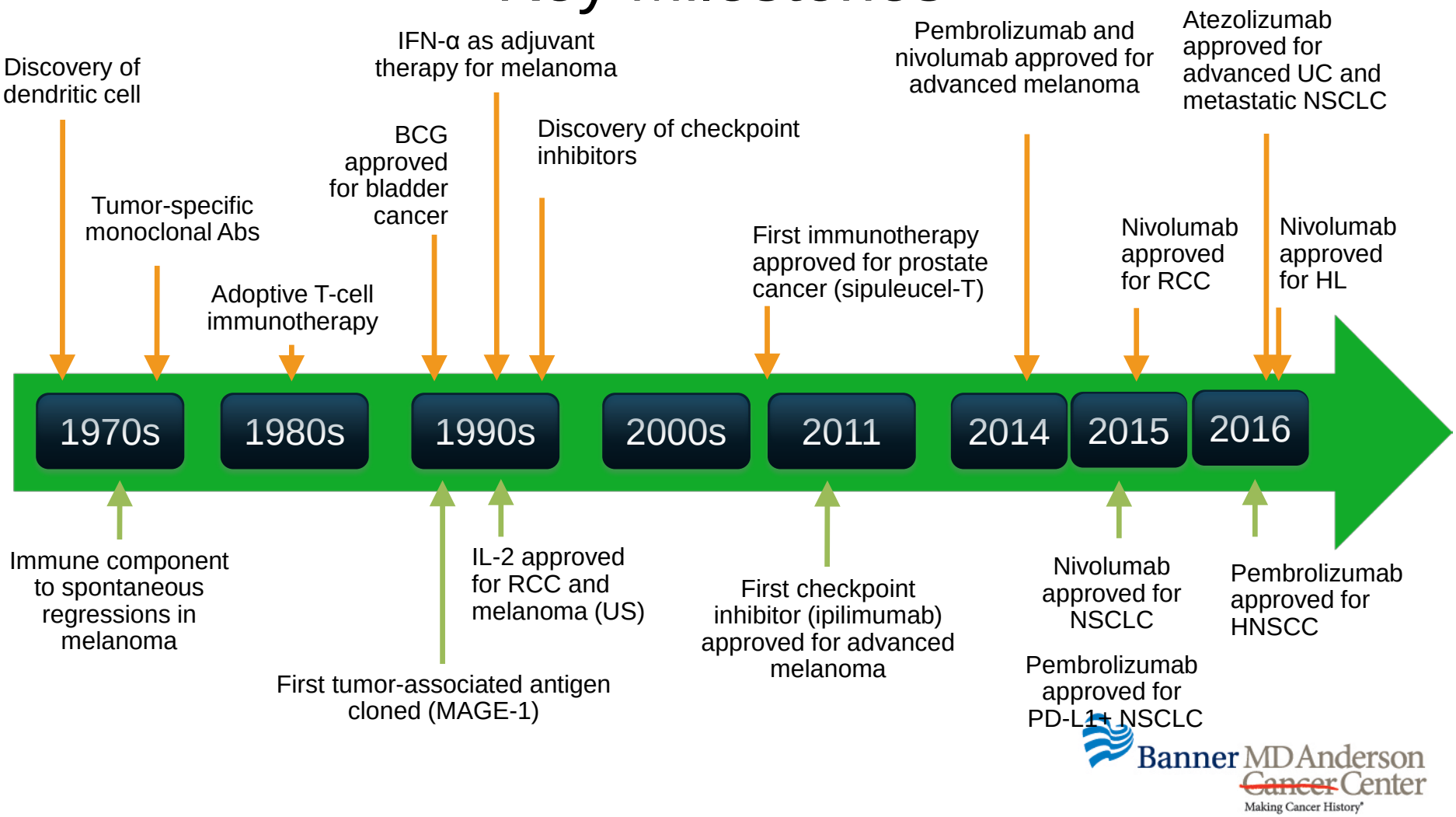
Kaplan-Meier analysis of overall survival



History of Cancer Immunotherapy: Key Milestones



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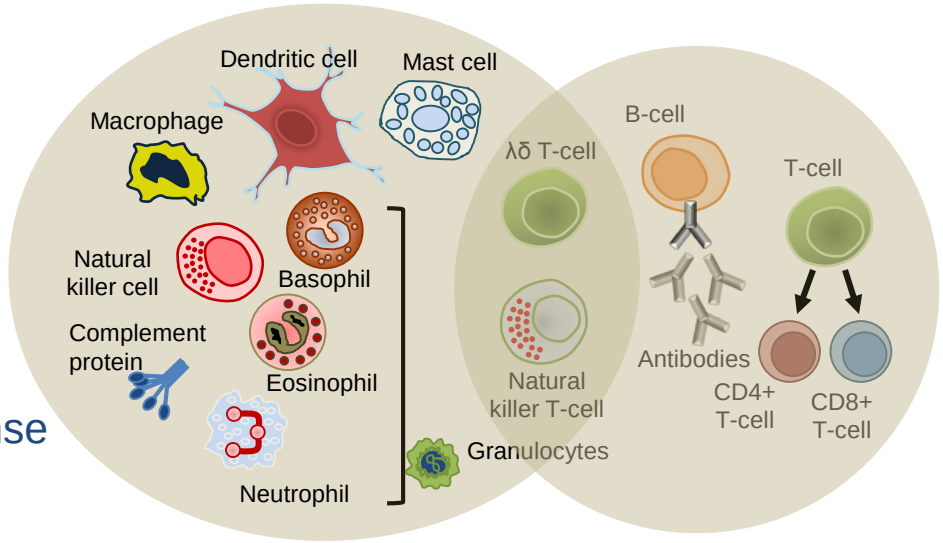
References in slidenotes.

Immune System Function and Immune Response

Identify and destroy foreign or abnormal cells in the body

Innate Immunity

- Nonspecific
- First line of defense
- WBCs (natural killer cells, neutrophils)
- Activation of adaptive response



Adaptive Immunity

- Specific
- Adapts specifically to diverse stimuli
- B-cell antibody production
- T-cell stimulation
- Memory functions

Immune surveillance:

- Involves both innate and adaptive immune mechanisms
- Goal of immunotherapy for cancer: to "educate and liberate" underlying anticancer immune responses

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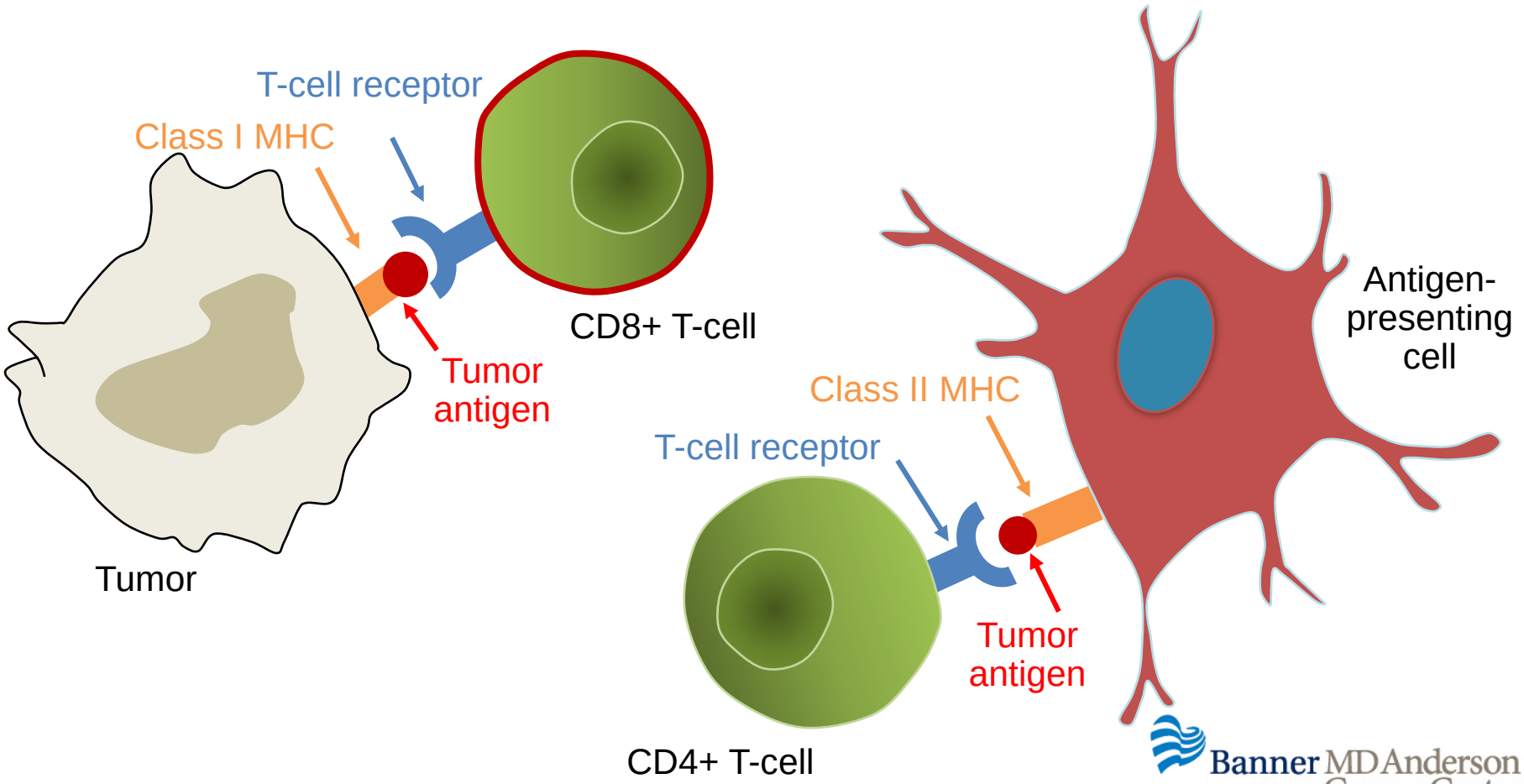
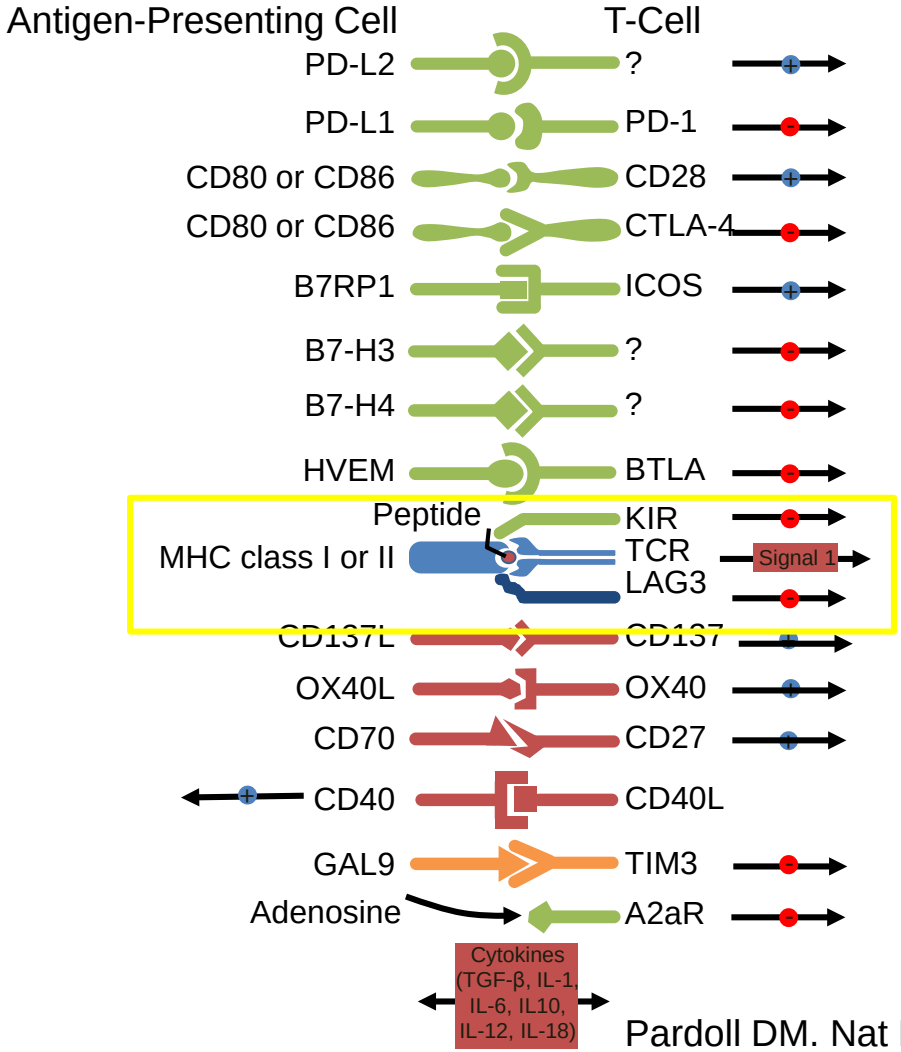
Janeway CA Jr, et al. Immunobiology: the immune system in health and disease. 2001.

T-Cell Response: First Signal



Adapted from: Snyder A, et al. Curr Opin Genet Dev. 2015;30:7-16.

T-Cell Regulation via Multiple Costimulatory and Inhibitory Interactions



- T-cell response to antigen is mediated by peptide-MHCs recognized specifically by TCR (first signal)
- B7 family of membrane-bound ligands binds both activating and inhibitory receptors (second costimulatory signal)
- Targeting CTLA-4 and PD-1 inhibitory receptors has been a major clinical focus

Pardoll DM. Nat Rev Cancer. 2012;12:252-264

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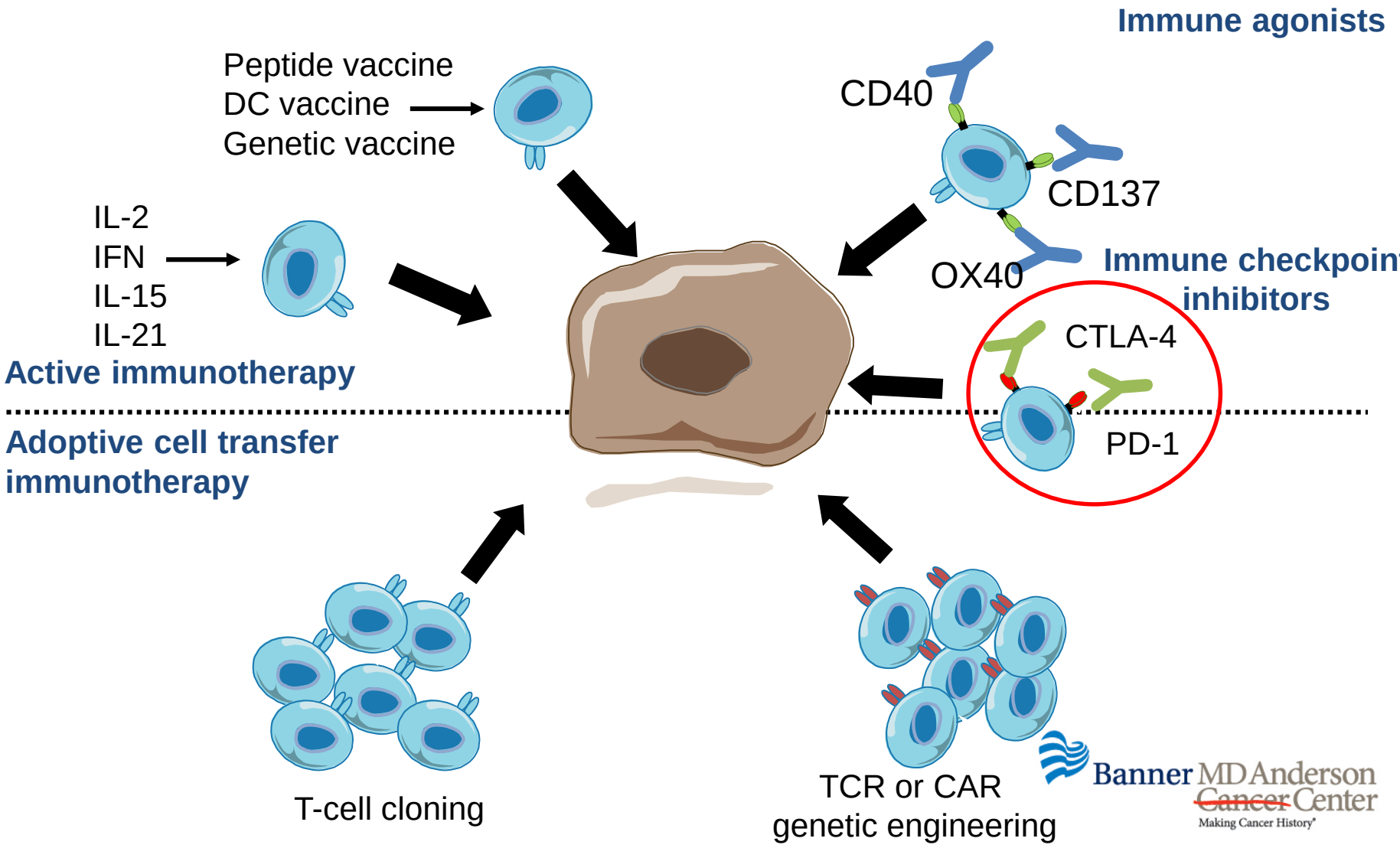
General Approaches for Cancer Immunotherapy



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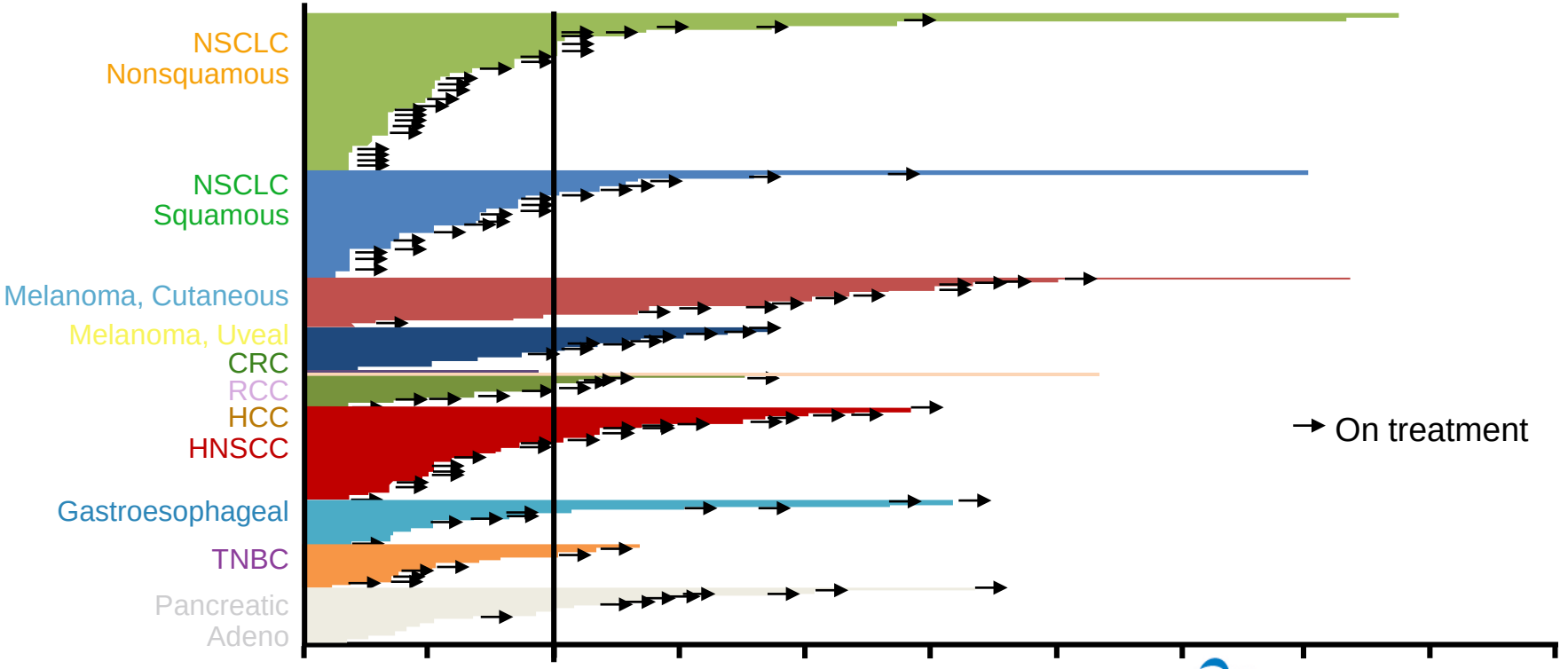
Durvalumab: Antitumor Activity in Multiple Solid Tumors

- All pts, all doses; N = 367



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Segal NH, et al. ASCO 2014. Abstract 3002.

Current trials in HCC with immunotherapy

Questions?

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