肺癌免疫治疗进展

Outline

1. Cancer Immunotherapy
2. Update of checkpoint Inhibitors in lung cancer therapy
3. Future Outlook

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2. Update of checkpoint Inhibitors in lung cancer therapy
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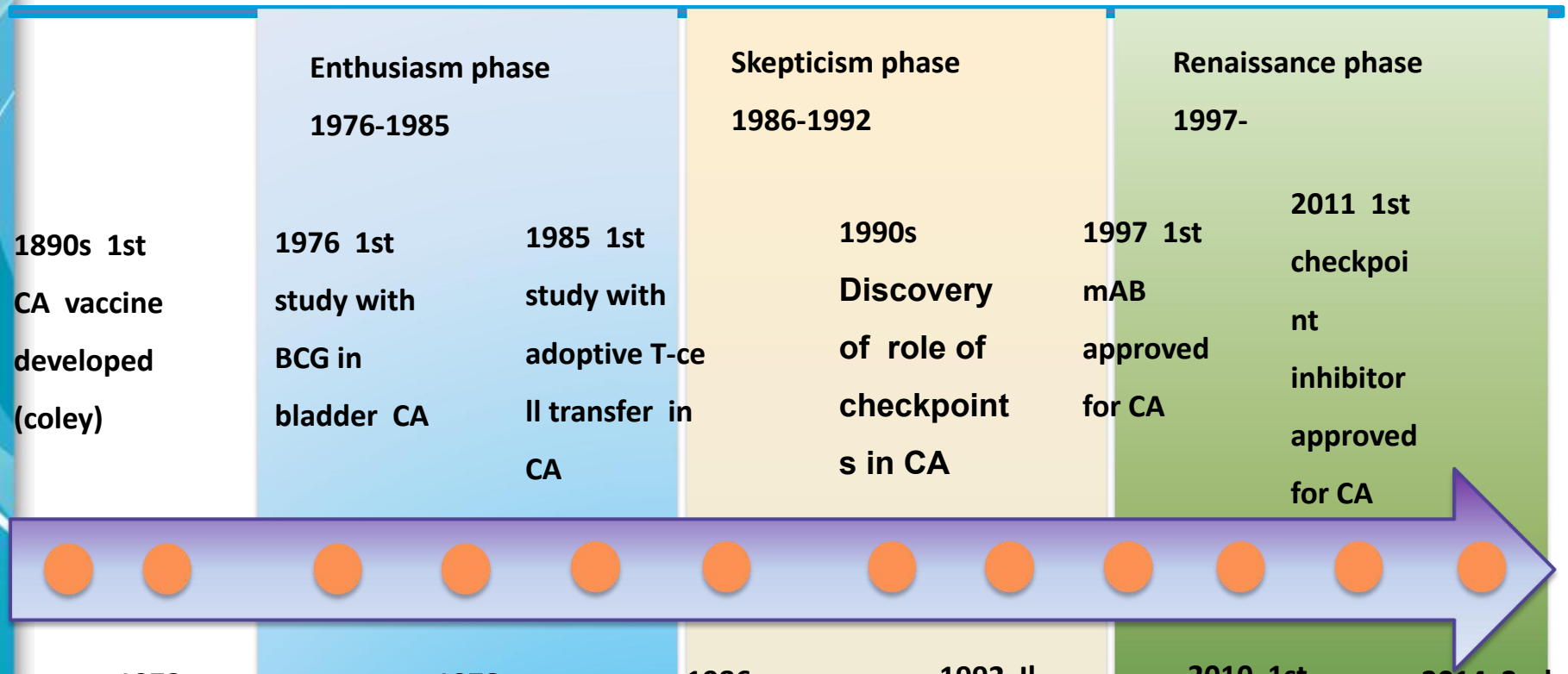
肿瘤免疫治疗—攻克肿瘤的新希望

人类抗击肿瘤的历史

肿瘤免疫治疗具有特异性和靶向性，一直为临床医师高度关注，近年进步显著，使得免疫治疗成为更具期待的领域

Key events in the history of cancer immunotherapy



美国《Science》杂志:

2013年六大值得关注的科学领域

单细胞测序

“普朗克”探测微波背景辐射

人类连接组计划

探索南极冰下世界

癌症免疫疗法

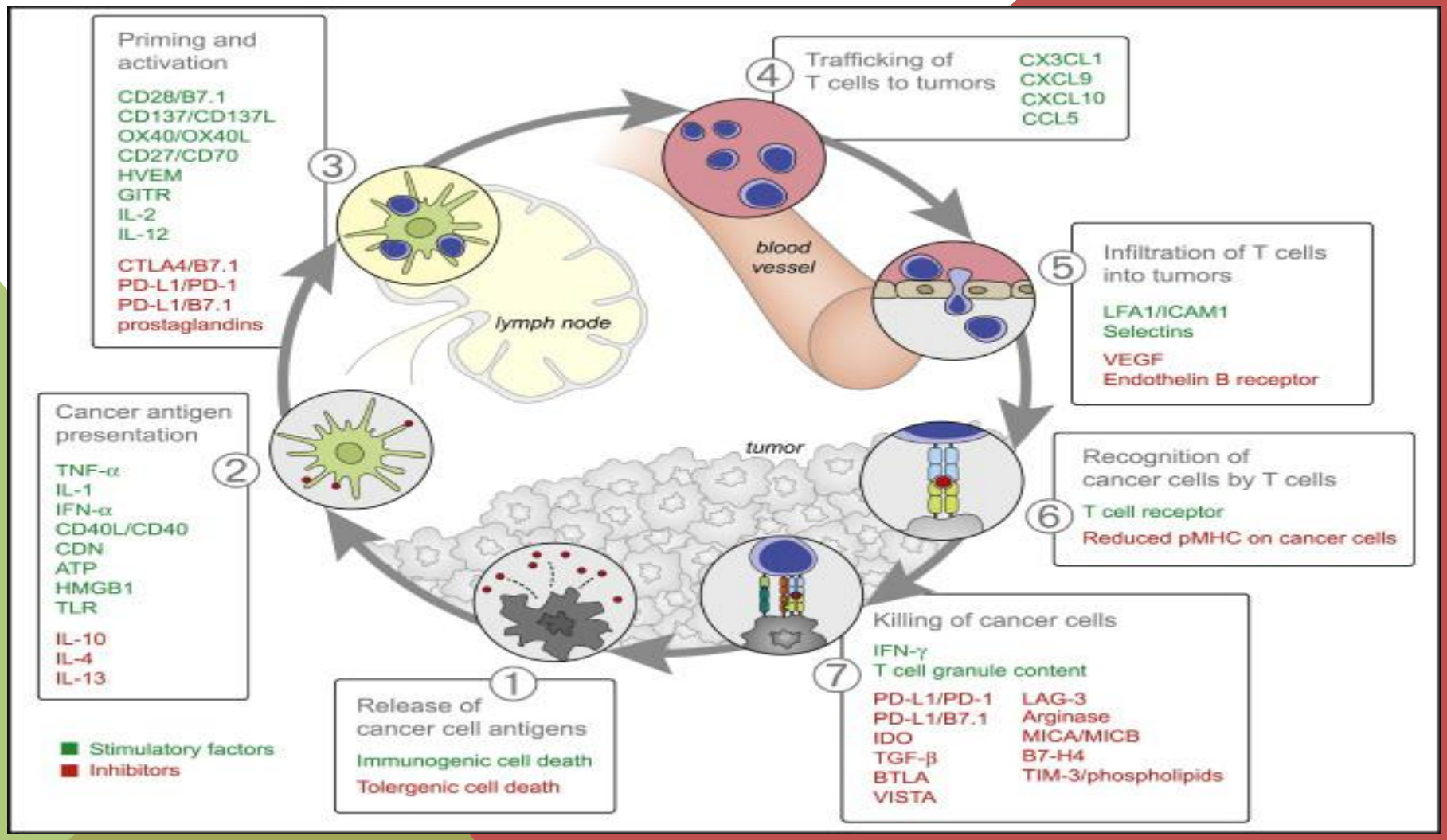
基础植物研究

Breakthrough of year

2013

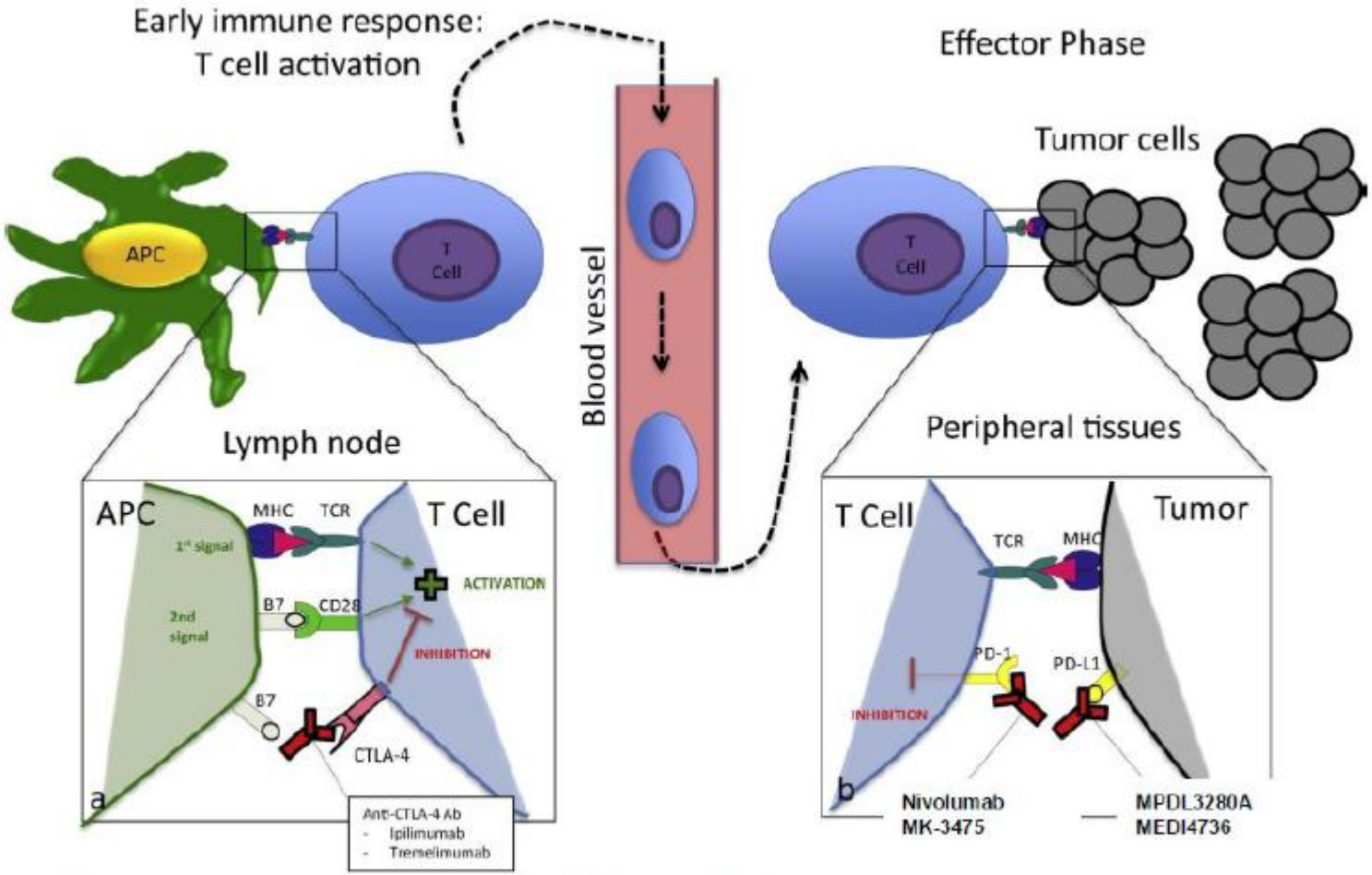
Science. 2013 Dec 20;342(6165):1432-3

Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle



Immunity. 39(1)25 July 2013, Pages 1–10

CTLA-4 and PD-1/PD-L1 checkpoint blockade for cancer treatment



Kyi C, Postow MA. FEBS Lett. 2014;588:368-376

CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

- **Immune checkpoint blockade includes agents targeting the negative regulators CTLA-4 and PD-1**

- **CTLA-4 attenuates the early activation of naive and memory T cells in the lymph nodes**
  - **Agents targeting CTLA-4 include ipilimumab and tremelimumab**

- **In contrast, PD-1 modulates the effector phase of T cell activity in peripheral tissues via interaction with PD-L1 and PD-L2**
- **Agents targeting PD-1 include nivolumab and MK-3475**
- **Agents targeting PD-L1 include MPDL3280A and MEDI4736**

Kyi C, et al. FEBS Lett. 2014;588:368-376

Comparing CTLA-4 and PD-1

	CTLA-4	PD-1
Biological function	▪ Inhibitory receptor	▪ Inhibitory receptor
Expression on	▪ T cells at the time of initial response to antigen (activated CD8+ T cells)	▪ Activated T cells, B cells, NK cells ▪ TILs in different tumor types
Major role	▪ Regulates the early stage of T-cell activation	▪ Limits T-cell activity in peripheral tissue after inflammatory response ▪ Limits autoimmunity
Ligands	▪ B7.1 (CD80) ▪ B7.2 (CD86)	▪ PD-L1 (B7-H1/CD274) ▪ PD-L2 (B7-CD/CD273)
Mechanism of action	After ligand binding: ▪Binding with PI3K, phosphatases SHP-2 and PP2A ▪Blockade of lipid-raft expression ▪Blockade of microcluster formation	After ligand binding: ▪Recruits inhibitory phosphatase, SHP-2 ▪Decreases expression of cell survival protein Bcl-xL ▪Inhibits kinases (PI3K/AKT) involved in T-cell activation

CTLA-4 and PD-1 have separate but complimentary roles in immune responses

Crit Rev Oncol Hematol. 2014;89:140-165.

Outline

1. Cancer Immunotherapy
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- **CTLA-4 Checkpoint Inhibitor**

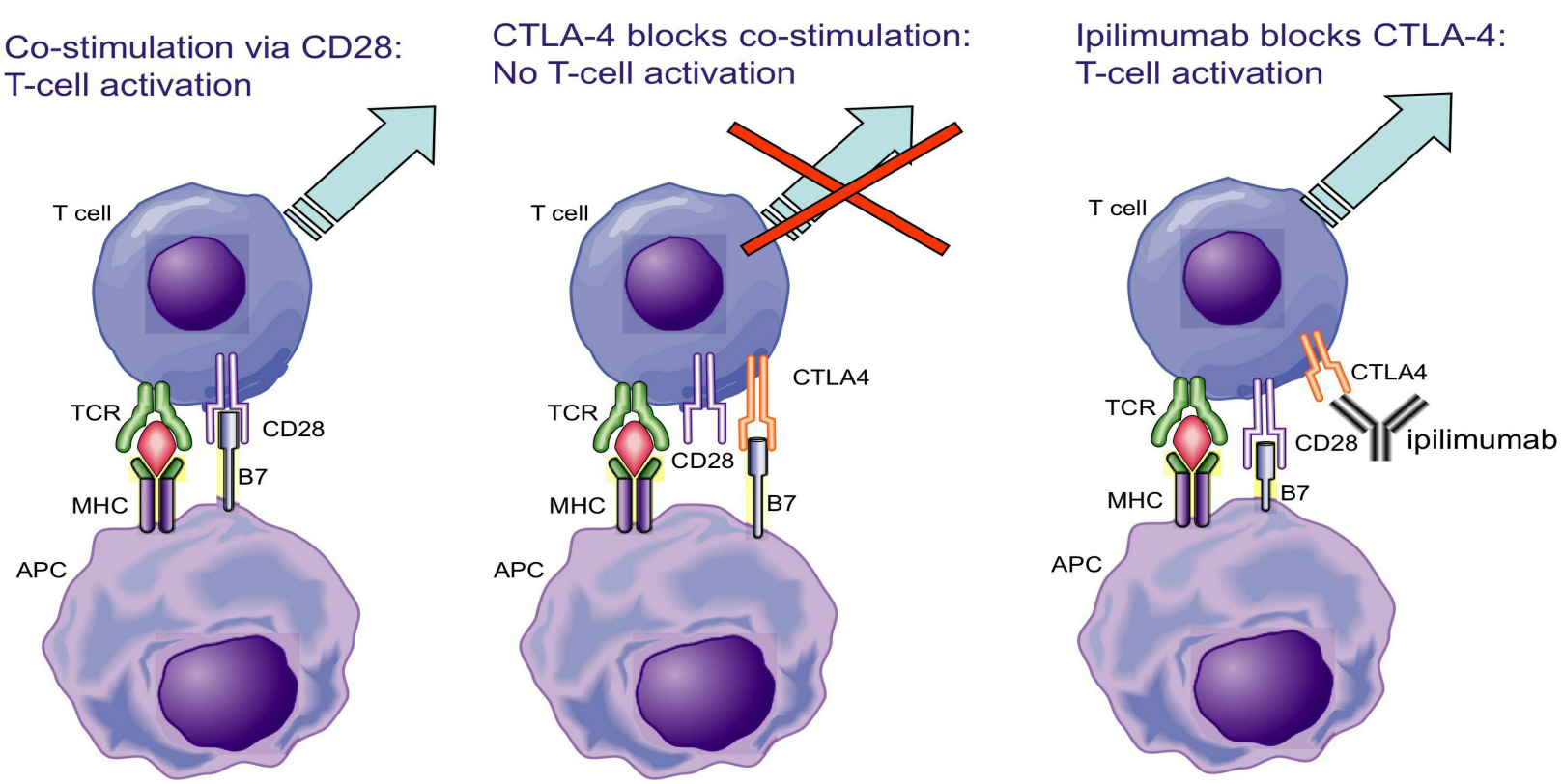
Anti-CTLA-4 antibodies can induce clinical response in a broad variety of cancer

Control pathogens

Prevent auto-immunity

- Ipilimumab – melanoma

Bladder
Renal
Esophageal



Adapted from Lebbé et al. ESMO 2008

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

Adapted form Lebbe et al. ESMO 2008

Presented By Lawrence Fong at 2014 ASCO Annual Meeting

VOLUME 30 · NUMBER 17 · JUNE 10 2012
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non–Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study

Thomas J. Lynch, Igor Bondarenko, Alexander Luft, Piotr Serwatowski, Fabrice Barlesi, Raju Chacko, Martin Sebastian, Joel Neal, Haolan Lu, Jean-Marie Cuillerot, and Martin Reck

See accompanying editorial on page 2025 and articles on pages 2055 and 2063

Annals of Oncology
original articles
Annals of Oncology 24: 75–83, 2013
doi:10.1093/annonc/mds213
Published online 2 August 2012

Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial†

M. Reck[1]*, I. Bondarenko[2], A. Luft[3], P. Serwatowski[4], F. Barlesi[5], R. Chacko[6], M. Sebastian[7], H. Lu[8], J. -M. Cuillerot[8] & T. J. Lynch[9]

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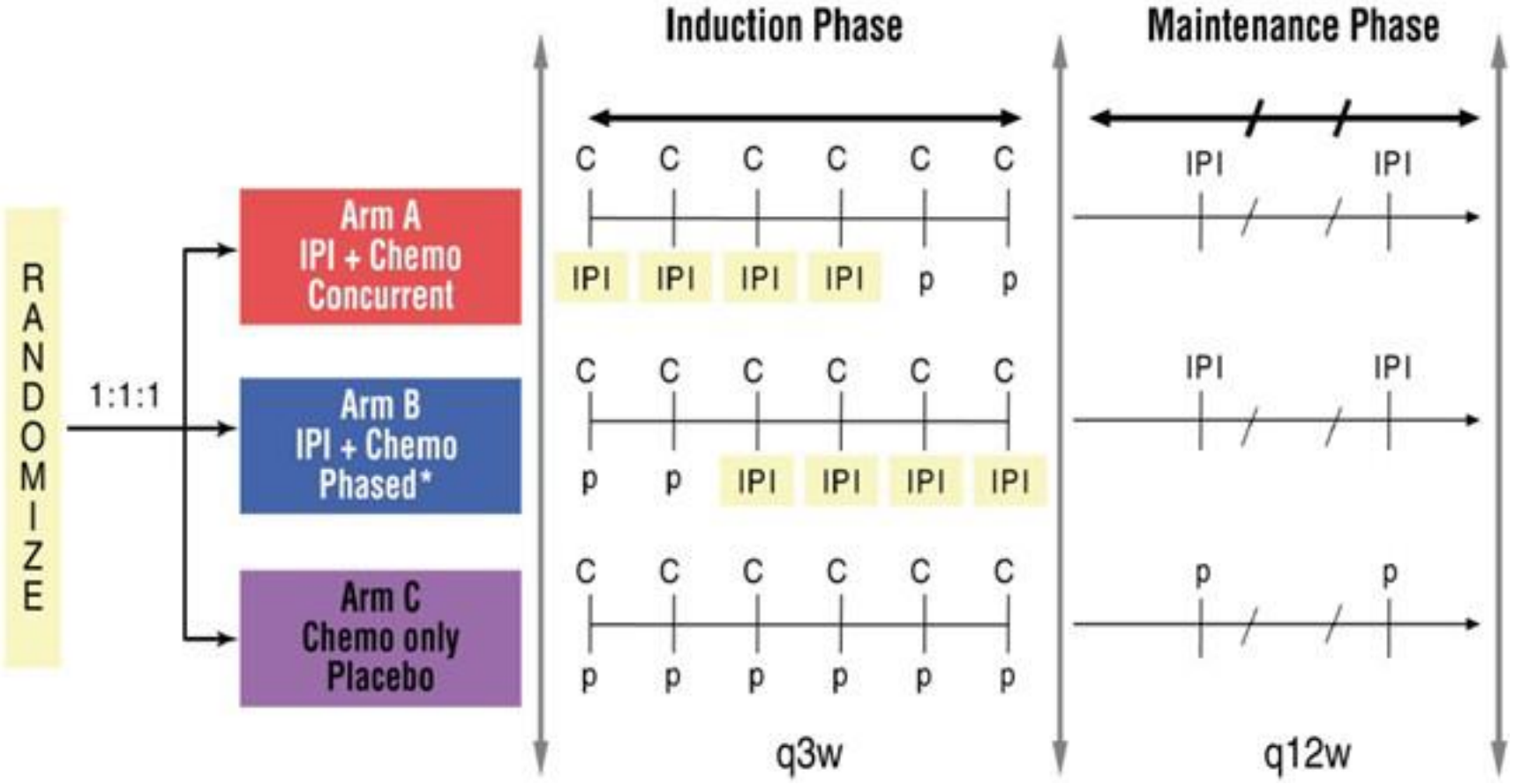
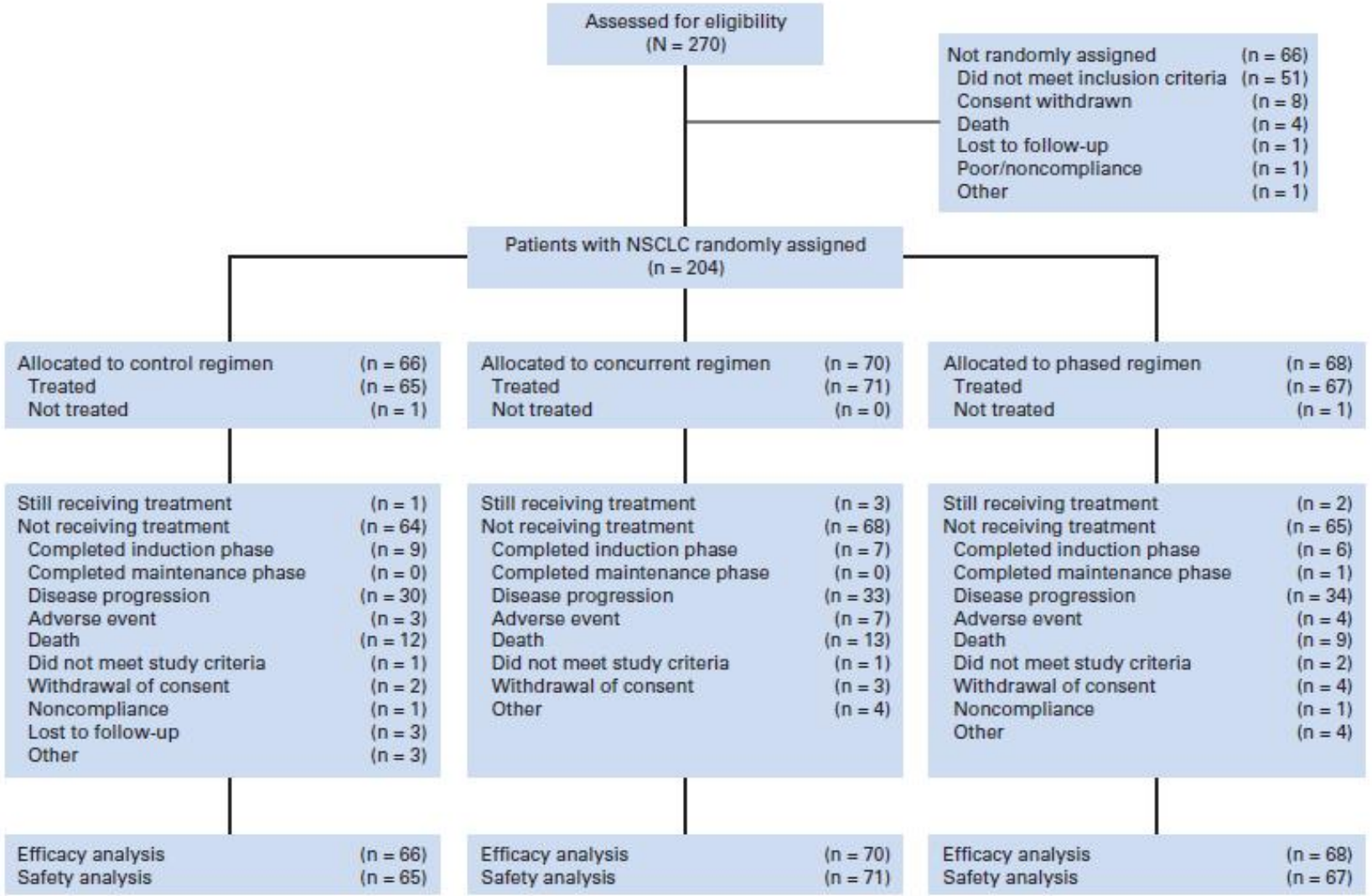


J Clin Oncol. 2012 Jun 10;30(17):2046-54
Ann Oncol. 2013 Jan;24(1):75-83

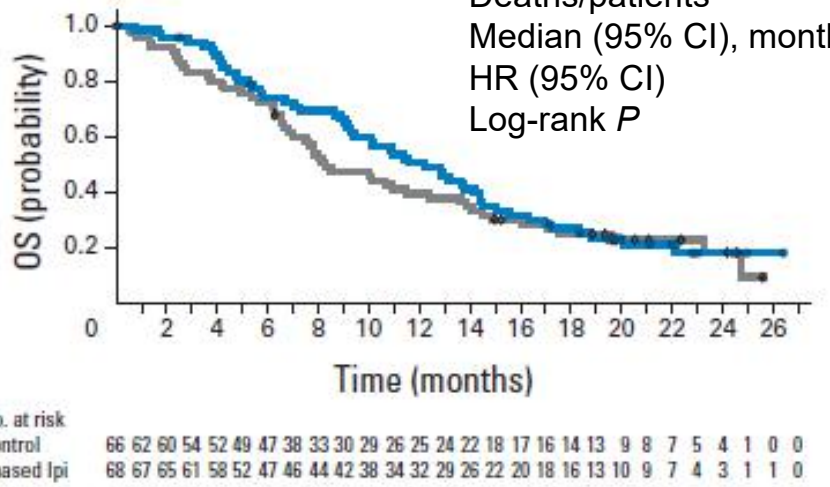
Ipilimumab in combination with PC as first-line therapy in stage IIIB/IV NSCLC



J Clin Oncol. 2012 Jun 10;30(17):2046-54

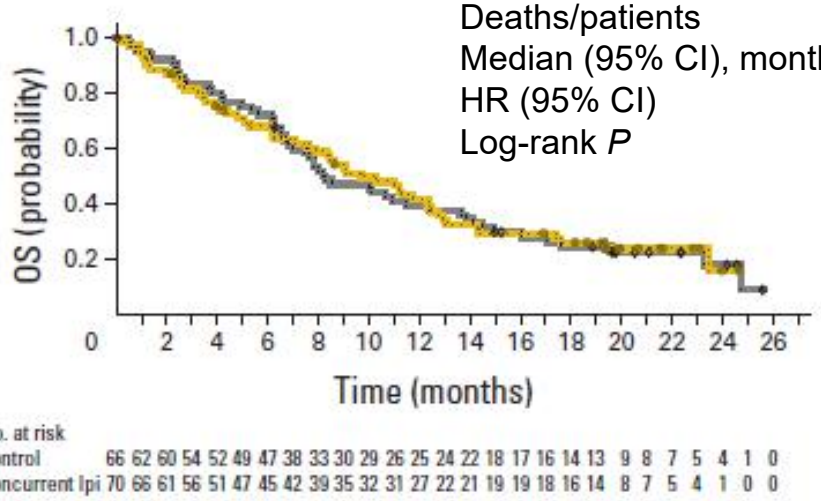
Kaplan–Meier plots for OS

A



	Control	Phased Ipi
Deaths/patients	51/66	51/68
Median (95% CI), months	8.28 (6.80 to 12.39)	12.22 (9.26 to 14.39)
HR (95% CI)		0.87 (0.59 to 1.28)
Log-rank *P*		*0* .23

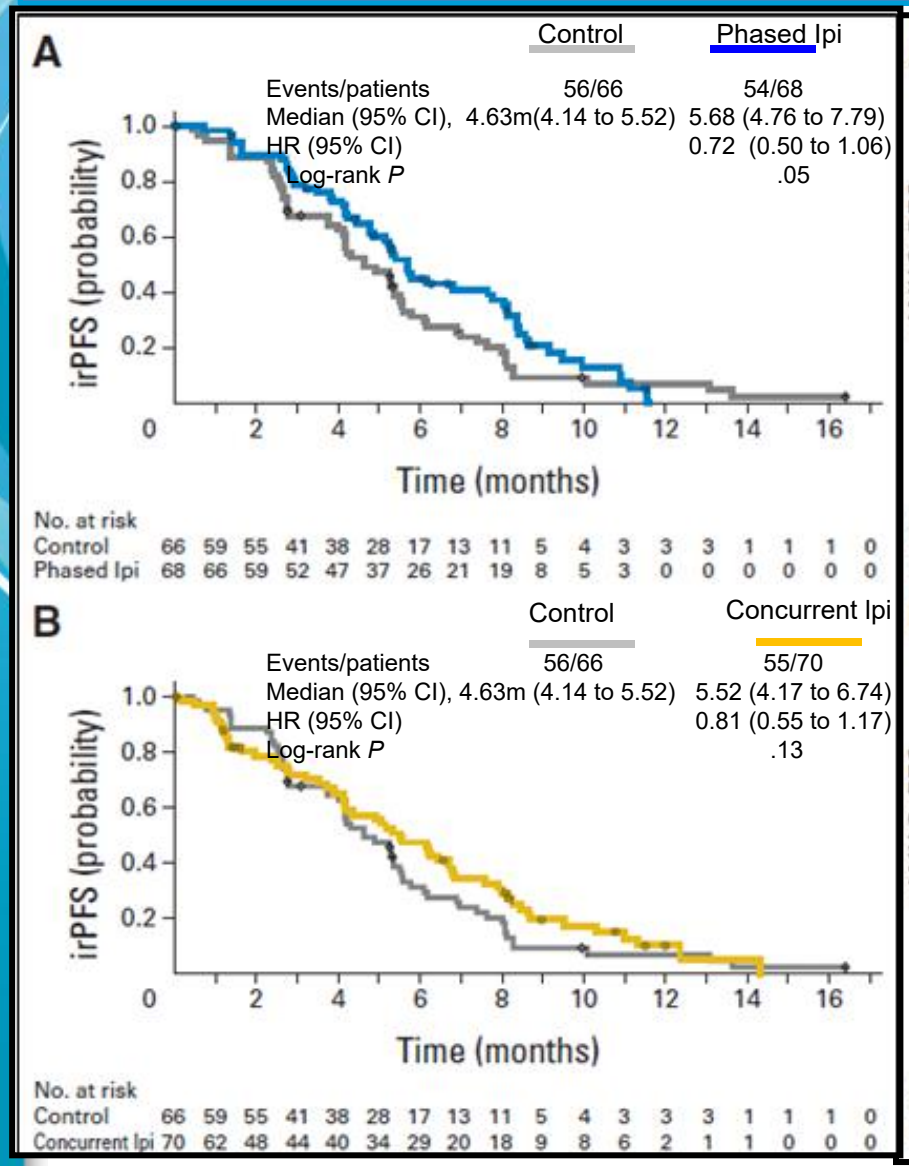
B

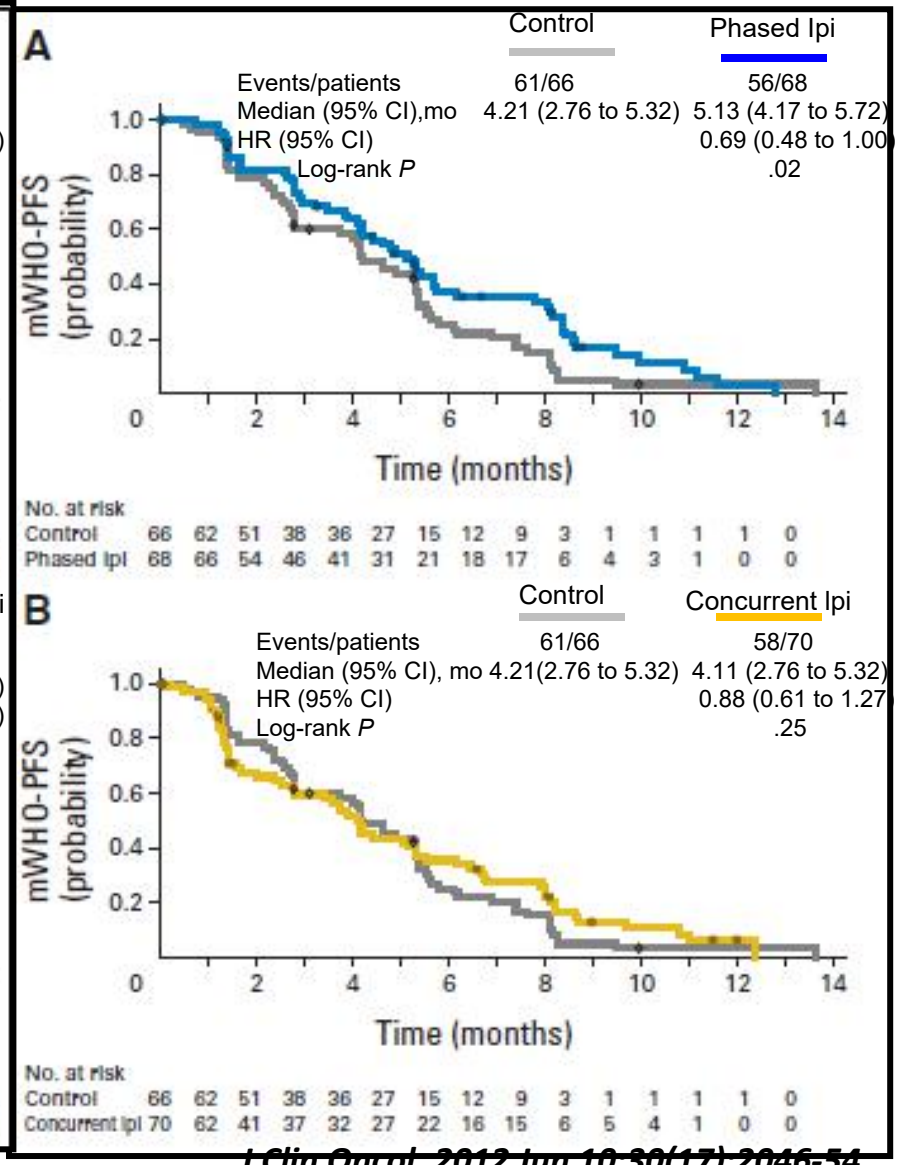


	Control	Concurrent Ipi
Deaths/patients	51/66	51/70
Median (95% CI), months	8.28 (6.80 to 12.39)	9.69 (7.59 to 12.48)
HR (95% CI)		0.99 (0.67 to 1.46)
Log-rank *P*		*0.48*

J Clin Oncol. 2012 Jun 10;30(17):2046-54

Kaplan–Meier plots for PFS per immune-related (ir) response criteria (irPFS) and modified WHO criteria (mWHO-PFS).





J Clin Oncol. 2012 Jun 10;30(17):2046-54

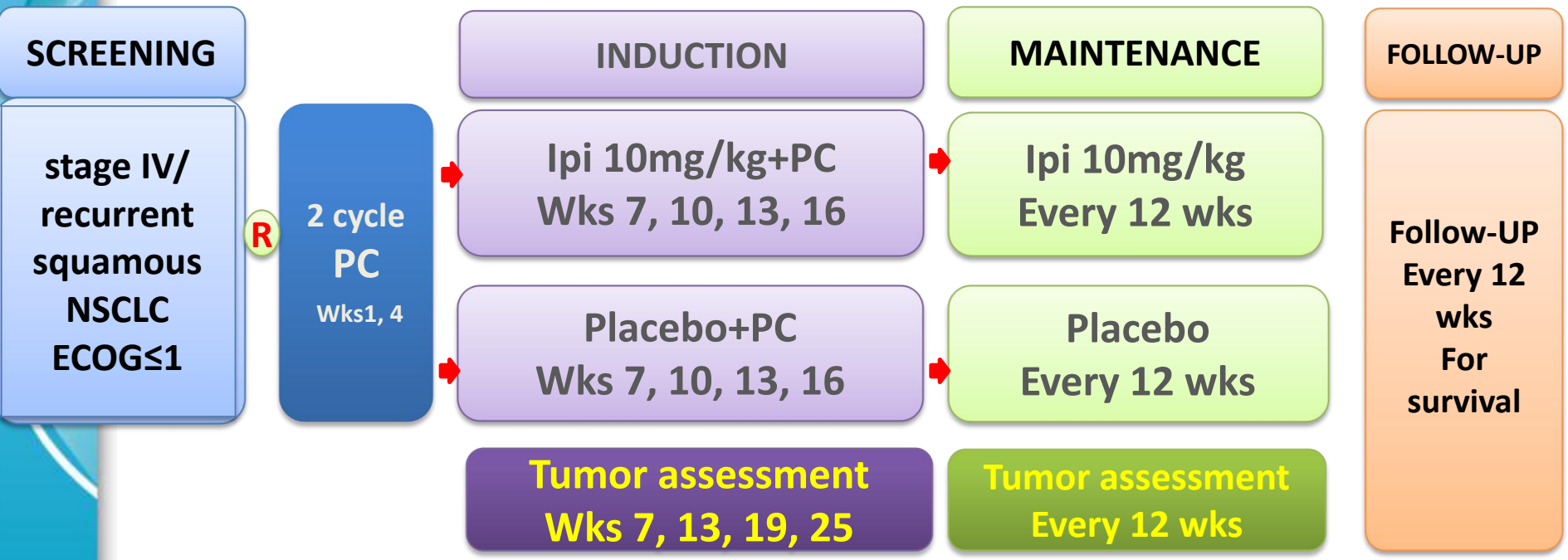
Adverse Events

Event	Control (n = 65)			Concurrent Ipilimumab (n = 71)			Phased Ipilimumab (n = 67)		
	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4
Any adverse event, %	31	29	11	16	30	27	19	42	12
Any treatment-related adverse event, %	43	29	8	35	24	17	43	31	8
Treatment-related non-hematologic adverse events, %									
Fatigue	22	5	0	20	7	1	19	5	0
Alopecia	46	NA	NA	34	NA	NA	45	NA	NA
Rash	8	2	0	25	3	0	10	3	0
Pruritus	5	2	0	17	0	0	8	0	0
Arthralgia	11	0	0	16	0	0	12	2	0
Asthenia	3	2	0	4	3	0	16	2	0
Diarrhea	14	3	0	23	7	0	18	5	0
Nausea	31	2	0	25	1	0	31	2	0
Vomiting	15	2	0	17	1	0	16	2	0
Peripheral neuropathy*	23	2	0	13	1	0	10	0	0
Peripheral sensory neuropathy*	11	2	0	8	0	0	16	3	0
Hematologic abnormalities, %†									
Thrombocytopenia	35	8	2	39	2	0	40	3	0
Neutropenia	32	8	2	26	5	3	34	2	0
Anemia	89	6	0	80	8	3	92	6	0
Liver-function enzymes, %†									
ALT	35	2	0	40	2	0	29	2	0
AST	32	2	0	25	2	0	31	2	0

NOTE. Adverse events listed were those (any grade) reported in ≥15% of patients in any arm. Patients could have more than one adverse event.
Abbreviation: NA, not applicable.
*As reported by investigators (standardized Medical Dictionary for Regulatory Activities query term scope).
†On the basis of laboratory results.

J Clin Oncol. 2012 Jun 10;30(17):2046-54

CA184-104: phase III trial comparing the the efficacy of ipilimumab (Ipi) with PC versus placebo with PC in patients (pts) with stage IV/recurrent NSCLC of squamous histology



Exclusion Criteria:
Brain Metastases
Autoimmune diseases

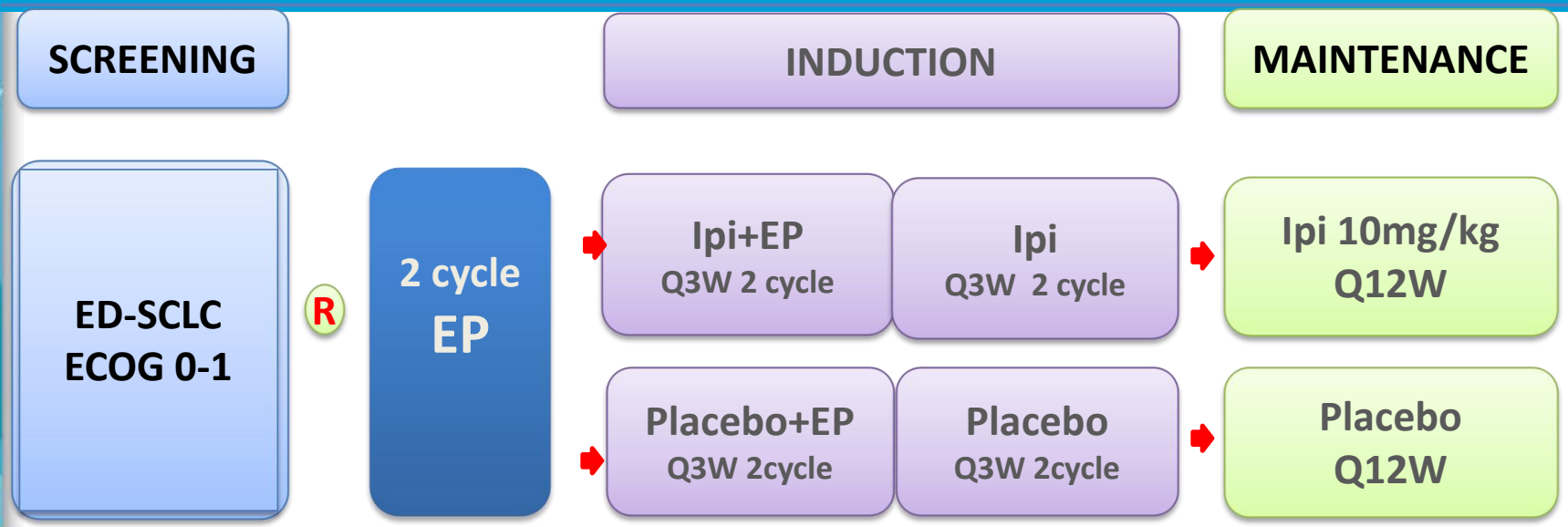
PC
Paclitaxel (175 mg/m², IV)
+Carboplatin (AUC=6, IV)

primary endpoint
- **OS**

secondary endpoints
- **OS among pts who receive blinded therapy**
- **PFS**
- **best overall response rate**

J Clin Oncol 31, 2013 (suppl; abstr TPS8117)

CA184-156: Phase III Trial Comparing the Efficacy of Ipi Plus Etoposide/Platinum Versus Etoposide/Platinum in Subjects With Newly Diagnosed ED-SCLC



Exclusion Criteria:

Prior systemic therapy for lung cancer

Symptomatic CNS metastases

History of autoimmune disease

primary endpoint

OS

secondary endpoints

OS among pts who receive blinded therapy

immune-related and mWHO PFS

best overall response rate

duration of response

EP:
etoposide (100 mg/m^2, IV on Days 1-3 Q3W) +cisplatin (75 mg/m^2, IV) or +carboplatin (AUC=5, IV) once Q3W
Ipi: (10 mg/kg, IV, Q3W)

J Clin Oncol 30, 2012 (suppl; abstr TPS7113)

A Phase III Study of Nivolumab in Combination with Yervoy in Patients with Advanced Non-Small Cell Lung Cancer

Clinical Trial Profile

A Phase III Study of Nivolumab in Combination with Yervoy in Patients with Advanced Non-Small Cell Lung Cancer	
Disease Type	Lung, Non-Small Cell
Patient Segment	First line, Stage III, Stage IV
Trial Tag / Attribute	N/A
Trial Phase	III
Sponsors	BMS, Ono Pharmaceutical
Primary Drugs	ipilimumab, nivolumab
Other Drugs	
Protocol ID / Trial Identifier	TrialTroveID-208893
Status	Planned
Trial Outcome(s)	N/A
Outcomes Details	N/A
Trial Objectives	**Objectives** To evaluate nivolumab in combination with yervoy in patients with advanced non-small cell lung cancer. **Primary Endpoint/Outcome measures/objectives** N/A **Other Endpoint/Outcome measures/objectives** N/A
Treatment Plan	**Study Design** N/A **Treatment Plan** Patients will receive nivolumab in combination with yervoy.

- **PD-1/PD-L1 Checkpoint Inhibitors**

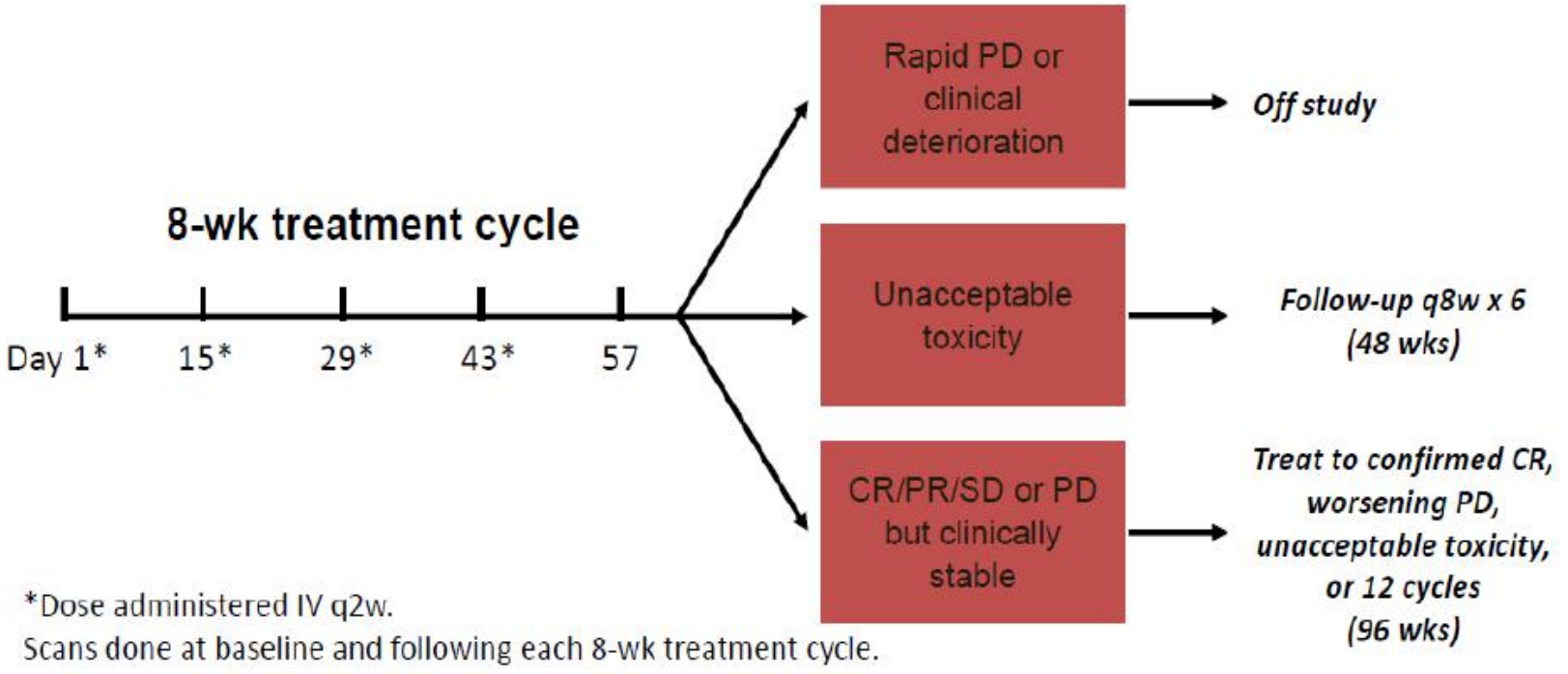
PD-1 and PD-L1 antibodies in phase III development

Agent	Class	Disease State
Anti-PD-L1		
MPDL3280A	Engineered IgG1	NSCLC[1]
MEDI4736	Modified IgG1	NSCLC[2]
Anti-PD-1		
Nivolumab	IgG4	Melanoma[3]; NSCLC[4]; RCC[5]
MK-3475 (Pembrolizumab)	IgG4 (humanized)	Melanoma[6]; NSCLC[7,8]

1. ClinicalTrials.gov. NCT02008227. 2. ClinicalTrials.gov. NCT02125461. 3. ClinicalTrials.gov. NCT01844505.
4. ClinicalTrials.gov. NCT01673867. 5. ClinicalTrials.gov. NCT01668784. 6. ClinicalTrials.gov. NCT01866319.
7. ClinicalTrials.gov NCT01905657. 8. ClinicalTrials.gov. NCT02142738.

Phase1 Nivolumab (anti-PD-1; BMS-936558, ONO-4538) multidose regimen

Eligibility:advcanced melanoma,NSCLC,RCC,CRC, or CRPC with PD after1-5 systemic therapies



Brahmer JR NEJM 2013

Select Aes(>1%) occuring in Pts with NSCLC treated with Nivolumab(N=129)

Drug-related pneumonitis(any grade) occurred in 8 NSCLC Pts(6%) VS 12 Pts(4%) in the overall study population
-3Pts (2%) with NSCLC had grade ¾ pneumonitis

Treatment-Related Select AE, % (n)		
	Any Grade*	Grade 3/4*
Any treatment-related select AE	41 (53)	5 (6)
Skin	16 (20)	0
Gastrointestinal	12 (15)	1 (1)
Pulmonary	7 (9)	2 (3)
Endocrinopathies	6 (8)	0
Hepatic	5 (6)	1 (1)
Infusion reaction	4 (5)	1 (1)
Renal	3 (4)	0

*AE severity was graded based on the Common Terminology Criteria for Adverse Events, v3.0

Brahmer JR, et al. ASCO 2013. Abstract 8030.

Efficacy of Nivolumab monotherapy in Pts treated with NSCLC

Dose, mg/kg	ORR, % (n/N)	Median DOR, Wks (Range)	SD Rate ≥ 24 Wks, % (n/N)	Median PFS, Mos (95% CI)	Median OS, Mos (95% CI)
All doses	17.1 (22/129)	74.0 (6.1+, 133.9+)	10.1 (13/129)	2.3 (1.9-3.7)	9.6 (7.8-12.4)
1	3.0 (1/33)	63.9 (63.9, 63.9)	15.2 (5/33)	1.9 (1.8-3.6)	9.2 (5.6-11.1)
3	24.3 (9/37)	74.0 (16.1+, 133.9+)	8.1 (3/37)	1.9 (1.7-7.3)	14.9 (9.5-NE)
10	20.3 (12/59)	83.1 (6.1+, 117.1+)	8.5 (5/59)	3.6 (1.9-3.8)	9.2 (5.2-12.4)

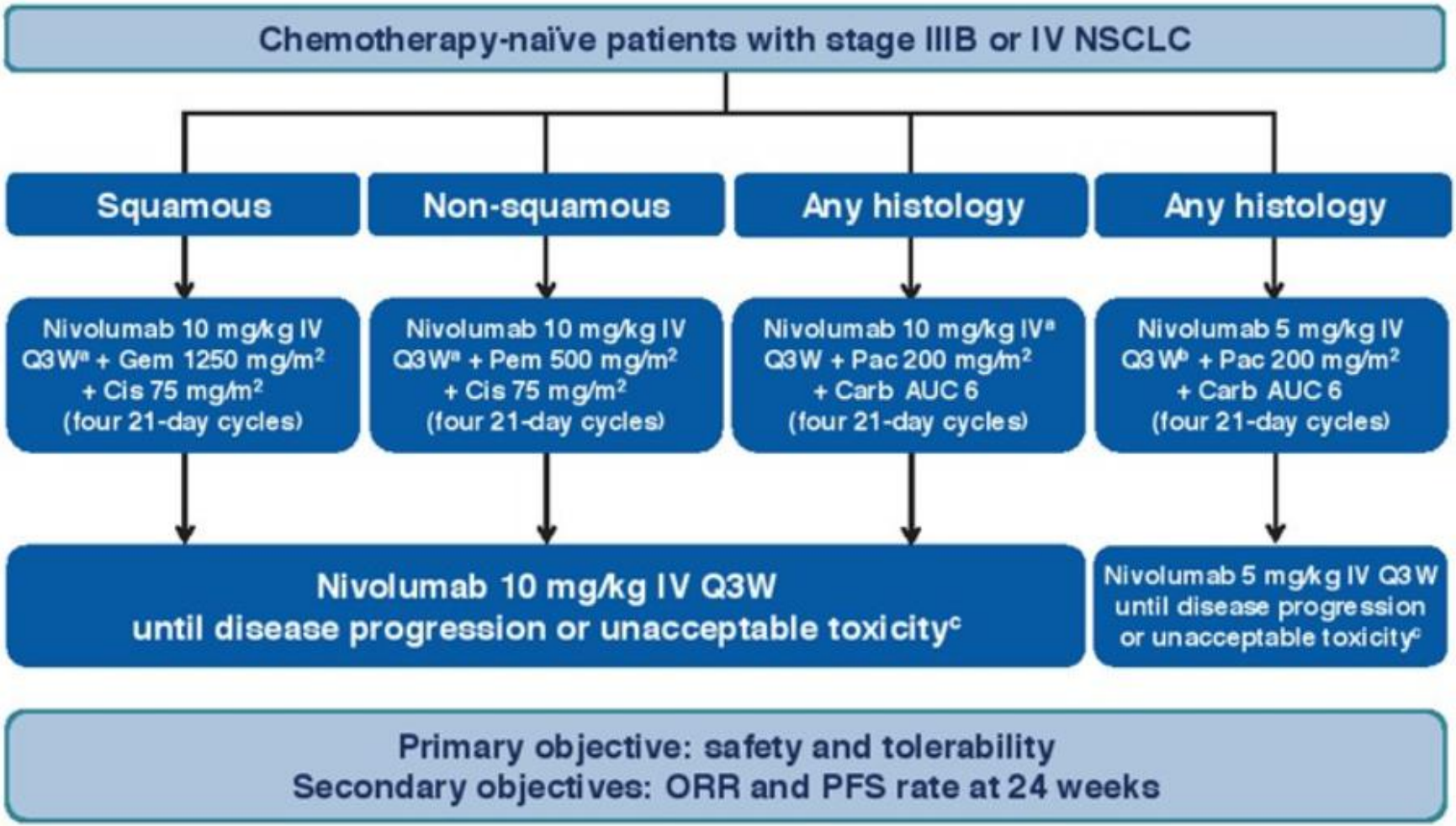
Durable responses: responses are ongoing in 45% of patients (10/22)

Rapid responses: 50% of responding pts had response at first assessment (8 weeks)

7/16 responders who discontinued for reasons other than disease progression responded for ≥16 wks; 6/7 remain in response

6 pts with unconventional “immune-related” responses were not included as responders

Nivolumab in combination with PT-DC in advanced NSCLC



Antonia SJ, et al. 2014 ASCO Abstract 8113.

Results and Conclusions

- 治疗的前6周没有发生剂量限制毒性
- 3-4级治疗相关不良事件发生率为45%
- ORR：33-50%
- 1年OS：59-87%

	Nivo 10+gem/cis 鳞癌	Nivo 10+pem/cis 非鳞癌	Nivo 10+pac/carb 鳞+非鳞癌	Nivo 5+pac/carb 鳞+非鳞癌
N	12	15	15	14
ORR, n (%)	4(33)	7(47)	7(47)	7(50)
mDOR (范围)，周	20.9 (12.1-41.7)	32.0 (13,1-42.1)	25.6 (11.4-39.0)	NA (11.4-37.3)
PD为BOR, n (%)	0	0	3(20)	1(7)
24周时PFS, %	36	71	38	57
1年OS,%	59	87	59	NA

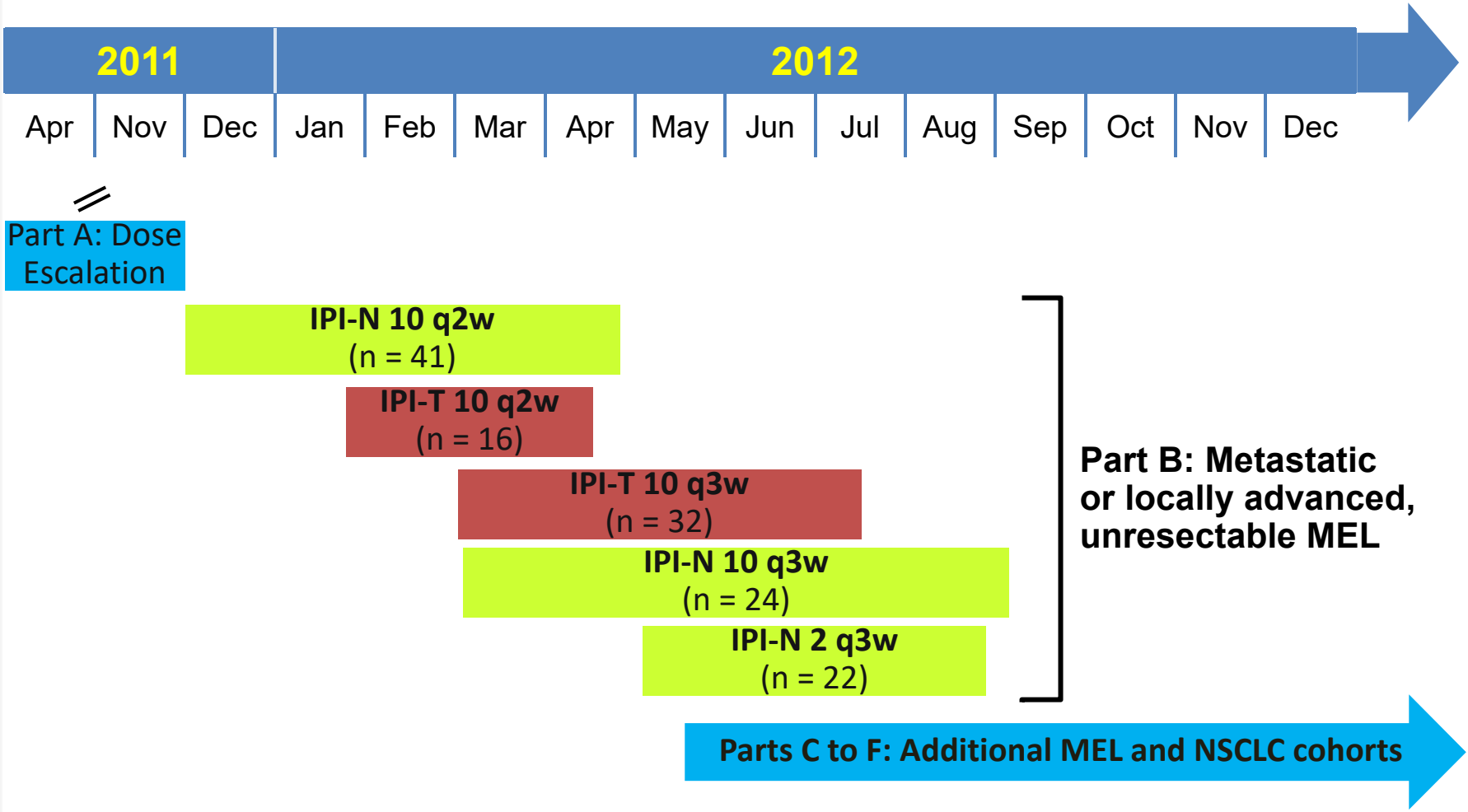
Antonia SJ, et al. 2014 ASCO Abstract 8113.

Ongoing Nivolumab Clinical Trials in Patients With NSCLC

Line of therapy	Phase	PD-L1 Selection	Comparator
Single agent Nivolumab			
1st line[1]	III	Yes	Chemotherapy
2nd line, squamous[2]	III	No	Docetaxel
2nd line, adeno[3]	III	Yes	Docetaxel
≥ 2nd line, squamous[4]	II	No	NA
Combination Nivolumab			
≥ 2nd line[5]	I	No	+ LAG3
≥ 2nd line[6]	I	No	+ lirilumab (KIR)
1st line[7]	I	No	Single agent; + chemotherapy; + bevacizumab; + erlotinib; + ipilimumab

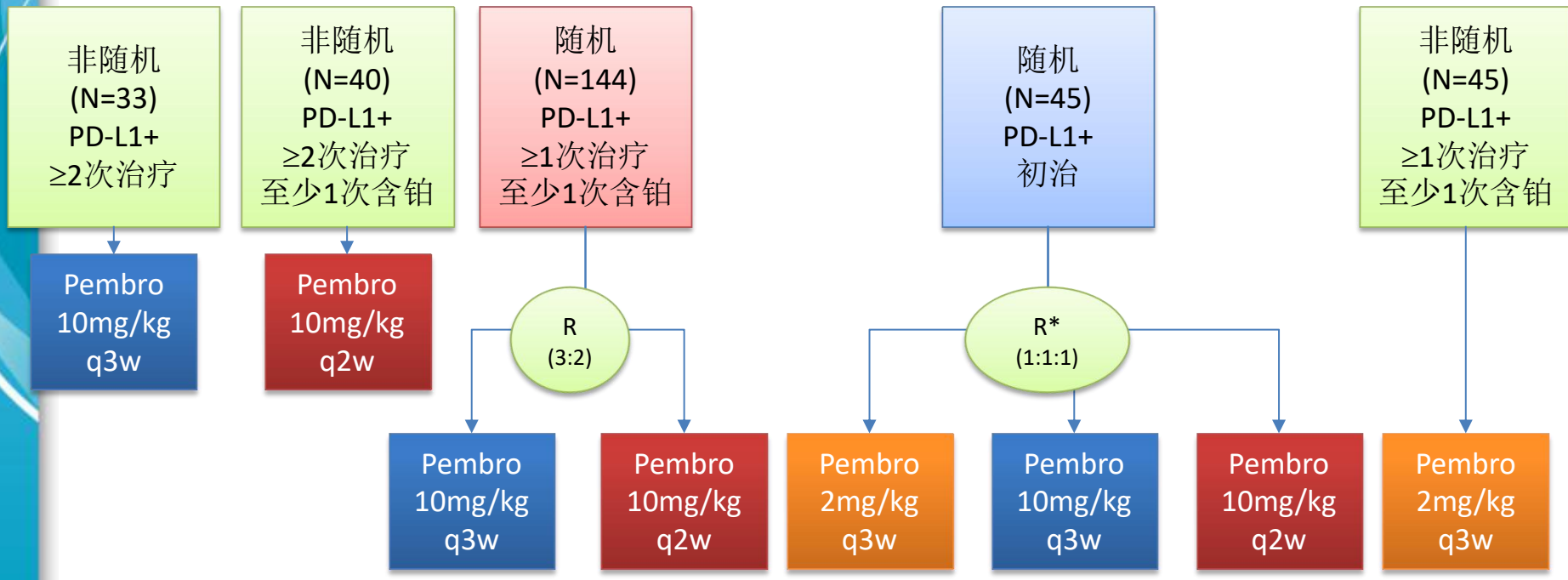
1. ClinicalTrials.gov. NCT02041533. 2. ClinicalTrials.gov. NCT01642004. 3. ClinicalTrials.gov. NCT01673867. 4. ClinicalTrials.gov. NCT01721759. 5. ClinicalTrials.gov. NCT01968109. 6. ClinicalTrials.gov. NCT01714739. 7. ClinicalTrials.gov. NCT01454102.

MK3475(Pembrolizumab , Anti-PD-1): Phase I Trial Design



Ribas A et al. ASCO 2013. Abstract 9009.

KEYNOTE-001：
NSCLC扩大队列研究设计 (N=307)



- 主要终点：**ORR (RECIST v1.1[独立中心评估])**
- 次要终点：免疫相关疗效标准(irRC)[研究者评估]
- **Pembrolizumab (MK3475)** 治疗持续直至PD，不可接受的毒性或死亡

*前11例患者随机分入2mg/kg q3w和10mg/kg q3w组，剩余34例患者随机接受10mg/kg q2w和10mg/kg q3w组
****非随机队列的45例接受2mg/kg q3w的患者分析截止日期为2014年9月11日
数据截止日期：2014年3月3日
Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：基线特征

特征	N=262
年龄，中位(范围)，岁	65(28-86)
男性	50%
ECOG PS：0/1/缺失	31%/68%/1%
人种：白种/黑人或非裔美国人/亚裔/其他	83%/4%/11%/2%
鳞癌	17%
既往接受治疗次数：0/>=1	17%/83%
分期：M0/M1a/M1b/未知	13%/28%/49%/11%
脑转移瘤史	5%
EGFR突变(N=250)	16%
KRAS突变(N=156)	26%
ALK基因重排(N=231)	3%
吸烟史：目前/曾经/从不/未知	5%/64%/28%/2%

Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：
治疗暴露与治疗相关不良事件汇总

治疗暴露	N=262
中位(范围)治疗时间(d)	85.5(1-400)
中位(范围)剂量(n)	5.5(1-23)
治疗相关不良事件总结(%)	
任何级别	67%
3-4级	9%
死亡	0.4%
终止	3%

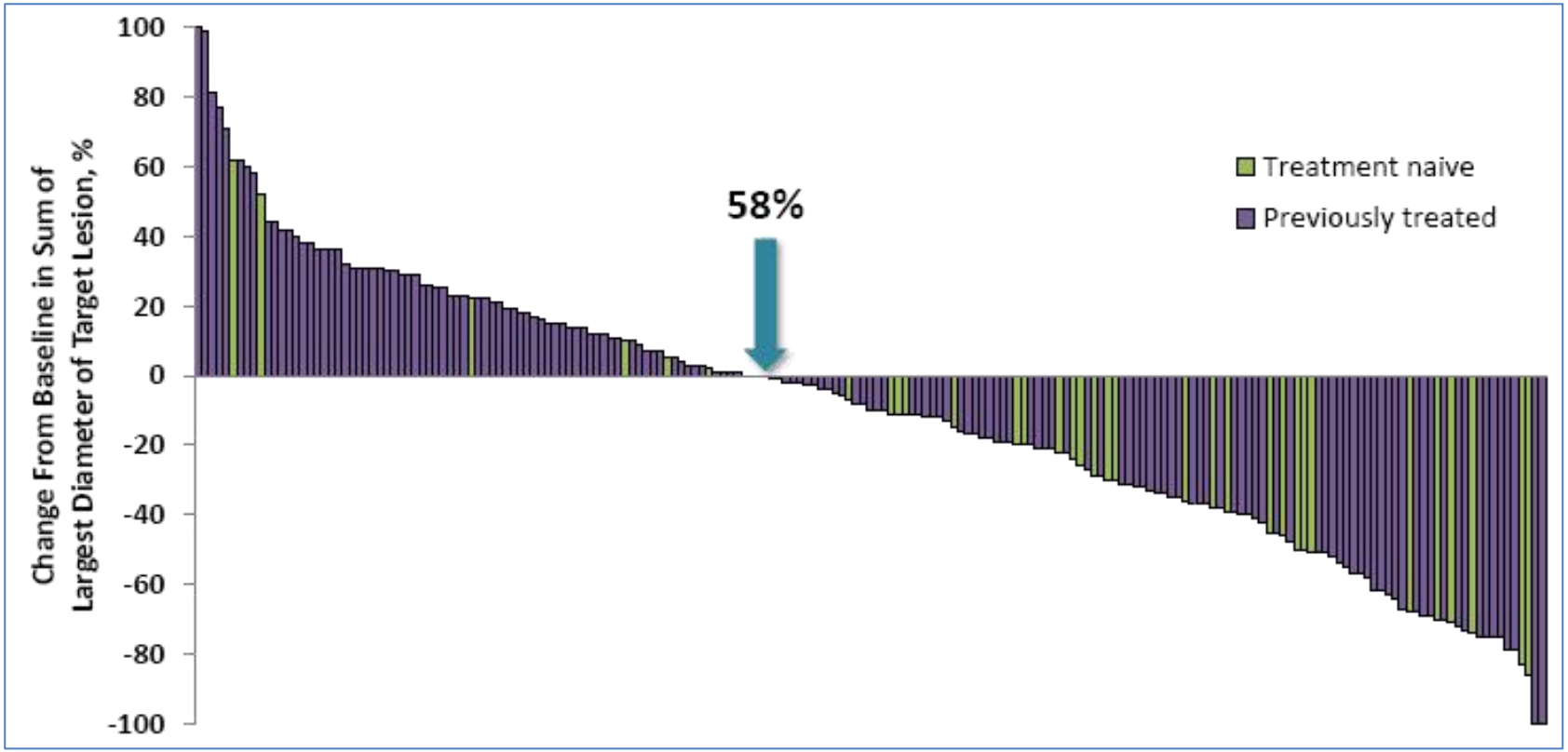
不良事件发生率	N=262	
	任何级别	3-5级
治疗相关不良事件(发生率≥5%)		
乏力	20%	<1%
瘙痒	9%	0
关节痛	8%	<1%
食欲减退	8%	0
腹泻	7%	0
甲状腺功能减退	6%	0
发热	6%	0
皮疹	6%	0
恶心	5%	<1%
其他关注的临床不良事件(发生率≥1%)		
肺炎	4%	2%
甲状腺功能亢进	2%	<1%

4例患者(1.5%)发生输注相关反应
发生率<1%的其他潜在免疫调节不良事件为结肠炎和低钠血症

Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：
肿瘤大小自基线最大变化*(%)

(RECIST v1.1，中心评估)



*可评估患者为根据中心评估基线有可测量病灶且至少接受一次基线后肿瘤评估

Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：抗肿瘤活性 (RECIST v1.1，中心评估)

	N	ORR %(95%CI)
总计	**236**	**21(16-27)**
治疗史	236	
未经治疗	42	26(14-42)
曾接受过治疗	194	20(15-26)
组织学	230	
非鳞癌	191	23(17-29)
鳞癌	39	18(8-34)
吸烟史	230	
目前/曾经	165	27(20-34)
从不	65	9(4-19)

	N	ORR %(95%CI)
给药方案	236	
2 Q3W	6	33(4-78)
10 Q3W	126	21(14-29)
10 Q2W	104	21(14-30)
PD-L1表达	236	
阳性	201	23(18-30)
阴性	35	9(2-23)
EGFR突变	36	14(5-30)
KRAS突变	39	28(15-45)
ALK基因重排	6	17(0-64)

[a]包括确认和未确认缓解；[b]数据截止日期为2014年3月3日

Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：抗肿瘤活性 (irRC，研究者评估)

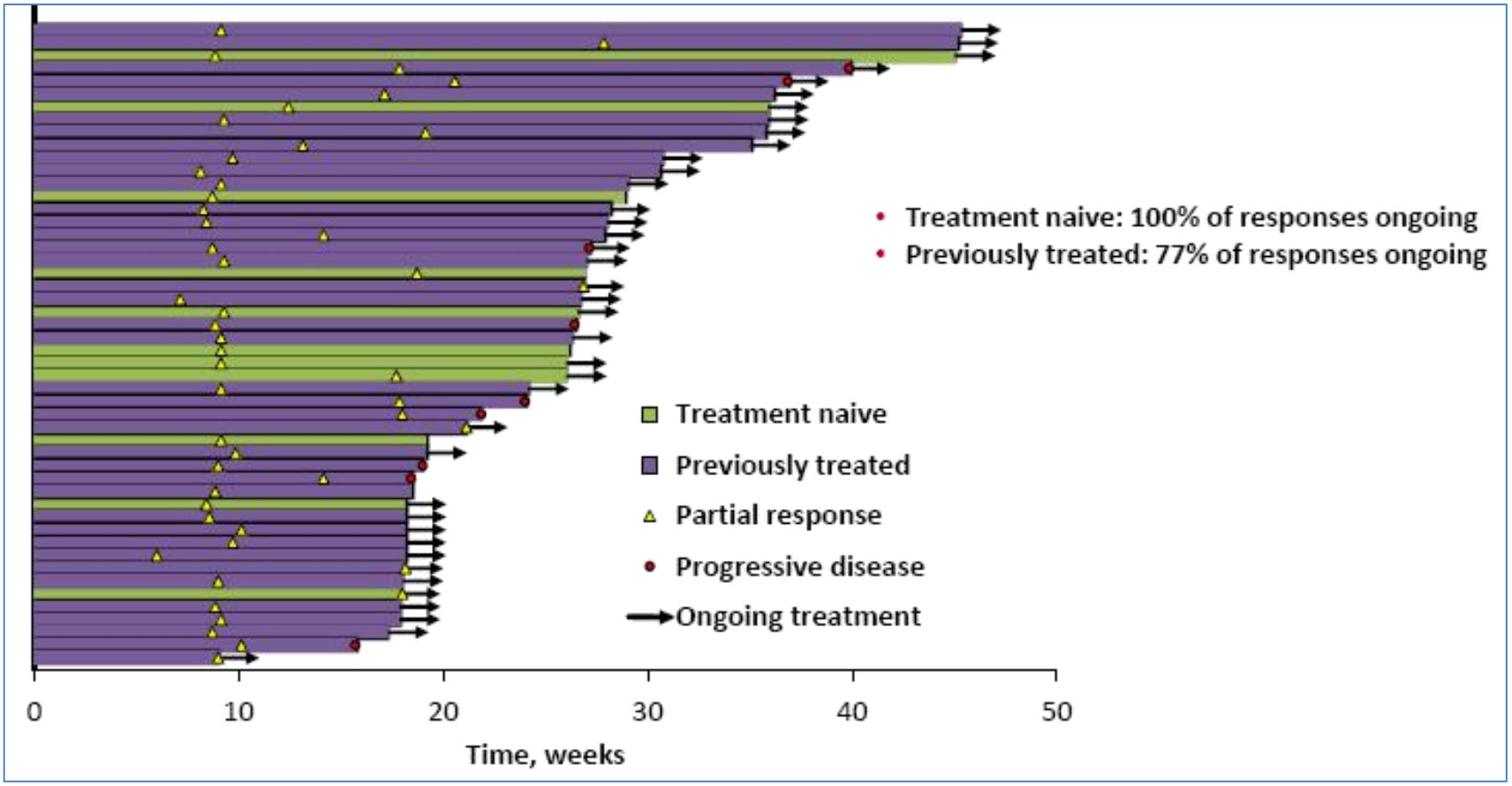
	N	ORR %(95%CI)		N	ORR %(95%CI)
总计	262	23(18-29)	给药方案	262	
治疗史	262		2 Q3W	6	67(22-96)
未经治疗	45	47(32-62)	10 Q3W	141	22(16-30)
曾接受过治疗	217	18(13-24)	10 Q2W	115	22(15-30)
组织学	258		PD-L1表达	262	
非鳞癌	212	23(17-29)	阳性	222	25(19-31)
鳞癌	44	25(13-40)	阴性	40	13(4-27)
吸烟史	256		EGRFR突变	41	12(4-26)
目前/曾经	182	27(21-34)	KRAS突变	41	32(18-48)
从不	74	14(7-24)	ALK重排	6	33(4-78)

- 额外45例接受2mg/kg q3w治疗的患者中，ORR[a]为20%(95%CI:10%-35%)[b]

[a]包括确认和未确认缓解；[b]数据截止日期为2014年9月11日

Garon EB, et al. 2014 ESMO Abstract LBA43.

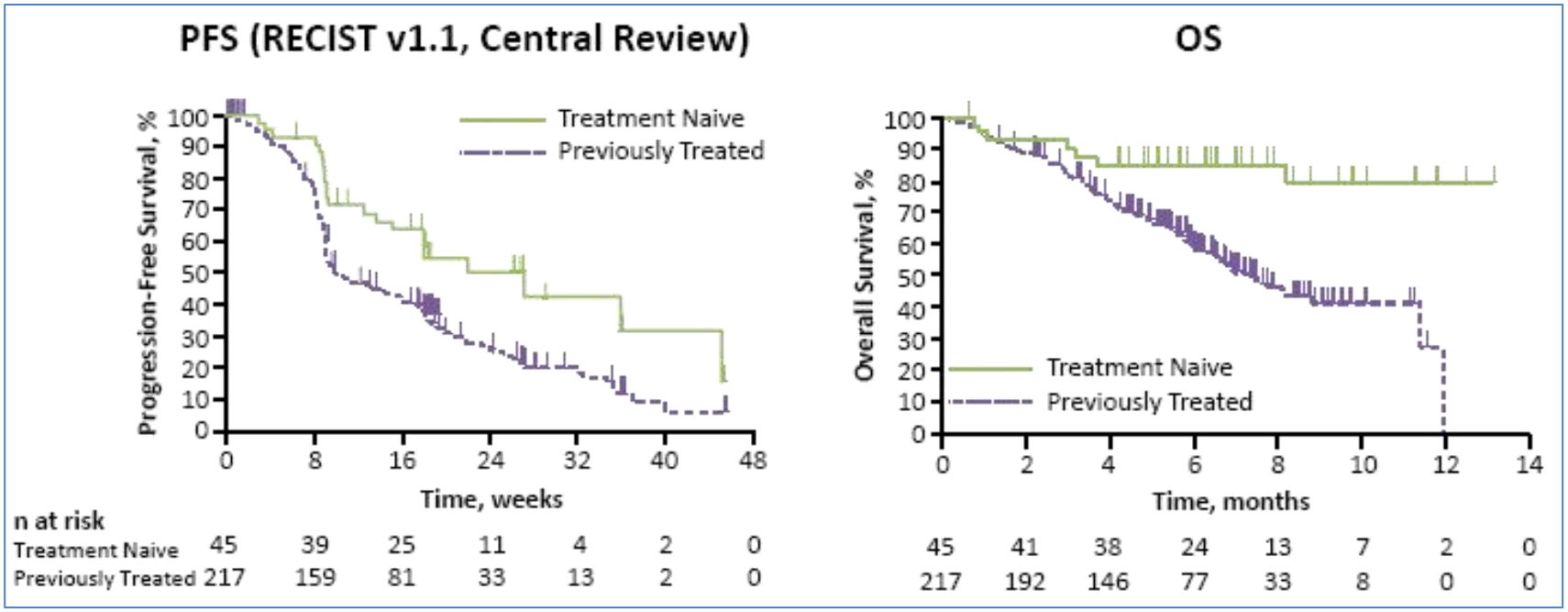
KEYNOTE-001：
至缓解时间 & 缓解持续时间



[a]包括确认和未确认缓解

Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：
生存期评估：初治 vs. 复治

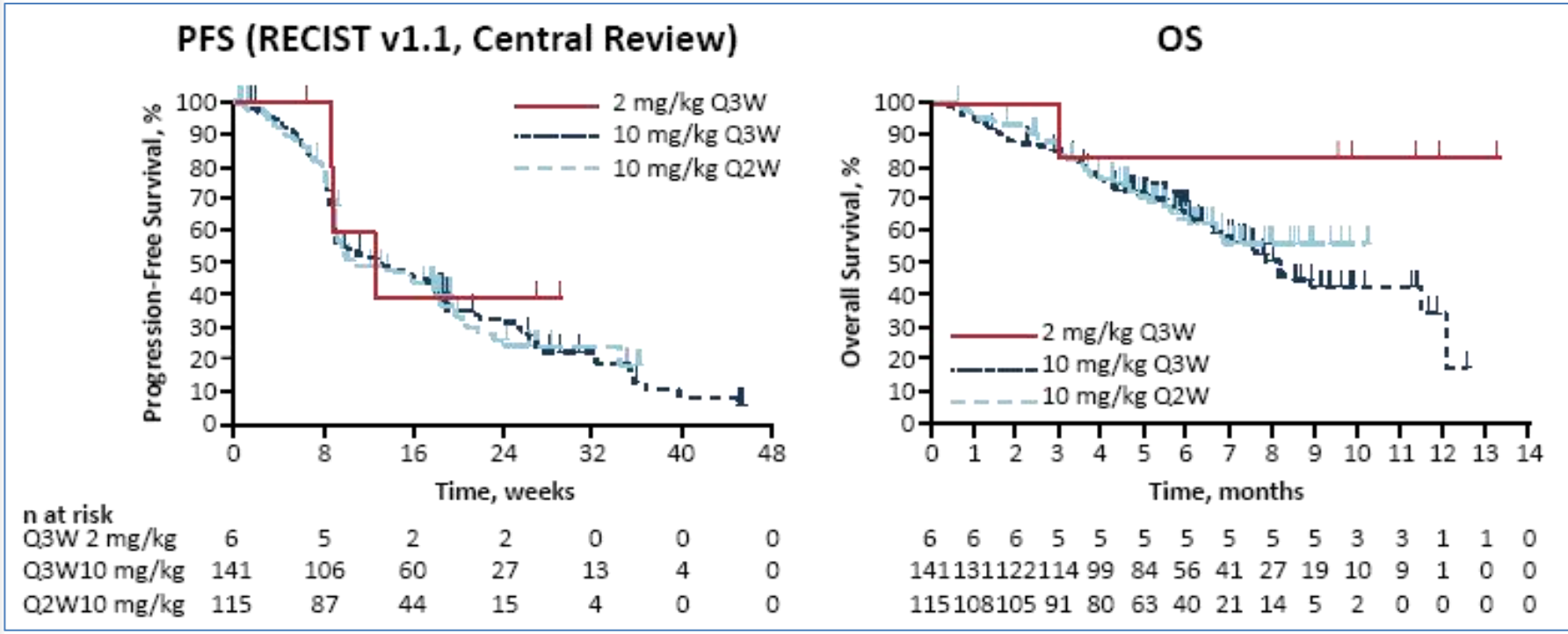


	初治	复治
中位PFS (周)	27	10
24周PFS (%)	51	26

	初治	复治
中位OS (月)	NR	8.2
6个月OS (%)	86	59

Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：
生存期评估：不同剂量

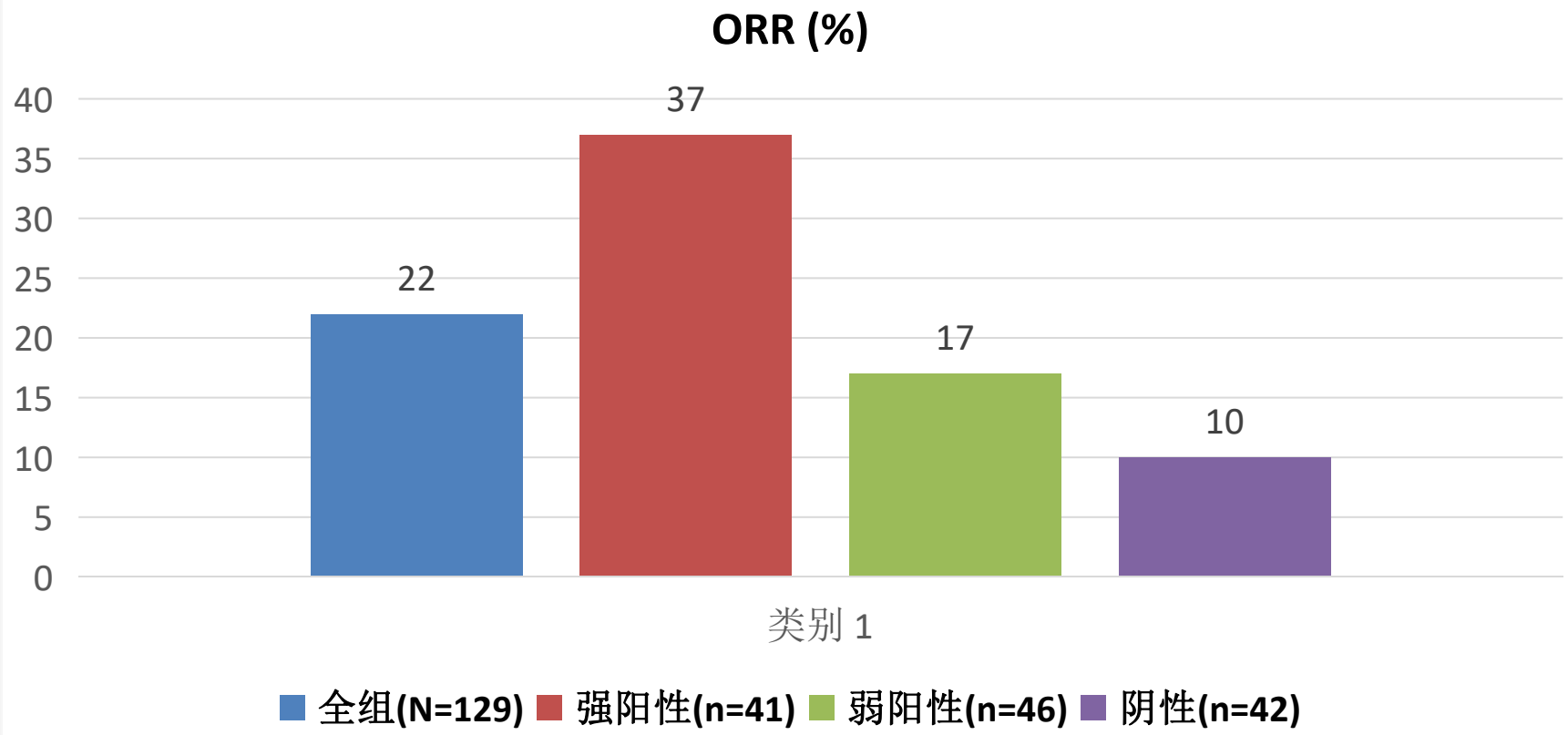


	全组人群
中位PFS (周)	13.0
24周PFS (%)	30

	全组人群
中位OS (月)	8.2
6个月OS (%)	64

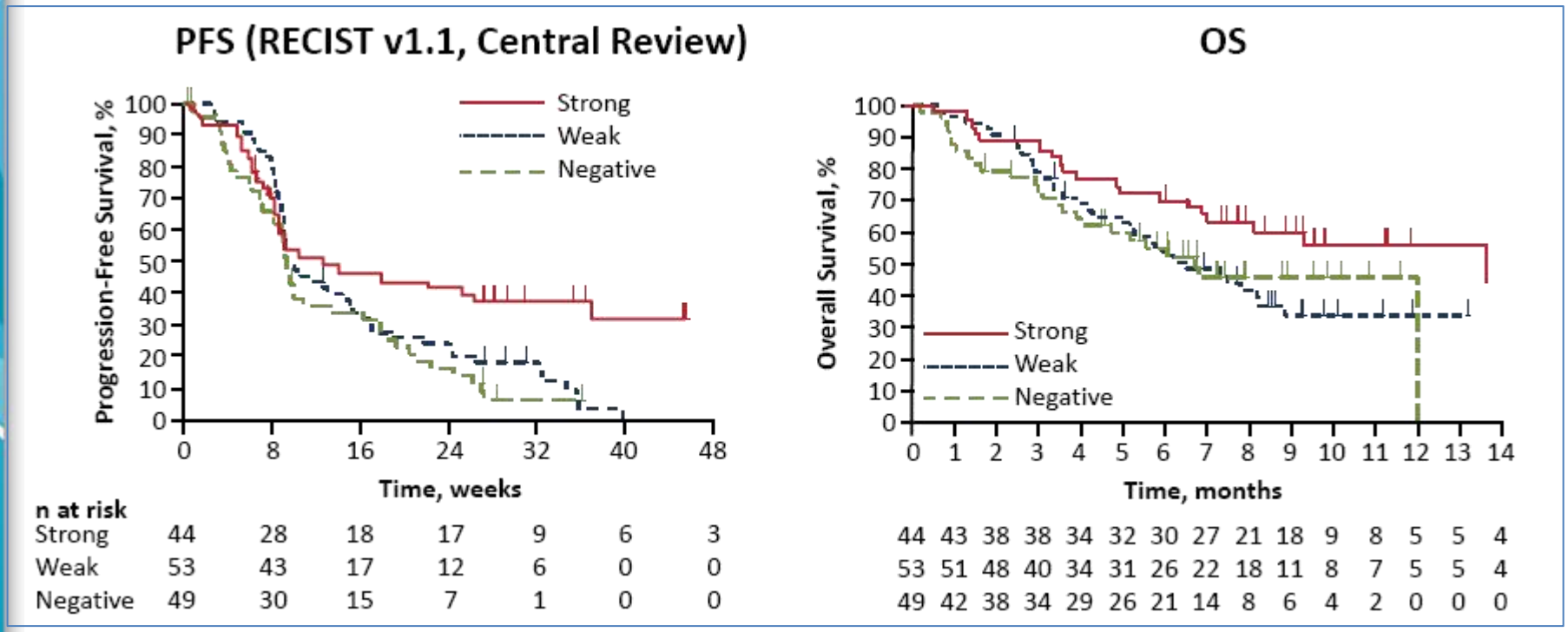
Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：
PD-L1表达水平与缓解率



Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：
生存期评估：PD-L1表达



- PD-L1强阳性患者较弱阳性/阴性患者的PFS更长(HR=0.52; 95%CI:0.33-0.80)
- PD-L1强阳性患者较弱阳性/阴性患者的OS更长(HR=0.59; 95%CI:0.35-0.99)

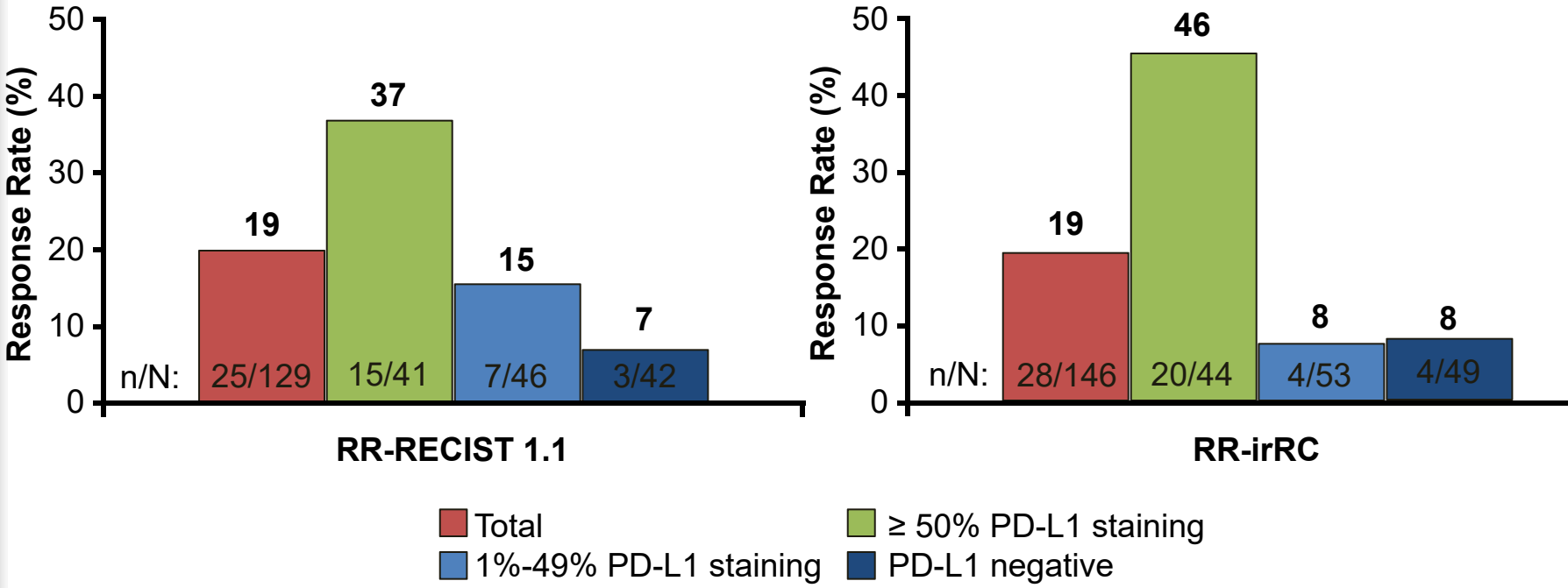
PD-L1强阳性：>=50%的肿瘤细胞
PD-L1弱阳性：1-49%的肿瘤细胞
染色阴性为PD-L1无表达
Garon EB, et al. 2014 ESMO Abstract LBA43.

KEYNOTE-001：总结与结论

- 在初治(ORR 26%)和复治(ORR 20%)晚期NSCLC患者中，所有剂量和方案都观察到很好的抗肿瘤活性
- 2mg/kg q3w剂量下，ORR为20%(irRC)
- 缓解持久
- 安全性及毒性可管理
- PD-L1强表达与缓解率(37%)、PFS(HR=0.52)、OS(HR=0.59)的改善相关
- 在KEYNOTE-001研究额外入组的300例患者中将前瞻性验证PD-L1的截点

Garon EB, et al. 2014 ESMO Abstract LBA43.

PD-L1 Identifies Pts With NSCLC Most Likely to Benefit From MK-3475(Pembrolizumab, Anti-PD-1)



Strong PD-L1 positive staining was considered ≥ 50% of tumor cells, and weak was defined as staining between 1% to 49% of positively staining tumor cells. Negative had no tumor staining for PD-L1.

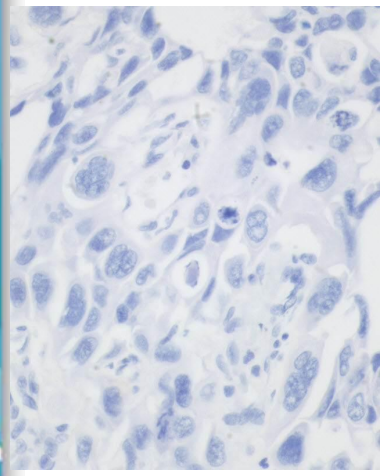
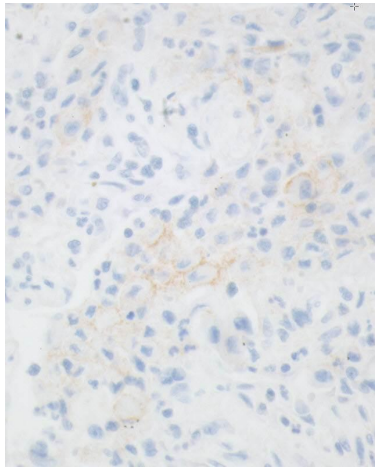
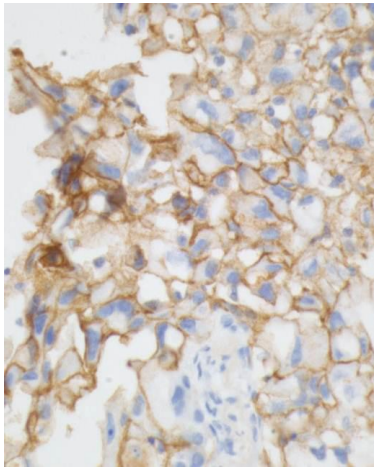
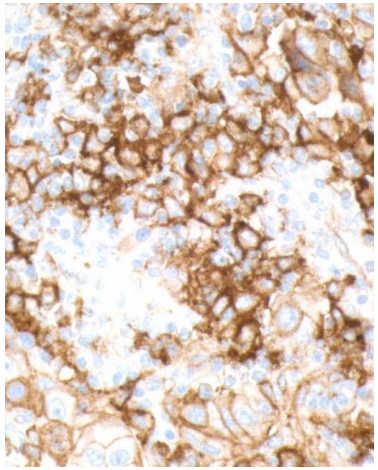
Gandhi L, et al. AACR 2014. Abstract CT105. Reprinted with permission.

Ongoing MK-3475(Pembrolizumab, Anti-PD-1) Clinical Trials in Patients With NSCLC

Line of Therapy	Phase	PD-L1 Selection	Comparator
Single-agent MK-3475			
1st line; ≥ 2nd line[1,2]	I/II	Both	NA
2nd line[3]	III	Yes	Docetaxel
1st line[4]	III	Yes	Chemotherapy
Combination MK-3475			
NA[5]	I/II	No	Single agent; + chemotherapy; + pemetrexed; + gefitinib; + erlotinib; + ipilimumab

1. ClinicalTrials.gov. NCT02085070. 2. ClinicalTrials.gov. NCT02129556. 3. ClinicalTrials.gov. NCT0190
4. ClinicalTrials.gov. NCT02142738. 5. ClinicalTrials.gov. NCT02039674.

Examples of PD-L1 NSCLC Sample IHC Staining*

Staining Intensity	0+	1+	2+	3+
PD-L1 Positivity, %	0	2	100	100
	PD-L1 Negative	**PD-L1 Positive**		

*Clinical trial assay.

Gandhi L, et al. AACR 2014. Abstract CT105. Reprinted with permission.

Phase I Study of MPDL3280A (Anti-PDL-1) in NSCLC

- MPDL3280A: anti–PD-L1 antibody engineered for enhanced safety and efficacy
- Patients with metastatic solid tumors
  - EGFR and KRAS status assessed at baseline
- Study design: MPDL3280A IV every 3 wks x 16 cycles (≈ 1 yr)
- Primary endpoint: safety
- Secondary endpoint: ORR by RECIST v1.1
- Baseline demographics

Characteristics	n = 85*
Median age, yrs (range)	60 (24-84)
Sex, male/female, n (%)	48 (56)/37 (44)
ECOG PS, 0 / 1, n (%)	27 (32)/58 (68)
Histology, n (%)	
Squamous	20 (24)
Nonsquamous	65 (76)

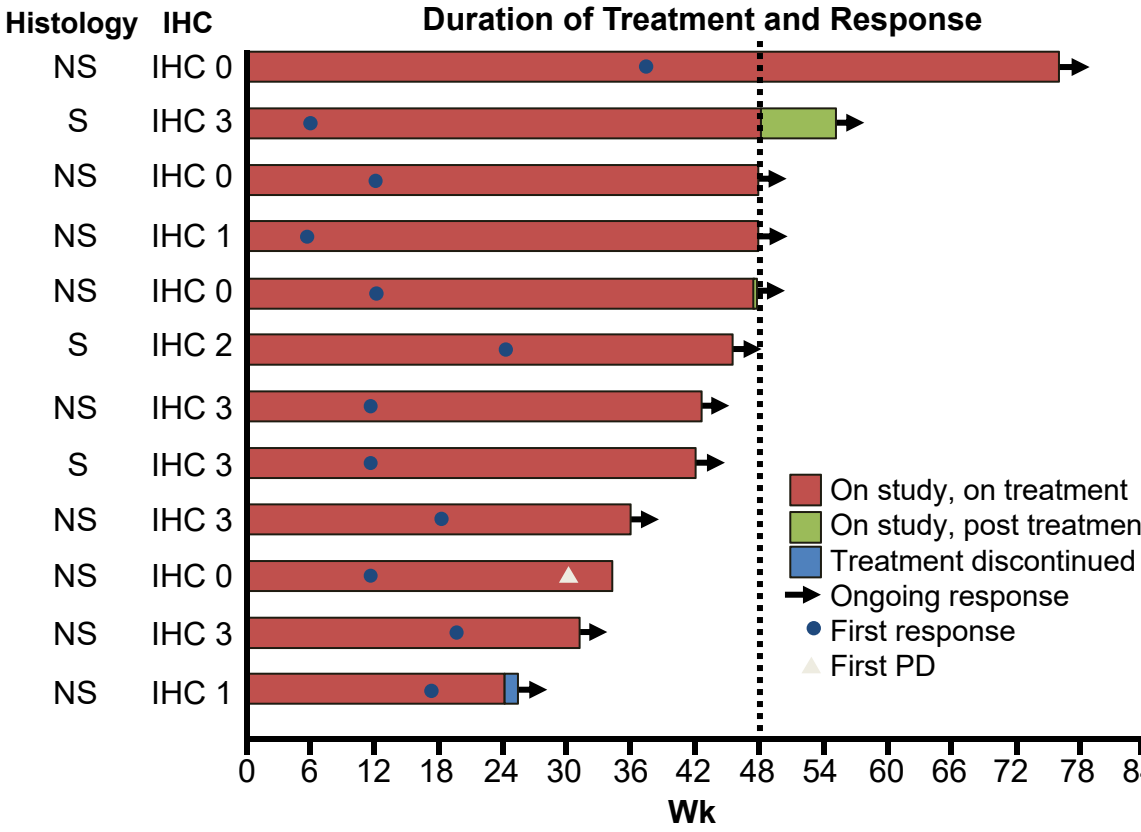
Characteristics, n (%)	n = 85*
Previous systemic regimens†	
1 or 2	36 (42)
≥ 3	47 (55)
Smoking status	
Current/previous	68 (80)
Never	17 (20)

*Safety evaluable patients (n = 85) with NSCLC. Data cutoff April 30, 2013.
†Systemic regimens administered in the metastatic, adjuvant or neoadjuvant setting. 3% of patients had no previous systemic regimens.

Horn L, et al. WCLC 2013. Abstract MO18. Reprinted with permission.

MPDL3280A(Anti-PDL-1) in NSCLC: Best Response by PD-L1 Status and DOT/DOR

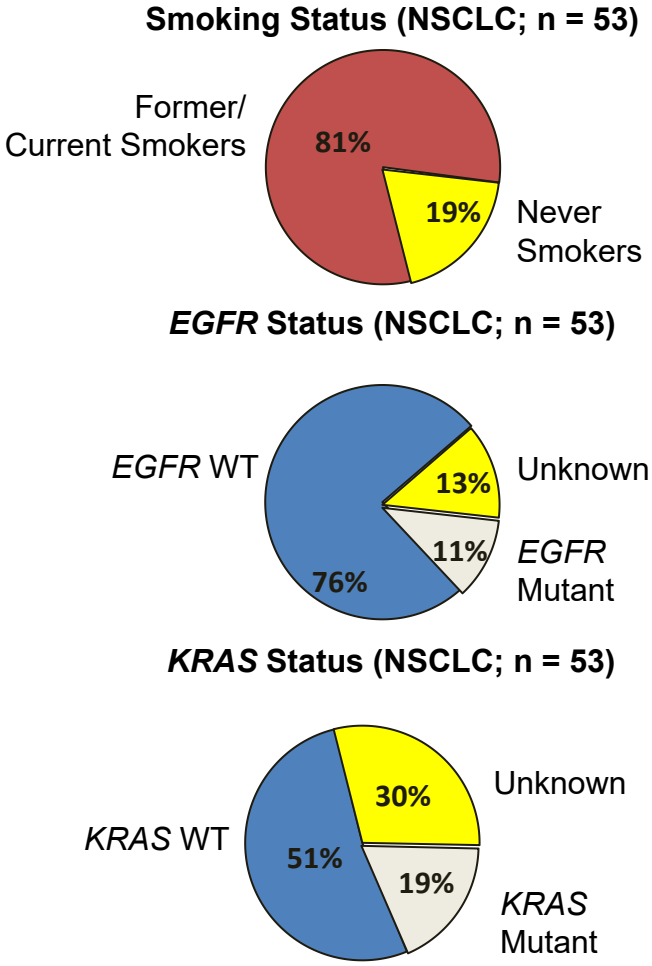
PD-L1 Status* (N = 53)	ORR,† % (n/N)	Pts With PD, % (n/N)
IHC 3 (n = 6)	83 (5/6)	17 (1/6)
IHC 2 and 3 (n = 13)	46 (6/13)	23 (3/13)
IHC 1/2/3 (n = 26)	31 (8/26)	38 (10/26)
All patients (IHC 0/1/2/3 and 7 patients with diagnostic unknown; N = 53)	23 (12/53)	40 (21/53)

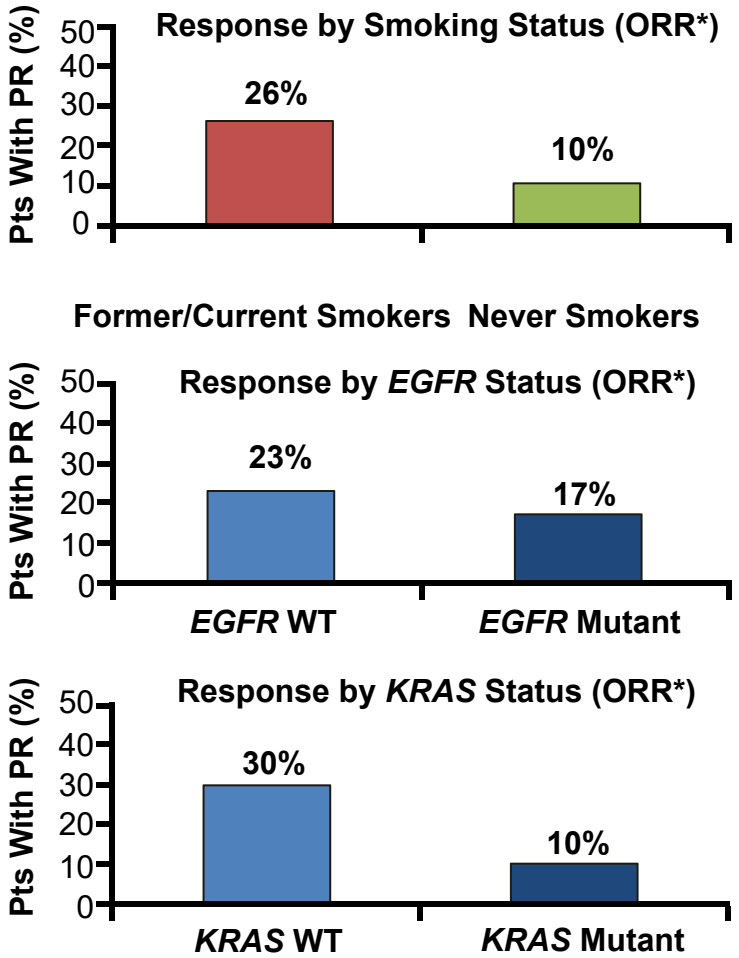


*PD-LI status determined using proprietary Genentech Roche IHC.
†ORR includes investigator-assessed unconfirmed and confirmed (u/c) PR per RECIST 1.1.
Patients first dosed at 1-20 mg/kg by October 1, 2012. Data cutoff April 30, 2013.

Horn L, et al. WCLC 2013. Abstract MO18. Reprinted with permission.

MPDL3280A (Anti-PDL-1)Phase Ia: Response by Smoking and Mutational Status





*ORR includes investigator-assessed u/c PR by RECIST 1.1. Patients first dosed at 1-20 mg/kg by October 1, 2012. Data cutoff April 30, 2013.

Horn L, et al. WCLC 2013. Abstract MO18. Reprinted with permission.

MPDL3280A(Anti-PDL-1): Treatment-Related Adverse Events in Patients With NSCLC

- Majority of AEs were grade 1/2 and did not require intervention
- No MTD or dose-limiting toxicities
- No grade 3-5 pneumonitis observed
- Treatment-related death (cardio-respiratory arrest) in 1 patient with sinus thrombosis and large tumor mass invading the heart at baseline
- Immune-related grade 3.4 AEs: 1 patient with large-cell neuroendocrine NSCLC (diabetes mellitus, 1%)

Adverse Event (n = 85)	Treatment Related, % (n)	
	Any Grade*	Grade 3/4†
Any AE	66 (56)	11 (9)
Fatigue	20 (17)	2 (2)
Nausea	14 (12)	1 (1)
Decreased appetite	12 (10)	0
Dyspnea	9 (8)	1 (1)
Diarrhea	8 (7)	0
Asthenia	7 (6)	0
Headache	7 (6)	0
Rash	7 (6)	0
Pyrexia	6 (5)	0
Vomiting	6 (5)	1 (1)
Upper respiratory tract infection	5 (4)	0

*AEs occurring in ≥ 5% of patients.
†Grade 3/4 treatment-related AEs listed include treatment-related AEs for which the any grade occurrence was ≥ 5% of patients.
Data cutoff April 30, 2013.

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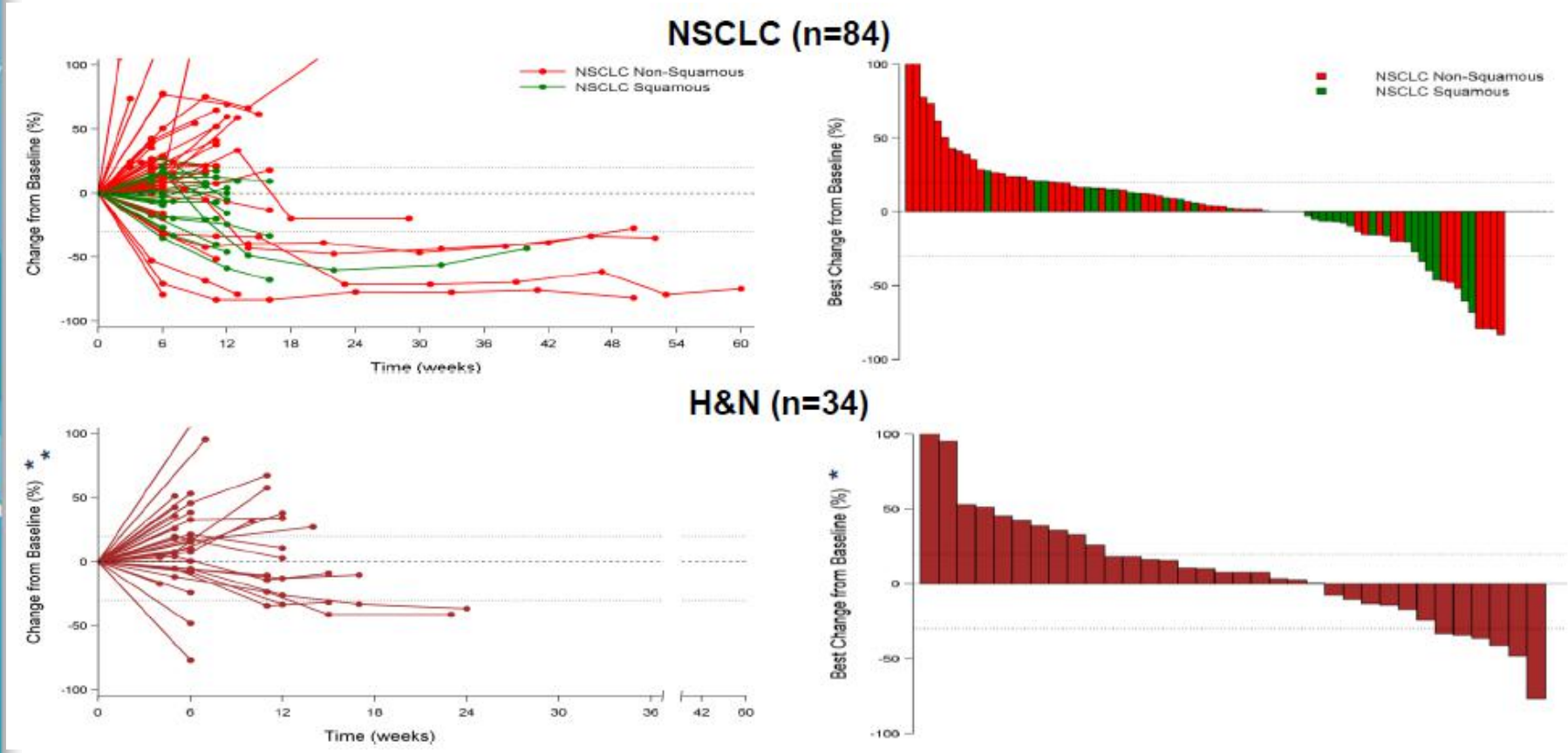
Ongoing MPDL3280A(Anti-PDL-1) Clinical Trials in Patients With NSCLC

Line of Therapy	Phase	PD-L1 Selection	Comparator
Single-agent MPDL3280A			
1st line; ≥ 2nd line[1]	II	Yes	NA
1st line; ≥ 2nd line[2]	II	Yes	NA
2nd line[3]	II	No	Docetaxel
≥ 2nd line[4]	III	No	Chemotherapy
Combination MPDL3280A			
Expansion: EGFRm TKI naive[5]	I	No	+ erlotinib
Expansion: KRAS NSCLC[6]	I	No	+ cobimetinib
NA[7]	I	No	+ chemotherapy; + bevacizumab

1. ClinicalTrials.gov. NCT02108652. 2. ClinicalTrials.gov. NCT01846416. 3. ClinicalTrials.gov. NCT01903993.
4. ClinicalTrials.gov. NCT01984242. 5. ClinicalTrials.gov. NCT02013219. 6. ClinicalTrials.gov. NCT01988896.
7. ClinicalTrials.gov. NCT01633970.

MED14736(Anti-PD-L1):Emerging promising clinical activity in select tumors



Jose Lutzky, Neil Howard Segal ASCO 2014

MED14736(Anti-PDL1) safety: No colitis, no high grade pneumonitis ,no drug-related deaths

Select drug-related AEs of interest*		MEDI4736 10 mg/kg q2w (N= 339)	
System Organ Class	**Event**	**All Grades, n (%)**	**Grade 3/4, n (%)**
Constitutional - General	Fatigue	44 (13)	2 (1)
	Pyrexia	9 (3)	0
Gastro-Intestinal	Vomiting	16 (5)	1 (<1)
	Diarrhea	15 (4)	0
	Abdominal Pain	7 (2)	0
Endocrine	Hypothyroidism	7 (2)	1 (<1)
	Hyperthyroidism	3 (1)	0
	Hyperglycemia	1 (<1)	1 (<1)
Skin	Rash	16 (5)	0
	Pruritus	13 (4)	1 (<1)
Respiratory	Dyspnea	14 (4)	0
	Pneumonitis	2 (1)	0
Hepatic	AST Elevation	7(2)	2 (1)
	ALT Elevation	7(2)	1 (<1)
Neurotoxicity	Peripheral neuropathy	3 (1)	0

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Ongoing MEDI4736 (Anti-PDL-1)Clinical Trials in Patients With NSCLC

Line of Therapy	Phase	PD-L1 Selection	Comparator
Single-agent MEDI4736			
≥ 2nd line[1]	II	Yes	NA
Post chemo-RT for IIIA NSCLC[2]	II	Yes	NA
Combination MEDI4736			
NA[3,4]	I	No	+ tremelimumab
≥ 2nd line for EGFR+ NSCLC[5]	I	No	+ gefitinib
NA[6]	I	No	+ MEDI0680 (PD-1)

1. ClinicalTrials.gov. NCT02087423. 2. ClinicalTrials.gov. NCT02125461. 3. ClinicalTrials.gov. NCT01975831
4. ClinicalTrials.gov. NCT02000947. 5. ClinicalTrials.gov. NCT02088112. 6. ClinicalTrials.gov. NCT02118337

NSCLC-other key PD-1/PD-L1 data presented at 2014 ASCO

2L/3L NSCLC Monotherapy

- **Nivolumab: Phl in 2L/3L NSCLC at pivotal dose (3mg/kg)**
  - ORR: 24%, 1 yr OS: 56%, 2 yr OS: 45% for pivotal dose
- **MK-3475: in Phl in 2L/3L NSCLC at 10mg/kg (Q2W and Q3W)**
  - ORR (by Recist) was 20% overall, 23% in PDL1+ and 9% in in PDL1-

1L NSCLC - Monotherapy

- **Nivolumab: in 1L PDL1+ NSCLC (PDL1+ defined as ≥5% PDL1 expression)**
  - Sizable difference in ORR between PDL1+ and PDL1- 1L NSCLC patients (50% vs 0%)
- **MK-3475: in 1L PDL1+ NSCLC**
  - ORR=26% (RECIST) in PDL1+, which represent 78% of pts (≥1% PDL1 expression).

1L NSCLC - Combinations

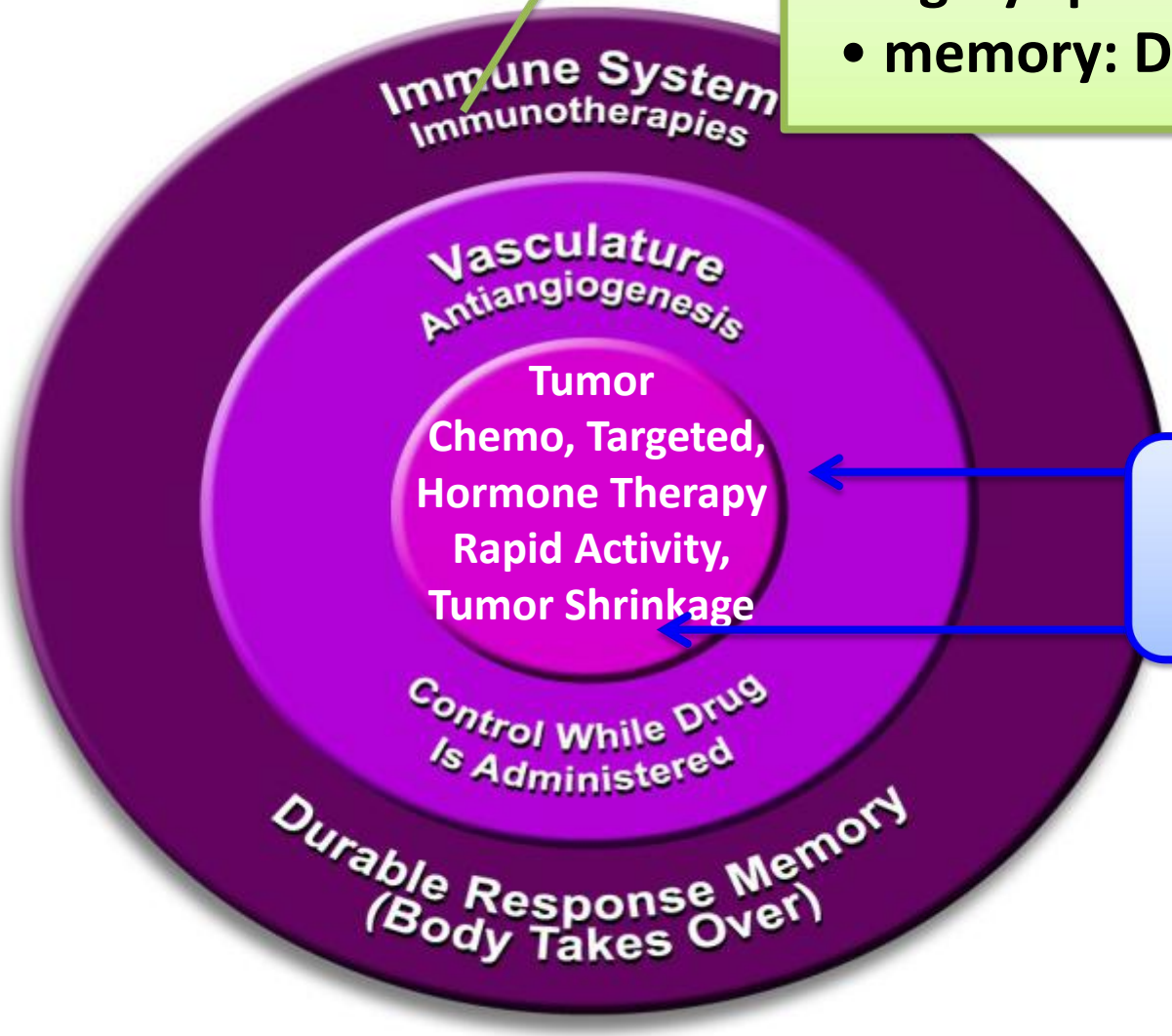
- **Nivo+Ipilimumab**
  - ORR was 16% (8/49); activity observed regardless of PD-L1 status; grade 3/4 AEs 49%
- **Nivo+erlotinib:** ORR was 19% (4/21 pts); Single TKI-naive patient had a CR
- **Nivo+chemo**
  - ORRs (across arms) were 33–50%; 1 yr OS rates were 59–87%; grade 3/4 AEs: 45%

Outline

1. Cancer Immunotherapy
2. Update of checkpoint Inhibitors in lung cancer therapy
3. **Future Outlook**

Understanding of Tumor Biology & Immunology Enables Rational Immuno-Combination

Targeting host immune system
- **highly specific anti-tumor immunity**
- **memory: Durable response (cure?)**



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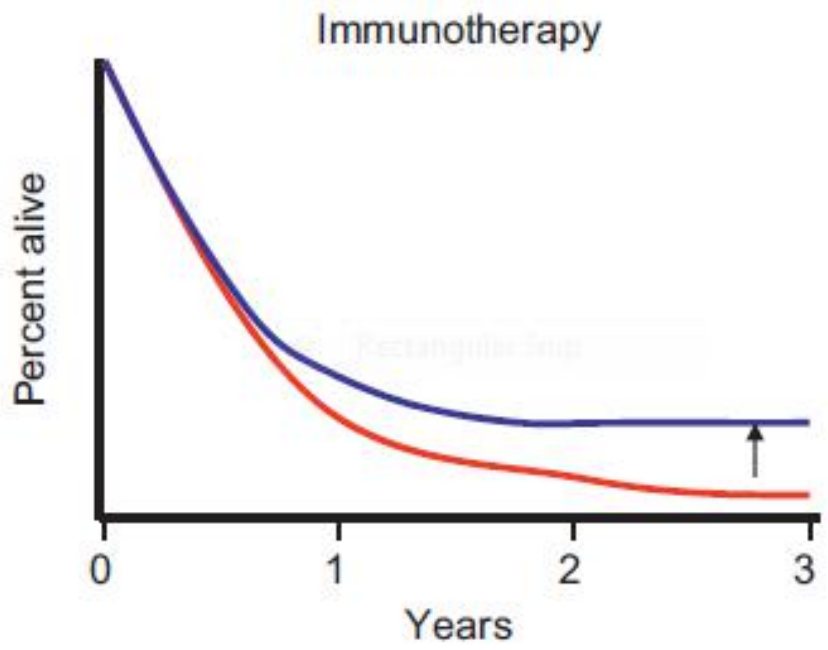
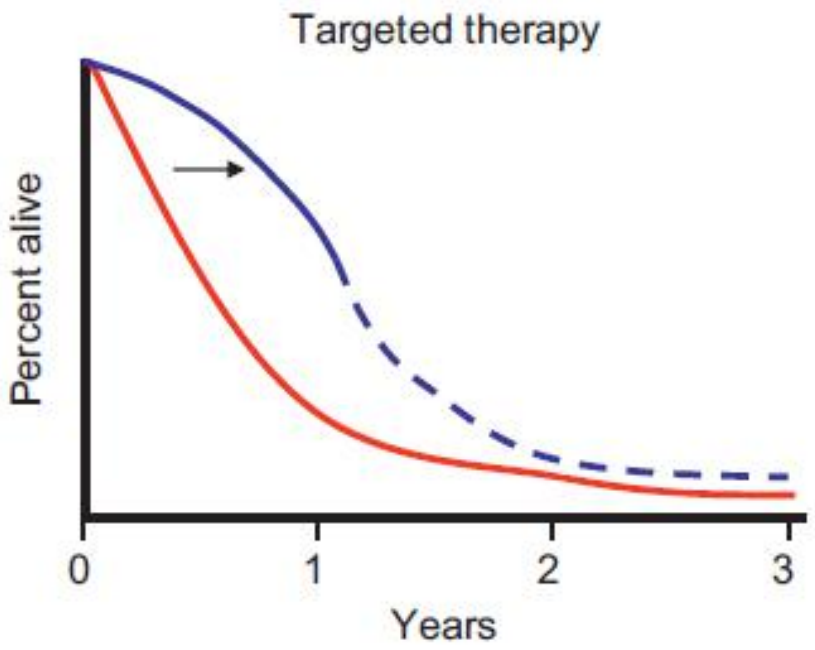
Targeting tumor and tumor microenvironment

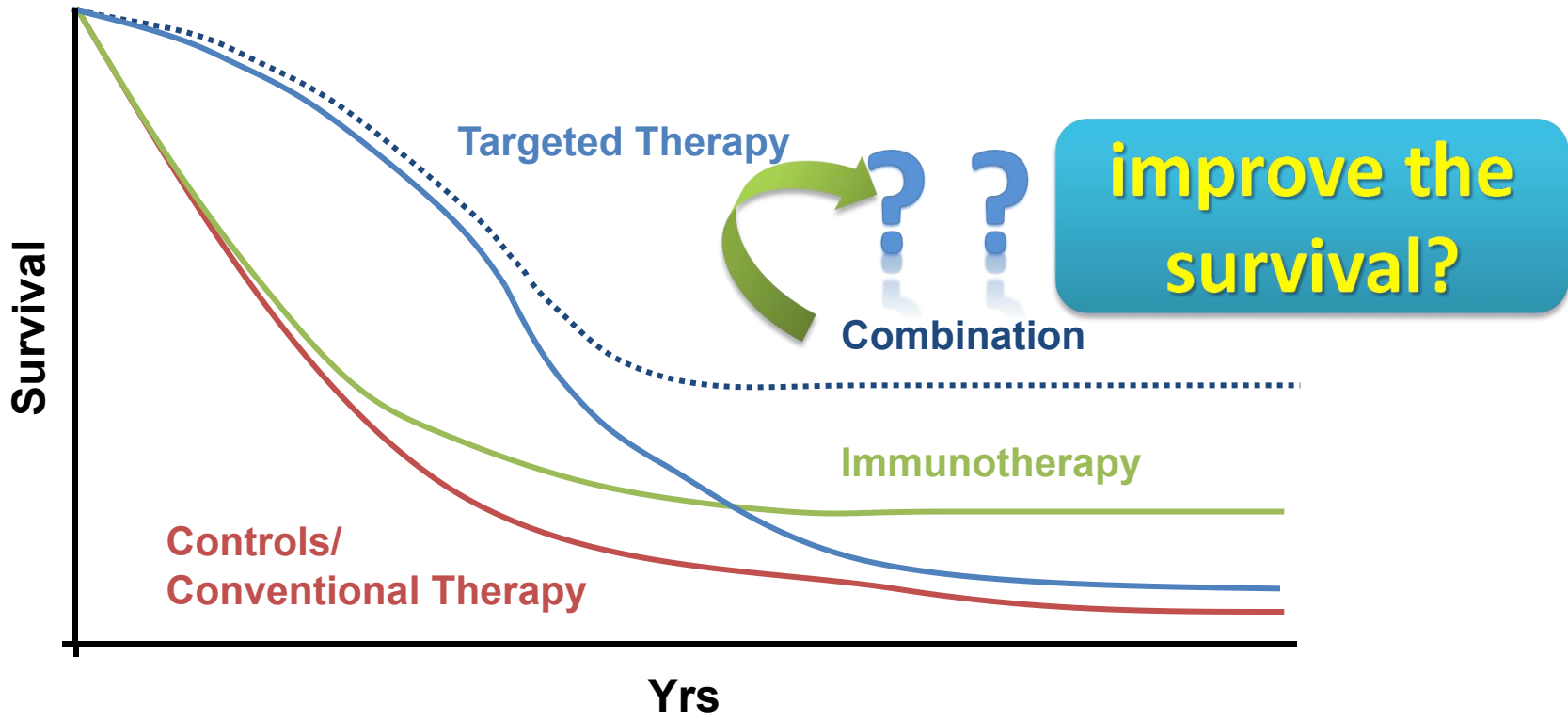
Effects of immunotherapy and targeted therapy on melanoma survival curves





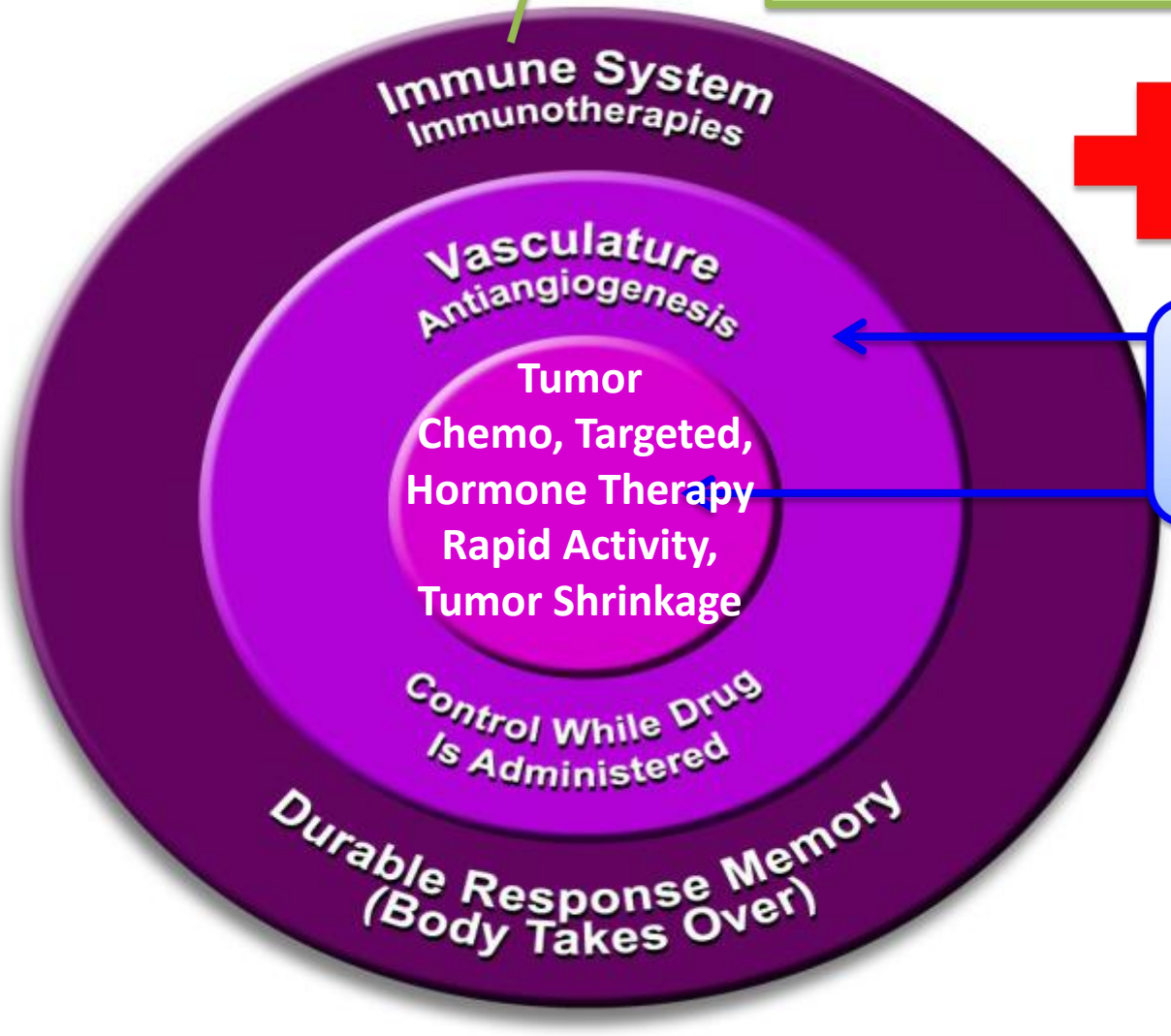
Clin Cancer Res. 2012;18:336-341.

Combining Immunotherapy and Conventional Therapies



Clin Cancer Res. 2012;18:336-341.

Targeting host immune system
- highly specific anti-tumor immunity
- memory: Durable response (cure?)



+ HOW?

Targeting tumor and tumor microenvironment

THANK YOU ！

谢谢！