一套 PPT 看尽 2015 年肺癌领域前沿进展

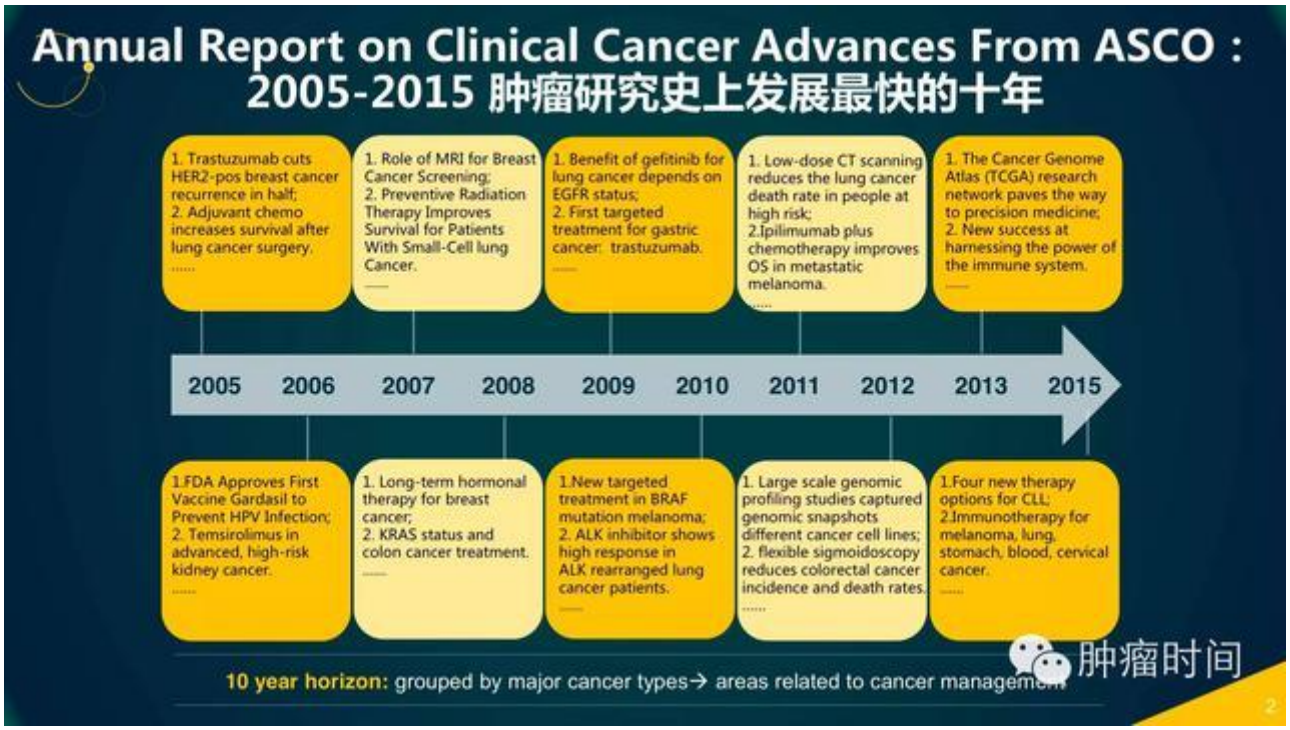
http://toutiao.com/news/6243682089456108034/?tt_from=weixin&utm_campaign=client_share&app=news_article&utm_source=weixin&iid=3484132199&utm_medium=toutiao_android&wxshare_count=1

时空科技 2016-01-25 19:15

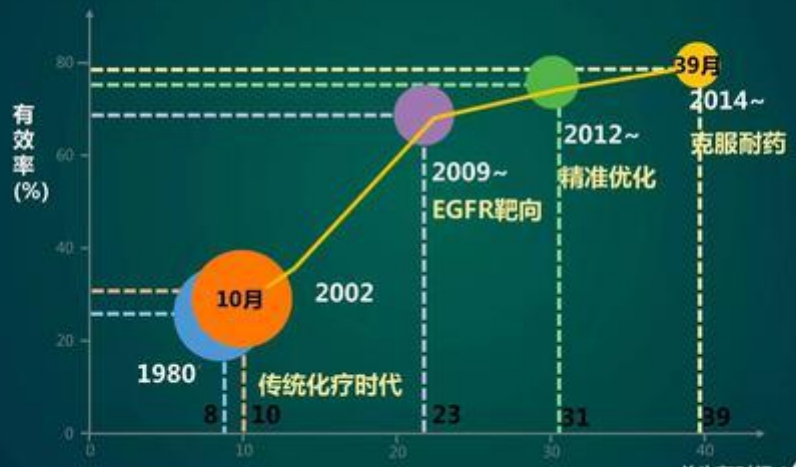
钟文昭

广东省人民医院 广东肺癌研究所

2015 年肺癌领域取得了哪些进展？让我们通过这组 PPT 一起来回顾一下吧。

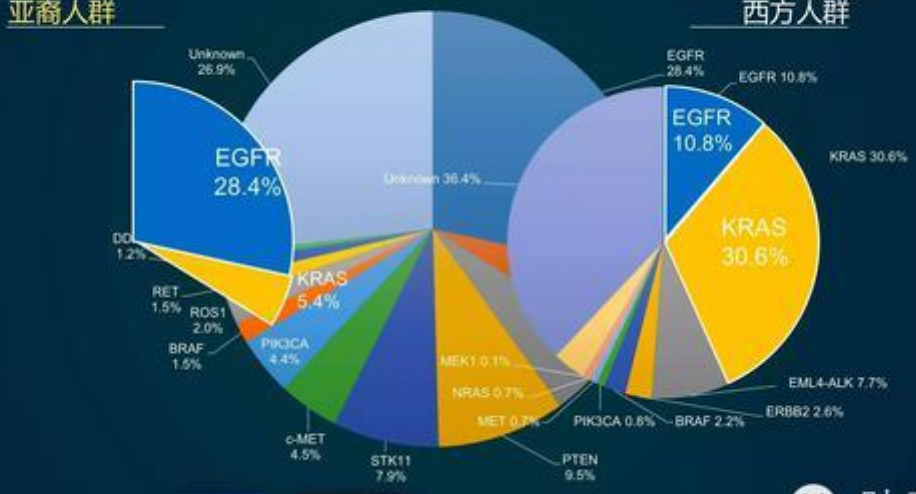


驱动基因突变肺癌逐渐成为临床可控的慢性疾病



中国肺癌驱动基因变异图谱

3个中心、1484例肺癌标本



Journal of Thoracic Oncology

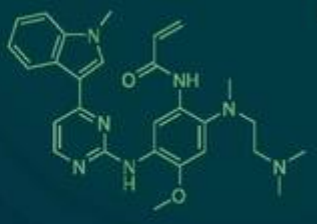
nature REVIEWS

J Clin Oncol 2010,28(30):4
J Thorac Oncol 2007, 2(5):430~439
Nat Rev Clin Oncol 2011,8(11):661-668

革新和优化

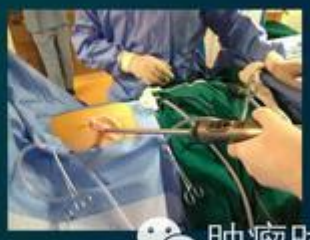
靶向：TKI从一代到三代

- Gefitinib
- Afatinib
- AZD 9291
- Erlotinib
- Lcotinib
- Dacomitinib



腔镜：切口从三个到一个

- 三孔
- 单操作孔
- 单孔



2015肺癌重要事件

影响临床实践

改变对肺癌理解

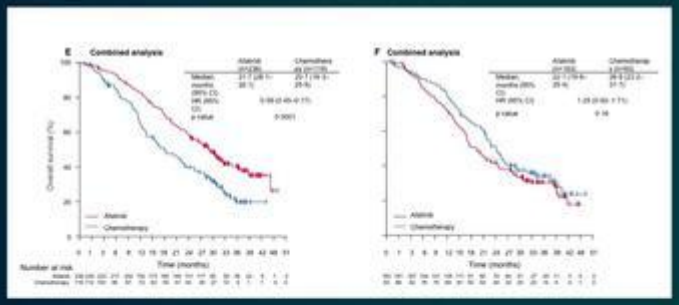
理念革新

细节优化

和其他癌肿相互借鉴

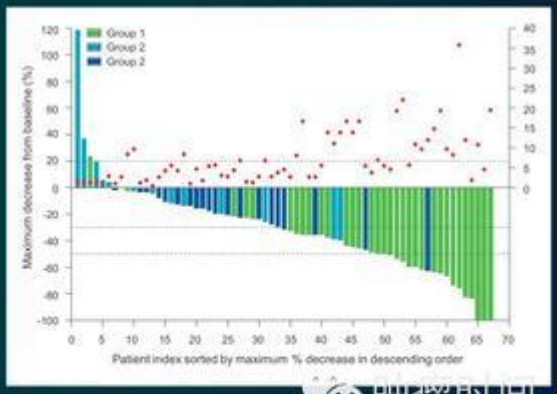
TKI治疗的优化

19 del和L858R需区别对待



Yang and Wu et al. Lancet Oncol. 2015 Feb;16(2):141-51

TKI在非常见突变L861Q/G719C的疗效

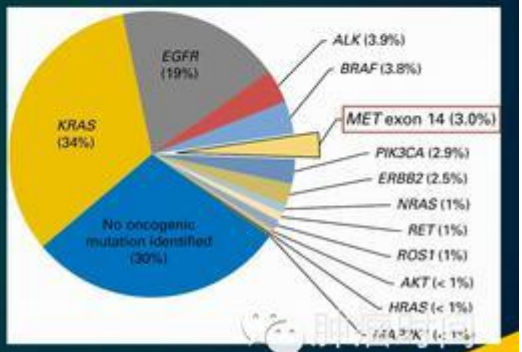


Wu and Yang et al. Lancet Oncol. 2015 Jul;16(7):830-8

驱动版图

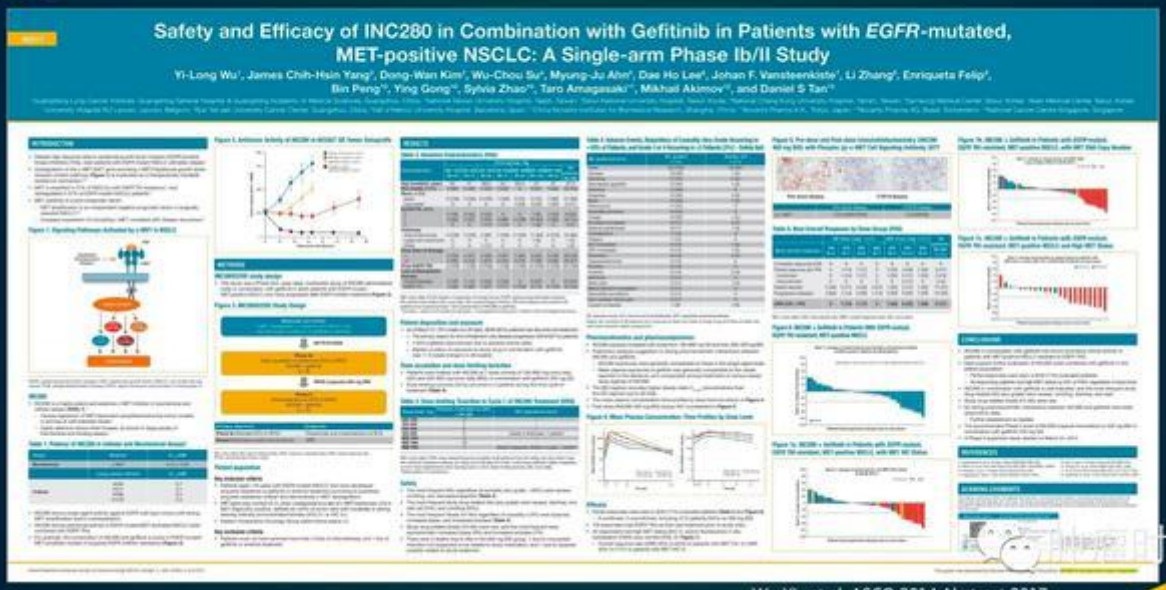
NSCLC：已临床应用及渐浮出水面的分子靶点及药物

分子靶点	药物
EGFR	一代：厄洛替尼、吉非替尼、埃克替尼 二代：阿法替尼 三代：CO-1686, AZD9291，Dacomitinib
ALK	一代：克唑替尼 二代：Alectinib，ceritinib
Met	Tivantinib(ARQ197), Onartuzumab(MetMab) Cabozantinib(XL184)
FGFR1	Nintedanib, XL999
HER-2	阿法替尼
RET/ROS融合基因	克唑替尼, AP 26113, ASP 3026
RAS/MAPK通路	Trametinib(GSK1120212), Pimastertib Refametinib, TAK733……
PI3K/PTEN/AKT	BEZ235, XL-765……
PD-1/PDL-1	Nivolumab,MPDL3280A
HSP 90 …..	Ganetespib



Awad MM, et al. J Clin Oncol. 2016 Jan 4. pii: JCO634600. . [Epub ahead of print]

Met抑制剂用于TKI耐药：旁路激活？

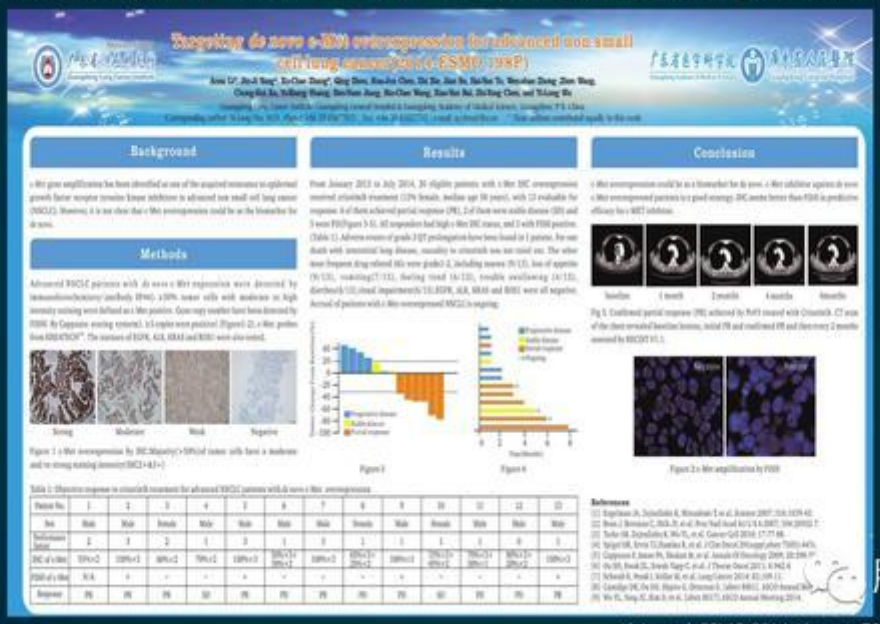


Safety and Efficacy of INC280 in Combination with Gefitinib in Patients with *EGFR*-mutated, MET-positive NSCLC: A Single-arm Phase Ib/II Study

Yi-Long Wu[1], James Chih-Hsin Yang[2], Dong-Wan Kim[3], Wu-Chou Su[4], Myung-Ju Ahn[5], Dae Ho Lee[6], Johan F. Vansteenkiste[7], Li Zhang[8], Enriqueta Felip[9], Bin Peng[10], Ying Gong[10], Sylvia Zhao[10], Taro Arnagasaki[10], Mikhail Akimov[10], and Daniel S Tan[11]

Wu YL, et al. ASCO 2014 Abstract 8017

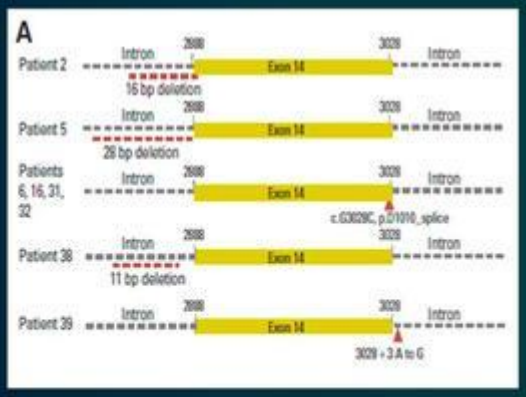
Met抑制剂用于deno vo met高表达肺癌（驱动基因?）



Li A, et al. ESMO 2014 Abstract 7229

Next-Generation Sequencing of Pulmonary Sarcomatoid Carcinoma Reveals High Frequency of Actionable MET Gene Mutations

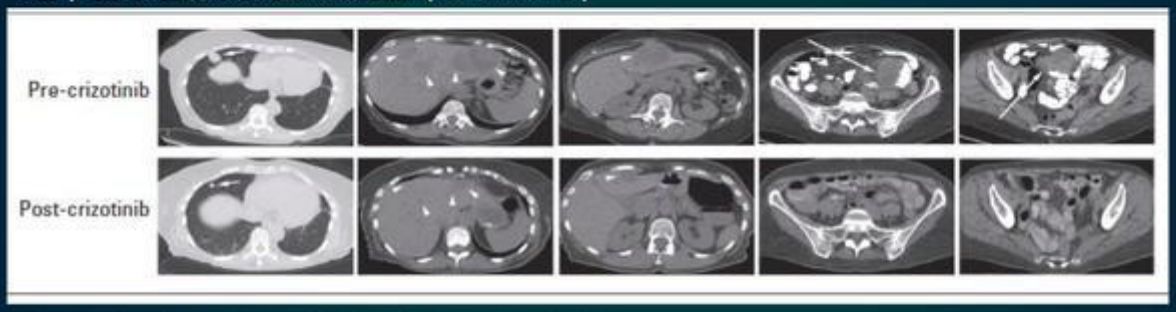
二代测序在肺肉瘤样癌中发现高频的靶点基因MET突变（22%， 8/36）



Xuewen Liu，et al .J Clin Oncol 33

肿瘤时间

在携带有MET exon 14 剪切突变的难治性PSC患者中，MET抑制剂（克唑替尼）显示出惊人的疗效反应（Dramatic）



上图：克唑替尼治疗前，多发脏器转移，肝脏巨大肿块
下图：克唑替尼治疗2月后，各脏器转移病灶明显缓解

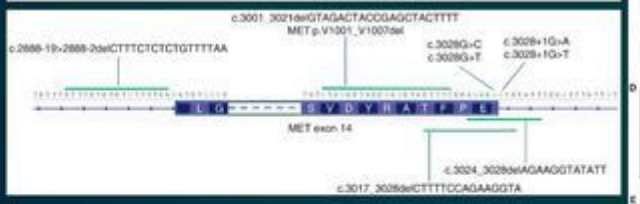
Xuewen Liu，et al .J Clin Oncol 33

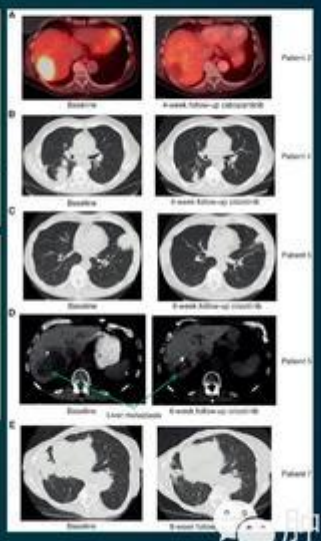
肿瘤时间

Met抑制剂对Met 14 skipping肺腺癌有效

Response to MET Inhibitors in Patients with Stage IV Lung Adenocarcinomas Harboring MET Mutations Causing Exon 14 Skipping

Paul K. Paik[1,2] , Alexander Drilon[1,2] , Pang-Dian Fan[3] , Helena Yu[1,2] , Natasha Rekhtman[3] , Michelle S. Ginsberg[4] , Laetitia Borsu [3] , Nikolaus Schultz[5,6] , Michael F. Berger[2,3,5] , Charles M. Rudin[1,2] ,and Marc Ladanyi[3,5]



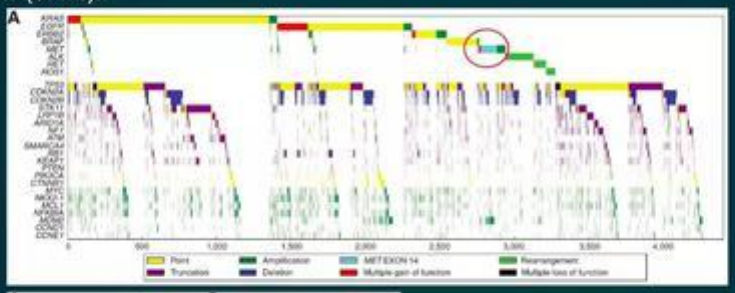


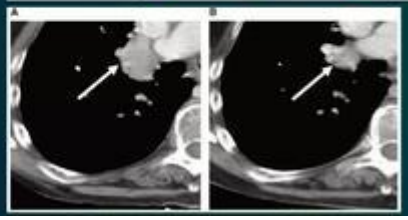
Met 14 skipping 4% in AC

Paik PK, et al. Cancer Discov. 2015 Aug;5(8):842-9.

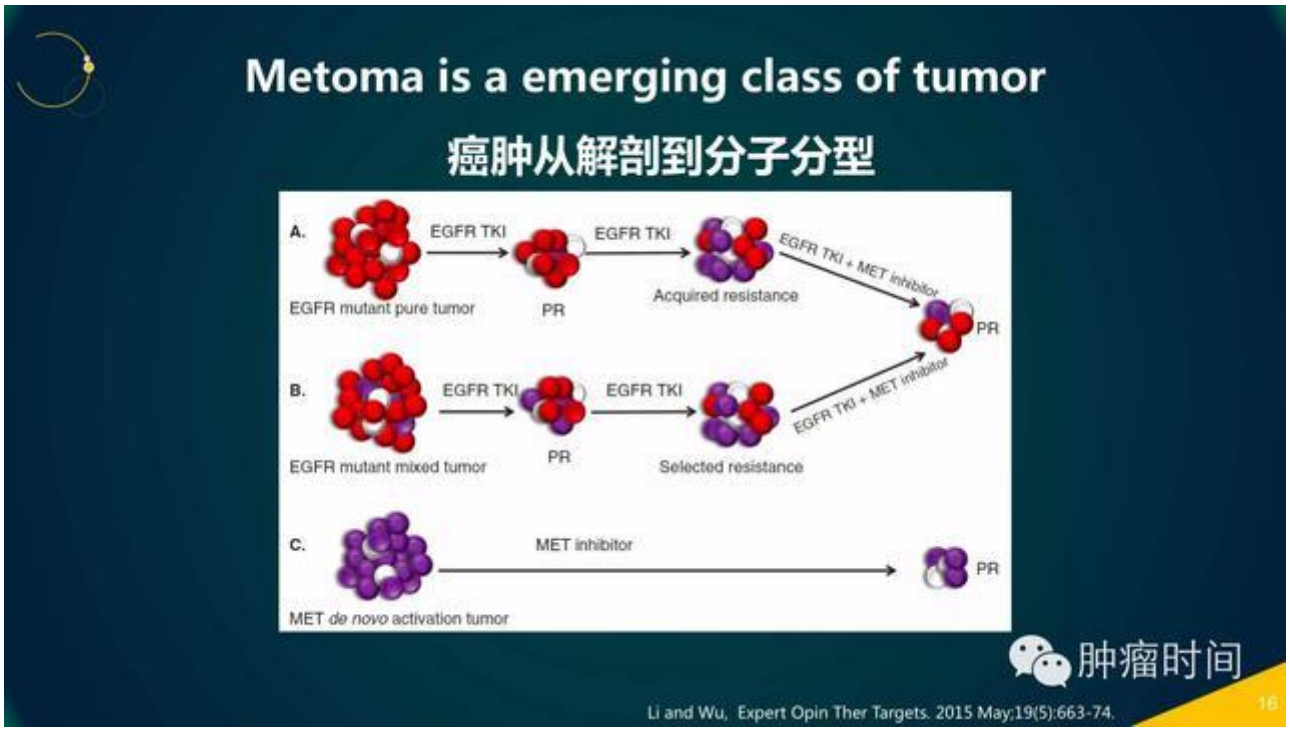
Met抑制剂对Met 14 skipping实体瘤有效

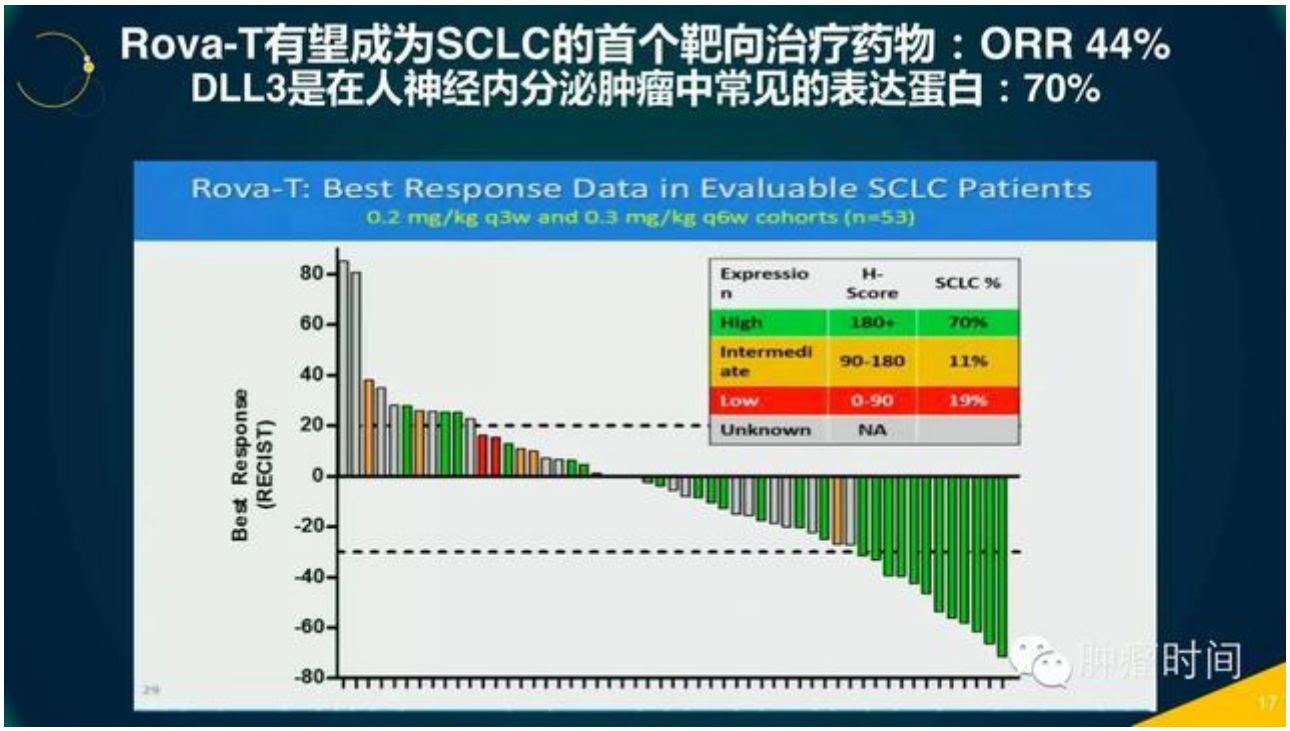
From 38,028 patients to identify 221 cases with *MET* ex14 mutations (0.6%), including 126 distinct sequence variants. *MET* ex14 mutations are detected most frequently in lung adenocarcinoma (3%), but also frequently in other lung neoplasms(2.3%), brain glioma (0.4%), and tumors of unknown primary origin (0.4%).





Frampton GM, et al. Cancer Discov. 2015 Aug;5(8):850-9.

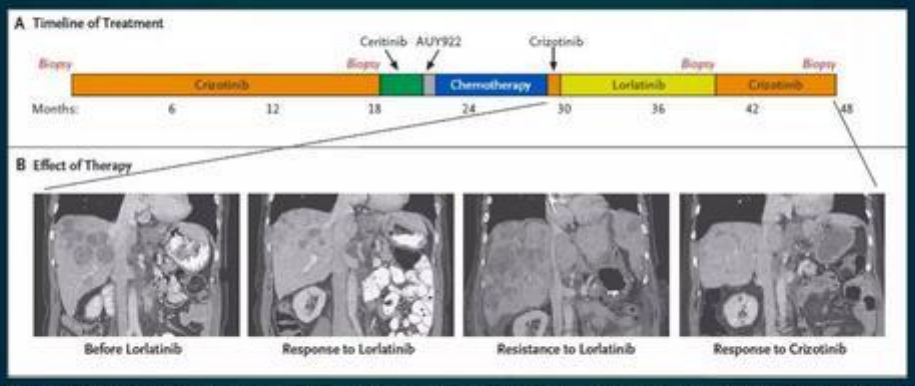

Metoma is a emerging class of tumor
癌肿从解剖到分子分型
A.
EGFR TKI
EGFR TKI
EGFR TKI + MET inhibitor
EGFR mutant pure tumor
PR
Acquired resistance
PR
B.
EGFR TKI
EGFR TKI
EGFR TKI + MET inhibitor
EGFR mutant mixed tumor
PR
Selected resistance
C.
MET inhibitor
PR
MET de novo activation tumor
肿瘤时间
Li and Wu, Expert Opin Ther Targets. 2015 May;19(5):663-74.


Rova-T有望成为SCLC的首个靶向治疗药物：ORR 44%
DLL3是在人神经内分泌肿瘤中常见的表达蛋白：70%
Rova-T: Best Response Data in Evaluable SCLC Patients
0.2 mg/kg q3w and 0.3 mg/kg q6w cohorts (n=53)
Best Response (RECIST)
80
60
40
20
0
-20
-40
-60
-80
Expression
H-Score
SCLC %
High
180+
70%
Intermediate
90-180
11%
Low
0-90
19%
Unknown
NA
肿瘤时间

靶向轮回

靶向轮回--ALK耐药与癌共舞

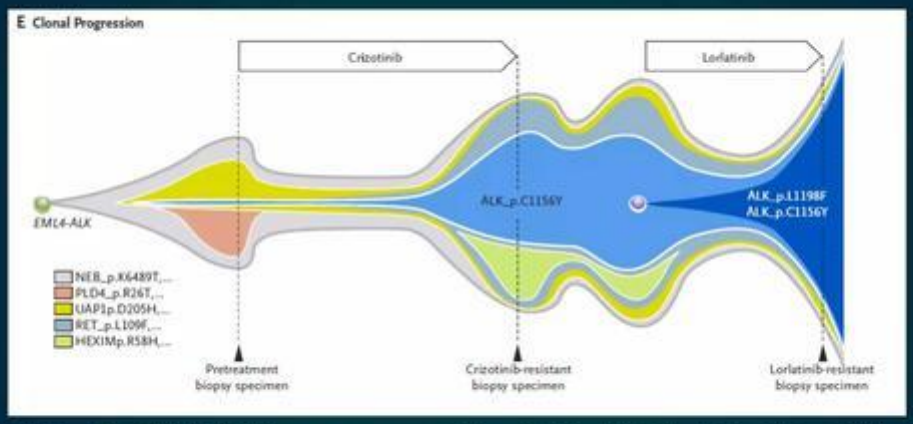
Resensitization to Crizotinib by the Lorlatinib *ALK* Resistance Mutation L1198F



52岁女性ALK阳性NSCLC患者的治疗历程，长达48个月，历经了第一代ALK抑制剂克唑替尼（PFS 18月），第二代ALK抑制剂色瑞替尼（PFS 5w），第三代抑制剂lorlatinib的治疗（PFS 9月），间或接受HSP90（热休克蛋白）和化疗，最终再次接受克唑替尼治疗，并从中获益

Alice T. Shaw ,et al NEJM 2015

靶向轮回--ALK耐药与癌共舞

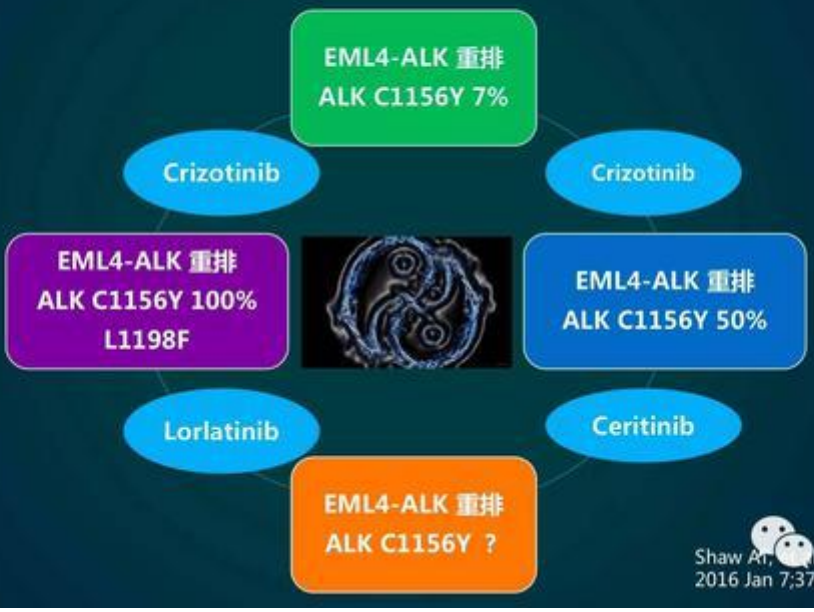


在治疗前的标本中，发现了低频的基线ALK C1156Y亚克隆；经过克唑替尼治疗后，该组亚克隆细胞增加到50%，从而导致肿瘤发生进展

lorlatinib对C1156Y敏感，但该克隆又获得了ALK 二次突变 L1198F，这种双突变的亚克隆细胞对lorlatinib不敏感，从而变成占主导的肿瘤细胞，肿瘤耐药进展再次发生，空间构想改变对克唑替尼再次敏感

Alice T. Shaw ,et al NEJM 2015

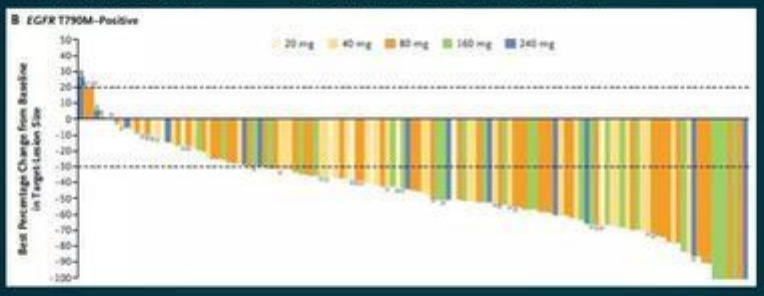
TKI 轮回 - ALK



Shaw AT, et al. N Engl J Med. 2016 Jan 7;374(1):54-61.

AZD9291：3rd TKI

- AZD9291是不可逆的、突变选择性的EGFR-TKI，对于敏感突变及T790M均有效[1]
- 正在进行的AZD9291I 期研究 (AURA, NCT01802632),在既往EGFR-TKI治疗后疾病进展的T790M突变阳性肺癌患者中的缓解率>60%[2]



- 我们最近报道的AZD9291的获得性耐药,可能是因为EGFR C797S突变和EGFR T790M缺失引起的[3]

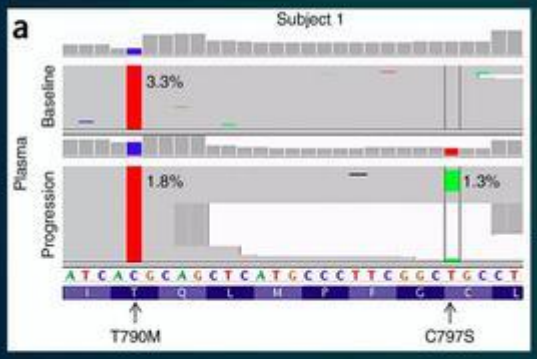
1. Cross DA, et al. Cancer Discov. 2014 Sep;4(9):1046-61.;
2. Jänne PA, et al. N Engl J Med. 2015 Apr 30;372(18):1689-99.
3. Thress KS, et al. Nat Med. 2015 Jun;21(6):560-2.

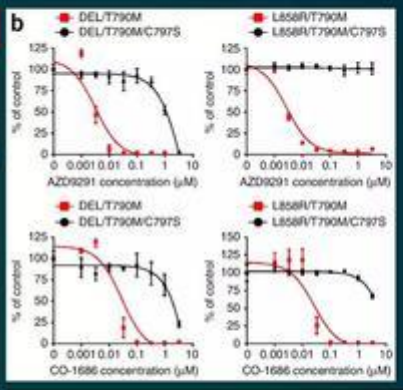
EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor

Geoffrey R.Oxnard,et al.2015 WCLC 17.07

再向前一步的探索—三代TKI耐药机制

Acquired *EGFR* C797S mutation mediates resistance to AZD9291 in non–small cell lung cancer harboring *EGFR* T790M





Six cases acquired the C797S mutation, five cases maintained the T790M mutation but did not acquire the C797S mutation and four cases lost the T790M mutation despite the presence of the underlying EGFR activating mutati

Thress KS, et al. Nat Med. 2015 Jun;21(6):560-2.

TKI 轮回 - EGFR

EGFR ex19 del

1st TKIs & 2nd TKI

1st TKIs

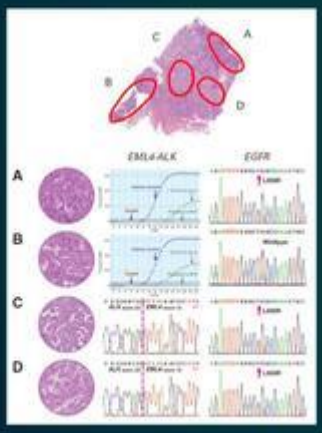
EGFR ex19 del
C797S+T790M -

EGFR ex19 del
T790M +

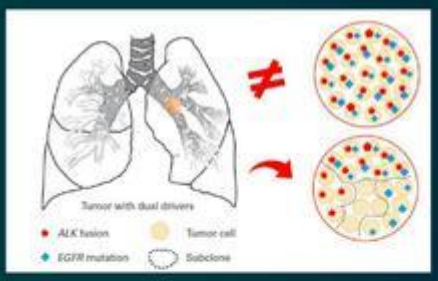
3rd TKIs

Intratumoral Heterogeneity of *ALK*-Rearranged and *ALK*/*EGFR* Coaltered Lung Adenocarcinoma

ALK/EGFR co-exist



2 models



J Clin Oncol. 2015 Sep 2[illegible]
JCO.2014.58.8293

肿瘤时间

Evolutionary Precision Medicine: A Role for Repeat Epidermal Growth Factor Receptor Analysis in ALK-Rearranged Lung Adenocarcinoma?

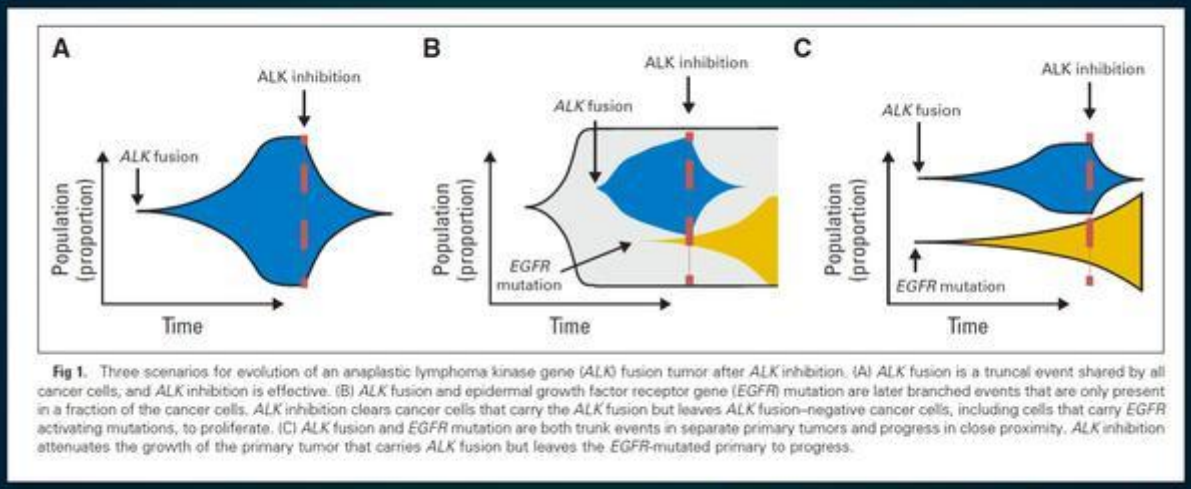


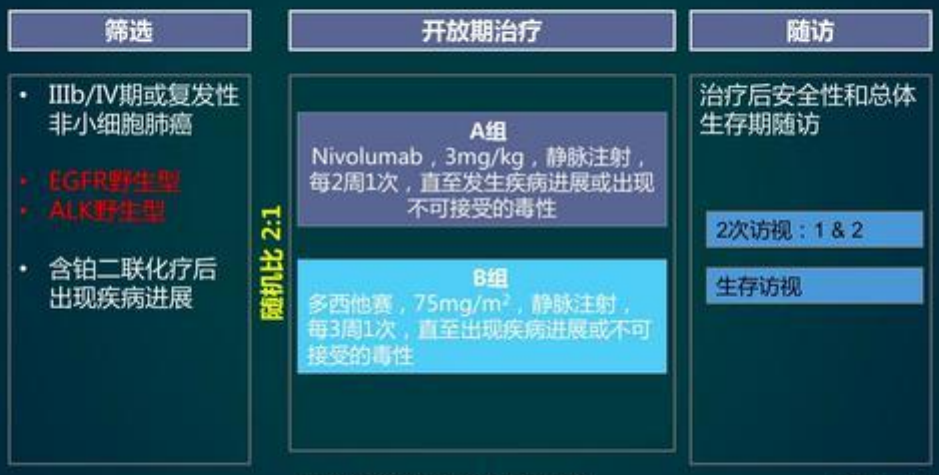
Fig 1. Three scenarios for evolution of an anaplastic lymphoma kinase gene (*ALK*) fusion tumor after *ALK* inhibition. (A) *ALK* fusion is a truncal event shared by all cancer cells, and *ALK* inhibition is effective. (B) *ALK* fusion and epidermal growth factor receptor gene (*EGFR*) mutation are later branched events that are only present in a fraction of the cancer cells. *ALK* inhibition clears cancer cells that carry the *ALK* fusion but leaves *ALK* fusion–negative cancer cells, including cells that carry *EGFR* activating mutations, to proliferate. (C) *ALK* fusion and *EGFR* mutation are both trunk events in separate primary tumors and progress in close proximity. *ALK* inhibition attenuates the growth of the primary tumor that carries *ALK* fusion but leaves the *EGFR*-mutated primary to progress.

J Clin Oncol. 2015 Sep 28. pii
JCO.2015.63.2976

肿瘤时间

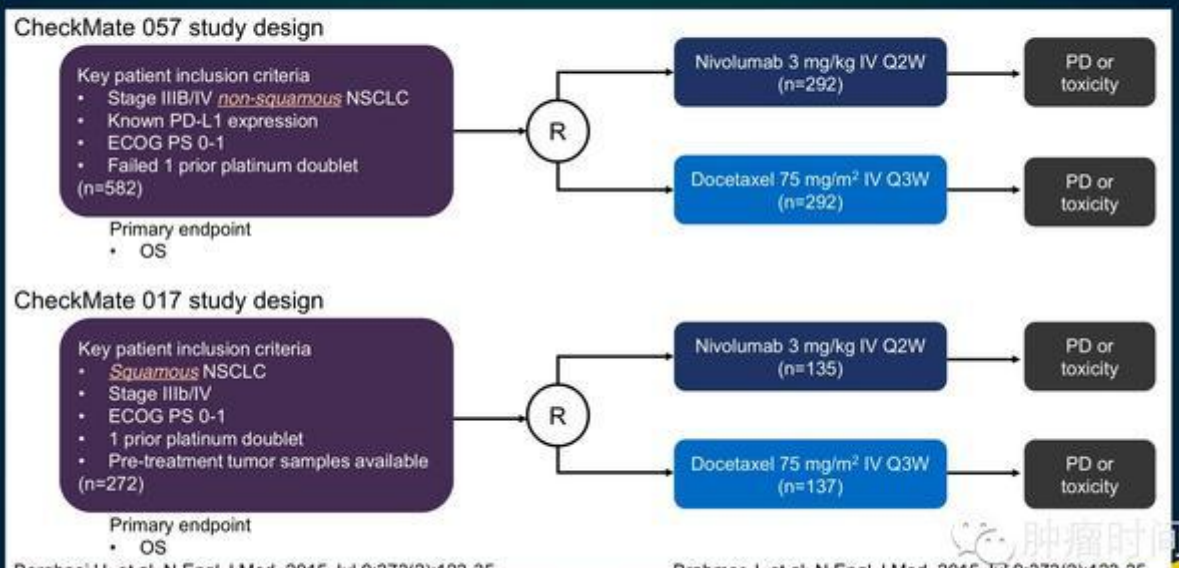
免疫曙光

研究设计3.1



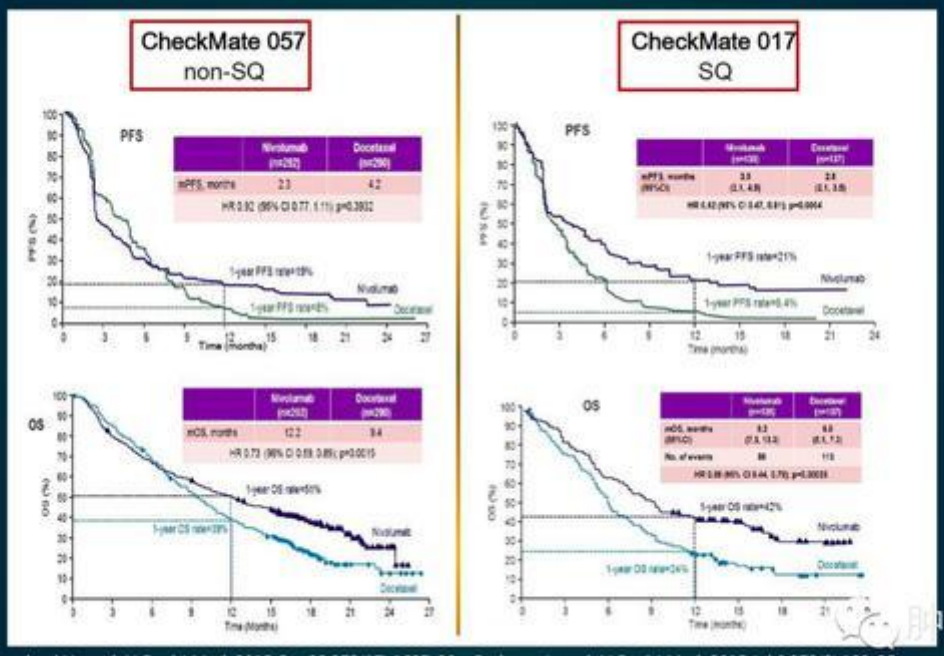
DMC将监督研究安全性和疗效

Nivolumab



Borghaei H, et al. N Engl J Med. 2015 Jul 9;373(2):123-35

Brahmer J, et al. N Engl J Med. 2015 Jul 9;373(2):123-35.



Borghaei H, et al. N Engl J Med. 2015 Oct 22;373(17):1627-39. Brahmer J, et al. N Engl J Med. 2015 Jul 9;373(2):123-35.

PD-L1抗体研究：
POPLAR：一项随机All-comer II期研究

转移性或局部晚期NSCLC（2L/3L）
经过含铂化疗治疗进展
N=287

分层因素：
- PD-L1 IC表达（0 vs.1vs.2vs.3）
- 组织学（鳞癌vs 非鳞癌）
- 既往化疗线数(1 vs 2)

R
1:1

Atezolizumab
1200mg IV q3w
直到临床无效

多西他赛
75 mg/m² q3w
直到疾病进展

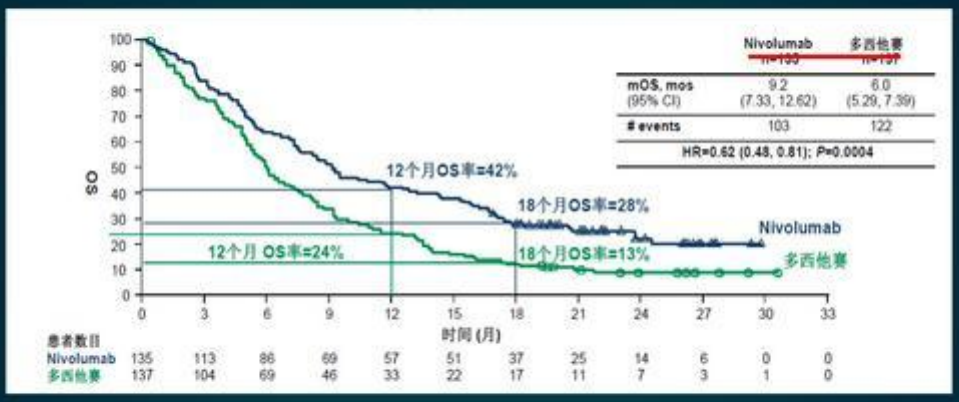
主要研究目的：
- **评估PD-L1选择人群和ITT人群的OS**

次要研究目的：
- 评估PD-L1选择人群和ITT人群的PFS，ORR和DOR
- 评估安全性

中期分析基于至少随访10个月的153例事件

Spira AI, et al. ASCO 2015 Abstract 8010.

总生存期（OS）



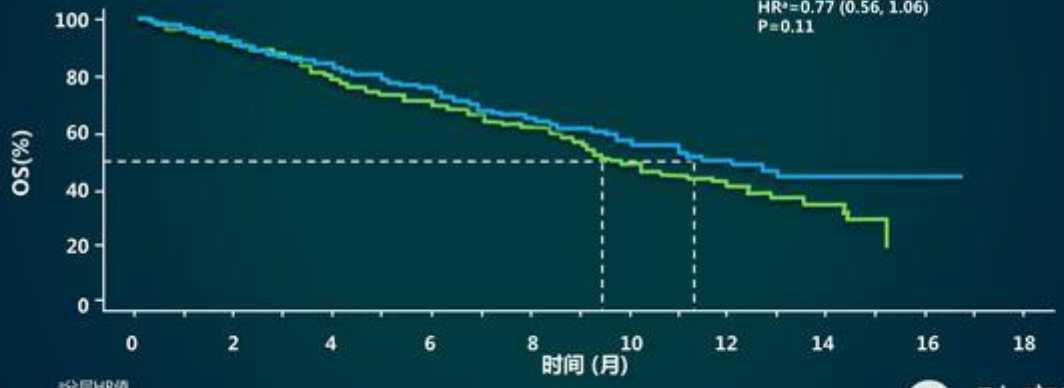
最短生存随访时间:18个月

K. Reckamp , et al. 2015WCLC

Ostoros G, et al. 2013 ESMO Abstract 3475.

总生存期OS（N=287）

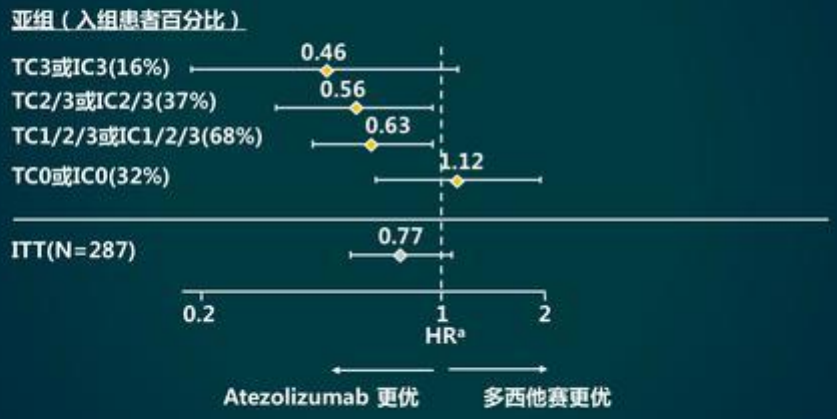
中位随访时间10个月



*分层HR值
数据截止时间：2015年1月30日

Spira AI, et al. ASCO 2015 Abstract 8010.

POPLAR：PD-L1 表达亚组中期OS



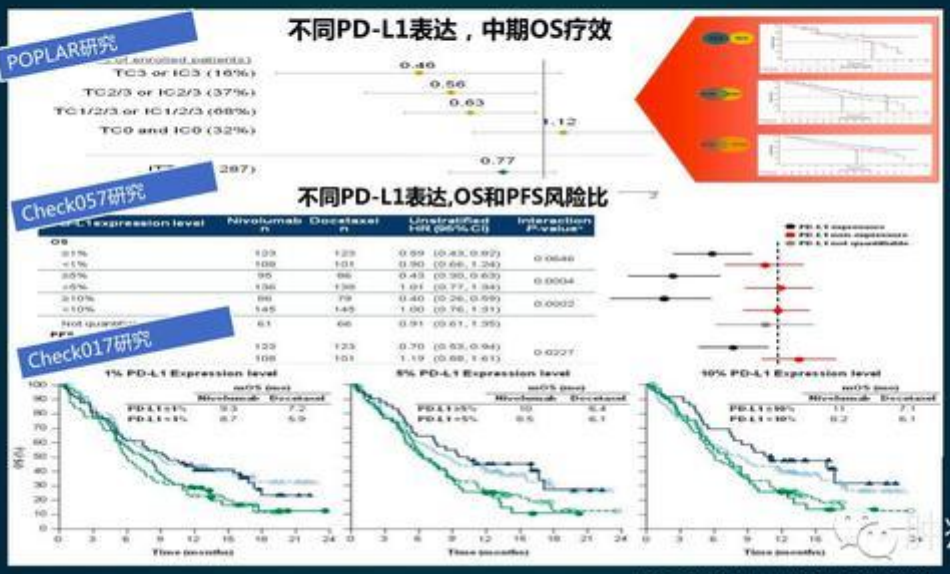
[a]亚组HR未分层；ITT人群HR分层
数据截止时间：2015年1月30日

肿瘤时间

Spira AI, et al. ASCO 2015 Abstract 8010.

31

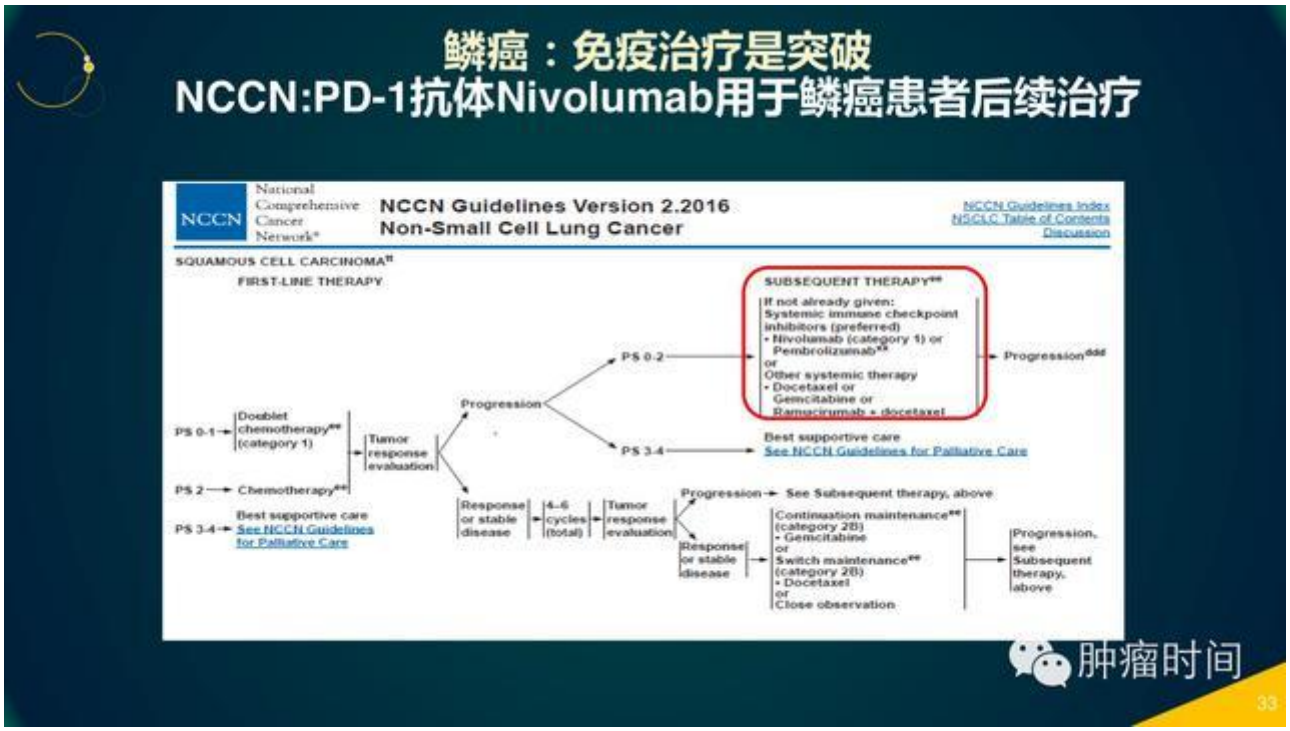
不同研究的结果不一致，无法明确疗效和PD-L1 表达相关性

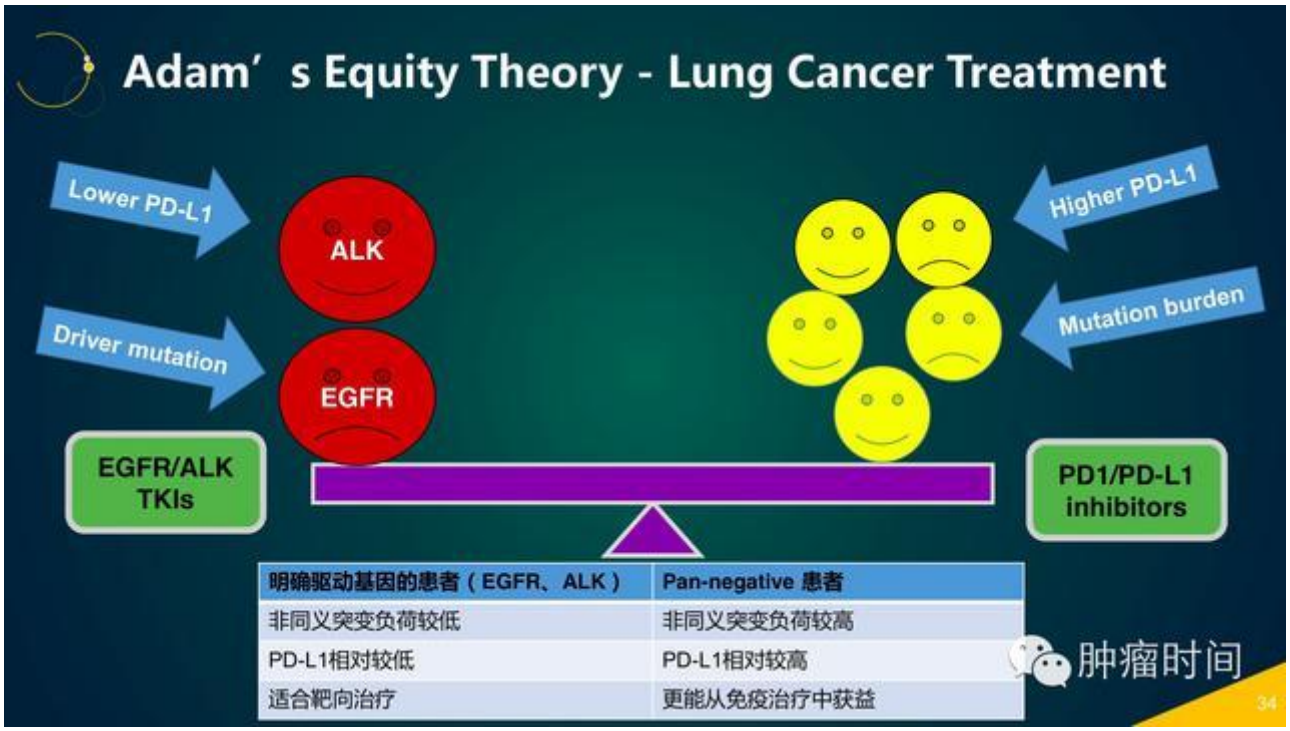


瘤时间

2015 ASCO abstract 8010/LBA109/8009

32


鳞癌：免疫治疗是突破
NCCN:PD-1抗体Nivolumab用于鳞癌患者后续治疗
NCCN Guidelines Version 2.2016
Non-Small Cell Lung Cancer
SQUAMOUS CELL CARCINOMA
FIRST-LINE THERAPY
SUBSEQUENT THERAPY
Progression
Best supportive care
See NCCN Guidelines for Palliative Care
肿瘤时间
33

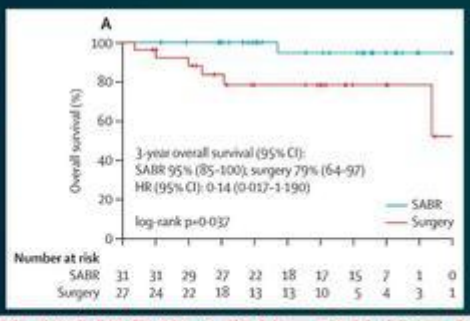

Adam’ s Equity Theory - Lung Cancer Treatment
Lower PD-L1
Driver mutation
ALK
EGFR
Higher PD-L1
Mutation burden
EGFR/ALK TKIs
PD1/PD-L1 inhibitors
明确驱动基因的患者（EGFR、ALK）
Pan-negative 患者
非同义突变负荷较低
非同义突变负荷较高
PD-L1相对较低
PD-L1相对较高
适合靶向治疗
更能从免疫治疗中获益
肿瘤时间
34

放疗挑战

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†*

ROSEL



- 入组
  - **cT1–2a (<4 cm)N0M0**
- 结果（SABR vs surgery）
  - 3y DFS 86% VS 80%
  - 3y OS 95% vs 79%（P=0.037）
- 不足
  - 样本量：58；
  - 随访：3年；
  - 病理：SABR组8例缺失

STARS

提出新的治疗选择争议（高龄，肺功能不良，惰性SBRT可选），并未[illegible]立新标准

Chang JY, et al. Lancet Oncol. 2015 Jun;16(6):630-7.

36

SBRT vs SBRT-I 研究设计违背伦理

对照组SBRT设置证据不足，肺叶切除仍是目前标准

主要入组标准：
- I 期或复发的孤立肺病灶
- N=180

R 1:1

- SBRT
- I-SBRT

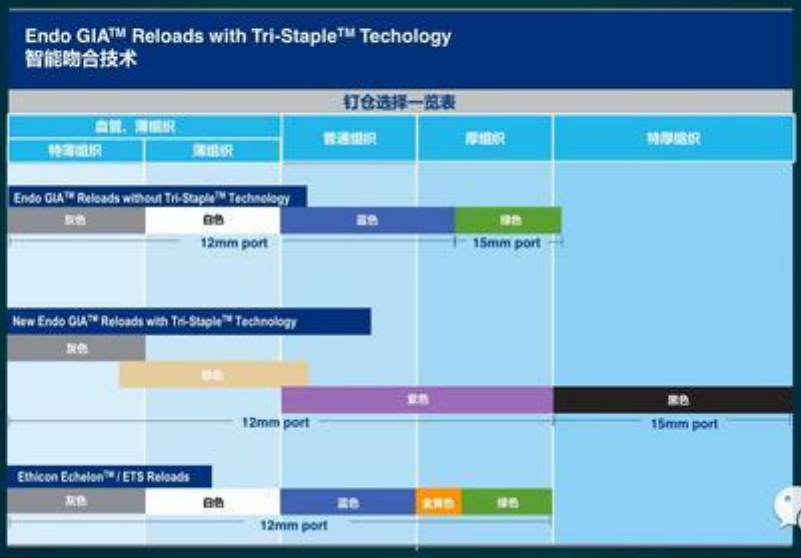
探索性分析：
- 免疫相关分子标志物
- 放射组学等预测指标
- I，immunotherapy

肿瘤时间

41

创新外科

肺癌外科技术发展伴随着创新外科发展



肺癌外科切除范围基于对生物行为的认识

JCOG 0804
- Ph II, single-arm trial (N = 334)
- Adenocarcinoma ≤ 2 cm
- GGO with < 25% solid component

→ Wedge resection

Endpoint:
- RFS

JCOG 0802
- Ph III, randomized trial (N = 1,100)
- Adenocarcinoma ≤ 2 cm
- GGO with 25-100% solid component

→ Lobectomy
→ Limited, sublobar resection
+ LN drop out → lobectomy

Endpoints:
- OS
- Pulmonary function

CALGB 140503
- Ph III, non-inferiority trial (N = 1,300)
- Peripheral carcinoma ≤ 2 cm with negative hilar nodes
- Stratification: smoking, histology, tumor size

→ Lobectomy
→ Sublobar resection (segmentectomy/ wedge)

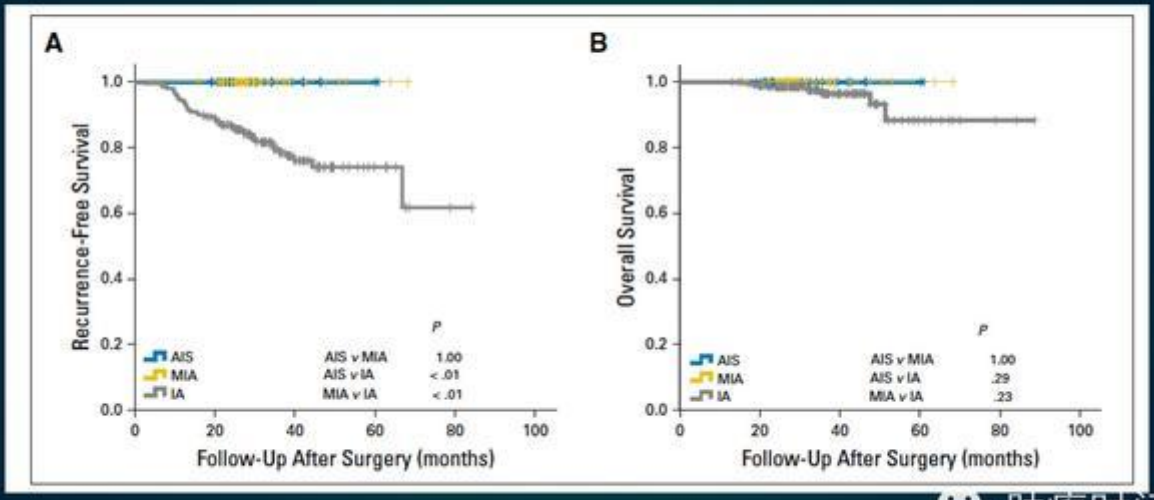
Endpoints
- Primary: OS
- Secondary: DFS, pulmonary function

JCOG 0804
GGO 25%-100%

JCOG 0802
GGO 0-75%

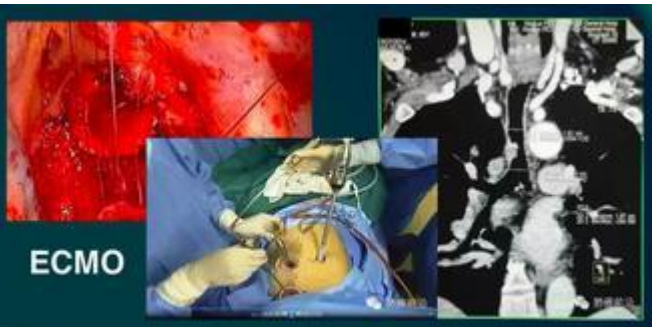
CALGB 140503 GGO 0-100%

术中冰冻切片的准确诊断，确定周围型小病灶肺腺癌的手术切除范围



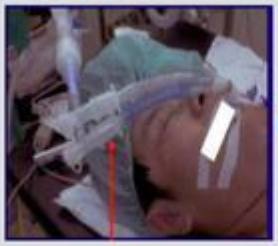
Liu S, Wang R, Zhang Y, et al. *J Clin Oncol* 2015

非气管插管-气管肿瘤手术

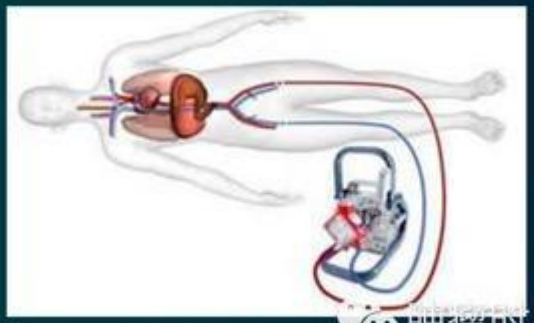


ECMO

非插管

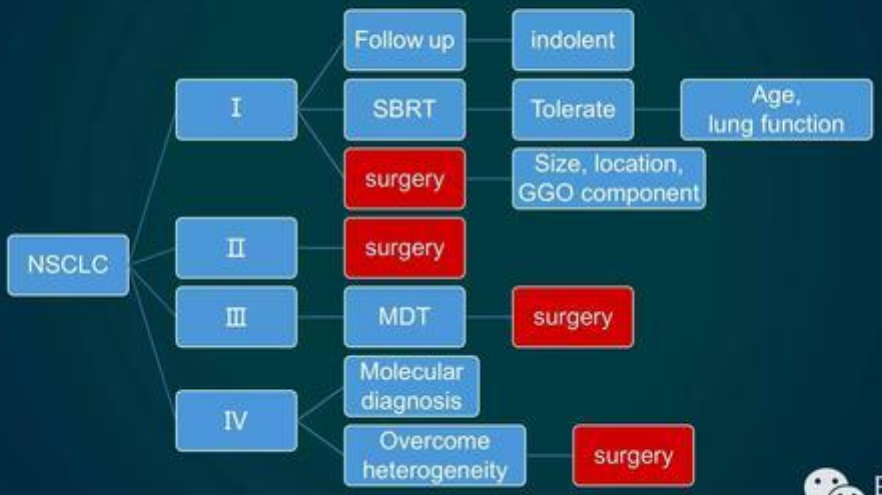


2015 WCLC Liu et al



2015 ESTS Yang et al

Role of surgery in lung cancer



The IASLC Lung Cancer Staging Project: The New Database to Inform the Eighth Edition of the TNM Classification of Lung Cancer

Ramón Rami-Porta, MD, FETCS,† Vanessa Bolejack, MPH,‡ Dorothy J. Giroux, MS,‡ Kari Chansky, MS,‡ John Crowley, PhD,‡ Hisao Asamura, MD,§ Peter Goldstraw, MBChB, FRCS,‖ on behalf of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Board Members and Participating Institutions?*

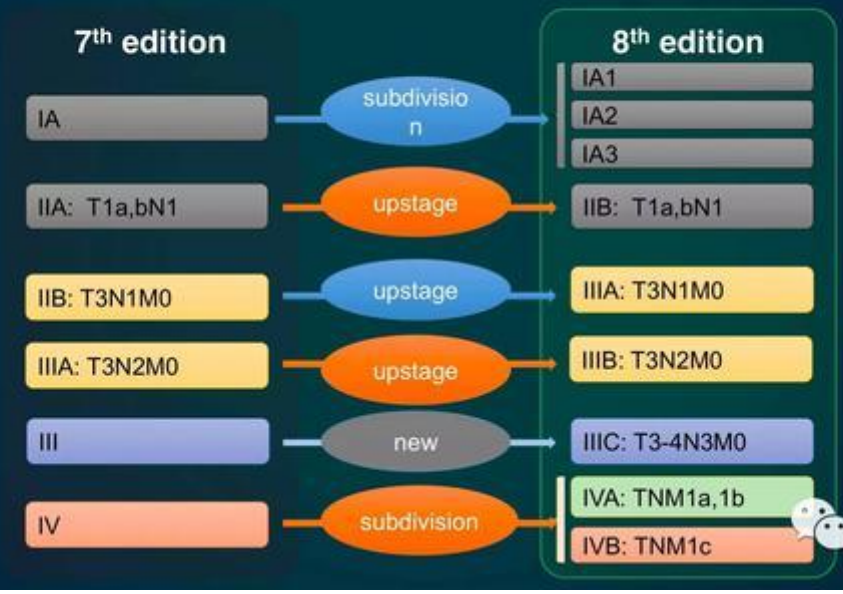
- 1999-2010的病例
- 16个 国家35个中心
- 94708 病例资料
- 77156 例参与分析
- Surgeon dominated

Hisao Asamura, MD,[1] Kari Chansky, MS,[2] JohnCrowley, PhD,[2] Peter Goldstraw, MBChb, FRCS,[3] ValerieW.Rusch, MD,[4] Johan F.Vansteenkiste, MD,[5] Hirokazu Watanabe, MD,[6] Yi-Long Wu, MD,[7] Marcin Zielinski, MD,[8] David Ball, MD,[9] and Ramon Rami-Porta, MD[10], onbehalf of the International Association for the Study of Lung Cancer Stagingand Prognostic Factors Committee, Advisory Board Members, and Participating Institutions[11]

Wilfried E.E. Eberhardt, MD[1], Alan Mitchell, MSc[2], John Crowley, PhD[2], Haruhiko Kondo, MD[3], Young Tae Kim, MD[4], Andrew turrisi IIIrd, MD[5], Peter Goldstraw, MBChB[6], Ramon Rami-Porta, MD[7], on behalf of the International Association the

Rami-Porta R, et al. J Thorac Oncol. 2014 Nov;9(11):1618-24.

2015 8TH TNM分期迁移



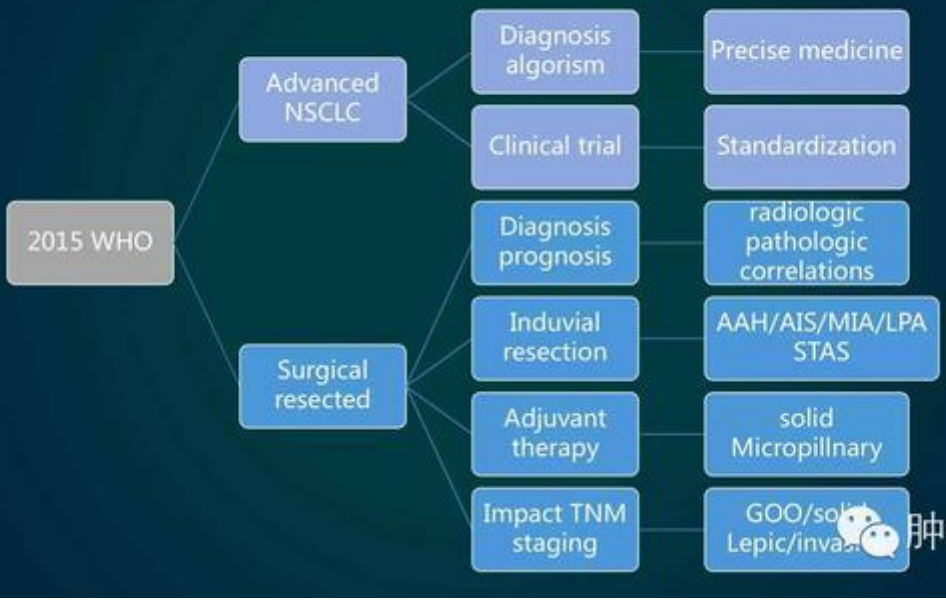
总体印象

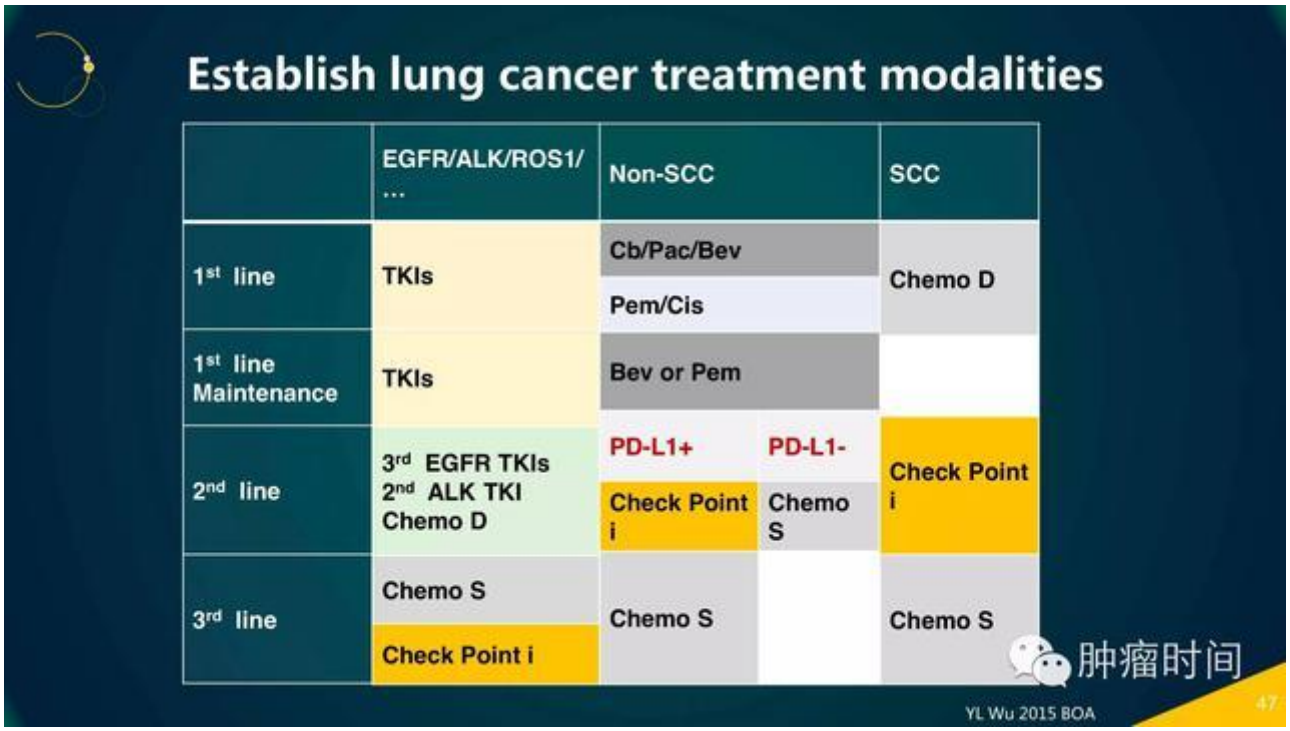
- 更为精确
- 更为繁琐
- 未纳入分子和病理分型
- 对临床实践的意义尚待阐明
  1. 非手术和手术的界限：3a to 3b
  2. 亚肺叶和肺叶的界限：T1a to T1b
  3. 辅助治疗的界限：1b to 1b-2a

2015年WHO肺癌分类的重要的改变

技术	• 免疫组化技术贯穿于整个分类 • 基因学研究成为新的重点
小活检和细胞学标本诊断标准与术语	• 大同小异：*vs.* 2011年IASLC/ATS/ERS 分类
手术切除标本分类	• 腺癌的分类：与在2011年IASLC/ATS/ERS • 大细胞癌的诊断：限定于手术切除缺乏明确形态学或免疫组化分化的肿瘤，将原大细胞癌亚型重新分为其他类型 • 鳞状细胞癌：重新分为角化型、非角化型以及基底细胞样三个亚型，非角化型肿瘤需要免疫组化证实存在鳞状分化 • 神经内分泌瘤：归为一类 • 增加NUT肿瘤

Impact on Clinical Practice: 2015 WHO





展望未来 **10** 年

关注肿瘤时间，对话框回复口令「**肺癌**」，即可获得 2016 版最新中文 NCCN 指南。