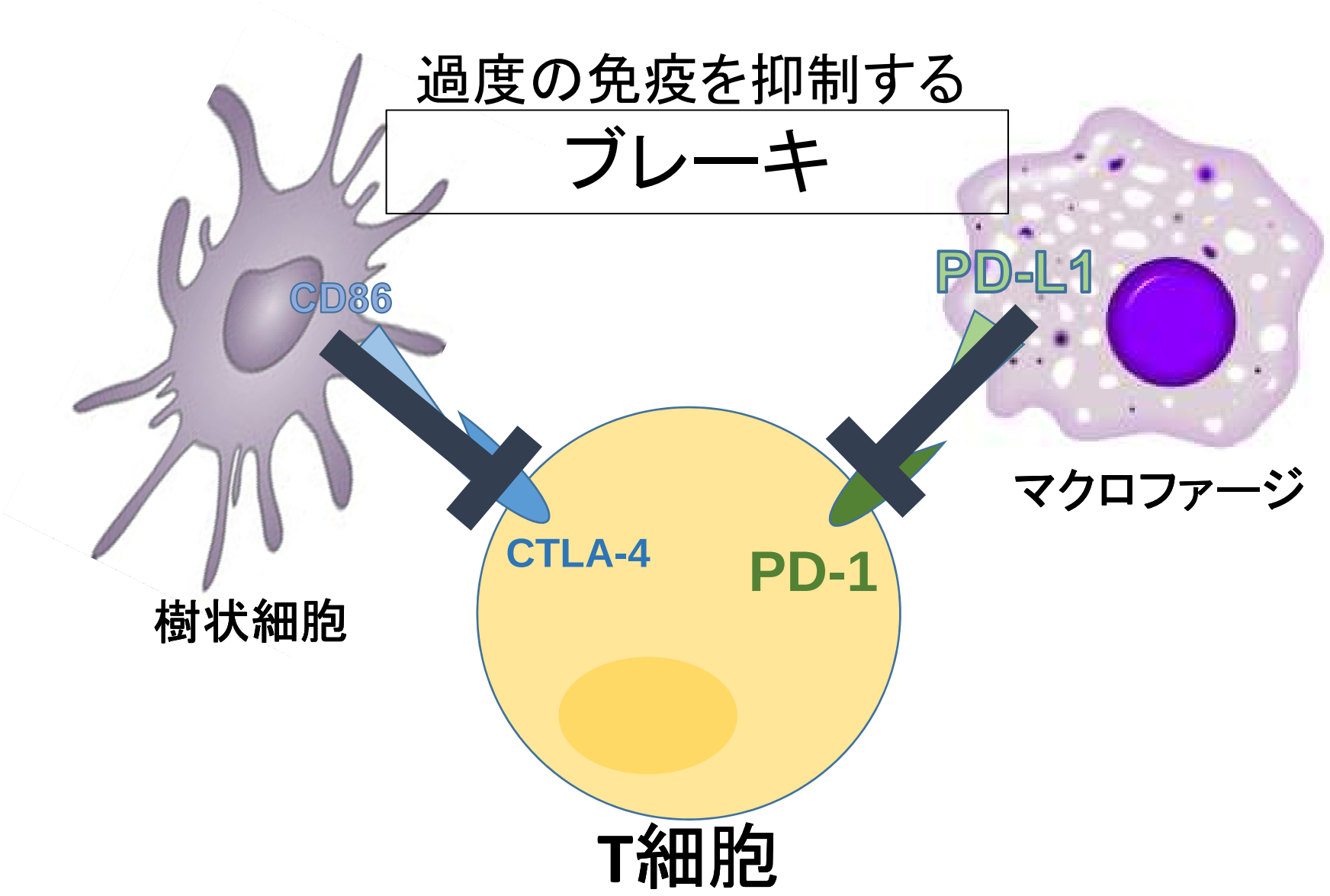
Medical & Surgical Grand Rounds

チェックポイント阻害剤

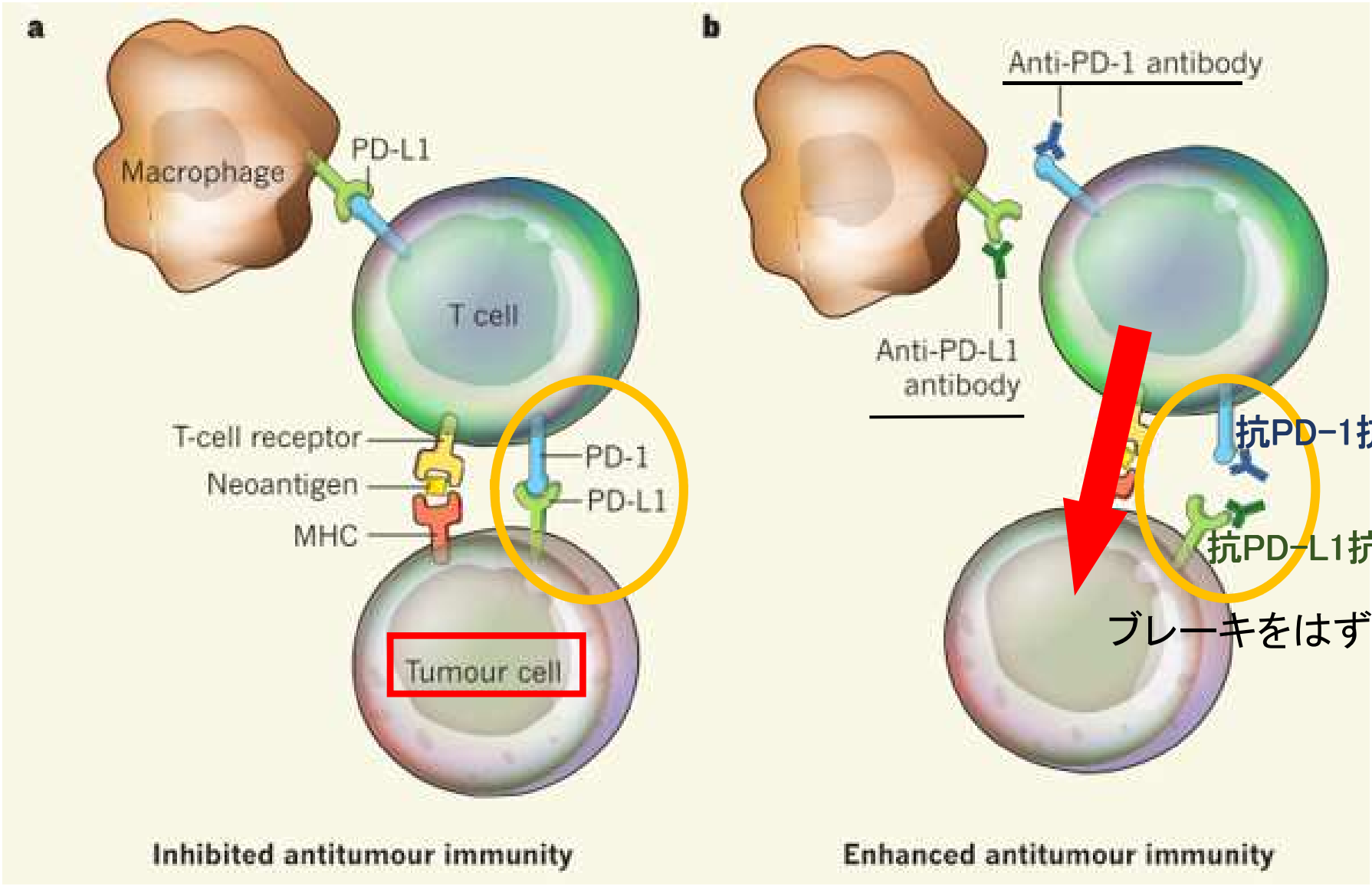
免疫チェックポイント

過度の免疫を抑制する

ブレーキ



癌細胞もPD-1/PD-L1を“悪用”していた



PD-1 Blockade 臨床応用

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph. Christine Mateus, M.D., Peter Boasberg, M.D., F. Bartosz Chmielowski, M.D., Ph.D., Scot W. E. Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and A.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., ik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., rn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., o, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D.,

nature International weekly journal of science

Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audio & Video | For

Archive > Volume 515 > Issue 7528 > Letters > Article

ARTICLE PREVIEW

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NATURE | LETTER

日本語要約

MPDL3280A (anti-PD-L1) treatment leads clinical activity in metastatic bladder cance

Thomas Powles, Joseph Paul Eder, Gregg D. Fine, Fadi S. Braiteh, Yohann Cruz, Joaquim Bellmunt, Howard A. Burris, Daniel P. Petrylak, Siew-leng T Shen, Zachary Boyd, Priti S. Hegde, Daniel S. Chen & Nicholas J. Vogelzan

Affiliations | Contributions | Corresponding author

Nature **515**, 558–562 (27 November 2014) | doi:10.1038/nature13904
Received 23 May 2014 | Accepted 30 September 2014 | Published online 26 N

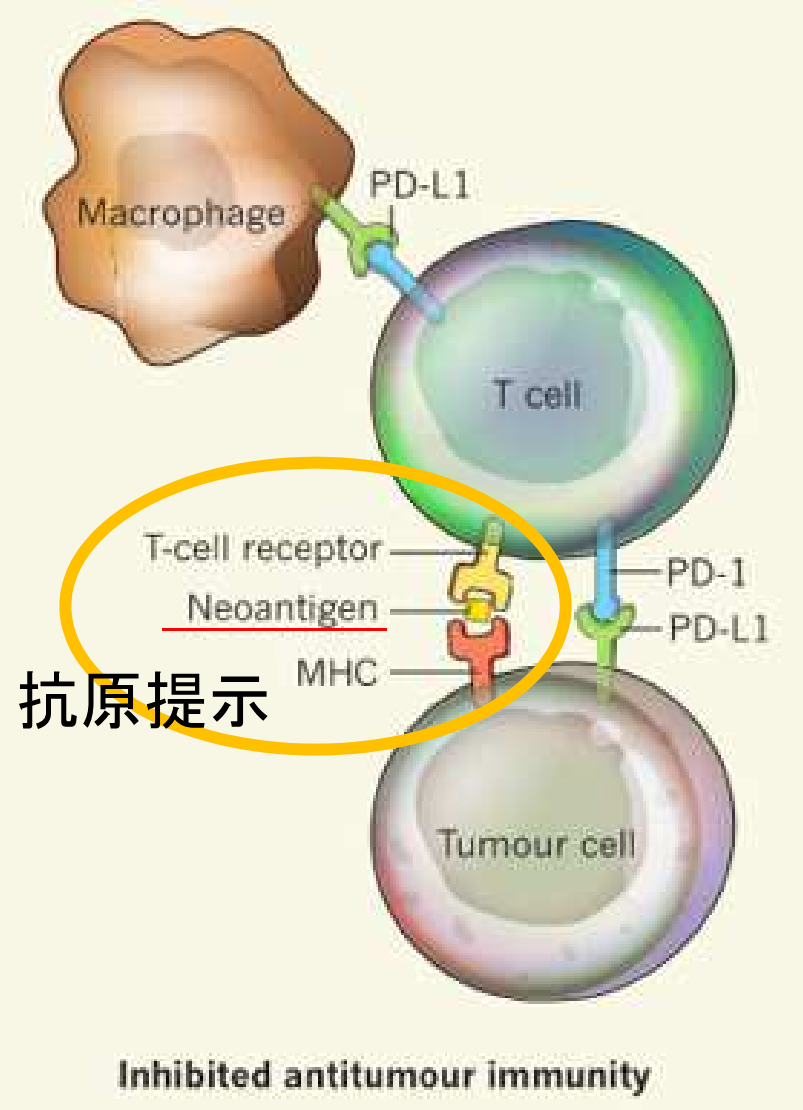
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 22, 2015 VOL. 372 NO. 4

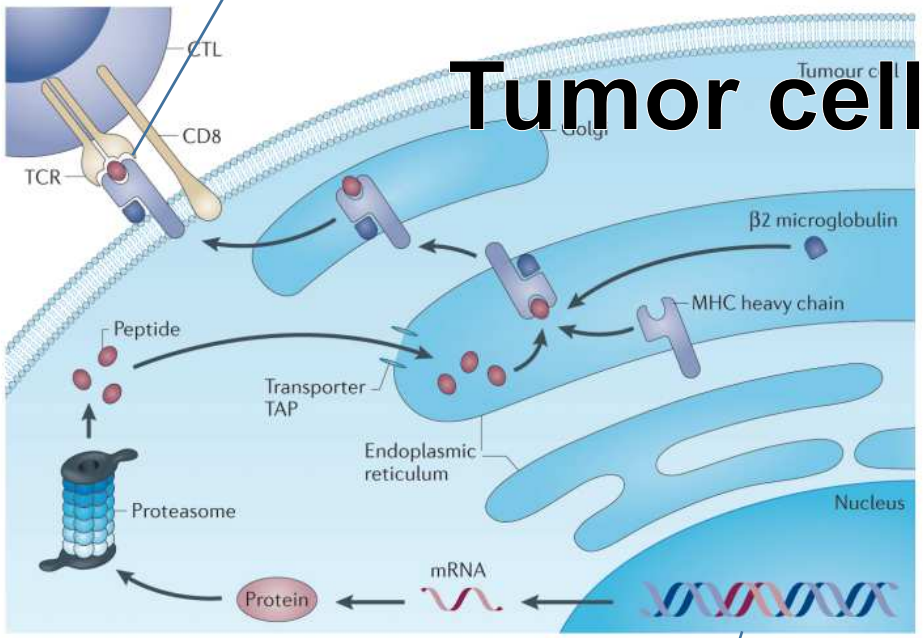
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

免疫応答には抗原提示が必要

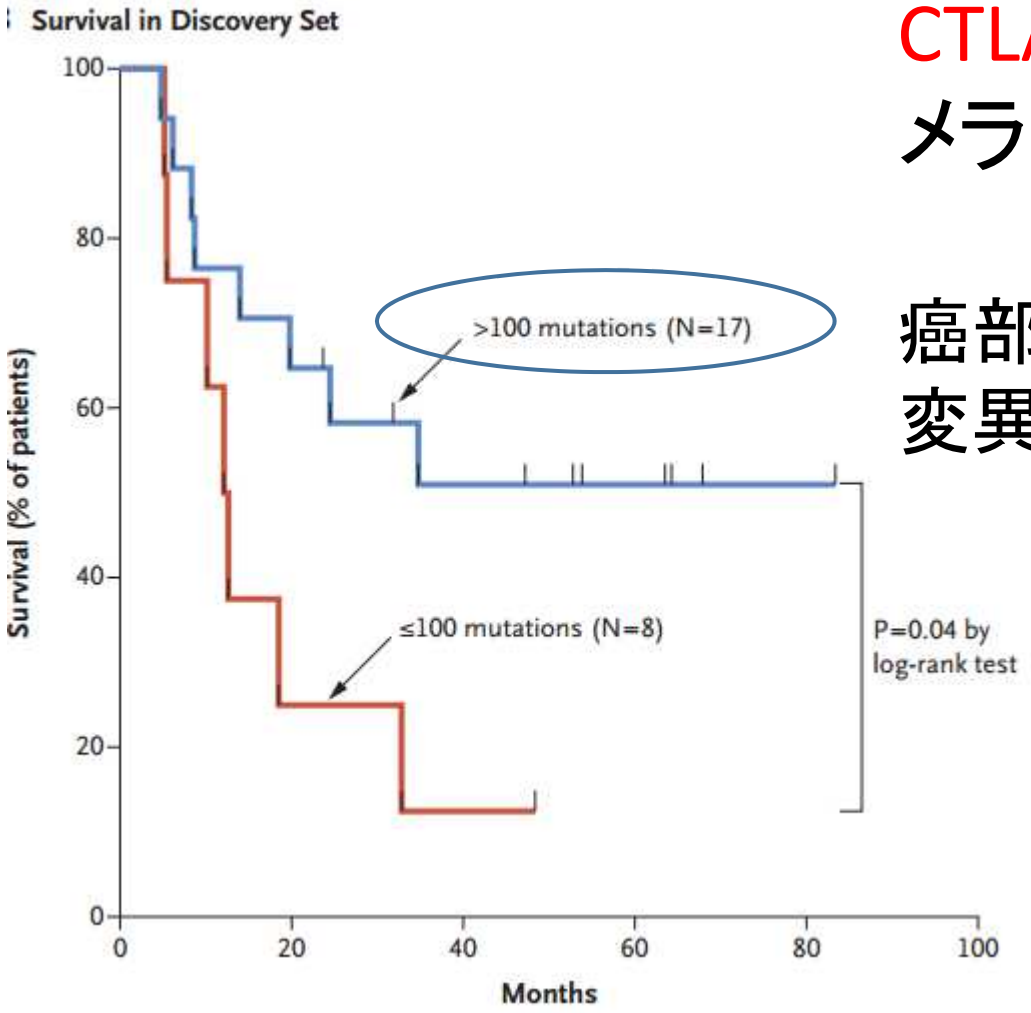


Neoantigen??



DNA mutation

癌の遺伝子変異数が多いほど
チェックポイント阻害剤の効果が高い



CTLA-4阻害剤

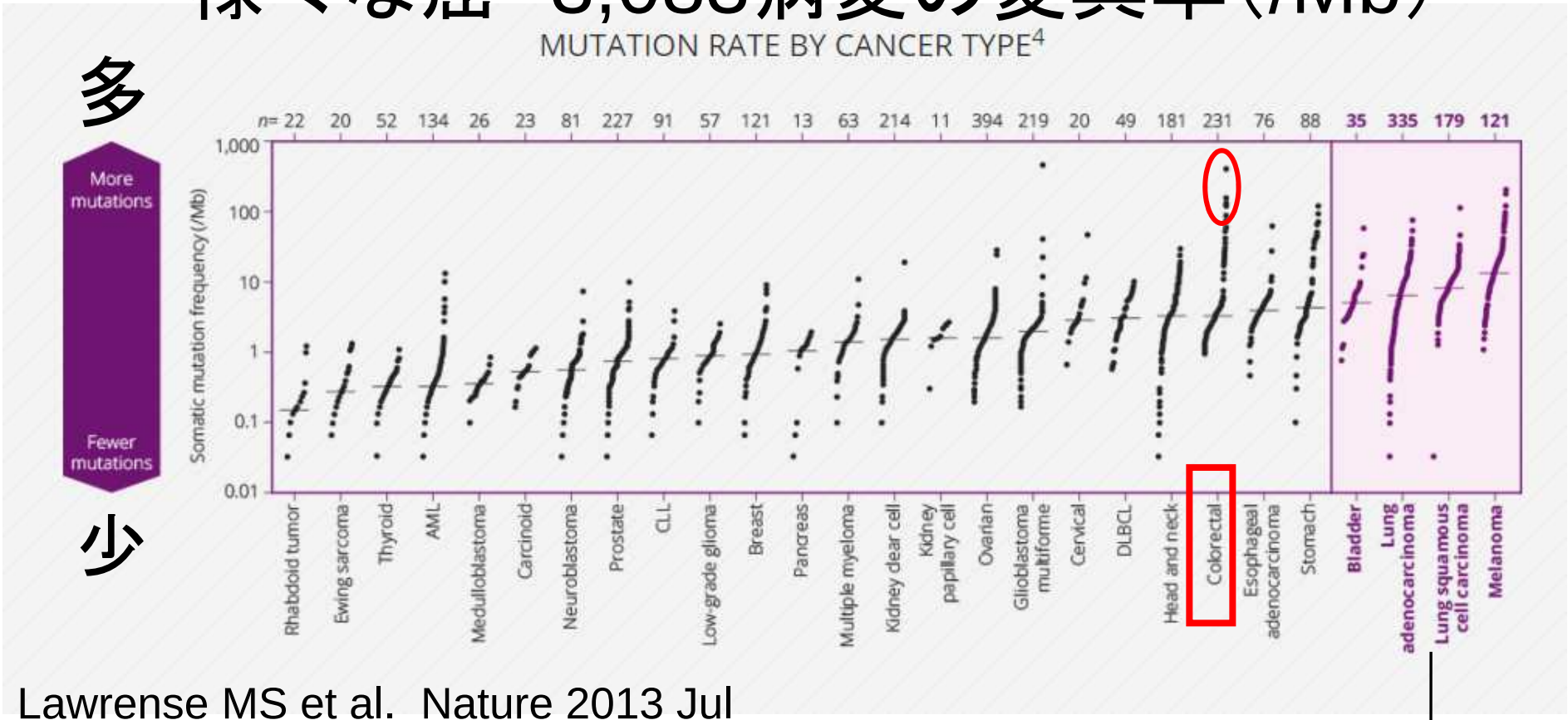
メラノーマ　n=25

癌部　Whole-exome sequence

変異数 >100 vs <100

Alexandra Snyder et al.
N Engl J Med 2014

様々な癌　3,083病変の変異率（/Mb）



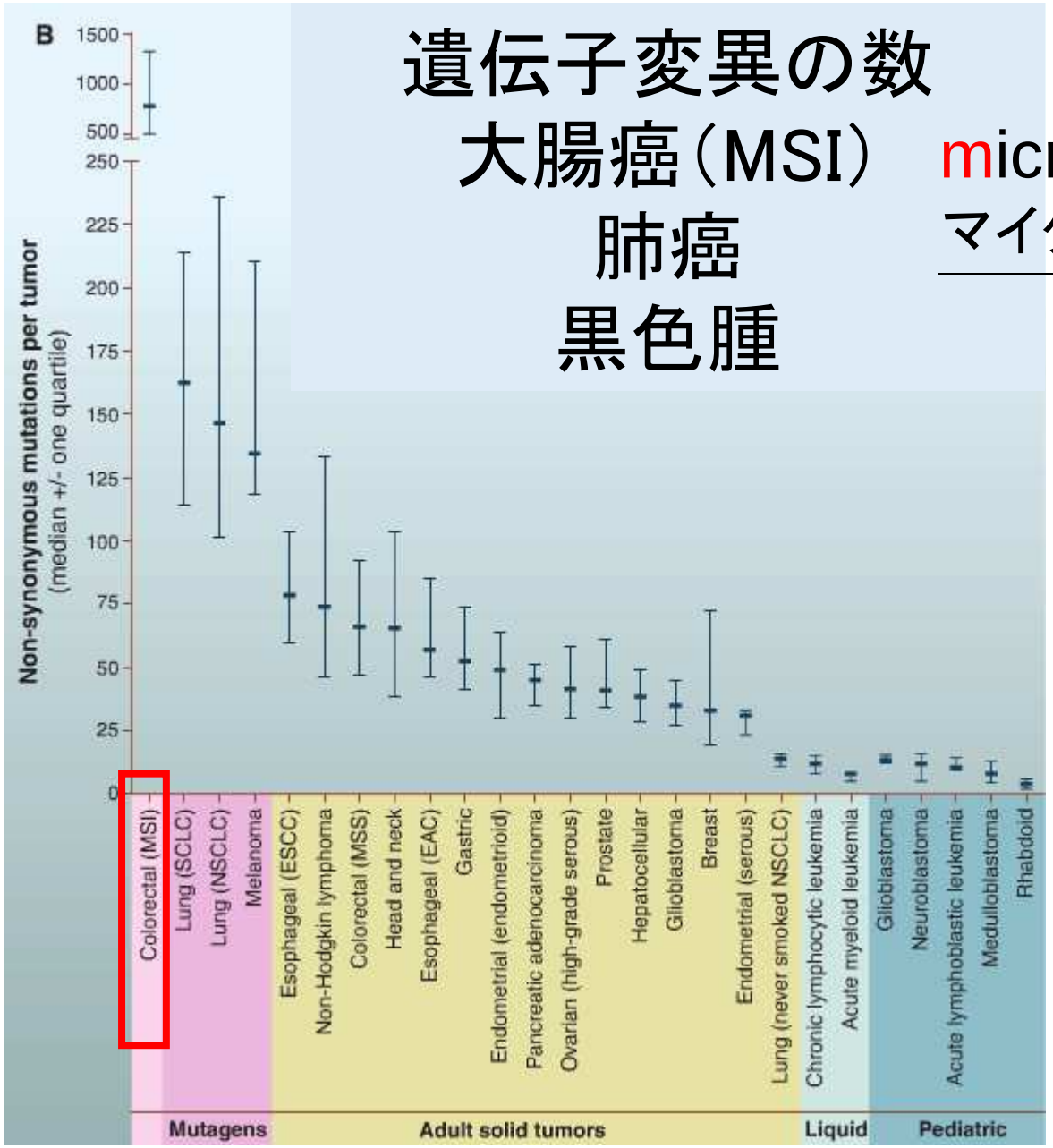
Lawrense MS et al. Nature 2013 Jul

mutagen

悪性黒色腫　―― 紫外線

非小細胞肺癌 ―― タバコ

遺伝子変異が多い癌



遺伝子変異の数
大腸癌（MSI）
肺癌
黒色腫

microsatellite instability
マイクロサテライト不安定性

遺伝子の塩基の繰り返し配列
（AAAAAAAやCACACACAなど）

---GGTAGCCAA A A A A (A)n CGATCCA---

---TCGCATGCA CA CA (CA)n ATTCGCA---

DNA複製エラーが起きやすい領域

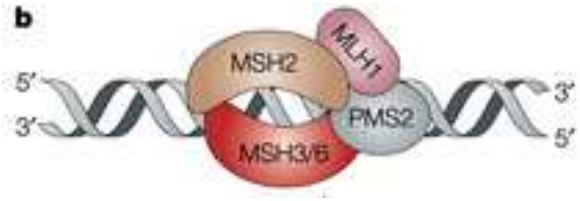
ミスマッチ修復システムで校正

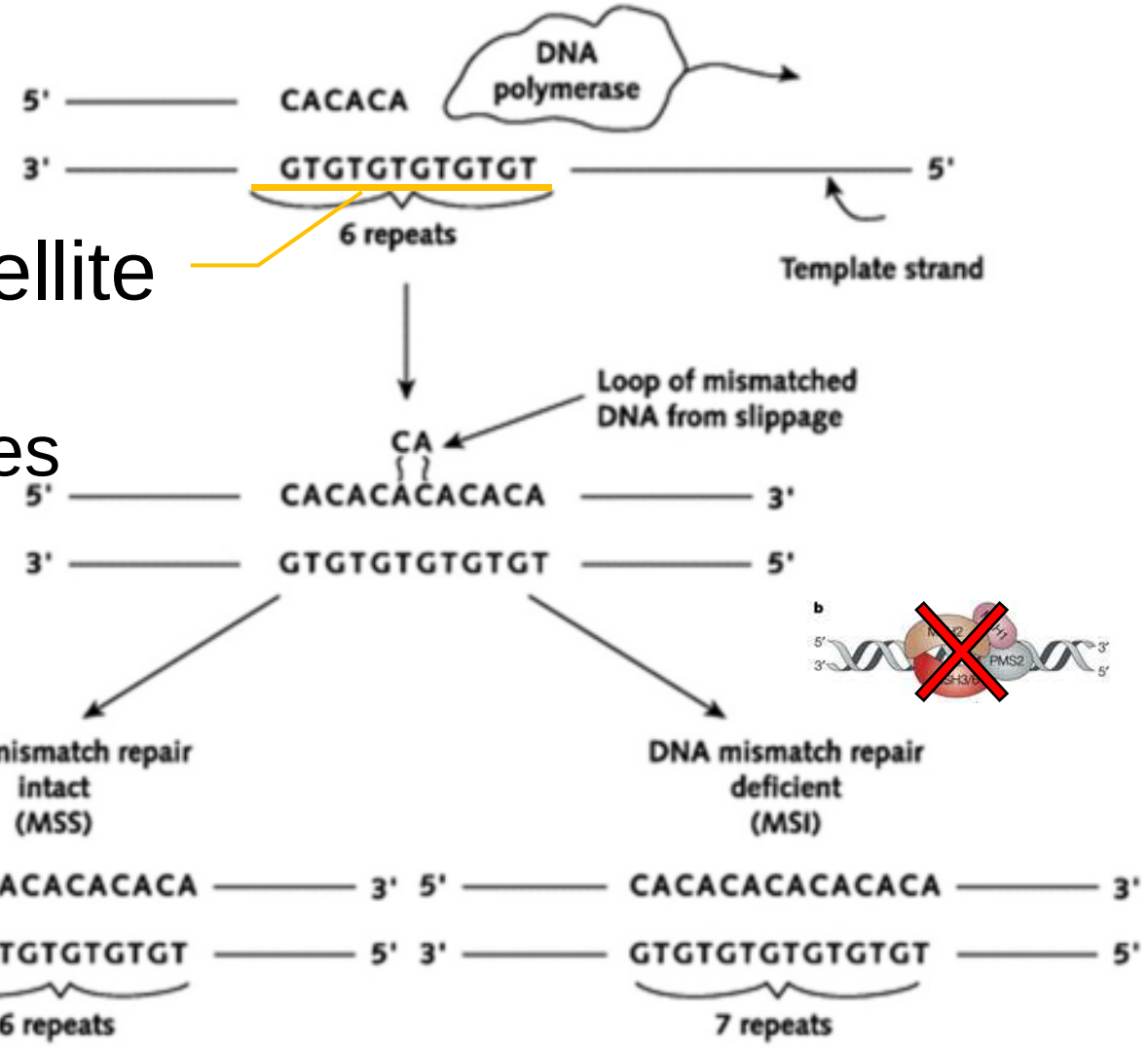
MSI　:
DNAミスマッチ修復が通常通り行われない状態
→　変異が起こりやすい状態

Cancer genome landscapes Vogelstein B et al. Science 2013 Mar

microsatellite

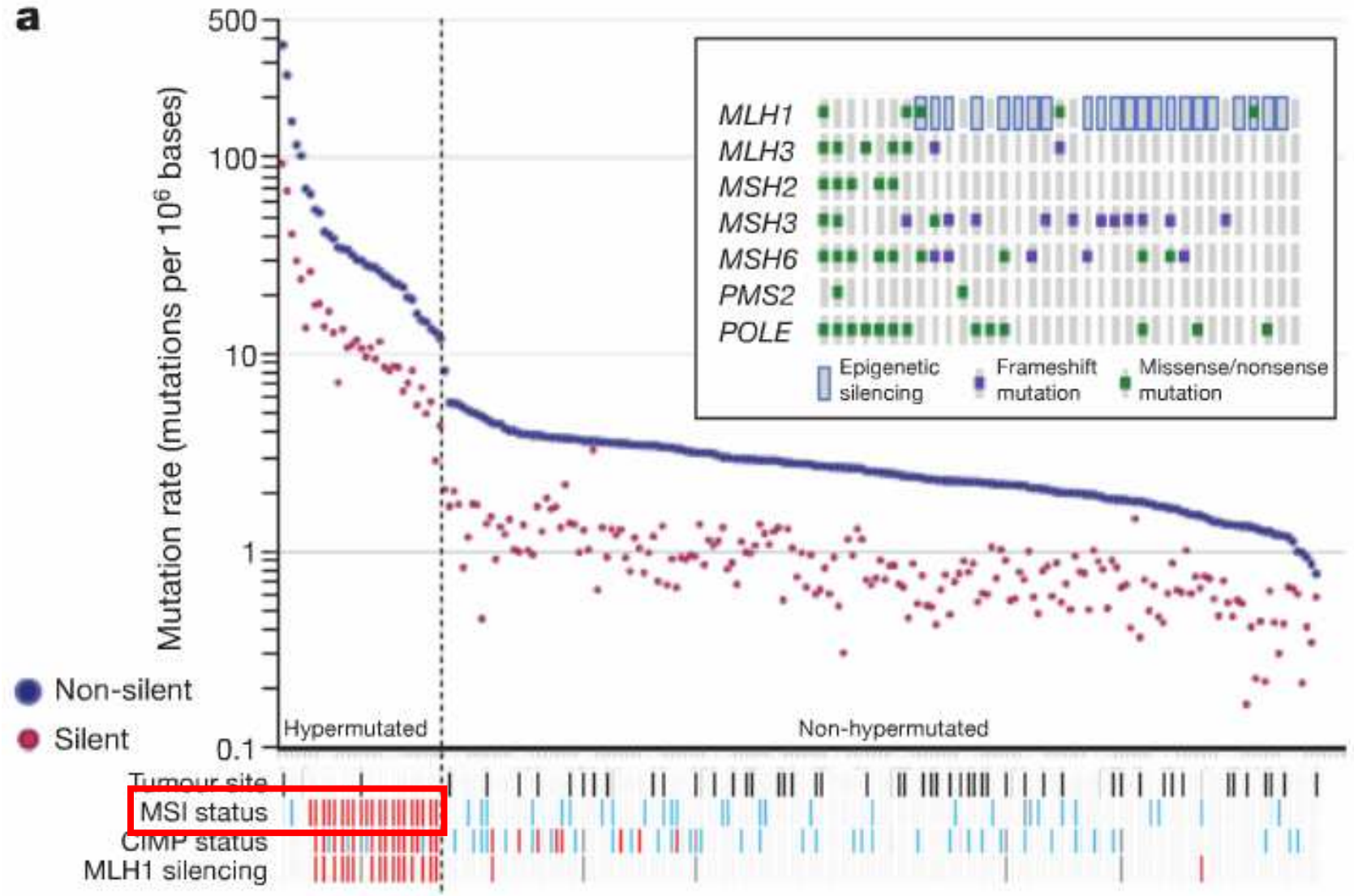
Mismatch repair genes





MSI

大腸癌276検体の97検体（16%）がHypermutator



Cancer genome atlas network. Nature 2012

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

The New England Jounal of Medicine
June,25,2015
Dung T. Le, M.D. and Outher

研修医2年目　名田屋　辰規
消化器内科　倉富　夏彦

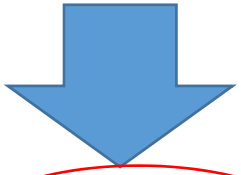
Our hypothesis

mismatch repair–deficient tumors are more responsive to PD-1 blockade than are mismatch repair–proficient tumors.

ミスマッチ修復異常（MMRd）を有する癌は、
免疫チェックポイント阻害剤
（PD-1阻害剤：Pembrolizmab）
に対し高い効果が期待できるのではないか？

ミスマッチ修復（MMR）の判定

5つのタイプのMicrosatteliiteで、
2タイプ以上変化しているもの



MSI≒MMRd

MSI　Analysis Sistem（Promega）

PATIENTS

Stage Ⅳ：41例

（September 2013 ― January 2015）

大腸癌：32例

cohort A
ミスマッチ修復異常
あり
11例

cohort B
ミスマッチ修復異常
なし
21例

非大腸癌

cohort C
ミスマッチ修復異常
あり
9例

胆管癌：4（44%）
子宮内膜癌：2（22%）
小腸癌：2（22%）
胃癌：1（11%）

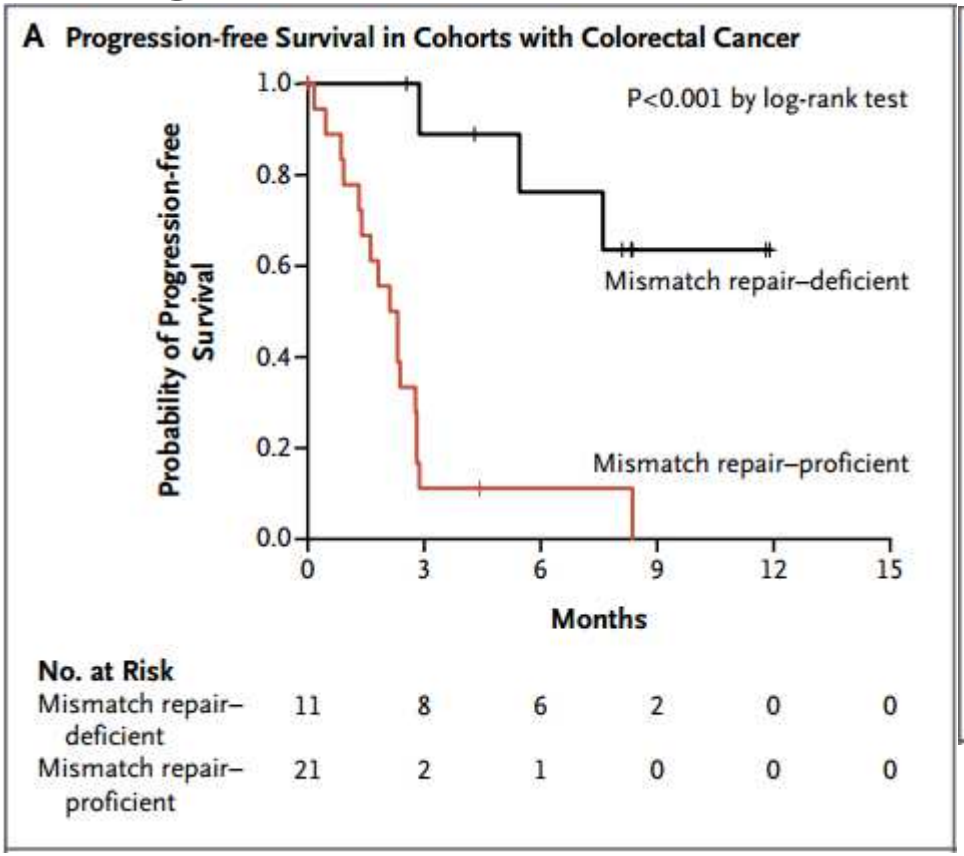
Objective response rate

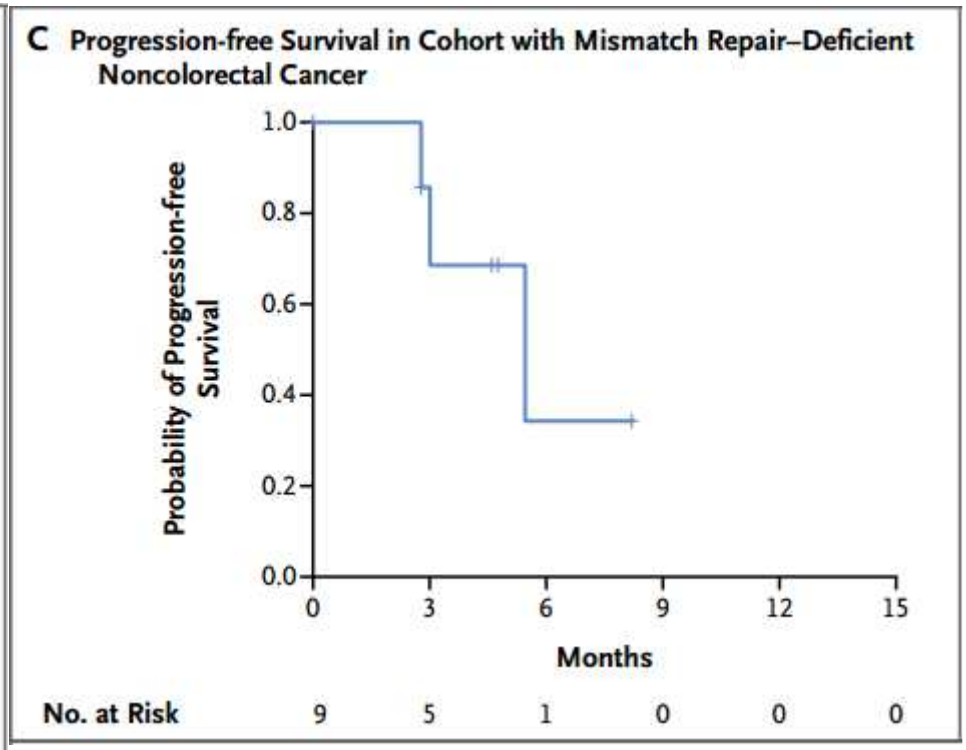
Table 2. Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

- 奏効率(CR + PR)
  - MMRd 大腸癌　40% (4/10人)
  - MMRp 大腸癌　0% (0/18人)
  - MMRd 非大腸癌　71% (5/7人)

Progression-free survival

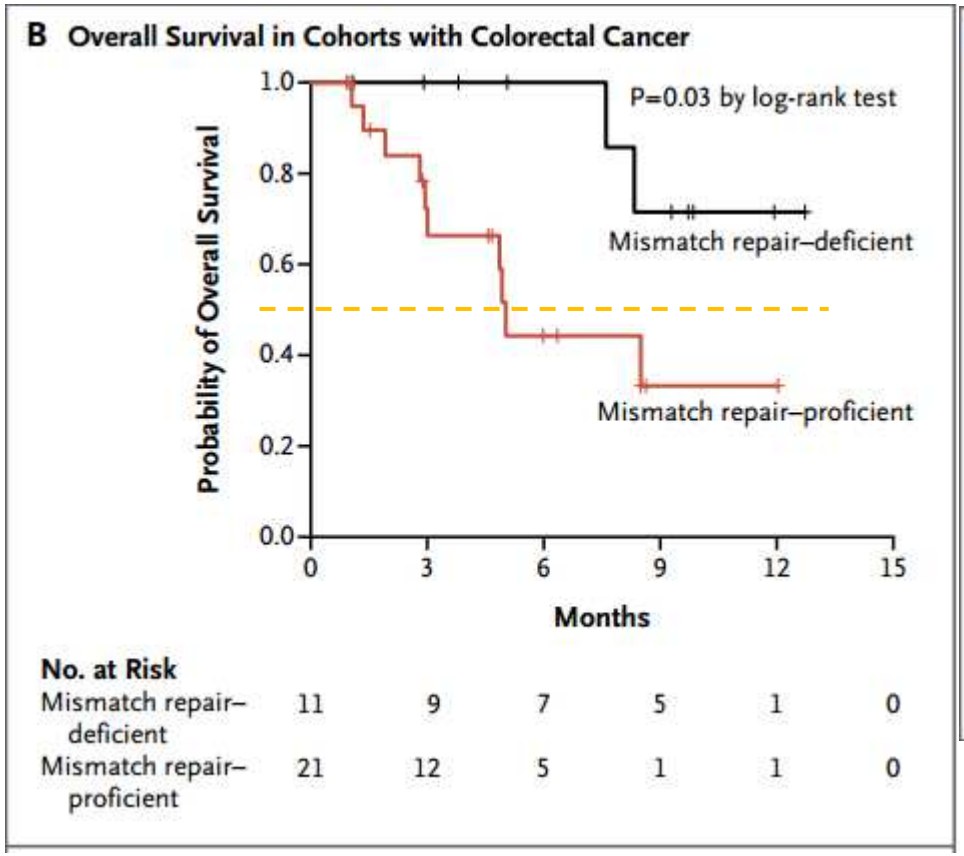


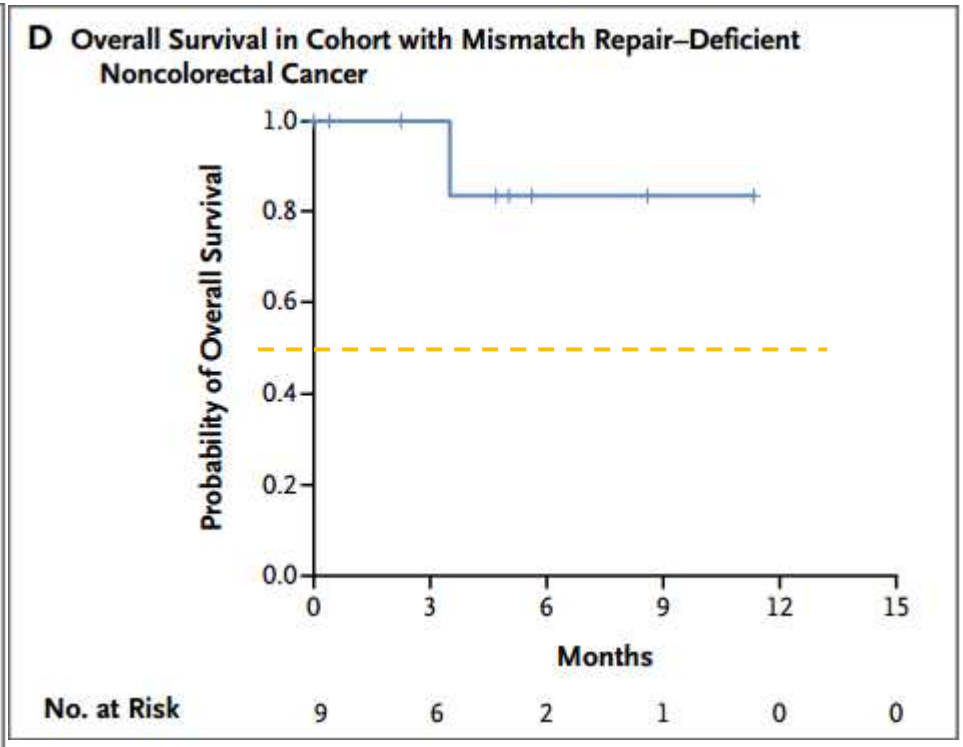


- 治療開始20週時点での無増悪生存率

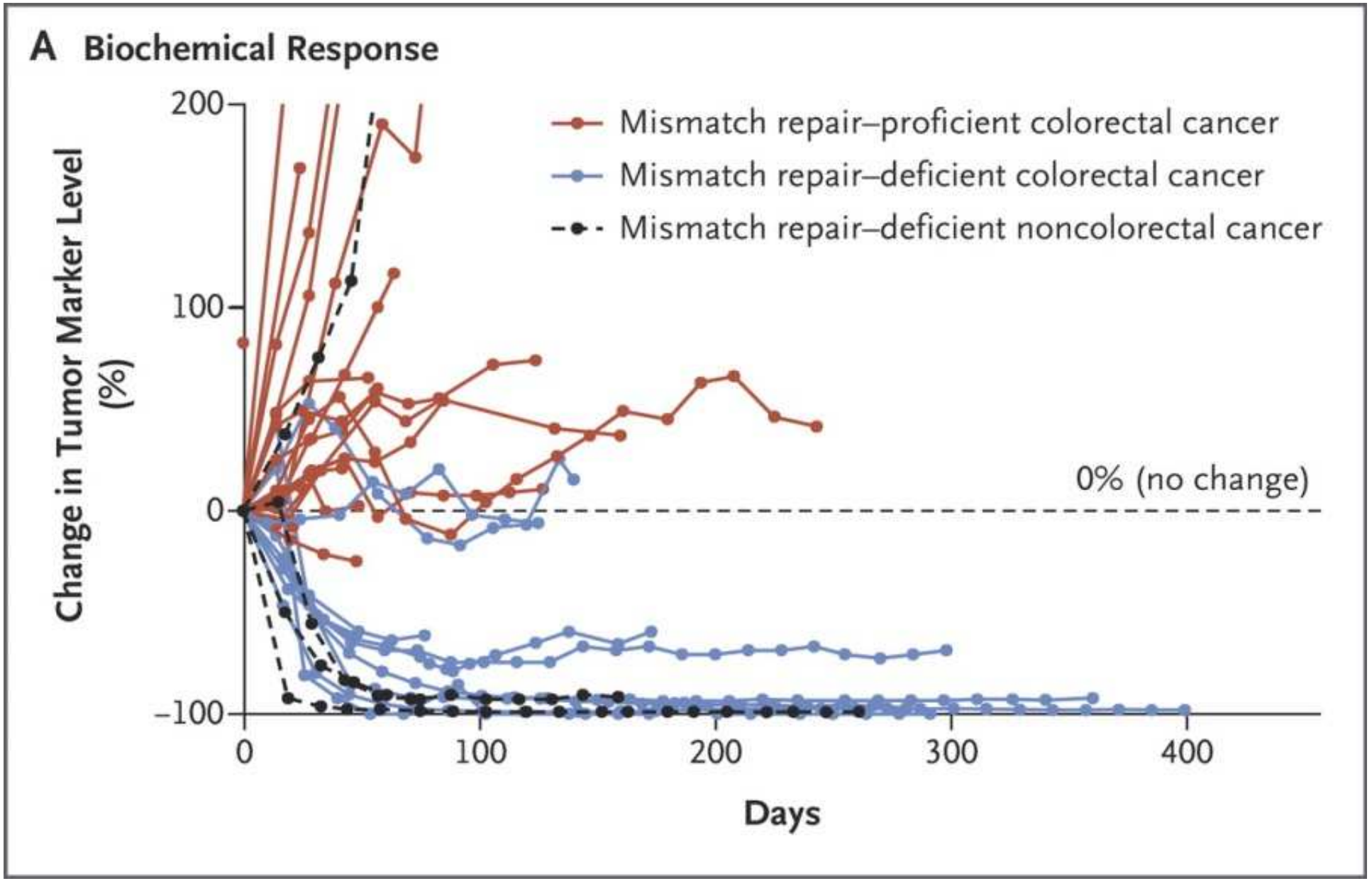
MMRd 大腸癌　78% (7/9人)
MMRp 大腸癌　11% (2/18人)　P <0.001
MMRd 非大腸癌　67% (4/6人)

Overall survival





- median OS
  - MMRd 大腸癌　not reached
  - MMRp 大腸癌　2.2 months (95%CI;1.4-2.8)
  - MMRd 非大腸癌　not reached

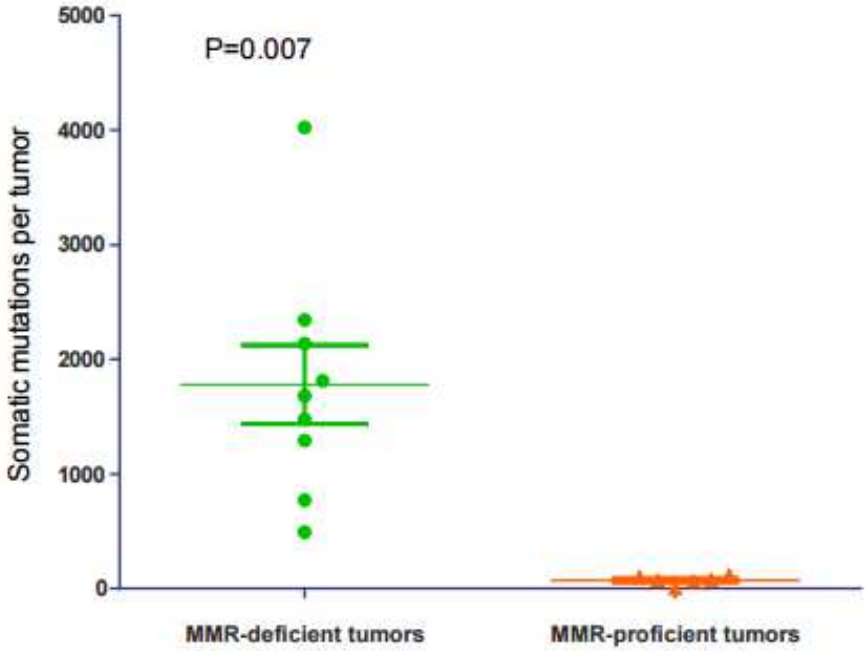

A Biochemical Response
Change in Tumor Marker Level (%)
200
100
0
−100
0
100
200
300
400
Days
Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer
0% (no change)

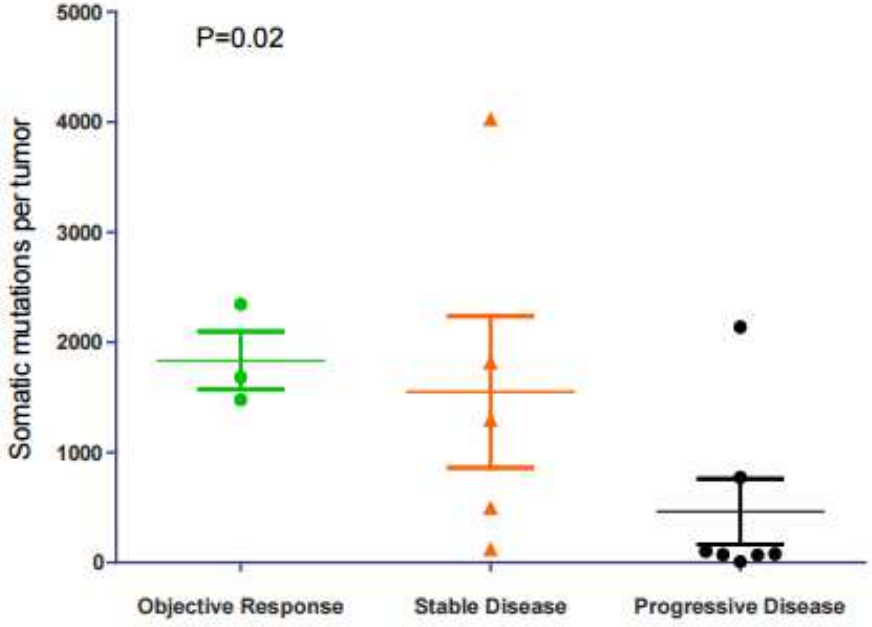
Genomic analysis

Whole-exome sequence

MMRd Cancer　9人　平均1782変異

MMRp Cancer　6人　平均73変異





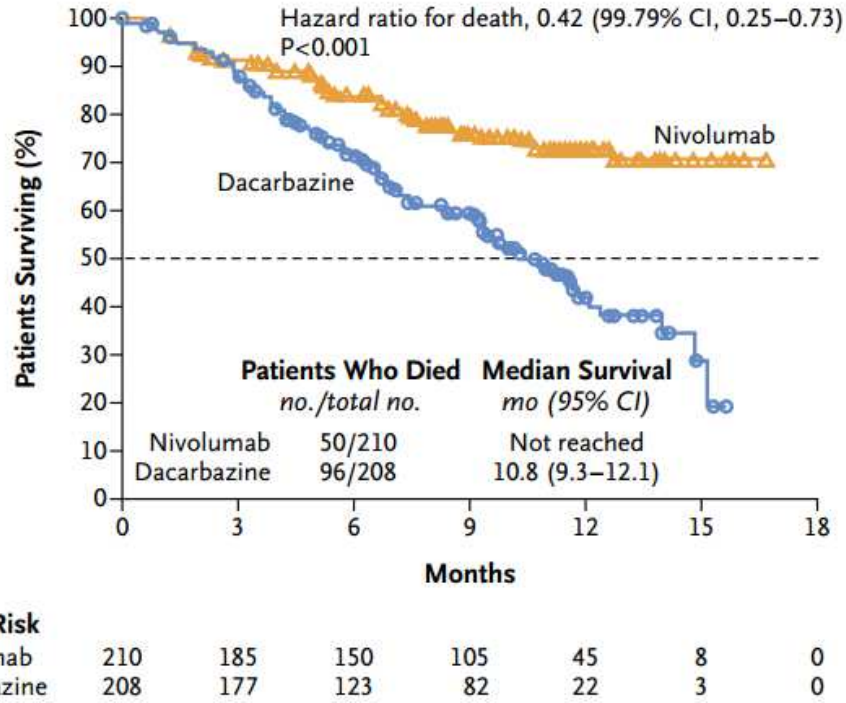
変異数が多いほど、治療効果が高い傾向

Nivolumab(抗PD−1抗体)が変えた癌治療

■メラノーマ

対象：BRAF変異を伴わない未治療の転移を有するメラノーマ

Intervention	n=	Overall rate of survival at 1 year
Nivolumab	210	72.9% (CI; 65.5-78.9)
Dacarbazine	208	42.1% (CI; 33.0-50.9)

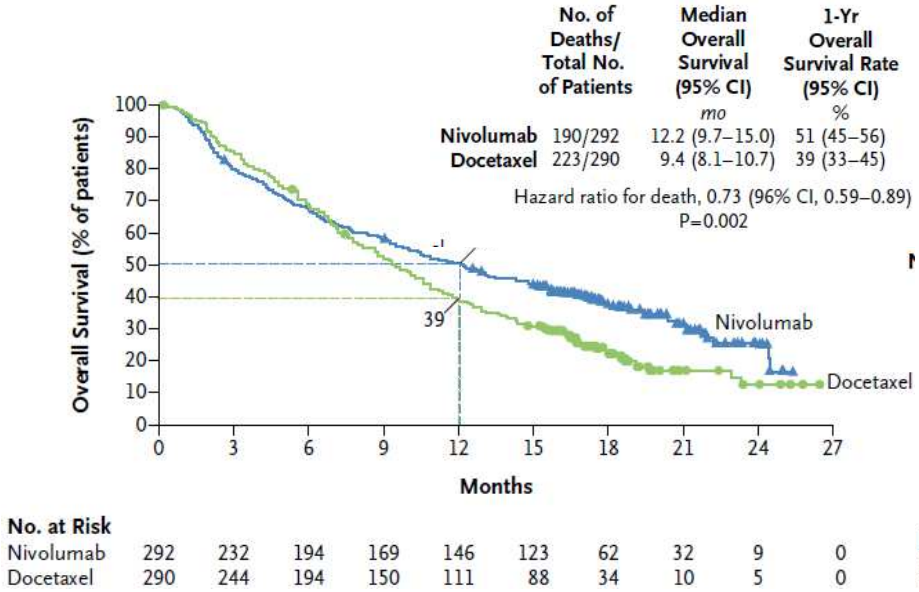


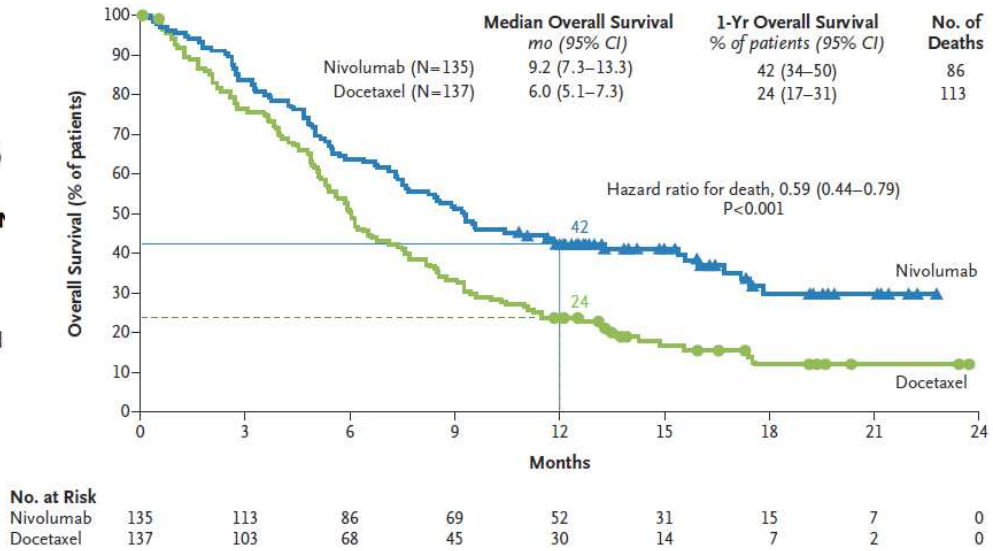
Caroline Robert et al.
N Engl J Med 2015 Jan

Nivolumab(抗PD−1抗体)が変えた癌治療

■非小細胞肺癌

対象：前治療のある切除不能肺癌





非扁平上皮肺癌

H. Borghaei et al.
N Engl J Med 2015 Oct

扁平上皮肺癌

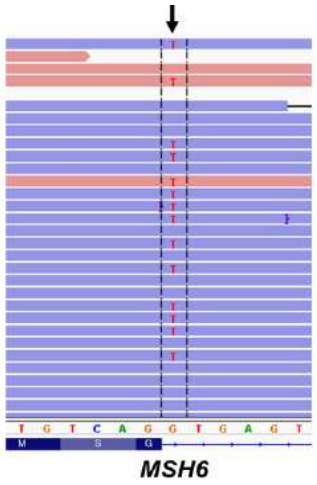
Julie Brahmer et al.
N Engl J Med 2015 Jul

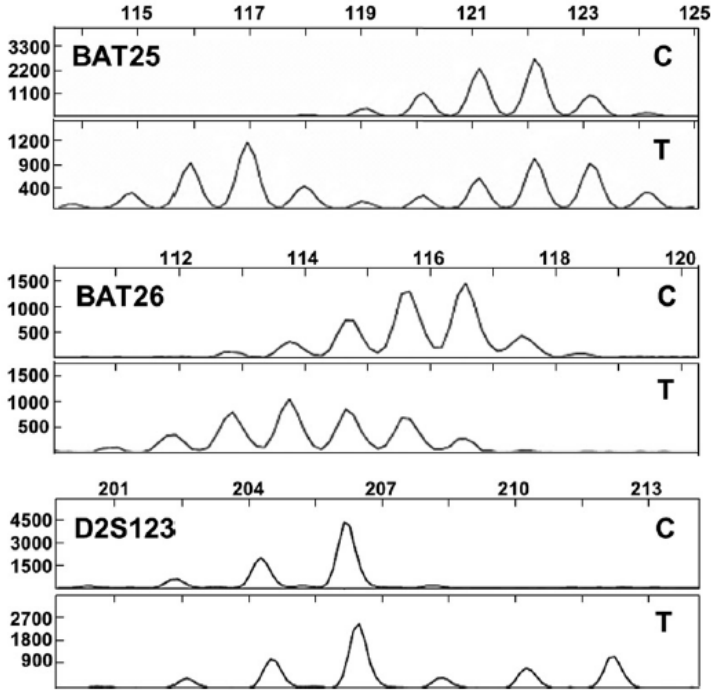
抗PD-1抗体を用いたPhase3試験

癌	薬剤	vs	登録数
胃癌	Nivolumab	N vs Placebo	480
肝細胞癌	Nivolumab	N vs Sorafenib	726
膠芽腫	Nivolumab	N vs Bevacizumab	440
食道癌	Nivolumab	N vs Placebo	390
腎細胞癌	Nivolumab	N vs Everolimus	822
頭頸部癌	Nivolumab	N vs Chemotherapy	360
胃癌	Pembrolizumab	P vs P+Chemotherapy vs Chemotherapy	750
肝細胞癌	Pembrolizumab	P vs BSC	408
食道癌	Pembrolizumab	P vs Standard Therapy	600
大腸癌	Pembrolizumab	P vs Standard Therapy	270
多発性骨髄腫	Pembrolizumab	P+Chemotherapy vs Chemotherapy	300
頭頸部癌	Pembrolizumab	P vs P+Chemotherapy vs Chemotherapy	780
乳癌	Pembrolizumab	P vs Chemotherapy	600
尿路上皮癌	Pembrolizumab	P vs Chemotherapy	470
ホジキンリンパ腫	Pembrolizumab	P vs Brentuximab Vedotin	300

チェックポイント阻害剤の適応 “Mismatch repair deficiency” を伴う様々な癌腫の解析

Gene	Chromosome
ATM	chr11
BARD1	chr2
BRIP1	chr17
CDH1	chr16
CHEK2	chr22
EPCAM	chr2
MLH1	chr3
MSH2	chr2
MSH6	chr2
NBN	chr8
PALB2	chr16
PMS2	chr7
PTEN	chr10
RAD51C	chr17
RAD51D	chr17
STK11 (LKB1)	chr19
TP53	chr17
MUTYH	chr1
MRE11A	chr11
RAD50	chr5
APC	chr5
BMPR1A	chr10
CDK4	chr12
CDKN2A	chr9
SMAD4	chr18





Yosuke Hirotsu et al.
Molecular Genetics
& Genomic Medcine
2015

遺伝性卵巣癌（Lynch症候群による）

- 自家製パネルを用いたGermline mutation解析
  - Mismatch repair genesを含む25遺伝子
- MSI解析

当院において全身化学療法を行ったStageⅣ大腸癌

（期間：2011年1月～2014年10月）

n= 69