2022年3月2日
WEB開催

第13回JBFシンポジウム

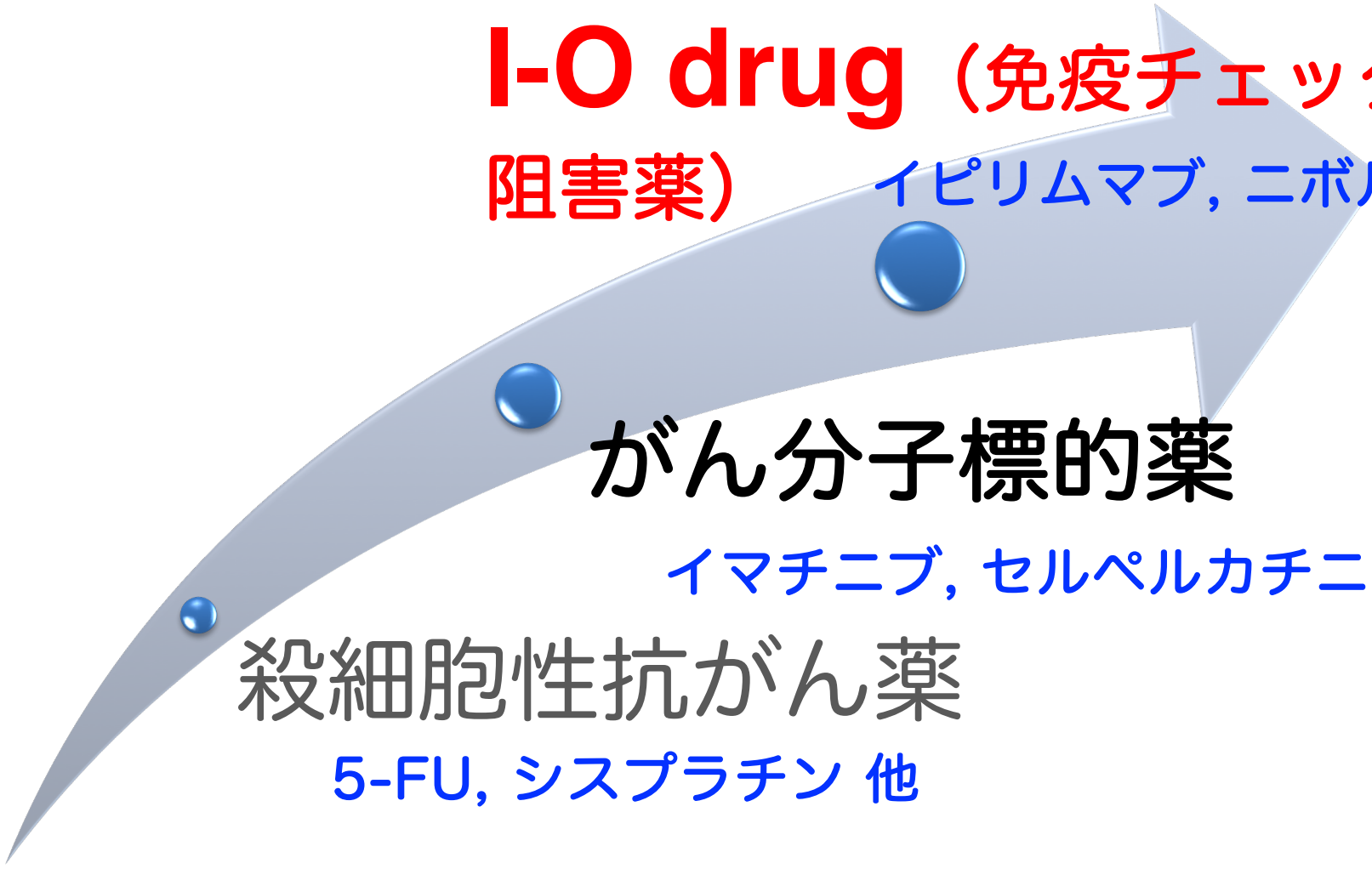
抗PD-1抗体薬ニボルマブとペムブロリズマブの薬物動態と免疫原性の長期観察研究

福土 将秀[1,2)]

1) 札幌医科大学附属病院　薬剤部
2) 旭川医科大学病院　薬剤部

今回の発表に関して、開示すべき利益相反はありません。

抗悪性腫瘍剤の推移



I-O drug（免疫チェックポイント阻害薬）

イピリムマブ，ニボルマブ 他

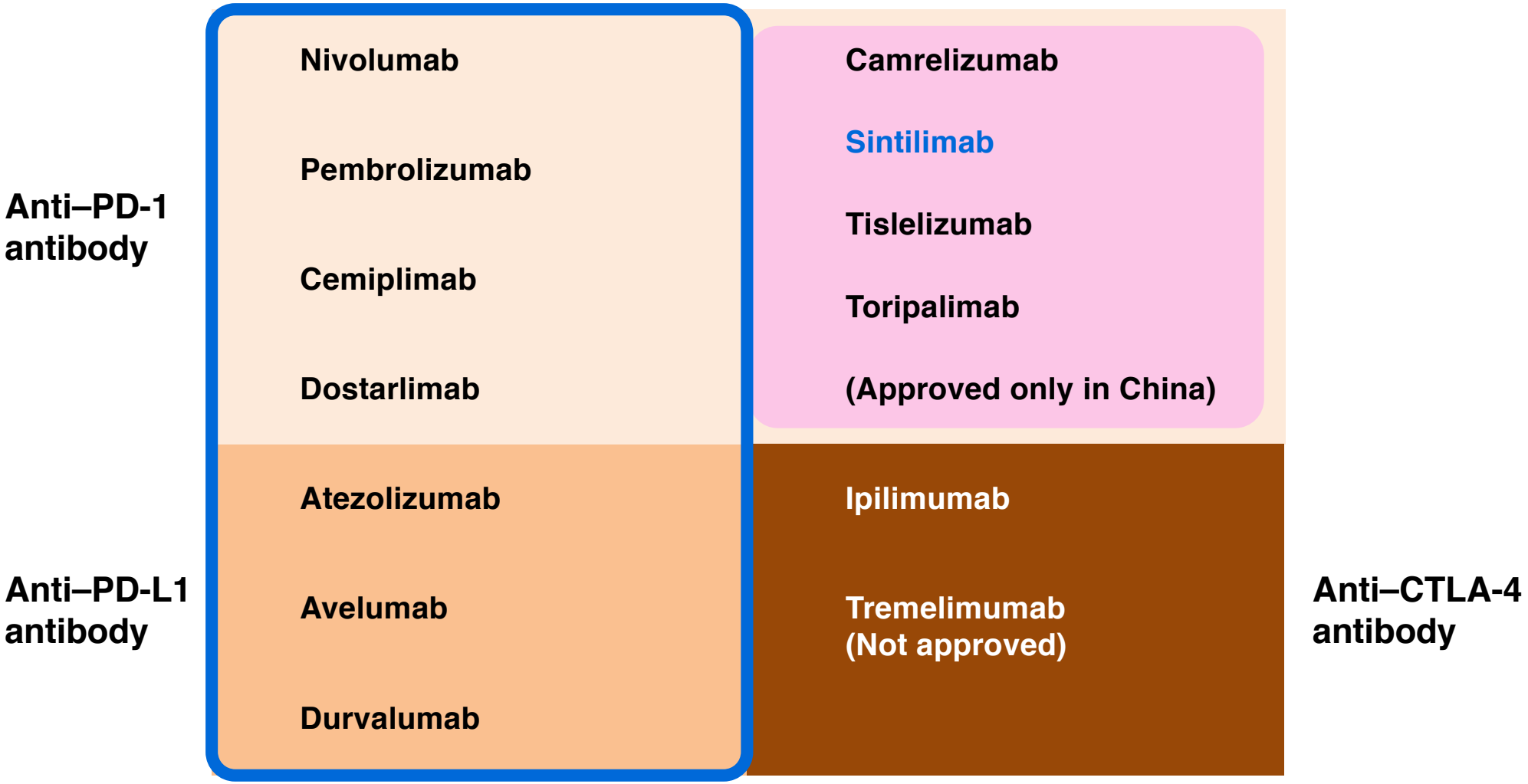
がん分子標的薬

イマチニブ，セルペルカチニブ 他

殺細胞性抗がん薬

5-FU，シスプラチン 他

Immuno-Oncology Drugs



7 mAbs

免疫チェックポイント阻害薬

Table 1. Pharmacodynamic and Pharmacokinetic Properties for Approved CTLA-4, PD-1, and PD-L1 Inhibitors[a]

	Ipilimumab	Nivolumab[b]	Pembrolizumab	Atezolizumab	Avelumab	Durvalumab
Dosing characteristics						
IgG type	IgG1 κ	IgG4 κ	IgG4 κ	Nonglycosylated IgG1 κ	IgG1 λ	IgG1 κ
Dose and dosing schedules tested	0.3, 3, or 10 mg/kg Q3W × 4	0.1–20 mg/kg as a single dose or as multiple doses Q2W or Q3W	1–10 mg/kg Q2W and 2–10 mg/kg Q3W	0.1–20 mg/kg and flat dose of 1200 mg	1–20 mg/kg Q2W	0.1–10 mg/kg Q2W, 15 mg/kg Q3W, and 20 mg/kg Q4W
Approved dose/dosing schedule	*Unresectable/ metastatic melanoma:* 3 mg/kg Q3W for a maximum of 4 doses *Melanoma adjuvant setting:* 10 mg/kg Q3W × 4, then 10 mg/kg Q12W for up to 3 years	*Melanoma (nivolumab monotherapy), NSCLC, RCC, and urothelial cancer:* 240 mg Q2W *Melanoma (combined with ipilimumab):* nivolumab 1 mg/kg, then ipilimumab on the same day, Q3W × 4, then nivolumab 240 mg Q2W *cHL and HNSCC:* 3 mg/kg Q2W	*Melanoma, NSCLC, HNSCC, cHL, and urothelial cancer:* 200 mg Q3W *Microsatellite instability-high cancer:* 200 mg Q3W (adults), 2 mg/kg Q3W (children)	*Urothelial cancer and NSCLC:* 1200 mg Q3W	*Merkel cell carcinoma:* 10 mg/kg Q2W	*Urothelial cancer:* 10 mg/kg Q2W

PD-1阻害薬

480 mg Q4W

400 mg Q6W

アキシチニブ併用
（腎細胞がん）

ベバシズマブ併用
（肝細胞がん）

アキシチニブ併用（腎細胞がん）
レンバチニブ併用（子宮内膜がん、腎細胞がん）

カボザンチニブ併用（腎細胞がん）

Sheng et al., *J Clin Pharmacol* 57:S26-S42, 2017

Overspending driven by oversized single dose vials of cancer drugs

Peter B Bach and colleagues call for an end to contradictory regulatory standards in the US that allow drug manufacturers to boost profits by producing single dose vials containing quantities that increase leftover drug

Bach et al., *BMJ* 352:i788, 2016



3 mg/kg, Q2W

Sep. 2016

240 mg/body, Q2W



用量/曝露量とレスポンスの関係が”フラット”である。

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 40–48; doi:10.1002/psp4.12133
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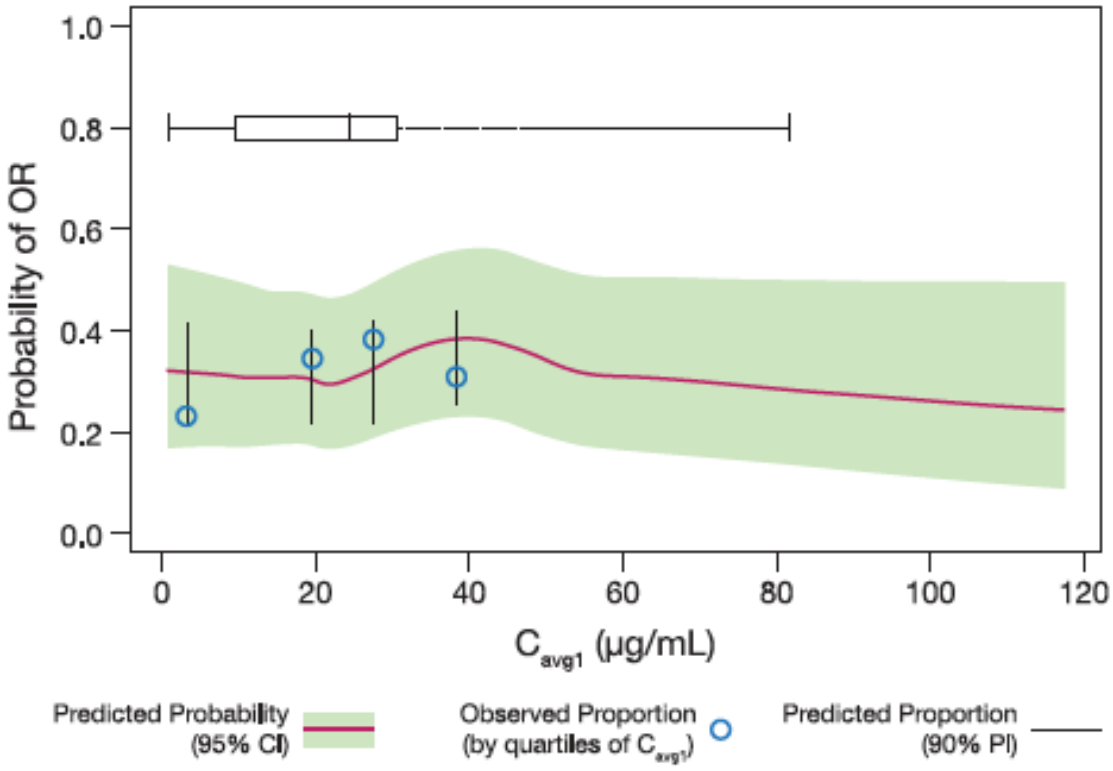
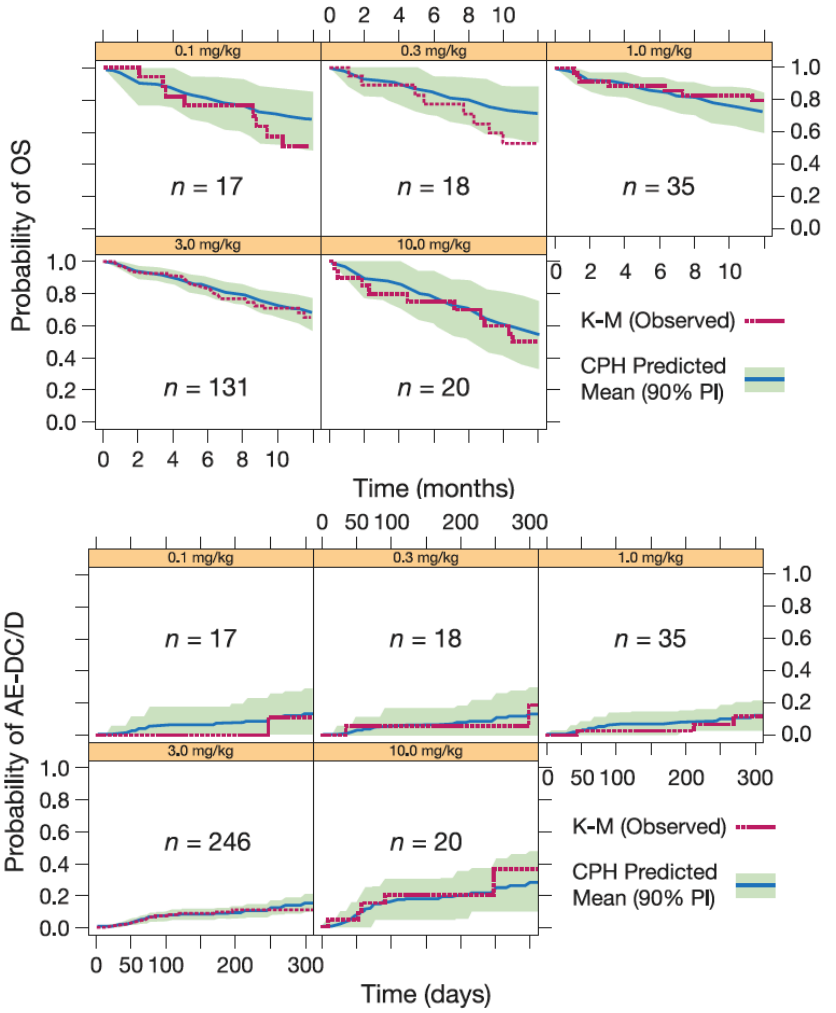
ORIGINAL ARTICLE

Quantitative Characterization of the Exposure–Response Relationship for Cancer Immunotherapy: A Case Study of Nivolumab in Patients With Advanced Melanoma

X Wang[1]*, Y Feng[1], G Bajaj[1], M Gupta[1], S Agrawal[1], A Yang[2], J-S Park[3], B Lestini[2] and A Roy[1]





European Journal of Cancer 109 (2019) 12–20

Available online at www.sciencedirect.com

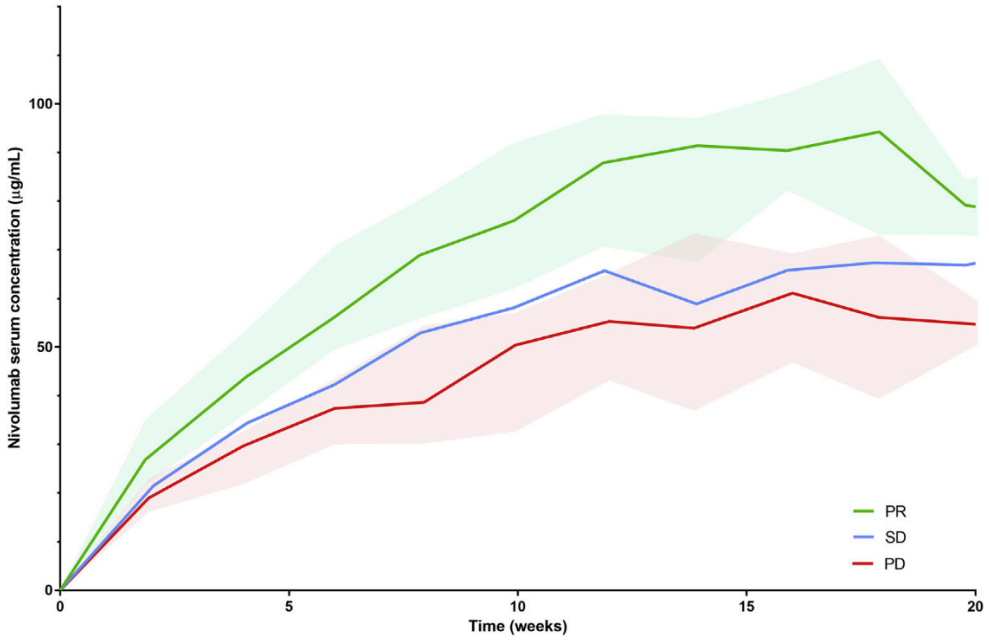
ScienceDirect

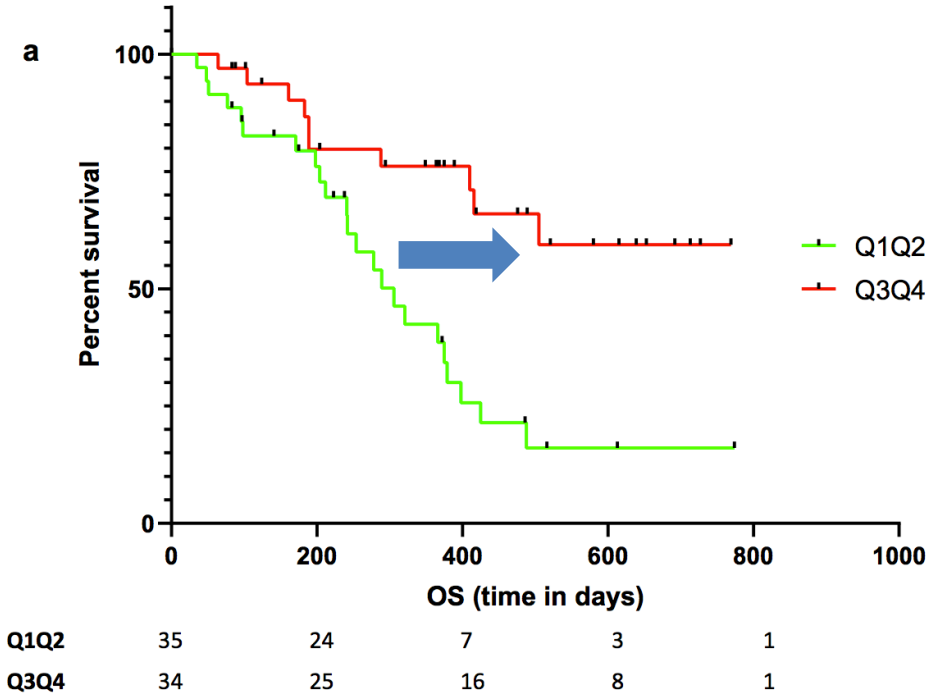
journal homepage: www.ejcancer.com

Original Research

Correlation between nivolumab exposure and treatment outcomes in non–small-cell lung cancer

Edwin A. Basak [a,*], Stijn L.W. Koolen [a,b], Daan P. Hurkmans [a], Marco W.J. Schreurs [c], Sander Bins [a], Esther Oomen — de Hoop [a], Annemarie J.M. Wijkhuijs [c], Ilse den Besten [d], Stefan Sleijfer [a], Reno Debets [a], Astrid A.M. van der Veldt [a], Joachim G.J.V. Aerts [d], Ron H.J. Mathijssen [a]





Immunogenicity

～抗体医薬品の永遠の課題～

抗体医薬品が抗原として作用し、治療した患者さんの体内で薬物に対する抗体（抗薬物抗体、**ADA**）の産生が誘導される性質。

場合によっては、**薬物動態（PK）**や**有効性・安全性**に影響を及ぼす可能性があるため、**免疫原性**について十分に理解し、評価することが重要。

- ✓ **Loss-of-Efficacy**
- ✓ **Gain-of-Toxicity**

免疫チェックポイント阻害薬の免疫原性

mAb	Patients *N*, regimen, tumor type	ADA assay	ADA %	NAb %	Reference	Year
Anti-PD-1	***Monotherapy***					
Nivolumab	*N* = 1086, pool of 6 clinical studies	ECL	12.7	0.8	Agrawal et al.	2017
	N = 2085	ECL	11.2	0.7	US PI	2018
	Nivo 3 mg/kg followed by ipi 1 mg/kg Q3W	NR	23.8-26 ADA to nivo	0.5–1.9 nivo NAb	US PI	2018
	Combo therapy					
	Nivo 1 mg/kg followed by ipi 3 mg/kg Q3W	NR	37.8 ADA to nivo	4.6 nivo NAb	US PI	2018
	Nivo followed by ipi	NR	4.1–8.4 ADA to ipi	0–0.3 ipi NAb	US PI	2018
Pembrolizumab	*N* = 1087	ECL	1.7	NR	Van Vugt et al.	2016
	NSCLC	ECL	2.5	NR	Van Vugt et al.	2016
	melanoma	ECL	0.7	NR	Van Vugt et al.	2016
	N = 1289[b]	ECL	2.1	0.5	US PI	2018
Cemiplimab	*N* = 398	ECL	1.3	NR	US PI	2018
Anti-CTLA-4						
Ipilimumab	*N* = 1024, melanoma	ECL	1.1	0	US PI	2018
	N = 144, melanoma[c]	ECL	4.9	0	US PI	2018
	Nivo and ipi, *N* = 499, RCC and mCRC	NR	5.4 ADA to ipi	0 ipi NAb	US PI	2018
	N = 31, melanoma	Bead-based assay	26	NR	Knerveland et al.	2018
Anti-PD-L1						
Atezolizumab	*N* = 2007	NR	39.1	NR	EMA	2017
	N = 111 (cohort 1), urothelial carcinoma	NR	48	NR	US PI	2018
	N = 275 (cohort 2), urothelial carcinoma	NR	42	NR	US PI	2018
	N = 565, NSCLC	NR	30	NR	US PI	2018
Avelumab	*N* = 1558	NR	4.1	NR	US PI	2017
	N = 1738[d]	NR	5.9	NR	EMA	2017
Durvalumab	*N* = 1570	NR	2.9	NR	US PI	2018
	Durvalumab + tremelimumab, *N* = 60	ECL	6.6 ADA to durva	NR	Antonia et al	2016
	Durvalumab + tremelimumab, *N* = 53	ECL	1.8 ADA to trem	NR	Antonia et al	2016

Davda *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:105

Evaluation of Immunogenicity of Nivolumab Monotherapy and Its Clinical Relevance in Patients With Metastatic Solid Tumors

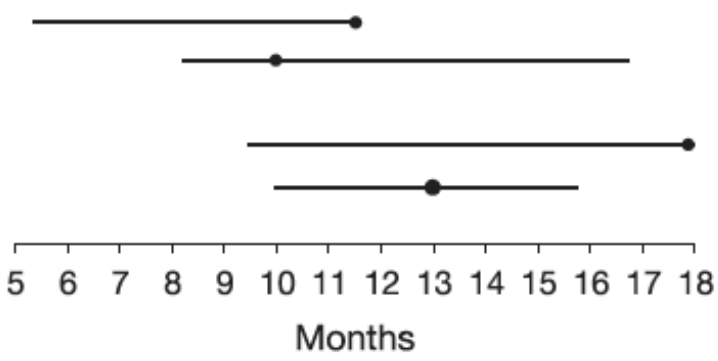
The Journal of Clinical Pharmacology
2017, 57(3) 394–400
© 2016, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.818

Table 3. Summary of Hypersensitivity/Infusion Reactions by Nivolumab ADA Status Across Studies

	Patients, n (%)	
Select Adverse Event Category: Hypersensitivity/Infusion Reaction	Nivolumab ADA Positive (N = 138)	Nivolumab ADA Negative (N = 948)
Total patients with an event	4 (2.9)	49 (5.1)
Anaphylactic shock	0	0
Bronchospasm	1 (0.7)	4 (0.4)
Hypersensitivity	1 (0.7)	25 (2.6)
Infusion-related reaction	2 (1.5)	23 (2.4)

NOT clinically relevant

	# Events (# Randomized)	Median OS (95% CI)
CA209017		
Nivo ADA positive	12 (21)	11.56 (5.36, NA)
Nivo ADA negative	55 (88)	9.99 (8.21, 16.69)
CA209057		
Nivo ADA positive	22 (43)	17.87 (9.43, NA)
Nivo ADA negative	134 (208)	12.98 (9.99, 15.74)



Vugt *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:212
https://doi.org/10.1186/s40425-019-0663-4

Journal for ImmunoTherapy of Cancer

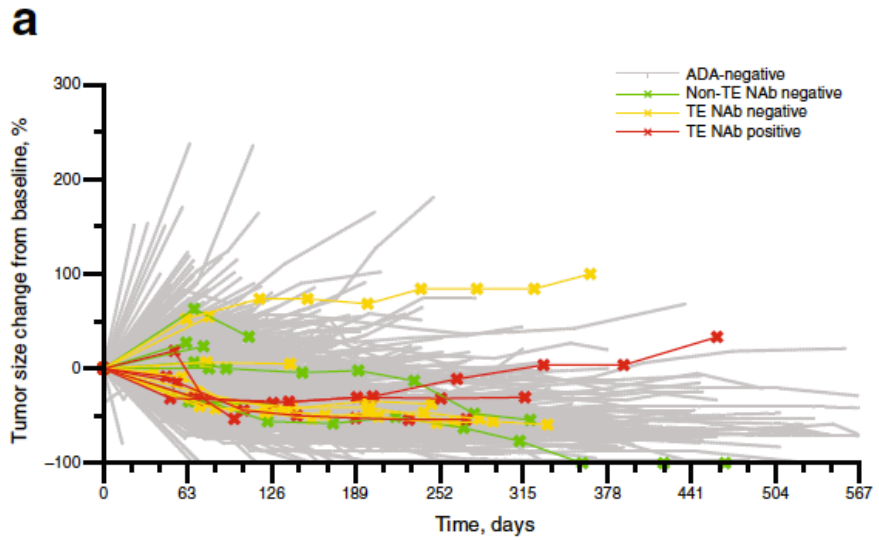
RESEARCH ARTICLE Open Access

Immunogenicity of pembrolizumab in patients with advanced tumors

Marianne J. H. van Vugt[1], Julie A. Stone[2], "Rik" H. J. M. M. De Greef[1], Ellen S. Snyder[2], Leslie Lipka[2], David C. Turner[2], Anne Chain[2], Mallika Lala[2], Mengyao Li[2], Seth H. Robey[2], Anna G. Kondic[3], Dinesh De Alwis[2], Kapil Mayawala[2], Lokesh Jain[2] and Tomoko Freshwater[2*]

Table 2 Summary of AEs by ADA category after pembrolizumab treatment

	ADA-negative patients	ADA-positive patients, *n* = 57				Total patients
		Non-TE NAb negative	Non-TE NAb positive	TE NAb negative	TE NAb positive	
Patients in population	1943	19	2	27	9	2000
Patients with drug-related[a] AE, n (%)	1338 (68.9)	11 (57.9)	2 (100)	21 (77.8)	6 (66.7)	1378 (68.9)
Patients with infusion-related reaction,[b] n (%)	43 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	43 (2.2)



NOT clinically relevant

ONCOIMMUNOLOGY
2018, VOL. 7, NO. 5, e1424674 (6 pages)
https://doi.org/10.1080/2162402X.2018.1424674

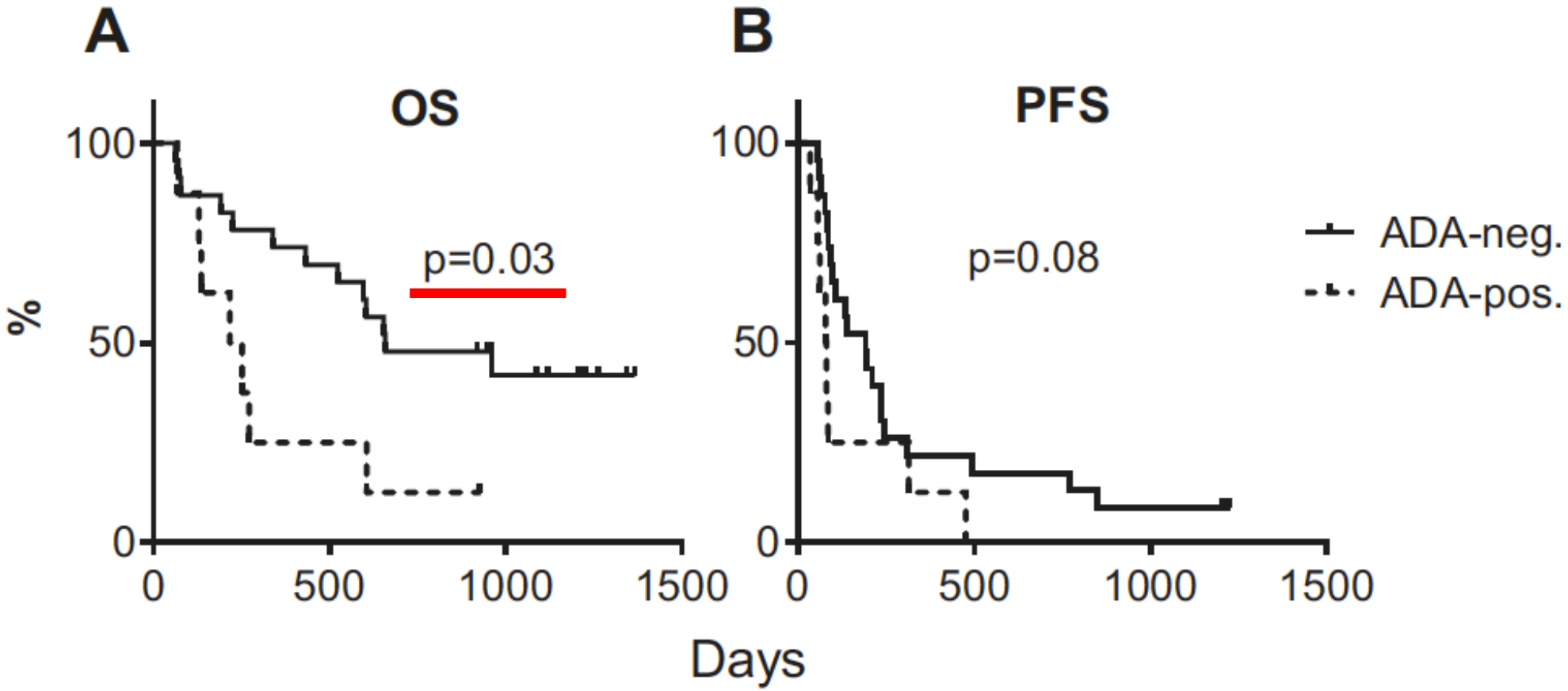
Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS
Check for updates

Development of anti-drug antibodies is associated with shortened survival in patients with metastatic melanoma treated with ipilimumab

Anders H. Kverneland[a,b], Christian Enevold[a], Marco Donia[b], Lars Bastholt[c], Inge Marie Svane[b,#], and Claus H. Nielsen[a,#]



➢Objective

- **To investigate the long-term PK and ADA profiles of nivolumab (Nivo) and pembrolizumab (Pembro), correlated with efficacy and safety in real-world practice.**

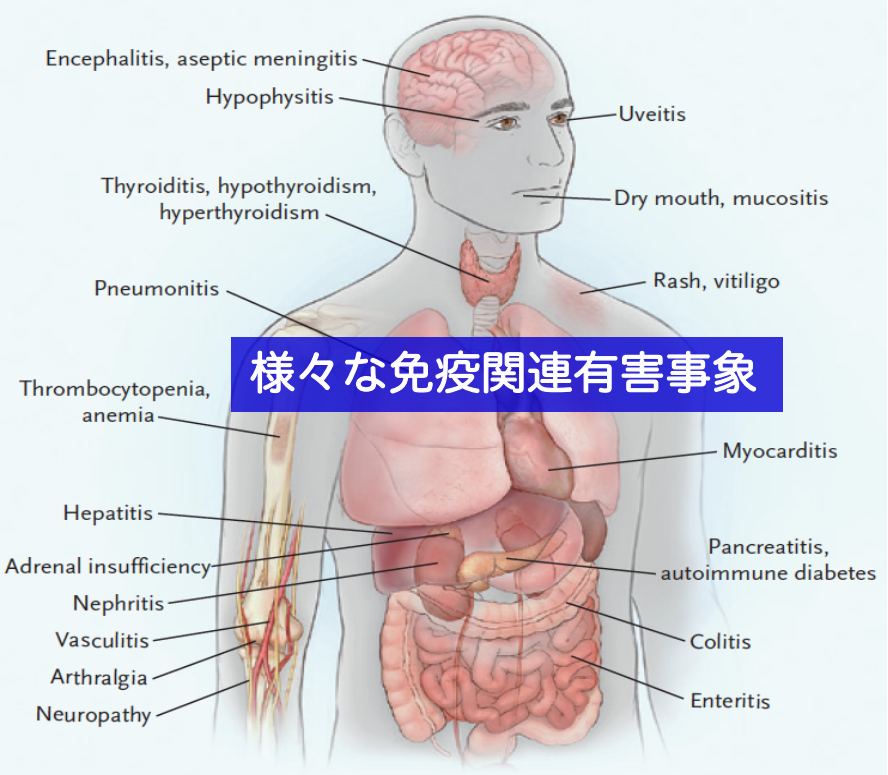
CHOPIN STUDY

A single-center study of CHeckpoint inhibitor Optimization based on PK/PD and ADA INvestigations

UMIN000033036

医師と看護師
薬剤師
検査技師
患者さん
からの協力のもとで
研究実施

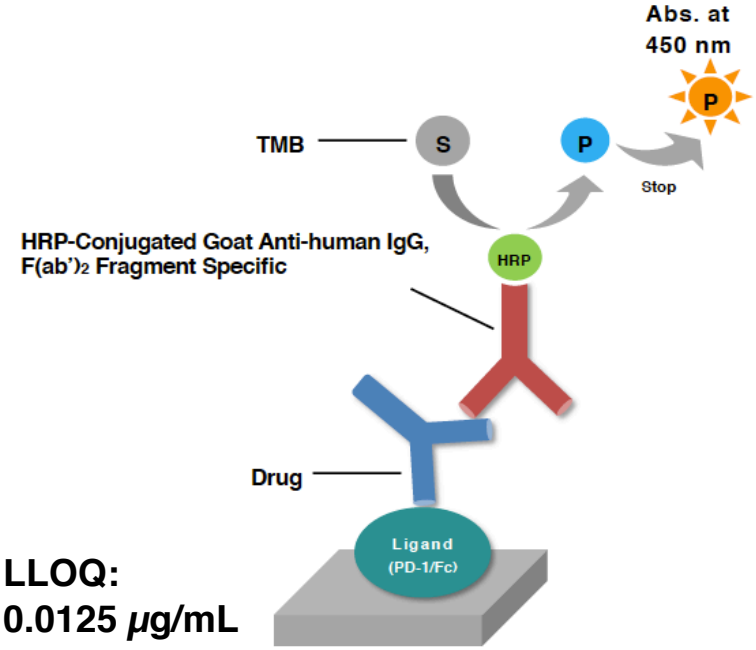




Postow et al., *N Engl J Med* 378:158-168, 2018

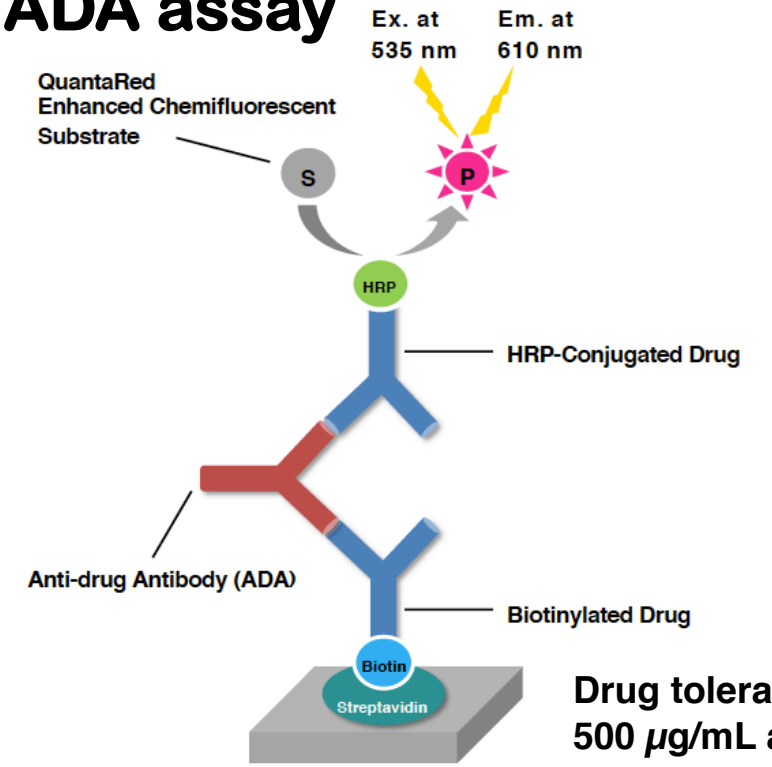
PD-1阻害薬の薬物動態および免疫原性の評価

PK assay

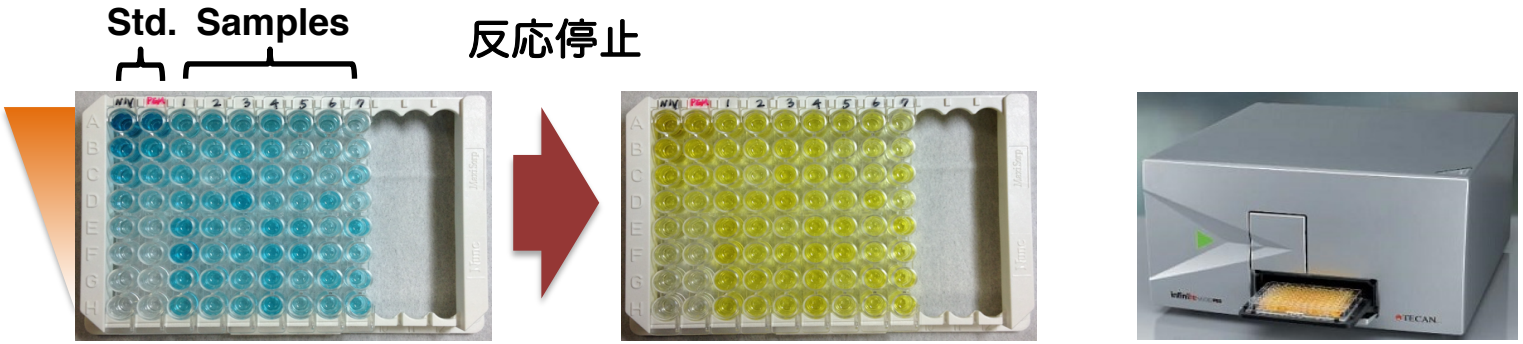


LLOQ:
0.0125 μg/mL

ADA assay



Drug tolerance level:
500 μg/mL at 250 ng/mL of ADAs



Plasma samples (2 μL) appropriately diluted with blank plasma were further diluted in assay buffer.

患者背景

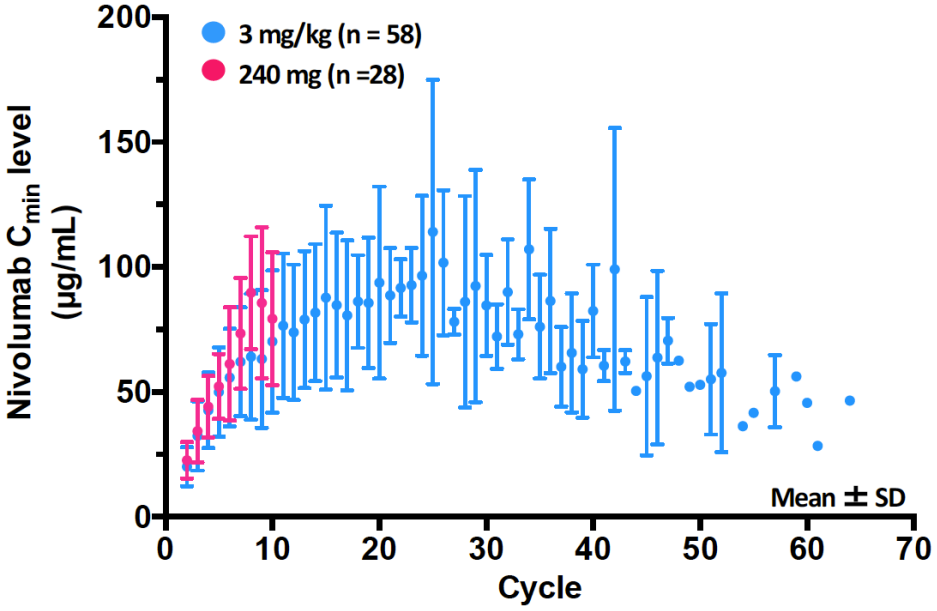
	Nivo (n = 98)	Pembro (n = 49)	All (n = 147)
Median age (range), y	68 (17-84)	68 (50-88)	68 (17-88)
Cancer type, n			
NSCLC/MPM	21/2	37*/0	58/2
SCCHN	21	0	21
Gastric cancer	21	0	21
RCC/Urothelial carcinoma	18†/0	0/10	18/10
MEL	15†	2	17
ECOG performance status			
0/1	92	46	138
≥2	6	3	9
Median follow-up (range), mo	5.6 (0.1-38.7)	6.5 (0.2-21.5)	6.0 (0.1-38.7)

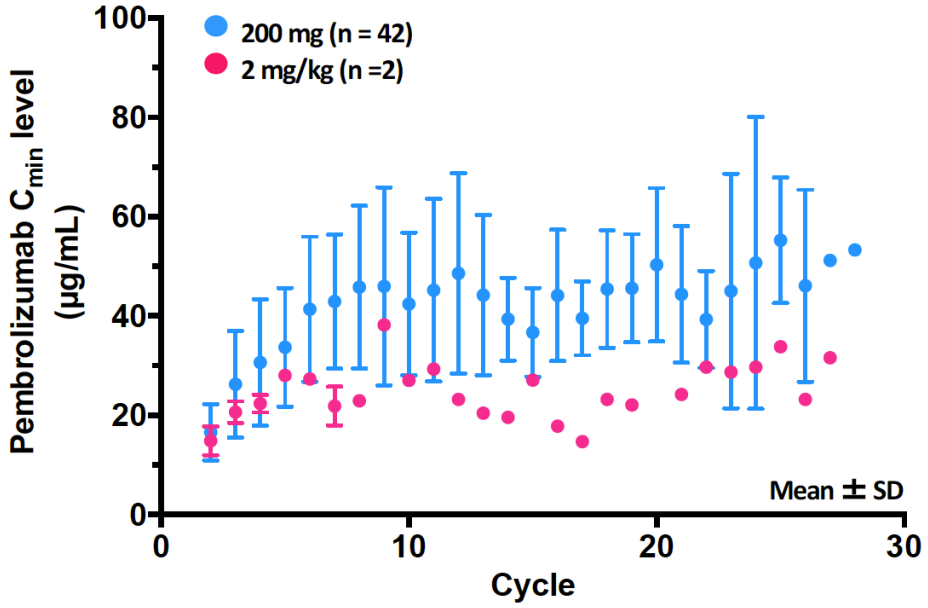
Abbreviations: ECOG, Eastern Cooperative Oncology Group; MEL, melanoma; MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck.

*Includes 2 in combo with chemotherapy.
†Includes 2 in combo with ipilimumab.

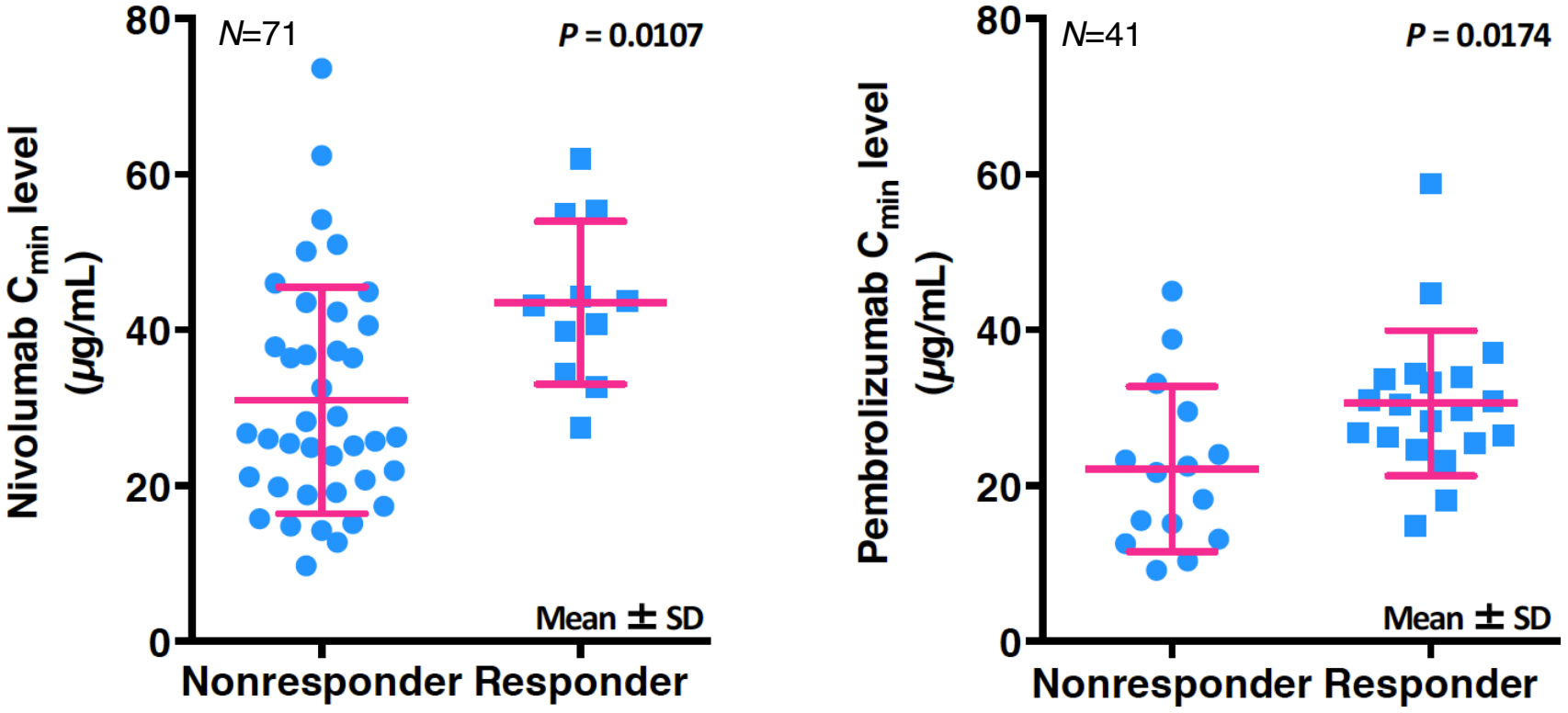
Blood samples collected (n = 1,718)

ニボルマブおよびペムブロリズマブのPKプロファイル





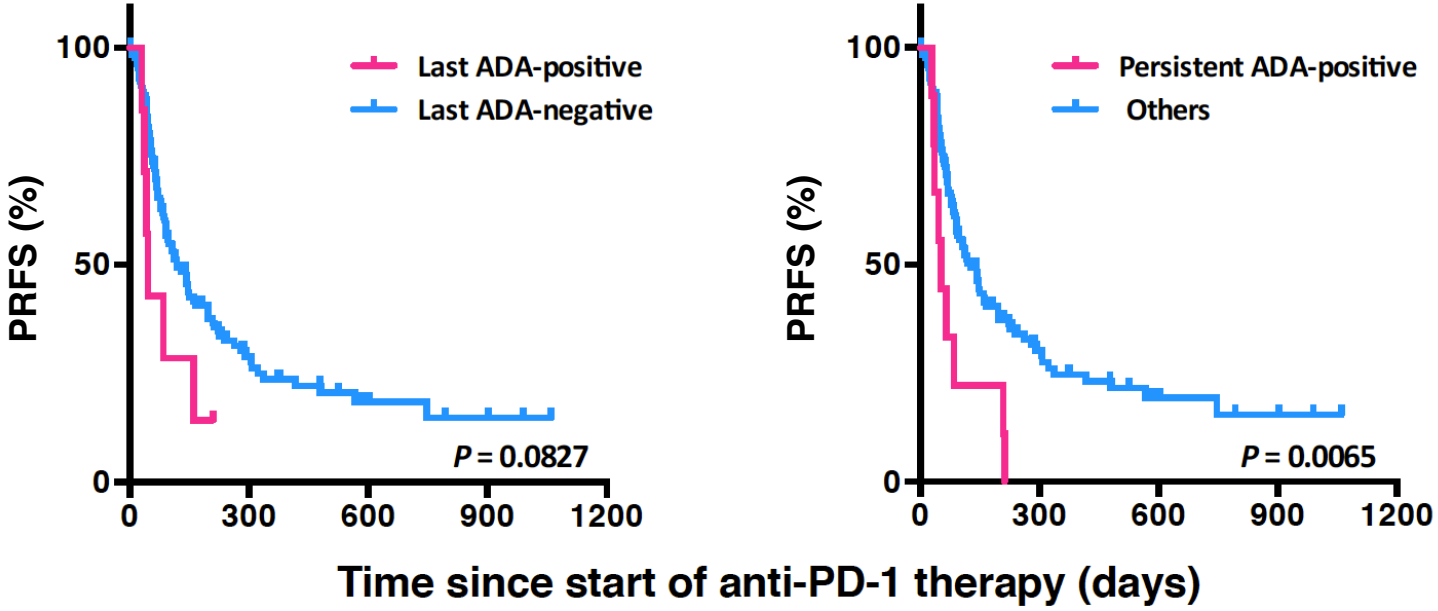
ニボルマブおよびペムブロリズマブの曝露量とレスポンスの関連



ニボルマブおよびペムブロリズマブの免疫原性

Patients, No. (%)	Nivo (n = 98)	Pembro (n = 49)
Baseline ADA positive	2 (2.0) [2 fever*]	2 (4.1) [1 fever*]
Treatment-emergent ADA positive	22 (22.4)	6 (12.2)
Persistent positive†	7 (7.1)	2 (4.1)
Only last sample positive	1 (1.0)	1 (2.0)
Transient positive‡	14 (14.3)	3 (6.1)
ADA negative	76 (77.6)	43 (87.8)

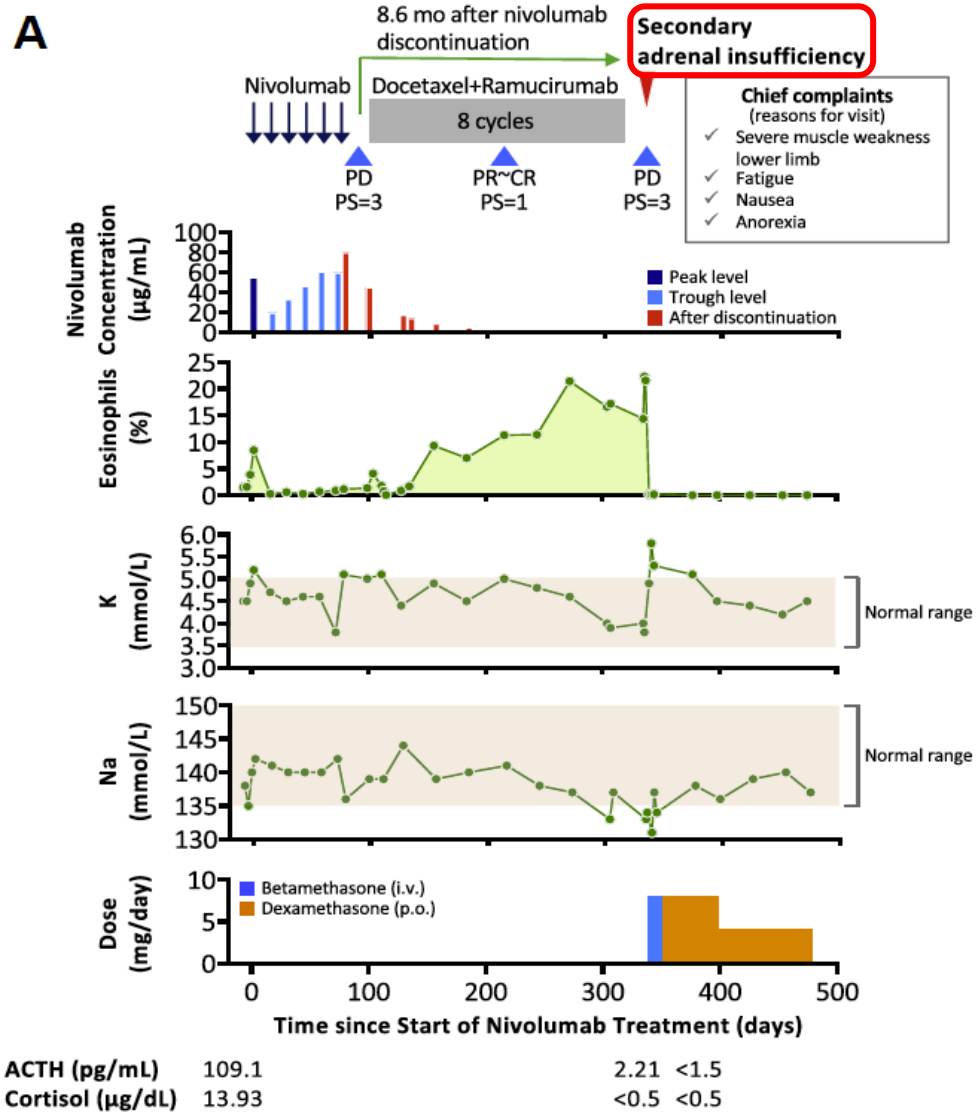
†Pts having ADA-positive samples at 2 or more consecutive time-points ≥4 weeks apart.
‡Pts not having persistent ADA-positive samples, with the last sample negative.

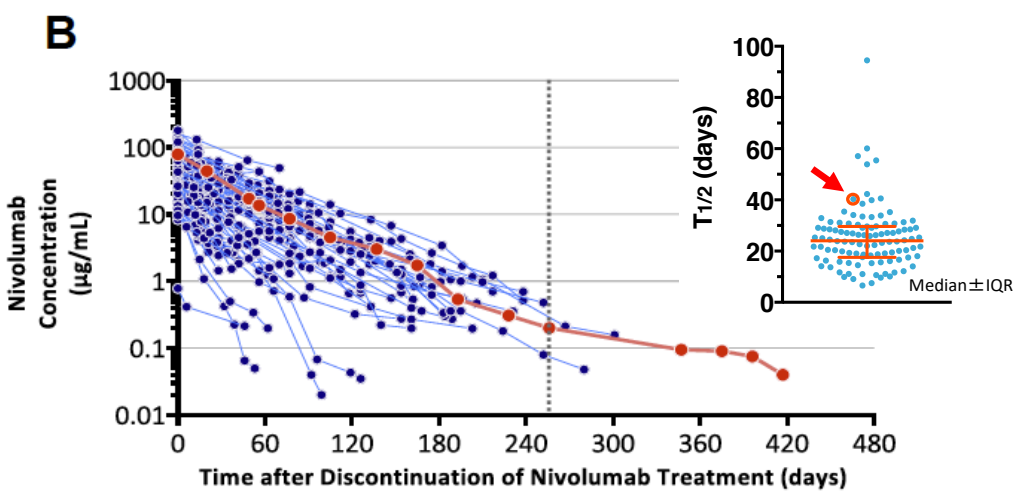


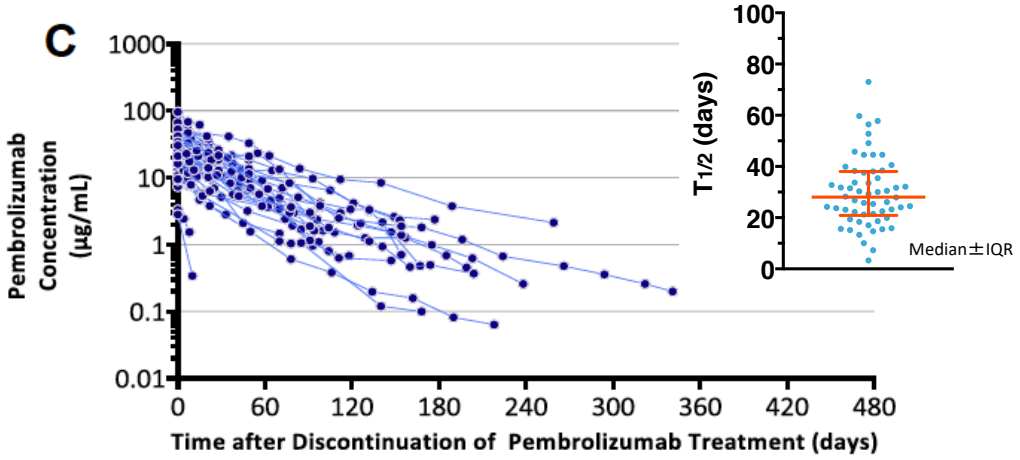
PD-1 Blockers: Staying Long in the Body and Delayed Toxicity Risks

To the Editor:

抗PD-1治療終了後においても、遅発性有害事象に対する注意が必要





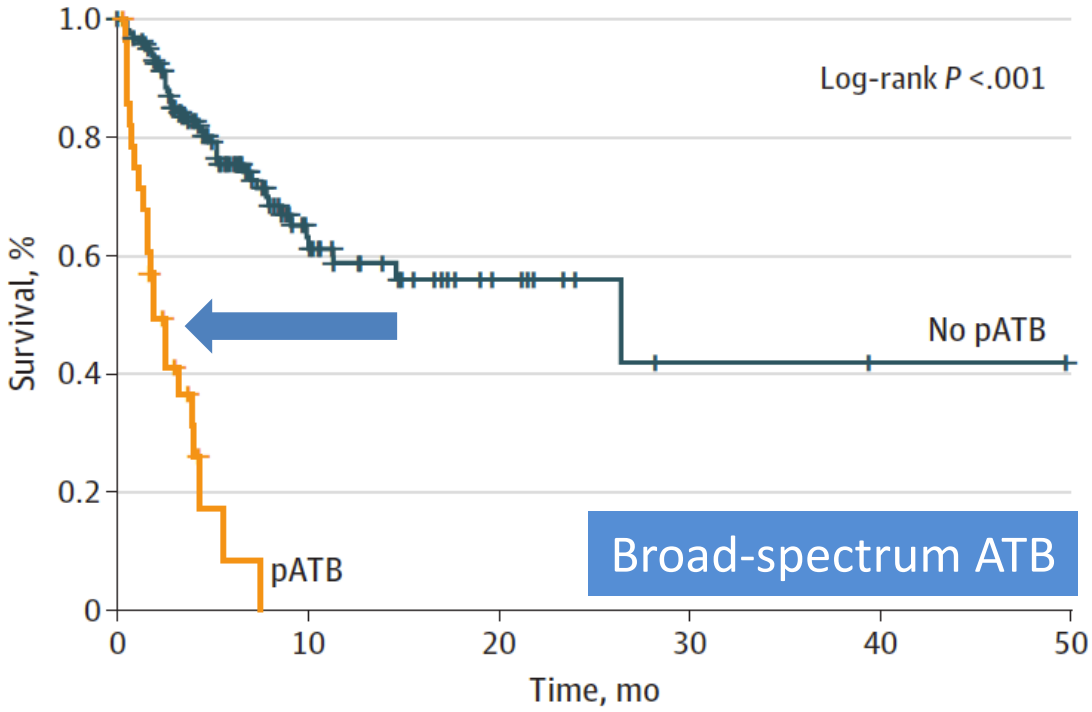


Fukudo et al., *J Thorac Oncol* 15:e42-e44, 2020

JAMA Oncology | Brief Report

Association of Prior Antibiotic Treatment With Survival and Response to Immune Checkpoint Inhibitor Therapy in Patients With Cancer

A Kaplan-Meier curves



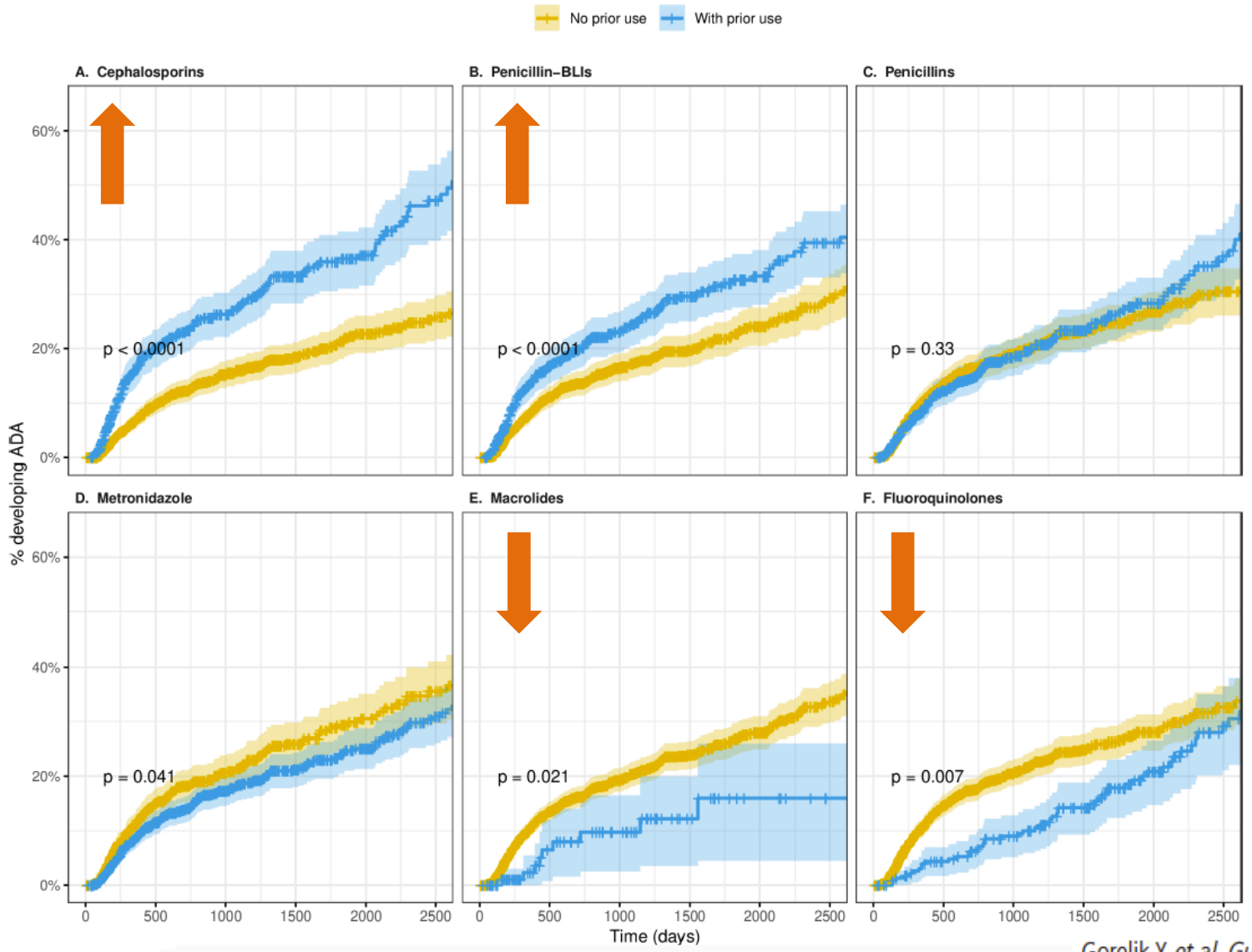
No. at risk						
No pATB	166	32	10	2	1	0
pATB	29	0	0	0	0	0

Pinato et al., JAMA Oncol. 2019;5(12):1774-1778.

BMJ Journals

Gut

Antibiotic use differentially affects the risk of anti-drug antibody formation during anti-TNFα therapy in inflammatory bowel disease patients: a report from the epi-IIRN



Gorelik Y, *et al*. *Gut* 2022;**71**:287–295.

➢ Key findings

- **Exposure to nivolumab as well as pembrolizumab was associated with early response.**

- **Persistent ADA-positive patients had a worse prognosis than others.**

➢ Conclusions

- **Immunogenicity of the PD-1 blockers Nivo and Pembro may potentially influence clinical outcomes.**
- **It may be possible to optimize dose in certain patients with lower drug exposure for improved efficacy.**

謝　辞

旭川医科大学病院
各診療科医師、看護師、検査部スタッフ
薬剤部諸氏
研究にご協力を頂いた全ての患者さん

国立医薬品食品衛生研究所　生物薬品部
石井明子　部長

臨床薬理研究振興財団、科研費（基盤・C）