InaJCC The Indonesian Journal of Cancer Control

Original Article

Efficacy and safety of neoadjuvant nivolumab and ipilimumab for resectable melanoma

Stephanie D Djuanda[1], Janice Suhartono[1], Tirza A Sutedjo[1], Nydia S Sucahyo[1], Steven Alvianto[1], Ketut K Winaya[2]

e-ISSN 2797-457X
DOI: 10.52830/inajcc.v4i2.112

Received: August 10, 2025
Accepted: October 17, 2025

Authors' affiliations:
[1]Doctor of Medicine, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia
[2]Department of Dermatology and Venereology, Faculty of Medicine, Udayana University / Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali, Indonesia

Corresponding author:
E-mail: *dr.kwartantayaw@unud.acl.id*

Abstract

Introduction: Neoadjuvant immunotherapy is an emerging strategy in the management of resectable melanoma, aiming to improve long-term outcomes by inducing early immune responses before surgery. The combination of nivolumab (PD-1 inhibitors) and ipilimumab (anti–CTLA-4) has shown promise.
Objective: To systematically review the efficacy and safety of neoadjuvant nivolumab and ipilimumab regimens in resectable melanoma patients.
Methods: A systematic search of databases was conducted following PRISMA 2020 guidelines. Studies were screened and selected based on the use of neoadjuvant nivolumab and ipilimumab combination for resectable melanoma. Risk of bias was assessed. Key outcomes included relapse-free survival (RFS), event-free survival (EFS), overall survival (OS), pathological response and grade ≥3 adverse events (AE). Seven studies comprising five randomized controlled trials (RCT), non-RCT and one retrospective cohort study with a total of 530 patients were included.
Results: The combination of neoadjuvant nivolumab and ipilimumab showed high efficacy, with RFS from 70% to 96%, EFS ≥90%, and OS ≥95% over median follow-up of 8-28 months. The most favorable outcomes were observed with low-dose ipilimumab (1 mg/kg) plus high-dose nivolumab (3 mg/kg). Pathological response rates were high, major/complete responses ≥70% of patients. Grade ≥3 treatment-related AE were common, including rash, colitis, elevated liver enzyme.
Conclusion: Neoadjuvant nivolumab with ipilimumab shows strong clinical and pathological response in resectable melanoma, with a potential to improve long-term outcomes. However, its use is limited by a significant risk of severe immune-related adverse events. Optimizing the dosing, lowering ipilimumab dosage, may enhance the risk-benefit profile.

Keywords: *Ipilimumab; melanoma; neoadjuvant therapy; nivolumab*

Abstrak

Pendahuluan: Imunoterapi neoadjuvan merupakan strategi yang sedang berkembang dalam penatalaksanaan melanoma yang dapat direseksi, dengan tujuan meningkatkan luaran jangka panjang melalui induksi respons imun dini sebelum pembedahan. Kombinasi nivolumab (inhibitor PD-1) dan ipilimumab (anti-CTLA-4) telah menunjukkan hasil yang menjanjikan.
Tujuan: Meninjau secara sistematis efektivitas dan keamanan regimen neoadjuvan nivolumab dan ipilimumab pada pasien melanoma yang dapat direseksi.
Metode: Penelusuran sistematis terhadap basis data dilakukan sesuai pedoman PRISMA 2020. Studi diseleksi berdasarkan penggunaan kombinasi neoadjuvan nivolumab dan ipilimumab pada melanoma yang dapat direseksi. Risiko bias dinilai secara sistematis. Luaran utama meliputi *relapse-free survival* (RFS), *event-free survival* (EFS), *overall survival* (OS), respons patologis, serta kejadian efek samping terkait terapi derajat ≥3. Sebanyak tujuh studi yang terdiri atas lima uji klinis teracak terkontrol (RCT), satu studi non-RCT, dan satu studi kohort retrospektif dengan total 530 pasien diikutsertakan dalam analisis.
Hasil: Kombinasi neoadjuvan nivolumab dan ipilimumab menunjukkan efektivitas yang tinggi, dengan RFS berkisar antara 70–96%, EFS ≥90%, dan OS ≥95% pada median tindak lanjut 8–28 bulan. Luaran terbaik ditemukan pada regimen ipilimumab dosis rendah (1 mg/kgBB) yang dikombinasikan dengan nivolumab dosis tinggi (3 mg/kgBB). Angka respons patologis tergolong tinggi, dengan respons mayor/komplet pada ≥70% pasien. Efek samping terkait terapi derajat ≥3 cukup sering dijumpai, termasuk ruam kulit, kolitis, dan peningkatan enzim hati.
Kesimpulan: Pemberian neoadjuvan nivolumab yang dikombinasikan dengan ipilimumab menunjukkan respons klinis dan patologis yang kuat pada melanoma yang dapat direseksi, serta berpotensi memperbaiki luaran jangka panjang. Namun, penggunaannya dibatasi oleh risiko efek samping imunologis berat yang signifikan. Optimalisasi regimen dosis, khususnya dengan penurunan dosis ipilimumab, berpotensi meningkatkan rasio manfaat–risiko terapi.

Background

Melanoma is a highly aggressive skin cancer that develops from melanocytes, the cells in the deepest layer of the skin responsible for producing melanin. Although it makes up just about 1% of all skin cancers, melanoma is responsible for more than 80% of deaths from skin cancer.[1] For individuals with resectable melanoma at stage IIIB or higher, the standard of care was surgery followed by adjuvant therapy.[2] Over the past decade, melanoma treatment has undergone significant transformation. To further improve clinical outcomes, neoadjuvant strategies (NAS) are now being explored.[3] Neoadjuvant therapy, especially immunotherapy, can change the way treatment works. It not only shrinks lesions but also makes surgery less necessary by boosting the body's immune response more effectively than adjuvant therapy. It also allows for more frequent monitoring, enabling timely assessment of treatment response and early detection of disease progression.[4] The International Neoadjuvant Melanoma Consortium (INMC) also highlighted several advantages of the NAS therapy approach. This helps identify good responders, potentially reducing the extent of surgery and need for further therapy.[3]

Previous studies have shown that adjuvant PD-1 inhibitors, such as nivolumab and pembrolizumab, improve relapse-free survival (RFS) when compared to ipilimumab or placebo. Despite of adjuvant therapy, patients still experience recurrence after surgery, and no approved adjuvant immunotherapies have demonstrated a significant benefit in overall survival (OS) after long-term follow-up.[5] A combination of immunotherapy drugs tends to offer superior long-term outcomes, particularly in terms of recurrence-free and OS.[6] Pre-clinical and phase 1 studies suggest neoadjuvant immune checkpoint inhibitors may be more effective than adjuvant therapy. The nivolumab ipilimumab combination shows strong potential in activating immune responses against tumor cells.[3,7]

The nivolumab–ipilimumab combination shows strong promise in neoadjuvant treatment for resectable melanoma, achieving high rates of pathological remission linked to improved long-term survival.[8] Despite promising results, no comprehensive review currently exists on this topic. Previous reviews have focused on adjuvant therapy or lacked synthesis of recent high-quality neoadjuvant trials. This study aims to evaluate the efficacy and safety of neoadjuvant nivolumab and ipilimumab in resectable melanoma.

Methods

This systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) on April 18th, 2025, with the following registration number: CRD420251033496. The study aimed to evaluate the efficacy and safety of nivolumab and ipilimumab as neoadjuvant for patients with resectable melanoma.

The review included all studies published in English up to April 2025, whether interventional or observational studies. Research that were classified as reviews, case reports, case series, conference abstracts, book sections, commentaries/editorials, or in vitro or in silico investigations were not included. The included studies focused on resectable melanoma patients who underwent therapy with Nivolumab and Ipilimumab as neoadjuvant. Patients with metastatic or unresectable melanoma and adjuvant only therapies were excluded. The primary outcomes of interest are relapse-free survival (RFS), event-free survival (EFS), overall survival (OS), pathological response and grade ≥3 adverse events (AE). Relevant studies were identified through searches on MEDLINE, EBSCO, ScienceDirect, ProQuest. Four independent authors searched for articles using the following keyword combination: ((“Nivolumab”) AND (“ipilimumab”) AND (“neoadjuvant”)) AND ((“melanoma” OR “cutaneous melanoma” OR “skin melanoma” OR “malignant melanoma”)).

All studies were imported into Rayyan software to remove duplicates. Titles and abstracts were independently screened by the authors, and studies that did not match the review objective were excluded. Full-text articles were then assessed based on the eligibility criteria. The authors independently extracted key information from each study. Due to the variety in study designs and reported outcomes, the limited data made a meta-analysis unfeasible.

Results

The systematic review process began with 662 potentially relevant articles, from which 559 remained after duplicates were removed. After screening titles and abstracts, 19 studies were selected for full-text review. Of these, 11 were excluded due to reasons such as wrong population (n = 2), outcomes (n = 3), interventions (n = 3),

study design (n = 2), and one ongoing study (Figure 1). Ultimately, 7 studies were included in the final analysis. Study quality was evaluated using the modified Newcastle-Ottawa Scale for cohort studies (Table 1), RoB 2 for RCT (Table 2), and ROBINS-I for non-RCT studies (Table 3). Overall, the included studies demonstrated a low risk of bias. These studies, published between 2018 and 2024, were conducted across diverse regions including Australia, Sweden, the Netherlands, Europe, and Brazil. The review comprised randomized controlled trials and a retrospective cohort study, involving a total of 530 patients. Patient performance status was assessed using either the Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO) criteria. Key demographic data, as well as survival outcomes including RFS, EFS, DMFS, OS and median follow-up duration, are detailed in **Table 4.**

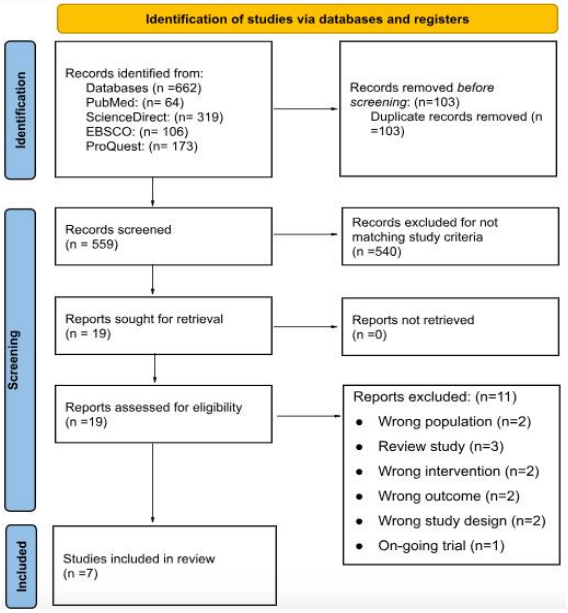

Figure 1. PRISMA 2020 flowchart

Neoadjuvant treatment with nivolumab and ipilimumab showed promising survival outcomes in resectable stage III melanoma. RFS rates were favorable across studies: the NADINA Phase 3 trial reported RFS of 95.1% in patients with major pathological response (MPR).[5] The OPACIN Phase 1B trial found 80% of patients relapse-free at a median follow-up of 25.6 months. The PRADO trial observed 85% RFS at 28.1 months.[9] Another cohort study reported a 96% RFS at 16 months, suggesting that relapse can be effectively prevented.10 Reijers et al. reported an 80% EFS, and the OpACIN and OpACIN-neo protocols showed 70% and 82% EFS, respectively.[9]

DMFS outcomes were also favorable. OS rates were consistently high: the PRADO trial reported 95% OS at 24 months, the OpACIN trial showed 90% 5-year OS (95% CI, 73% to >99%), and the OpACIN-neo trial demonstrated 92% 3-year OS (95% CI, 86% to 98%) across all arms.[9,13,14] In Blank et al. (2024), 90% of patients were alive at 25.6 months, reflecting durable long-term benefits.[5] Pathological responses to neoadjuvant immuno-therapy were also strong. The OpACIN-neo trial identified ipilimumab 1 mg/kg plus nivolumab 3 mg/kg for two cycles as the optimal regimen, achieving a 74% total pathological response, including a high rate of complete responses.[11]

Treatment-related toxicity, especially grade ≥3 AEs, remains a significant concern. OPACIN trial reported a 90% incidence of severe AEs, while PRADO trial observed only 22%.[9,14] Immune-related AEs (irAEs) such as rash, elevated liver enzymes and colitis were common, due to T-cell activation from checkpoint inhibitors.[16] While neoadjuvant ipilimumab and nivolumab are effective, careful management of irAEs is essential.

Table 1. Risk of bias for included Cohort Study

Journal	Selection (4 stars)				Comparability (2 stars)	Outcome (3 stars)			Total
	Represen-tativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertain-ment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Silva et al, 2024	*	-	*	*	-	*	*	*	Satisfactory Studies

Very Good Studies: 9-10 stars
Good Studies: 7-8 stars
Satisfactory Studies: 5-6 stars
Unsatisfactory Studies: 0-4 stars

Table 2. Risk of bias for included Randomized Controlled Trials

Study	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result
Blank et al., 2024	Low	Some	Low	Low	Low
Blank et al., 2018	Low	Some	Low	Some	Low
Versluis et al., 2023	Low	Low	Some	Low	Some
Rozeman et al., 2019	Low	Low	Low	Low	Low
Rozeman et al., 2021	Low	Low	Some	Low	Low

Table 3. Risk of bias for included Non-randomized Controlled Trials

Study	Bias due to confounding	Bias in classifi-cation of inter-ventions	Bias in selection of participants into the study (or into the analysis)	Bias due to deviations from intended interventions	Bias due to missing data	Bias arising from measurement of the outcome	Bias in selection of the reported result
Reijers et al., 2022	Moderate	Low	Moderate	Moderate	Low	Moderate	Moderate

Table 4. Study Characteristics and Survival Outcome

Author, year	Study/ Registration	Patients (M/F)	Median Age	Perfu-sion Status	Stage	BRAF Status	Lymph Node	Previous Treatment	Inter-vention	RFS	EFS	DMFS	OS	MPR	pCR	Near-pCR	Partial Response	Non-Response	Non-Evalua-tion	Follow-up (months)
Blank et al., 2018	OPACIN (NCT0243 7279)	6/4	54	0=10*	IIIB=7, IIIC=3	V600=6	N/A	SND=2, LND=0, ST=0	IPI3+NIV O1 x2 pre/post-op	80%	N/A	N/A	90%	N/A	3	3	1	2	1	25.6
Rozeman et al., 2019	OpACIN-neo (NCT0297 7052)	49/37	N/A	0=85, 1=1*	T1a= 22 T1b= 7 T2a=6 T2b= 3 T3a= 7 T3b= 7 T4a= 2 T4b=8 Unkno wn=24	N/A	Neck= 14 Axilla=44 Axilla and Neck= 3 Groin=24 Epitrochle ar= 1	SND=26, LND=5	Arms A=IPI3 + NIVO1 x3 Arms B=IPI1 + NIVO3 x3 Arms C=IPI3 x3 + NIVO3 x2	PR=1 00% Non= 57%	Not reach ed	N/A	N/A	N/A	37	15	12	21	1	8.3
Rozeman et al., 2021	OpACIN-neo (NCT0297 7052)	49/37	N/A	0=85, 1=1*	Idem Rozeman 2019	N/A	N/A	N/A	Follow-up from 2019 study	84%	82%	N/A	95%	N/A	N/A	N/A	N/A	N/A	N/A	24.6
Reijers et al., 2022	PRADO (NCT0297 7052)	65/34	58	0=94, 1=5†	T1a/b = 17 T2a/b = 26 T3a/b = 20 T4a/b = 21 Tx = 2 Unknown = 13	Yes = 45 No = 43 VE1 - = 9 Unknown = 2	Neck=24 Axilla=39 Groin=36	SND=24, LND=2	IPI1+NIV O3 week 0 & 3	85%	80%	89%	95%	61	48	12	11	N/A	N/A	28.1
Versluis et al., 2023	OpACIN / OpACIN-neo	55/41	57	N/A	N/A	V600=43	Neck=14 Axilla=49 Groin=29 Epitrochle ar=1	N/A	OPACIN = 2 cycles neoadjuv ant OpACIN-neo-Arms A=IPI3 + NIVO1 x3 Arms B=IPI1 + NIVO3 x3 Arms C=IPI3 x3 + NIVO3 x2	70 - 82%	70– 87%	80– 88%	90– 92%	58	N/A	N/A	13	23	2	OpACIN =69 OpACIN -neo = 47

Blank et al., 2024	NADINA (NCT04949113)	71/141	60	0=192, 1=20*	T1= 25 T2= 41 T3= 41 T4= 52 Tx = 7 Unknown = 46	V600E=95 V600K=17 Other = 5 Wild type = 95	Neck=55 Axilla=86 Groin=66	SND = 75 LND = 1 None = 136	IPI80mg + NIVO240 mg x3	MPR = 95,7%	N/A	N/A	N/A	125	100	25	17	56	14	9.9
Silva et al., 2024	Retrospective cohort	25/12	58	N/A	IIIB=23, IIIC=12, IIID=2	V600=25	N/A	N/A	IPI1+NIVO3 x2, surgery + adj.	96%	73%	N/A	N/A	23	N/A	N/A	12	2	N/A	16.1

† Eastern Cooperative Oncology Group (ECOG) Performance Status; * World Health Organization (WHO) Performance Status; SND= Sentinel Node Procedure ; LNP= Lymph Node Dissection; ST= Systemic Therapy; F= female; M = male; RFS=Relapse-Free Survival; EFS=Event-Free Survival; DMFS=Distant Metastasis-Free Survival; OS=Overall Survival; IPI=Ipilumumab; NIVO=Nivolumab; MPR=Major Pathological Response; N/A=Not Available; pNR=Pathological Non-Response; pCR=pathological complete response; pPR=pathological partial response

Discussion

This systematic review provides a comprehensive summary of the efficacy and safety of neoadjuvant nivolumab and ipilimumab in patients with resectable melanoma. The included studies consistently reported high OS and RFS rates, with durable responses over extended follow-up periods. These findings suggest that the combination therapy may significantly improve long-term outcomes. However, the treatment is also associated with a high rate of grade ≥3 treatment-related adverse events (AEs), such as rash, elevated liver enzyme and colitis as the highest. The exact pathophysiology of immune-mediated colitis is unknown, however, the hyperproliferation and hyperactivation of T cells and lymphocyte infiltration are proposed mechanisms. Studies by Rozeman et al. and Silva et al. highlighted the need to balance efficacy with toxicity. Lowering the dose of ipilimumab, particularly the 1 mg/kg ipilimumab plus 3 mg/kg nivolumab regimen used in Arm B of several trials, was found to reduce toxicity.[10,12]

Standard treatment for resectable stage III melanoma typically involves surgery, but recurrence and metastasis remain concerns. Neoadjuvant immunotherapy offers several advantages: it allows assessment of treatment efficacy, reduces tumor size preoperatively, and uses pathological response as a surrogate marker for long-term survival outcomes.[5] Wolchok et al. confirmed the clinical feasibility and benefit of this approach. PD-1, found on T cells, downregulates immune activity when binding to PD-L1/PD-L2 on antigen-presenting cells. In cancer, tumor-expressed PD-L1 suppresses PD-1+ T cells, helping tumors evade the immune system. Nivolumab blocks PD-1, restoring T-cell activity and enabling tumor destruction. Ipilimumab targets CTLA-4, preventing its interaction with B7 and allowing continued CD28-mediated costimulation. This enhances T-cell activation and proliferation, promoting an antitumor immune response, making their combination particularly effective.[16]

This is the first systematic to provide an overview focused specifically on neoadjuvant nivolumab and ipilimumab for resectable melanoma. It includes all relevant studies to date and presents a detailed analysis of efficacy and grade ≥3 safety outcomes. However, limitations include the inability to conduct a meta-analysis due to insufficient pooled data, exclusion of ongoing trials, and incomplete pathological response reporting in some studies. Future research should focus on directly comparing different dosing strategies especially reduced-dose ipilimumab regimens to optimize the balance between efficacy and tolerability. Long-term follow-up data are essential. Additionally, studies involving more diverse populations and real-world clinical environments are needed to enhance the generalizability of current findings.

Conclusion

This systematic review highlights the promise of neoadjuvant nivolumab and ipilimumab in resectable melanoma, with high response rates and improved survival, especially in high-risk patients. However, significant grade ≥3 immune-related adverse events may impact adherence and quality of life. Lower-dose ipilimumab (1 mg/kg) with higher-dose nivolumab (3 mg/kg) appears to offer a better safety-efficacy balance. Further randomized trials are needed to confirm the optimal dosing strategy.

Conflict of Interests

All the authors declare no conflict of interest..

References

1. Saginala K, Barsouk A et al. Epidemiology of melanoma. Med Sci (Basel). 2021 Oct 20;9(4):63.
2. Ellebaek E, Donia M, Svane IM. Neoadjuvant or perioperative immunotherapy for resectable melanoma: The need for biomarkers. Eur J Cancer. 2025 Feb 25;217:115257.
3. Kuijpers AMJ, van Akkooi ACJ. Neo-adjuvant therapy for metastatic melanoma. Cancers (Basel). 2024 Mar 22;16(7):1247.
4. Bushara O, Tidwell J, Wester JR, Miura J. The current state of neoadjuvant therapy in resectable advanced stage melanoma. Cancers (Basel). 2023 Jun 26;15(13):3344.
5. Blank CU, Lucas MW, Scolyer RA, Van de Wiel BA, Menzies AM et al. Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. N Engl J Med. 2024 Nov 7;391(18):1696-1708.
6. Menzies AM, Amaria RN, Rozeman EA et al. Pathological response and survival with neoadjuvant therapy in melanoma: A pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). Nat Med. 2021 Feb;27(2):301-309.
7. Sharon CE, Karakousis GC. Neoadjuvant therapy for resectable melanoma. Clin Exp Metastasis. 2024 Aug;41(4):461-464.
8. Hieken TJ, Kreidieh F, Aedo-Lopez V et al. Neoadjuvant immunotherapy in melanoma: The paradigm shift. Am Soc Clin Oncol Educ Book. 2023 Jan;43:e390614.
9. Reijers ILM, Menzies AM, van Akkooi ACJ et al. Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and

nivolumab in high-risk stage III melanoma: the PRADO trial. Nat Med. 2022 Jun;28(6):1178-1188.
10. Silva MJ, Tavares MC, Lima JPSN, et al. Analysis of neoadjuvant nivolumab and ipilimumab for clinical stage III melanoma using the SWOG S1801 event-free survival definition. J Clin Oncol. 2024;42(16_suppl):e21563.
11. Rozeman EA, Menzies AM, van Akkooi AC et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): A multicentre, phase 2, randomised, controlled trial. The lancet oncology. 2019;20(7):948–60.
12. Rozeman EA, Hoefsmit EP, Reijers ILM et al. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med. 2021 Feb;27(2):256–63.
13. Versluis JM, Menzies AM et al Survival update of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma in the OpACIN and OpACIN-neo trials. Ann Oncol. 2023 Apr;34(4):420-430.
14. Blank CU, Rozeman EA et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018 Nov;24(11):1655-1661.
15. Coutzac C, Adam J, Soularue E, et al. Colon immune-related adverse events: anti-CTLA-4 and anti-PD-1 blockade induce distinct immunopathological entities. J Crohns Colitis. 2017;11:1238–1246.
16. Wolchok JD, Chiarion-Sileni V et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017 Oct 5;377(14):1345-1356. doi: 10.1056/NEJMoa1709684. Epub 2017 Sep 11. Erratum in: N Engl J Med. 2018 Nov 29;379(22):218.