

BRIEF REPORT



## Nivolumab plus ipilimumab in metastatic uveal melanoma: a real-life, retrospective cohort of 47 patients

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### ABSTRACT

Although combined PD-1/CTLA-4 inhibition showed limited efficacy in single-arm, phase II trials in metastatic uveal melanoma (mUM), such combination appears frequently used in mUM patients. We here report our experience with nivolumab/ipilimumab in mUM. A retrospective cohort of 47 mUM patients, 24 men and 23 women, received nivolumab/ipilimumab between October 2019 and December 2021, mostly first line (94%). Two regimens were used: nivolumab 1 mg/kg + ipilimumab 3 mg/kg (nivo1ipi3, 49% of patients) and nivolumab 3 mg/kg + ipilimumab 1 mg/kg (nivo3ipi1, 51% of patients). Median follow-up was 37 and 88 weeks in nivo3ipi1 and nivo1ipi3 cohorts, respectively. We observed partial response in two patients (4%) and stable disease in 14 patients (30%), with no significant difference between the two regimens. Median progression-free survival was 13.6 weeks and 11.9 weeks in the nivo1ipi3 and nivo3ipi1 cohorts, respectively ( $p = 0.49$ ). Severe adverse events (grade 3 or 4) were observed in seven patients (15%) among which five treated with nivo1ipi3 (22%) and two treated with nivo3ipi1 (8%). These data suggest that nivolumab/ipilimumab combination does not improve clinical outcomes compared to other therapies but is more toxic. In the absence of controlled clinical trials, we would not recommend this combination as a standard treatment in all mUM patients but rather as an option. Patients for whom the benefit–risk ratio could justify the combination need to be defined.

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## Introduction

Uveal melanoma (UM) is the most frequent primary intraocular malignancy in adults. Metastases occur in one-third to half of UM patients, predominantly in the liver.<sup>1</sup> Once metastatic, UM is associated with poor prognosis, with a median overall survival (OS) of 12–16 months.<sup>2,3</sup> Alkylating agents have been the main therapeutic option for the last decades. More recently, immune checkpoint inhibitors (ICI) such as nivolumab or pembrolizumab have been used, but overall response rate (ORR) is usually less than 5%, and no benefit on survival has been reported.<sup>4,5</sup> Very recently, tebentafusp, a bispecific T-cell engager that redirects the cells toward gp100-positive melanocytes, has become the standard of care for HLA-A02:01-positive metastatic patients where available.<sup>2</sup> However, there is currently no standard of care neither for HLA-A02:01-positive patients who progress on tebentafusp nor for HLA-A02:01-negative metastatic patient in first line.

Combined PD-1/CTLA-4 inhibition showed a significantly enhanced efficacy in metastatic skin melanoma patients and other cancer types compared to each monotherapy individually.<sup>6–8</sup> Given these encouraging results, the combination has been tested in UM as well. Modest clinical activity was reported in two single-arm phase II trials and in two

retrospective studies,<sup>9–12</sup> with ORR between 12% and 18% (Table 1). Median progression-free survival (PFS) ranged from 2.7 to 3.0 months in most studies<sup>9,10,12</sup> although Pelster *et al.* reported a median PFS of 5.5 months.<sup>11</sup> OS were comparable to recent historical series including the standard arm of the IMCgp100-202 study, ranging from 15.1 to 19.1 months.<sup>9–12</sup> This modest clinical activity came at the price of important toxicities with grade 3/4 adverse events in up to 58% of patients. Due to the high risk of grade 3–4 toxicities and in the absence of comparative study, use of the nivolumab–ipilimumab combination remains controversial in mUM. In this study, we present clinical outcomes of 47 metastatic UM patients treated with the combination of nivolumab and ipilimumab at Institut Curie, a reference center for UM.

## Materials and methods

We retrospectively identified patients who received combined treatment with nivolumab and ipilimumab for the treatment of unresectable mUM at Institut Curie, Paris, France. Informed consent was obtained from all individual participants included in the study. This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by

**Table 1.** Studies investigating the nivolumab/ipilimumab combination in metastatic uveal melanoma patients.

	Type of study	Nb pts	nivo1ipi3	nivo3ipi1	ipi1pembro2	FU (weeks)	ORR	PFS (months)	OS (months)	SAE
Heppt <sup>9</sup>	Retrospective cohort	64	59 (92.2%)	0 (0%)	5 (7.8%)	40.0 [33.9–46.11]	15.6%	3.0 [2.4–3.6]	16.1 [12.9–19.3]	39.1%
Najjar <sup>10</sup>	Retrospective cohort	89	89 (100%)	0 (0%)	0 (0%)	40.0	11.6%	2.7 [2.6–3.3]	15 [10.9–20.6]	30%
Pelster <sup>11</sup>	Phase II trial, single-arm	33	33 (100%)	0 (0%)	0 (0%)	56.6 [5.7–189.2]	18%	5.5 [3.4–9.5]	19.1 [9.6–NR]	40%
Piulats <sup>12</sup>	Phase II trial, single-arm	52	52 (100%)	0 (0%)	0 (0%)	58.3 [3.5–153.1]	11.5%	3.0 [2.0–4.1]	12.7 [7.1–18.3]	57.7%
Salaün	Retrospective cohort	47	23 (49%)	24 (51%)	0 (0%)	42.9 [38.9–51.3]	4%	2.9 [2.6–3.8]	14.9 [12.4 –NR]	14.9%

Nb pts: number of patients.

SAE: severe adverse events grade 3 or 4.

the Internal Review Board of Institut Curie, Paris, France (reference: OBS160034). ORR was defined as the best response according to RECIST 1.1 criteria; clinical benefit was defined as the sum of complete response, partial response, and stable disease after four cycles of treatment (12 weeks). PFS was defined as the time between the start of the nivolumab–ipilimumab combination and the date of progression, relapse, death, or last news, whichever occurred first. OS was defined as the time between the start of the nivolumab–ipilimumab combination and death or last news. Median follow-up was estimated with the reverse Kaplan–Meier method. Differences between groups were tested with Fisher’s test for qualitative variables. PFS and OS were estimated by the Kaplan–Meier method. For the calculation of PFS, patients without any event were censored at the date of last news; for the calculation of OS, patients still alive were censored at the date of last news. The survival data were compared with a log-rank test. Adverse events were assessed according NCI CTCAE version 4.03. All statistical tests were two-sided, and *p*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using R® software.

## Results

This retrospective study included consecutive patients who initiated treatment with nivolumab and ipilimumab for the treatment of unresectable mUM between October 2019 and December 2021. Patients’ characteristics are presented in Table 2 and were balanced. A total of 47 patients were included among which were 24 men (51%) and 23 women (49%). Median age at mUM diagnosis was 59 y old [49–64]. Among these 47 patients, 46 presented hepatic metastases

(98%). Nivolumab + ipilimumab was administered in first line in 44 patients (94%; no liver-directed therapy except liver surgeries) and in third line in three patients (6%). Patients in third-line treatment previously received pembrolizumab and fotemustine for two patients (one patient in nivo1ipi3 and one patient in nivo3ipi1 group) and dacarbazine and nivolumab for one patients in nivo1ipi3 group. After four combined infusions of nivolumab and ipilimumab, nivolumab was continued alone if disease was stable or in response and in case of no toxicities. Because the combination of nivolumab 1 mg/kg + ipilimumab 3 mg/kg (nivo1ipi3) was deemed too toxic after treating the first 23 patients, most of the following ones since late 2020 were initiated at nivolumab 3 mg/kg + ipilimumab 1 mg/kg (nivo3ipi1) in accordance with the results of the Checkmate 511 trial reporting diminished toxicity but similar clinical benefit with nivo3ipi1 regimen in skin melanoma patients.<sup>13</sup> Administration regimen was nivo3ipi1 for 24 patients (51%) and nivo1ipi3 for 23 patients (49%).

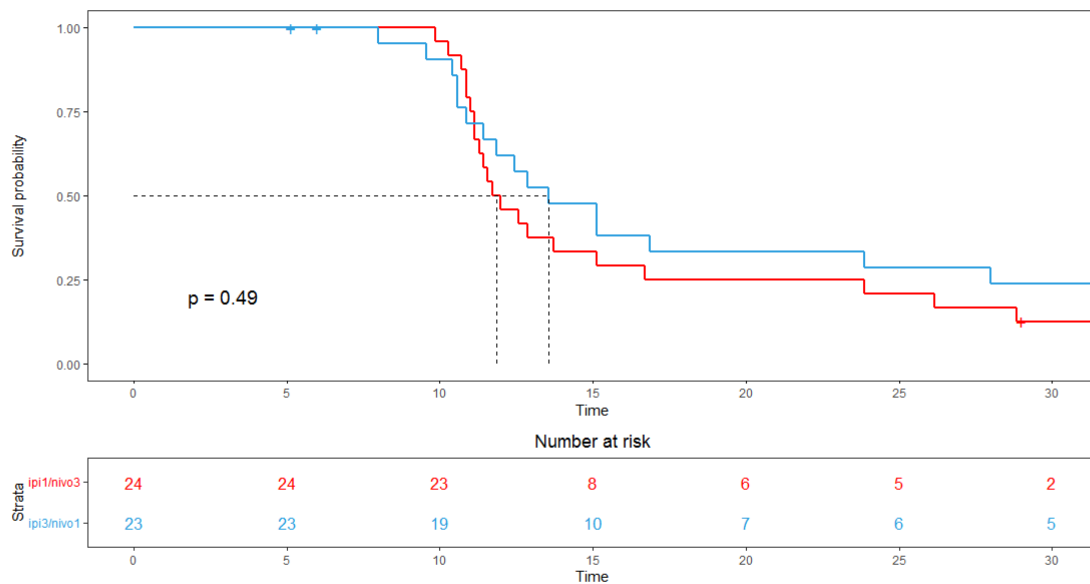
We observed two partial responses (4%), both with nivo1ipi3 treatment (9% in the nivo1ipi3 cohort). Both patients had metastatic choroid melanomas with disomies 3 and 8q gains and are still on nivolumab maintenance, 2 y after starting the combination. Stable disease was observed for 14 patients (30%) including eight patients in the nivo3ipi1 cohort (33%) and six patients in the nivo1ipi3 cohort (27%). Altogether, these combinations were associated with similar clinical benefit (defined as rate of responses plus stable diseases): 33% and 36% in the nivo3ipi1 and nivo1ipi3 cohorts, respectively (Fisher’s exact test *p*-value = 1). Median follow-up was 37 and 88 weeks in the nivo3ipi1 and nivo1ipi3 cohorts, respectively. Median

**Table 2.** Patient characteristics.

	Total	Nivolumab 3 +ipilimumab 1	Nivolumab 1 + ipilimumab 3	<i>p</i>
Patients	47	24 (51%)	23 (49%)	
Men	24 (51%)	16 (67%)	8 (35%)	0.3
Women	23 (49%)	8 (33%)	15 (65%)	0.2
Median age (years old)	59 [49–64]	61 [55–64]	55 [46–63]	0.09
Enucleation	27 (57%)	13 (54%)	14 (61%)	1
Performance status 0	39 (83%)	19 (79%)	20 (87%)	1
Performance status 1	8 (17%)	5 (21%)	3 (13%)	0.7
LDH > upper limit of normal <sup>a</sup>	10 (21%)	7 (29%)	3 (13%)	0.3
LDH < upper limit of normal <sup>a</sup>	27 (58%)	14 (48%)	13 (47%)	1
Hepatic metastases	46 (98%)	24 (100%)	22 (96%)	1
Other metastatic sites	11 (23%)	7 (29%)	4 (17%)	0.5
First-line treatment	44 (94%)	23 (96%)	21 (91%)	1
Third-line treatment	3 (6%)	1 (4%)	2 (9%)	1

<sup>a</sup>LDH was unknown for 10 patients (21%): three patients receiving nivo3ipi1 (13%) and seven patients receiving nivo1ipi3 (30%).

*p*-Values were calculated with Mann–Whitney test for qualitative variable (median age) and with Fisher’s test for quantitative variable (other variables).



**Figure 1.** Progression-free survival (in weeks) in metastatic uveal melanoma patients treated with either nivolumab 1 mg/kg + ipilimumab 3 mg/kg (blue line) or nivolumab 3 mg/kg + ipilimumab 1 mg/kg (red line).

PFS was 12.6 weeks in the whole cohort. Median PFS was 11.9 weeks in the nivo3ipi1 cohort compared to 13.6 weeks in the nivo1ipi3 cohort (log-rank  $p$ -value = 0.49; Figure 1). OS at 37 weeks (corresponding to the median follow-up of the nivo3ipi1 group) was 81% in the whole cohort, but survivals were not compared between the two dosing groups as the follow-up was too short. Severe adverse events (grade 3 or 4) were observed in seven patients (15%) including two who were treated with nivo3ipi1 (9%) and five who were treated with nivo1ipi3 (22%, Fisher's exact  $p$ -value = 0.24) confirming the better tolerance of the nivo3ipi1 regimen. Severe adverse events consisted in liver, endocrine, and dermatological adverse events for two patients and colitis, myositis, and polyarthritis in one patient. Two patients experienced both skin and liver adverse events, requiring treatment discontinuation. Two patients experienced partial response to nivolumab–ipilimumab treatment; both had prolonged response with PFS of 12 and 20 months. The patient with the 20-month PFS was the only patient in the whole cohort without hepatic metastasis (only lung metastases).

## Discussion

In our experience, double immune checkpoint inhibition with nivolumab and ipilimumab in real life resulted in a lower response rate (4.3%) than previous combination studies.<sup>9–12</sup> In fact, this low response rate is comparable to the one observed with ICI monotherapy, including in a recently published cohort of 300 patients treated in our institution (4.0% response rate).<sup>5,6,9,10,12,14</sup> In contrast, median PFS was similar, but when clinical benefit rate is of 50% or less, median PFS then corresponds to the delay to the first radiological assessment and varies according to the frequency of imaging and not to the response rate. The fact that we frequently observe lower response rates in our institution than in literature probably derives from the fact that we almost systematically assess tumor

burden with liver MRI (including diffusion-weighted sequences and use of gadolinium-based agents) in this disease, a more specific and sensitive modality than CT.<sup>15</sup> Response rate differences may not only be influenced by patient and tumor characteristics but also by dosing regimens as half of our patients received nivo1ipi3 and the other half nivo3ipi1 regimen. However, numbers are too low to directly compare the efficacy in these two groups (two responder patients *versus* none). Furthermore, if the ipi3nivo1 combination was superior to the ipi1nivo3, we would expect a higher rate of stable disease and, consequently, a higher rate of patients deriving a clinical benefit. Nevertheless, the rate of clinical benefit was exactly the same in both groups. This observation is in line with the CheckMate 511 trial, which showed similar efficacy of the two regimens in skin melanoma patients in response rate (45.6% in the nivo3ipi1 versus 50.6% in the nivo1ipi3;  $p$  = .35) as well as in median PFS (9.92 months versus 8.94 months; HR = 1.06, 95% CI = 0.79–1.42).<sup>13</sup> In fact and in line with CheckMate 511, which showed a significant increase in treatment-related grade 3–5 adverse events with nivo1ipi3 (48%) *versus* nivo3ipi1 (34%;  $p$  = 0.006), there was a trend for less severe adverse events with the nivo3ipi1 regimen in our series. Understanding the underlying mechanisms implicated in response to immune checkpoint inhibitors in UM remains an important field of research. Compared to skin melanoma, UM carries a more than tenfold lower somatic mutation burden, limiting the number of immunogenic neoepitopes and, subsequently, chances to generate an immune response.<sup>16,17</sup> Strong hepatotropism is another characteristic of metastatic UM that may participate to this low immune response as liver environment is known to be associated with colder tumors and lower response rates to ICI.<sup>18</sup> In this sense, the patient with the most prolonged response to the combination was the only one in this cohort not having liver metastases when the treatment was debuted. In conclusion, the data presented here, although monocentric and retrospective with all

the inherent biases of such series, do not support a wide use of nivolumab/ipilimumab combination as standard treatment in metastatic UM patients. Moreover, a significant fraction of patients experienced important toxicities, even when using the nivo3ipi1 regimen, interfering with their quality of life, if not life threatening. In the absence of a controlled clinical trial demonstrating a superior efficacy of the combination over monotherapy, we would not recommend this combination as a standard treatment in metastatic UM patients. Patient subgroups for which the risk–benefit ratio could justify this combo are to be defined in future works.

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## Abbreviations

ICI: immune checkpoint inhibitors; UM: metastatic uveal melanoma; MRI: magnetic resonance imaging; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; UM: uveal melanoma











## Disclosure statement

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## Author contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by Hélène Salaün, Mathilde Saint-Ghislain, and Agathe Garcia. The first draft of the manuscript was written by Manuel Rodrigues, Hélène Salaün, and Leanne de Koning. All authors read and approved the final manuscript.

## Ethics approval

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Internal Review Board of Institut Curie, Paris, France (reference: OBS160034).

## Consent to participate

Informed consent was obtained from all individual participants included in the study.

## Data availability statement

The data that support the findings of this study are available on request from the corresponding author, M.R. The data are not publicly available due to restrictions related to the privacy of the patients.

## References

- Jager MJ, Shields CL, Cebulla CM, Abdel-Rahman MH, Grossniklaus HE, Stern MH, Carvajal RD, Belfort RN, Jia R, Shields JA, et al. Uveal melanoma. *Nat Rev Dis Primer.* 9 avr 2020 6: 1. 125.
- Nathan P, Hassel JC, Rutkowski P, Baurain J-F, Butler MO, Schlaak M, Sullivan RJ, Ochsenreither S, Dummer R, Kirkwood JM, et al. Overall survival benefit with tebentafusp in metastatic uveal melanoma. *N Engl J Med.* 23 sept 2021, 385 (13):1196206. doi:10.1056/NEJMoa2103485.
- Khoja L, Atenafu EG, Suciú S, Leyvraz S, Sato T, Marshall E, Keilholz U, Zimmer L, Patel SP, Piperno-Neumann S, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. *Ann Oncol Off J Eur Soc Med Oncol.* 1 août 2019 30: 8. 137080.
- Heppt MV, Steeb T, Schlager JG, Rosumeck S, Dressler C, Ruzicka T, Nast A, Berking C. Immune checkpoint blockade for unresectable or metastatic uveal melanoma: a systematic review. *Cancer Treat Rev.* 2017 nov;60:44-52. doi:10.1016/j.ctrv.2017.08.009.
- Rossi E, Pagliara MM, Orteschi D, Dosa T, Sammarco MG, Caputo CG, Petrone G, Rindi G, Zollino M, Blasi MA, et al. Pembrolizumab as first-line treatment for metastatic uveal melanoma. *Cancer Immunol Immunother CII.* 2019;68 (7):1179–1185. juill. doi:10.1007/s00262-019-02352-6.
- Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob -J-J, Rutkowski P, Cowey CL, Lao CD, Schadendorf D, Wagstaff J, Dummer R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol.* 2018 nov;19(11):1480–1192. doi:10.1016/S1470-2045(18)30700-9.
- Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med.* 21 nov 2019, 381 (21):2020–1131. doi:10.1056/NEJMoa1910231.
- Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med.* 2018 avr 5;378 (14):1277–1190. doi:10.1056/NEJMoa1712126.
- Heppt MV, Amaral T, Kähler KC, Heinzerling L, Hassel JC, Meer M, Kreuzberg N, Loquai C, Reinhardt L, Utikal J, et al. Combined immune checkpoint blockade for metastatic uveal melanoma: a retrospective, multi-center study. *J Immunother Cancer.* 13 nov 2019, 7(1):299. doi:10.1186/s40425-019-0800-0.
- Najjar YG, Navrazhina K, Ding F, Bhatia R, Tsai K, Abbate K, Durden B, Eroglu Z, Bhatia S, Park S, et al. Ipilimumab plus nivolumab for patients with metastatic uveal melanoma:

- a multicenter, retrospective study. *J Immunother Cancer*. Juin. 2020;8(1):e000331. doi:10.1136/jitc-2019-000331.
11. Pelster MS, Gruschkus SK, Bassett R, Gombos DS, Shephard M, Posada L, Glover MS, Simien R, Diab A, Hwu P, et al. Nivolumab and ipilimumab in metastatic uveal melanoma: results from a single-arm phase ii study. *J Clin Oncol Off J Am Soc Clin Oncol*. 2021 févr 20;39(6):599-607. doi:10.1200/JCO.20.00605.
  12. Piulats JM, Espinosa E, de la Cruz Merino L, Varela M, Alonso Carrión L, Martín-Algarra S, López Castro R, Curiel T, Rodríguez-Abreu D, Redrado M, et al. Nivolumab plus ipilimumab for treatment-naïve metastatic uveal melanoma: an open-label, multicenter, phase II trial by the spanish multidisciplinary Melanoma group (GEM-1402). *J Clin Oncol Off J Am Soc Clin Oncol*. 2021 févr 20;39(6):586-98. doi:10.1200/JCO.20.00550.
  13. Lebbé C, Meyer N, Mortier L, Marquez-Rodas I, Robert C, Rutkowski P, Menzies AM, Eigentler T, Ascierto PA, Smylie M, et al. Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: results from the phase IIIb/IV checkMate 511 Trial. *J Clin Oncol Off J Am Soc Clin Oncol*. 2019 avr 10;37(11):867-75. doi:10.1200/JCO.18.01998.
  14. Saint-Ghislain M, Derrien AC, Geoffrois L, Gastaud L, Lesimple T, Negrier S, Penel N, Kurtz JE, Le Corre Y, Dutriaux C, et al. MBD4 deficiency is predictive of response to immune checkpoint inhibitors in metastatic uveal melanoma patients. *Eur J Cancer Oxf Engl*. 1990. 18 1990 2022. 173: 10512.
  15. Balasubramanya R, Selvarajan SK, Cox M, Joshi G, Deshmukh S, Mitchell DG, O'Kane P. Imaging of ocular melanoma metastasis. *Br J Radiol*. 2016 sept;89(1065):20160092. doi:10.1259/bjr.20160092.
  16. Robertson AG, Shih J, Yau C, Gibb EA, Oba J, Mungall KL, Hess JM, Uzunangelov V, Walter V, Danilova L, et al. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. *Cancer Cell*. 2017 août 14;32(2):204-220.e15. doi:10.1016/j.ccell.2017.07.003.
  17. Rodrigues M, Mobuchon L, Houy A, Alsafadi S, Baulande S, Mariani O, Marande B, Ait Rais K, Van der Kooij MK, Kapiteijn E, et al. Evolutionary routes in metastatic uveal melanomas depend on MBD4 alterations. *Clin Cancer Res Off J Am Assoc Cancer Res*. 15 sept 2019, 25(18):5513-1124. doi:10.1158/1078-0432.CCR-19-1215.
  18. Yu J, Green MD, Li S, Sun Y, Journey SN, Choi JE, Rizvi SM, Qin A, Waninger JJ, Lang X, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med*. janv. 2021;27(1):152-64.