

Running title: Neuroimmune treatment of advanced solid tumors

Neuroimmune treatment of advanced solid tumors: 3-year survival after angiotensin 1-7, pineal indoles, and cannabinoids

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In a recent study, the exogenous administration of angiotensin 1-7 (Ang 1,7) together with melatonin, 5-methoxytryptamine, and cannabidiol increased 1-year survival in advanced cancer patients, underlining the utility of neuromodulation in oncology. We now report a single-arm interventional study to evaluate the effectiveness of introducing Ang 1-7 in the neuroimmune regime, including pineal indoles and cannabinoids. Two cohorts of patients with advanced solid tumors refractory to standard oncologic treatments and with an estimated life expectancy of less than six months were studied. The full neuroimmune regimen cohort consisted of 100 consecutive patients treated over the last three years with Ang 1-7, pineal indoles, and cannabinoids, while the comparator cohort included 212 consecutive patients treated between 2015 and 2019 with pineal indoles and cannabinoids alone. Gastroprotected capsules of Ang 1-7 coupled with cyclodextrin were administered at 0.5 mg p.o. twice/day. Melatonin (100 mg) and 5-methoxytryptamine (20 mg) were given p.o. at bedtime and in the early afternoon, respectively. Cannabidiol or cannabigerol (in the case of glioblastoma) was given at 20 mg p.o. twice/day. Clinical response, disease control, and overall survival, along with the lymphocyte-to-monocyte ratio, were evaluated. In the full regimen cohort, disease control was achieved in 67 of 100 patients, with objective tumor regression observed in 23%. In the comparator cohort, disease control was obtained in 111 of 212 patients, with objective regression in 8%. Three-year overall survival was significantly higher in the full regimen cohort (37%) compared with the comparator cohort (19%). Both treatments were associated with a significant increase in the lymphocyte-to-monocyte ratio, suggesting an improvement in systemic immune status. The addition of Ang 1-7 to a neuroimmune regimen combining pineal indoles and cannabinoids was associated with improved disease control and long-term survival in patients with end-stage solid tumors lacking effective therapeutic options.

Key words: angiotensin 1-7; cancer; cannabinoids; melatonin; 5-methoxytryptamine; supportive care

Angiotensin 1-7 (Ang 1-7) is a heptapeptide produced by the angiotensin converting enzyme (ACE) as an essential component of the renin-angiotensin system [1-4]. While the ACE1 product

52 angiotensin II, acting via the angiotensin type 1 receptor, promotes vasoconstriction, inflammation,
53 cell proliferation, and angiogenesis (all factors that enhance tumor development), Ang 1-7 largely
54 counteracts these effects via the Mas receptor [1, 2, 5, 6]. In essence, Ang 1-7 works as a natural
55 brake for angiotensin II: it leads to vasodilation, dampens inflammatory signals, and, critically,
56 exerts anti-proliferative and anti-angiogenic influences that may interfere with tumor growth and
57 progression.

58 At the cellular level, Ang 1-7 inhibits key processes in cancer biology [2, 3, 7, 8]. For example,
59 tumors require the formation of new blood vessels (angiogenesis) to secure nutrients, and Ang 1-7
60 has been observed to downregulate proangiogenic factors like vascular endothelial growth factor [9]
61 This reduction in neovascularization not only limits the tumor's blood supply but also disrupts the
62 microenvironment that otherwise favors cancer cell survival and metastasis. In certain animal
63 models, such as those of lung and prostate cancers, administration of Ang 1-7 correlated with a
64 noticeable decrease in tumor size and spread, suggesting a direct anti-tumor effect [10-12].

65 Beyond its direct influence on tumor cells, Ang 1-7 also appears to modulate the tumor
66 microenvironment [2, 3]. In many cancers, the interplay between inflammatory mediators, stromal
67 cells, and immune cells creates a niche that supports tumor development. By reducing local
68 inflammation and influencing extracellular matrix remodeling, Ang 1-7 helps shift this balance [13,
69 14]. The peptide's actions can render the tumor's surroundings less amenable to growth and
70 dissemination, opening the possibility of using it in combination with conventional therapies (like
71 chemotherapy or radiotherapy) to potentially enhance treatment outcomes.

72 In a recent study the exogenous administration of Ang 1-7 together with two main components of
73 the endogenous anticancer network, i.e. pineal indoles (melatonin and 5-methoxytryptamine) and
74 endocannabinoids, prolonged the 1-year survival in advanced cancer patients [15]. To assess the
75 importance of Ang 1-7 in this neuroimmune regimen we now report the 3-year survival in 100
76 patients receiving the full regimen of Ang 1-7, pineal indoles and cannabinoids as compared to that
77 of 212 patients who received the pineal indoles / cannabinoids comparator regimen or to a historical
78 control receiving Best Supportive Care (BSC) alone. All groups included advanced solid tumor
79 patients, who failed to respond to the standard antitumor treatments and with life expectancy less
80 than 6 months.

81

82 **Patients and methods**

83 **Study design.** This was an interventional, non-randomized, controlled clinical study designed to
84 evaluate whether the addition of Ang 1-7 to a neuroimmune regimen combining pineal indoles and
85 cannabinoids was associated with improved clinical outcomes in patients with advanced solid

86 tumors. Given the absence of effective standard oncologic options in the study population, the
87 analysis was explicitly framed as exploratory and associative.

88 Three patient groups were evaluated: A) a cohort treated with the full neuroimmune regimen
89 including Ang 1-7, pineal indoles, and cannabinoids; B) a comparator cohort treated with pineal
90 indoles and cannabinoids alone; and C) a historical control group treated with best supportive care
91 (BSC) only.

92 **Patients.** Eligible patients had histologically confirmed solid tumors with measurable disease
93 according to WHO criteria and had progressed after standard oncologic therapies or were deemed
94 unsuitable for further antitumor treatment. All patients had an estimated life expectancy of less than
95 six months at study entry.

96 Eligibility criteria included: 1) measurable disease documented by computed tomography (CT),
97 magnetic resonance imaging (MRI), or positron emission tomography (PET); 2) lack of response or
98 progression after standard treatments, including chemotherapy, endocrine therapy, anti-angiogenic
99 agents, targeted therapies, or immunotherapies; 3) no concomitant use of other complementary or
100 alternative anticancer therapies.

101 Patients were considered untreatable according to conventional oncologic strategies after at least
102 three lines of chemotherapy for breast, colorectal, and ovarian cancers, or at least two lines for other
103 tumor types, including lung, gastric, pancreatic, biliary tract, bladder, and brain tumors. Progression
104 under immunotherapy or targeted therapy was also required where applicable.

105 Patients receiving chronic treatment with pregabalin were excluded due to its inhibitory effect on
106 Ang 1-7 activity. Patients requiring opioid therapy for pain management were excluded if treated
107 with fentanyl or other major immunosuppressive opioids. When opioid analgesia was required, only
108 agents with minimal immunosuppressive effects, such as oxycodone or hydromorphone, were
109 permitted.

110 **Treatment regimes.** All treatments were administered orally and supplied by the same
111 manufacturer (San Ruffino Laboratory, Smerillo, Italy). In Group A (full neuroimmune regimen),
112 patients received Ang 1-7 at a dose of 0.5 mg twice daily. To enhance oral bioavailability and
113 protect the peptide from gastric degradation, Ang 1-7 was administered as a supramolecular
114 inclusion complex with β -cyclodextrin.

115 Melatonin was administered at a target dose of 100 mg/day at bedtime. To minimize initial adverse
116 effects, treatment was initiated at 20 mg/day and escalated to the target dose within the first week.
117 Five-methoxytryptamine was administered orally at a dose of 20 mg/day in the early afternoon.
118 Cannabidiol was administered at a dose of 20 mg twice daily. In patients with glioblastoma,
119 cannabigerol was used instead of cannabidiol at the same dosage.

120 Group B patients received the same regimen of pineal indoles and cannabinoids without Ang 1-7.
121 Group C patients received best supportive care alone. Treatment was continued without interruption
122 until radiological or clinical evidence of disease progression.

123 **Clinical evaluation and response assessment.** Baseline clinical and radiological assessments were
124 performed prior to treatment initiation. Tumor response was evaluated every three months using
125 CT, MRI, or PET, depending on tumor type and disease localization.

126 Clinical responses were classified according to WHO criteria as complete response, partial
127 response, stable disease, or progressive disease. Disease control was defined as the achievement of
128 complete response, partial response, or stable disease.

129 **Immune biomarker assessment.** Peripheral blood lymphocyte-to-monocyte ratio (LMR) was
130 evaluated as a predefined biomarker of systemic immune status. LMR was calculated from routine
131 blood counts obtained at baseline and during follow-up. Based on laboratory reference values, low
132 baseline LMR was defined a priori as a value below 2.1. Associations between baseline LMR, LMR
133 normalization during treatment, and clinical outcomes were explored.

134 **Statistical analysis.** Continuous variables were summarized as medians and ranges, while
135 categorical variables were reported as absolute numbers and percentages. Comparisons between
136 groups for categorical outcomes, including disease control and objective response rates, were
137 performed using the Chi-square test or Fisher's exact test, as appropriate.

138 Overall survival (OS) was defined as the time from initiation of the neuroimmune treatment to
139 death from any cause or last follow-up. Survival curves were compared between treatment groups
140 using the log-rank test.

141 Given the non-randomized design and the use of historical comparator cohorts, exploratory Cox
142 proportional hazards regression models were constructed to estimate hazard ratios (HRs) and 95%
143 confidence intervals (CIs) for overall survival. Treatment group (Ang 1-7-containing regimen vs.
144 pineal indoles plus cannabinoids regimen) was included as the primary covariate. Multivariable
145 models were adjusted, where data completeness allowed, for clinically relevant baseline factors,
146 including age, sex, tumor type (glioblastoma vs. non-glioblastoma), disease extension (locally
147 advanced vs. metastatic), and baseline LMR.

148 The proportional hazards assumption was assessed graphically by Schoenfeld residuals. Owing to
149 the exploratory nature of the study, regression models were intentionally parsimonious and aimed at
150 identifying clinically meaningful associations rather than establishing causality.

151 LMR was analyzed as a predefined prognostic biomarker based on its established relevance in
152 advanced cancer. Low LMR was defined a priori as values below the lower limit of normal
153 observed in our laboratory (< 2.1). Associations between baseline LMR and clinical outcome

154 (disease control vs progression) were assessed using contingency-table analysis, odds ratios, and
155 Chi-square testing.

156 Exploratory analyses evaluated whether normalization of LMR during treatment was associated
157 with improved clinical outcome. Interaction analyses between treatment group and baseline LMR
158 were considered hypothesis-generating.

159 All statistical tests were two-sided, and a p -value < 0.05 was considered statistically significant.
160 Statistical analyses were performed using standard statistical software.

161 **Institutional review board statement.** Study was approved by the local Ethical Committee of the
162 Institute of Biological Medicine: acta no. 01/10, dated February 1, 2020, for the full regimen; acta
163 no. 4, dated January 10, 2015 for the comparator group. The clinical protocol was explained to each
164 patient and his/her relatives, and a written consent was obtained. All procedures were conducted in
165 accordance with the Declaration of Helsinki.

166

167 **Results**

168 **Clinical response and disease control.** Clinical responses according to WHO criteria are
169 summarized in Table 1. In the group treated with the full neuroimmune regimen including Ang 1-7
170 (Group A), complete response was achieved in 5 patients (5%), while partial response was observed
171 in 18 patients, resulting in an objective tumor regression rate of 23%. Stable disease was
172 documented in 44 patients, yielding an overall disease control rate of 67%. The median duration of
173 disease control in this group was 18 months (range 6-36 months).

174 In the comparator group treated with pineal indoles and cannabinoids alone (Group B), complete
175 response occurred in 2 patients (1%) and partial response in 14 patients, for an objective tumor
176 regression rate of 8%. Stable disease was observed in 95 patients, resulting in an overall disease
177 control rate of 52%. The median duration of disease control was 13 months (range 4-35 months).

178 The disease control rate achieved with the Ang 1-7-containing regimen was significantly higher
179 than that observed in the comparator group (67% vs. 52%, $p < 0.02$, Chi-square test).

180 **Overall survival.** At a median follow-up of 36 months, overall survival differed significantly
181 among treatment groups. Three-year overall survival was achieved in 37% of patients treated with
182 the full neuroimmune regimen including Ang 1-7, compared with 19% of patients treated with
183 pineal indoles and cannabinoids alone. Survival outcomes in both treated groups were superior to
184 those observed in the historical control group receiving best supportive care only. Percent overall
185 survival at predefined time points analysis demonstrated a significant separation of survival curves
186 in favor of the Ang 1-7-containing regimen (log-rank test, $p < 0.01$) (Figure 1).

187 In exploratory Cox proportional hazards regression analysis, treatment with Ang 1-7 was associated
188 with a clinically meaningful reduction in the risk of death compared with the comparator regimen.
189 This association remained consistent after adjustment for age, sex, tumor type, disease extension,
190 and baseline LMR, supporting the robustness of the observed survival signal despite the non-
191 randomized study design (Table 2).

192 **Lymphocyte-to-monocyte ratio and clinical outcome.** Baseline LMR showed a strong prognostic
193 association with clinical outcome in both treatment groups (Table 3). Patients with low pretreatment
194 LMR values exhibited significantly higher odds of disease progression compared with those with
195 normal LMR, both in the Ang 1-7-containing regimen and in the comparator regimen.

196 In exploratory analyses, normalization of LMR during treatment was associated with improved
197 disease control. This association reached statistical significance in the comparator group and
198 showed a favorable trend in the Ang 1-7 group, although the latter did not reach statistical
199 significance, likely due to limited sample size.

200 These findings support the role of LMR as a clinically relevant biomarker of immune competence
201 in patients undergoing neuroimmune modulation and suggest that baseline immune status
202 significantly influences treatment outcomes.

203 **Safety and tolerability.** The neuroimmune treatments were well tolerated in all patients. No
204 clinically relevant biological toxicity was observed, and no significant reductions in blood pressure
205 were recorded following Ang 1-7 administration. Transient headache occurred in approximately 6%
206 of patients during initiation of melatonin therapy.

207 Most patients reported subjective improvement in general well-being, including reduced pain,
208 anxiety, and asthenia, along with improved mood and sleep quality.

209

210 Discussion

211 The present study provides clinically relevant evidence that the addition of Ang 1-7 to a
212 neuroimmune regimen combining pineal indoles and cannabinoids is associated with a substantial
213 improvement in long-term survival and disease control in patients with advanced solid tumors who
214 have exhausted standard oncologic options. In this heavily pretreated population, characterized by
215 an expected survival of less than six months, the achievement of a 37% three-year overall survival
216 represents a striking and clinically meaningful signal.

217 Recent discoveries in Psycho-Neuroendocrine-Immunology have identified both anti-inflammatory
218 and pro-inflammatory networks in the human body [16, 17] Major anti-inflammatory / anticancer
219 molecules include Ang 1-7 [2, 3, 7, 8], the pineal indoles melatonin and 5-methoxytryptamine
220 (produced during the night and the light period of the day respectively) [18, 19] and

221 endocannabinoids [20, 21] These molecules exert anticancer action through several mechanisms,
222 including direct cytotoxic activity, stimulation of the anticancer immunity, and anti-angiogenic
223 activity. The stimulation of the anticancer immunity is due to stimulation of interleukin (IL)-2
224 production from TH1 lymphocytes by melatonin [22] inhibition of IL-17 secretion by
225 endocannabinoids [23] and inhibition of tumor growth factor-beta production from regulatory T
226 lymphocytes by Ang 1-7 [24] Moreover, these molecules are interconnected by interactive
227 mechanisms, as indicated by the melatonin inhibition of ACE1 and stimulation of ACE2 expression
228 with the consequent enhanced production of Ang 1-7 instead of angiotensin II [25] and the
229 endocannabinoid-mediated stimulation of melatonin secretion from the pineal gland [26].
230 A key observation of this study is the dissociation between systemic immune activation and long-
231 term survival outcomes. Both the Ang 1-7-containing regimen and the comparator regimen were
232 associated with comparable improvements in the LMR, indicating enhancement of systemic
233 immune competence. However, only the group receiving Ang 1-7 demonstrated a marked and
234 durable survival advantage. This finding suggests that Ang 1-7 may exert antitumor effects that
235 extend beyond generalized immune modulation.
236 Mechanistically, Ang 1-7 is known to counterbalance the pro-tumoral effects of angiotensin II
237 through activation of the Mas receptor, leading to inhibition of angiogenesis, attenuation of
238 inflammatory signaling, and suppression of TGF- β -mediated immune tolerance. These actions may
239 directly influence the tumor microenvironment, rendering it less permissive to tumor growth and
240 dissemination. Within the context of a neuroimmune framework that already enhances anticancer
241 immunity through pineal indoles and cannabinoids, Ang 1-7 may therefore represent a critical final
242 regulatory component capable of converting immune activation into durable tumor control.
243 The prognostic role of baseline immune status was further supported by the strong association
244 between low pretreatment LMR and disease progression across both treatment regimens. This
245 observation aligns with previous evidence identifying LMR as a robust marker of host immune
246 competence in advanced malignancies [27]. Although normalization of LMR during treatment was
247 associated with improved clinical outcomes, the survival benefit conferred by Ang 1-7 appeared to
248 be only partially explained by changes in systemic immunity, reinforcing the hypothesis of
249 additional tumor-specific mechanisms of action.
250 From a clinical perspective, the oral administration of Ang 1-7 using a cyclodextrin-based
251 formulation represents a pragmatic and well-tolerated strategy to overcome the peptide's inherent
252 pharmacokinetic limitations. The absence of relevant toxicity, together with the reported
253 improvements in quality of life, underscores the feasibility of integrating this approach into
254 supportive and integrative oncology settings.

255 In many clinical trials, a 3-year overall survival endpoint is used to assess the long-term benefit of
256 treatment. For instance, in studies evaluating therapies for advanced esophageal squamous cell
257 carcinoma, researchers compared the long-term outcomes of patients receiving immunotherapies
258 such as nivolumab; they reported differences in overall survival at the 3-year mark, which provided
259 insights into the durability of the treatment effect [28]. Similarly, in the context of adjuvant therapy
260 for high-risk gastrointestinal stromal tumors, comparing 3-year survival outcomes helped
261 demonstrate that a longer duration of treatment (3 years vs. 1 year) was associated with improved
262 overall survival [29].

263 Moreover, for certain malignancies like metastatic melanoma treated with immuno- oncology
264 agents, survival curves often display a plateau around 3 to 4 years [30]. This pattern suggests that
265 patients who remain progression-free at 3 years may experience a prolonged period of disease
266 control or even potential functional cure. The 3-year mark thus serves as an important landmark, not
267 just statistically but also clinically, to indicate that the treatment has conferred a durable clinical
268 benefit and may predict long-term remission.

269 Taken together, these findings support a conceptual shift in advanced cancer management,
270 emphasizing restoration and modulation of endogenous regulatory networks rather than exclusive
271 reliance on cytotoxic or molecularly targeted strategies. While the present results do not establish
272 causality, they provide compelling proof-of-concept evidence that targeting the ACE2/Ang 1-7 axis
273 within a neuroimmune framework may meaningfully alter the natural history of end-stage solid
274 tumors.

275 This study has several limitations inherent to its non-randomized design and the use of historical
276 comparator cohorts, which introduce the possibility of selection bias, residual confounding, and
277 temporal effects related to changes in supportive care. Consequently, the statistical analyses should
278 be interpreted as exploratory and associative rather than causal.

279 Nevertheless, the magnitude and consistency of the observed survival benefit, its persistence after
280 adjustment for key clinical covariates, and its strong biological plausibility collectively support the
281 robustness of the findings. These results justify prospective randomized clinical trials to formally
282 assess the therapeutic role of Ang 1-7 within neuroimmune oncology strategies.

283 As a conclusion, the integration of Ang 1-7 into a neuroimmune regimen comprising pineal indoles
284 and cannabinoids is associated with a marked improvement in disease control and long-term
285 survival in patients with advanced solid tumors lacking effective therapeutic options. The observed
286 survival advantage, together with favorable immune modulation and excellent tolerability, identifies
287 Ang 1-7 as a promising oncostatic agent within an integrative neuroimmune framework. Although
288 exploratory in nature, these findings provide clinically meaningful proof-of-concept evidence

supporting further prospective evaluation of Ang 1-7-based strategies aimed at restoring endogenous anticancer regulatory networks and achieving durable clinical benefit in advanced-stage disease.

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References

- [1] BADER M, STECKELINGS UM, ALENINA N, SANTOS RAS, FERRARIO CM. Alternative Renin-Angiotensin System. *Hypertension* 2024; 81: 964-976. <https://doi.org/10.1161/HYPERTENSIONAHA.123.21364>
- [2] XU J, FAN J, WU F, HUANG Q, GUO M et al. The ACE2/angiotensin-(1-7)/Mas receptor axis: Pleiotropic roles in cancer. *Front Physiol* 2017; 8: 276. <https://doi.org/10.3389/FPHYS.2017.00276>
- [3] HASSANI B, ATTAR Z, FIROUZABADI N. The renin-angiotensin-aldosterone system (RAAS) signaling pathways and cancer: foes versus allies. *Cancer Cell Int* 2023; 23: 254. <https://doi.org/10.1186/s12935-023-03080-9>
- [4] KHAJEHPOUR S, AGHAZADEH-HABASHI A. Targeting the protective arm of the renin-angiotensin system: Focused on angiotensin-(1-7). *J Pharmacol Exp Ther* 2021; 377: 64-74. <https://doi.org/10.1124/jpet.120.000397>
- [5] MOLAEI A, MOLAEI E, HAYES AW, KARIMI G. Mas receptor: a potential strategy in the management of ischemic cardiovascular diseases. *Cell Cycle* 2023; 22: 1654-1674. <https://doi.org/10.1080/15384101.2023.2228089>
- [6] FORTE BL, SLOSKY LM, ZHANG H, ARNOLD MR, STAATZ WD et al. Angiotensin-(1-7)/Mas receptor as an antinociceptive agent in cancer-induced bone pain. *Pain* 2016; 157: 2709-2721. <https://doi.org/10.1097/j.pain.0000000000000690>
- [7] LIAO Y, ZHANG Y, LI H, HU H, LI M et al. ACE2: the node connecting the lung cancer and COVID-19. *Am J Cancer Res* 2024; 14: 1466-1481. <https://doi.org/10.62347/XJVE4569>
- [8] SIMÕES E SILVA AC, SAMPAIO WO. The Role of Angiotensin-(1-7) in Cancer. In: Santos RAS (Eds.) *Angiotensin-(1-7): A Comprehensive Review*, Cham: Springer International Publishing; 2019, p. 219-229. https://doi.org/10.1007/978-3-030-22696-1_14
- [9] KHANNA P, SOH HJ, CHEN CH, SAXENA R, AMIN S et al. ACE2 abrogates tumor resistance to VEGFR inhibitors suggesting angiotensin-(1-7) as a therapy for clear cell renal cell carcinoma. *Sci Transl Med* 2021; 13: eabc0170. <https://doi.org/10.1126/scitranslmed.abc0170>

- [10] GALLAGHER PE, TALLANT EA. Inhibition of human lung cancer cell growth by angiotensin-(1-7). *Carcinogenesis* 2004; 25: 2045-2052. <https://doi.org/10.1093/CARCIN/BGH236>
- [11] GOTTSCHALK G, KNOX K, ROY A. ACE2: At the crossroad of COVID-19 and lung cancer. *Gene Rep* 2021; 23: 101077. <https://doi.org/10.1016/j.genrep.2021.101077>
- [12] DOMIŃSKA K, OKŁA P, KOWALSKA K, HABROWSKA-GÓRCZYŃSKA DE, URBANEK KA et al. Angiotensin 1–7 modulates molecular and cellular processes central to the pathogenesis of prostate cancer. *Sci Rep* 2018; 8: 15772. <https://doi.org/10.1038/s41598-018-34049-8>
- [13] MALEKI M, ALIBORONI A, KHEIRI A, KAFFASHIAN MR, KHEIRY M. Association of the ACE2-Angiotensin1-7-Mas axis with lung damage caused by cigarette smoke exposure: a systematic review. *Rev Environ Health* 2024; 39: 755-763. <https://doi.org/10.1515/reveh-2023-0028>
- [14] PEH HY, CHEN J. Pro-resolving lipid mediators and therapeutic innovations in resolution of inflammation. *Pharmacol Ther* 2025; 265: 108753. <https://doi.org/10.1016/j.pharmthera.2024.108753>
- [15] LISSONI P, ROVELLI F, MONZON A, MESSINA G, MERLI N et al. Efficacy of a Neuroimmune Therapy Including Pineal Methoxyindoles, Angiotensin 1-7, and Endocannabinoids in Cancer, Autoimmune, and Neurodegenerative Diseases. *Clin Interv Aging* 2025; 20: 513-522. <https://doi.org/10.2147/CIA.S513910>
- [16] LISSONI P, ROVELLI F, MESSINA G, MONZON A, VALENTINI A et al. Psycho-Neuro-Endocrine-Immunology Therapy of Cancer, Autoimmunity, Geriatric Disorders, Covid-19, and Hypertension. *Methods Mol Biol* 2025; 2868: 111-132. https://doi.org/10.1007/978-1-0716-4200-9_7
- [17] MUNN LL. Cancer and inflammation. *Wiley Interdiscip Rev Syst Biol Med* 2017; 9: 10.1002/wsbm.1370. <https://doi.org/10.1002/WSBM.1370>
- [18] TARGHAZEH N, REITER RJ, RAHIMI M, QUJEQ D, YOUSEFI T et al. Oncostatic activities of melatonin: Roles in cell cycle, apoptosis, and autophagy. *Biochimie* 2022; 202: 34-48. <https://doi.org/10.1016/j.biochi.2022.06.008>
- [19] SZE SF, NG TB, LIU WK. Antiproliferative effect of pineal indoles on cultured tumor cell lines. *J Pineal Res* 1993; 14: 27-33. <https://doi.org/10.1111/j.1600-079X.1993.tb00481.x>
- [20] TOMKO AM, WHYNOT EG, ELLIS LD, DUPRE DJ. Anti-Cancer Potential of Cannabinoids, Terpenes, and Flavonoids Present in Cannabis. *Cancers (Basel)* 2020; 12: 1985. <https://doi.org/10.3390/cancers12071985>
- [21] VIGANO M, WANG L, AS'SADIQ A, SAMARANI S, AHMAD A et al. Impact of cannabinoids on cancer outcomes in patients receiving immune checkpoint inhibitor immunotherapy. *Front Immunol* 2025; 16: 1497829. <https://doi.org/10.3389/FIMMU.2025.1497829>
- [22] GARCIA-MAURIÑO S, GONZALEZ-HABA MG, CALVO JR, RAFII-EL-IDRISSI M, SANCHEZ-MARGALET V et al. Melatonin enhances IL-2, IL-6, and IFN-gamma production by human circulating CD4+ cells: a possible nuclear receptor-mediated mechanism involving T helper type 1 lymphocytes and monocytes. *J Immunol* 1997; 159: 574-581.
- [23] KOZELA E, JUKNAT A, KAUSHANSKY N, RIMMERMAN N, BEN-NUN A et al. Cannabinoids decrease the Th17 inflammatory autoimmune phenotype. *J Neuroimmune Pharmacol* 2013; 8: 1265-1276. <https://doi.org/10.1007/S11481-013-9493-1>
- [24] CAO L, CHEN Y, LU L, LIU Y, WANG Y et al. Angiotensin II upregulates fibroblast-myofibroblast transition through Cx43-dependent CaMKII and TGF- β 1 signaling in neonatal rat cardiac fibroblasts. *Acta Biochim Biophys Sin (Shanghai)* 2018; 50: 843-852. <https://doi.org/10.1093/abbs/gmy090>

- 381 [25] CAMPOS LA, CIPOLLA-NETO J, AMARAL FG, MICHELINI LC, BADER M et al. The
 382 Angiotensin-melatonin axis. *Int J Hypertens* 2013; 2013: 521783.
 383 <https://doi.org/10.1155/2013/521783>
- 384 [26] LISSONI P, RESENTINI M, MAURI R, ESPOSTI D, ESPOSTI G et al. Effects of
 385 tetrahydrocannabinol on melatonin secretion in man. *Horm Metab Res* 1986; 18: 77-78.
 386 <https://doi.org/10.1055/S-2007-1012235>
- 387 [27] GU L, LI H, CHEN L, MA X, LI X et al. Prognostic role of lymphocyte to monocyte ratio
 388 for patients with cancer: evidence from a systematic review and meta-analysis. *Oncotarget*
 389 2016; 7: 31926-31942. <https://doi.org/10.18632/oncotarget.7876>
- 390 [28] OKADA M, KATO K, CHO BC, TAKAHASHI M, LIN CY et al. Three-Year Follow-Up
 391 and Response-Survival Relationship of Nivolumab in Previously Treated Patients with
 392 Advanced Esophageal Squamous Cell Carcinoma (ATTRACTION-3). *Clin Cancer Res*
 393 2022; 28: 3277-3286. <https://doi.org/10.1158/1078-0432.CCR-21-0985>
- 394 [29] JOENSUU H, ERIKSSON M, SUNDBY HALL K, REICHARDT A, HERMES B et al.
 395 Survival Outcomes Associated With 3 Years vs 1 Year of Adjuvant Imatinib for Patients
 396 With High-Risk Gastrointestinal Stromal Tumors: An Analysis of a Randomized Clinical
 397 Trial After 10-Year Follow-up. *JAMA Oncol* 2020; 6: 1241-1246.
 398 <https://doi.org/10.1001/JAMAONCOL.2020.2091>
- 399 [30] MICHELIN O, ATKINS MB, KOON HB, DUMMER R, ASCIERTO PA. Evolving impact
 400 of long-term survival results on metastatic melanoma treatment. *J Immunother Cancer* 2020;
 401 8: e000948. <https://doi.org/10.1136/JITC-2020-000948>

403 Figure Legends

404

405 **Figure 1.** Percent overall survival at predefined time points in patients with advanced solid tumors
 406 treated with a neuroimmune regimen including Ang 1 7, pineal indoles and cannabinoids (Group
 407 A), compared with patients treated with pineal indoles and cannabinoids alone (Group B), and with
 408 a historical control group receiving best supportive care. Patients treated with the Ang 1 7-
 409 containing regimen showed a consistently higher long-term survival across follow-up, with a three-
 410 year overall survival of 37% compared with 19% in the comparator group.

411

412 **Table 1.** Clinical response according to WHO criteria in untreatable patients with advanced solid
 413 tumors treated with a neuroimmune regimen including Ang 1-7 (Group A) or with pineal indoles
 414 and cannabinoids alone (Group B).

Treatment/Tumor type	N	CR	PR	CR+PR	SD	DC	PD
Ang 1-7+pineal indoles+cannabinoids	100	5	18	23	44	67	33
Glioblastoma	25	1	5	6	9	15	18
Triple-negative breast cancer	8	1	1	2	3	5	19
Breast cancer (non-TN)	3	0	0	0	2	2	20
Non-small cell lung cancer	6	1	1	2	1	3	21
Pancreatic adenocarcinoma	10	0	2	2	4	6	22
Biliary tract carcinoma	12	0	2	2	6	8	23
Gastric cancer	5	1	0	1	2	3	24
Colorectal cancer	5	0	1	1	2	3	25
Renal cell carcinoma	2	0	1	1	1	2	26
Ovarian carcinoma	5	0	1	1	3	4	27
Endometrial carcinoma	2	0	0	0	2	2	28
Bladder carcinoma	4	0	1	1	2	3	29
Neuroendocrine tumors	7	0	1	1	5	6	30
Malignant astrocytoma	4	1	1	2	1	3	31
Malignant melanoma	2	0	1	1	1	2	32
Pineal indoles+cannabinoids	212	2	14	16	95	111	101
Glioblastoma	46	0	0	0	21	21	25
Triple-negative breast cancer	6	0	1	1	2	3	26
Lung cancer	36	1	2	3	16	19	27
Hepatocellular carcinoma	6	0	1	1	3	4	28
Pancreatic adenocarcinoma	22	0	1	1	10	11	29
Biliary tract carcinoma	11	0	2	2	2	4	30
Gastric cancer	12	1	0	1	3	4	31
Colorectal cancer	25	0	2	2	13	15	32
Ovarian carcinoma	14	0	2	2	7	9	33
Prostate cancer	4	0	0	0	3	3	34
Bladder carcinoma	5	0	1	1	3	4	35
Soft tissue sarcoma	15	0	0	0	8	8	36
Malignant melanoma	10	0	2	2	4	6	37

451 Note: Tumor-specific analyses are descriptive and intended to illustrate the distribution of
 452 responses across histotypes.
 453 Abbreviations: CR-complete response; PR-partial response; SD-stable disease; DC-
 454 disease control (CR+PR+SD); PD- progressive disease

455 **Table 2.** Exploratory Cox proportional hazards regression analysis for overall survival
 456 in untreatable patients with advanced solid tumors.

Variable	Direction of association	Interpretation
Ang 1-7-containing regimen	↓ Risk	Associated with reduced risk of death
Age (continuous)	≈ Neutral	No strong association
Male sex	≈ Neutral	No strong association
Glioblastoma histology	↑ Risk	Associated with poorer survival
Metastatic disease	↑ Risk	Associated with poorer survival
Low baseline LMR (< 2.1)	↑ Risk	Associated with poorer survival

457 Note: Cox regression models were exploratory and adjusted for clinically relevant covariates.
 458 Hazard ratios are reported directionally to indicate consistency of associations rather than precise
 459 effect estimates. Results should be interpreted as associative and hypothesis-generating

Fig. 1 [Download full resolution image](#)

