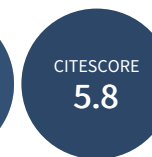


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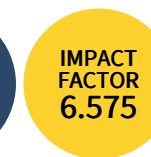
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Authored by:

Sia Pei Ling; Long Chiau Ming; Jagjit Singh Dhaliwal; Madhu Gupta; Chrismawan Ardianto; Khang Wen Goh;
Zahid Hussain; Naeem Shafqat

Published in:

Cancers 2022, Volume 14, Issue 21, 5205



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Article Information Overview

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Article type	Systematic Review
Title	Role of Immunotherapy in the Treatment of Cancer: A Systematic Review
Journal	Cancers (https://www.mdpi.com/journal/cancers)
Volume	14
Issue	21
Section	Cancer Drug Development (https://www.mdpi.com/journal/cancers/sections/Cancer_Drug_Development)
Special Issue	Advances in Anticancer Drugs and Pharmacotherapy of Cancer (https://www.mdpi.com/journal/cancers/special_issues/2XZ7916841)
Abstract	Tremendous progress has been made in cancer research over the years, and, as a result, immunotherapy has emerged as an important therapy for the treatment of cancer, either as a stand-alone treatment or in conjunction with other cancer therapies. Immunotherapy has demonstrated encouraging outcomes and offers a viable strategy for not only enhancing the quality of life but also dramatically boosting the overall survival rate of cancer patients. The objective of this systematic review was to assess the efficacy of immunotherapy in the treatment of cancer. Databases such as PubMed and Science Direct were searched from their inception until September 2021, using the following keywords: cancer immunotherapy, cancer recurrence, cancer treatment options, and cancer therapies. The systematic review was conducted in accordance with the PRISMA protocol. There were a total of 599 articles; however, after applying the inclusion and exclusion criteria, the final review ended up with 34 publications. In conclusion, the studies have demonstrated that immunotherapy is a viable alternative treatment option for patients with recurrent or metastatic cancer, since the overall survival rate and progression-free survival rate were shown to be successful.
Keywords	cancer cell; breast cancer; neoplasm; non-small cell lung cancer; glioblastoma; antineoplastic agent; preventable death; medicine; biological therapy; immunomodulation



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Author Information

Submitting Author	Long Chiau Ming
Corresponding Authors	Chrismawan Ardianto, Naeem Shafqat
Author #1	Sia Pei Ling (ID: https://orcid.org/0000-0001-7155-4922)
Affiliation	1. PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Gadong BE1410, Brunei
E-Mail	19b3021@ubd.edu.bn (co-author email has not been published)



Author #2 Long Chiau Ming ([iD](https://orcid.org/0000-0002-6971-1383))
Affiliation 1. PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Gadong BE1410, Brunei
2. Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, Indonesia
E-Mail longchiauming@gmail.com (co-author email has not been published)

Author #3 Jagjit Singh Dhaliwal ([iD](https://orcid.org/0000-0002-3357-388X))
Affiliation 1. PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Gadong BE1410, Brunei
E-Mail jagjit.dhaliwal@ubd.edu.bn (co-author email has not been published)

Author #4 Madhu Gupta ([iD](https://orcid.org/0000-0002-8503-0609))
Affiliation 3. School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University (DPSRU), New Delhi 110017, India
E-Mail madhugupta98@gmail.com (co-author email has not been published)

Author #5 Chrismawan Ardianto ([iD](https://orcid.org/0000-0003-3713-7900))
Affiliation 2. Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, Indonesia
E-Mail chrismawan-a@ff.unair.ac.id (corresponding author email)

Author #6 Khang Wen Goh ([iD](https://orcid.org/0000-0001-6686-7019))
Affiliation 4. Faculty of Data Science and Information Technology, INTI International University, Nilai 71800, Malaysia
E-Mail khangwen.goh@newinti.edu.my (co-author email has not been published)

Author #7 Zahid Hussain
Affiliation 5. Faculty of Health, University of Canberra, Bruce, ACT 2617, Australia
E-Mail zahid.hussain@canberra.edu.au (co-author email has not been published)

Author #8 Naeem Shafqat ([iD](https://orcid.org/0000-0002-1468-4082))
Affiliation 1. PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Gadong BE1410, Brunei
E-Mail sheikh.shafqat@ubd.edu.bn (corresponding author email)

Manuscript Information

Received Date 26 August 2022
Revised Date 14 October 2022
Accepted Date 15 October 2022
Published Date 24 October 2022
Submission to First Decision (Days) 18
Submission to Publication (Days) 58
Round of Revision 2
Size of PDF 674 KiB
Word Count 6009
Page Count 18
Figure Count 1
Table Count 2
Reference Count 70

Editor Decision

Decision Accept in current form
Comments The authors provided the requested changes.
Decision Date 14 October 2022

Review Report

Reviewer 1 Review Report (Round 1) (/user/manuscripts/review/30047549?report=22236292)
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Total Payment Amount: 0.00 CHF

Previously Published Papers

Khotib, J.; Gani, M.A.; Budiati, A.S.; Lestari, M.L.A.D.; Rahadiansyah, E.; Ardianto, C. Signaling Pathway and Transcriptional Regulation in Osteoblasts during Bone Healing: Direct Involvement of Hydroxyapatite as a Biomaterial. *Pharmaceuticals* **2021**, *14*, 615. doi: 10.3390/ph14070615 (<https://doi.org/10.3390/ph14070615>)

Gani, M.A.; Budiati, A.S.; Lestari, M.L.A.D.; Rantam, F.A.; Ardianto, C.; Khotib, J. Fabrication and Characterization of Submicron-Scale Bovine Hydroxyapatite: A Top-Down Approach for a Natural Biomaterial. *Materials* **2022**, *15*, 2324. doi: 10.3390/ma15062324 (<https://doi.org/10.3390/ma15062324>)

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Khan, F.B.; Singh, P.; Jamous, Y.F.; Ali, S.A.; Abdullah; Uddin, S.; Zia, Q.; Jena, M.K.; Khan, M.; Owais, M.; Huang, C.Y.; Chanukuppa, V.; Ardianto, C.; Ming, L.C.; Alam, W.; Khan, H.; Ayoub, M.A. Multifaceted Pharmacological Potentials of Curcumin, Genistein, and Tanshinone IIA through Proteomic Approaches: An In-Depth Review. *Cancers* **2023**, *15*, 249. doi: 10.3390/cancers15010249 (<https://doi.org/10.3390/cancers15010249>)

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Sevilla-Ortega, L.; Ferrández-Pulido, L.; Palazón-Carrión, N.; Álamo de la Gala, M.C.; de Toro-Salas, R.; Garnacho-Montero, J.; Marcos-Rodríguez, J.A.; Agudo Martínez, A.; Aráji-Tiliani, O.; Calvo-Morón, M.C.; Barquero-Aroca, J.M.; Fernández-López, A.R.; Jaime-Borrego, J.M.; Santos-Jiménez, J.C.; Moreno-Ramírez, D.; de la Cruz-Merino, L. Role of Isolated Limb Perfusion in the Era of Targeted Therapies and Immunotherapy in Melanoma. A Systematic Review of The Literature. *Cancers* **2021**, *13*, 5485. doi: 10.3390/cancers13215485 (<https://doi.org/10.3390/cancers13215485>)

Henriques, B.; Mendes, F.; Martins, D. Immunotherapy in Breast Cancer: When, How, and What Challenges? *Biomedicines* **2021**, *9*, 1687. doi: 10.3390/biomedicines9111687 (<https://doi.org/10.3390/biomedicines9111687>)

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Journal Cancers (https://www.mdpi.com/journal/cancers) (ISSN 2072-6694)
 Manuscript ID cancers-1909099
 Type Systematic Review
 Title Role of immunotherapy in the treatment of cancer: A systematic review (https://www.mdpi.com/2072-6694/14/21/5205)
 Authors Sia Pei Ling , Long Chiau Ming , Jagjit Singh Dhaliwal , Madhu Gupta , Chrismawan Ardianto * , Khang Wen Goh , Zahid Hussain , Naeem Shafqat *
 Section Cancer Drug Development (https://www.mdpi.com/journal/cancers/sections/Cancer_Drug_Development)

Special Issue Advances in Anticancer Drugs and Pharmacotherapy of Cancer (https://www.mdpi.com/journal/cancers/special_issues/2XZ7916841)
 Abstract A tremendous progress has been made in cancer research over the year and as a result, immunotherapy has emerged as an important therapy for the treatment of cancer, either as a stand-alone treatment or in conjunction with other cancer therapies. Immunotherapy has demonstrated encouraging outcomes and offers a viable strategy for not only enhancing the quality of life, but also dramatically boosting the overall survival rate of cancer patients. The objective of this systematic review was to assess the efficacy of immunotherapy in the treatment of cancer. The databases such as PubMed and Science Direct were searched from their inception until September 2021 using the following keywords: cancer immunotherapy, cancer recurrence, cancer treatment options, and cancer therapies. The systematic review was conducted in accordance with the PRISMA protocol. There were a total of 599 articles. However, after applying the inclusion and exclusion criteria, the final review included 34 publications. In conclusion, the studies have demonstrated that immunotherapy is a viable alternative treatment option for patients with recurrent or metastatic cancer, since the overall survival rate and progression-free survival rate were shown to be successful.

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Authors' Responses to Reviewer's Comments (Reviewer 1)

Author's Notes Dear reviewer,

We would like to thank you for your careful and thorough reading of this manuscript as well as for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We have carefully edited the manuscript according to your inputs. We truly hope that the revised manuscript is clear to follow. The response and amendment for each comment are as below.

The manuscript focuses on a meta analysis of literature data about the role on immunotherapy in the treatment of cancer patients is well written and requires minor considerations to be accpeted for the publication

Replies: Thank you for your valuable comments, we really appreciate it .

- In the text, the authors elucidate the role of IC in the cancer patients. in particular they also show the ipact of this approach on different soldi tumor patients. IN addition, could the authors also point on the clinical setting (first, second or other lines) where IC is applied?

Replies: Thank you for your valuable comments, we have edited the text. We presume that IC here you are referring to Cancer immunotherapy (CI)

Clinical practice guideline of using CI

- In the text, could the authors also focus on AE derived from IC approach?

Replies: Thank you for your valuable comments, we have edited the text.

- Could the authors verify style of table 1?

Replies: Thank you for your valuable comments, however, the comments are somewhat vague. Nevertheless, we have reformatted Table 1 to enhance its readability.

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- Quality of English () English very difficult to understand/incomprehensible
- Language () Extensive editing of English language and style required
- () Moderate English changes required



(x) English language and style are fine/minor spell check required
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Are the conclusions supported by the results?	(x)	()	()	()

Comments and Suggestions for Authors
The manuscript focuses on a meta analysis of literature data about the role on immunotherapy in the treatment of cancer patients is well written and requires minor considerations to be accepted for the publication.


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Journal [Cancers \(/https://www.mdpi.com/journal/cancers\)](https://www.mdpi.com/journal/cancers) (ISSN 2072-6694)
Manuscript ID [cancers-1909099](#)
Type [Systematic Review](#)
Title [Role of immunotherapy in the treatment of cancer: A systematic review \(/https://www.mdpi.com/2072-6694/14/21/5205\)](https://www.mdpi.com/2072-6694/14/21/5205)
Authors [Sia Pei Ling](#) , [Long Chiau Ming](#) , [Jagjit Singh Dhaliwal](#) , [Madhu Gupta](#) , [Chrismawan Ardianto *](#) , [Khang Wen Goh](#) , [Zahid Hussain](#) , [Naeem Shafqat *](#)
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Abstract A tremendous progress has been made in cancer research over the year and as a result, immunotherapy has emerged as an important therapy for the treatment of cancer, either as a stand-alone treatment or in conjunction with other cancer therapies. Immunotherapy has demonstrated encouraging outcomes and offers a viable strategy for not only enhancing the quality of life, but also dramatically boosting the overall survival rate of cancer patients. The objective of this systematic review was to assess the efficacy of immunotherapy in the treatment of cancer. The databases such as PubMed and Science Direct were searched from their inception until September 2021 using the following keywords: cancer immunotherapy, cancer recurrence, cancer treatment options, and cancer therapies. The systematic review was conducted in accordance with the PRISMA protocol. There were a total of 599 articles. However, after applying the inclusion and exclusion criteria, the final review included 34 publications. In conclusion, the studies have demonstrated that immunotherapy is a viable alternative treatment option for patients with recurrent or metastatic cancer, since the overall survival rate and progression-free survival rate were shown to be successful.

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Authors' Responses to Reviewer's Comments (Reviewer 2)

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Author's Notes

Dear reviewer,

We would like to thank you for your careful and thorough reading of this manuscript as well as for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We have carefully edited the manuscript according to your inputs. We truly hope that the revised manuscript is clear to follow. The response and amendment for each comment are as below.

The authors set out to conduct a systematic review of the literature on the efficacy of immunotherapy as a second-line treatment for numerous oncological diseases. The topic has been addressed by several authors over time, which means that the review does not add much knowledge to what the scientific community already possesses. Nevertheless, it is interesting and the article could benefit from some modifications during a major review.

Replies: Thank you for your valuable comments, we have edited the text.

1) In some passages, the English used is deficient and has errors. A major revision of the text is suggested to make it more pleasant to read.

Replies: Thank you for your valuable comments, we have edited the text.

2) The section on methods should be improved. The criteria used to select the studies to be included in the review are not sufficiently described. The authors should clearly indicate the search strategy used. (The section on search strategy mentions some keywords used, but there is no consistency between those listed at the beginning of the paragraph and those listed at the end. It is unclear whether the articles initially considered (n=599) represent the sum of what was found in the two databases examined or the articles recorded in both. It is not clear which time interval the articles refer to (what does the term 'inception' refer to?). Why does the search exclude articles possibly published in 2022?)

Replies: Thank you for your valuable comments, we have edited the text. However, the articles that we have gathered from the two databases were from the beginning of whichever the year the available article was from in two of the databases (which refers to inception) up until September, 2021. We did not include any articles that could have possibly been published in 2022 was because this systematic review was written towards the end of September 2021. Hope this explanation helps.

Similarly, the criteria used by the 'single reviewer' for the selection and collection of data are unclear.

Replies: Thank you for your valuable comments, we have edited the text.

3) Although the authors provide a table on the risk of bias in clinical trials, they do not discuss the point enough. The discussion would benefit from a discussion along these lines.

Replies: Thank you for your valuable comments. We have taken extra steps to revise the manuscript.



4) The authors report an "overall efficacy of immunotherapy" against "reduced side effects". However, side effects of immunotherapy are still one of the main problems in its large-scale application. The authors should discuss this point, comparing the side effects of first-line treatment with those caused by immunotherapy and discussing the benefits of this new line of treatment not only in terms of survival, but also in terms of quality of life.

Replies: We appreciate your comments. The text has been extensively revised. Thank you for your valuable comments.

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Quality of English Language English very difficult to understand/incomprehensible
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2) The section on methods should be improved. The criteria used to select the studies to be included in the review are not sufficiently described. The authors should clearly indicate the search strategy used. (The section on search strategy mentions some keywords used, but there is no consistency between those listed at the beginning of the paragraph and those listed at the end. It is unclear whether the articles initially considered (n=599) represent the sum of what was found in the two databases examined or the articles recorded in both. It is not clear which time interval the articles refer to (what does the term 'inception' refer to?). Why does the search exclude articles possibly published in 2022?

Similarly, the criteria used by the 'single reviewer' for the selection and collection of data are unclear.

3) Although the authors provide a table on the risk of bias in clinical trials, they do not discuss the point enough. The discussion would benefit from a discussion along these lines.

4) The authors report an "overall efficacy of immunotherapy" against "reduced side effects". However, side effects of immunotherapy are still one of the main problems in its large-scale application. The authors should discuss this point, comparing the side effects of first-line treatment with those caused by immunotherapy and discussing the benefits of this new line of treatment not only in terms of survival, but also in terms of quality of life.

Submission Date 26 August 2022
 Date of this review 11 Sep 2022 11:13:53



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Journal Cancers (https://www.mdpi.com/journal/cancers) (ISSN 2072-6694)

Manuscript ID cancers-1909099

Type Systematic Review

Title Role of immunotherapy in the treatment of cancer: A systematic review (https://www.mdpi.com/2072-6694/14/21/5205)

Authors Sia Pei Ling , Long Chiau Ming , Jagjit Singh Dhaliwal , Madhu Gupta , Chrismawan Ardianto * , Khang Wen Goh , Zahid Hussain , Naeem Shafqat *

Section Cancer Drug Development (https://www.mdpi.com/journal/cancers/sections/Cancer_Drug_Development)

Special Issue Advances in Anticancer Drugs and Pharmacotherapy of Cancer (https://www.mdpi.com/journal/cancers/special_issues/2XZ7916841)

Abstract A tremendous progress has been made in cancer research over the year and as a result, immunotherapy has emerged as an important therapy for the treatment of cancer, either as a stand-alone treatment or in conjunction with other cancer therapies. Immunotherapy has demonstrated encouraging outcomes and offers a viable strategy for not only enhancing the quality of life, but also dramatically boosting the overall survival rate of cancer patients. The objective of this systematic review was to assess the efficacy of immunotherapy in the treatment of cancer. The databases such as PubMed and Science Direct were searched from their inception until September 2021 using the following keywords: cancer immunotherapy, cancer recurrence, cancer treatment options, and cancer therapies. The systematic review was conducted in accordance with the PRISMA protocol. There were a total of 599 articles. However, after applying the inclusion and exclusion criteria, the final review included 34 publications. In conclusion, the studies have demonstrated that immunotherapy is a viable alternative treatment option for patients with recurrent or metastatic cancer, since the overall survival rate and progression-free survival rate were shown to be successful.

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Authors' Responses to Reviewer's Comments (Reviewer 2)

Author's Notes Dear Reviewer,

Following your constructive suggestions and advice in improving the overall quality of the manuscript, we are resubmitting a thoroughly reviewed full text version (with corrected language and typo errors) of systematic review entitled "Role of immunotherapy in the treatment of cancer: A systematic review".

We hope that the manuscript has now incorporated all the changes as suggested by the reviewers and is ready to be considered for publication in Cancer.

Thank you.

Sincerely,

Dr. Sheikh Naeem Shafqat

PAP Rashidah Sa'adatul Bolkiah Institute of Health Sciences, Universiti Brunei Darussalam, BE1410

Brunei Darussalam

Author's Notes File Report Notes (/user/review/displayFile/30047559/gVZCx7H5?file=author-coverletter&report=23219756)

Review Report Form

- Quality of English Language
- English very difficult to understand/incomprehensible
 - Extensive editing of English language and style required
 - Moderate English changes required
 - English language and style are fine/minor spell check required
 - I am not qualified to assess the quality of English in this paper

Yes Can be improved Must be improved Not applicable



Does the introduction provide sufficient background and include all relevant references?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Are all the cited references relevant to the research?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Is the research design appropriate?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Are the methods adequately described?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Are the results clearly presented?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Are the conclusions supported by the results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments and Suggestions for Authors I appreciate the work done by the authors to answer the questions raised during the review. In my opinion, the work has gained in value. Nevertheless, there are still issues with the English language (ex. Line 296 'cutaneous' instead of 'cutaneous'). It is suggested that the authors review the text in full in order to correct any typos.

Submission Date 26 August 2022
Date of this review 10 Oct 2022 16:19:09

