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ACCESS TO ONCOLOGY COMBINATION THERAPIES IN EUROPE: MOVING FORWARD

Medical Rationale Supporting Patient Access to Novel Oncology Combination Therapies

March 2024

Contents

1. Introduction

The cancer treatment landscape has undergone significant advances over recent decades.[1,2] Although all-cancer incidence rates have increased in recent years[3], overall cancer mortality rates in Europe have seen a decline. [4] For instance, the European Society for Medical Oncology (ESMO) projected a 6% decrease in cancer mortality rates in men and a 4% decrease in cancer mortality rates in women in 2022, compared to mortality rates in 2017. [5]However, despite these advances, a high level of unmet need persists. In 2020, cancer was the second-leading cause of death in the EU, accounting for 23.0 % of the total number of deaths in the EU.[6]

One reason for a high level of unmet need in some cancer patients is the susceptibility to drug resistance-related relapse during treatment with monotherapies and/or combinations containing chemotherapies.[7,8,9] Considering this limitation, a new wave of novel oncology combination therapies (combination therapies composed of two or more innovative medicines used together) may be well-positioned to address these patients' unmet needs.[10,11] Given their unique benefits (such as a 'multi-pronged' approach targeting different pathways and potential synergistic effects between the constituents), an increasing number of these novel combination therapies continue to enter the oncology pipeline and oncology treatment paradigms, and such therapies are providing significant medical benefits to patients.[12]

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1 Danko, D., Blay, J. Y., & Garrison, L. P. (2019). Challenges in the value assessment, pricing and funding of targeted combination therapies in oncology. Health Policy, 123(12), 1230-1236.

2 Briggs, Doyle, Schneider, Taylor, Roffe, Low, Davis, Kaiser, Hatswell, Rabin, Podkonjak. An Attribution of Value Framework for Combination Therapies. (January 2021)

3 Ferlay J, Colombet M and Bray F. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2018. Available from: http://ci5.iarc.fr.

4 Dalmartello M;La Vecchia C;Bertuccio P;Boffetta P;Levi F;Negri E;Malvezzi M; European cancer mortality predictions for the year 2022 with focus on ovarian cancer [Internet]. U.S. National Library of Medicine; [cited 2023 Jul 26]. Available from: https://pubmed.ncbi.nlm.nih.gov/35090748/

5 European Society for Medical Oncology (ESMO). (2022) Death Rates from Ovarian Cancer will Fall in the EU and UK in 2022 [Annals of Oncology Press Release]. Accessed 28th July 2023. Available at: https://www.esmo.org/newsroom/press-releases/death-rates-from-ovarian-cancer-will-fall-in-the-eu-and-uk-in-2022

6 European Comission: Eurostat Cancer Statistics [Internet]. [cited 2023 Jul 24]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cancer_statistics#:~:text=healthcare%20and%20equipment-,Deaths%20from%20cancer,among%20women%20(20.0%20%25).

7 Khdair A, Chen D, Patil Y, Ma L, Dou QP, Shekhar MP, Panyam J. Nanoparticle-mediated combination chemotherapy and photodynamic therapy overcomes tumor drug resistance. J Control Release. 2010;141:137-44.

8 Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer. 2002;2:48-58.

9 Jardim DL, De Melo Gagliato D, Nikanjam M, Barkauskas DA, Kurzrock R. Efficacy and safety of anticancer drug combinations: a meta-analysis of randomized trials with a focus on immunotherapeutics and gene-targeted compounds. Oncoimmunology. 2020 Jan 1;9(1):1710052.

10 Mokhtari, R.B., Homayouni, T.S., Baluch, N., Morgatskaya, E., Kumar, S., Das, B. and Yeger, H., 2017. Combination therapy in combating cancer. Oncotarget, 8(23), p.38022.

11 Boshuizen, J. and Peeper, D.S. (2020) "Rational cancer treatment combinations: An urgent clinical need," Molecular Cell, 78(6), pp. 1002–1018.

12 Mokhtari, R.B., Homayouni, T.S., Baluch, N., Morgatskaya, E., Kumar, S., Das, B. and Yeger, H., 2017. Combination therapy in combating cancer. Oncotarget, 8(23), p.38022.

Between 2015 and 2022, approximately 35 novel combination therapies were approved in Europe.[13] These therapies have typically targeted major tumour types such as breast cancer, non-small-cell lung cancer (NSCLC) and colorectal cancer.[14] Given their unique therapeutic potential, many novel oncology combination therapies are expected to launch during the coming years, with 77 phase 2 and 3 trials planned (i.e., 'active', 'currently recruiting', or 'not yet recruiting') for oncology combination therapies, as of August 2022.[15]

However, despite providing significant medical benefits to patients, novel oncology combination therapies continue to face challenges associated with patient access due to value assessment and pricing and reimbursement complexities.[16,17,18,19,20] Although multiple stakeholder groups have debated such access challenges, there is still limited awareness about the issues, and access to novel oncology combinations has lagged behind access to oncology medicines in general.[21] This lack of awareness is partly due to the complexity of the topic, the tendency to associate novel oncology combinations with combinations containing only one innovative constituent, and the misperception of the value they can deliver.

To incentivise the development of feasible and impactful solutions to ensure patient access to novel oncology combination therapies, it is essential to consider and acknowledge such treatments' benefits.

To provide an overview of these benefits, the EFPIA Oncology Platform (EOP) commissioned this consensus document (Box 1). This document describes the mechanistic advantages of oncology combination therapies and highlights the medical benefits of oncology combination therapies that cannot be delivered by monotherapies. Several examples of effective oncology combination therapies have also been presented to demonstrate the clinical benefits provided to patients.

13 CRA analysis (June 2023)

14 Jardim DL, De Melo Gagliato D, Nikanjam M, Barkauskas DA, Kurzrock R. Efficacy and safety of anticancer drug combinations: a meta-analysis of randomized trials with a focus on immunotherapeutics and gene-targeted compounds. Oncoimmunology. 2020 Jan 1;9(1):1710052.

15 CRA analysis, August 2022

16 Danko, D., Blay, J. Y., & Garrison, L. P. (2019). Challenges in the value assessment, pricing and funding of targeted combination therapies in oncology. Health Policy, 123(12), 1230-1236.

17 Briggs, Doyle, Schneider, Taylor, Roffe, Low, Davis, Kaiser, Hatswell, Rabin, Podkonjak. An Attribution of Value Framework for Combination Therapies. (January 2021)

18 OECD. Addressing the challenges in access to oncology medicines. (2020)

19 Latimer N, Pollard D, Towse A, Henshall C. Challenges in valuing and paying for combination regimens in oncology. Report of an international workshop convened by Bellberry, held on November 18-20, in Sydney, Australia. (May 2020)

20 Danko, D., Blay, J. Y., & Garrison, L. P. (2019). Challenges in the value assessment, pricing and funding of targeted combination therapies in oncology. Health Policy, 123(12), 1230-1236.

21 Latimer N, Pollard D, Towse A, Henshall C. Challenges in valuing and paying for combination regimens in oncology. Report of an international workshop convened by Bellberry, held on November 18-20, in Sydney, Australia. (May 2020)

Box 1: The overall purpose and intended audience of this report

Purpose and scope of this report
The document aims to summarise the mechanistic advantages of combination therapies and their medical benefits for patients. This report is primarily intended for policymakers to incentivise the development and introduction of impactful solutions to improve patient access. Specific challenges for patient access to novel oncology combination therapies will be briefly covered, but this will not be a key focus of this consensus document; the EFPIA Oncology Platform has reported on such challenges extensively in previous work developed in 2022.

2. Methodology

The methodology used to develop this consensus document was designed to obtain a comprehensive understanding of oncology combination therapies: a three-step approach was adopted to inform this analysis.

Firstly, a brief literature review was undertaken to identify the most recent peer-reviewed articles on the benefits of oncology combination therapies. The literature review focused primarily on recent publications on combination therapies (published in the last six years, 2017-2022); some earlier-dated publications (2002-2014) were also reviewed to provide insights on the unmet need that could not be satisfied with monotherapies. Articles were identified by researching keywords (such as: “oncology combinations”, “medical benefits”, “immunotherapy combination”, and “clinical trial oncology combinations”) through Google, Google Scholar, PubMed, and selected websites. A total of 28 papers were selected for review including academic journals, clinical trial reports and articles. Where necessary, additional analyses were performed to gain further insights into the clinical benefits of combination therapies. The findings from the literature review were consolidated to form a draft consensus document.

Secondly, medical experts from eight member companies of the EOP's combination therapies working group were interviewed between April and July 2023 to validate the findings of the draft consensus document and provide additional guidance.

Finally, interviews with six leading non-industry experts were held to review the consensus document, gain additional insights, and finalise the report. These experts included a variety of stakeholders, such as medical oncologists, policymakers, health economists and patient advocacy group representatives.

3. Combination therapies vs monotherapies: biological mechanisms

3.1. Current monotherapy oncology treatment approaches

Although chemotherapy has been the mainstay of cancer treatments for decades, these treatments have shown limitations in efficacy. For example, chemotherapies have not demonstrated the ability to eliminate cancer stem cells, due to their fewer specific mechanisms of action. Consequently, neoplasms remain capable of self-renewing, de-differentiating, and becoming metastatic (having the potential to invade/spread to other body tissues) due to their high mutation rates.[22]

Over recent decades, there has been a shift in cancer treatment paradigms towards more targeted therapies, such as tyrosine kinase inhibitors, and more personalised therapies, such as immunotherapies. Immunotherapies, although targeting the immune system non-specifically, can augment the response of the body's natural immune system, leading to a more targeted immune response against the tumour.[23] However, despite these treatments providing improvements in efficacy compared to chemotherapies, limitations still exist for some patients including susceptibility to drug resistance. The heterogeneous nature of cancer means that some cancer cells can evade the anti-cancer effects of treatment. These cells are induced to utilise alternative signalling pathways to evade the immune system, avoiding the anti-cancer effects of the monotherapy and forming drug resistance.[24,25] They are described as 'therapy-induced resistant cancer cells' (or 'cancer stem cells') and can multiply and drive the growth of the tumour (Figure 1). [26]

22 Chen K, Huang YH, Chen JL. Understanding and targeting cancer stem cells: therapeutic implications and challenges. Acta Pharmacol Sin. 2013;34:732-40.

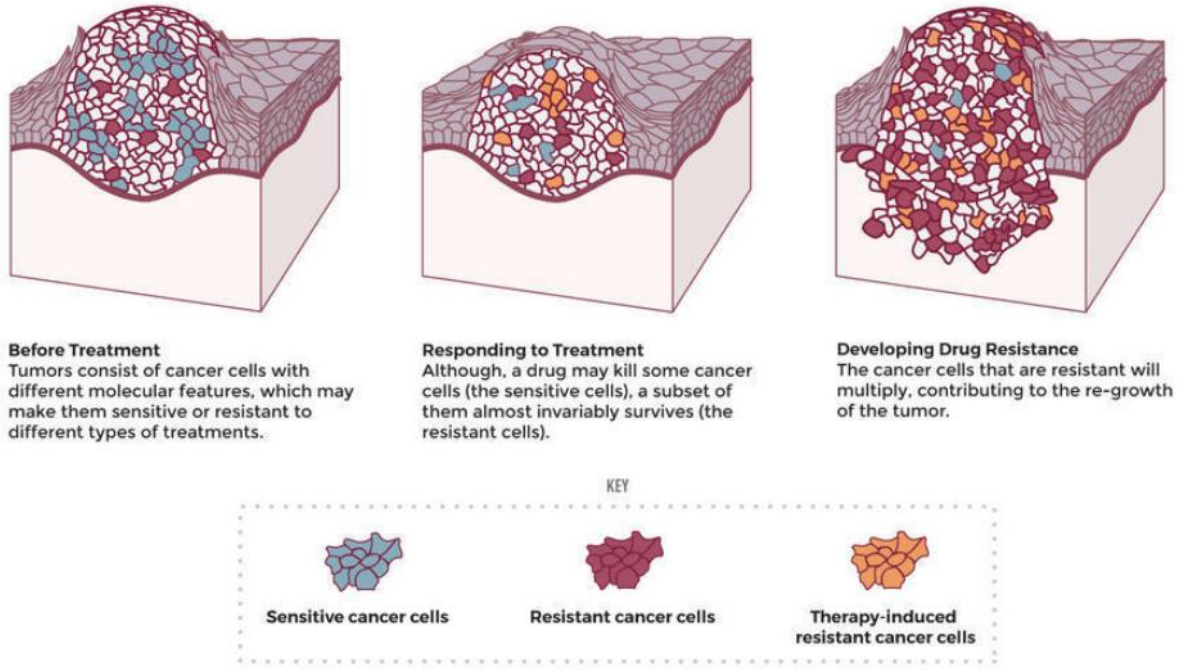
23 Akkın S, Varan G, Bilensoy E. A review on cancer immunotherapy and applications of nanotechnology to chemoimmunotherapy of different cancers. Molecules. 2021 Jun 3;26(11):3382.

24 Khdair A, Chen D, Patil Y, Ma L, Dou QP, Shekhar MP, Panyam J. Nanoparticle-mediated combination chemotherapy and photodynamic therapy overcomes tumor drug resistance. J Control Release. 2010;141:137-44.

25 Jardim DL, De Melo Gagliato D, Nikanjam M, Barkauskas DA, Kurzrock R. Efficacy and safety of anticancer drug combinations: a meta-analysis of randomized trials with a focus on immunotherapeutics and gene-targeted compounds. Oncoimmunology. 2020 Jan 1;9(1):1710052.

26 National Cancer Institute (2016) Why Do Cancer Treatments Stop Working? Overcoming Treatment Resistance. Available at: https://www.cancer.gov/about-cancer/treatment/research/drug-combo-resistance (Accessed: April 15, 2023).

Figure 1 – Treatment-induced drug resistance in cancer cells. *As the tumour responds to treatment, some cancer cells will be capable of utilising alternative signalling pathways to avoid destruction by the treatment. Subsequently, these cells will proliferate and contribute to the re-growth of the tumour.*[27]



Source: National Cancer Institute (2016) Why Do Cancer Treatments Stop Working? Overcoming Treatment Resistance. Available at: https://www.cancer.gov/about-cancer/treatment/research/drug-combo-resistance (Accessed: April 15, 2023)

Patient susceptibility to drug resistance associated with monotherapy treatment is demonstrated by studies showing that some patients who initially respond to immunotherapy treatment can experience drug-resistant relapse within months or years.[28] Therefore, there is a clear medical need to enhance the effectiveness of current constituents via alternative treatment strategies such as combining novel constituents, to provide more robust and durable responses against the tumour.

3.2. Mechanistic advantages of combination therapies

Combination therapies often demonstrate superior clinical benefits for some cancer patients compared to monotherapies.[34,35,29] Such superior efficacy is underpinned by the mechanistic benefits of combination therapies that monotherapies lack, such as their ability to target multiple signalling pathways simultaneously.[58] Essentially, our understanding of cancer biology is growing, and this is allowing more efficacious therapies to be developed. For example, certain constituents may act to 'prime' the tumour microenvironment, allowing the

27 National Cancer Institute (2016) Why Do Cancer Treatments Stop Working? Overcoming Treatment Resistance. Available at: https://www.cancer.gov/about-cancer/treatment/research/drug-combo-resistance (Accessed: April 15, 2023).

28 Syn, N.L.; Teng, M.W.L.; Mok, T.S.K.; Soo, R.A. De-novo and acquired resistance to immune checkpoint targeting. Lancet Oncol. 2017, 18, e731–e741.

29 Briggs, Doyle, Schneider, Taylor, Roffe, Low, Davis, Kaiser, Hatswell, Rabin, Podkonjak. An Attribution of Value Framework for Combination Therapies. (January 2021)

other constituent within the combination therapy to exert a more efficacious anti-cancer effect. [30]

Compared to monotherapies, combination therapies generally reduce the probability of the tumour developing drug resistance. This results from the cancer cells not adapting rapidly enough to utilise alternative signalling pathways to evade being targeted by the combination therapy.[31] For example, combination therapies that contain constituents targeting cancer stem cells have been shown to reduce the risk of relapse compared to monotherapies.[32] The constituents of combination therapies may also work synergistically (i.e., exerting a greater therapeutic effect than the sum of their individual effects, possibly by targeting multiple signalling pathways) to enhance the anti-cancer effects of each medicine (i.e., CTLA-4 and PD-1 combination blockade has been proven to enhance natural immune responses and improve patient response rates).[33,34] Not only does this mechanism contribute to improved efficacy of the treatments versus monotherapies, but the individual constituents are often administered in smaller dosages, possibly reducing toxicity and limiting the dosing burden for patients.[35,36] Overall, novel oncology combination therapies possess clear mechanistic, biological benefits over monotherapies that translate to improved medical outcomes for some cancer patients.

30 Chyuan IT, Chu CL, Hsu PN. Targeting the Tumor Microenvironment for Improving Therapeutic Effectiveness in Cancer Immunotherapy: Focusing on Immune Checkpoint Inhibitors and CombinationTherapies. Cancers (Basel). 2021;13(6).

31 Zimmermann GR, Lehar J, Keith CT. Multi-target therapeutics: when the whole is greater than the sum of the parts. Drug Discov Today. 2007;12:34-42.

32 Takebe N, Miele L, Harris PJ, Jeong W, Bando H, Kahn M, Yang SX, Ivy SP. Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update. Nat Rev Clin Oncol. 2015;12:445-64.

33 Hellmann, M.D., Paz-Ares, L., Bernabe Caro, R., Zurawski, B., Kim, S.-W., Car- cereny Costa, E., Park, K., Alexandru, A., Lupinacci, L., de la Mora Jimenez, E., et al. (2019). Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N. Engl. J. Med. 381, 2020–2031.

34 Gide, T.N., Quek, C., Menzies, A.M., Tasker, A.T., Shang, P., Holst, J., Madore, J., Lim, S.Y., Velickovic, R., Wongchenko, M., et al. (2019). Distinct Immune Cell Populations Define Response to Anti-PD-1 Monotherapy and Anti-PD- 1/Anti-CTLA-4 Combined Therapy. Cancer Cell 35, 238–255.e6.

35 Albain KS, Nag SM, Calderillo-Ruiz G, Jordaan JP, Llombart AC, Pluzanska A, Rolski J, Melemed AS, Reyes-Vidal JM, Sekhon JS, Simms L, O'Shaughnessy J. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol. 2008;26:3950-7.

36 Mokhtari RB, Kumar S, Islam SS, Yazdanpanah M, Adeli K, Cutz E, Yeger H. Combination of carbonic anhydrase inhibitor, acetazolamide, and sulforaphane, reduces the viability and growth of bronchial carcinoid cell lines. BMC Cancer. 2013;13:378.

4. Medical benefits of oncology combination therapies

Importantly, the mechanistic advantages of oncology combination therapies underpin medical benefits for some cancer patients including improved clinical efficacy compared to monotherapies and an increased likelihood of the patients overcoming drug resistance, thereby extending the duration of the anti-cancer effects. [37,38,39,40,41]

In terms of improved clinical efficacy, a meta-analysis of 95 clinical trials of combination therapies completed between 2001-2018 showed that novel oncology combination therapies of non-chemotherapeutic (e.g., small molecules, immunotherapies and/or hormonal therapies) medicines provide statistically significant improvements in median overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) compared to non-chemotherapeutic monotherapies.[42] Clinical trials comparing combination therapies versus the current standard of care have also demonstrated compelling medical benefits for cancer patients. For example, a triple-novel combination (a combination therapy containing three novel constituents) of encorafenib, binimetinib and cetuximab has shown significant improvements in OS and ORR in colorectal cancer. The 'doublet' combination of encorafenib and cetuximab also demonstrated clinical superiority over cetuximab plus generic chemotherapy.[43,44] These findings demonstrate how novel combination therapies can provide anti-cancer effects, superior to that of monotherapies, to achieve positive clinical responses.

Additionally, a combination of monoclonal antibodies, nivolumab and ipilimumab, has demonstrated strong superiority in median OS and treatment-free survival, in patients with advanced melanoma, over both constituents as monotherapies.[45] The nivolumab and ipilimumab also showed superior OS achieved over both constituents as monotherapies after

37 Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N. Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer. New England Journal of Medicine. 2019 Oct 24;381(17):1632-43.

38 Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40(2):127-137. doi:10.1200/JCO.21.02229

39 Janjigian YY, Kawazoe A, Yanez PE, Luo S, Lonardi S, Kolesnik O, Barajas O, Bai Y, Shen L, Tang Y, Wyrwicz L. Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction (G/GEJ) cancer: Initial findings of the global Phase 3 KEYNOTE-811 study.

40 ClinicalTrials.gov (2023) NCT03615326. Available at: https://clinicaltrials.gov/ct2/show/record/NCT03615326 (Accessed: April 12, 2023).

41 Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, Mandalà M, Demidov L, Stroyakovskiy D, Thomas L, de la Cruz-Merino L, Dutriaux C, Garbe C, Sovak MA, Chang I, Choong N, Hack SP, McArthur GA, Ribas A. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014 Nov 13;371(20):1867-76. doi: 10.1056/NEJMoa1408868

42 Jardim DL, De Melo Gagliato D, Nikanjam M, Barkauskas DA, Kurzrock R. Efficacy and safety of anticancer drug combinations: a meta-analysis of randomized trials with a focus on immunotherapeutics and gene-targeted compounds. Oncoimmunology. 2020 Jan 1;9(1):1710052.

43 Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N. Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer. New England Journal of Medicine. 2019 Oct 24;381(17):1632-43.

44 Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N. Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer. New England Journal of Medicine. 2019 Oct 24;381(17):1632-43.

45 Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40(2):127-137. doi:10.1200/JCO.21.02229

a minimum of 77 months follow-up period.[46] Further examples of the strong clinical superiority of novel combination therapies are provided in Box 2.

Box 2: Novel combination therapies with superior efficacy over alternative standard-of-care therapies

Examples of double/triple-novel combination therapies with superior efficacy over standard of care
Dabrafenib and trametinib A phase 3 trial was performed including 423 previously untreated patients with unresectable stage III or stage IV melanoma with a BRAF V600E or V600K mutation receiving a combination of dabrafenib and trametinib, or dabrafenib and placebo.[47] This was one of the first studies highlighting the superior efficacy of a novel oncology combination therapy (dabrafenib and trametinib) over dabrafenib or trametinib monotherapies. At 6 months, the interim overall survival rate was 93% within the combination group and 85% within the dabrafenib-only group. The combination group also demonstrated a lower rate of cutaneous squamous-cell carcinoma, a known and challenging toxicity of monotherapy BRAF inhibition, (2% vs 9%) compared with the dabrafenib plus placebo group.
Nivolumab and ipilimumab Nivolumab and ipilimumab are currently approved in combination for the treatment of six different tumour types.[48] In a phase III trial, this combination therapy demonstrated durable, improved clinical outcomes versus either constituent as a monotherapy for patients with advanced melanoma.[49] Specifically, nivolumab and ipilimumab provided a 51% greater median OS (72.1 vs 36.9 months) to patients compared to nivolumab alone, and a 72% greater median OS (72.1 vs 19.9 months) compared to ipilimumab alone. The combination also showed strong superiority in treatment-free survival over both monotherapies; in patients who discontinued treatment, the median treatment-free interval was 27.6, 2.3, and 1.9 months for the combination, nivolumab alone and ipilimumab alone, respectively. [50]

46 Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40(2):127-137. doi:10.1200/JCO.21.02229

47 Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. New England Journal of Medicine. 2014;371(20):1877–88. doi:10.1056/nejmoa1406037

48 EMA (2023) Opdivo, European Medicines Agency. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/opdivoda (Accessed: April 15, 2023).

49 Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40(2):127-137. doi:10.1200/JCO.21.02229

50 Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40(2):127-137. doi:10.1200/JCO.21.02229

Lenvatinib plus pembrolizumab or everolimus

A phase 3 trial was performed including 1069 patients with advanced renal cell carcinoma and no previous systemic therapy. Patients received lenvatinib plus pembrolizumab, lenvatinib plus everolimus, or sunitinib alone.[51] This study highlighted the superior efficacy of the novel combination therapy (lenvatinib plus pembrolizumab) over lenvatinib plus everolimus or sunitinib monotherapy. The lenvatinib plus pembrolizumab achieved a longer PFS of 23.9 vs. 14.7 vs 9.2 months compared to lenvatinib plus everolimus and sunitinib monotherapy. 40% of the patients in the lenvatinib plus pembrolizumab group also reached median OS, compared to 31.4% and 18.8% of patients in the lenvatinib plus everolimus group, or the sunitinib-alone group respectively.

Encorafenib, binimetinib and cetuximab

An open-label, phase 3 trial was performed including 665 patients with BRAF V600E–mutated metastatic colorectal cancer who had had disease progression after one or two previous regimens.[52] This study highlighted the superior efficacy of a triple-novel therapy (encorafenib, binimetinib, cetuximab) over the standard of care (cetuximab plus generic chemotherapy). The triple-novel combination therapy provided a 37% increase in OS (9.0 months vs 5.4 months) versus standard of care and achieved significantly higher overall response rates in patients versus standard of care (26% vs 2%).[53]

Vemurafenib and cobimetinib

Vemurafenib and cobimetinib are currently approved in combination for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation.[54] In a phase 3 study of 495 patients, the combination therapy demonstrated strong clinical superiority over vemurafenib as a monotherapy; providing a 60% increase in median PFS (9.9 vs 6.2 months) and a greater complete/partial response (68% vs 45%) against the monotherapy. Additionally, patients receiving the combination therapy did not experience a significantly higher incidence of grade 3 and above adverse events compared with the monotherapy

51 Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, Grünwald V, Hutson TE, Kopyltsov E, Méndez-Vidal MJ, Kozlov V, Alyasova A, Hong SH, Kapoor A, Alonso Gordoa T, Merchan JR, Winquist E, Maroto P, Goh JC, Kim M, Gurney H, Patel V, Peer A, Procopio G, Takagi T, Melichar B, Rolland F, De Giorgi U, Wong S, Bedke J, Schmidinger M, Dutcus CE, Smith AD, Dutta L, Mody K, Perini RF, Xing D, Choueiri TK; CLEAR Trial Investigators. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021 Apr 8;384(14):1289-1300. doi: 10.1056/NEJMoa2035716. Epub 2021 Feb 13. PMID: 33616314.

52 Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N. Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer. New England Journal of Medicine. 2019 Oct 24;381(17):1632-43.

53 Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N. Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer. New England Journal of Medicine. 2019 Oct 24;381(17):1632-43.

54 EMA (2023) Cotellic, European Medicines Agency. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/cotellic (Accessed: April 15, 2023).

group (65% vs. 59%), and the number of secondary cutaneous cancers decreased with the combination therapy. [55]

Pembrolizumab and trastuzumab

Pembrolizumab has entered many various combination therapies in oncology and is approved by the EMA for the treatment of eleven different tumour types.[56] Currently, pembrolizumab is being evaluated in combination with trastuzumab and generic chemotherapies, versus trastuzumab and generic chemotherapy alone, for the treatment of HER2+ metastatic gastric or gastroesophageal junction (G/GEJ) cancer. [57] Initial trial results (estimated n=732) have shown the addition of pembrolizumab to (trastuzumab plus generic chemotherapies) to provide a substantial, statistically significant increase in overall response rate (ORR) (74% vs 52%).[58]

It should be noted that meta-analyses have shown that some combination therapies may increase rates of adverse events. However, the rate of adverse events and levels of toxicity associated with the combination therapies did not show a linear increase (i.e., the rates of rate of adverse events and toxicity did not double in patients treated with combination therapies compared to those treated with monotherapies) and it was concluded that the increased safety risk was outweighed by the strong clinical efficacy benefits provided by the combinations. [59]

55 Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, Mandalà M, Demidov L, Stroyakovskiy D, Thomas L, de la Cruz-Merino L, Dutriaux C, Garbe C, Sovak MA, Chang I, Choong N, Hack SP, McArthur GA, Ribas A. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014 Nov 13;371(20):1867-76. doi: 10.1056/NEJMoa1408868

56 EMA (2023) Keytruda, European Medicines Agency. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda (Accessed: April 12, 2023).

57 ClinicalTrials.gov (2023) NCT03615326. Available at: https://clinicaltrials.gov/ct2/show/record/NCT03615326 (Accessed: April 12, 2023).

58 Janjigian YY, Kawazoe A, Yanez PE, Luo S, Lonardi S, Kolesnik O, Barajas O, Bai Y, Shen L, Tang Y, Wyrwicz L. Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction (G/GEJ) cancer: Initial findings of the global Phase 3 KEYNOTE-811 study.

59 Jardim DL, De Melo Gagliato D, Nikanjam M, Barkauskas DA, Kurzrock R. Efficacy and safety of anticancer drug combinations: a meta-analysis of randomized trials with a focus on immunotherapeutics and gene-targeted compounds. Oncoimmunology. 2020 Jan 1;9(1):1710052.

5. Ongoing challenges for patient access: intervention is needed today

Novel oncology combination therapies are providing clear medical benefits to many patients, underpinned by biological and mechanistic advantages over alternative monotherapies. Given the large number of combinations expected to launch in the coming years,**Error! R eference source not found.**[60] it is likely that such therapies will continue to advance the standards of cancer care. However, alongside this promising outlook, there are significant access challenges that must be addressed to ensure patient availability of these highly effective therapies.[61,62,71]

One major challenge lies in the current health technology assessment (HTA) frameworks that generally do not have specific approaches for evaluating combination therapies.[63] Therefore, it is challenging to determine the proportional value that each constituent brings to the combination therapy and consequently, the manufacturer of the last constituent to the market is called to demonstrate the value for money of the whole combination but would only be able to leverage the price of the last constituent as a negotiation tool. For instance, in cost-effectiveness-focused markets (e.g., the UK), some combinations may not be cost-effective even if the second therapy is priced at zero, as the first ('backbone') constituent may already be reimbursed near the willingness to pay threshold of the payer, leaving little headroom to pay for the second ('add-on') constituent. [64]

Complexities for pricing negotiation and concerns with competition laws also pose challenges for combination therapies. Current pricing frameworks often discourage the participation of some manufacturers. For the price of the combination therapy to be aligned with the combination's value from the payer's perspective, a price reduction for the first constituent may be required.[71] However, if the constituents are owned by different manufacturers, the manufacturer of the first constituent may not be able to provide further price reductions, especially if the first constituent is already marketed for other indications. Manufacturers are also hesitant to discuss access strategies due to concerns about infringing competition law, often leaving the manufacturer of the add-on therapy solely responsible for negotiating reimbursement for the combination with no knowledge of the backbone therapy's economic or clinical data.

Additional barriers to access further complicate the situation. The lack of adequate payment mechanisms limits manufacturers' ability to negotiate access effectively.[70,71] There is limited use of novel payment mechanisms, such as specific prices for use in combinations, which could help address access challenges without affecting the backbone constituent's price in

60 CRA analysis, August 2022

61 OECD. Addressing the challenges in access to oncology medicines. (2020)

62 Latimer N, Pollard D, Towse A, Henshall C. Challenges in valuing and paying for combination regimens in oncology. Report of an international workshop convened by Bellberry, held on November 18-20, in Sydney, Australia. (May 2020)

63 Danko, D., Blay, J. Y., & Garrison, L. P. (2019). Challenges in the value assessment, pricing and funding of targeted combination therapies in oncology. Health Policy, 123(12), 1230-1236.

64 Latimer NR, Towse A, Henshall C. Not cost-effective at zero price: valuing and paying for combination therapies in cancer. Expert Review of Pharmacoeconomics & Outcomes Research. 2021 May 4;21(3):331-3.

other indications. Furthermore, the ability to track therapy usage in combinations versus monotherapies is essential for implementing novel pricing models, such as combination-specific pricing. However, an absence of usage-tracking infrastructure in many European countries also restricts the potential implementation of access solutions.

Although multiple stakeholder groups have debated the problem and the potential solutions, there is still limited awareness about the challenges to patient access and progress has been slow in trying to solve it in practice. If no policy interventions are undertaken, the limitations on treatment availability and consequences for patients are expected to worsen as an increasing number of combinations are in development and aim to launch over the coming years. Furthermore, manufacturers may be disincentivised to invest in the development of combination therapies, limiting the potential of future research.

Considering these challenges, it is crucial for stakeholders, including policymakers, payers, and pharmaceutical companies, to collaboratively develop innovative and adaptive solutions. Addressing the reimbursement, pricing, and competition law concerns surrounding novel oncology combination therapies will be key to ensuring that patients can readily access these highly effective treatments, leading to improved cancer outcomes and better quality of life for patients.