

Supplementary information

Metabolites as agents and targets for cancer immunotherapy

**In the format provided by
the authors and unedited**

Supplementary Table 1: List of clinical trials employing metabolites and metabolic interventions discussed in this review. For each pathway and metabolite, the clinical trials discussed in this review are shown including their clinical trial registration number, indication, drugs used for combinations, the clinical trial phase and status. When results have been rendered publicly available, we shortly summarized the main outcome of each trial with its DOI references. RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer. The contents of this table are meant only for research and educational purposes and not for any medical decisions.

Drug	Target	Indication	Combination	Trial ID - Phase	Status	Main Result	Ref
Tryptophan / Kynurenic acid pathway							
Epacadostat	IDO1	Unresectable or metastatic melanoma	Pembrolizumab	NCT02752074 - III	Completed	No benefit	1
Epacadostat	IDO1	Locally advanced or metastatic RCC	Pembrolizumab	NCT03260894 - III	Active, not recruiting	No benefit	2
Epacadostat	IDO1	Recurrent or metastatic HNSCC	Pembrolizumab	NCT03358472 - II	Active, not recruiting	No significant benefit	3
BMS-986205	IDO1	NSCLC stage IV or recurrent	Nivolumab with or without chemotherapy	NCT03417037 - III	Withdrawn	None reported	
BMS-986205	IDO1	Recurrent or metastatic HNSCC	Nivolumab	NCT03386838 - III	Withdrawn	None reported	
Navoximod	IDO1	Locally advanced or metastatic solid tumors	Atezolizumab	NCT02471846 - I	Completed	Well tolerated, no apparent benefit	4
Navoximod	IDO1	Advanced solid tumors	Stereotactic body radiotherapy	NCT05469490 - I	Withdrawn	None reported	
Navoximod	IDO1	Advanced solid tumors	none	NCT02048709 - I	Completed	Well tolerated	5
AT-0174	IDO1, TDO	Advanced solid tumors	none	ACTRN12623000956606 - I	Recruiting		
Indoximod	mTOR, Tryptophan depletion	Metastatic breast cancer	Chemotherapy	NCT01792050 - II	Completed	No benefit	6
Indoximod	mTOR, Tryptophan depletion	Advanced or metastatic melanoma	Ipilimumab, Pembrolizumab or Nivolumab	NCT02073123 - I, II	Completed	Well tolerated, favorable response rate	7
Indoximod	mTOR, Tryptophan depletion	Pediatric patients with progressive primary malignant brain tumors	Temozolomide	NCT02502708 - II	Completed	Well tolerated, favorable response rate	8
Indoximod	mTOR, Tryptophan depletion	Refractory metastatic prostate cancer	Sipuleucel-T	NCT01560923 - II	Completed	Well tolerated, significant clinical improvement	9
Indoximod	mTOR, Tryptophan depletion	Adult patients with primary malignant brain tumors	Temozolomide	NCT02052648 - II	Completed	Maximum tolerated dose found (results on clinicaltrials.gov)	10
Indoximod	mTOR, Tryptophan depletion	Metastatic breast cancer	Adenovirus dendritic cell vaccine	NCT01042535 - I/II	Completed	Well tolerated potential effects	11
Indoximod	mTOR, Tryptophan depletion	Metastatic pancreatic cancer	Gemcitabine and Nab-Paclitaxel	NCT02077881 - II	Completed	Well tolerated, did not meet primary	12

						response goal, promising responses and immunological correlates	
Indoximod	mTOR, Tryptophan depletion	Relapsed brain tumors or newly diagnosed DIPG	Chemotherapy and radiation	NCT04049669 - II	Recruiting		
Indoximod	mTOR, Tryptophan depletion	Pediatric brain cancer	Ibrutinib and Chemotherapy	NCT05106296 - I	Recruiting		
Glutamine pathway							
CB-839 (Telaglenastat)	Glutaminase	Melanoma, clear cell RCC and NSCLC	Nivolumab	NCT02771626 - I, II	Terminated	No benefit	
CB-839 (Telaglenastat)	Glutaminase	Advanced or metastatic renal cell carcinoma	Cabozantinib	NCT03428217 - II	Completed	No benefit	¹³
CB-839 (Telaglenastat)	Glutaminase	Advanced or metastatic renal cell carcinoma	Everolimus	NCT03163667 - II	Completed	Well tolerated, improved PFS	¹⁴
CB-839 (Telaglenastat)	Glutaminase	Advanced-stage non-small cell lung cancer	Sapanisertib	NCT04250545 - I	Active, not recruiting		
CB-839 (Telaglenastat)	Glutaminase	KEAP1/NRF2-mutated, stage IV NSCLC	Standard of care pembrolizumab and chemotherapy	NCT04265534 - II	Terminated	Terminated for lack of efficacy	
DRP-104 (Sirpiglenastat)	Glutaminase	Advanced solid tumors	Atezolizumab	NCT04471415 - I, II	terminated	None reported	
DRP-104 (Sirpiglenastat)	Glutaminase	Advanced stage fibrolamellar carcinoma	Durvalumab	NCT06027086 - I, II	Recruiting		
IPN60090	Glutaminase	Advanced solid tumors	none	NCT03894540 - I	Terminated	Well tolerated, biological activity observed	¹⁵
IPN60091	Glutaminase	Advanced solid tumors	Bevacizumab and Paclitaxel	NCT05039801 - I	Recruiting		
Glutarate pathway							
Ivosidenib	mIDH1	IDH1-mutated acute myeloid leukemia	Azacitidine	NCT03173248 - III	Completed	Significant benefit on PFS	¹⁶
Ivosidenib	mIDH2	Nonresectable or metastatic IDH1 mutant cholangiocarcinoma	Nivolumab or Ipilimumab	NCT05921760 - I, II	Recruiting		
Vorasidenib	mIDH1, mIDH2	Grade 2 IDH-mutant glioma	none	NCT04164901 - III	Active, not recruiting	Significant benefit on PFS	¹⁷
Vorasidenib	mIDH1, mIDH3	Recurrent or progressive mIDH1 glioma	Pembrolizumab	NCT05484622 - I	Recruiting		
Arginine pathway and amino acid derivatives							
INCB001158 (Numidargistat)	extracellular Arginase	Advanced or metastatic solid tumours	With and without Pembrolizumab	NCT02903914 - I	Completed	Well tolerated, no benefit	¹⁸
INCB001158 (Numidargistat)	extracellular Arginase	Advanced solid tumors	With and without retifanlimab	NCT03910530 - Ib	Completed	Well tolerated, no apparent benefit	¹⁹

OATD-02	Arginase 1, Arginase 2	advanced or metastatic solid tumours	none	NCT05759923 - I	Recruiting		
Fluoxetine	Serotonin Transporter	Colorectal cancer	Neoadjuvant	NCT06225011 - I	Not yet recruiting		
Adenosine pathway							
Oleclumab (MEDI9447)	CD73	Unresectable stage III NSCLC	Durvalumab	NCT03822351 - II	Completed	Significant benefit on PFS	20
Oleclumab (MEDI9447)	CD73	Unresectable stage III NSCLC	Durvalumab, Chemoirradiation	NCT05221840 - III	Recruiting		
Quemliclustat (AB680)	CD73	Treatment-naive metastatic pancreatic adenocarcinoma	Zimberelimab, Nab-Paclitaxel and Gemcitabine	NCT04104672 - I	Recruiting	Well tolerated, promising OS improvement	21
Quemliclustat (AB680)	CD73	Metastatic castrate-resistant prostate cancer	Etrumadenant, Zimberelimab, Docetaxel	NCT04381832 - Ib/II	Completed	First phase completed, ongoing	
LY3475070	CD73	Advanced solid tumors	Pembrolizumab	NCT04148937 - I	Completed	Maximum tolerated doses found	
BMS-986179	CD73	Advanced solid tumors	Nivolumab	NCT02754141 - I	Completed	Well tolerated	
CPI-006	CD73	Advanced solid tumors	Pembrolizumab with and without Ciforadenant	NCT03454451 - I	Completed	Well tolerated	
NZV930	CD73	Advanced solid tumors	NZV930, PDR001	NCT03549000 - I	Terminated	Low likelihood of benefit	
TTX-030	CD39	Advanced solid tumors	budigalimab and FOLFOX	NCT04306900 - I	Completed	Locally advanced or metastatic gastric/GEJ cancer: safe and promising activities	22
TTX-030	CD39	Metastatic pancreatic adenocarcinoma patients	Chemotherapy With or Without Budigalimab	NCT06119217 - II	Active, not recruiting		23
SRF617	CD39	Advanced solid tumors	Gemcitabine and Nab-Paclitaxel, or Pembrolizumab	NCT04336098 - I	Completed	Well tolerated, target engagement	24
SRF617	CD39	Metastatic castration resistant prostate cancer	Etrumadenant, Zimberelimab	NCT05177770 - I	Terminated for strategic reasons		
IPH5201	CD39	Advanced solid tumors	With and without Nivolumab	NCT04261075 - I	Completed	Well tolerated, target engagement	25
IPH5201	CD39	Resectable NSCLC	Durvalumab, chemotherapy; neoadjuvant and adjuvant	NCT05742607 - II	Recruiting		
Etrumadenant (AB928)	AA2R	Metastatic colorectal cancer	Combinations of Zimberelimab, mFOLFOX-6, Bevacizumab	NCT04660812 - I, II	Active, not recruiting	Manageable toxicity profile and improvements in PFS and OS	26

Ciforadenant	AA2R	Treatment-refractory renal cell cancer and prostate cancer	Atezolizumab	NCT02655822 - I	Completed	Well tolerated, potential benefit	27
Ciforadenant	AA2R	First-line advanced renal cell carcinoma	Ipilimumab and Nivolumab	NCT05501054 - I, II	Recruiting		
AZD4635	AA2R	Progressive, metastatic, castration-resistant prostate cancer	Durvalumab and Cabazitaxel	NCT04495179 - II	Completed	Well tolerated, no benefit	28
Taminadenant (NIR178)	AA2R	Advanced or metastatic NSCLC	With and without PDR001	NCT02403193 - I	Completed	Well tolerated, potential signs of benefit	29
Taminadenant (NIR178)	AA2R	Solid tumors and non-Hodgkin lymphoma	PDR001	NCT03207867 - II	Terminated	No benefit	

Lactate pathway and mitochondrial metabolism							
AZD3965	MCT1	Advanced cancers	none	NCT01791595 - I	Completed	Tolerated at doses with target engagement	30
IACS-010759	Mitochondria I complex I	Relapsed/refractory acute myeloid leukemia	none	NCT02882321 - I	Terminated for lack of efficacy	Dose-limiting toxicity hindering target engagement	31
IACS-010759	Mitochondria I complex I	Advanced solid tumors		NCT03291938 - I	Completed	Dose-limiting toxicity hindering target engagement	31
CPI-613 (devimistat)	ketoglutarate dehydrogenase and pyruvate dehydrogenase	Advanced hematological malignancies	none	NCT01034475 - I	Completed	Maximum tolerated dose found, potential signs of response	32
CPI-613 (devimistat)	ketoglutarate dehydrogenase and pyruvate dehydrogenase	Metastatic pancreatic adenocarcinoma	Modified Folfirinox	NCT03504423 - III	Completed	No benefit	33
CPI-613 (devimistat)	ketoglutarate dehydrogenase and pyruvate dehydrogenase	Pancreatic adenocarcinoma	Gemcitabine and radiation therapy	NCT05325281 - I	Recruiting		
CPI-613 (devimistat)	ketoglutarate dehydrogenase and pyruvate dehydrogenase	Advanced chemorefractory solid tumors	Hydroxychloroquine and 5-Fluorouracil or Gemcitabine	NCT05733000 - II	Recruiting		
CPI-613 (devimistat)	ketoglutarate dehydrogenase and pyruvate dehydrogenase	Relapsed/refractory T-cell non-Hodgkin lymphoma	Bendamustine	NCT04217317 - II	Recruiting		

Diet and Microbiota

High Fiber Diet	Gut Microbiota Modulation	Metastatic or unresectable stage III-IV melanoma	Pembrolizumab or Nivolumab	NCT04645680 - II	Active, not recruiting		34
Ketogenic Diet	Diet	Locally advanced and metastatic breast cancer	Chemotherapy	IRCT20171105037259N2 - Na	Completed	Reduction in tumor size and fasting insulin	35
Ketogenic Diet	Diet	Locally advanced and metastatic breast cancer	Radiotherapy	NCT02516501 - Na	Completed	Decreased body weight and fat mass, preserved muscle mass	36
Ketogenic Diet	Diet	Metastatic renal cell carcinoma	Nivolumab and Ipilimumab	NCT05119010 - Na	Terminated		
Urolithin A	Gut Microbiota Modulation	Healthy volunteers	Na	NCT05735886 - Na	Completed	Changes in immune cell numbers and phenotype in the blood	37
Camu-Camu Berry powder	Gut Microbiota Modulation	Advanced NSCLC and melanoma	Standard-of-care ICI (Pembrolizumab, Nivolumab, and or Ipilimumab)	NCT05303493 - I	Recruiting		
Autologous natural dendritic cells pulsed with synthetic peptides	Gut Microbiota Modulation	Melanoma stage IIIB/C	Adjuvant application	NCT02993315 - III	Active, not recruiting	Well tolerated, no apparent benefit	38
Ursodeoxycholic acid	Liver Immunomodulation	Hematological malignancies	Allogeneic stem-cell transplantation	NA - not reported	not reported	Significant benefit on GvHD and survival	39
High-Fiber, High-Fruit and Vegetable, low-fat diet	Gut Microbiota Modulation	Removed confirmed colorectal adenomatous polyp	None	NCT00339625 - III	completed	Baseline bile acids correlated with adenoma recurrence. No significant effect of dietary intervention on bile acid concentrations.	40
High-SCFA diet	SCFA	Healthy adults	Na	ACTRN12618001054202 - Na	Completed	Increase in fecal and serum SCFAs.	41
Metformin	AMPK and energy regulation	Esophageal squamous cell carcinoma	Neoadjuvant	ChiCTR-ICR-15005940- II	Completed	Increased number of CD8+ T cells, CD20+ B cells, CD11+ macrophages and less CD163+ macrophages in tumor.	42
Metformin	AMPK and energy regulation	Advanced pancreatic cancer	Gamcitabine and erlotinib chemotherapy	NCT01210911 - II	Completed	No significant survival benefit	43

Metformin	AMPK and energy regulation	Operable nonmetastatic breast cancer patients without diabetes	Standard of care	NCT01101438 - III	Completed	No benefit of metformin on invasive disease-free survival. Subgroup analysis showed benefit in rs11212617 C allele ERBB2+ patients.	44
Metformin	AMPK and energy regulation	ERBB2+ breast cancer	Neoadjuvant chemotherapy, trastuzumab	EudraCT 2011-000490-30 - II	Ongoing	Significant correlation between rs11212617 SNV genotype and complete pathological response in metformin-containing arm	45
Vitamin D	Immune stimulation	People >60 years old	None	ACTRN1261300074 3763 - III	Active, not recruiting	No change in mortality. Subgroup analysis showed increased cancer mortality	46
Vitamin D	Immune stimulation	Men >50 , women > 55 years old	None	NCT01169259 - III	Active, not recruiting	No change in cancer incidence, benefit on advanced cancers	47
Vitamin D	Immune stimulation	Advanced solid tumor, advanced stage disease	Checkpoint blockade	Not reported	Not reported	Compared to retrospective control, vitamin D improved overall survival.	48

References Supplementary Information

1. Long, G. V. *et al.* Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. *Lancet Oncol* **20**, 1083–1097 (2019).
2. Lara, P. N. *et al.* A randomized, open-label, phase 3 trial of pembrolizumab plus epacadostat versus sunitinib or pazopanib as first-line treatment for metastatic renal cell carcinoma (KEYNOTE-679/ECHO-302). *BMC Cancer* **23**, 1253 (2024).
3. Cho, B. C. *et al.* Pembrolizumab plus epacadostat in patients with recurrent/metastatic head and neck squamous cell carcinoma (KEYNOTE-669/ECHO-304): a phase 3, randomized, open-label study. *BMC Cancer* **23**, 1–12 (2024).
4. Jung, K. H. *et al.* Phase I study of the indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor navoximod (GDC-0919) administered with PD-L1 inhibitor (atezolizumab) in advanced solid tumors. *Clinical Cancer Research* **25**, 3220–3228 (2019).
5. Nayak-Kapoor, A. *et al.* Phase Ia study of the indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor navoximod (GDC-0919) in patients with recurrent advanced solid tumors. *J Immunother Cancer* **6**, 61 (2018).
6. Mariotti, V. *et al.* Effect of Taxane Chemotherapy With or Without Indoximod in Metastatic Breast Cancer: A Randomized Clinical Trial. *JAMA Oncol* **7**, 61–69 (2021).

7. Zakharia, Y. *et al.* Phase 2 trial of the IDO pathway inhibitor indoximod plus checkpoint inhibition for the treatment of patients with advanced melanoma. https://doi.org/10.1200/JCO.2018.36.15_suppl.9512 **36**, 9512–9512 (2018).
8. Johnson, T. S. *et al.* Indoximod-based chemo-immunotherapy for pediatric brain tumors: A first-in-children phase I trial. *Neuro Oncol* **26**, 348–361 (2024).
9. Jha, G. G. *et al.* A phase II randomized, double-blind study of sipuleucel-T followed by IDO pathway inhibitor, indoximod, or placebo in the treatment of patients with metastatic castration resistant prostate cancer (mCRPC). https://doi.org/10.1200/JCO.2017.35.15_suppl.3066 **35**, 3066–3066 (2017).
10. Colman, H. *et al.* A phase 1b/2 study of the combination of the IDO pathway inhibitor indoximod and temozolomide for adult patients with temozolomide-refractory primary malignant brain tumors: Safety analysis and preliminary efficacy of the phase 1b component. https://doi.org/10.1200/jco.2015.33.15_suppl.2070 **33**, 2070–2070 (2015).
11. Soliman, H. *et al.* A phase-1/2 study of adenovirus-p53 transduced dendritic cell vaccine in combination with indoximod in metastatic solid tumors and invasive breast cancer. *Oncotarget* **9**, 10110–10117 (2018).
12. Bahary, N. *et al.* Phase 2 trial of the IDO pathway inhibitor indoximod plus gemcitabine / nab-paclitaxel for the treatment of patients with metastatic pancreas cancer. https://doi.org/10.1200/JCO.2018.36.15_suppl.4015 **36**, 4015–4015 (2018).
13. Tannir, N. M. *et al.* Efficacy and Safety of Telaglenastat Plus Cabozantinib vs Placebo Plus Cabozantinib in Patients with Advanced Renal Cell Carcinoma: The CANTATA Randomized Clinical Trial. *JAMA Oncol* **8**, 1411–1418 (2022).
14. Lee, C. H. *et al.* Telaglenastat plus Everolimus in Advanced Renal Cell Carcinoma: A Randomized, Double-Blinded, Placebo-Controlled, Phase II ENTRATA Trial. *Clinical Cancer Research* **28**, 3248–3255 (2022).
15. Yap, T. A. *et al.* First-in-human biomarker-driven phase I trial of the potent and selective glutaminase-1 (GLS1) inhibitor IACS-6274 (IPN60090) in patients (pts) with molecularly selected advanced solid tumors. *Journal of Clinical Oncology* **39**, 3001–3001 (2021).
16. Montesinos, P. *et al.* Ivosidenib and Azacitidine in IDH1 -Mutated Acute Myeloid Leukemia. *New England Journal of Medicine* **386**, 1519–1531 (2022).
17. Naing, A. *et al.* First-in-human phase 1 study of the arginase inhibitor INCB001158 alone or combined with pembrolizumab in patients with advanced or metastatic solid tumours. *BMJ Oncology* **3**, e000249 (2024).
18. Kuboki, Y. *et al.* PD-1 inhibition with retifanlimab and/or arginase inhibition with INCB001158 in Japanese patients with solid tumors: A phase I study. *Cancer Med* **13**, (2024).
19. Herbst, R. S. *et al.* COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination with Oleclumab or Monalizumab in Patients with Unresectable, Stage III Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology* **3**, (2022).
20. Wainberg, Z. A. *et al.* ARC-8: Phase 1/1b randomized study of quemliclustat + gemcitabine/nab-paclitaxel ± zimberelimab in patients with treatment-naïve metastatic pancreatic adenocarcinoma. https://doi.org/10.1200/JCO.2024.42.3_suppl.665 **42**, 665–665 (2024).
21. Wainberg, Z. *et al.* Abstract CT015: Safety and efficacy of TTX-030, an anti-CD39 antibody, in combination with chemoimmunotherapy for the first line treatment of locally advanced or metastatic gastric/GEJ cancer. *Cancer Res* **82**, CT015–CT015 (2022).
22. Wainberg, Z. *et al.* Abstract CT015: Safety and efficacy of TTX-030, an anti-CD39 antibody, in combination with chemoimmunotherapy for the first line treatment of locally advanced or metastatic gastric/GEJ cancer. *Cancer Res* **82**, CT015–CT015 (2022).
23. Patnaik, A. *et al.* 135P First-in-human phase I trial of SRF617, a potent inhibitor of CD39 activity, as monotherapy or in combination, in patients (pts) with advanced solid tumors. *Annals of Oncology* **32**, S1435–S1436 (2021).
24. Imbimbo, M. *et al.* 188P IPH5201 as monotherapy or in combination with durvalumab (D) in advanced solid tumours. *Immuno-Oncology and Technology* **16**, 100300 (2022).

25. Wainberg, Z. A. *et al.* ARC-9: A randomized study to evaluate etrumadenant based treatment combinations in previously treated metastatic colorectal cancer (mCRC). https://doi.org/10.1200/JCO.2024.42.16_suppl.3508 **42**, 3508–3508 (2024).
26. Fong, L. *et al.* Adenosine 2A receptor blockade as an immunotherapy for treatment-refractory renal cell cancer. *Cancer Discov* **10**, 40–53 (2020).
27. Alonso-Gordoa, T. *et al.* A phase II study (AARDVARC) of AZD4635 in combination with durvalumab and cabazitaxel in patients with progressive, metastatic, castration-resistant prostate cancer. *ESMO Open* **9**, 103446 (2024).
28. Chiappori, A. A. *et al.* Phase I Study of Taminadenant (PBF509/NIR178), an Adenosine 2A Receptor Antagonist, with or without Spartalizumab (PDR001), in Patients with Advanced Non-Small Cell Lung Cancer. *Clinical Cancer Research* **28**, 2313–2320 (2022).
29. Halford, S. *et al.* A Phase I Dose-Escalation Study of AZD3965, an Oral Monocarboxylate Transporter 1 Inhibitor, in Patients with Advanced Cancer. *Clinical Cancer Research* **29**, 1429–1439 (2023).
30. Yap, T. A. *et al.* Complex I inhibitor of oxidative phosphorylation in advanced solid tumors and acute myeloid leukemia: phase I trials. *Nature Medicine* **29**, 115–126 (2023).
31. Pardee, T. S. *et al.* A phase I study of the first-in-class antimitochondrial metabolism agent, CPI-613, in patients with advanced hematologic malignancies. *Clinical Cancer Research* **20**, 5255–5264 (2014).
32. Study Evaluating Efficacy and Safety of FFX Versus Combination of CPI-613 With mFFX in Patients With Metastatic Adenocarcinoma of the Pancreas | ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT03504423?tab=results>.
33. Farias, R. *et al.* The DIET study: A randomized controlled trial of a high fiber diet in cancer patients (pts) receiving immune checkpoint blockade (ICB). *Journal of Clinical Oncology* **41**, TPS9609–TPS9609 (2023).
34. Khodabakhshi, A. *et al.* Effects of Ketogenic metabolic therapy on patients with breast cancer: A randomized controlled clinical trial. *Clinical Nutrition* **40**, 751–758 (2021).
35. Klement, R. J. *et al.* Impact of a ketogenic diet intervention during radiotherapy on body composition: III - Final results of the KETOCOMP study for breast cancer patients. *Breast Cancer Research* **22**, 1–14 (2020).
36. Denk, D. *et al.* Impact of urolithin A supplementation, a mitophagy activator on mitochondrial health of immune cells (MitoIMMUNE): A randomized, double-blind, placebo-controlled trial in healthy adults. *Journal of Clinical Oncology* **42**, e14562–e14562 (2024).
37. Alves Costa Silva, C. *et al.* Influence of microbiota-associated metabolic reprogramming on clinical outcome in patients with melanoma from the randomized adjuvant dendritic cell-based MIND-DC trial. *Nature Communications* **15**, 1–16 (2024).
38. Ruutu, T. *et al.* Improved survival with ursodeoxycholic acid prophylaxis in allogeneic stem cell transplantation: long-term follow-up of a randomized study. *Biol Blood Marrow Transplant* **20**, 135–138 (2014).
39. Byrd, D. A. *et al.* Circulating Bile Acids and Adenoma Recurrence in the Context of Adherence to a High-Fiber, High-Fruit and Vegetable, and Low-Fat Dietary Intervention. *Clin Transl Gastroenterol* **13**, e00533 (2022).
40. Gill, P. A., Muir, J. G., Gibson, P. R. & Van Zelm, M. C. A randomized dietary intervention to increase colonic and peripheral blood SCFAs modulates the blood B- and T-cell compartments in healthy humans. *Am J Clin Nutr* **116**, 1354 (2022).
41. Wang, S. *et al.* Low-Dose Metformin Reprograms the Tumor Immune Microenvironment in Human Esophageal Cancer: Results of a Phase II Clinical Trial. *Clinical Cancer Research* **26**, 4921–4932 (2020).
42. Kordes, S. *et al.* Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol* **16**, 839–847 (2015).
43. Goodwin, P. J. *et al.* Effect of Metformin vs Placebo on Invasive Disease-Free Survival in Patients With Breast Cancer: The MA.32 Randomized Clinical Trial. *JAMA* **327**, 1963–1973 (2022).

44. Cuyàs, E. *et al.* The C allele of ATM rs11212617 associates with higher pathological complete remission rate in breast cancer patients treated with neoadjuvant metformin. *Front Oncol* **9**, 443988 (2019).
45. Neale, R. E. *et al.* The D-Health Trial: a randomised controlled trial of the effect of vitamin D on mortality. *Lancet Diabetes Endocrinol* **10**, 120–128 (2022).
46. Chandler, P. D. *et al.* Effect of Vitamin D3 Supplements on Development of Advanced Cancer: A Secondary Analysis of the VITAL Randomized Clinical Trial. *JAMA Netw Open* **3**, e2025850–e2025850 (2020).
47. Bersanelli, M. *et al.* Systematic vitamin D supplementation is associated with improved outcomes and reduced thyroid adverse events in patients with cancer treated with immune checkpoint inhibitors: results from the prospective PROVIDENCE study. *Cancer Immunol Immunother* **72**, 3707–3716 (2023).