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（分担研究報告書）
国内外の情報の質を担保する規制を含めた諸要件の整理：
保険適用外のがん免疫療法のシステマティックレビュー

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研究要旨
がんを心配して情報を探し始める場面から適切にがん拠点病院等につながり、患者らが必要に応じて正しい情報を入手できるよう、国内外の情報の質を担保する規制を含む諸要件を検討することを目的としている。この中で、自由診療等で行われている保険適用外のがん免疫療法に関するシステマティックレビューを行い、有効性・安全性に関する現時点のエビデンスを明確化し、患者さん・ご家族が、がん免疫療法を判断する際の手がかりとなることを目指す。

A. 研究目的

本研究では、がんを心配して情報を探し始める場面から適切にがん拠点病院等につながり、患者らが必要に応じて正しい情報を入手できるよう、国内外の情報の質を担保する規制を含む諸要件を検討することを目的としている。この中で、自由診療等で行われている保険適用外のがん免疫療法に関するシステマティックレビューを行った。

B. 研究方法

日本臨床腫瘍学会のがん免疫療法ガイドライン第3版改訂に合わせて、「がんワクチン療法」と「がんエフェクターT細胞療法」について、文献検索された情報をもとに、各がん種のシステマティックレビューを行った。

（倫理面への配慮）

本研究は、個人情報などを扱う内容ではなく、特に倫理面の配慮の必要はない。

C. 研究結果

がん免疫療法ガイドライン第3版（日本臨床腫瘍学会編）のガイドライン委員会委員長の岡山大学の堀田先生の許可を得て（JSMOに提出した概要書：資料1）、日本臨床腫瘍学会からの外部委託という形で、システマティックレビューを実施することとなった（資料1、文献検索結果；資料2-4）。

研究協力者として、西川医師、星野医師、瀬田医師、横山医師、中村医師に参画いただいた。

１）文献検索について

がん免疫療法ガイドライン第2版の方法を踏襲して実施された。Pubmedを用いて、2017年10月から2021年6月の期間で検索した。

エフェクターT細胞療法の検索式：neoplasms[majr] AND ("effector t cell" OR "t-lymphocyte subsets"[mesh] OR "NK cell" OR "killer cells, natural "[mesh] OR TIL OR "lymphocytes, tumor-infiltrating"[mesh] OR TCR OR "t-cell receptor"[tw] engineered OR chimeric OR " Induced Pluripotent Stem Cells"[mesh] OR iPS OR "Receptors, Chimeric Antigen"[mesh] OR "Induced Pluripotent Stem Cells"[mesh]) AND ("randomized controlled trial"[pt] OR meta-analysis[pt] OR "syste

matic review"[pt]) AND humans AND 2017/10:2021/05[dp] AND (English[la] OR japanese[la])。
ワクチン療法の検索式 : neoplasms[majr] AND ("effector t cell" OR "t-lymphocyte subsets"[mesh] OR "NK cell" OR "killer cells, natural"[mesh] OR TIL OR "lymphocytes, tumor-infiltrating"[mesh] OR TCR OR "t-cell receptor"[tw] engineered OR chimeric OR " Induced Pluripotent Stem Cells"[mesh] OR iPS OR "Receptors, Chimeric Antigen"[mesh] OR "Induced Pluripotent Stem Cells"[mesh]) AND ("randomized controlled trial"[pt] OR meta-analysis[pt] OR "systematic review"[pt]) AND humans AND 2017/10:2021/05[dp] AND (English[la] OR japanese[la])
であった。

この結果、がんワクチン療法では418文献、エフェクターT細胞療法は44件の文献がヒットした（資料3, 4）。

２）一次スクリーニングについて

Phase2以上のエビデンスレベルのRCTを検索することとした。2名の分担研究者が独立して割り当てられた部分の文献をスクリーニングして、ワクチン療法は49文献、エフェクターT細胞療法は2文献がのこった。ただし、特に造血器腫瘍についてはエフェクターT細胞療法はPhase2試験で薬事承認を受けており、実臨床で使用されていることを鑑みて、Phase2試験についても抽出することとした。

３）二次スクリーニング以後の対応

各臓器ごとに、ワクチン療法とエフェクターT細胞療法の担当を決めて、各文献のエビデンスの強さ等を評価して、必要に応じてメタアナリシスも実施した。その結果をもとに、ガイドラインの各臓器の部分に追記することとなった（資料2）。

ガイドライン自体は、2022年6月までのエビデンスを追記して、最終版とするため、現時点ではほぼほぼ完成版として各臓器について作成済みであるが、ガイドライン自体は作成途中である。

D. 考察

前回までのがん免疫療法ガイドライン第2版においても、エフェクターT細胞療法やワクチン療法の有効性が示されているがん種はほとんど存在しなかった。今回は、造血器腫瘍やメラノーマなど、一部のがんでエフェクターT細胞療法やワクチン療法の有効性が示されており、今後発展の可能性がある。

一方で、現時点では、殆どのがん種で、ワクチン療法の種類もまちまちで、RCTで対照群と比較して有効な結果を示しているものはほとんどなかった。

一部有望な結果が出ている研究については、細胞製剤の調整の方法が詳細に示されておらず、再現性に疑問が生じる部分があった。

今後、今回のデータをもとに、実際に巷で実施されている自由診療下での免疫療法のエビデンスについて評価を進めてまいりたい。

E. 結論

がん免疫療法ガイドラインの作成の手法に則って、エビデンスの評価を行った。現時点では、ガイドライン作成のために、公表はできないが、ほとんどのがん種においてワクチン療法やエフェクターT細胞療法が有効であるというRCTの結果は出ていない。

F. 健康危険情報

特になし

G. 研究発表

1. 論文発表　なし

2. 学会発表　なし

H.知的財産権の出願・登録状況
（予定を含む）

1. 特許取得　　なし

2. 実用新案登録 なし

3. その他　　なし

資料１

2021 年 4 月 18 日

科学的根拠に基づくがん情報の迅速な作成と提供のための体制整備のあり方に関する研究（20EA1008）若尾班(2020-22 年度)の中山小班と JSMO との連携について

国立研究開発法人国立がん研究センター　がん対策情報センター　センター長　若尾　文彦
京都大学大学院医学研究科　社会健康医学系専攻　健康情報学分野教授　中山　健夫

【目的】
若尾班では、がんを心配して情報を探し始める場面から適切にがん拠点病院等につながり、患者らが必要に応じて正しい情報を入手できるよう、以下の 3 つの検討から All Japan による情報提供に関する方策を提言する（詳細については添付の研究計画書参照)。

若尾班では、以下の 3 つの大項目について検討予定としている。
１．国、国立がん研究センター、関係学会等との連携による持続可能な情報作成体制（All Japan がん情報コンソーシアム）とそれに関わる諸要件の検討
　SG1 企業等との協働による財源・情報作成・活用・提供・普及の仕組みのパイロット事業による検討
　SG2 国内外の情報の質を担保する規制を含む諸要件の検討（担当：中山健夫［京都大学］）
２．情報検索会社等との連携による、情報探索パターン等に応じた正しい情報にたどり着きやすくするシステムの開発
３．相談員のための診療ガイドライン・データベースの作成と活用促進に向けた検討

【SG2 中山小班で実施する検討内容】
- 患者さんに正しい情報を提供するため、自由診療等で行われている保険適応外のがん免疫療法に関するシステマティックレビューを行う。
- 有効性・安全性に関する現時点のエビデンスを明確化し、患者さん・ご家族が、がん免疫療法を判断する際の手がかりとなることを目指す。

【日本臨床腫瘍学会　がん免疫療法ガイドラインとの共同研究についてのご依頼事項】
- 現在、進められている日本臨床腫瘍学会・がん免疫療法ガイドラインの改訂作業と連携させて頂く予定である（一部作成をお手伝いさせていただく)。
- 本研究班で担当させていただく項目候補は、保険適用外の「がんワクチン療法」と「エフェクターT 細胞療法」を想定しているが、詳細については、がん免疫療法ガイドライン委員会との協議に基づいて決定させていただく。

以上

資料 2

付表

臓器	**ワクチン療法/エフェクター細胞療法**
造血器腫瘍	中村先生　エフェクターあり、ワクチンなし
食道がん	なし
胃がん	なし
大腸がん	瀬田先生　ワクチンあり、エフェクターなし
肝・胆・膵がん	西川先生　膵臓癌　ワクチンあり
	肝・胆については文献検索なかったが免疫チェックポイント阻害薬等で見つかった文献を下井が対応
肺がん・悪性胸膜中皮腫・MSI-H	西川先生　肺がん　ワクチンあり、 中村先生　肺がん　エフェクターあり
	西川先生　中皮腫　ワクチンあり、 中皮腫　エフェクターなし
頭頸部がん	なし
婦人科がん	星野先生　ワクチンあり、エフェクターなし
腎細胞がん・尿路上皮がん・前立腺がん （腎障害）	中村先生　前立腺がん　ワクチンあり、 エフェクターなし
	横山先生　腎細胞がん　ワクチンあり、 エフェクターなし
	尿路上皮なし
脳腫瘍・小児腫瘍	横山先生　脳腫瘍　ワクチンあり、エフェクターなし
皮膚悪性腫瘍（悪性黒色腫・メルケル細胞がん）	瀬田先生　メラノーマ　ワクチンあり、 エフェクターなし
	その他なし
骨軟部腫瘍・原発不明がん	なし
乳がん	星野先生　ワクチンあり、エフェクターなし

資料3．ワクチン療法（Pubmed） 一部抜粋

ID	Language	Authors	Title	Journal	Year	Volume	Pages	Pub. Type	Abstract	Memo	MeSH
34011097	eng	Li YX, Luo HX, Wang W, Wang Z, Zhao WH, Hao	Diagnostic accuracy of novel folate receptor-mediated staining solution detection (FRD) for CIN2+: A systematic review and meta analysis.	Medicine (Baltimore)	2021	100(20)	e26004	Comparative Study; Evaluation Study; Journal Article; Meta-Analysis; Systematic Review	BACKGROUND: Early detection and diagnosis of high-grade cervical intraepithelial neoplasia grade 2 or higher (CIN2+) is critical for a good prognosis and appropriate treatment. The chief aim of our study was to evaluate the diagnostic performance of folate receptor-mediated staining solution detection (FRD) for CIN2+. METHODS: We conducted a systematic review and meta-analysis by searching the PubMed and EMBASE databases for studies published until May 2020, which assessed the diagnostic accuracy of FRD, human papilloma virus (HPV) testing, and ThinPrep cytology test (TCT) for the detection of CIN2+. Bivariate models were used to compare the diagnostic performance of FRD, HPV, and TCT. RESULTS: Six studies involving 2817 patients were included in this meta-analysis. The pooled specificity of FRD was higher than that of HPV and TCT for detecting CIN2+ (0.65, 0.12, and 0.39, respectively). The summary area under the receiver operating characteristic curve values using FRD, HPV, and TCT for detecting CIN2+ were 0.79, 0.95, and 0.77, respectively, indicating that FRD was superior to TCT. The diagnostic odds ratios of FRD, HPV, and TCT were 6 (95% CI: 5-7), 3 (95% CI: 2-5), and 3 (95% CI: 2-4), respectively, demonstrating that FRD had good diagnostic accuracy. CONCLUSION: FRD showed good diagnostic accuracy and higher specificity than HPV and TCT for detecting CIN2+. Based on our results, we propose that FRD could be a candidate for cervical screening, especially in underdeveloped countries.		Alphapapillomavirus; Cervical Intraepithelial Neoplasia/*diagnosis/pathology/virology; Cervix Uteri/pathology/virology; Early Detection of Cancer/*methods; Female; Folate Receptor 1/metabolism; Folic Acid/chemistry/metabolism; Humans; Papillomavirus Infections/*diagnosis/pathology/virology; Sensitivity and Specificity; Staining and Labeling/*methods; Uterine Cervical Neoplasms/*diagnosis/pathology/virology; Vaginal Smears/methods
33882206	eng	Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, Brufsky A, Sardesai SD, Kalinsky K, Zelnak AB, Weaver R, Traina T, Dalenc F, Aftimos P, Lynce F, Diab S, Cortes J, O'Shaughnessy J, Dieras V, Ferrario C, Schmid P, Carey LA, Gianni L, Piccart MJ, Loibl S, Goldenberg DM, Hong Q, Olivo MS, Itri LM, Rugo	Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer.	N Engl J Med	2021	384(16)	1529-1541	Clinical Trial, Phase III; Comparative Study; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't	BACKGROUND: Patients with metastatic triple-negative breast cancer have a poor prognosis. Sacituzumab govitecan is an antibody-drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), which is expressed in the majority of breast cancers, coupled to SN-38 (topoisomerase I inhibitor) through a proprietary hydrolyzable linker. METHODS: In this randomized, phase 3 trial, we evaluated sacituzumab govitecan as compared with single-agent chemotherapy of the physician's choice (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with relapsed or refractory metastatic triple-negative breast cancer. The primary end point was progression-free survival (as determined by blinded independent central review) among patients without brain metastases. RESULTS: A total of 468 patients without brain metastases were randomly assigned to receive sacituzumab govitecan (235 patients) or chemotherapy (233 patients). The median age was 54 years; all the patients had previous use of taxanes. The median progression-free survival was 5.6 months (95% confidence interval [CI], 4.3 to 6.3; 166 events) with sacituzumab govitecan and 1.7 months (95% CI, 1.5 to 2.6; 150 events) with chemotherapy (hazard ratio for disease progression or death, 0.41; 95% CI, 0.32 to 0.52; P<0.001). The median overall survival was 12.1 months (95% CI, 10.7 to 14.0) with sacituzumab govitecan and 6.7 months (95% CI, 5.8 to 7.7) with chemotherapy (hazard ratio for death, 0.48; 95% CI, 0.38 to 0.59; P<0.001). The percentage of patients with an objective response was 35% with sacituzumab govitecan and 5% with chemotherapy. The incidences of key treatment-related adverse events of grade 3 or higher were neutropenia (51% with sacituzumab govitecan and 33% with chemotherapy), leukopenia (10% and 5%), diarrhea (10% and <1%), anemia (8% and 5%), and febrile neutropenia (6% and 2%). There were three deaths owing to adverse events in each group; no deaths were considered to be related to sacituzumab govitecan treatment. CONCLUSIONS: Progression-free and overall survival were significantly longer with sacituzumab govitecan than with single-agent chemotherapy among patients with metastatic triple-negative breast cancer. Myelosuppression and diarrhea were more frequent with sacituzumab govitecan. (Funded by Immunomedics; ASCENT ClinicalTrials.gov number, NCT02574455; EudraCT number, 2017-003019-21.).		Adult; Aged; Aged, 80 and over; Antibodies, Monoclonal, Humanized/adverse effects/*therapeutic use; Antigens, Neoplasm; Antineoplastic Agents/adverse effects/*therapeutic use; Camptothecin/adverse effects/*analogs & derivatives/therapeutic use; Cell Adhesion Molecules/*antagonists & inhibitors; Drug Resistance, Neoplasm; Female; Humans; Immune Checkpoint Inhibitors/therapeutic use; Immunoconjugates/adverse effects/*therapeutic use; Male; Middle Aged; Neoplasm Recurrence, Local/drug therapy; Progression-Free Survival; Survival Analysis; Triple Negative Breast Neoplasms/*drug therapy/mortality; Tumor Burden

33832309	eng	Zhu T, Peng X, Cheng Z, Xing D, Zhang	Diagnostic rather than prognostic markers-relationship between EpCAM overexpression and lung cancer: a meta-analysis.	Ann Palliat Med	2021	10(4)	4025-4036	Journal Article; Meta-Analysis	BACKGROUND: Epithelial cell adhesion molecule (EpCAM) is one of the most commonly used markers of cancer stem cells (CSCs). However, the diagnostic and prognostic significance of EpCAM in lung cancer remains largely undetermined. In the present study, we systematically summarized and elucidated the correlation between EpCAM overexpression and lung cancer through a meta-analysis. METHODS: Six databases (PubMed, Web of Science, Cochrane Library, and Embase, CnKI and Wanfang Database) were systematically searched. Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria were adopted to assess the qualities of the included studies. Relevant data were extracted for meta-analysis using the Stata12.0 software. Unadjusted mixed odds ratios (ORs) or hazard ratios (HRs) with 95% confidence interval (95% CI) were estimated to evaluate the correlation between EpCAM overexpression and lung cancer. The sensitivity and specificity of the included studies were used to construct the summary receiver operator characteristic (SROC) curve and calculate the area under the SROC curve (AUC). RESULTS: A total of 14 studies consisting of 2,658 lung cancer patients were included following the PICOS principle. We found that the EpCAM expression was significantly higher in lung cancer patients compared with normal controls, including patients with benign pulmonary diseases (OR =63.71, 95% CI, 14.59-278.21, P=0.003) and healthy individuals (OR =520.08, 95% CI, 16.38-16,510.80, P=0.002), and its overexpression was negatively associated with the TNM stage (III + IV) (OR =0.41, 95% CI, 0.21-0.82, P=0.073. The combined sensitivity and specificity of EpCAM overexpression in the diagnosis of lung cancer were 0.79 (95% CI, 0.59-0.90) and 0.98 (95% CI, 0.95-0.99), respectively, and the SROC-AUC was 0.98 (95% CI, 0.97-0.99). Multivariate analysis of 322 lung cancer patients showed that there was no significant correlation between the EpCAM overexpression and prognosis of lung cancer (HR =2.28, 95% CI, 0.80-6.51, P=0.002). Deeks' funnel plot analysis showed the existence of publication bias (P=0.000). CONCLUSIONS: Our present findings suggested that EpCAM overexpression was not sensitive enough to predict the prognosis of lung cancer. Moreover, it was also a potential diagnostic indicator for lung cancer and correlated with TNM staging of lung cancer.	Epithelial Cell Adhesion Molecule/genetics; Humans; *Lung Neoplasms/diagnosis/genetics; Prognosis; Proportional Hazards Models; Sensitivity and Specificity
33787569	eng	Yuan X, Zhang AZ, Ren YL, Wang XL, Jiang CH, Yang L, Liu CX, Liang WH, Pang LJ, Gu WY, Li F, Hu	Cytokine-induced killer cells/dendritic cells and cytokine-induced killer cells immunotherapy for the treatment of esophageal cancer: A meta-analysis.	Medicine (Baltimore)	2021	100(13)	e24519	Journal Article; Meta-Analysis; Systematic Review	OBJECTIVES: This meta-analysis was designed to systematically evaluate whether autologous cytokine-induced killer cells (CIK) or dendritic cells and cytokine-induced killer cells (DC-CIK) immunotherapy combined with chemotherapy can improve the therapeutic effect and safety of chemotherapy in esophageal cancer (EC). MATERIALS AND METHODS: Randomized controlled trials (RCTs) were electronically searched databases including CNKI, WanFang, WeiPu, CBMDisc, PubMed, Web of Science, EMbase, the Cochrane Library, and Clinical Trials. The databases were searched for articles published until June 2019. Two researchers independently screened the literature, extracted data, and evaluated the quality of the included literature. Meta-analysis was performed using RevMan5.3. RESULTS: Seventeen studies (1416 participants) were included. The differences between CIK/DC-CIK combination chemotherapy and chemotherapy alone were significant. The results displayed that the number of CD3+, CD4+, CD4+/CD8+, and NK cells was significantly increased after 1 to 2 weeks of treatment with CIK/DC-CIK cells in the treatment group (all $P < .05$). In addition, the results shown that 1-year overall survival was significantly prolonged ($P < .0001$) and quality of life was improved ($P = .001$) in EC chemotherapy combined with immunotherapy groups compared with conventional treatment. Furthermore, cytokine expression levels of interleukin 2 (IL-2), tumor necrosis factor α (TNF-α), and interleukin 12 (IL-12) were significantly increased (P=.0003) as well as the levels of immunoglobulins were elevated ($P < .00001$). Serum levels of tumor marker molecules, carcinoembryonic antigen (CEA), carbohydrate antigen (CA)-199, and CA-125 were lower in treatment groups than that of control groups ($P < .00001$). No fatal adverse reactions were noted ($P = .04$). CONCLUSIONS: It is safe and effective for patients to use chemotherapy combined with CIK/DC-CIK immunotherapy. Immunotherapy can simultaneously improve the antitumor immune response. Specifically, DC-CIK cells can increase T lymphocyte subsets, CIK cells, NK cells, and immunoglobulins in peripheral blood to enhance antitumor immunity. Therefore, combination therapy enhances the immune function and improves the therapeutic efficacy of patients with EC.	Adaptive Immunity/*immunology; Aged; Antineoplastic Agents/*immunology; Combined Modality Therapy; Cytokine-Induced Killer Cells/*immunology; Dendritic Cells/*immunology; Esophageal Neoplasms/immunology/*therapy; Female; Humans; Male; Middle Aged; Randomized Controlled Trials as Topic; Treatment Outcome

33667587	eng	Pen SL, Shan YS, Hsiao CF, Liu TW, Chen JS, Ho CL, Chou WC, Hsieh RK, Chen LT, Ch'ang	High expression of krüppel-like factor 10 or Smad4 predicts clinical benefit of adjuvant chemoradiotherapy in curatively resected pancreatic adenocarcinoma: From a randomized phase III trial.	Radiother Oncol	2021	158	146-154	Clinical Trial, Phase III; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't	PURPOSE: Our previous studies have demonstrated that krüppel-like factor 10 (Klf10) modulated tumor radiation resistance and helps to predict clinical outcomes of pancreatic adenocarcinoma (PDAC). This study aimed to evaluate whether the expression levels of Klf10, Smad4 and Runx3 can help predict the benefits of adjuvant chemoradiotherapy (CRT) in resected PDAC. METHODS AND MATERIALS: Tissue specimens were collected from 111 patients with curatively resected PDAC who were enrolled into a randomized trial comparing adjuvant gemcitabine with or without CRT. Immunohistochemical expression of biomarkers was quantified by pathologists blinded to patient outcomes through a grading system based on the extent and intensity of staining. The predictive value of biomarkers was analyzed using SAS statistical software. RESULTS: In total, 56 and 55 patients received adjuvant gemcitabine alone and additional CRT, respectively. The expression levels of Klf10, Smad4 and postoperative CA19-9 were significantly correlated with overall survival (OS) (p=0.013, 0.045, and 0.047, respectively). Multivariable analysis showed that the expression level of postoperative serum CA19-9 and tumor tissue Klf10 expression level were significant predictors for OS (p=0.038, and 0.028, respectively). Patients with high Klf10 or Smad4 (n=55), had a significantly better local recurrence-free survival (oo vs 19.8months; p=0.026) and a longer OS (33.0 vs 23.0months; p=0.12) if they received additional adjuvant CRT than gemcitabine only. The results were similar after adjusted by postoperative level of CA19-9. CONCLUSION: Patients with curatively resected PDAC and a high expression of either Klf10 or Smad4 have high chances of benefiting from adjuvant CRT. Combining Klf10 and Smad4 to predict the benefits of adjuvant CRT in resected PDAC deserves further validation.	*Adenocarcinoma/therapy; CA-19-9 Antigen; Chemoradiotherapy, Adjuvant; Chemotherapy, Adjuvant; Humans; Kruppel-Like Transcription Factors; *Pancreatic Neoplasms/therapy; Smad4 Protein
33648449	eng	Zeng M, Zhou J, Wen L, Zhu Y, Luo Y, Wang	The relationship between the expression of Ki-67 and the prognosis of osteosarcoma.	BMC Cancer	2021	21(1)	210	Journal Article; Meta-Analysis; Systematic Review	BACKGROUND: A number of studies have linked positive Ki-67 expression with the prognosis of osteosarcoma (OS) patients. However, the results have been conflicting. To address this controversy, we conducted an analysis using a meta-analysis and a TCGA dataset to estimate the value of Ki-67 expression in the prognosis of OS. METHODS: A comprehensive search for relevant papers was conducted using NCBI PubMed, Embase, Springer, ISI Web of Knowledge, the Cochrane Library, and CNKI regardless of the publication year. The associations between Ki-67 expression and the clinical features and main prognostic outcomes of OS were measured. The TCGA dataset was also analyzed. The pooled odds ratio (OR) and its 95% confidential intervals (CIs) were utilized for statistical analysis. RESULTS: Overall, a total of 12 studies with 500 cases were included, and the results indicated that the expression of Ki-67 was significantly associated with Enneking stage (OR = 6.88, 95% CI: 2.92-16.22, p < .05), distant metastasis (OR = .04, 95% CI: 1.51-6.12, p = .05) and overall survival (OR = .82, 95% CI: 4.68-16.65, p < .05) in OS patients. Additionally, we observed no significant heterogeneity among all retrieved studies. Associations between Ki-67 expression and overall survival and disease-free survival of sarcoma were confirmed using the TCGA and Kaplan-Meier plotter datasets. CONCLUSION: The present study strongly suggests that positive Ki-67 expression was associated with Enneking stage, distant metastasis, and overall survival of OS, and it may be used as a potential biomarker to predict prognosis and guide clinical therapy for OS.	Antigens, Neoplasm/*analysis/biosynthesis/genetics; Bone Neoplasms/genetics/*metabolism/mortality/pathology; Datasets as Topic; Disease-Free Survival; Gene Expression Regulation, Neoplastic; Humans; Kaplan-Meier Estimate; Ki-67 Antigen/*analysis/biosynthesis/genetics; Neoplasm Metastasis; Neoplasm Staging; Osteosarcoma/genetics/*metabolism/mortality/pathology; Prognosis; Publication Bias; Sarcoma/genetics/metabolism/mortality/pathology; Up-Regulation
33381588	eng	Li J, Yin J, Zhong J, Yang Z, Tang A, Li	Clinicopathological and Prognostic Significance of PRAME Overexpression in Human Cancer: A Meta-Analysis.	Biomed Res Int	2020	2020	8828579	Journal Article; Meta-Analysis	Numerous studies have demonstrated that preferentially expressed antigen in melanoma (PRAME) is abnormally expressed in various solid tumours. However, the clinicopathological features and prognostic value of the PRAME expression in patients with cancer remain unclear. Accordingly, we performed a meta-analysis to accurately assess the association of the expression level of PRAME with clinicopathological features and cancer prognosis. Relevant study collection was performed in PubMed, Web of Science, and Embase until 28 February 2020. A total of 14 original studies involving 2,421 patients were included. Our data indicated that the PRAME expression was significantly associated with tumour stage (OR = 1.99, 95% CI: 1.48-2.67, P < 0.001) and positive lymph node metastasis (OR = 3.14, 95% CI: 1.99-4.97, P < 0.001). Pooled results showed that overexpression of PRAME is positively correlated with poor disease-free survival (HR = 1.60, 95% CI: 1.36-1.88, P < 0.001), progression-free survival (HR = 1.88, 95% CI: 1.02-3.46, P = 0.042), metastasis-free survival (HR = 1.86, 95% CI: 1.05-3.31, P = 0.034), and overall survival (HR = 1.75, 95% CI: 1.53-1.99, P < 0.001). In summary, these data are suggesting that PRAME is tumorigenic and may serve as a prognostic biomarker for cancer.	Antigens, Neoplasm/*metabolism; Biomarkers, Tumor; Disease-Free Survival; *Gene Expression Regulation, Neoplastic; Humans; Kaplan-Meier Estimate; Lymphatic Metastasis; Melanoma/*metabolism/mortality; Neoplasm Metastasis; Prognosis; Progression-Free Survival; Skin Neoplasms/*metabolism/mortality

33615628	eng	Kondo S, Shimizu T, Koyama T, Sato J, Iwasa S, Yonemori K, Fujiwara Y, Shimomura A, Kitano S, Tamura K, Yamamoto	First-in-human study of the cancer peptide vaccine TAS0313 in patients with advanced solid tumors.	Cancer Sci	2021	112(4)	1514-1523	Clinical Trial, Phase I; Clinical Trial, Phase II; Journal Article; Multicenter Study; Randomized Controlled Trial	TAS0313, a novel cancer vaccine cocktail, was developed to overcome the disadvantages of previously developed short and long peptide vaccines; it comprises several long peptides targeting multiple cancer antigens. We evaluated TAS0313 monotherapy in Japanese patients with advanced solid tumors for which no other therapies were available. In the dose-finding cohort, patients received TAS0313 (9 or 27mg) on days 1, 8, and 15 of cycles 1 and 2, and then on day 1 of each subsequent 21-day cycle. The primary objective was the evaluation of safety and tolerability. Secondary objectives were evaluation of efficacy, tumor responses, and immune activation (CTL, IgG, and tumor-infiltrating lymphocyte [TIL] levels). The full analysis set contained 10 patients in the 9-mg group and seven in the 27-mg group. No dose-limiting toxicities were reported in cycle 1. All adverse drug reactions (ADRs) were grade 1 or 2; the most common ADRs were injection site-related events. The best response was stable disease in four of 17 patients. The median progression-free survival (PFS) duration was 2.2 (95% confidence interval, 1.0-2.3) months overall; patients with baseline low lymphocyte counts (<750/μL) had shorter PFS. Compared with baseline, TILs were increased in five patients. Although CTLs, IgG, and TILs were induced, no correlative pattern with clinical outcomes was observed. The safety, tolerability, and induction of immune responses in patients with advanced solid tumors receiving TAS0313 were confirmed. Further evaluation of TAS0313's efficacy as monotherapy or in combination with pembrolizumab is underway. The study is registered at www.clinicaltrials.jp (JapicCTI-183824).	Aged; Antibodies, Monoclonal, Humanized/adverse effects/therapeutic use; Antineoplastic Agents, Immunological/therapeutic use; Antineoplastic Combined Chemotherapy Protocols/adverse ; Cancer Vaccines/*immunology; Cohort Studies; Drug-Related Side Effects and Adverse Reactions/immunology; Female; Humans; Immunoglobulin G/immunology; Lymphocytes, Tumor-Infiltrating/drug effects/immunology; Male; Middle Aged; Neoplasms/drug therapy/*immunology/therapy; Peptides/*immunology; Progression-Free Survival; Vaccines, Subunit/*immunology
33568208	eng	Makarov DV, Feuer Z, Ciprut S, Lopez NM, Fagerlin A, Shedlin M, Gold HT, Li H, Lynch G, Warren R, Ubel P, Ravenell	Randomized trial of community health worker-led decision coaching to promote shared decision-making for prostate cancer screening among Black male patients and their providers.	Trials	2021	22(1)	128	Journal Article; Randomized Controlled Trial	BACKGROUND: Black men are disproportionately affected by prostate cancer, the most common non-cutaneous malignancy among men in the USA. The United States Preventive Services Task Force (USPSTF) encourages prostate-specific antigen (PSA) testing decisions to be based on shared decision-making (SDM) clinician professional judgment, and patient preferences. However, evidence suggests that SDM is underutilized in clinical practice, especially among the most vulnerable patients. The purpose of this study is to evaluate the efficacy of a community health worker (CHW)-led decision-coaching program to facilitate SDM for prostate cancer screening among Black men in the primary care setting, with the ultimate aim of improving/optimizing decision quality. METHODS: We proposed a CHW-led decision-coaching program to facilitate SDM for prostate cancer screening discussions in Black men at a primary care FQHC. This study enrolled Black men who were patients at the participating clinical site and up to 15 providers who cared for them. We estimated to recruit 228 participants, ages 40-69 to be randomized to either (1) a decision aid along with decision coaching on PSA screening from a CHW or (2) receiving a decision aid along with CHW-led interaction on modifying dietary and lifestyle to serve as an attention control. The independent randomization process was implemented within each provider and we controlled for age by dividing patients into two strata: 40-54 years and 55-69 years. This sample size sufficiently powered the detection differences in the primary study outcomes: knowledge, indicative of decision quality, and differences in PSA screening rates. Primary outcome measures for patients will be decision quality and decision regarding whether to undergo PSA screening. Primary outcome measures for providers will be acceptability and feasibility of the intervention. We will examine how decision coaching about prostate cancer screening impact patient-provider communication. These outcomes will be analyzed quantitatively through objective, validated scales and qualitatively through semi-structured, in-depth interviews, and thematic analysis of clinical encounters. Through a conceptual model combining elements of the Preventative Health Care Model (PHM) and Informed Decision-Making Model, we hypothesize that the prostate cancer screening decision coaching intervention will result in a preference-congruent decision and decisional satisfaction. We also hypothesize that this intervention will improve physician satisfaction with counseling patients about prostate cancer screening. DISCUSSION: Decision coaching is an evidence-based approach to improve decision quality in many clinical contexts, but its efficacy is incompletely explored for PSA screening among Black men in primary care. Our proposal to evaluate a CHW-led decision-coaching program for PSA screening has high potential for scalability and public health impact. Our results will determine the efficacy, cost-effectiveness, and sustainability of a CHW intervention in a community clinic setting in order to inform subsequent widespread dissemination, a critical research area highlighted by USPSTF. TRIAL REGISTRATION: The trial was registered prospectively with the National Institute of Health registry (www.clinicaltrials.gov), registration number NCT03726320 , on October 31, 2018.	Adult; African Americans; Aged; Community Health Workers; Decision Making; Early Detection of Cancer; Humans; Male; *Mentoring; Middle Aged; Prostate-Specific Antigen; *Prostatic Neoplasms/diagnosis/therapy; United States

33496795	eng	Vaishampayan UN, Heilbrun LK, Monk P 3rd, Tejwani S, Sonpavde G, Hwang C, Smith D, Jasti P, Dobson K, Dickow B, Heath EI, Semaan L, Cher ML, Fontana JA, Chinni	Clinical Efficacy of Enzalutamide vs Bicalutamide Combined With Androgen Deprivation Therapy in Men With Metastatic Hormone-Sensitive Prostate Cancer: A Randomized Clinical Trial.	JAMA Netw Open	2021	4(1)	e2034633	Clinical Trial, Phase II; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't	IMPORTANCE: Black patients have been underrepresented in prospective clinical trials of advanced prostate cancer. This study evaluated the efficacy of enzalutamide compared with bicalutamide, with planned subset analysis of Black patients with metastatic hormone-sensitive prostate cancer (mHSPC), which is a disease state responsive to androgen deprivation therapy (ADT). OBJECTIVE: To compare the efficacy of enzalutamide vs bicalutamide in combination with ADT in men with mHSPC, with a subset analysis of Black patients. DESIGN, SETTING, AND PARTICIPANTS: In this randomized clinical trial, a phase 2 screening design enabled a nondefinitive comparison of the primary outcome by treatment. Patients were stratified by race (Black or other) and bone pain (present or absent). Accrual of at least 30% Black patients was required. This multicenter trial was conducted at 4 centers in the US. Men with mHSPC with no history of seizures and adequate marrow, renal, and liver function were eligible. Data analysis was performed from February 2019 to March 2020. INTERVENTIONS: Participants were randomized 1:1 to receive oral enzalutamide (160 mg daily) or bicalutamide (50 mg daily) in addition to ADT. MAIN OUTCOMES AND MEASURES: The primary end point was the 7-month prostate-specific antigen (PSA) response (SMPR) rate, a previously accepted surrogate for overall survival (OS) outcome. Secondary end points included adverse reactions, time to PSA progression, and OS. RESULTS: A total of 71 men (median [range] age, 65 [51-86] years) were enrolled; 29 (41%) were Black, 41 (58%) were White, and 1 (1%) was Asian. Thirty-six patients were randomized to receive enzalutamide, and 35 were randomized to receive bicalutamide. Twenty-six patients (37%) had bone pain and 37 patients (52%) had extensive disease. SMPR was achieved in 30 of 32 patients (94%; 95% CI, 80%-98%) taking enzalutamide and 17 of 26 patients (65%; 95% CI, 46%-81%) taking bicalutamide (P = .008) (difference, 29%; 95% CI, 5%-50%). Among Black patients, the SMPR was 93% (95% CI, 69%-99%) among those taking enzalutamide and 42% (95% CI, 19%-68%) among those taking bicalutamide (P = .009); among non-Black patients, the SMPR was 94% (95% CI, 74%-99%) among those taking enzalutamide and 86% (95% CI, 60%-96%) among those taking bicalutamide. The 12-month PSA response rates were 84% with enzalutamide and 34% with bicalutamide. CONCLUSIONS AND RELEVANCE: The findings of this randomized clinical trial comparing enzalutamide with bicalutamide suggest that enzalutamide is associated with improved outcomes compared with bicalutamide, in terms of the rate and duration of PSA response, in Black patients with mHSPC. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02058706.	*African Americans; Aged; Aged, 80 and over; Androgen Antagonists/*therapeutic use; Anilides/*therapeutic use; Antineoplastic Agents/*therapeutic use; Biomarkers, Tumor/blood; Drug Therapy, Combination; Humans; Male; Middle Aged; Nitriles/*therapeutic use; Phenylthiohydantoin/*analogs & derivatives/therapeutic use; Prostate-Specific Antigen/blood; Prostatic Neoplasms/*drug therapy/ethnology; Tosyl Compounds/*therapeutic use; Treatment Outcome
33485895	eng	Chick RC, Clifton GT, Hale DF, Vreeland TJ, Hickerson AT, Kemp Bohan PM, McCarthy PM, Litton JK, Alatrash G, Murthy RK, Qiao N, Philips A, Lukas J, Holmes JP, Mittendorf EA, Peoples	Subgroup analysis of nelipepimut-S plus GM-CSF combined with trastuzumab versus trastuzumab alone to prevent recurrences in patients with high-risk, HER2 low-expressing breast cancer.	Clin Immunol	2021	225	108679	Clinical Trial, Phase II; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't	HER2-targeted therapy has not benefited patients with low levels of HER2 expression; however, combination therapy may be effective. Primary analysis of a phase IIb trial investigating the HER2-derived vaccine nelipepimut-S (NPS) did not benefit the intention-to-treat population, but subset analysis showed a benefit in triple-negative breast cancer (TNBC) patients. The subset analysis of this multicenter, randomized, single-blind, phase IIb trial identified significant improvement in 36-month disease-free survival (DFS) between NPS (n=55) and placebo (n=44) in TNBC (HR 0.25, p=0.01) and those who express HLA-A24 (HR 0.41, p=0.05). The TNBC cohort demonstrated improved 36-month DFS in those with HER2 1+ expression (HR 0.17, p=0.01), HLA-A24 positivity (HR 0.08, p<0.01), or in those who received neoadjuvant chemotherapy (HR 0.21, p<0.01). NPS vaccination with trastuzumab was associated with improved 36-month DFS among patients with TNBC. The observed benefit to this high-risk subgroup warrants confirmation in a phase III trial.	Adult; Antineoplastic Combined Chemotherapy Protocols/*therapeutic use; Cancer Vaccines/*immunology; Cohort Studies; Female; Gene Expression Regulation, Neoplastic; Granulocyte-Macrophage Colony-Stimulating Factor/*immunology; HLA-A24 Antigen/metabolism; Humans; Immunotherapy/*methods; Intention to Treat Analysis; Neoplasm Recurrence, Local; Peptide Fragments/*immunology; Placebo Effect; Precision Medicine; Receptor, ErbB-2/genetics/*immunology/metabolism; Risk; Survival Analysis; Trastuzumab/*therapeutic use; Triple Negative Breast Neoplasms/immunology/mortality/*therapy
33472645	eng	Wang X, Zhang Y, Ji Z, Yang P, Tian	Old men with prostate cancer have higher risk of Gleason score upgrading and pathological upstaging after initial diagnosis: a systematic review and meta-analysis.	World J Surg Oncol	2021	19(1)	18	Journal Article; Meta-Analysis; Review; Systematic Review	BACKGROUND: To evaluate the predictive performance of age for the risk of Gleason score change and pathologic upstaging. EVIDENCE ACQUISITION: Ovid MEDLINE, Ovid Embase, and the Cochrane Library were searched from inception until May 2020. Quality of included studies was appraised utilizing the Newcastle-Ottawa Quality Assessment Scale for case-control studies. The publication bias was evaluated by funnel plots and Egger's tests. EVIDENCE SYNTHESIS: Our search yielded 27 studies with moderate-to-high quality including 84296 patients with mean age of 62.1 years. From biopsy to prostatectomy, upgrading and upstaging occurred in 32.3% and 9.8% of patients, respectively. Upgrading from diagnostic biopsy to confirmatory biopsy was found in 16.8%. Older age was associated with a significant increased risk of upgrading (OR 1.04, 95% CI 1.03-1.05), and similar direction of effect was found in studies focused on upgrading from diagnostic biopsy to confirmatory biopsy (OR 1.06, 95% CI 1.04-1.08). For pathologic upstaging within older men compared with younger, the pooled odds was 1.03 (95% CI 1.01-1.04). CONCLUSION: Thorough consideration of age in the context of effect sizes for other factors not only prompts more accurate risk stratification but also helps providers to select optimal therapies for patients with prostate cancer.	Aged; Biopsy; Humans; Male; Middle Aged; Neoplasm Grading; Neoplasm Staging; Prognosis; Prostate-Specific Antigen; Prostatectomy; *Prostatic Neoplasms/pathology/surgery; Retrospective Studies

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ID	Languag	Authors	Title	Journal	Year	Volume	Pages	Pub. Type	Abstract	Memo	MeSH
34017005	eng	Andreatta M, Corria-Osorio J, Müller S, Cubas R, Coukos G, Carmona SJ	Interpretation of T cell states from single-cell transcriptomics data using reference atlases.	Nat Commun	2021	12(1)	2965	Journal Article; Meta-Analysis; Research Support, Non-U.S. Gov't	Single-cell RNA sequencing (scRNA-seq) has revealed an unprecedented degree of immune cell diversity. However, consistent definition of cell subtypes and cell states across studies and diseases remains a major challenge. Here we generate reference T cell atlases for cancer and viral infection by multi-study integration, and develop ProjecTILs, an algorithm for reference atlas projection. In contrast to other methods, ProjecTILs allows not only accurate embedding of new scRNA-seq data into a reference without altering its structure, but also characterizing previously unknown cell states that "deviate" from the reference. ProjecTILs accurately predicts the effects of cell perturbations and identifies gene programs that are altered in different conditions and tissues. A meta-analysis of tumor-infiltrating T cells from several cohorts reveals a strong conservation of T cell subtypes between human and mouse, providing a consistent basis to describe T cell heterogeneity across studies, diseases, and species.		Animals; Cell Differentiation/immunology; Cohort Studies; Disease Models, Animal; Gene Expression Regulation/immunology; Humans; Lymphocytes, Tumor-Infiltrating/immunology; Mice; Neoplasms/blood/*immunology/pathology; RNA-Seq/*methods; Reference Values; Single-Cell Analysis/*methods; Software; Species Specificity; T-Lymphocyte Subsets/immunology; T-Lymphocytes/*immunology; Tumor Microenvironment/immunology; Virus Diseases/blood/*immunology
33751401	eng	Song Y, Zhou H, Zhang H, Liu W, Shuang Y, Zhou K, Lv F, Xu H, Zhou J, Li W, Wang H, Zhang H, Huang H, Zhang Q, Xu W, Ge Z, Xiang Y, Wang S, Gao D, Yang S, Lin J, Wang L, Zou L, Zheng M, Liu J, Shao Z, Pang Y, Xia R, Chen Z, Hou M, Yao H, Feng R, Cai Z, Zhang M, Ran W, Liu L, Zeng S, Yang W, Liu P, Liang A, Zuo X, Zou Q, Ma J, Sang W, Guo Y, Zhang W, Cao Y, Li Y, Feng J, Du X, Zhang X, Zhao H, Zhou H, Yu J, Sun X, Zhu J, Qiu L	Efficacy and Safety of the Biosimilar IBI301 Plus Standard CHOP (I-CHOP) in Comparison With Rituximab Plus CHOP (R-CHOP) in Patients with Previously Untreated Diffuse Large B-Cell Lymphoma (DLBCL): A Randomized, Double-Blind, Parallel-Group, Phase 3 Trial.	Adv Ther	2021	38(4)	1889-1903	Clinical Trial, Phase III; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't	INTRODUCTION: Patients with diffuse large B-cell lymphoma (DLBCL) have limited access to rituximab. IBI301 is a recombinant chimeric murine/human anti-CD20 monoclonal antibody and is a candidate biosimilar to rituximab. This study aimed to assess the therapeutic equivalence of IBI301 and rituximab in previously untreated patients with diffuse large B-cell lymphoma (DLBCL). METHODS: This multicenter, randomized, double-blind, parallel-group, phase 3 trial compared IBI301 and rituximab, both plus the chemotherapy of doxorubicin, cyclophosphamide, vindesine, and prednisone (CHOP), was conducted in 68 centers across China. Eligible patients with untreated CD20 positive (CD20(+)) DLBCL randomly received IBI301 (375mg/m(2)) plus the standard CHOP or rituximab (375mg/m(2)) plus the standard CHOP for six cycles of a 21-day cycle. The primary end point was the overall remission rate (ORR). Efficacy equivalence was defined if 95% CIs for the ORR difference between the two groups were within a±2.0% margin. RESULTS: Between August 22, 2016, and September 5, 2018, 419 patients were randomly allocated into the IBI301 group (N = 209) and rituximab group (N = 210). In the full analysis set, the ORR was 89.9% and 93.8% in the IBI301 and rituximab groups, respectively, and the ORR difference was -3.9% (95% CI -9.1%-1.3%), falling within a ± ・2.0% margin. The occurrences of treatment-emergent adverse events (TEAEs) (100% vs. 99.0%) and AEs of grade > 3 (87.1% vs. 83.3%) were similar in the two groups (P >.05). CONCLUSIONS: IBI301 had a non-inferiority efficacy and a comparable safety compared with rituximab. IBI301 plus CHOP could be suggested as a candidate treatment regimen for untreated patients with CD20(+) DLBCL. TRIAL REGISTRATION: This trial is registered on ClinicalTrials.gov (NCT02867566).		Animals; Antineoplastic Combined Chemotherapy Protocols/therapeutic use; *Biosimilar Pharmaceuticals/therapeutic use; China; Humans; *Lymphoma, Large B-Cell, Diffuse/drug therapy; Mice; Reference Standards; Rituximab/therapeutic use; Treatment Outcome; Vincristine/therapeutic use
33610734	eng	Sahin U, Türeci ・, Manikhas G, Lordick F, Rusyn A, Vynnychenko I, Dudov A, Bazin I, Bondarenko I, Melichar B, Dhaene K, Wiechen K, Huber C, Maurus D, Arozullah A, Park JW, Schuler M, Al-Batran SE	FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma.	Ann Oncol	2021	32(5)	609-619	Clinical Trial, Phase II; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't	BACKGROUND: Claudin 18.2 (CLDN18.2) is contained within normal gastric mucosa epithelial tight junctions; upon malignant transformation, CLDN18.2 epitopes become exposed. Zolbetuximab, a chimeric monoclonal antibody, mediates specific killing of CLDN18.2-positive cells through immune effector mechanisms. PATIENTS AND METHODS: The FAST study enrolled advanced gastric/gastro-oesophageal junction and oesophageal adenocarcinoma patients (aged ≧τ8 years) with moderate-to-strong CLDN18.2 expression in ≧χ0% tumour cells. Patients received first-line epirubicin+ oxaliplatin+ capecitabine (EOX, arm 1, n= 84) every 3 weeks (Q3W), or zolbetuximab+ EOX (loading dose, 800 mg/m(2) then 600 mg/m(2) Q3W) (arm 2, n= 77). Arm 3 (exploratory) was added after enrolment initiation (zolbetuximab+ EOX 1000 mg/m(2) Q3W, n= 85). The primary endpoint was progression-free survival (PFS) and overall survival (OS) was a secondary endpoint. RESULTS: In the overall population, both PFS [hazard ratio (HR)= 0.44; 95% confidence interval (CI), 0.29-0.67; P < 0.0005] and OS (HR= 0.55; 95% CI, 0.39-0.77; P < 0.0005) were significantly improved with zolbetuximab+ EOX (arm 2) compared with EOX alone (arm 1). This significant PFS benefit was retained in patients with moderate-to-strong CLDN18.2 expression in ≧ ・0% of tumour cells (HR= 0.38; 95% CI, 0.23-0.62; P < 0.0005). Significant improvement in PFS was also reported in the overall population of arm 3 versus arm 1 (HR= 0.58; 95% CI, 0.39-0.85; P= 0.0114) but not in high CLDN18.2-expressing patients; no significant improvement in OS was observed in either population. Most adverse events (AEs) related to zolbetuximab+ EOX (nausea, vomiting, neutropenia, anaemia) were grade 1-2. Grade ≧φ AEs showed no substantial increases overall (zolbetuximab+ EOX versus EOX alone). CONCLUSIONS: In advanced gastric/gastro-oesophageal junction and oesophageal adenocarcinoma patients expressing CLDN18.2, adding zolbetuximab to first-line EOX provided longer PFS and OS versus EOX alone. Zolbetuximab+ EOX was generally tolerated and AEs were manageable. Zolbetuximab 800/600 mg/m(2) is being evaluated in phase III studies based on clinical benefit observed in the overall population and in patients with moderate-to-strong CLDN18.2 expression in ≧ ・0% of tumour cells.		*Adenocarcinoma/drug therapy; Adolescent; Adult; Antibodies, Monoclonal/therapeutic use; Antineoplastic Combined Chemotherapy Protocols/therapeutic use; Capecitabine/therapeutic use; Claudins/genetics/therapeutic use; *Esophageal Neoplasms/drug therapy; Esophagogastric Junction; Humans; *Stomach Neoplasms/drug therapy
33606005	eng	Mohyuddin GR, Rooney A, Balmaceda N, Aziz M, Sborov DW, McClune B, Kumar SK	Chimeric antigen receptor T-cell therapy in multiple myeloma: a systematic review and meta-analysis of 950 patients.	Blood Adv	2021	5(4)	1097-1101	Journal Article; Meta-Analysis; Systematic Review			Cell- and Tissue-Based Therapy; Humans; Immunotherapy, Adoptive; *Multiple Myeloma/therapy; *Receptors, Chimeric Antigen/genetics; T-Lymphocytes

33598857	eng	Shah N, Sussman M, Crivera C, Valluri S, Benner J, Jagannath S	Comparative Effectiveness Research for CAR-T Therapies in Multiple Myeloma: Appropriate Comparisons Require Careful Considerations of Data Sources and Patient Populations.	Clin Drug Investig	2021	41(3)	201-210	Systematic Review	BACKGROUND AND OBJECTIVE: Registrational trials for ciltacabtagene autoleucel [cilta-cel]) and idecabtagene vicleucel [ide-cel] chimeric antigen receptor T-cell (CAR-T) therapies were single-arm studies conducted with relapse refractory multiple myeloma (MM) patients who were triple-class-exposed (TCE) or triple-class-refractory (TCR). It is critical for researchers conducting comparative effectiveness research (CER) to carefully consider the most appropriate data sources and comparable patient populations. The aim of this study was to identify potential data sources and populations for comparing to single-arm CAR-T trials CARTITUDE-1 (cilta-cel) and KarMMa (ide-cel). METHODS: A 2-part global systematic literature search produced a review of (1) clinical trials of National Comprehensive Cancer Network (NCCN) guideline preferred regimens in previously treated MM, and (2) real-world data cohorts of TCE or TCR populations, published between 1/1/2015 and 12/10/2020, with sample sizes of >50 patients and reporting survival-related outcomes. Implications on CER and accepted best practices are discussed. RESULTS: Nine clinical trials of NCCN preferred regimens were identified along with five real-world data-based publications. No clinical trials evaluated patients with TCE or TCR MM. Among the real-world data-based publications, two evaluated patients exclusively with TCR MM, two analyzed a mixed population of patients with TCE or TCR MM, and one publication assessed patients exclusively with TCE MM. Real-world data treatment patterns were heterogeneous. CONCLUSION: Current NCCN preferred regimens were not specifically studied in TCE or TCR MM patients, although some studies do include a proportion of these types of patients. Therefore, appropriate matching of populations using either real-world data or patient level clinical trial data is critical to putting trials of novel CAR-Ts (i.e., CARTITUDE-1 or KarMMa) into appropriate comparative context.	Comparative Effectiveness Research; Humans; Immunotherapy, Adoptive/*methods; Information Storage and Retrieval; Multiple Myeloma/*therapy; Receptors, Chimeric Antigen/*immunology
33587155	eng	Hu L, Charwudzi A, Li Q, Zhu W, Tao Q, Xiong S, Zhai Z	Anti-CD19 CAR-T cell therapy bridge to HSCT decreases the relapse rate and improves the long-term survival of R/R B-ALL patients: a systematic review and meta-analysis.	Ann Hematol	2021	100(4)	1003-1012	Journal Article; Meta-Analysis; Systematic Review	Chimeric antigen receptor (CAR) T cell therapy improves the remission rate of refractory/relapsed B-acute lymphoblastic leukemia (R/R B-ALL) patients, but the relapse rate remains high. Recent studies suggest patients who underwent post-chimeric antigen receptor T cell therapy hematopoietic stem cell transplantation (post- HSCT) would achieve durable remission and better survival, but this remains controversial. To this end, we conducted a meta-analysis to assess the role of post-HSCT in R/R B-ALL. The Cochrane Library, Embase, and PubMed were used to identify relevant studies; the latest search update was on July 05, 2020. We used the Cochran Q test and I-squared statistics to test for heterogeneity among the studies analyzed. The fixed model and random model were used to combine results when appropriate. We performed all statistical analyses with Stata 12, and $P < 0.05$ was considered statistically significant. We included 18 studies with 758 patients in the meta-analysis. Our results indicated that post-HSCT was associated with lower relapse rate (RR: 0.40, 95% CI: 0.32-0.50, P = 0.000), better overall survival (HR: 0.37, 95% CI: 0.19-0.71, P = 0.003), better leukemia-free survival (HR: 0.20, 95% CI: 0.10-0.40, P = 0.000). However, post-HSCT did not influence OS in Caucasians, and CAR-T cells with CD28 co-stimulation factor bridged to HSCT did not influence OS. Post-HSCT decreased the relapse rate and improved the long-term survival of R/R B-ALL patients. R/R B-ALL patients would benefit from post-HSCT after CAR-T cell therapy.	Antigens, CD19/immunology; Asian Continental Ancestry Group; Disease-Free Survival; Epidemiologic Studies; European Continental Ancestry Group; *Hematopoietic Stem Cell Transplantation; Humans; *Immunotherapy, Adoptive; Precursor Cell Lymphoblastic Leukemia-Lymphoma/ethnology/mortality/*therapy; Prognosis; Recurrence; Remission Induction; *Salvage Therapy; Treatment Outcome
33581791	eng	Li T, Zhang GQ, Li Y, Dong SA, Wang N, Yi M, Qi Y, Zhai H, Yang L, Shi FD, Yang CS	Efficacy and safety of different dosages of rituximab for refractory generalized AChR myasthenia gravis: A meta-analysis.	J Clin Neurosci	2021	85	6-12	Journal Article; Meta-Analysis	BACKGROUND: Rituximab (RTX) is a mouse-human chimeric anti-CD20 monoclonal antibody and has been increasingly used for preventing relapses in myasthenia gravis (MG). However, the appropriate dose for maximizing the beneficial effects in refractory MG with acetylcholine receptor (AChR) autoantibody is a long-standing and critical debating question. METHODS: We performed a meta-analysis to evaluate the efficacy and safety of the different doses of RTX in 260 refractory AChR-MG patients. RESULTS: The AChR-MG patients were divided into low or routine RTX dose groups. An overall proportion of 77% (p=0.000) AChR-MG patients demonstrated improved clinical status as indicated by the Myasthenia Gravis Foundation of America post-intervention scale (MGFA-PIS). There were 77.1% patients showed improved clinical status in lower dose of RTX group (p=0.000) and 76.8% in routine protocol group (p=0.000). Although we found there was no significant difference in the proportion of AChR-MG patients with improved clinical status or adverse reactions between the two groups, adverse reactions might be lower in the lower dose RTX group. CONCLUSION: Most of refractory MG patients with anti-AChR autoantibody were well responsive and tolerated to RTX treatment. Repeated application of lower dose of RTX was effective and might be more appropriate for refractory AChR-MG patients with potential lower side effects.	Adult; Aged; Autoantibodies/immunology; Dose-Response Relationship, Drug; Female; Humans; Immunologic Factors/*administration & dosage/adverse effects; Male; Middle Aged; Myasthenia Gravis/*drug therapy/immunology; Receptors, Cholinergic/immunology; Rituximab/*administration & dosage/adverse effects

33308471	eng	Benjamin R, Graham C, Yallop D, Jozwik A, Mirci-Danicar OC, Lucchini G, Pinner D, Jain N, Kantarjian H, Boissel N, Maus MV, Frigault MJ, Baruchel A, Mohty M, Gianella-Borradori A, Binlich F, Balandraud S, Vitry F, Thomas E, Philippe A, Fouliard S, Dupouy S, Marchiq I, Almena-Carrasco M, Ferry N, Arnould S, Konto C, Veys P, Qasim W	Genome-edited, donor-derived allogeneic anti-CD19 chimeric antigen receptor T cells in paediatric and adult B-cell acute lymphoblastic leukaemia: results of two phase 1 studies.	Lancet	2020	396(10266)	1885-1894	Clinical Trial, Phase I; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't	BACKGROUND: Genome-edited donor-derived allogeneic anti-CD19 chimeric antigen receptor (CAR) T cells offer a novel form of CAR-T-cell product that is available for immediate clinical use, thereby broadening access and applicability. UCART19 is one such product investigated in children and adults with relapsed or refractory B-cell acute lymphoblastic leukaemia. Two multicentre phase 1 studies aimed to investigate the feasibility, safety, and antileukaemic activity of UCART19 in children and adults with relapsed or refractory B-cell acute lymphoblastic leukaemia. METHODS: We enrolled paediatric or adult patients in two ongoing, multicentre, phase 1 clinical trials to evaluate the safety and antileukaemic activity of UCART19. All patients underwent lymphodepletion with fludarabine and cyclophosphamide with or without alemtuzumab, then children received UCART19 at 1・1-2・3 ×10(6) cells per kg and adults received UCART19 doses of 6 × 10(6) cells, 6-8 × 10(7) cells, or 1・8-2・4× 10(8) cells in a dose-escalation study. The primary outcome measure was adverse events in the period between first infusion and data cutoff. These studies were registered at ClinicalTrials.gov, NCT02808442 and NCT02746952. FINDINGS: Between June 3, 2016, and Oct 23, 2018, seven children and 14 adults were enrolled in the two studies and received UCART19. Cytokine release syndrome was the most common adverse event and was observed in 19 patients (91%); three (14%) had grade 3-4 cytokine release syndrome. Other adverse events were grade 1 or 2 neurotoxicity in eight patients (38%), grade 1 acute skin graft-versus-host disease in two patients (10%), and grade 4 prolonged cytopenia in six patients (32%). Two treatment-related deaths occurred; one caused by neutropenic sepsis in a patient with concurrent cytokine release syndrome and one from pulmonary haemorrhage in a patient with persistent cytopenia. 14 (67%) of 21 patients had a complete response or complete response with incomplete haematological recovery 28 days after infusion. Patients not receiving alemtuzumab (n=4) showed no UCART19 expansion or antileukaemic activity. The median duration of response was 4・1 months with ten (71%) of 14 responders proceeding to a subsequent allogeneic stem-cell transplant. Progression-free survival at 6 months was 27%, and overall survival was 55%. INTERPRETATION: These two studies show, for the first time, the feasibility of using allogeneic, genome-edited CAR T cells to treat patients with aggressive leukaemia. UCART19 exhibited in-vivo expansion and antileukaemic activity with a manageable safety profile in heavily pretreated paediatric and adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia. The results this study are an encouraging step forward for the field of allogeneic CAR T cells, and UCART19 offers the opportunity to treat patients with rapidly progressive disease and where autologous CAR-T-cell therapy is unavailable. FUNDING: Servier.	Adult; Antigens, CD19/*immunology; Child, Preschool; Cytokine Release Syndrome/etiology; Feasibility Studies; Female; Gene Editing; Humans; Immunotherapy, Adoptive/adverse effects; Male; Precursor Cell Lymphoblastic Leukemia-Lymphoma/*therapy; Receptors, Chimeric Antigen/*therapeutic use
33272302	eng	Roex G, Timmers M, Wouters K, Campillo-Davo D, Flumens D, Schroyens W, Chu Y, Berneman ZN, Lion E, Luo F, Anguille S	Safety and clinical efficacy of BCMA CAR-T-cell therapy in multiple myeloma.	J Hematol Oncol	2020	13(1)	164	Journal Article; Meta-Analysis; Research Support, Non-U.S. Gov't; Systematic Review	BACKGROUND: B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR)-T-cell therapy is an emerging treatment option for multiple myeloma. The aim of this systematic review and meta-analysis was to determine its safety and clinical activity and to identify factors influencing these outcomes. METHODS: We performed a database search using the terms "BCMA," "CAR," and "multiple myeloma" for clinical studies published between 01/01/2015 and 01/01/2020. The methodology is further detailed in PROSPERO (CRD42020125332). RESULTS: Twenty-three different CAR-T-cell products have been used so far in 640 patients. Cytokine release syndrome was observed in 80.3% (69.0-88.2); 10.5% (6.8-16.0) had neurotoxicity. A higher neurotoxicity rate was reported in studies that included more heavily pretreated patients: 19.1% (13.3-26.7; I(2) = 5%) versus 2.8% (1.3-6.1; I(2) = 0%) (p < .0001). The pooled overall response rate was 80.5% (73.5-85.9); complete responses (CR) were observed in 44.8% (35.3-54.6). A pooled CR rate of 71.9% (62.8-79.6; I(2) = 0%) was noted in studies using alpaca/llama-based constructs, whereas it was only 18.0% (6.5-41.1; I(2) = 7%) in studies that used retroviral vectors for CAR transduction. Median progression-free survival (PFS) was 12.2 (11.4-17.4) months, which compared favorably to the expected PFS of 1.9 (1.5-3.7) months (HR 0.14; p < .0001). CONCLUSIONS: Although considerable toxicity was observed, BCMA-targeted CAR-T-cell therapy is highly efficacious even in advanced multiple myeloma. Subgroup analysis confirmed the anticipated inter-study heterogeneity and identified potential factors contributing to safety and efficacy. The results of this meta-analysis may assist the future design of CAR-T-cell studies and lead to optimized BCMA CAR-T-cell products.	B-Cell Maturation Antigen/*immunology; Cytokine Release Syndrome/etiology/immunology; Humans; Immunotherapy, Adoptive/*adverse effects/methods; Multiple Myeloma/immunology/*therapy; Neurotoxicity Syndromes/etiology/immunology; Progression-Free Survival; Receptors, Chimeric Antigen/immunology/*therapeutic use; Treatment Outcome

33091355	eng	Anagnostou T, Riaz IB, Hashmi SK, Murad MH, Kenderian SS	Anti-CD19 chimeric antigen receptor T-cell therapy in acute lymphocytic leukaemia: a systematic review and meta-analysis.	Lancet Haematol	2020	7(11)	e816-e826	Journal Article; Meta-Analysis; Systematic Review	BACKGROUND: Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy has shown remarkable activity in patients with refractory or relapsed acute lymphocytic leukaemia. Various anti-CD19 CAR T-cell constructs have been trialled and responses vary widely among different studies. We aimed to systematically analyse the outcomes of patients with acute lymphocytic leukaemia treated with anti-CD19 CAR T cells and identify factors associated with differences in outcomes. METHODS: We did a systematic review and meta-analysis of published and unpublished clinical trials that reported data on the outcomes of adult or paediatric patients that were treated with anti-CD19 CAR T cells for relapsed or refractory B-cell acute lymphocytic leukaemia, reported between Jan 1, 2012, and April 14, 2020. Studies with two patients or fewer were excluded and summary data were extracted from the reports. The primary outcome was the number of patients who had complete remission at any time after anti-CD19 CAR T-cell infusion. This study is not registered in PROSPERO. FINDINGS: From 1160 studies, we identified 40 potentially appropriate studies, 35 (88%) of which met the eligibility criteria and were included in the final analysis (n=953 patients). The pooled complete remission was 80% (95% CI 75・5-84・8) and heterogeneity between studies was moderate (I(2)=56・96%). In the prespecified subgroup analyses, 195 (75% [95% CI 66・9-82・9, I(2)=35・22%]) of 263 patients in adult studies and 242 (81% [72・9-87・2, I(2)=54・45%]) of 346 patients in paediatric studies achieved complete remission, p=0・24. The pooled complete remission did not significantly differ with anti-CD19 CAR T-cell construct type or single-chain variable fragment clone, but was higher with autologous T-cell origin (727 [83%, 78・5-86・5, I(2)=44・34%] of 901 patients), compared with allogeneic T-cell origin (29 [55%, 30・6-79・0, I(2)=62・64%] of 52 patients; p=0・018). 242 (26% [95% CI 18・5-34・1]) of 854 patients developed grade 3 or worse cytokine release syndrome and 97 (12% [6・6-19・2]) of 532 developed grade 3 or worse neurotoxicity. There was no difference in the proportion of patients who achieved complete remission or who had cytokine release syndrome or neurotoxicity between different anti-CD19 CAR T-cell constructs. The risk of bias was assessed as low in 17 studies and moderate in 18 studies. INTERPRETATION: The high response rates after anti-CD19 CAR T-cell therapy can be used to guide the use of therapy in patients with relapsed or refractory acute lymphocytic leukaemia. Comparison studies are required to further determine differences in efficacy between different anti-CD19 CAR T-cell constructs in the setting of relapsed or refractory acute lymphocytic leukaemia. FUNDING: National Cancer Institute, National Comprehensive Cancer Network, Mayo Clinic K2R Research Pipeline, and Mayo Clinic Center for Individualized Medicine.	Antigens, CD19/*immunology; Cytokine Release Syndrome/etiology; Humans; *Immunotherapy, Adoptive/adverse effects; Neoplasm, Residual; Precursor Cell Lymphoblastic Leukemia-Lymphoma/mortality/*therapy; Progression-Free Survival; Receptors, Chimeric Antigen/therapeutic use; Remission Induction; Transplantation, Autologous
32432755	eng	Cao HH, Wang LL, Geng CK, Mao WW, Yang LL, Ma Y, He M, Zhang R, Zhou YY, Liu LQ, Hu XJ, Yu JX, Yang L, Shen XF, Yin LF, Gu XZ, Shen ZL	Therapeutic effects of chimeric antigen receptor T cells (CAR-T) on relapse/refractory diffuse large B-cell lymphoma (R/R DLBCL): a meta-analysis.	Eur Rev Med Pharmacol Sci	2020	24(9)	4921-4930	Journal Article; Meta-Analysis; Research Support, Non-U.S. Gov't	OBJECTIVE: Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL). This study aimed to systematically evaluate the efficacy of chimeric antigen receptor T cells (CAR-T) in treating relapse/refractory DLBCL (R/R DLBCL) and associated complete-remission rate (CR). MATERIALS AND METHODS: PubMed, Cochrane Library, CNKI, VIP, CBM, and Wanfang databases were searched, and literature was collected up to January 2019. According to inclusion criteria and exclusion criteria, two researchers independently reviewed and screened literature, extracted required data and crossly checked them. This meta-analysis was conducted using RevMan 5.3 software. RESULTS: This study finally included 13 English literatures and 263 cases. There was no heterogeneity among all these studies, therefore, fixed effect model was used. Meta-analysis findings showed that total CR rate of R/R DLBCL treated with CAR-T was 46.8% (95% CI: 0.408-0.533). Subgroup analysis showed that CR rate of CD28 group was slightly higher [52.5%, with 95% confidence interval (CI): 0.441-0.602] compared to that of 4-1BB group (41.5%, with 95% CI: 0.324-0.510). CR rate of CD19 group was slightly higher (49.2%, with 95% CI: 0.429-0.556) compared to that of CD20 group (42.2%, with 95% CI: 0.231-0.639). Funnel chart of total CR rate, co-stimulatory factor, and target antigen demonstrated fundamental symmetry. Moreover, age, HSCT administration, CAR-T cell counts, and drug pre-treatment also affected immunotherapy on CAR-T on R/R DLBCL. CONCLUSIONS: CAR-T treatment for R/R DLBCL demonstrated evident curative effect and high complete remission rate. CAR-T cell immunotherapy would be expected to become mainstream therapy for hematolymph system tumors.	Humans; Lymphoma, Large B-Cell, Diffuse/immunology/*therapy; Receptors, Chimeric Antigen/*immunology; Software
32305113	eng	Cao JX, Wang H, Gao WJ, You J, Wu LH, Wang ZX	The incidence of cytokine release syndrome and neurotoxicity of CD19 chimeric antigen receptor-T cell therapy in the patient with acute lymphoblastic leukemia and lymphoma.	Cytotherapy	2020	22(4)	214-226	Journal Article; Meta-Analysis	Our objective was to summarize the side effect of chimeric antigen receptor (CAR)-T cell therapy in patients with acute lymphocytic leukemia (ALL) and lymphoma. Two independent reviewers extracted relevant data. A total of 35 hematologic malignancy studies with CD19 CAR-T cell were included (1412 participants). Severe cytokine release syndrome (sCRS) proportion was experienced by 18.5% (95% confidence interval [CI], 0.128-0.259; P=0.000) of 982 patients with the National Cancer Institute/Lee/common terminology criteria for adverse events grading system. The pooled neurotoxicity proportion was 21.7% (95% CI, 0.167-0.287; P=0.000) of 747 patients with the same grading system. For all of the 25 clinical trials with the same grading system, subgroup analysis was performed. Based on the different disease type, a pooled prevalence of 35.7% was observed with event rate (ER) of 0.358 (95% CI, 0.289-0.434; P=0.000) for ALL in 12 clinical trials. For lymphoma, a pooled prevalence of 13% was observed with ER of 0.073 (95% CI, 0.028-0.179; P=0.000) in eight clinical trials. It was demonstrated that the patients who were older than 18 years of age have the lower sCRS incidence of 16.1% (95% CI, 0.110-0.250; P=0.000) compared with 28.6% of the remaining population who were younger than 18 years of age (95% CI, 0.117-0.462: P=0.023) in our analysis. Based on the different co-stimulatory domain, the sCRS of 16.5% was observed with ER of 0.175 (95% CI, 0.090-0.312; P=0.000) for 4-1BB. The sCRS of 22.2% was observed with ER of 0.193 (95% CI, 0.107-0.322; P=0.000) for CD28. For both the CD28 and 4-1BB, the sCRS of 17.3% was observed with ER of 0.170 (95% CI, 0.067-0.369; P=0.003). Sub-analysis sCRS of the impact with cell dose and specific disease indication were also demonstrated. Limitations include heterogeneity of study populations, as well as high risk of bias of included studies. These results are helpful for physicians, patients and the other stakeholders to understand the adverse events and to further promote the improvement of CAR-T cell therapy in the future.	Adolescent; Adult; Aged; Aged, 80 and over; Antigens, CD19/*immunology; CD28 Antigens/immunology; Cell- and Tissue-Based Therapy/*adverse effects/methods; Child; Cytokine Release Syndrome/*epidemiology; Female; Hematologic Neoplasms/*therapy; Humans; Immunotherapy, Adoptive/*adverse effects/methods; Incidence; Lymphoma/*therapy; Male; Middle Aged; Precursor Cell Lymphoblastic Leukemia-Lymphoma/*therapy; Receptors, Chimeric Antigen/*immunology; Treatment Outcome; Young Adult

32298202	eng	Frey NV, Gill S, Hexner EO, Schuster S, Nasta S, Loren A, Svoboda J, Stadtmauer E, Landsburg DJ, Mato A, Levine BL, Lacey SF, Melenhorst JJ, Veloso E, Gaymon A, Pequignot E, Shan X, Hwang WT, June CH, Porter DL	Long-Term Outcomes From a Randomized Dose Optimization Study of Chimeric Antigen Receptor Modified T Cells in Relapsed Chronic Lymphocytic Leukemia.	J Clin Oncol	2020	38(25)	2862-2871	Clinical Trial, Phase II; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't	PURPOSE: To describe long-term outcomes of anti-CD19 chimeric antigen receptor T (CART) cells in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). METHODS: Between January 2013 and June 2016, 42 patients with relapsed or refractory CLL were enrolled in this study and 38 were infused with anti-CD19 CART cells (CART-19). Of these, 28 patients were initially randomly assigned to receive a low (5・10(7)) or high (5・10(8)) dose of CART-19, and 24 were evaluable for response assessment. After an interim analysis, 10 additional patients received the selected (high) dose and of these, eight were evaluable for response. Patients were followed for a median 31.5 months (range, 2 to 75 months). RESULTS: At 4 weeks, the complete and overall responses for the 32 evaluable patients were 28% (90% CI, 16% to 44%) and 44% (90% CI, 29% to 60%), respectively. The median overall survival (OS) for all patients was 64 months; there was no statistically significant difference between low- and high-dose groups (P = .84). Regardless of dose, prolonged survival was observed in patients who achieved a CR versus those who did not (P = .035), with median OS not reached in patients with CR versus 64 months in those without CR. The median progression-free survival was 40.2 months in patients with CR and 1 month in those without a CR (P < .0001). Toxicity was comparable in both dose groups. CONCLUSION: In patients with advanced CLL, a 5・10(8) dose of CART-19 may be more effective than 5・10(7) CART-19 at inducing CR without excessive toxicity. Attainment of a CR after CART-19 infusion, regardless of cell dose, is associated with longer OS and progression-free survival in patients with relapsed CLL.	Aged; Antigens, CD19/immunology; Cytokine Release Syndrome/immunology; Dose-Response Relationship, Immunologic; Female; Humans; Immunotherapy, Adoptive/adverse effects/*methods; Leukemia, Lymphocytic, Chronic, B-Cell/immunology/*therapy; Male; Middle Aged; Progression-Free Survival; Receptors, Chimeric Antigen/immunology; Recurrence; Survival Rate; T-Lymphocytes/immunology/transplantation
32107374	eng	Hasegawa D, Imamura T, Yumura-Yagi K, Takahashi Y, Usami I, Suenobu SI, Nishimura S, Suzuki N, Hashii Y, Deguchi T, Moriya-Saito A, Kato K, Kosaka Y, Hirayama M, Iguchi A, Kawasaki H, Hori H, Sato A, Kudoh T, Nakahata T, Oda M, Hara J, Horibe K	Risk-adjusted therapy for pediatric non-T cell ALL improves outcomes for standard risk patients: results of JACLS ALL-02.	Blood Cancer J	2020	10(2)	23	Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't	This study was a second multicenter trial on childhood ALL by the Japan Childhood Leukemia Study Group (JACLS) to improve outcomes in non-T ALL. Between April 2002 and March 2008, 1138 children with non-T ALL were enrolled in the JACLS ALL-02 trial. Patients were stratified into three groups using age, white blood cell count, unfavorable genetic abnormalities, and treatment response: standard risk (SR), high risk (HR), and extremely high risk (ER). Prophylactic cranial radiation therapy (PCRT) was abolished except for CNS leukemia. Four-year event-free survival (4yr-EFS) and 4-year overall survival (4yr-OS) rates for all patients were 85.4%±・.1% and 91.2%±・.9%, respectively. Risk-adjusted therapy resulted in 4yr-EFS rates of 90.4%±・.4% for SR, 84.9%±・.6% for HR, and 66.5%±・.0% for ER. Based on NCI risk classification, 4yr-EFS rates were 88.2% in NCI-SR and 76.4% in NCI-HR patients, respectively. Compared to previous trial ALL-97, 4yr-EFS of NCI-SR patients was significantly improved (88.2% vs 81.2%, log rank p=.0004). The 4-year cumulative incidence of isolated (0.9%) and total (1.5%) CNS relapse were significantly lower than those reported previously. In conclusion, improved EFS in NCI-SR patients and abolish of PCRT was achieved in ALL-02.	Adolescent; Antineoplastic Combined Chemotherapy Protocols/*therapeutic use; Central Nervous System Neoplasms/*mortality/pathology/therapy; Child; Child, Preschool; Combined Modality Therapy; Cranial Irradiation/*mortality; Female; Follow-Up Studies; Humans; Infant; Male; Neoplasm Recurrence, Local/*mortality/pathology/therapy; Precursor Cell Lymphoblastic Leukemia-Lymphoma/*mortality/pathology/therapy; Prognosis; Risk Adjustment/*methods; Survival Rate
32034661	eng	Braun T, von Jan J, Wahnschaffe L, Herling M	Advances and Perspectives in the Treatment of T-PLL.	Curr Hematol Malig Rep	2020	15(2)	113-124	Journal Article; Research Support, Non-U.S. Gov't; Systematic Review	PURPOSE OF REVIEW: T cell prolymphocytic leukemia (T-PLL) is a rare mature T cell tumor. Available treatment options in this aggressive disease are largely inefficient and patient outcomes are highly dissatisfactory. Current therapeutic strategies mainly employ the CD52-antibody alemtuzumab as the most active single agent. However, sustained remissions after sole alemtuzumab-based induction are exceptions. Responses after available second-line strategies are even less durable. More profound disease control or rare curative outcomes can currently only be expected after a consolidating allogeneic hematopoietic stem cell transplantation (allo-HSCT) in best first response. However, only 30-50% of patients are eligible for this procedure. Major advances in the molecular characterization of T-PLL during recent years have stimulated translational studies on potential vulnerabilities of the T-PLL cell. We summarize here the current state of "classical" treatments and critically appraise novel (pre)clinical strategies. RECENT FINDINGS: Alemtuzumab-induced first remissions, accomplished in ≧・0% of patients, last at median ≧・2months. Series on allo-HSCT in T-PLL, although of very heterogeneous character, suggest a slight improvement in outcomes among transplanted patients within the past decade. Dual-action nucleosides such as bendamustine or cladribine show moderate clinical activity as single agents in the setting of relapsed or refractory disease. Induction of apoptosis via reactivation of p53 (e.g., by inhibitors of HDAC or MDM2) and targeting of its downstream pathways (i.e., BCL2 family antagonists, CDK inhibitors) are promising new approaches. Novel strategies also focus on inhibition of the JAK/STAT pathway with the first clinical data. Implementations of immune-checkpoint blockades or CAR-T cell therapy are at the stage of pre-clinical assessments of activity and feasibility. The recommended treatment strategy in T-PLL remains a successful induction by infusional alemtuzumab followed by a consolidating allo-HSCT in eligible patients. Nevertheless, long-term survivors after this "standard" comprise only 10-20%. The increasingly revealed molecular make-up of T-PLL and the tremendous expansion of approved targeted compounds in oncology represent a "never-before" opportunity to successfully tackle the voids in T-PLL. Approaches, e.g., those reinstating deficient cell death execution, show encouraging pre-clinical and first-in-human results in T-PLL, and urgently have to be transferred to systematic clinical testing.	Alemtuzumab/adverse effects/*therapeutic use; Animals; Antineoplastic Agents, Immunological/adverse effects/*therapeutic use; Diffusion of Innovation; Forecasting; Hematopoietic Stem Cell Transplantation/adverse effects/mortality/*trends; Humans; Immunotherapy, Adoptive/trends; Leukemia, Prolymphocytic, T-Cell/diagnosis/immunology/mortality/*therapy; Molecular Targeted Therapy/adverse effects/mortality/*trends; Receptors, Chimeric Antigen/immunology; Treatment Outcome