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Schweizer Onkologiepflege-Kongress 2024

Less is more bei medikamentösen Tumortherapien

Manuela Lang und Oliver Gautschi
Medizinische Onkologie Luzerner Kantonsspital

Kompetenz, die lächelt.

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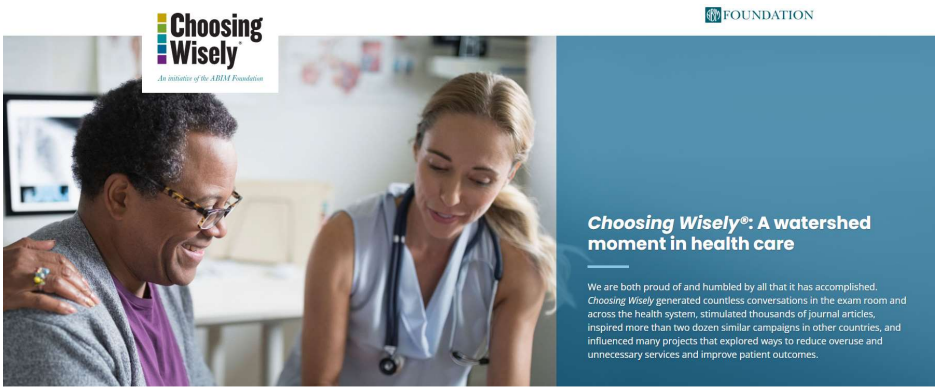
Choosing wisey: American Board of Internal Medicine



https://www.choosingwisely.org/

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Choosing Wisely
An initiative of the ABIM Foundation

American Society of Clinical Oncology
ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Five Things Physicians and Patients Should Question

The American Society of Clinical Oncology (ASCO) is a medical professional oncology society committed to conquering cancer through research, education, prevention and delivery of high-quality patient care. ASCO recognizes the importance of evidence-based cancer care and making wise choices in the diagnosis and management of patients with cancer. After careful consideration by experienced oncologists, ASCO highlights ten categories of tests, procedures and/or treatments whose common use and clinical value are not supported by available evidence. These test and treatment options should not be administered unless the physician and patient have carefully considered if their use is appropriate in the individual case. As an example, when a patient is enrolled in a clinical trial, these tests, treatments and procedures may be part of the trial protocol and therefore deemed necessary for the patient's participation in the trial.

These items are provided solely for informational purposes and are not intended to replace a medical professional's independent judgment or as a substitute for consultation with a medical professional. Patients with any specific questions about the items on this list or their individual situation should consult their health care provider. New evidence may emerge following the development of these items. ASCO is not responsible for any injury or damage arising out of or related to any use of these items or to any errors or omissions.

1. **Don't use cancer-directed therapy for solid tumor patients with the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anti-cancer treatment.**
   - Studies show that cancer directed treatments are likely to be ineffective for solid tumor patients who meet the above stated criteria.
   - Exceptions include patients with functional limitations due to other conditions resulting in a low performance status or those with disease characteristics (e.g., mutations) that suggest a high likelihood of response to therapy.
   - Implementation of this approach should be accompanied with appropriate palliative and supportive care.
2. **Don't perform PET, CT, and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.**
   - Imaging with PET, CT, or radionuclide bone scans can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival.
   - Evidence does not support the use of these scans for staging of newly diagnosed low grade carcinoma of the prostate (Stage T1c/T2a, prostate-specific antigen (PSA) <10 ng/ml, Gleason score less than or equal to 6) with low risk of distant metastasis.
   - Unnecessary imaging can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.
3. **Don't perform PET, CT, and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.**
   - Imaging with PET, CT, or radionuclide bone scans can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival.
   - In breast cancer, for example, there is a lack of evidence demonstrating a benefit for the use of PET, CT, or radionuclide bone scans in asymptomatic individuals with newly identified ductal carcinoma in situ (DCIS), or clinical stage I or II disease.
   - Unnecessary imaging can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.
4. **Don't perform surveillance testing (biomarkers) or imaging (PET, CT, and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.**
   - Surveillance testing with serum tumor markers or imaging has been shown to have clinical value for certain cancers (e.g., colorectal). However for breast cancer that has been treated with curative intent, several studies have shown there is no benefit from routine imaging or serial measurement of serum tumor markers in asymptomatic patients.
   - False-positive tests can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.
5. **Don't use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20 percent risk for this complication.**
   - ASCO guidelines recommend using white cell stimulating factors when the risk of febrile neutropenia, secondary to a recommended chemotherapy regimen, is approximately 20 percent and equally effective treatment programs that do not require white cell stimulating factors are unavailable.
   - Exceptions should be made when using regimens that have a lower chance of causing febrile neutropenia if it is determined that the patient is at high risk for this complication (due to age, medical history, or disease characteristics).

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Five More Things Physicians and Patients Should Question

6. **Don't give patients starting on a chemotherapy regimen that has a low or moderate risk of causing nausea and vomiting antiemetic drugs intended for use with a regimen that has a high risk of causing nausea and vomiting.**
   - Over the past several years, a large number of effective drugs with fewer side effects have been developed to prevent nausea and vomiting from chemotherapy. When successful, these medications can help patients avoid spending time in the hospital, improve their quality of life and lead to fewer changes in the chemotherapy regimen.
   - Oncologists customarily use different antiemetic drugs depending on the likelihood (low, moderate or high) for a particular chemotherapy program to cause nausea and vomiting. For chemotherapy programs that are likely to produce severe and persistent nausea and vomiting, there are new agents that can prevent this side effect. However, these drugs are very expensive and not devoid of side effects. For this reason, these drugs should be used only when the chemotherapy drugs that have a high likelihood of causing severe or persistent nausea and vomiting.
   - When using chemotherapy that is less likely to cause nausea and vomiting, there are other effective drugs available at a lower cost.
7. **Don't use combination chemotherapy (multiple drugs) instead of chemotherapy with one drug when treating an individual for metastatic breast cancer unless the patient needs a rapid response to relieve tumor-related symptoms.**
   - Although chemotherapy with multiple drugs, or combination chemotherapy, for metastatic breast cancer may slow tumor growth for a somewhat longer time than occurs when treating with a single agent, use of combination chemotherapy has not been shown to increase overall survival. In fact, the trade-offs of more frequent and severe side effects may have a net effect of worsening a patient's quality of life, necessitating a reduction in the dose of chemotherapy.
   - Combination chemotherapy may be useful and worth the risk of more side effects in situations in which the cancer burden must be reduced quickly because it is causing significant symptoms or is life threatening. As a general rule, however, giving effective drugs one at a time lowers the risk of side effects, may improve a patient's quality of life, and does not typically compromise overall survival.
8. **Avoid using PET or PET-CT scanning as part of routine follow-up care to monitor for a cancer recurrence in asymptomatic patients who have finished initial treatment to eliminate the cancer unless there is high-level evidence that such imaging will change the outcome.**
   - PET and PET-CT are used to diagnose, stage and monitor how well treatment is working. Available evidence from clinical studies suggests that using these tests to monitor for recurrence does not improve outcomes and therefore generally is not recommended for this purpose.
   - False positive tests can lead to unnecessary and invasive procedures, overtreatment, unnecessary radiation exposure and incorrect diagnoses.
   - Until high level evidence demonstrates that routine surveillance with PET or PET-CT scans helps prolong life or promote well-being after treatment for a specific type of cancer, this practice should not be done.
9. **Don't perform PSA testing for prostate cancer screening in men with no symptoms of the disease when they are expected to live less than 10 years.**
   - Since PSA levels in the blood have been linked with prostate cancer, many doctors have used repeated PSA tests in the hope of finding "early" prostate cancer in men with no symptoms of the disease. Unfortunately, PSA is not as useful for screening as many have hoped because many men with prostate cancer do not have high PSA levels, and other conditions that are not cancer (such as benign prostate hyperplasia) can also increase PSA levels.
   - Research has shown that men who receive PSA testing are less likely to die specifically from prostate cancer. However when accounting for deaths from all causes, no lives are saved, meaning that men who receive PSA screening have not been shown to live longer than men who do not have PSA screening. Men with medical conditions that limit their life expectancy to less than 10 years are unlikely to benefit from PSA screening as their probability of dying from the underlying medical problem is greater than the chance of dying from asymptomatic prostate cancer.
10. **Don't use a targeted therapy intended for use against a specific genetic aberration unless a patient's tumor cells have a specific biomarker that predicts an effective response to the targeted therapy.**
    - Unlike chemotherapy, targeted therapy can significantly benefit people with cancer because it can target specific gene products, i.e., proteins that cancer cells use to grow and spread, while causing little or no harm to healthy cells. Patients who are most likely to benefit from targeted therapy are those who have a specific biomarker in their tumor cells that indicates the presence or absence of a specific gene alteration that makes the tumor cells susceptible to the targeted agent.
    - Compared to chemotherapy, the cost of targeted therapy is generally higher, as these treatments are newer, more expensive to produce and under patent protection. In addition, like all anti-cancer therapies, there are risks to using targeted agents when there is no evidence to support their use because of the potential for serious side effects or reduced efficacy compared with other treatment options.

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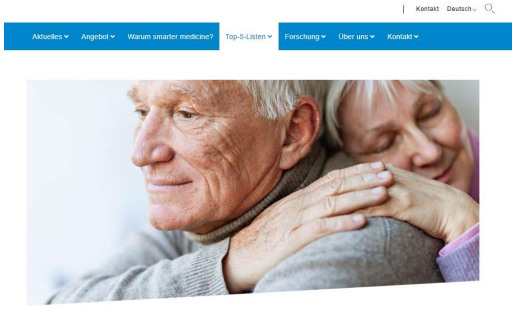
Smarter Medicine / Choosing Wisely Switzerland

smartermedicine
Choosing Wisely Switzerland



Schweizer Gesellschaft für Medizinische Onkologie SGMO
Adaptation der ASCO-TOP-5 Liste:

1. Keine Tumortherapie bei bettlägerigen, pflegebedürftigen Patienten am Lebensende (PS=3+4).
2. Keine Stimulation der weissen Blutzellen bei allen Chemotherapien.
3. Keine prophylaktische Gabe von Antiemetika bei allen Chemotherapien.
4. Keine PET-Untersuchungen in der Nachsorge.
5. Kein ungezielter Einsatz von molekular-gezielten Therapien.

https://www.smartermedicine.ch/de/top-5-listen/ueber-top-5-listen

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972 (44) 10.4414/smf.2023.09307 | 2023;23(12):972–977 | Swiss Medical Forum
Übersichtsartikel | Peer reviewed article

«Choosing wisely»

«Less is more» bei medikamentösen Tumortherapien

Der Fortschritt bei medikamentösen Tumortherapien ist gross und wichtig, birgt aber auch die Gefahr von Überbehandlung. Die zunehmende Komplexität erschwert das kritische Abwägen von Therapieoptionen durch Grundversorgende sowie Patientinnen und Patienten. Die Kampagne «choosing wisely» und das Prinzip «less is more» gewinnen an Bedeutung.

Dr. med. (HU) Magdalena Hecz, Prof. Dr. med. Stefan Aebi, KD Dr. med. Beat Müller, Dr. med. Thilo Zander, Dr. med. Christian Riklin, Dr. med. Ralph Winterhalder, Dr. med. Daniela Weiler, Dr. med. Kristin Zeidler, Dr. med. Veronika Blum, Dr. med. Philipp Niederberger, Dr. med. Benedetta Campana, Prof. Dr. med. Oliver Gautschi
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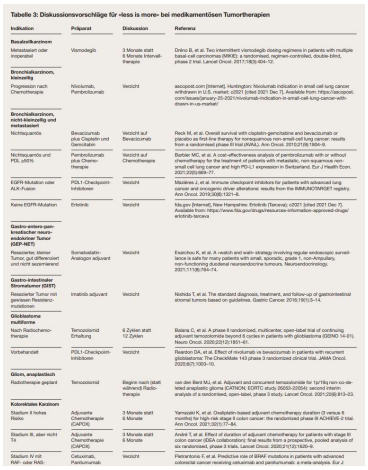

Tabelle 3: Diskussionsvorschläge für «less is more» bei medikamentösen Tumortherapien

Indikation	Präparat	Diskussion	Referenz
Basalzellkarzinom			
Metastasiert oder inoperabel	Vismodegib	3 Monate statt 9 Monate Intervall-therapie	Dréno B, et al. Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKE): a randomised, regimen-controlled, double-blind, phase 2 trial. Lancet Oncol. 2017;18(3):404–12.
Bronchialkarzinom, kleinzellig			
Progression nach Chemotherapie	Nivolumab, Pembrolizumab	Verzicht	ascopost.com [Internet]. Huntington: Nivolumab indication in small cell lung cancer withdrawn in U.S. market. c2021 [cited 2021 Dec 7]. Available from: https://ascopost.com/issues/january-25-2021/nivolumab-indication-in-small-cell-lung-cancer-withdrawn-in-us-market/
Bronchialkarzinom, nicht-kleinzellig und metastasiert			
Nichtsquamös	Bevacizumab plus Cisplatin und Gemcitabin	Verzicht auf Bevacizumab	Reck M, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol. 2010;21(9):1804–9.
Nichtsquamös und PDL-1/ETN	Pembrolizumab plus Chemo-therapie	Verzicht auf Chemotherapie	Barlesi MC, et al. A cost-effectiveness analysis of pembrolizumab with or without chemotherapy for the treatment of patients with metastatic, non-squamous non-small cell lung cancer and high PD-L1 expression in Switzerland. Eur J Health Econ. 2021;22(6):869–77.
EGFR-Mutation oder ALK-Fusion	PDL1-Checkpoint-Inhibitoren	Verzicht	Mazieres J, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol. 2019;30(8):1321–8.
Keine EGFR-Mutation	Erlotinib	Verzicht	Nia.gov [Internet]. New Hampshire: Erlotinib (Tarceva); c2021 [cited 2021 Dec 7]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/erlotinib-tarceva
Gastro-entero-pankreatischer neuro-endokriner Tumor (GEP-NET)			
Resezierter, kleiner Tumor, gut differenziert und nicht sezerniernd	Somatostatin-Analogen adjuvant	Verzicht	Exarchou K, et al. A «watch and wait» strategy involving regular endoscopic surveillance is safe for many patients with small, sporadic, grade 1, non-Ampullary, non-functioning duodenal neuroendocrine tumours. Neuroendocrinology. 2021;111(8):764–74.
Gastro-intestinaler Stromatumor (GIST)			
Resezierter Tumor mit geringem Rezidiv-risikoboren	Imatinib adjuvant	Verzicht	Nishida T, et al. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer. 2016;19(1):3–14.
Glioblastome multiforme			
Stadium II hohes Risiko	Temozolomid Erhaltung	6 Zyklen statt 12 Zyklen	Balana C, et al. A phase II randomized, multicenter, open-label trial of continuing adjuvant temozolomide beyond 6 cycles in patients with glioblastoma (GDNG 14-01). Neuro Oncol. 2020;22(12):1831–41.
Vorbehandelt	PDL1-Checkpoint-Inhibitoren	Verzicht	Reardon DA, et al. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: The CheckMate 143 phase 3 randomized clinical trial. JAMA Oncol. 2020;6(7):1003–10.
Gliom, anaplastisch			
Radiotherapie geplant	Temozolomid	Beginn nach (statt während) Radio-therapie	van den Bent MJ, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2021;22(6):813–23.
Kolorektales Karzinom			
Stadium II hohes Risiko	Adjuvante Chemotherapie (CAPOX)	3 Monate statt 6 Monate	Yamazaki K, et al. Oxaliplatin-based adjuvant chemotherapy duration (3 versus 6 months) for high-risk stage II colon cancer: the randomized phase III ACHIEVE-2 trial. Ann Oncol. 2021;32(1):77–84.
Stadium III, aber nicht T4	Adjuvante Chemotherapie (CAPOX)	3 Monate statt 6 Monate	André T, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. Lancet Oncol. 2020;21(12):1620–9.
Stadium IV mit RAF- oder RAS-	Cetuximab, Panitumumab	Verzicht	Pietrantonio F, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. Eur J

https://smf.swisshealthweb.ch/fileadmin/assets/SMF/2023/smf.2023.09307/smf-2023-09307.pdf

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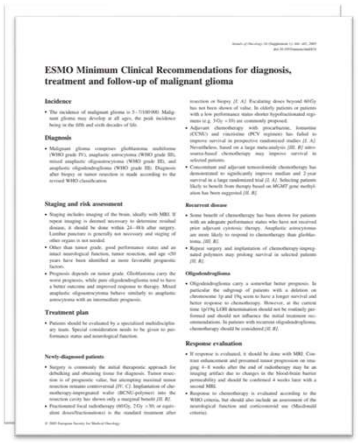
Beispiel: Richtlinien Hirntumorbehandlung früher und heute



ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of malignant glioma

Incidence

Diagnosis

Staging and risk assessment

Treatment plan

Newly-diagnosed patients

Recurrent disease

Oligodendroglioma

Response evaluation

clinical practice guidelines

High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

incidence and epidemiology

diagnosis and pathology

www.esmo.org

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Häufigkeit von Überbehandlung in der Onkologie

Tumor-gerichteten Therapien
- Zytostatika
- Biologika
- Endokrine Therapien
- Radiojodtherapie

Supportiven Therapien:
- Antiemetika
- G-CSF

Schleicher, Lancet Oncol 2018

	Type of evidence	Sample size (patients)	Findings
Chemotherapy			
USA, adults with stage I colorectal cancer	Direct	10 998	Overuse of chemotherapy ranged from 3·1% (for low spending areas) to 6·3% (in highest spending areas)[30]
USA, adults with stage II colorectal cancer	Indirect (variation)	16 371	Geographical variation in chemotherapy, ranging from 18% to 22·6%[34]
USA, adults with colorectal cancer	Indirect (intervention)	910	Patients treated on pathway had lower chemotherapy costs (adjuvant setting: US$60 787 to $22 564; metastatic setting: $65 358 to $41 894). 3-year disease free survival and 1-year overall survival were higher for patients on a clinical pathway[35]
USA, adults with cancer receiving >$200 in chemotherapy payments	Indirect (variation)	397 644	Approximately 1·7 times higher spending on pemetrexed in practices with the highest overall spending quartile compared to those in the lowest[33]
USA (Dana-Farber Cancer Institute), adults with stage IV non-small-cell lung cancer	Indirect (intervention)	370	Clinical pathway use reduced antineoplastic medication spending from mean $44 237 to $31 846[36]
Canada, adults with surgically resected non-small-cell lung cancer	Indirect (variation)	3354	Proportion of patients receiving adjuvant cisplatin-vinorelbine chemotherapy varied from 20% to 43% by geographical region[37]
USA, adults with newly diagnosed lung cancer	Indirect (intervention)	222 478	During the year after the Medicare Chemotherapy Reimbursement change in January, 2005, prescribing rates of carboplatin decreased from 55·9% to 53·7%, paclitaxel decreased from 30·0% to 26·2%, and docetaxel increased from 9·2% to 9·7%[38]
USA (rural Georgia), adults with early stage breast cancer	Direct	868	Overuse of endocrine therapy, chemotherapy, and radiation therapy ranged from 11·5% to 18·2%*[39]
Biological agents			
USA, adults with cancer receiving >$200 in chemotherapy payments	Indirect (variation)	397 644	Approximately 2·2 times higher spending on bevacizumab and a 1·7 times higher spending on cetuximab in practices with the highest overall spending quartile compared with those in the lowest[33]
USA, adults with localised breast cancer	Direct	775	Among women without a positive HER2 test, 3·9% still received trastuzumab[40]
USA, elderly adults with breast cancer who received trastuzumab	Direct	2984	Among women who received trastuzumab, 4·7% had no documentation of HER2 testing; use was associated with increased heart failure with no survival benefit[41]

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WZW: Wirksamkeit

Unsere «Standards» basieren oft auf Studien mit:

- Therapie-Maximierung statt -Optimierung
- Selektionierten Patienten
- Surrogat-Endpunkten und kurzer Beobachtungszeit
- Fehlendem oder inadäquatem Vergleichsarm
- Statistischer Signifikanz statt klinischer Relevanz
- Fehlender Validierung durch mehrere Phase III Studien

➢ Wir müssen Resultate beurteilen und einordnen können («journal clubs»)
➢ Zulassung ≠ Therapierichtlinie ≠ Indikation im Einzelfall

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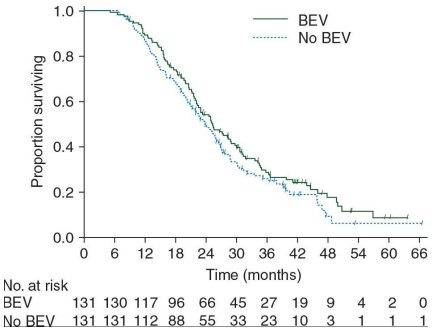
SAKK Studien zu *«less is more»*

- **SAKK 19/09** (Gautschi): Bevacizumab nach Chemotherapie beim Bronchialkarzinom hat keinen Effekt auf das Überleben
- **SAKK 41/06** (Koeberle): Bevacizumab nach Chemotherapie beim Kolonkarzinom hat keinen Effekt auf das Überleben
- **SAKK 07/17** (Stenner): Absetzen von Ipilimumab bei Therapieansprechen ändert Ansprechrate nicht
- **SAKK 39/16** (Zander): Alternative Dosierung von Pomalidomid beim Myelom reduziert Nebenwirkungen und Kosten
- **SAKK 96/12** (von Moos): Laufende Studie mit längeren Intervallen von Denosumab bei Knochenmetastasen



Gautschi, Clin Lung Cancer 2017

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Multiples Myelom: Pomalidomid

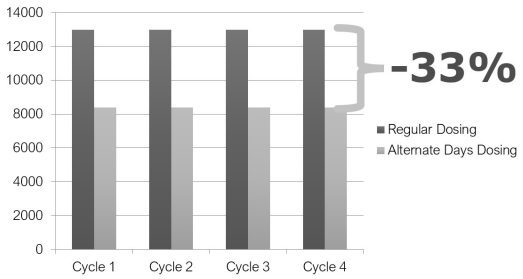
Pomalidomid Einnahme/28d

Swissmedic Zulassung: 21 Kapseln

Experimentell: 14 Kapseln

	Phase II Richardson et al.:	Phase III MM-003; 2013	OptiPOM
n	113	302	34
ORR (MR)	33%	40%	29%
Minor Response	12%	8%	3%
SD	37%	43%	44%
Median PFS	4.2 months	4.0 months	4.2 months
Median No of prior therapies	5	5	3

First FDA approval (2013) based on ORR in this Phase II trial



Zander Leukemia 2023

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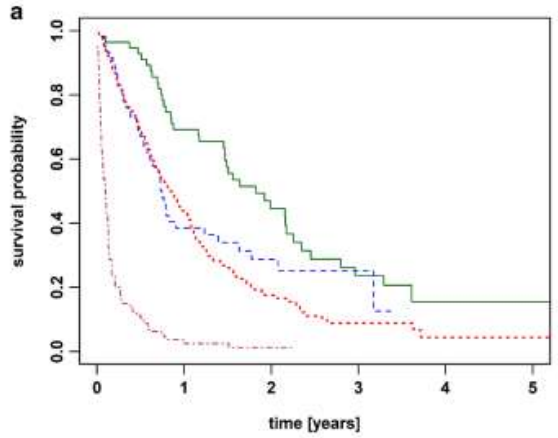
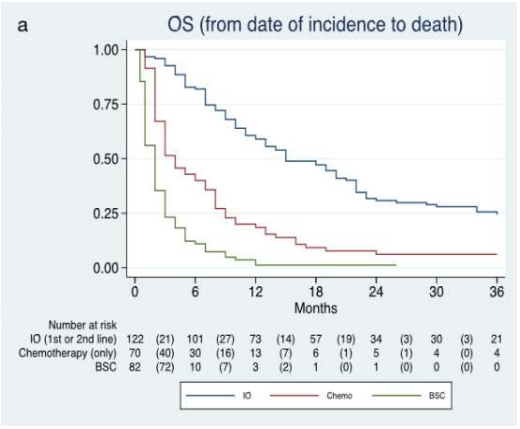
Real-World-Evidence RWE: Luzerner Studien

Molekular-gezielte Therapie (Schwegler, 2018)



Immun-Therapie (Allmann, 2023)



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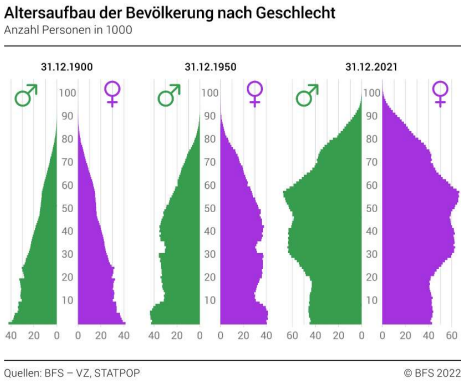
WZW: Zweckmässigkeit

Widersprüche:

- Therapiestandards entwickeln sich schnell
- Bestehende Zulassungen werden kaum revidiert

- Patienten werden immer älter und gebrechlicher
- Diese sind in Zulassungsstudien untervertreten

- Lebens-Ende ist schwierig vorauszusehen
- Therapie bis ans Lebens-Ende vermeiden



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Beispiele für überholte Zulassungen

Erbitux

Inf Lös 100 mg/20ml
(Cetuximabum 100 mg)

[1] ***Limitatio:***
Die Behandlung bedarf der Kostengutsprache durch den Krankenversicherer nach vorgängiger Konsultation des Vertrauensarztes:

Vergütung bei Patienten mit metastasiertem Kolorektalkarzinom mit nicht-mutiertem Wildtyp-Ras-Gen:
- In Kombination mit FOLFIRI oder FOLFOX
- Als Monotherapie, wenn eine Therapie auf Oxaliplatin- und Irinotecan-Basis versagt hat oder eine Irinotecan-Intoleranz vorliegt.

Tarceva

Filmtabl 100 mg
(Erlotinibum 100 mg)

[1] ***Limitatio:***
Nach Kostengutsprache durch den Krankenversicherer nach vorgängiger Konsultation des Vertrauensarztes.
Zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasierendem nichtkleinzelligem Lungenkrebs, bei denen mindestens eine vorgängige Chemotherapie wirkungslos geblieben ist.
Erstlinienbehandlung und Erhaltungsbehandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligem Lungenkarzinom (NSCLC) mit EGFR-aktivierenden Mutationen.

Fachinformation

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Objektive Beurteilung der Gebrechlichkeit

ECOG Performance Status Scale

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Einschluss in alle Studien

Nur «PS2-Studien»

Keine Studien

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982 Dec;5(6):649-655. PMID: 7165009.

https://ecog-acrin.org/resources/ecog-performance-status/

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Tabelle 2: G8-Screening-Fragebogen [4]*

	Fragen	Mögliche Antworten (Score)
1	Hat die Nahrungsaufnahme in den letzten 3 Monaten infolge Kauen oder Schlucken abgenommen?	0 = stark reduziert 1 = moderat reduziert 2 = normal
2	Gewichtsabnahme in den letzten 3 Monaten?	0 = Gewichtsabnahme ≥3 kg 1 = weiss nicht 2 = Gewichtsabnahme 1–3 kg 3 = keine
3	Mobilität	0 = kann nur sitzen oder liegen 1 = steht auf, geht aber nicht nach draussen 2 = geht nach draussen
4	Neuropsychologische Probleme	0 = schwere Demenz oder Depression 1 = leichte Demenz oder Depression 2 = keine
5	Body-Mass-Index (BMI)	0 = BMI <19 kg/m² 1 = 19 ≤ BMI < 21 kg/m² 2 = 21 ≤ BMI < 23 kg/m² 3 = BMI ≥23 kg/m²
6	Medikamenteneinnahme: ≥3 Präparate?	0 = ja 1 = nein
7	Einschätzung des eigenen Gesundheitszustands im Vergleich zu Gleichaltrigen	0 = weniger gut 0,5 = weiss nicht 1 = gleich gut 2 = besser
8	Alter	0 = >85 Jahre 1 = 80–85 Jahre 2 = <80 Jahre
	Gesamt-Score	0–17 (<14: Gebrechlichkeit)

* Aus [4]: Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, Soubeyran PL. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012;23(8):2166–72. © 2012 European Society for Medical Oncology. Published by Elsevier Inc. https://www.sciencedirect.com/journal/annals-of-oncology. Nachdruck und Übersetzung mit freundlicher Genehmigung.

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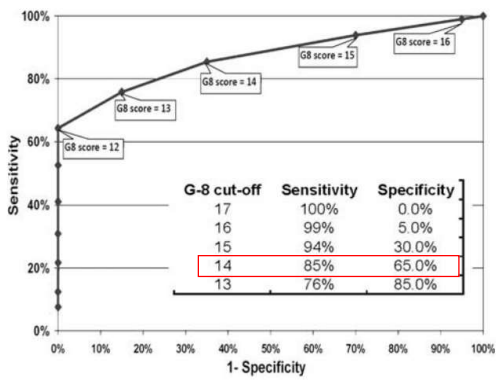

Figure 1. Receiver operating curve (sensitivity versus 1-specificity) for the G-8 screening tool against the reference exam consisting of seven comprehensive geriatric assessment questionnaires (at least one abnormal score versus none).

Bellera, Annals Oncol 2012

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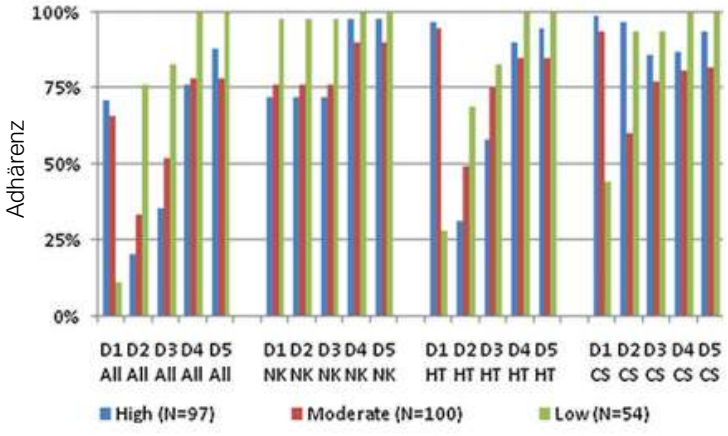
Prophylaxe der Chemotherapie-induzierten Emesis



Vor niedrig-emetogenen Chemotherapie wurden früher zu häufig Steroide und Serotonin-Antagonisten verschrieben

Dies führte möglicherweise zu unnötigen Nebenwirkungen und Kosten

Elektronisch Verordnungssysteme mit Richtlinien-getreuer Prämedikation verringern die Gefahr von Überbehandlung

Burmeister, Support Care Cancer 2011

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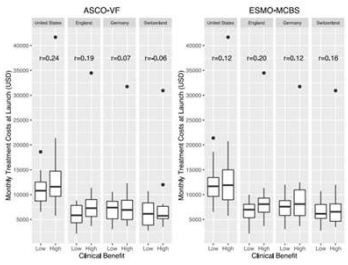
WZW: Wirtschaftlichkeit

Ist für die Leistungserbringenden schlecht beurteilbar weil:

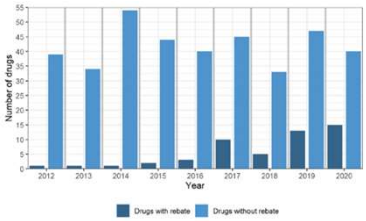
- Kein offizieller «willingness to pay threshold» in der CH
- Kaum unabhängige Kosten-Effektivitäts-Analysen
- Ausländische Daten lassen sich schlecht übertragen
- Preis korreliert nicht mit Nutzen
- Geheime Rabatte nehmen zu

➢ Bei ähnlicher Wirksamkeit die günstigere Option wählen

Vokinger, Lancet und JAMA 2021



Notes: Figure shows country-specific boxplots of monthly treatment costs at launch, adjusted for inflation and currency, by high versus low clinical benefit based on the ASCO value framework (left) and ESMO-MCBS (right) as applied at the time of regulatory approval. Correlation coefficients (r) are overlaid on the figure.



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Kosten-Effektivitäts-Analysen (CEA) aus Basel & Luzern

PharmacoEconomics
https://doi.org/10.1007/s40273-023-01305-3

ORIGINAL RESEARCH ARTICLE

Cost Effectiveness and Budget Impact of Nivolumab Plus Ipilimumab Versus Platinum Plus Pemetrexed (with and Without Bevacizumab) in Patients with Unresectable Malignant Pleural Mesothelioma in Switzerland

Michaela Carla Barbier[1] · Alicia Fengler[2] · Esther Pardo[2] · Arjun Bhadhuri[1] · Niklaus Meier[1] · Oliver Gautschi[2,3]

Accepted: 18 July 2023

Abstract

Background Malignant pleural mesotheliomas (MPMs) are aggressive and often unresectable. In the past, chemotherapy was the standard for palliative treatment. However, immunotherapy with nivolumab+ipilimumab has recently received marketing approval.

Objectives This study evaluated the cost effectiveness of nivolumab+ipilimumab versus pemetrexed+platinum (with/without bevacizumab) for Swiss patients with unresectable MPM, overall and by histological subtype.

Methods We developed a three-state Markov cohort model with a cycle length of 1 month, a 30-year time horizon, and a discount rate of 3% per year for costs and benefits. The model included the updated survival and treatment-dependent utility results from the Checkmate-743 and MAPS registration trials. A Swiss statutory health insurance perspective was considered with unit costs for 2022 from publicly available and real-world sources. We assumed a willingness-to-pay (WTP) threshold of CHF100,000/QALY. Model robustness was explored in sensitivity and scenario analyses.

Results Compared with chemotherapy, nivolumab+ipilimumab incurred additional costs of CHF109,115 and 0.57 additional quality-adjusted life-years (QALYs), yielding an incremental cost-effectiveness ratio (ICER) of CHF192,585/QALY (i.e. USD201,829/QALY) gained. Relative to their 2022 list price, nivolumab+ipilimumab may be cost effective if priced at 48% across all histologies. Assuming cisplatin-based instead of carboplatin-based chemotherapy reduced the ICER to CHF158,911/QALY (i.e. USD166,539/QALY). For the non-epithelioid subtype, nivolumab+ipilimumab was cost effective compared with chemotherapy (ICER of CHF97,894/QALY, i.e. USD102,593/QALY). Chemotherapy+bevacizumab was often a dominated strategy or would require a bevacizumab cost reduction to 28%.

Conclusions Our model projected nivolumab+ipilimumab to be cost effective for the non-epithelioid subtype but not for all histologies. Substantial discounts for nivolumab+ipilimumab would be necessary to achieve cost effectiveness for all histologies.

The European Journal of Health Economics
https://doi.org/10.1007/s10198-021-01282-4

ORIGINAL PAPER

A cost-effectiveness analysis of pembrolizumab with or without chemotherapy for the treatment of patients with metastatic, non-squamous non-small cell lung cancer and high PD-L1 expression in Switzerland

Michaela Carla Barbier[1] · Esther Pardo[2] · Cédric Michael Panje[3] · Oliver Gautschi[2,4] · Judith Eva Lupatsch[1] · for the Swiss Group for Clinical Cancer Research (SAKK)

Received: 13 May 2020 / Accepted: 26 February 2021

Abstract

Introduction Pembrolizumab monotherapy or in combination with chemotherapy are two new treatment options for patients with metastatic non-squamous non-small cell lung cancer (NSCLC) and high (≥ 50%) programmed death ligand 1 (PD-L1) expression. We conducted a cost-effectiveness analysis for Switzerland comparing these two options but also pembrolizumab to chemotherapy.

Methods We constructed a 3-state Markov model with a time horizon of 10 years. Parametric functions were fitted to Kaplan–Meier overall survival (OS) and progression-free survival (PFS) using 2-year follow-up data from the KN-024 and KN-189 registration trials. We included estimated costs for further treatment lines and costs for best supportive care. Costs were assessed from the Swiss healthcare payer perspective. We used published utility values.

Results Combination therapy resulted in an expected gain of 0.17 quality-adjusted life years (QALYs) per patient and incremental costs of Swiss Francs (CHF) 81,085 as compared to pembrolizumab. These estimates led to an incremental cost-effectiveness ratio (ICER) of CHF 475,299/QALY. Pembrolizumab in comparison to chemotherapy was estimated to generate mean incremental QALYs of 0.83 and incremental costs of CHF 56,585, resulting in an ICER of CHF 68,580/QALY. Results were most sensitive to changes in costs of 1L pembrolizumab and combination therapy, together with changes in PFS. In the probabilistic sensitivity analysis, we estimated combination therapy was cost-effective in 4.9% of the simulations and pembrolizumab monotherapy in 82.9%, assuming a willingness-to-pay threshold of CHF 100,000 per QALY gained.

Conclusions Pembrolizumab is likely to be cost-effective from the Swiss healthcare payer perspective, whereas pembrolizumab plus chemotherapy is not.

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Alternative Dosierungen

The Drug-Dosing Conundrum in Oncology — When Less Is More

Mirat Shah, M.D., Atiqur Rahman, Ph.D., Marc R. Theoret, M.D., and Richard Pazdur, M.D.

In May 2021, the Food and Drug Administration (FDA), where we work, approved sotorasib (Lumakras) for metastatic non–small-cell lung cancers (NSCLCs) harboring the *KRAS* p.G12C mutation. Sotorasib, which was approved on the basis of the phase 2 portion of the CodeBreaK100 trial, is the first drug to target *KRAS*, which had been considered "undruggable" and was investigated unsuccessfully for decades.[1] Despite this achievement, the drug's development was hampered by a lack of robust dose exploration, which led the FDA to require the sponsors to conduct a postmarketing trial to evaluate lower doses. This decision was based on data showing similar pharmacokinetic drug exposure (levels of drug in the body), target saturation, and tumor response rates among patients treated with the dose used in the registration trial and those treated with lower doses.

It's not unusual for doses and schedules of oncology drugs to be inadequately characterized before sponsors initiate registration trials (see table). The default decision to select the highest dose that has been evaluated reflects both the desire to make oncology drugs rapidly available to patients who have limited options and the belief that higher drug doses will have better therapeutic activity. Often, small cohorts of patients are assigned to receive escalating doses and are assessed for severe or life-threatening dose-limiting toxic effects for one treatment cycle to identify the maximum tolerated dose. We believe this practice should be reexamined for targeted drugs and biologic therapies.

Advances in cancer biology and molecular genetics have driven the development of multiple targeted therapies, including kinase inhibitors, monoclonal antibodies, and antibody–drug conjugates.[2] These drugs have extended survival among patients with various cancers, including NSCLC, melanoma, and breast cancer, and their introduction in the adjuvant setting has provided a potential for cure. With targeted drugs, increasing doses beyond a certain level may not enhance antitumor activity, dose-limiting toxic effects may not be observed at clinically active doses, and serious toxic effects may occur only after multiple cycles of experimental treatment. Patients may use targeted drugs for months or years, which increases the importance of evaluating long-term tolerability. And yet, the "more is better" paradigm is still used for dose selection for

Examples of Drugs Whose Doses or Schedules Were Modified for Safety or Tolerability after Approval.*

Drug	Initial Dose and Trials	Modified or Added Dose and Trials	Reason for Modified or Added Dose
Small-molecule drugs			
Ceritinib (Zykadia)	750 mg PO daily fasted (ASCEND-1)	450 mg PO daily with food (ASCEND-8)	Reduce gastrointestinal toxic effects
Dasatinib (Sprycel)	70 mg PO twice daily (CA180013, CA180005, CA180006, and CA180015)	100 mg PO daily (CA180034)	Reduce hematologic toxic effects and fluid retention
Niraparib (Zejula)	300 mg PO daily (NOVA)	200 mg PO daily (PRIMA)	Reduce thrombocytopenia in patients with a lower platelet count or lower body weight
Ponatinib (Iclusig)	45 mg PO daily (PACE)	45 mg PO daily, then 15 mg PO daily once ≤1% *BCR-ABL* is achieved (OPTIC)	Reduce vascular occlusive events
Chemotherapy			
Cabazitaxel (Jevtana)	25 mg/m² IV every 3 wk (TROPIC)	20 mg/m² IV every 3 wk (PROSELICA)	Reduce hematologic toxic effects and infections
Antibody–drug conjugates			
Gemtuzumab ozogamicin (Mylotarg)	9 mg/m² IV on days 1 and 15 (Study 201, Study 202, and Study 203)	3 mg/m² IV on days 1, 4, and 7 (Mylofrance-1)	Reduce veno-occlusive disease and treatment-related mortality

* Adapted from the Food and Drug Administration.[2] IV denotes intravenous, and PO by mouth.

Prostatakarzinom: Dosis von Abirateron

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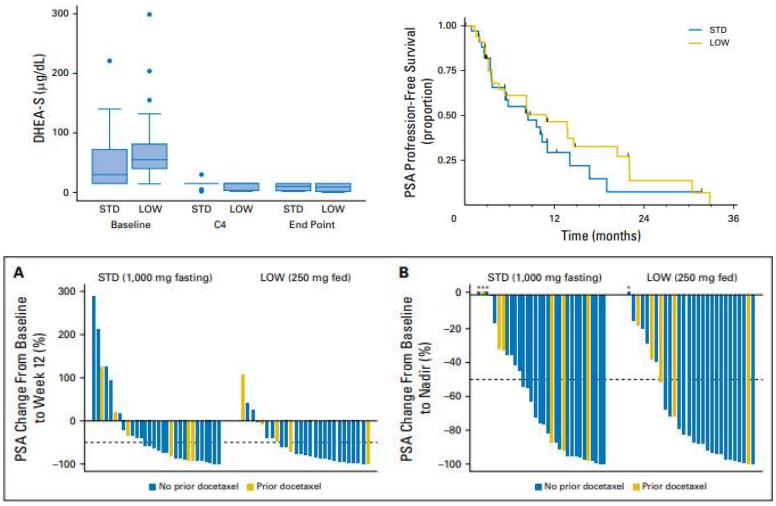
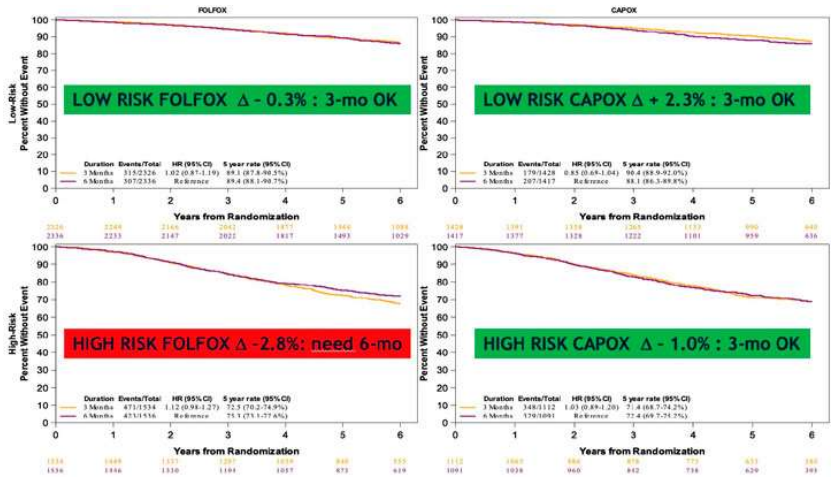


Szmulewitz J Clin Oncol. 2018

Darmkrebs: Dauer der adjuvanten Chemotherapie



Grothey NEJM 2018

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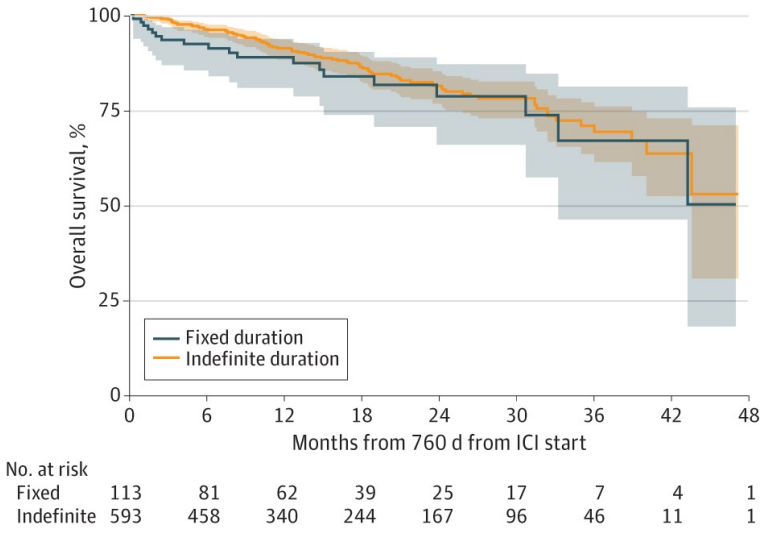
Lungenkrebs: Dauer der palliativen Immuntherapie



No. at risk

Fixed	113	81	62	39	25	17	7	4	1
Indefinite	593	458	340	244	167	96	46	11	1

Sun JAMAoncology 2023

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Fazit und Ausblick

- Smarter medicine / Less is more / choosing wisely = evidenzbasierte Medizin plus «shared decision making»
- Evidenz kommt von klinischen Studien = vergleichende (randomisierte) Studien bleiben wichtig
- Hürden (Gewinnorientierung) und Ausreden (vermeindlicher «Patientenwunsch») gibt es viele
- Eigene Fortbildung und Patientenaufklärung (inkl. Alternativen/Optionen) bleiben unerlässlich

- Patienten haben Anrecht auf Information, Selbstbestimmung, Achtung und Würde
- «Hippokratischer Eid» und «Genfer Gelöbnis» reichen offenbar nicht
- Es braucht auch neue wirtschaftliche Anreizsysteme