MOLECULAR HEALTH

Molecular pathology / Oncology

Guideline Check for molecular tumor diagnostics

Median survival time 4 years instead of 18 months for NSCLC stage IV? Targeted therapy based on molecular tumor diagnostics forms the backbone of treatment.[1] This overview provides an insight into the current status and prospects of precision oncology in keeping with current guidelines.

NSCLC: 30% of patients with treatable driver mutations

The data in the initial example relates to the metastatic non-small cell lung cancer (NSCLC) with treatable driver mutations such as ALK[a] and ROS[b] translocations, BRAF[c] and EGFR[d] aberrations.[1] Targeted therapy is now available for approximately one third of these NSCLC patients with adenocarcinoma[2] which prolongs survival time for over 4 years after diagnosis.[1] Until now, survival could only be extended for 8 to 18 months with non-selective treatments such as chemotherapy.[1]

The S3 guideline for lung cancer therefore recommends a molecular pathological examination for all non-curable, non-squamous NSCLC and squamous cell carcinomas in non-smokers and light smokers.[1] According to the latest data from the German CRISP[e] registry, about 77% of these tumors are currently being tested specifically for EGFR – 50% for a BRAF mutation.[3]

Four examples: Guideline Recommendations for molecular tumor diagnostics

Besides NSCLC, patients with other oncological diseases may also benefit from targeted therapy based on molecular tumor diagnostics. Here are 4 examples based on current guidelines:

➔ **Metastatic breast cancer & HER2: Remission rate of up to 80%**

Evidence of HER2[f] overexpression, present in approximately 20% of invasive ductal tumors. forms the basis of standard therapy in keeping with guidelines. Targeted therapy with HER2-specific antibodies may increase the remission rate in patients with metastatic HER2-positive breast cancer – depending on therapy:[4]

Therapy with HER2-specific antibodies	Remission rate
Monotherapy	20 %
Combination therapy with chemotherapy regimen	> 50 %
Triple therapy with 2 HER2 antibodies and taxanes	80 %

➔ **Metastatic colon cancer & RAS: Lower risk of progression**

The S3 guideline makes it clear that molecular pathology characterization is the primary objective of initial diagnosis in metastatic colon cancer. This status of the following mutations is of importance:[5]

Activating mutation	Percentage of patients
RAS (KRAS or NRAS)[g]	50 %
BRAF	8 % - 12 %

RAS and BRAF mutations are mutually exclusive.[5]
Combination therapy with EGFR-specific antibodies and chemotherapy regimens for tumors with an RAS wild type (no mutation) may reduce the risk of progression or death depending on the site of the primary tumor (-22% or -25%).[5]

The addition of a specific protein kinase inhibitor in patients with a BRAF mutation may prolong progression-free survival by 2.4 months.[6] The S3 guideline suggests HER2-specific treatment options in the absence of response to EGFR or BRAF-targeted therapy.[5]

➔ **Metastatic melanoma & BRAF: Doubling overall survival**

The S3 guideline recommends testing for BRAF gene mutations in patients with stage IIIB melanomas and higher, as well as for NRAS and, in certain melanomas, for c-kit[h] in case of BRAF wild type. Targeted therapies are available for these aberrations[7] and can significantly prolong median overall survival, especially in patients with non-resectable metastatic melanoma.
This was a mere 6 to 10 months with previously used chemotherapy regimens.[8] Today, patients on combination therapy with BRAF and MET[i] inhibitors can achieve a median survival time of over 22 months.[7]

➔ **CML & BCR-ABL: Almost normal life expectancy instead of a maximum of 7 years**
Pioneering work has been done in molecular tumor diagnostics in patients with chronic myeloid leukemia (CML). Breakage and subsequent translocation of chromosomes 9 and 22 gives rise to the fusion gene for the specifically treatable BCR-ABL[j] tyrosine kinase (TKI).[9] Guidelines recommend the use of specific TKI inhibitors, due to which the life expectancy of patients with CML now approximates that of the normal population.[10] Previously, the median survival time of CML patients on standard interferon therapy was 3 to 7 years.[11]

Next steps: Tumor-specific gene panels instead of hotspot mutations

The four established molecular pathology examples mentioned above involved identification of single mutations (hotspot mutations) or translocations using PCR or specific in situ hybridization. However, the rapid development of knowledge regarding clinically important mutations requires more comprehensive methods, such as next generation sequencing (NGS).

Advanced molecular tumor diagnostic testing with NGS enables, among other things, the sequencing of

- Tumor-specific DNA panels
- Tumor-specific RNA panels
- Whole exome sequencing (WES)
- Whole genome sequencing (WGS)

Analogous to FISH, the analysis of special gene panels allows identification of rare aberrations such as chromosomal breaks or relocations.[12] NGS analytics also enable examination of a larger number of potentially relevant genes in parallel. This provides a more comprehensive overview of tumor biology, and when such gene alterations are detected, patients may be included in a suitable clinical study in order to find individual therapeutic approaches.[13]

Precision oncology: Opportunities for advanced molecular diagnostics

These extensive genomic analyses form the basis for the first crucial steps towards precision oncology. In the future, this will have to do with linking genetic data with the constantly changing clinical knowledge regarding specific treatment options.

Specific software solutions support these demanding genome-based therapy decisions, which analyze complex genetic information and derive clinically relevant, future-oriented recommendations, based on the latest developments in available options.

Abbreviations

[a] Anaplastic lymphoma kinase
[b] c-ros oncogene
[c] B-isoform of the rapidly accelerated fibrosarcoma
[d] Epidermal growth factor receptor
[e] Clinical research platform into molecular testing, treatment and outcome of (non-)small cell lung carcinoma patients
[f] Human epidermal growth factor Receptor 2
[g] Kirsten rat sarcoma viral oncogene homolog / neuroblastoma RAS viral oncogene homolog
[h] Tyrosine kinase KIT
[i] Mesenchymal epithelial transition factor
[j] Breakpoint cluster region Abelson

Sources

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms, Langversion 1.0, Februar 2018, AWMF-Registernummer: 020/007OL. Unter: https://www.leitlinienprogramm-onkologie.de/leitlinien/lungenkarzinom/ (abgerufen am 31.03.2020).
2. Pakkala S, Ramalingam SS. Personalized therapy for lung cancer: striking a moving target, JCI Insight. 2018;3(15):e120858. Unter: https://insight.jci.org/articles/view/120858 (abgerufen am 31.03.2020).
3. Griesinger F. Clinical research platform into moecular testing, treatment and outcome of NSCLC (CRISP), Vortrag anlässlich des Deutschen Krebskongresses am 22.02.2020 in Berlin.
4. Onkopedia-Leitlinie Mammakarzinom der Frau, Stand: Januar 2018. Unter: https://www.onkopedia.com/de/onkopedia/guidelines/mammakarzinom-der-frau/@@guideline/html/index.html#ID0E6RAG (abgerufen am 31.03.2020).
5. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Kolorektales Karzinom, Langversion 2.1.– Januar 2019, AWMF-Registernummer: 021/007OL. Unter: https://www.awmf.org/uploads/tx_szleitlinien/021-007OLl_S3_Kolorektales-Karzinom-KRK_2019-01.pdf (abgerufen am 31.03.2020).
6. Onkopedia-Leitlinie Kolonkarzinom, Stand: Oktober 2018. Unter: https://www.onkopedia.com/de/onkopedia/guidelines/kolonkarzinom/@@guideline/html/index.html#ID0EX4AE (abgerufen am 31.03.2020).
7. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms, Version 3.2 – Oktober 2019, AWMF-Register-Nummer: 032/024OL. Unter: https://www.awmf.org/uploads/tx_szleitlinien/032-024OLl_S3_Melanom-Diagnostik-Therapie-Nachsorge_2020-01.pdf (abgerufen am 31.03.2020).
8. Karimkhani C et al. Novel therapies for unresectable and metastatic melanoma. BMJ. 2017;359:j5174. Unter: https://www.bmj.com/content/359/bmj.j5174 (abgerufen am 31.03.2020).
9. Qualitätsgesicherte Molekulardiagnostik in der Onkologie, zielgerichtet – integriert, Positionspapier der Deutschen Gesellschaft für Hämatologie und Onkologie (DGHO) e. V., Januar 2019. Unter: https://www.dgho.de/publikationen/stellungnahmen/gute-aerztliche-praxis/molekulare-diagnostik/molekulare-diagnostik-positionspapier-2019-1.pdf (abgerufen am 31.03.2020).
10. Onkopedia-Leitlinie Chronische Myeloische Leukämie (CML), Stand: Juni 2018. Unter: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-myeloische-leukaemie-cml/@@guideline/html/index.html#ID0EVIAG (abgerufen am 31.03.2020).
11. Deutsches Ärzteblatt, Chronisch myeloische Leukämie: Imatinib könnte langfristig Lebenserwartung normalisieren, 10.03.2017. Unter: https://www.aerzteblatt.de/nachrichten/73550/Chronisch-myeloische-Leukaemie-Imatinib-koennte-langfristig-Lebenserwartung-normalisieren (abgerufen am 31.03.2020).
12. Berger MF, Mardis ER. The emerging clinical relevance of genomics in cancer medicine. Nat Rev Clin Oncol. 2018;15(6):353–365. unter: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6658089 (abgerufen am 31.03.2020).
13. Brusco LL et al. Physician interpretation of genomic test results and treatment selection. Cancer. 2018;124(5):966–972. unter: https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.3111 (abgerufen am 14.04.2020).

Image source: istock