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Acute Promyelocytic Leukemia (APL)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Bauhofstr. 12
D-10117 Berlin

Executive chairman: Prof. Dr. med. Andreas Hochhaus

Phone: +49 (0)30 27 87 60 89 - 0

info@dgho.de
www.dgho.de

Contact person

Prof. Dr. med. Bernhard Wörmann
Medical superintendent

Source

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Table of contents

Acute Promyelocytic Leukemia (APL)

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- Guideline
- Conflict of interests

Authors: Eva Lengfelder, Konstanze Döhner, Anna Hecht-So, Sabine Kayser, Jean-Francois Lambert, David Nachbaur, Uwe Platzbecker, Richard F. Schlenk, Wolfgang Reinhard Sperr, Felicitas Thol
Previous authors: Dietger Niederwieser, Bernhard Wörmann

1 Summary

Acute promyelocytic leukemia (APL) is a rare subtype of acute myeloid leukemia that leads rapidly to death if untreated. The characteristic morphology of promyelocytic blasts in combination with the genetic detection of the chromosome translocation t(15;17)(q22;q21) or the fusion gene *PML::RARA* allow the clear diagnosis of APL.

Once a diagnosis of APL was suspected, initiation of supportive therapy to reduce the risk of bleeding complications, rapid confirmation of diagnosis, and prompt initiation of antileukemic therapy are essential.

The therapeutic goal of APL is curative. The prerequisite for a durable remission and cure is the achievement of a molecular remission. Due to continuous advances in therapy (anthracyclines, all-trans-retinoic acid (ATRA), arsenic derivatives), the chances of cure in therapy studies with arsenic trioxide (ATO)-based therapy are over 90%.

For patients with a pretherapeutic leukocyte count ≤10 000/µl, the chemotherapy-free combination of ATRA and ATO represents the current standard therapy. ATO is not approved for higher initial leukocyte counts (high-risk APL). ATRA and anthracycline-based combination therapy remains the standard of care in this setting. Transplantation procedures (autologous or allogeneic stem cell transplantation) are restricted to relapse or therapy failure.

2 Basics

2.1 Definition and basic information

Acute promyelocytic leukemia (APL) is a myeloid neoplasm. In the FAB classification, it was listed as AML M3; in the current WHO or ICC classification, it is classified under the heading 'Acute myeloid leukemia with defining genetic abnormalities' or as 'AML with percentage of blasts required for diagnosis' [1, 2]. APL can be diagnosed microscopically due to the characteristic morphology of the blasts. The microgranular variant (AML M3v) is a special morphologic sub-type, mostly associated with elevated leukocyte counts. A confirmation of the genetic diagnosis is mandatory and can be made by molecular detection of the fusion gene *PML::RARA* or by conventional karyotyping (translocation t(15;17)(q22;q21)). Very rarely, cytogenetic/ molecular variants are found (see chapter 6.3.1.).

Untreated APL is characterized by a rapidly increasing bleeding risk due to coagulopathy and the frequently present thrombocytopenia. Suspected APL should always be managed as a hematologic emergency that requires immediate diagnostic confirmation and immediate initiation of therapy [3]. It should be emphasized that initiation of therapy with ATRA is recom-

mended already in cases of suspected APL. In cases presenting with high leukocyte counts, ATRA should be combined with idarubicin to reduce the risk of early mortality.

The combination of ATRA and ATO represents the current standard of care for front line therapy of low- and intermediate-risk APL (collectively referred to as standard-risk APL or 'non-high-risk APL' with pretherapeutic leukocyte counts ≤10 000/µl). In cases with standard-risk APL, ATRA and ATO reduced the early death rate and the relapse rate, and improved overall survival to more than 95% as compared with conventional ATRA/anthracycline-based therapy [4- 7].

ATO is also highly effective in high-risk APL (pretherapeutic leukocyte count >10 000/µl). However, the number of cases with high-risk APL included in clinical trials is small, and a survival benefit over conventional therapy has not yet been demonstrated. In Europe, ATO is not approved for the treatment of high-risk APL and its use is only off-label. Therefore, ATRA and chemotherapy remain the standard of care in these patients. Cohort analyses also show good efficacy of ATRA and ATO in other high-risk settings, such as advanced age or therapy-related APL [8, 9].

Despite these positive developments, the risk of death from bleeding complications in the early phase of the disease remains almost unchanged. Hence, the high early mortality of APL is still an unresolved problem. This becomes particularly evident by non-selected patient data from population-based registries, which show substantially higher early death rates and significantly worse overall survival compared to trial results. [10].

2.2 Epidemiology

APL is rare and accounts for approximately 5% of cases of newly diagnosed acute myeloid leukemia (AML). A higher incidence has been reported in Southern Europe, and in North, Central and South America. The incidence increases to a constant level in young adults after the age of 10 and decreases after the age of 60. The mean age of onset is between 40 and 50 years. Men and women are nearly equally affected.

2.3 Pathogenesis

In approximately 98% of cases with the characteristic morphology of APL, the reciprocal chromosomal translocation t(15;17)(q22;q12) involving the retinoic acid receptor-alpha (*RARA) gene* on chromosome 17 and the promyelocytic leukemia gene (*PML)* on chromosome 15 is genetically detectable. Expression of *PML::RARA* in hematopoietic progenitor cells induces the differentiation block, which is characteristic for APL [11]. The chromosomal translocation involving *RARA* and *PML* and the generation of the fusion gene *PML::RARA* leads to the malignant transformation.

In a small percentage of cases with the cytological picture of APL, molecular variants are present, each involving genes of retinoic acid receptors, quite predominantly of RARA [12].

2.4 Risk factors

The cause of APL is mostly unexplained, as are the different regional and ethnic frequencies. The proportion of therapy-induced APL after chemotherapy, especially after topoisomerase (topo)-II inhibitors (e.g., mitoxantrone for multiple sclerosis therapy) or after alkylating agents, shows an increasing trend compared with previous studies [13]. Hotspots are located in the breakpoint regions of *PML* and *RARA* as preferential sites of topo-II-induced DNA damage [14]. Several observations indicate an increased incidence of APL in severe overweight/obesity and a less favorable disease course (etiology unclear to date).

3 Prevention and early diagnosis

As with all acute leukemias, there are no effective measures for prevention and early detection of APL. It is important to consider a possible APL, if a bleeding tendency appears, as the delay of diagnosis is associated with an increase of the risk of early mortality.

4 Clinical presentation

In more than half of the cases with APL, there are concomitant coagulation disorders and respective clinical symptoms (life-threatening cerebral hemorrhage, bleeding into the lungs, skin and mucous membranes and gastrointestinal tract). Depending on the severity of thrombocytopenia, the bleeding tendency is increased. As with all other forms of acute leukemia, anemia-related symptoms and an increased risk for infection may occur. The increased risk of severe thrombosis due to the coagulopathy is to be emphasized.

5 Diagnosis

5.1 Diagnostics

Due to the high risk of life-threatening complications in the early phase of APL, rapid diagnosis is required. In addition to the basic investigations required in all acute leukemias, special investigations are necessary to detect APL (Table 1). Immediate confirmation of the diagnosis by molecular genetic techniques such as polymerase chain reaction (PCR), preferably quantitative real time PCR (qPCR), by interphase cytogenetics, by fluorescence in situ hybridization (FISH), or by immunofluorescence microscopy (diagnostic use of monoclonal antibodies against PML) is mandatory. These methods are assessed equivalent in the context of confirming the diagnosis. Determination of the *PML::RARA isoform* (bcr1, bcr2, bcr3) by PCR is required for subsequent molecular monitoring of measurable residual disease (MRD). Importantly, the monitoring is not possible by any other method. Supplementary investigations are required at onset of therapy (Table 2).

Table 1: Diagnostics for suspected APL

Investigation	Note
Medical history and physical examination	signs of bleeding, anemia symptoms, infections
Blood count and differential blood count	
Bone marrow aspirate	cytology cytochemistry immunophenotyping FISH or immunofluorescence qPCR from *PML::RARA* conventional cytogenetics (*FLT3* mutation, only in studies, not obligatory in routine diagnostics)
Bone marrow biopsy	only, if punctio sicca
Coagulation status	prothrombin time (INR, Quick value), aPTT, fibrinogen, D-dimers, factor XIII, if necessary ATIII

Table 2: Necessary supplementary examinations at therapy initiation

Investigation	Note
General condition	ECOG/WHO Score
Evaluation of comorbidities	consider anthracycline exposition pre-therapy in case of secondary APL.
Clinical chemistry, urin alysis	if necessary, correction of electrolytes before ATO (potassium values above 4 mEq/l and magnesium values above 1.8 mg/dl).
Pregnancy testing/sperm cryopreservation Fertility protective measures incl. GnRH analogues	if applicable
X-ray/ CT thorax if necessary	
ECG	important for QTc- (QTcF-) time determination *
Echocardiography	obligatory in case of previous cardiac disease and in case of previous anthracycline therapy, recommended when anthracyclines are administered as part of APL therapy.

Legend:
** It is recommended to determine the QTc time according to the Fridericia correction method: QTcF (QTcF=QT/cube root of RR), because the mostly common determination according to the Bazett correction method QTcB=QT/square root of RR) may lead to unnecessary interruptions of ATO therapy [15].*

5.1.1 Morphology / Cytochemistry / Immunophenotyping

The characteristic morphology of APL blasts usually allows the prompt diagnosis of APL (examples in eLCH - eLearning Curriculum Hematology for Bone Marrow Cytology using Virtual Microscopy; https://ehaematology.com/). Microscopically, two subtypes are distinguished, the much more common hypergranular form (AML M3) and the rare hypo- (micro-) granular variant (M3v). The most important features are listed in Table 3.

Table 3: Characteristics of APL subtypes.

	APL (hypergranular, FAB M3)	APL variant (microgranular, FAB M3v)
Relative frequency (%)	90-95	5-10
Peripheral blood count	leukocytopenia[2]	leukocytosis[2]
Morphology	• large blasts • closely packed large granules • Auer rods, often in bundles • 'faggot cells'	• monocytoid blasts (reniform or bilobed nucleus) • microgranular • few or none Auer rods • 'faggot cells' (relatively rare)
Cytochemistry	POX strongly positive	POX strongly positive
Immunophenotype[1]	CD2-, CD13+, CD33+, CD34-, CD117+, HLA-DR-	CD2+, CD13+, CD33+, CD34+, CD117+, HLA-DR-.

Legend:

[1] according to CD classification - Cluster of differentiation,
[2] mostly, but exceptions possible. The description of the immunophenotype corresponds to the pattern characteristic of the two subtypes. Deviations from the expression of HLA-DR, CD2 and CD34 shown here were reported in both subtypes [16].

5.1.2 Cytogenetics / Molecular Biology

If the typical morphological features of APL are present, the underlying genetic defect corresponds in about 98% to the translocation t(15;17)(q22;q12), with the resulting fusion gene *PML::RARA*. Also rare but possible are cryptic genetic alterations that are invisible in conven-

tional cytogenetics but can be detected by FISH and PCR (normal karyogram but *PML::RARA-positive*). The reciprocal fusion gene *RARA::PML* is detectable in only a subset of cases. It is therefore not appropriate for routine diagnosis. In addition to *PML::RARA,* other concomitant mutations with as yet uncertain influence on disease progression have been described, including in the *FLT3*, *WT1*, *NRAS, ARID1A,* and *KRAS* genes [17]. The prognostic impact of additional cytogenetic aberrations is controversial.

Only very few patients have other fusion variants, where instead of the *PML gene* another partner gene fuses with the retinoic acid receptor alpha gene (*RARA*) (see chapter 6.3.1., table 6). The most common variant is the translocation t(11;17)(q23;q21), which corresponds at the molecular level to a fusion of the *ZBTB16* (former name *PLZF) gene* and the *RARA* gene. More recently, single APL forms involving other retinoic acid receptors (RARB or RARG) have also been described [12].

5.2 Differential diagnosis

The differential diagnosis of APL primarily concerns other subtypes of AML, in particular AML FAB M2 or M4 (according to the current WHO classification assigned to the rubric 'AML defined by differentiation', according to ICC to 'AML with percentage of blasts required for diagnosis'), which are morphologically difficult to distinguish from APL in some cases [1, 2]. In addition, the differential diagnosis includes a number of hematologic and non-hematologic disorders with pancytopenia (Table 4), which should be considered as a differential diagnosis, especially in aleukemic APL. In this context, the history and clinical examination are often suggestive and helpful. Bone marrow aspiration with detection of the characteristic morphology (chapter 5.1.1.) usually allows a rapid diagnosis of APL.

Table 4: Important differential diagnoses of APL in peripheral pancytopenia.

• Other forms of acute leukemia (myeloid, lymphoid)
• Myelodysplastic syndrome
• Aplastic anemia
• Primary myelofibrosis
• Non-Hodgkin's lymphoma with bone marrow infiltration
• Hairy cell leukemia
• Hypersplenia syndrome of various causes
• Reactive / toxic bone marrow changes
• Vitamin B 12 - deficiency
• Paroxysmal nocturnal hemoglobinuria (PNH)
• Viral infections
• Sepsis

5.3 Prognosis

5.3.1 Early mortality

The high rate of early mortality, especially before the start of therapy or shortly after therapy initiation, remains a major challenge in the treatment of APL. According to data from a Swedish registry study, 63% of early deaths occurred within the first week after diagnosis [10].
Prominent risk factors for early death include older age (approximately 60 years or older) and high leukocyte/blast count before initiation of therapy, and comorbidity. Elevated creatinine and male gender have also been described as risk factors [10, 18]. Data suggest that these risk factors, originally reported under ATRA and chemotherapy, are also valid for treatment with ATO [19]. Factors influencing fatal bleeding complications are described in Chapter 6.2.5.1.

5.3.2 Risk of relapse

During therapy with ATRA and anthracyclines (AIDA protocol of the Italian GIMEMA and Spanish PETHEMA), the combination of pre-therapeutic leukocyte and platelet count (Sanz score) proved to be a significant risk factor for the occurrence of a relapse [20]. This internationally used score (originally developed basing on ATRA and anthracycline therapy) distinguishes three risk groups (Table 5). Concerning protocols with ATRA and anthracycline therapy, the score allows a significant estimation of relapse risk and stratification of therapy intensity [20]. Other unfavorable prognostic factors detected under therapy with ATRA and anthracyclines (e.g., *FLT3 length mutations*, bcr3 isoform, CD56 expression, and cytogenetic additional aberrations) have not gained significance with respect to therapy stratification.

Low-risk and intermediate-risk (each with initial leukocyte count ≤10 000/µl without consideration of platelet count) are now summarized under the term standard-risk or 'non-high-risk', as the separation into low- and intermediate-risk had not proven to be significant in ATO-based therapy. Literature results make clear that the Sanz score is not applicable to protocols that include high doses of cytosine arabinoside (Ara-C) or ATO [21- 24]. Furthermore, *FLT3 length mutation* or cytogenetic additional aberrations had no prognostic significance in the therapy trials with ATO and ATRA [23- 26].

Table 5: APL risk score (Sanz score) [20].

Risk group	low	intermediate	high
Leukocytes/ µl	≤ 10 000	≤ 10 000	> 10 000
Platelets/ µl	> 40 000	≤ 40 000	

6 Therapy

6.1 Therapy structure

If APL is suspected, attention should be paid to adequate substitution therapy to stabilize coagulopathy and thrombocytopenia (see chapter 6.2.5.1.).

In addition to supportive therapy, the immediate start of APL-specific antileukemic therapy is important. ATRA should be started when APL is suspected, if necessary before genetic confirmation of the diagnosis is available, because any delay of the start of therapy increases the risk of bleeding complications and of early death. If the leukocyte count is high, ATRA is not to be started as monotherapy, and idarubicin should be initiated simultaneously. Due to the rarity

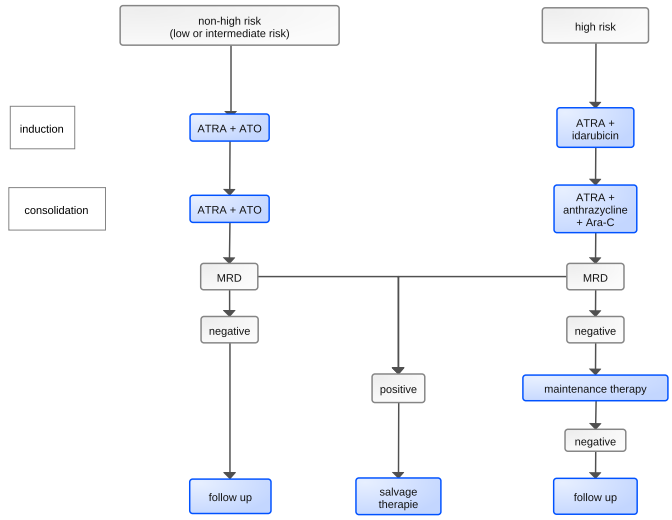
of APL, therapy at a hematology center and, if available, as part of a registry or therapy study is recommended (see Chapter 10).

The goal of induction therapy is the induction of a complete hematologic remission (CR). The goal of consolidation therapy is to achieve complete molecular remission. Consolidation therapy consists of a varying number of cycles depending on the protocol chosen. Maintenance therapy is exclusive to ATO-free regimens. Since only patients in molecular remission remain disease-free in the long term, the achievement of molecular remission after completion of consolidation therapy is the primary therapeutic goal (see Chapter 6.1.1.).

6.1.1 First-line therapy

First-line therapy of APL is stratified by the pre-therapeutic leukocyte count (Sanz Score, Figure 1). In the absence of high risk, current standard (chemotherapy-free) therapy consists of ATRA and ATO. For high-risk APL, conventional treatment with ATRA plus anthracycline-containing chemotherapy remains the standard of care (Figure 1). Use of ATO is only possible off-label in this setting.

Figure 1: Therapy algorithm for first-line therapy.



Legend:
curative intended therapy
** See Table 5*
for risk score, low and intermediate risk are collectively referred to as standard risk or 'non-high-risk'; ATRA - all-trans retinoic acid, ATO - arsenic trioxide, MRD - measurable residual disease.

6.1.1.1 Therapy for standard risk: ATRA plus ATO

6.1.1.1.1 Induction therapy for standard risk

In patients with APL that are assigned to standard risk, the simultaneous administration of ATRA and ATO corresponds to the current therapeutic standard. The establishment of this therapeutic concept was preceded by two randomized therapy trials testing similar therapeutic concepts with ATRA and ATO versus conventional therapy (Italian-German APL0406 trial of GIMEMA, SAL and AMLSG in cases with pre-therapeutic leukocyte count ≤10 000/µ (standard risk APL) and British AML17-APL trial in all risk groups) [4, 5].

Both protocols were superior to conventional ATRA/antracycline therapy with regard to antileukemic efficacy and toxicity. Long-term results showed significant advantages in overall survival, event-free survival, and cumulative incidence of relapse with ATRA and ATO, as well as quality of life [6, 7, 27]. Meanwhile, the excellent efficacy of this therapy was confirmed by 'real

life' registry data in standard risk APL [26]. In this setting, conventional ATRA/antracycline therapy is no longer the treatment of choice and should only be given, if contraindications to ATO exist.

6.1.1.1.2 Consolidation therapy at standard risk

Consolidation therapy consists of a combination of ATRA and ATO. In total, there are four blocks of ATO therapy and seven ATRA blocks, some of which are applied simultaneously. The intended total duration of consolidation therapy is 28 weeks [4]. Molecular remission (MRD negativity) should be achieved at the latest after the last consolidation course. If the PCR is still positive, treatment failure is to be assumed (see chapter 6.1.2.).

6.1.1.1.3 Maintenance therapy for standard risk

Maintenance therapy is not provided.

6.1.1.2 High-risk therapy: ATRA and chemotherapy

6.1.1.2.1 Induction therapy for high risk

The use of ATRA and anthracycline-based chemotherapy is very effective in high-risk APL and still represents the standard of care for high-risk patients. Since the majority of study results indicate an improvement in prognosis (reduction of relapse rate) with the addition of higher-dose Ara-C, the inclusion of Ara-C is considered standard in high-risk APL up to approximately 65 years of age [21,22,28-31]. In Germany, the corresponding high-risk protocol of the Italian study group GIMEMA is now widely used (Figure 1) [29].

Therapy with ATRA and ATO is also very effective in high-risk APL. There is widespread consensus that ATRA and ATO should be combined with anthracyclines or gemtuzumab ozogamicin in this setting to lower the high leukocyte count and reduce the risk of APL differentiation syndrome (ADS). Historical comparisons with the combination of ATRA and chemotherapy suggest that relapse rates are also reduced in high-risk APL by ATO-based approaches. However, no improvement in survival prognosis has been derived [5, 23, 24]. A randomized comparison of both regimens is the subject of the now-closed European trial for high-risk APL (APOLLO NCT02688140). Since ATO is not approved for the primary therapy of high-risk patients in Europe and the USA, its use can only be off-label.

6.1.1.2.2 Consolidation therapy for high risk

Consolidation therapy, is required to stabilize remission. Depending on the protocol chosen, up to three consolidation cycles consisting of ATRA and chemotherapy are common [29, 30].

6.1.1.2.3 Maintenance therapy for high risk

After first-line therapy with ATRA and chemotherapy, two years of maintenance therapy with methotrexate, mercaptopurine, and ATRA is common in cases that are MRD-negative after consolidation (determination of thiopurine methyltransferase (TPMT) activity may be possible). This

recommendation is based on the results of a randomized trial from the 1990s (French/European APL93 trial), in which the role of maintenance therapy was investigated. The initial publication of the study results as well as the long-term data showed a significant reduction of the recurrence rate when maintenance therapy was applied. This effect was particularly evident in patients with higher initial leukocyte counts (>5 000/µl) [31]. The necessity of maintenance therapy was repeatedly questioned in the course of subsequent years, but a definitive recommendation for abandoning it was never derived [32].

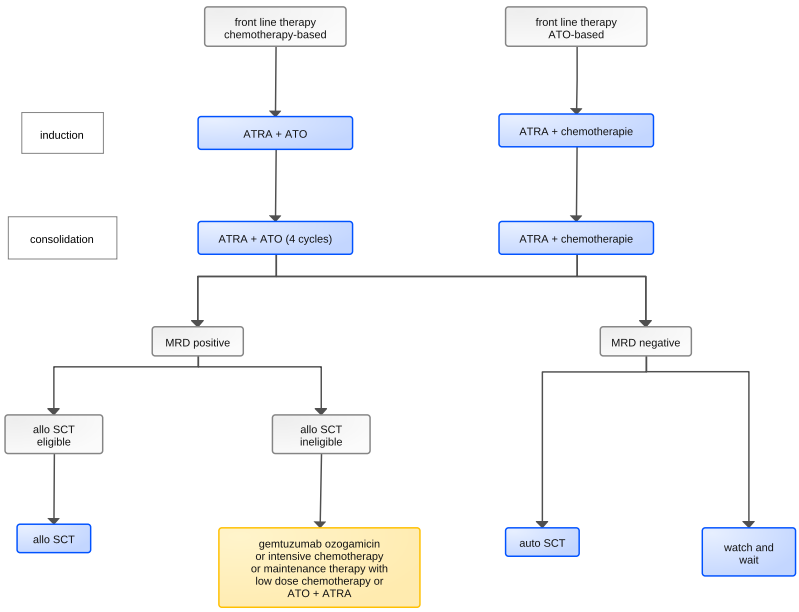
Autologous or allogeneic peripheral blood stem cell transplantation (SZT) is not indicated in first remission when molecular remission has been achieved.

6.1.2 Relapsed or refractory APL

In medullary or extramedullary relapse of *PML::RARA-positive* APL, as well as in the rare case of primary resistance (persistence of a positive PCR after consolidation), long-lasting remissions and cure can be achieved by salvage therapy. In APL relapse, the achievement of a renewed molecular remission is also the critical therapeutic goal (as it is in front-line therapy). Data indicate that when salvage therapy is initiated already in molecular relapse, a reduction in early and all-cause mortality can be assumed compared with therapy in full hematologic relapse [33, 34]. In case of cytological evidence of a possible relapse (blast detection), molecular APL diagnostics should always be repeated to exclude the development of *PML-RARA* negative secondary AML or MDS.

An algorithm for second-line therapy is shown in Figure 2.

Figure 2: Algorithm for second-line therapy in acute promyelocytic leukemia.



Legend:
curative intended therapy, palliative intended therapy
ATO - arsenic trioxide; ATRA - all-trans retinoic acid; MRD - measurable residual disease; SCT - stem cell transplant;
gemtuzumab ozogamicin (only off label).

The choice of therapy in the first hematologic or molecular relapse of APL depends primarily on the composition of the primary therapy and the duration of the initial remission (see Figure 2). Thus, after primary treatment with ATRA and chemotherapy, ATO-based relapse therapy is recommended and vice versa. If remission is prolonged (over approximately 2 years), primary therapy may also be repeated (not evidence-based) [32].

In **relapse after primary therapy with ATRA and chemotherapy,** ATO in combination with ATRA is the therapy of choice due to its high antileukemic efficacy [35]. Usually, remission induction consists of a course of ATO and ATRA. Consolidation therapy analogous to primary therapy with ATO has been established with four consolidation cycles of ATO/ATRA (see chapter 6. 1. 1. 2.).

For **ATO-based primary therapy,** there are no evidence-based recommendations for the treatment of relapse. The focus is on conventional ATRA-plus-chemotherapy regimens, usually including higher doses of Ara-C. Longer lasting remission durations (at least 2 years) after ATO therapy are considered as possible exceptions in which ATO can be used again [32]. Also, in individual cases with shorter remission durations that cannot be exposed to the toxicity of intensive chemotherapy or, when the time to allogeneic stem cell transplantation (SCT) needs to be bridged, re-therapy with ATO may be considered. In individual cases, testing for PML mutations with arsenic resistance may be helpful in decisions to use ATO again [36].

The further therapy steps (postconsolidation therapy) are to be adapted to the individual case. For suitable patients in second molecular remission, **autologous SCT** is considered the therapy of choice [37- 39]. Although molecular remission is the general consensus prerequisite for autologous SZT, long-term remissions of MRD-positive cases have also been observed [40]. Also of note are reports of cases that received second-line therapy with ATO and ATRA after primary therapy with ATRA and chemotherapy and remained in stable remission without autologous SCT [7, 41]. Here, the majority (as far as information is available) were patients with longer initial remission duration [41]. These observations may be helpful in making difficult case-by-case decisions.

Pronounced risk constellations, such as the rare failure to achieve molecular remission after first-line therapy or second and subsequent relapses, usually represent an indication for the use of **allogeneic SCT** [39]. If allogeneic SCT is not feasible, the decision must be made on an individually. In this case, further treatment with ATO or chemotherapy or with the combination of both, if necessary as 'low dose' continuous therapy or experimental therapy can be performed (Figure 2). In this context, special reference should be made to the high efficacy of the toxin-coupled anti-CD33 antibody gemtuzumab ozogamicin (GO) in multiply pretreated APL [42]. GO is approved by the U.S. Food and Drug Administration (FDA) and subsequently by the EMA for selected AML patients, but not for APL. Starting in Japan, synthetic retinoids (tamibarotene, not available in Germany) with improved efficacy compared to ATRA were used [43].

6.1.3 CNS prophylaxis and therapy of CNS relapse

The CNS is by far the most common site of extramedullary relapse. These are isolated CNS relapses or hematologic or molecular bone marrow relapses involving the CNS. Although there are no formal data on the use of intrathecal (i.th.) CNS prophylaxis (either for chemotherapy or ATO-based therapy), if chosen, it should be restricted to high-risk APL. In particular, if the leukocyte count is high, CNS prophylaxis should be given only after hematologic remission has been achieved to avoid complications, especially bleeding [3, 32].

For local CNS relapse, repeated weekly i.th. triple therapy with methotrexate, Ara-C, and hydrocortisone is recommended until blast clearance, followed by 6 to 10 dilated applications for consolidation [3]. For prophylaxis or treatment of the usually subsequent or simultaneous medullary relapse, systemic therapy with good CNS penetration (ATO or high-dose ARA-C) should be administered. For consolidation with autologous or allogeneic SCT, the recommendations of medullary relapse apply. In addition, there is the option of craniospinal irradiation [3, 32].

6.1.4 Molecular monitoring

Molecular monitoring by quantitative REAL-time PCR (qPCR) of *PML::RARA* is an obligatory control parameter to assess treatment response as well as for early detection of molecular relapse.

The primary goal of molecular monitoring is to record the remission status after the end of consolidation therapy and, in the further course, the early detection of a molecular relapse even before the transition to a hematological relapse.
For **standard risk APL,** the following approach is recommended depending on the therapy:

1. in case of therapy with **ATRA and ATO**, a routine control by means of bone marrow aspirate with the aim of detecting molecular remission is obligatory after the end of consolidation therapy. (The individual course of the values of qPCR during the induction and consolidation phase has no influence on the therapy management, the result after consolidation therapy is essential). Once molecular remission is achieved after consolidation, follow-up monitoring is no longer routinely recommended due to the very low recurrence rate (<5%).
2. in therapy with **ATRA and chemotherapy,** the clinical benefit of molecular monitoring is assessed differently, so that the decision here must be made individually [32, 44].

In **high-risk APL, molecular** follow-up should always be performed after molecular remission has been achieved, regardless of the primary therapy chosen. It is also recommended **after relapse** [32, 44].

Molecular monitoring can be performed either by 3-monthly controls from bone marrow aspirate or by shorter-term controls (e.g., 4- to 6-weekly) from peripheral blood, although analysis from peripheral blood is less sensitive. There is no evidence for the **duration of monitoring.** Given the relative rarity of subsequent relapses, a duration of 2 years is considered sufficient [32, 44].

With qPCR, which is the current standard method for molecular monitoring, the quantity of transcripts and the kinetics of MRD is detectable much more accurately than with nested RT-PCR, which was used formerly. (Should nested RT-PCR still be used, a sensitivity of at least 10^{-4} is required.)

In case of recurrence of a positive transcript detection after originally achieved qPCR negativity or an increase above 1Log, a developing relapse is suspected. In such cases, short-term monitoring of the results (after approximately 2 to 4 weeks) in the context of a new bone marrow aspiration is recommended. However, interpretation of the result in high-sensitivity qPCR can sometimes be difficult if the number of transcripts is low. In this case, the increase in transcripts with further controls is the most reliable marker of "true" positivity [32].

6.2 Therapy modalities

6.2.1 All-trans retinoic acid (ATRA)

ATRA, a derivative of vitamin A acid, causes an abrogation of the differentiation block of promyelocytic blasts at the molecular level and induces maturation into mature neutrophilic granulocytes, associated with a regression of coagulopathy within a few days. The exceptionally high efficacy of ATRA is APL-specific. ATRA is an obligatory component of induction therapy in APL. With ATRA monotherapy, 80% to 90% of patients with newly diagnosed APL achieve hematologic remission. Because ATRA alone does not induce durable remissions, ATRA monotherapy is usually restricted to palliative treatment goals.

Therapeutic intervention under ATRA monotherapy is primarily required in the occurrence of the APL differentiation syndrome (ADS, formerly ATRA syndrome) and in the event of a rapid leukocyte increase (Chapter 6.2.5.2. and Chapter 6.2.5.3.). Pseudotumor cerebri is observed mainly in children and young adults and is a potentially threatening complication requiring dose reduction of ATRA [3]. Dose adjustments may also be required in the presence of impaired hepatic or renal function.

6.2.2 Arsenic trioxide

Arsenic compounds represent the most effective monosubstance with curative potential in APL. The greatest clinical experience is with arsenic trioxide (As_2 O_3 ; ATO). ATO has predominantly apoptosis-inducing properties in addition to a differentiating effect. ATO targets the PML portion of the PML::RARA protein, whereas the RARA portion is the target of ATRA. The combination of the two synergistically acting compounds enhances antileukemic efficiency and leads to degradation of the PML::RARA fusion protein and, as a consequence, to apoptosis of APL blasts. Complete eradication of the APL clone (curative effect) can only be achieved by ATO [3, 11].

The onset of action of ATO is accompanied in about 50% of cases by an increase in the leukocyte count (hyperleukocytosis, see chapter 6.2.5.2.) and by increased numbers of precursors of granulopoiesis in the peripheral blood. A potentially dangerous side effect of therapy is ADS, which is observed in up to 25% of cases (see Chapter 6.2.5.3.). Concurrent use of ATRA may increase the risk of ADS. During therapy with ATO, ECG changes with prolongations of QTcF time (Fridericia correction method, Table 2) and electrolyte shifts requiring substitution, especially of potassium and magnesium, require special attention (see Chapter 5.1). Potassium should be above 4 mmol/l and magnesium above 1.8 mg/dl. Regular ECG checks are indicated. If the QTcF interval exceeds 500 msec, therapy is discontinued because of the risk of cardiac arrhythmias (torsade des pointes) [32]. After regression, treatment should be continued at 50% of the previously given daily dose (for further information on ECG and electrolyte monitoring, see EMA approval text of ATO: Trisenox, INN-arsenic trioxide (europa.eu)).

Comedication with drugs that, like ATO, can prolong QTcF time should be avoided and, if unavoidable, requires intensified ECG monitoring.

Relatively common, usually non-life-threatening side effects include liver dysfunction and increase in transaminases, nausea, vomiting, exanthema, fatigue, fever, neuropathy, and diarrhea. Reactivations of herpes zoster infections are more frequent. Regarding herpes prophylaxis (including vaccination), there are no firm recommendations. Detailed information and instructions for action in case of adverse effects of ATO are provided in the expert information of arsenic trioxide (Trisenox^{TM}) [45].

Oral arsenic compounds are highly effective, as is the intravenous route of administration. They are not available in the EU but are widely used in China [43].

6.2.3 Chemotherapy

APL blasts are highly sensitive to anthracyclines. Daunorubicin, which was originally used, has now been largely replaced by idarubicin, as this agent was found to be more effective in APL therapy. Data suggest that the inclusion of medium-high to high-dose Ara-C in high-risk APL reduces the relapse rate [21, 22][25- 28]. The spectrum of side effects of chemotherapy regimens is similar to that of AML therapy.

6.2.4 Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is an antibody-drug conjugate. It consists of a monoclonal antibody directed against CD33 covalently bound to the cytotoxic agent calicheamicin. Calicheamicin induces double-strand breaks in target cells, comparable to the effect of conventional chemotherapy. GO was shown to be highly effective in the relapse and primary therapy of APL [42]. However, the compound can only be used off-label in APL because the approval for CD33-positive AML does not include APL.

6.2.5 Supportive therapy

6.2.5.1 Coagulopathy

Bleeding complications are the most common cause of high early mortality. Risk factors for lethal bleeding even before the start of therapy or in the first days after the start of induction therapy include pre-existing active bleeding, hypofibrinogenemia (<100 mg/dl), elevated levels of D-dimers or fibrin cleavage products, prolonged prothrombin time or PTT, high peripheral leukocyte or blast counts, marked thrombocytopenia, elevated creatinine levels, and poor general health [20]. These risk factors remain relevant in the ATO era [19]. Procedures associated with potential bleeding complications, such as lumbar puncture, central venous catheter, invasive examinations (e.g. bronchoscopy) should be avoided before or during induction therapy if possible.

Coagulation status is monitored with the global tests of activated partial thromboplastin time (aPTT), prothrombin time (INR, Quick), as well as fibrinogen level and platelet count. The relevant coagulation status parameters and platelet count should be monitored once or twice daily at least until the coagulation disorders have regressed. Substitution is performed with fibrinogen, FFP (fresh frozen plasma) and platelet concentrates. The goal is fibrinogen levels between 100 to 150 mg/dl and platelet levels between 30 000 to 50 000/µl [32].

Treatment with the antifibrinolytic tranexamic acid, substitution of factor XIII or, if necessary, ATIII can be considered in individual cases. There is no proven benefit for prophylactic heparinization and administration of anticoagulants or antifibrinolytics. Recombinant soluble thrombomodulin is used in Japan for therapy of disseminated intravascular coagulation and reduced early deaths from bleeding in a retrospective analysis. However, prospective controlled studies are lacking [47].

The recommended supportive measures apply regardless of the therapy used.

6.2.5.2 Hyperleukocytosis,

A high leukocyte count (>10 000/µl) should be controlled by the immediate use of chemotherapy (idarubicin, hydroxyurea), both at the start of therapy with ATRA and ATO and when leukocytes rise during therapy. The speed of the leukocyte increase should also be considered. If the doubling time is rapid (e.g., daily), the use of hydroxyurea should be considered already at leukocytes below 5 000/µl. Leukapheresis should be avoided because of the possible favoring of bleeding complications. Steroid prophylaxis to prevent ADS is possible (Chapter 6.2.5.3.) [3, 32].

6.2.5.3 APL Differentiation Syndrome (ADS)

After initiation of therapy with ATRA or ATO, AD syndrome may develop very rapidly. Usually, the syndrome appears within the first 2 weeks after the start of therapy, but later time points are also possible. ADS is diagnosed solely on the basis of clinical criteria. ADS is considered definite when three of the following symptoms are present; suspicion exists with the presence of even a single symptom:

- Weight gain
- Shortness of breath
- Fever of unexplained cause
- Pulmonary Infiltrates
- Pleural or pericardial effusion

Prophylactic steroid administration (prednisone 0.5 mg/kg/day) to prevent AD concomitant with induction therapy with ATO analogous to the APL0406 trial is recommended [4, 6]. Steroid prophylaxis is also optional in the treatment of high-risk APL with chemotherapy-containing regimens [3, 32].

In manifest ADS, the use of dexamethasone (10 mg i.v., every 12 hours) is mandatory. Without the use of high-dose steroids, ADS had a lethality of over 30%. Therefore, dexamethasone therapy should be initiated promptly even if ADS is suspected. The use of dexamethasone is also explicitly recommended when it is not possible to distinguish with certainty between ADS and other differential diagnoses (e.g., pneumonia, heart failure). The therapy should be continued for at least three days or until the symptoms disappear. Additional diuretic therapy is recommended.

In a mild form of ADS under combination of ATRA and ATO, therapy with both drugs can be continued under dexamethasone protection. If the syndrome is severe or very severe, e.g. with respiratory insufficiency requiring ventilation, progressive renal insufficiency or need for intensive care due to other symptoms, therapy is interrupted and can be restarted at 50% dosage in each case after symptoms have resolved: If clinically stable, the full ATO/ATRA dose can be restarted in the further course [48]. When therapy is resumed, the leukocyte count should be reduced to at least <10 000/µl, or better still stable in lower ranges (see also chapter 6.2.5.2.).

6.2.5.4 Infections

For prophylaxis and therapy of infections, please refer to the specific Onkopedia guidelines of the AGIHO Fungal Infections-Primary Prophylaxis and Febrile Neutropenia.

6.3 Special situations

6.3.1 APL molecular variants

A selection of overall very rare molecular variants of APL including RARA is shown in Table 6. The most common variant with the translocation t(11;17)(q23;q21) is usually not sensitive to therapy with ATRA or ATO. Other variants show partial sensitivity to ATRA and/or ATO. However, this experience is based only on small case collections or individual cases, which should be considered when making treatment decisions. In cases of resistance, chemotherapy is recommended as in AML. In some of these rare variants of APL, molecular monitoring by the standard method, qPCR, is not possible. In such cases, an NGS-based MRD method may be helpful to provide insight into the status of residual disease.

More recently, APL forms involving other retinoic acid receptors (RARB or RARG) have also been described. Where studied, they showed no sensitivity to ATRA or ATO [12]. A comprehensive review of genetic alterations in atypical APL was published by an Italian research group [49].

Table 6: Molecular variants of APL [12].

Fusion protein	Translocation	ATRA sensitivity	ATO sensitivity
ZBTB16::RARA (formerly PLZF/RARA)	t(11;17)(q23;q21)	resistant	resistant
BCoR::RARA	t(X;17)(p11;q21)	resistant	resistant
FIP1L1::RARA	t(4;17)(q12;q21)	sensitive	n.a.
FNDC3B::RARA	t(3;17)(q26;q21)	unsafe	n.a.
GTF2I::RARA	t(7;17)(q11;q21)	resistant	resistant
IRF2BP2::RARA	t(1;17)(q42;q21)	probably	resistant
NABP1::RARA	t(2;17)(q32;q21)	unsafe	n.a.
NPM1::RARA	t(5;17)(q35;q21)	sensitive	n.a.
NuMA::RARA	t(11;17)(q13;q21)	probably	n.a.
PRKAR1A::RARA	del(17)(q21;q24)	unsafe	unsafe
STAT3::RARA	t(17;17)(q21;q21)	resistant	resistant
STAT5b::RARA	t(17;17)(q21;q21)	resistant	resistant
TLBR1::RARA	t(3;17)(q26;q21)	resistant	resistant
TGF::RARA	t(3;14;17)(q12;q11;q21)	sensitive	n.a.

Legend:
***n**.a.: not available*

6.3.2 Higher age

Even in advanced age, a curative therapy approach should be pursued in the case of APL [9, 50]. The sensitivity of blasts to therapy does not differ from that of younger patients. Comorbidity and therapy-associated toxicity, especially when conventional ATRA-plus-chemotherapy concepts are used, are therapy-limiting in older patients. According to an analysis of registry data, older patients benefit from the use of ATO-based therapy in terms of remission and relapse rates. This applies to cases with standard and high-risk APL (off-label for high-risk APL) [9].

6.3.3 Secondary APL

Secondary, therapy-associated APL should be treated as primary APL with the goal of cure. Prior anthracycline exposure is to be considered in the choice of therapy. The use of ATO-based primary therapy proved to be advantageous over ATRA-plus chemotherapy in a retrospective comparison, allowing a curative approach without administration of further chemotherapy [9].

6.3.4 Pregnancy

The care of pregnant APL patients must be interdisciplinary. Even if APL is diagnosed during pregnancy, the patient has a chance of recovery. The stage of pregnancy is decisive for the therapeutic procedure. While it is usually not possible to successfully terminate the pregnancy

in the first trimester, there is a good chance to successfully terminate the pregnancy in the second and especially in the last trimester.

ATRA and ATO have a high teratogenic potential. Options in the first trimester are termination of pregnancy (cave bleeding complications) or mono-chemotherapy with daunorubicin. After abortion, standard risk-adapted therapy can be started immediately.

In the second and third trimesters, there are no contraindications to combined treatment with ATRA and anthracyclines. A summary of published cases of all AML types shows no increased maternal risk and no increased risk of malformations in the child. However, there is an increased rate of miscarriage, premature birth, and low birth weight neonates [51, 52]. Because these complications are associated with chemotherapy, in low- or intermediate-risk pregnant women with APL, the time until after delivery can be bridged by monotherapy with ATRA, if possible. In high risk patients, combination therapy of ATRA and anthracyclines (preferably daunorubicin) is indicated despite the associated risks. In all cases, close follow-up and gynecologic co-management are required.

7 Follow-up

For molecular monitoring by PCR of *PML::RARA* in the context of remission monitoring, please refer to chapter 6.1.4.

Molecular genetic confirmation of APL is always required to prove relapse and to differentiate secondary leukemia/MDS. In the case of proven relapse, the recommended diagnostics in the context of the initial manifestation are recommended (Table 1 and Table 2).

Most relapses occur up to about 2 years after completion of primary therapy. Relapses after five years of remission are rare; isolated late recurrences after more than 10 years have been observed. To detect late toxicity, late relapses or secondary leukemia and other second malignancies, long-term monitoring with once-yearly check-ups of the blood count and other individually adjusted parameters is recommended.

For guidance on COVID-19, please refer to the Onkopedia COVID-19 Guideline. With regard to therapy or control and follow-up examinations, there are no changes due to the SARS-CoV-2 pandemic.

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10 Active studies / registers

Napoleon Register:

Prof. Dr. med. Uwe Platzbecker
Medical Clinic and Polyclinic I (Hematology, Cell Therapy, Hemostaseology)
University Hospital Leipzig
Liebigstraße 22,
04103 Leipzig
Uwe.Platzbecker@medizin.uni-leipzig.de

14 Links

Therapy recommendation for primary therapy of APL and relapse (German AML/APL Intergroup): available through the AML Study Groups and the Competence Network Acute and Chronic Leukemia http://www.kompetenznetz-leukaemie.de;

http://www.kompetenznetz-leukaemie.de/content/aerzte/aml/therapieempfehlungen/apl

15 Authors' Affiliations

Prof. Dr. med. Konstanze Döhner
Universitätsklinikum Ulm
Innere Medizin III
Albert-Einstein-Allee 23
89081 Ulm
konstanze.doehner@uniklinik-ulm.de

PD Dr. med. Anna Hecht-So
Klinikum rechts der Isar der Technischen Universität München
Klinik und Poliklinik für Innere Medizin III
Ismaninger Str. 22
81675 München
anna.hecht@mri.tum.de

PD Dr. med. Sabine Kayser
Institut für Transfusionsmedizin und Immunologie
Medizinische Fakultät Mannheim, Universität Heidelberg
DRK-Blutspendedienst Baden-Württemberg Hessen gGmbH
Friedrich-Ebert-Str. 107
68167 Mannheim
Sabine.Kayser@medma.uni-heidelberg.de

Dr. Jean-Francois Lambert
Groupement Hospitalier de l'Ouest Lémanique
site de Nyon 10, ch. de Monastier
CH-1260 Nyon Suisse
jeanfrancois.lambert@ghol.ch

Prof. Dr. med. Eva Lengfelder
Universitätsklinikum Mannheim
Medizinische Fakultät Mannheim d. Uni Heidelberg
III. Medizinische Klinik
Theodor-Kutzer-Ufer 1-3
68167 Mannheim
eva.lengfelder@medma.uni-heidelberg.de

Univ.-Prof. Dr. David Nachbaur
Medizinische Universität Innsbruck
Innere Medizin
Hämatologie und Onkologie
Anichstr. 35
A-6020 Innsbruck
david.nachbaur@i-med.ac.at

Prof. Dr. med. Uwe Platzbecker
Universitätsklinikum Leipzig
Medizinische Klinik und Poliklinik I
Hämatologie und Zelltherapie
Liebigstr. 22, Haus 7
04103 Leipzig
Uwe.Platzbecker@medizin.uni-leipzig.de

Prof. Dr. Richard F. Schlenk
Nationales Centrum für Tumorerkrankungen (NCT)
Marsilius Arkaden
Turm West 9 Stock
Im Neuenheimer Feld 330.3
69120 Heidelberg
richard.schlenk@nct-heidelberg.de

Prof. Dr. med. Wolfgang Reinhard Sperr
Medizinische Universität Wien
Klinik für Innere Medizin I
Abt.f. Hämatologie und Hämostaseologie
Währinger Gürtel 18-20
A-1090 Wien
wolfgang.r.sperr@meduniwien.ac.at

Prof. Dr. med. Felicitas Thol
Medizinische Hochschule Hannover
Klinik für Hämatologie, Hämostaseologie
Onkologie und Stammzelltransplantation
Carl-Neuberg-Str. 1
30625 Hannover
thol.felicitas@mh-hannover.de

16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License[4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Döhner, Konstanze	Universitätsklinikum Ulm, Albert-Einstein Allee 23, 89081 Ulm	**Yes** Advisory Board: Novartis, Janssen, Celgene/BMS, Daiichi Sankyo, JAZZ, Roche, ABBVIE, GSK	**No**	**No**	**Yes** Advisory Board: Novartis, Janssen, Celgene/BMS, Daiichi Sankyo, JAZZ, Roche, ABBVIE, GSK	**Yes** Novartis, Celgene7BMS, Astellas, Agios	**No**	**No**
Hecht-So, Anna	Früher Universitätsmedizin Mannheim, jetzt Klinikum rechts der Isar, Technische Universität München	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Kayser, Sabine	vormals Universitätsklinikum Leipzig, aktuell Institut für Transfusionsmedizin und Immunologie Medizinische Fakultät Mannheim, Universität Heidelberg DRK-Blutspendedienst Baden-Württemberg – Hessen gGmbH	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Lambert, Jean-Francois	GHOL-Nyon Hospital, CH1260 Nyon	**Yes** Abbvie, Gilead, Incyte, Janssen, Novartis, OrphaSwiss, Sanofi, Takeda, Vifor	**No**	**No**	**No**	**No**	**No**	**No**

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Lengfelder, Eva	Universitätsmedizin Mannheim, Medizinische Fakultät der Universität Heidelberg	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Nachbaur, David	Medizinische Universität Innsbruck Innere Medizin Hämatologie und Onkologie	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Platzbecker, Uwe	Universitätsklinikum Leipzig	**Yes** BMS, Abbvie, Curis	**No**	**No**	**Yes** BMS, Abbvie, Curis, Jazz, Gilead	**Yes** BMS, Curis, Jazz, Gilead	**No**	**No**
Schlenk, Richard F.	Universitätsklinikum Heidelberg	**Yes** Daiichi Sankyo, Pfizer, Astellas, and Novartis;	**No**	**No**	**Yes** AbbVie	**Yes** PharmaMar,AstraZeneca, Pfizer, Roche, Boehringer Ingelheim, Daiichi Sankyo;	**No**	**No**
Sperr, Wolfgang Reinhard	AKH Wien Klinik f. Innere Medizin I Abt.f. Hämatologie und Hämostaseologie	**No**	**No**	**No**	**Yes** AbbVie, BMS, Daiichi Sankyo, Jazz, Novartis, Pfizer, Thermo Fisher, Stem Line	**Yes** Pfizer	**No**	**No**
Thol, Felicitas	Medizinische Hochschule Hannover	**Yes** Ad Board: Celgene/ BMS, Abbvie, Novartis, Jazz, Astellas, Pfizer	**No**	**No**	**No**	**Yes** Studie: Celgene/BMS	**No**	**No**

Legend:

[1] - Current employer, relevant previous employers in the last 3 years (institution/location).

[2] - Activity as a consultant or expert or paid participation in a scientific advisory board of a company in the health care industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract research organization, or an insurance company.

[3] - Ownership of business shares, stocks, funds with participation of companies of the health care industry.

[4] - Relates to drugs and medical devices.

[5] - Honoraria for lecturing and training activities or paid authors or co-authorships on behalf of a company in the health care industry, a commercially oriented contracting institute or an insurance company.

[6] *- Financial support (third-party funds) for research projects or direct financing of employees of the institution by a company in the health care industry, a commercially oriented contract institute or an insurance company.*

[7] *- Other financial relationships, e.g., gifts, travel reimbursements, or other payments in excess of 100 euros outside of research projects, if paid by an entity that has an investment in, license to, or other commercial interest in the subject matter of the investigation.*

[8] *- Personal relationship with an authorized representative(s) of a healthcare company.*