# DNA repair in cancer therapy beneficial or harmful?

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# Agenda

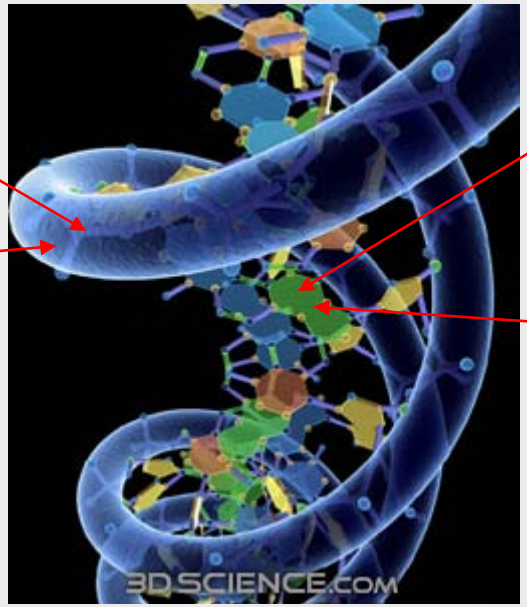
- DNA damage as therapeutic mechanism
- DNA repair pathways
- Repair of topo inhibitor-induced DNA damage
- Chromosomal rearrangements
- Clinical relevance

# DNA: main target of chemotherapy

- DNA damaging drugs

**Topoisomerase inhibitors:**
Strand breaks

**Bleomycin:**
Strand breaks

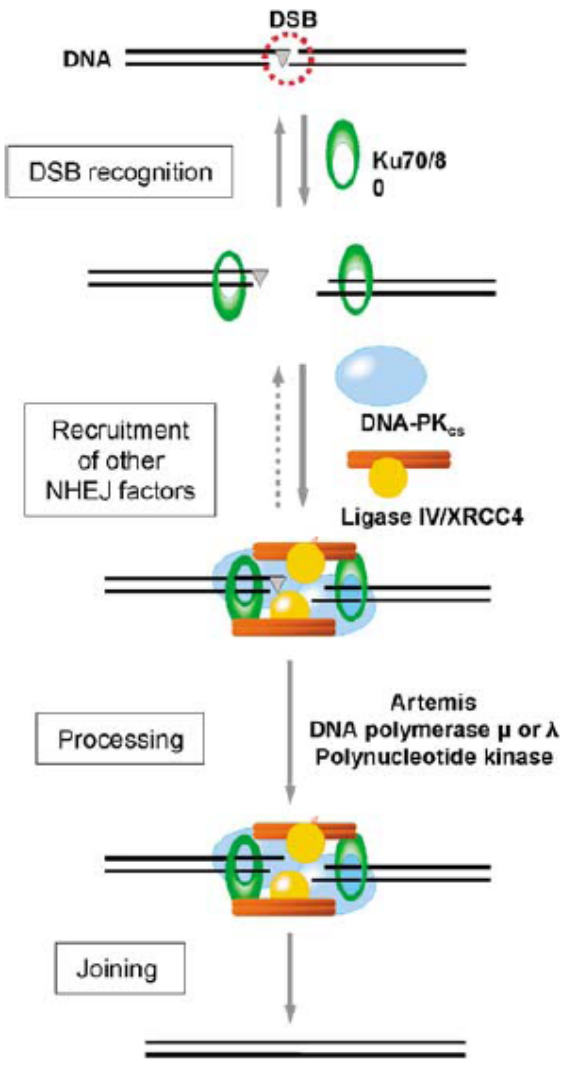



**Alkylating agents:**
1) Alkyl adducts
2) Strand breaks

**Platinum agents:**
1) Pt-adducts
2) Strand breaks

**Antimetabolites:**
Synthesis (replication, transcription, DNA repair)

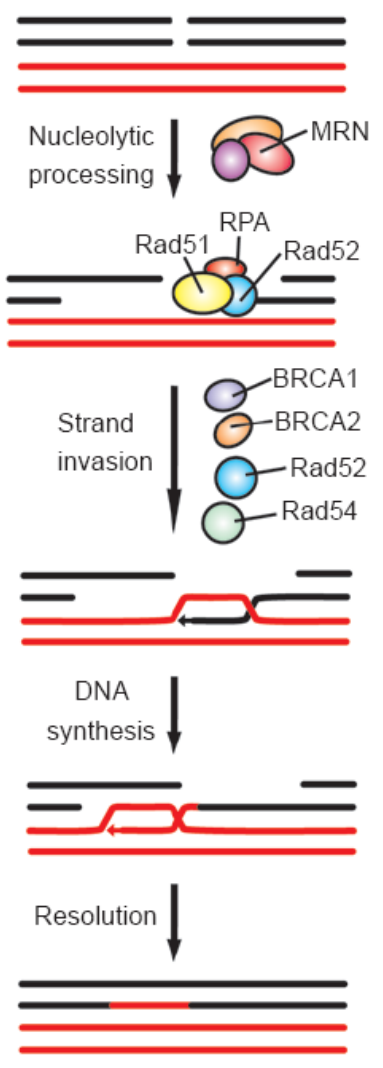
# DNA double strand break repair




- Non-homologous end joining (NHEJ)
- Most important repair mechanism
- Direct joining of free DNA ends (at most short microhomologies)
- errorfree, IF few breaks are present

[van Gent & van der Burg, Oncogene (2007) 26, 7731–7740; Lieberman, Current Medicinal Chemistry (2008) 15, 360-367]

# DNA double strand break repair

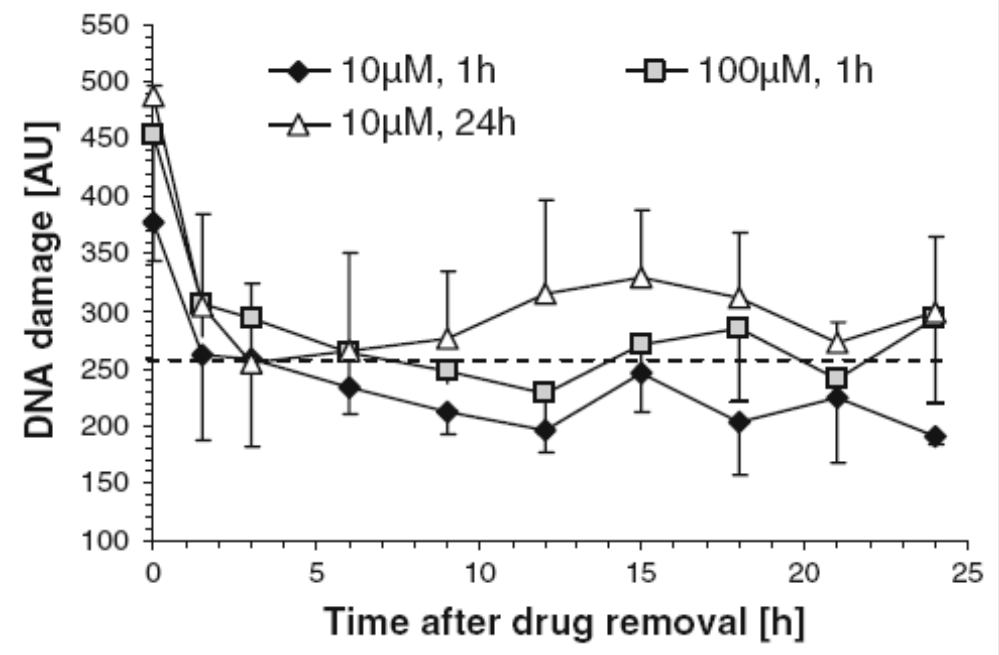



- Homologous recombination (HR)
- Greatest activity in late S and $G_2$ phase
- Requires homologous sequence
- Fills broken DNA strand according to intact homologous template
- Enables mostly correct repair

[Weterings & Chen, Cell Research (2008) 18, 114-124; Lieberman, Current Medicinal Chemistry (2008) 15, 360-367]

# Etoposide-induced DNA damage

- HT29; human Colon-Ca
- Etoposide
- Drug removal
- Incubation for 0-24h
- Comet-Assay [pH10/pH13]

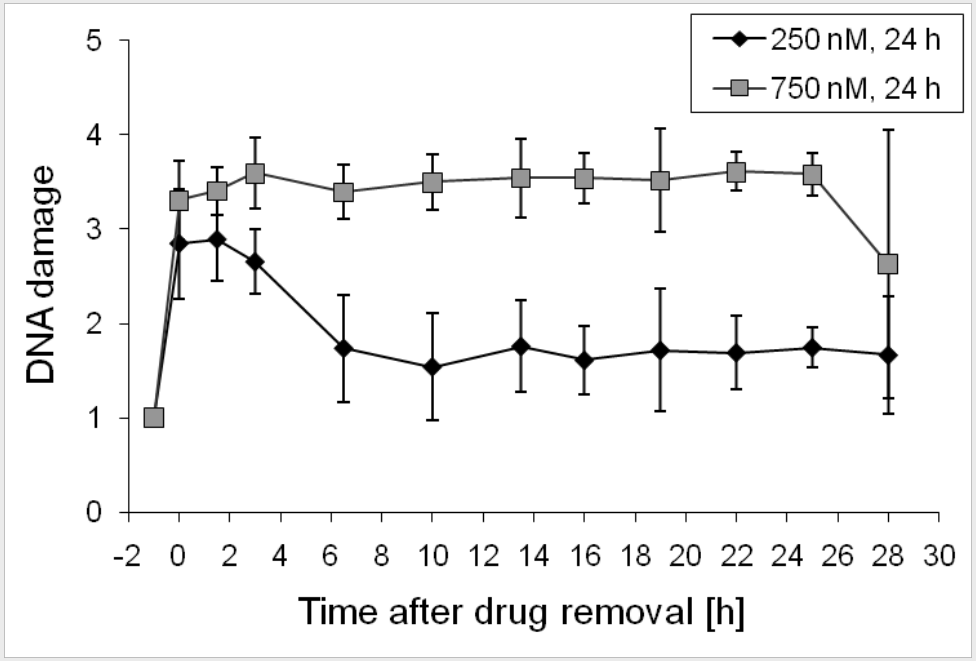



**... and repair!**

Schonn, Hennesen, Dartsch: Apoptosis 2009, DOI 10.1007/s10495-009-0440-9

# Doxorubicin-induced DNA damage

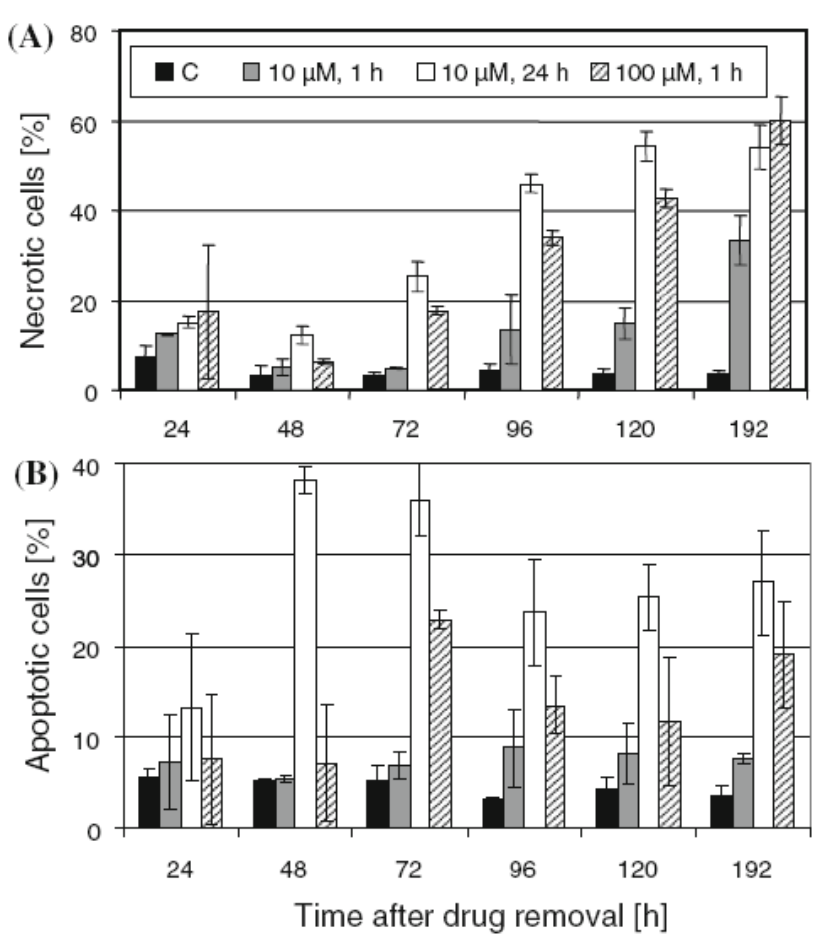
- HT29; human Colon-Ca
- Doxorubicin, 24h
- Drug removal
- Incubation for 0-28h
- Comet-Assay [pH10/pH13]

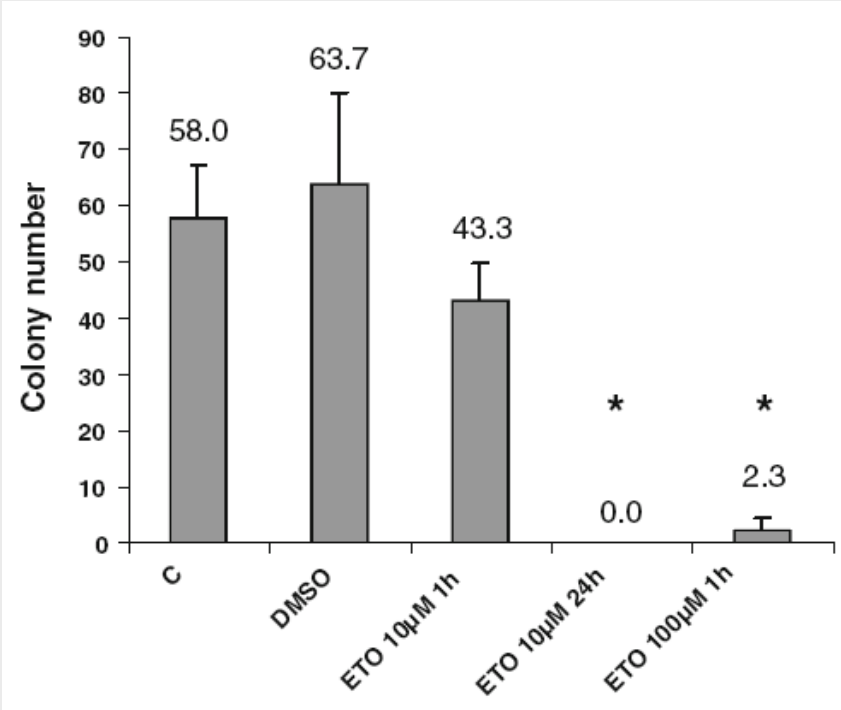



**... and repair!**

Schonn, Hennesen, Dartsch: manuscript in progress

# Etoposide-induced cell death

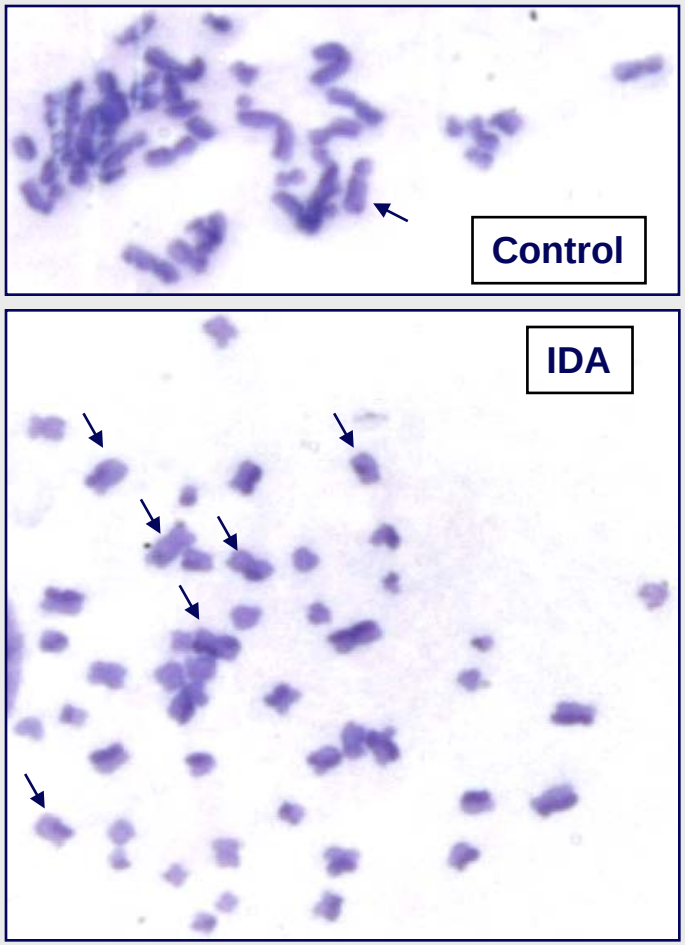


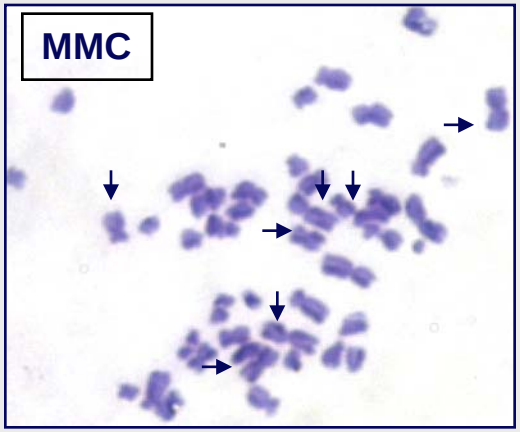



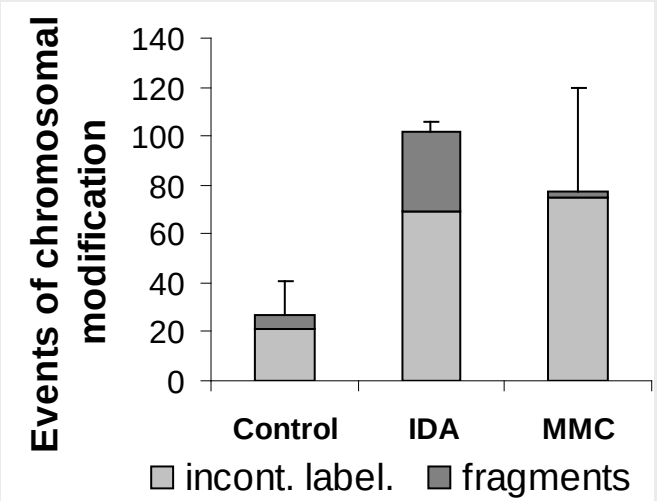

**... in spite of repair!**

Schonn, Hennesen, Dartsch: Apoptosis 2009, DOI 10.1007/s10495-009-0440-9

# Incorrect DNA repair

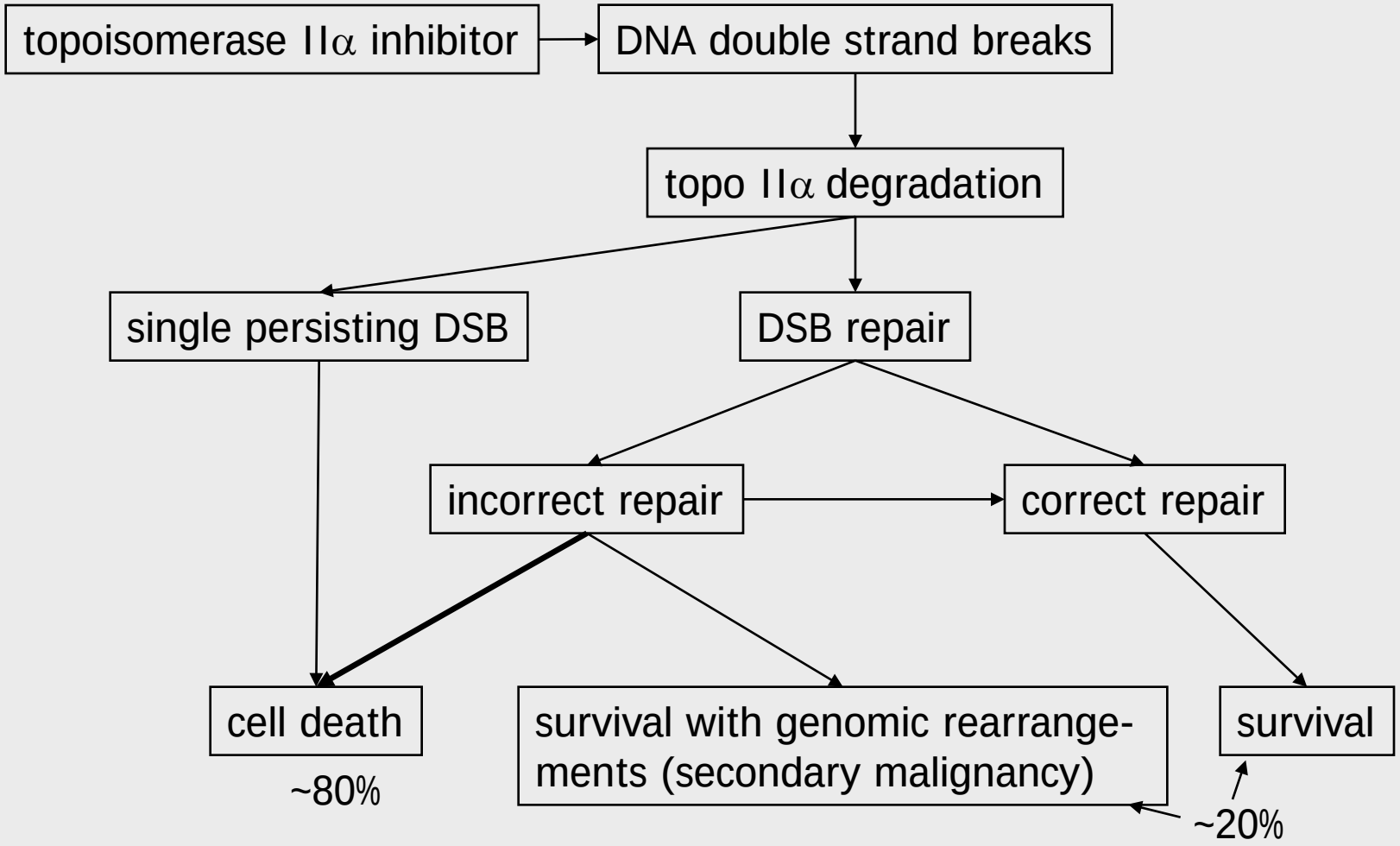


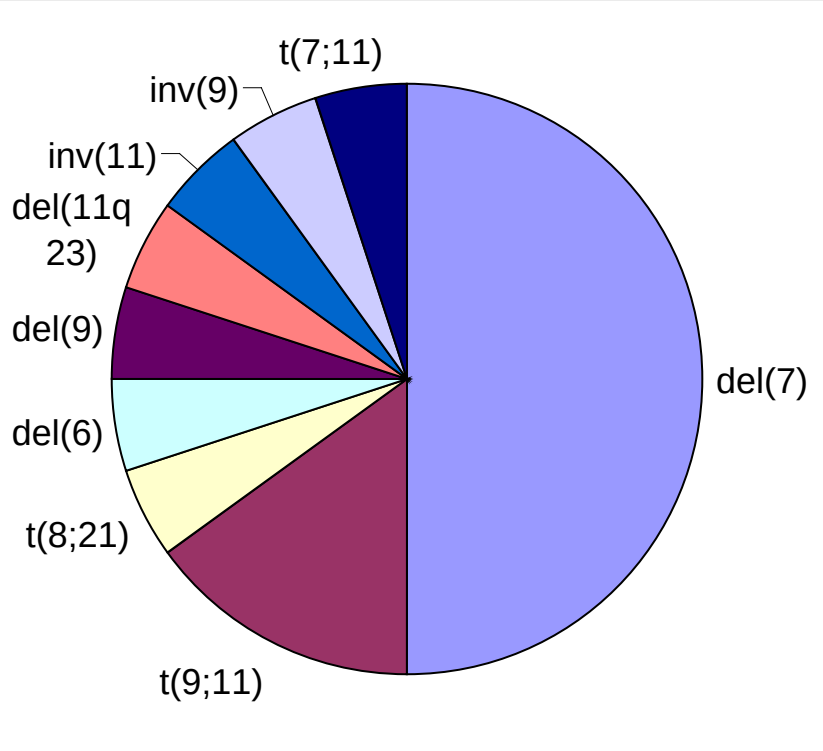

Dartsch & Gieseler, DNA Repair 6 (2007), 1618-1628

# DNA repair beneficial or harmful?



# DNA damage in secondary malignancies

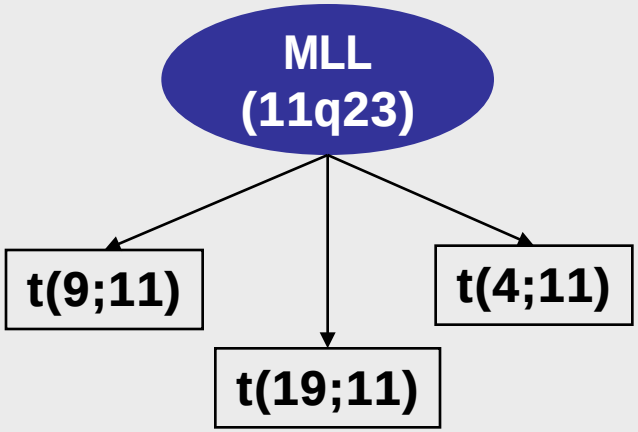
- In a study from MDACC, none of the 22 children with therapy-related MDS/AML had normal cytogenetics:

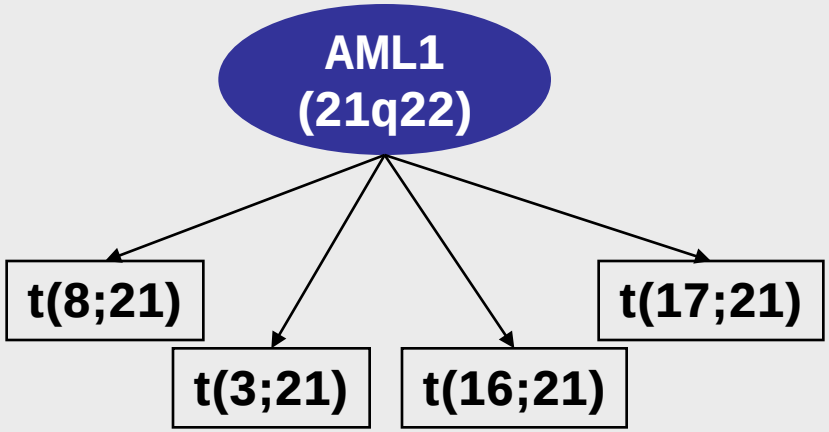


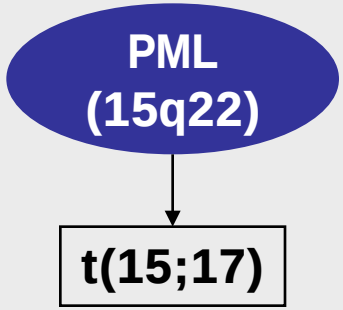

[data from: Aguilera DG: Pediatric Therapy-related Myelodysplastic Syndrome/Acute Myeloid Leukemia - The MD Anderson Cancer Center Experience. J Pediatr Hematol Oncol 2009;31:803–811]

# Chromosomal rearrangements

Frequency of tAML patients with chromosomal rearrangements: > 90%




t(8;16)

inv(16)

t(9;22)

**Unbalanced aberrations:**

-5/-7

-5q/-7q

+8

# Frequency of secondary tumours in childhood cancer survivors

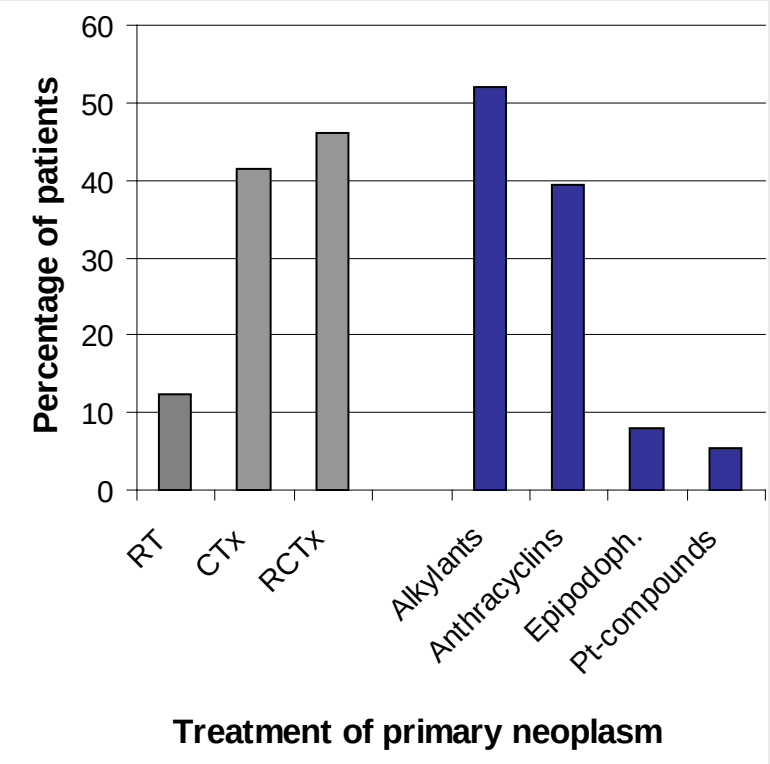
| Primary Diagnosis | Total cases (n) | No. of SMN (%) | Breast (%) | Thyroid (%) | CNS (%) | Sarco-ma (%) | Bone (%) | Leuke-mia (%) | Melano-ma (%) | Lympho-ma (%) | GIT (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HL | 1,927 | 12.82 | 4.88 | 1.87 | 0.36 | 0.99 | 0.31 | 0.73 | 0.57 | 0.73 | 0.73 |
| Leukemia | 4,829 | 3.15 | 0.33 | 0.48 | 0.93 | 0.08 | 0.08 | 0.19 | 0.23 | 0.21 | 0.04 |
| Soft tissue sarc. | 1,245 | 6.43 | 0.80 | 0.56 | 0.24 | 1.45 | 0.96 | 0.24 | 0.48 | 0.16 | 0.16 |
| Bone | 1,188 | 6.23 | 1.77 | 0.76 | 0.25 | 0.42 | 0.76 | 0.51 | 0.42 | 0.08 | 0.59 |
| CNS | 1,877 | 3.62 | 0.16 | 0.64 | 0.96 | 0.32 | 0.27 | 0.16 | 0.21 | 0.21 | 0.11 |
| NHL | 1,081 | 3.98 | 0.56 | 0.65 | 0.37 | 0.19 | 0.46 | 0.19 | 0.19 | 0.37 | 0.19 |
| Neuroblastoma | 955 | 3.46 | 0.21 | 0.84 | 0.10 | 0.42 | 0.00 | 0.42 | 0.00 | 0.10 | 0.00 |
| Wilms | 1,256 | 2.63 | 0.40 | 0.16 | 0.00 | 0.56 | 0.40 | 0.16 | 0.24 | 0.00 | 0.32 |

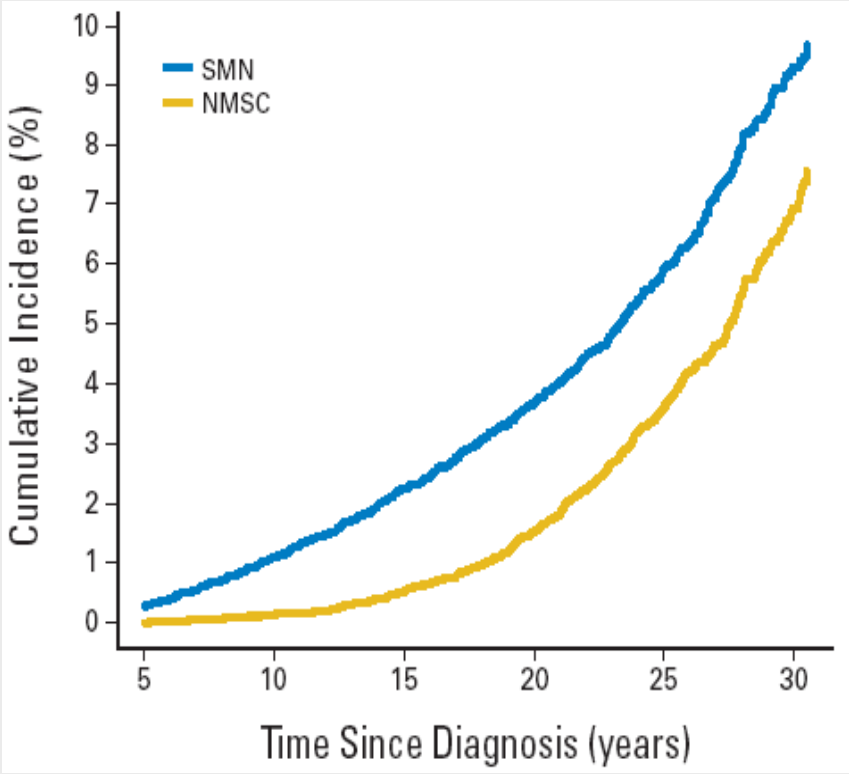
Abbr.: SMN – secondary malignant neoplams; CNS – central nervous system; GIT – gastrointestinal tract; HL – Hodgkin Lymphoma; NHL – Non-Hodgkin Lymphoma

Patients: 14,363 5 year survivors of childhood cancer treated between 1970 and 1986

[data from: Meadows AT: Second Neoplasms in Survivors of Childhood Cancer: Findings From the Childhood Cancer Survivor Study Cohort. J Clin Oncol 2009, 27:2356-2362]

# Latency of secondary tumours in childhood cancer survivors




[data from: Meadows AT: Second Neoplasms in Survivors of Childhood Cancer: Findings From the Childhood Cancer Survivor Study Cohort. J Clin Oncol 2009, 27:2356-2362]

# Clinical Studies with DNA repair inhibitors

Table 1 | **Ongoing clinical trials of small-molecule inhibitors of the DNA damage response and related signalling pathways**

| Agent (company) | Target molecule or pathway | Monotherapy or combination therapy agent(s) | Phase of clinical trial planned, ongoing or recently completed | Reference |
|---|---|---|---|---|
| AZD-2281 (Astra Zeneca) | PARP | Gemcitabine<br>Carboplatin<br>Topotecan<br>Monotherapy | Phase I<br>Phase I<br>Phase I<br>Phase II | http://www.astrazenecaclinicaltrials.com/article/525925.aspx |
| AG014699 (Pfizer) | PARP | Temozolomide<br>antibody<br>Temozolomide | Phase I<br><br>Phase II | http://www.eddn.org/clinicalTr_caResUK.html |
| INO-1001 (Inotek) | PARP | Temozolomide | Phase I | http://www.inotekcorp.com/content/ino-1001.asp |
| BSI-201 (Bipar Sciences) | PARP | Monotherapy<br>Gemcitabine–carboplatin | Phase I<br>Phase II | http://www.biparsciences.com/BSI201.html |
| ABT-888 (Abbott Laboratories) | PARP | Temozolomide | Phase I | NCT00526617 |
| TRC-102 (Tracon Pharma) | BER | Temozolomide<br>Pemetrexed | Phase I<br>Phase I planned | http://www.traconpharma.com/content/pipeline_overview.html |
| Lomeguatrib (Astra Zeneca) | MGMT | Irinotecan<br>Temozolomide | Phase I<br>Phase II | http://www.astrazenecaclinicaltrials.com/article/525925.aspx |
| $O^6$-Benzylguanine | MGMT | Temozolomide | Phase II | http://clinicalstudies.info.nih.gov/cgi/detail.cgi?A_2006-C-0089.html |
| Decitabine (MGI Pharma[121]) | Hypermethylation of mismatch repair genes | Epirubicin, cisplatin, 5-fluorouracil<br>Carboplatin | Phase I<br><br>Phase II | http://pfsearch.ukcrn.org.uk/StudyDetail.aspx?TopicID=&StudyID=2192 |
| XL844 (Exilixis[122]) | CHK1, CHK2 | Gemcitabine | Phase I planned | http://www.exelixis.com/pipeline_xl844.shtml |

The recent or current stage of development of clinical trials is indicated for individual compounds, which are grouped by molecular target. BER, base excision repair; CHK, checkpoint kinase; MGMT, O-6-methylguanine methyltransferase; PARP, poly(ADP-ribose) polymerase.

[Helleday et al., Nat Rev Cancer 8 (2008) 193-204]

# For the moment…

Treatment decisions reflecting concern about secondary malignancy are recommended as follows:

1. Find an effective therapy
2. If effective alternatives exist, choose ‚safer' drugs, e.g.
   - antimetabolites or MT-directed agents instead of alkylants or topo inhibitors
   - cyclophosphamide instead of busulphane
   - doxorubicine instead of mitoxanthrone

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