= Neuroblastoma =

Neuroblastoma (NB) is the most common extracranial solid cancer in childhood and the most common cancer in infancy , with an incidence of about 650 cases per year in the U.S. , and 100 cases per year in the UK . Nearly half of neuroblastoma cases occur in children younger than two years . It is a neuroendocrine tumor , arising from any neural crest element of the sympathetic nervous system (SNS) . It most frequently originates in one of the adrenal glands , but can also develop in nerve tissues in the neck , chest , abdomen , or pelvis .

Neuroblastoma is one of the few human malignancies known to demonstrate spontaneous regression from an undifferentiated state to a completely benign cellular appearance . It is a disease exhibiting extreme heterogeneity , and is stratified into three risk categories : low , intermediate , and high risk . Low @-@ risk disease is most common in infants and good outcomes are common with observation only or surgery , whereas high @-@ risk disease is difficult to treat successfully even with the most intensive multi @-@ modal therapies available .

Esthesioneuroblastoma , also known as olfactory neuroblastoma , is believed to arise from the olfactory epithelium and its classification remains controversial . However , since it is not a sympathetic nervous system malignancy , esthesioneuroblastoma is a distinct clinical entity and is not to be confused with neuroblastoma .

= = Signs and symptoms = =

The first symptoms of neuroblastoma are often vague making diagnosis difficult . Fatigue , loss of appetite , fever , and joint pain are common . Symptoms depend on primary tumor locations and metastases if present :

In the abdomen , a tumor may cause a swollen belly and constipation .

A tumor in the chest may cause breathing problems .

A tumor pressing on the spinal cord may cause weakness and thus an inability to stand , crawl , or walk .

Bone lesions in the legs and hips may cause pain and limping .

A tumor in the bones around the eyes or orbits may cause distinct bruising and swelling .

Infiltration of the bone marrow may cause pallor from anemia .

Neuroblastoma often spreads to other parts of the body before any symptoms are apparent and 50 to 60 % of all neuroblastoma cases present with metastases .

The most common location for neuroblastoma to originate (i.e. , the primary tumor) is in the adrenal glands . This occurs in 40 % of localized tumors and in 60 % of cases of widespread disease . Neuroblastoma can also develop anywhere along the sympathetic nervous system chain from the neck to the pelvis . Frequencies in different locations include : neck (1 %) , chest (19 %) , abdomen (30 % non @-@ adrenal) , or pelvis (1 %) . In rare cases , no primary tumor can be discerned .

Rare but characteristic presentations include transverse myelopathy (tumor spinal cord compression , 5 % of cases) , treatment @-@ resistant diarrhea (tumor vasoactive intestinal peptide secretion , 4 % of cases) , Horner 's syndrome (cervical tumor , 2 @.@ 4 % of cases) , opsoclonus myoclonus syndrome and ataxia (suspected paraneoplastic cause , 1 @.@ 3 % of cases) , and hypertension (catecholamine secretion or renal artery compression , 1 @.@ 3 % of cases) .

= = Cause = =

The etiology of neuroblastoma is not well understood . The great majority of cases are sporadic and non @-@ familial . About 1 ? 2 % of cases run in families and have been linked to specific gene mutations . Familial neuroblastoma in some cases is caused by rare germline mutations in the anaplastic lymphoma kinase (ALK) gene . Germline mutations in the PHOX2A or KIF1B gene have been implicated in familial neuroblastoma as well . Neuroblastoma is also a feature of

neurofibromatosis type 1 and the Beckwith @-@ Wiedemann syndrome .

MYCN oncogene amplification within the tumor is a common finding in neuroblastoma . The degree of amplification shows a bimodal distribution : either 3- to 10 @-@ fold , or 100- to 300 @-@ fold . The presence of this mutation is highly correlated to advanced stages of disease .

Duplicated segments of the LMO1 gene within neuroblastoma tumor cells have been shown to increase the risk of developing an aggressive form of the cancer .

Neuroblastoma has been linked to copy @-@ number variation within the NBPF10 gene , which results in the 1q21.1 deletion syndrome or 1q21.1 duplication syndrome .

Several risk factors have been proposed and are the subject of ongoing research . Due to characteristic early onset many studies have focused on parental factors around conception and during gestation . Factors investigated have included occupation (i.e. exposure to chemicals in specific industries) , smoking , alcohol consumption , use of medicinal drugs during pregnancy and birth factors ; however , results have been inconclusive .

Other studies have examined possible links with atopy and exposure to infection early in life , use of hormones and fertility drugs , and maternal use of hair dye .

= = Diagnosis = =

The diagnosis is usually confirmed by a surgical pathologist , taking into account the clinical presentation , microscopic findings , and other laboratory tests .

= = = Biochemistry = = =

In about 90 % of cases of neuroblastoma , elevated levels of catecholamines or their metabolites are found in the urine or blood . Catecholamines and their metabolites include dopamine , homovanillic acid (HVA) , and / or vanillylmandelic acid (VMA) .

= = = Imaging = = =

Another way to detect neuroblastoma is the mIBG scan (meta @-@ iodobenzylguanidine) , which is taken up by 90 to 95 % of all neuroblastomas , often termed " mIBG @-@ avid . " The mechanism is that mIBG is taken up by sympathetic neurons , and is a functioning analog of the neurotransmitter norepinephrine . When it is radio @-@ ionated with I @-@ 131 or I @-@ 123 (radioactive iodine isotopes) , it is a very good radiopharmaceutical for diagnosis and monitoring of response to treatment for this disease . With a half @-@ life of 13 hours , I @-@ 123 is the preferred isotope for imaging sensitivity and quality . I @-@ 131 has a half @-@ life of 8 days and at higher doses is an effective therapy as targeted radiation against relapsed and refractory neuroblastoma .

= = = Histology = = =

On microscopy , the tumor cells are typically described as small , round and blue , and rosette patterns (Homer Wright rosettes) may be seen . Homer Wright rosettes are tumor cells around the neuropil , not to be confused with pseudorosettes , which are tumor cells around a blood vessel . They are also distinct from the pseudorosettes of an ependymoma which consist of tumor cells with glial fibrillary acidic protein (GFAP) ? positive processes tapering off toward a blood vessel (thus a combination of the two) . A variety of immunohistochemical stains are used by pathologists to distinguish neuroblastomas from histological mimics , such as rhabdomyosarcoma , Ewing 's sarcoma , lymphoma and Wilms ' tumor .

Neuroblastoma is one of the peripheral neuroblastic tumors (pNTs) that have similar origins and show a wide pattern of differentiation ranging from benign ganglioneuroma to stroma @-@ rich ganglioneuroblastoma with neuroblastic cells intermixed or in nodules , to highly malignant neuroblastoma . This distinction in the pre @-@ treatment tumor pathology is an important

prognostic factor , along with age and mitosis @-@ karyorrhexis index (MKI) . This pathology classification system (the Shimada system) describes " favorable " and " unfavorable " tumors by the International Neuroblastoma Pathology Committee (INPC) which was established in 1999 and revised in 2003 .

= = = Staging = = =

The " International Neuroblastoma Staging System " (INSS) established in 1986 and revised in 1988 stratifies neuroblastoma according to its anatomical presence at diagnosis :

Stage 1 : Localized tumor confined to the area of origin .

Stage 2A : Unilateral tumor with incomplete gross resection ; identifiable ipsilateral and contralateral lymph node negative for tumor .

Stage 2B : Unilateral tumor with complete or incomplete gross resection ; with ipsilateral lymph node positive for tumor ; identifiable contralateral lymph node negative for tumor .

Stage 3 : Tumor infiltrating across midline with or without regional lymph node involvement ; or unilateral tumor with contralateral lymph node involvement ; or midline tumor with bilateral lymph node involvement .

Stage 4 : Dissemination of tumor to distant lymph nodes , bone marrow , bone , liver , or other organs except as defined by Stage 4S .

Stage 4S : Age < 1 year old with localized primary tumor as defined in Stage 1 or 2 , with dissemination limited to liver , skin , or bone marrow (less than 10 percent of nucleated bone marrow cells are tumors) .

Although international agreement on staging (INSS) has been used , the need for an international consensus on risk assignment has also been recognized in order to compare similar cohorts in results of studies . Beginning in 2005 , representatives of the major pediatric oncology cooperative groups have met to review data for 8 @,@ 800 neuroblastoma patients treated in Europe , Japan , USA , Canada , and Australia between 1990 and 2002 . This task force has proposed the International Neuroblastoma Risk Group (INRG) classification system . Retrospective studies revealed the high survival rate of 12 ? 18 month old age group , previously categorized as high @-@ risk , and prompted the decision to reclassify 12 ? 18 month old children without N @-@ myc (also commonly referred to as MYCN) amplification to intermediate risk category .

The new INRG risk assignment will classify neuroblastoma at diagnosis based on a new International Neuroblastoma Risk Group Staging System (INRGSS) :

Stage L1 : Localized disease without image @-@ defined risk factors .

Stage L2 : Localized disease with image @-@ defined risk factors .

Stage M : Metastatic disease .

Stage MS : Metastatic disease " special " where MS is equivalent to stage 4S .

The new risk stratification will be based on the new INRGSS staging system , age (dichotomized at 18 months) , tumor grade , N @-@ myc amplification , unbalanced 11q aberration , and ploidy into four pre @-@ treatment risk groups : very low , low , intermediate , and high risk .

= = Screening = =

Urine catecholamine level can be elevated in pre @-@ clinical neuroblastoma . Screening asymptomatic infants at three weeks , six months , and one year has been performed in Japan , Canada , Austria and Germany since the 1980s . Japan began screening six @-@ month @-@ olds for neuroblastoma via analysis of the levels of homovanillic acid and vanilmandelic acid in 1984 . Screening was halted in 2004 after studies in Canada and Germany showed no reduction in deaths due to neuroblastoma , but rather caused an increase in diagnoses that would have disappeared without treatment , subjecting those infants to unnecessary surgery and chemotherapy .

= = Treatment = =

When the lesion is localized , it is generally curable . However , long @-@ term survival for children with advanced disease older than 18 months of age is poor despite aggressive multimodal therapy (intensive chemotherapy , surgery , radiation therapy , stem cell transplant , differentiation agent isotretinoin also called 13 @-@ cis @-@ retinoic acid , and frequently immunotherapy with anti @-@ GD2 monoclonal antibody therapy) .

Biologic and genetic characteristics have been identified , which , when added to classic clinical staging , has allowed patient assignment to risk groups for planning treatment intensity . These criteria include the age of the patient , extent of disease spread , microscopic appearance , and genetic features including DNA ploidy and N @-@ myc oncogene amplification (N @-@ myc regulates microRNAs) , into low , intermediate , and high risk disease . A recent biology study (COG ANBL00B1) analyzed 2687 neuroblastoma patients and the spectrum of risk assignment was determined : 37 % of neuroblastoma cases are low risk , 18 % are intermediate risk , and 45 % are high risk . (There is some evidence that the high- and low @-@ risk types are caused by different mechanisms , and are not merely two different degrees of expression of the same mechanism .)

The therapies for these different risk categories are very different .

Low @-@ risk disease can frequently be observed without any treatment at all or cured with surgery alone .

Intermediate @-@ risk disease is treated with surgery and chemotherapy .

High @-@ risk neuroblastoma is treated with intensive chemotherapy , surgery , radiation therapy , bone marrow / hematopoietic stem cell transplantation , biological @-@ based therapy with 13 @-@ cis @-@ retinoic acid (isotretinoin or Accutane) and antibody therapy usually administered with the cytokines GM @-@ CSF and IL @-@ 2 .

With current treatments , patients with low and intermediate risk disease have an excellent prognosis with cure rates above 90 % for low risk and 70 ? 90 % for intermediate risk . In contrast , therapy for high @-@ risk neuroblastoma the past two decades resulted in cures only about 30 % of the time . The addition of antibody therapy has raised survival rates for high @-@ risk disease significantly . In March 2009 an early analysis of a Children 's Oncology Group (COG) study with 226 high @-@ risk patients showed that two years after stem cell transplant 66 % of the group randomized to receive ch14.18 antibody with GM @-@ CSF and IL @-@ 2 were alive and disease @-@ free compared to only 46 % in the group that did not receive the antibody . The randomization was stopped so all patients enrolling on the trial will receive the antibody therapy .

Chemotherapy agents used in combination have been found to be effective against neuroblastoma . Agents commonly used in induction and for stem cell transplant conditioning are platinum compounds (cisplatin , carboplatin) , alkylating agents (cyclophosphamide , ifosfamide , melphalan) , topoisomerase II inhibitor (etoposide) , anthracycline antibiotics (doxorubicin) and vinca alkaloids (vincristine) . Some newer regimens include topoisomerase I inhibitors (topotecan and irinotecan) in induction which have been found to be effective against recurrent disease .

= = Prognosis = =

Between 20 % and 50 % of high @-@ risk cases do not respond adequately to induction high @-@ dose chemotherapy and are progressive or refractory . Relapse after completion of frontline therapy is also common . Further treatment is available in phase I and phase II clinical trials that test new agents and combinations of agents against neuroblastoma , but the outcome remains very poor for relapsed high @-@ risk disease .

Most long @-@ term survivors alive today had low or intermediate risk disease and milder courses of treatment compared to high @-@ risk disease . The majority of survivors have long @-@ term effects from the treatment . Survivors of intermediate and high @-@ risk treatment often experience hearing loss . Growth reduction , thyroid function disorders , learning difficulties , and greater risk of secondary cancers affect survivors of high @-@ risk disease . An estimated two of three survivors of childhood cancer will ultimately develop at least one chronic and sometimes life @-@ threatening health problem within 20 to 30 years after the cancer diagnosis .

= = = Cytogenetic profiles = = =

Based on a series of 493 neuroblastoma samples , it has been reported that overall genomic pattern , as tested by array @-@ based karyotyping , is a predictor of outcome in neuroblastoma :
Tumors presenting exclusively with whole chromosome copy number changes were associated with excellent survival .
Tumors presenting with any kind of segmental chromosome copy number changes were associated with a high risk of relapse .
Within tumors showing segmental alterations , additional independent predictors of decreased overall survival were N @-@ myc amplification , 1p and 11q deletions , and 1q gain .
Earlier publications categorized neuroblastomas into three major subtypes based on cytogenetic profiles :
Subtype 1 : favorable neuroblastoma with near triploidy and a predominance of numerical gains and losses , mostly representing non @-@ metastatic NB stages 1 , 2 and 4S .
Subtypes 2A and 2B : found in unfavorable widespread neuroblastoma , stages 3 and 4 , with 11q loss and 17q gain without N @-@ myc amplification (subtype 2A) or with N @-@ myc amplification often together with 1p deletions and 17q gain (subtype 2B) .
Virtual karyotyping can be performed on fresh or paraffin @-@ embedded tumors to assess copy number at these loci . SNP array virtual karyotyping is preferred for tumor samples , including neuroblastomas , because they can detect copy neutral loss of heterozygosity (acquired uniparental disomy) . Copy neutral LOH can be biologically equivalent to a deletion and has been detected at key loci in neuroblastoma . ArrayCGH , FISH , or conventional cytogenetics cannot detect copy neutral LOH .

= = Epidemiology = =

Neuroblastoma comprises 6 ? 10 % of all childhood cancers , and 15 % of cancer deaths in children . The annual mortality rate is 10 per million children in the 0- to 4 @-@ year @-@ old age group , and 4 per million in the 4- to 9 @-@ year old age group .
The highest incidence is in the first year of life , and some cases are congenital . The age range is broad , including older children and adults , but only 10 % of cases occur in people older than 5 years of age . A large European study reported less than 2 % of over 4000 neuroblastoma cases were over 18 years old .

= = History = =

In 1864 German physician Rudolf Virchow was the first to describe an abdominal tumor in a child as a " glioma " . The characteristics of tumors from the sympathetic nervous system and the adrenal medulla were then noted in 1891 by German pathologist Felix Marchand . In 1901 the distinctive presentation of stage 4S in infants (liver but no bone metastases) was described by William Pepper . In 1910 James Homer Wright understood the tumor to originate from primitive neural cells , and named it neuroblastoma . He also noted the circular clumps of cells in bone marrow samples which are now termed " Homer Wright rosettes " . Of note , " Homer @-@ Wright " with a hyphen is grammatically incorrect , as the eponym refers to just Dr. Wright .

= = Society and culture = =

= = = Legislative efforts = = =

U.S. Representative Chet Edwards of Waco , Texas , successfully introduced legislation to earmark $ 150 million toward a cure for neuroblastoma and other cancers . The measure was signed into law in July 2008 by U.S. President George W. Bush . Edwards was inspired in the endeavor by the

illness and subsequent death of Erin Channing Buenger (1997 ? 2009) of Bryan , daughter of one of his constituents , Walter L. Buenger , head of the history department at Texas A & M University .

= = = Fundraising = = =

Several organizations fundraise for research into neuroblastoma . GLOBAL VISION cancer care NGO a pioneer non profit organisation in India supporting poor cancer patients since 2009 [1] . Tom Hanks is the Honorary Patron of the James Fund , a leading fundraising organization in support of clinical research . On December 31 , 2014 , SickKids Foundation took over stewardship of The James Funds . The Cincinnati Bengals announced in 2014 that they would donate proceeds from the jersey sales of defensive lineman Devon Still 's jersey to the Cincinnati Children 's Hospital , and presented a check from more than $ 1 @.@ 3 million to Still 's daughter Leah during Thursday night 's game on November 6 , 2014 . Cincinnati Bengals defensive lineman Devon Still 's jersey is the 11th @-@ most popular in the NFL

= = Research = =

= = = Preclinical models = = =

Neuroblastoma patient derived tumor xenografts (PDXs) have been created by orthotopic implantation of patient tumor samples into immunodeficient mice . PDX models have several advantages over conventional cancer cell lines (CCL) s . Neuroblastoma PDXs retain the genetic hallmarks of their corresponding patient tumors and PDXs display infiltrative growth and metastasis to distant organs . PDX models are more predictive of clinical outcome as compared to conventional cancer cell line xenografts . Neuroblastoma PDXs might thus serve as clinically relevant models to identify effective compounds against neuroblastoma .

= = = Treatments = = =

Recent focus has been to reduce therapy for low and intermediate risk neuroblastoma while maintaining survival rates at 90 % . A study of 467 intermediate risk patients enrolled in A3961 from 1997 to 2005 confirmed the hypothesis that therapy could be successfully reduced for this risk group . Those with favorable characteristics (tumor grade and response) received four cycles of chemotherapy , and those with unfavorable characteristics received eight cycles , with three @-@ year event free survival and overall survival stable at 90 % for the entire cohort . Future plans are to intensify treatment for those patients with aberration of 1p36 or 11q23 chromosomes as well as for those who lack early response to treatment .

By contrast , focus the past 20 years or more has been to intensify treatment for high @-@ risk neuroblastoma . Chemotherapy induction variations , timing of surgery , stem cell transplant regimens , various delivery schemes for radiation , and use of monoclonal antibodies and retinoids to treat minimal residual disease continue to be examined . Recent phase III clinical trials with randomization have been carried out to answer these questions to improve survival of high @-@ risk disease :

1982 ? 1985 : European Neuroblastoma Study Group (ENSG1) enrolled 167 children and randomized to melphalan autologous bone marrow transplant or no further therapy (no radiation therapy given to any) . Transplant and no @-@ transplant arms each had 65 patients , and recent long @-@ term follow @-@ up report revealed significantly better 5 year event @-@ free survival for stage 4 over 1 year old in melphalan @-@ transplant group versus no further treatment : 33 % versus 17 % respectively .

1990 ? 1999 : European study (EU @-@ 20592 or CCLGNB @-@ 1990 @-@ 11) randomized 262 high @-@ risk children over 1 year old and revealed higher survival rate for rapid sequence induction (10 @-@ day cycle) versus standard induction (21 @-@ day cycle) with same total

dose . Ten @-@ year event free survival was 27 % and 18 % respectively with non @-@ aggressive surgical approach , no radiotherapy , and melphalan @-@ only autologous bone marrow or stem cell transplant for both groups .

1991 ? 1996 : Phase III trial with two sequential randomizations for 379 high @-@ risk NB patients was carried out by the Children 's Cancer Group (CCG @-@ 3891) which demonstrated improved survival with myeloablative therapy (with total body irradiation) and 13 @-@ cis @-@ retinoic acid (Accutane) with 50 patients in each of the four arms of the study . ,

1996 ? 2003 : The German (GPOH) study NB97 compared outcomes of 295 high @-@ risk NB patients randomized for stem cell transplant or consolidation chemotherapy . Results showed increased survival with transplant .

2000 ? 2006 : The recent study (COG @-@ A3973) questioned the need for purged stem cells for CEM @-@ LI (carboplatin , etoposide , melphalan , with local irradiation) transplant , and accrued 486 patients . Purging stem cells was not found to improve survival

2000 ? 2012 : A concurrent study (COG @-@ ANBL0032) determined in early review that the antibody ch14.18 with interleukin 2 and GMCSF (studied retrospectively in German GPOH NB90 and NB 97 at a lower dose and without cytokines) improved survival , and will accrue a total of 423 patients . A follow on Phase III study COG @-@ ANBL0931 opened Jan 2010 to accrue 105 patients to gather further safety and efficacy data for FDA approval .

2002 ? 2008 : SIOP (International Society of Paediatric Oncology) formed the European SIOP Neuroblastoma Group (SIOPEN) in 1994 and activated a phase III high @-@ risk NB protocol in 2002 (SIOP @-@ EUROPE @-@ HR @-@ NBL @-@ 1) using " rapid " COJEC (8 cycles of chemotherapy given at 10 @-@ day intervals) followed by transplant randomization to CEM (carboplatin , etoposide , melphalan) or BuMel (busulfan , melphalan) and the study has been recently amended to randomize children to ch14.18 antibody treatment with or without subcutaneous IL2 (without GM @-@ CSF as given in the COG) . This antibody was remanufactured in chinese hamster ovary (CHO) cells and shows molecular and functional differences compared to ch14.18 used in the COG trial . This study recently reported the benefit of growth factors (GCSF) , and all patients receive retinoic acid . This trial will accrue 1000 patients (175 per year) .

2005 ? 2010 : The current German NB2004 randomization will include MIBG therapy and randomize topotecan use in up @-@ front therapy and will accrue a total of 642 for all risk groups (roughly half will be high @-@ risk) . After transplant , the high @-@ risk protocol includes six months of cis @-@ retinoic acid , a three @-@ month break , and another three months of retinoic acid .

2007 : The COG phase III ANBL0532 trial opened December 2007 for accrual of 495 and will compare single versus tandem transplants , and induction begins with two cycles of topotecan .

In addition to these phase III studies , some research institutions offer pilot treatment protocols . For example , St Jude 's recently finished (2007) testing a new up @-@ front chemotherapy regimen in 23 children which included irinotecan and gefitinib with 16 months of maintenance chemotherapy after stem cell transplant with alternating oral 13 @-@ cis @-@ retinoic acid and topotecan . Memorial Sloan @-@ Kettering Cancer Center in New York offers treatment that includes a mouse @-@ derived monoclonal antibody , 3F8 , used in protocols since the mid @-@ 1980s . This antibody is used for treating minimal residual disease or consolidation instead of stem cell transplant . A new pilot protocol COG @-@ ANBL09P1 available for newly diagnosed (high @-@ risk) children at several Children 's Oncology Group (COG) centers will offer MIBG radiotherapy and chemotherapy for the transplant regimen .

= = = Refractory and relapsed neuroblastoma = = =

Some children (particularly in high @-@ risk cases) do not respond completely to frontline treatment (with a complete response or very good partial response) and are labeled refractory . These children are removed from the frontline therapy (clinical trial) and are eligible for clinical trials using new therapies . Many high @-@ risk children have a good response to frontline therapy and

achieve a remission , but later the disease recurs (relapse) . These children are also eligible for new therapies being tested in clinical trials .

Chemotherapy with topotecan and cyclophosphamide is frequently used in refractory setting and after relapse . A randomized study (2004) with 119 patients (comparing topotecan alone to topotecan and cyclophosphamide) revealed a 31 % complete or partial response rate with two @-@ year progression @-@ free survival at 36 % in the topotecan and cyclophosphamide group . Irinotecan (intravenous or oral) and oral temozolomide are also used in refractory and recurrent neuroblastoma .

Many phase I and phase II trials are currently testing new agents against neuroblastoma in children who have relapsed or are resistant to initial therapy . Investigators are currently studying new agents , alone and in new combinations , using small molecule targeted therapy , 131 @-@ I MIBG radiation therapy , angiogenesis agents , new monoclonal antibodies , vaccines , oncolytic viruses , as well as new myeloablative regimens .

A group of 16 children 's hospitals in the United States known as the New Advances in Neuroblastoma Therapy (NANT) consortium coordinates the I @-@ 131 MIBG radiation therapy trials . The NANT consortium also offers trials using an oral powder formulation of fenretinide , intravenous fenretinide , bisphosphonate (Zometa) with other agents , and combining I @-@ 131 MIBG with the inhibitor vorinostat .

The SIOPEN group investigated a new delivery method for anti @-@ GD2 antibody ch14.18 / CHO given as long term continuous infusion mostly combined with cytokine IL2 (Ref 1) in order to achieve a better tolerated treatment regimen .

Other research study groups such as The Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC) also conduct clinical trials to treat relapse neuroblastoma . Institutions in Europe are studying novel therapies to treat relapse , including haploidentical stem cell transplant . Many hospitals conduct their own institutional studies as well .

The protein p53 is believed to play a role in the development of resistance to chemotherapy . A November 2009 study in mice shows that activating the tumor suppressor p53 with a new drug , nutlin @-@ 3 , may slow tumor growth . In this study , physician Tom Van Maerken of Ghent University Hospital in Belgium and his colleagues used nutlin @-@ 3 to neutralize MDM2 , a protein that binds to the p53 protein and obstructs p53 's ability to trigger programmed cell death . Earlier studies have shown that nutlin @-@ 3 can specifically prevent MDM2 from disabling p53 .