Rhabdomyosarcoma: Review of the Children’s Oncology Group (COG) Soft-Tissue Sarcoma Committee Experience and Rationale for Current COG Studies

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Abstract

The prognosis for children and adolescents with rhabdomyosarcoma (RMS) has improved with refinements in multi-modal therapy. Since 1972, the Intergroup Rhabdomyosarcoma Study Group (now the Children’s Oncology Group Soft-Tissue Sarcoma Committee) has conducted serial studies for RMS. This review describes the IRSG and COG experience with RMS, presents the current risk stratification definitions, and provides rationale for the current generation of COG RMS studies.

Keywords
pediatric; rhabdomyosarcoma; soft-tissue sarcoma

INTRODUCTION

Soft-tissue sarcomas as a group comprise the most common type of extra-cranial solid tumor type in children [1]. The majority of soft-tissue sarcomas diagnosed in children are rhabdomyosarcoma (RMS). The two major histologic subtypes, embryonal and alveolar, appear to be biologically distinct. Patients with embryonal RMS (ERMS) differ from those with alveolar RMS (ARMS) in terms of age of onset, primary tumor sites, propensity for metastases, and long-term outcome.

Since formation of the Intergroup Rhabdomyosarcoma Study Group (IRSG) in 1972, outcome for patients with RMS has improved dramatically. Survival was less than 25% prior to consistent use of multi-agent chemotherapy beginning in the early 1970s [2]. Overall survival (OS) for patients with localized RMS, has improved from 55% on IRS-I to 71% on IRS-IV [3,4], which may be attributed to better staging, use of risk stratification, improved local therapy, and better supportive care. However, despite several randomized
studies, systemic chemotherapy for most patients has largely remained unchanged since the 1970s.

With formation of the Children’s Oncology Group (COG) in 2000, the efforts of the IRSG were continued in the COG Soft-Tissue Sarcoma (COG-STS) Committee. The IRS-Vor “D” series of studies conducted by COG used the concept of risk stratification to conduct separate studies based on clinical and biologic prognostic factors. The purpose of this article is to summarize the recent IRSG and COG-STS experience. We discuss current risk stratification, local and systemic treatment strategies, and outcome for each sub-group. We also analyze biologic and clinical prognostic features as well as outcome from IRS-V trials as rationale for the current COG-STS trials for RMS.

RISK STRATIFICATION

Clinical and Biologic Factors Used to Determine Risk Stratification

Risk stratification for RMS is based on both a pretreatment (TNM) staging system and a surgical/pathologic clinical grouping system established by the IRSG [3,5]. The clinical “group” is determined after the initial surgical procedure(s) prior to systemic therapy and is primarily based on the extent of residual tumor after surgery with consideration of regional lymph node involvement (Table I). The IRSG group system is highly predictive of outcome [6]. Three-year failure-free survival (FFS) rates for patients on IRS-IV were 83% for group I, 86% for group II, and 73% for group III ($P < 0.001$) [4]. Patients with group IV (metastatic) RMS have long-term FFS rates of <30% [7,8].

The IRS staging system for RMS is based on tumor size, invasiveness, nodal status, and importantly, site of primary tumor (Table II) [5]. As with clinical group, stage is a strong prognostic factor in RMS. On IRS-IV, 3-year FFS rates were 86% for stage 1, 80% for stage 2, and 68% for stage 3 ($P < 0.001$) [4].

Two other prognostic factors in RMS are age at diagnosis and tumor histology. Age correlates to some degree with tumor histology and primary site. Patients <10 years old more commonly have ERMS, and those ≥10 years old are more likely to have ARMS and an extremity primary site [9]. However, age is also an independent prognostic factor in RMS. After adjusting for histology, stage, and group, patients ≥10 years old did worse than younger patients on IRS-III and IRS-IV [10]. Outcome is even worse for adults with a 5-year OS of 27% [11]. FFS is also lower for infants due to higher rates of local failure [12,13].

The differential prognosis between ARMS and ERMS has been known since the early IRS studies [14]. Subsequent studies have used histologic subtype in risk stratification and have assigned more intensive therapy for ARMS. However, characterization of histologic subtype may be subjective, and small biopsy samples can result in misinterpretation. Moreover, the definition of histologic subtype has changed over time. Since 1995, any amount of alveolar histology observed in a tumor specimen has been considered sufficient evidence for ARMS [15].
Recent analyses have focused on molecular characterization based on PAX/FOXO1 fusion gene status. The balanced chromosomal translocations t(2;13)(q35;q14) or t(1;13)(p36;q14) that result in PAX3/FOXO1 and PAX7/FOXO1 fusion genes occur in 80% of cases of histologically diagnosed ARMS [16]. Gene expression analyses of fusion gene-negative ARMS cases show expression signatures similar to ERMS, but distinguishable from fusion gene-positive ARMS [17,18]. Moreover, the clinical features and outcome for patients with fusion gene-negative ARMS are similar to those for patients with ERMS [18].

Current Risk Stratification

The IRS-V or “D” series conducted by the COG-STS committee included D9602 for “low-risk” RMS, D9803 for “intermediate-risk” RMS, and D9802 for “high-risk” RMS. Data from IRS-III and IRS-IV provided rationale for risk stratification [19]. Patients with clinical and biologic features that placed them in the low-risk category had a 3-year FFS of 88% on these studies. Treatment was further tailored on D9602 by dividing the low-risk group into two subsets based on stage, group, and primary site. Patients in the low-risk Subset A (5-year FFS 90% on IRS-III and IRS-IV) included those with stage 1, group I/IIA; stage 2, group I; and stage 1, group III (orbit only) ERMS. Low-risk Subset B (5-year FFS rate of 87% on IRS-III and IRS-IV) included patients with stage I, group IIB/IIC or group III (nonorbit). The remaining patients with nonmetastatic ERMS (stage 2 or 3, group III) were considered to have “intermediate-risk” RMS and had a 5-year FFS of 73% on IRS-III and IRS-IV. In addition, patients with ARMS (stage 1–3, groups I–III), with a 5-year FFS of 65%, were included in the “intermediate-risk” category. Finally, an analysis from IRS-IV revealed a sub-group of patients with stage 4, group IVMRMS who had a more favorable prognosis [20]. Patients <10 years old with metastatic ERMS had outcomes similar to the intermediate-risk group and were eligible for D9803. All other patients with stage 4, group IV RMS (ERMS, ≥10 years of age and ARMS of any age) have an estimated FFS of less than 20% and were treated on D9802 in the IRS-V series.

Summary of Data From IRS-V by Risk Group

D9602 was a nonrandomized study for low-risk RMS [21]. Patients in Subset A received chemotherapy for 45 weeks with vincristine and actinomycin-D (VA), and those with group II or III tumors also received local radiation therapy (RT). The 5-year FFS and OS for this subset were 89% and 97%, respectively. Patients with Group III orbital tumors had a 5-year FFS of 86% with reduced RT to 45 Gy. Patients in Subset B received 45 weeks of chemotherapy with vincristine, actinomycin-D, and 2.2 g/m² cycle cyclophosphamide (VAC) along with RT. The 5-year FFS and 5-year OS were 85% and 93%, respectively. Patients with stage 1, group IIB/IIC and those with stage 2, group II tumors had better outcome compared to the rest of Subset B.

D9803 was a randomized study for patients with intermediate-risk RMS [22]. Patients were randomized to receive 42 weeks of VAC or VAC alternating with cycles of vincristine/topotecan/cyclophosphamide (VTC). Cyclophosphamide was 2.2 g/m² for 1 day per VAC cycle and 250 mg/m²/day for 5 days per VTC cycle. All patients received 36–50.4 Gy RT (with the rare exception of amputative resection at diagnosis). There was no difference
between the randomized arms, with a 4-year FFS of 73% with VAC versus 68% with VAC/VTC.

The COG D9802 study evaluated up-front window treatments with irinotecan and vincristine/irinotecan (VI) for high-risk RMS [23]. The irinotecan alone window showed a progressive disease (PD) rate of 32%. Following a study amendment to add vincristine to the irinotecan window, the PD rate was only 8%, with a combined complete and partial response rate of 70%. The VI response rate was better than any other phase II window drug pair tested by the IRSG or COG-STS [24]. This finding, along with the feasibility of interval compression to dose-intensify chemotherapy, which was later shown to improve outcome for localized Ewing sarcoma [25], formed the rationale for the COG ARST0431 study. ARST0431 treated patients with metastatic RMS using an intensive combination of VI, interval-compressed vincristine/doxorubicin/cyclophosphamide alternating with ifosfamide/etoposide in addition to VAC chemotherapy. One hundred nine patients with stage 4, group IV RMS (including those <10 years old with embryonal histology) were enrolled and received 54 weeks of therapy. Preliminary results show an 18-month FFS of 66% and OS of 80% [26]. By comparison, a recent pooled analysis of studies from Europe and North America show an 18-month FFS of 41% for a similar cohort of patients with metastatic RMS [8]. While preliminary results appear favorable, further follow-up is necessary to determine if outcome is improved with ARST0431 therapy.

RATIONAL FOR CURRENT COG STUDIES: SYSTEMIC THERAPY

The current series of COG studies uses the previously defined risk stratification to ask separate study questions for low-risk, intermediate-risk, and high-risk RMS. The rationale for each study builds on previous experience and data from IRS-V.

Low-Risk RMS

The recent study for low-risk RMS (COG ARST0331) sought to maintain the excellent outcome for these patients while minimizing acute and long-term toxicities. The study treated two subsets of patients similar to Subsets A and B as defined in D9602. However, due to improved outcome for patients with stage 1, group IIB/C and stage 2, group II ERMS, these patients were treated in Subset 1 on ARST0331, which includes all patients with stages 1–2, groups I–II and stage 1, group III orbit tumors (Table III). Subset 2 consists of the remaining low-risk patients (stage 3, groups I–II and stage 1, group III nonorbit). As in D9602, only ERMS are considered low-risk.

Patients eligible for Subset A had a 5-year FFS of 93% with VAC chemotherapy (2.2 g/m² cyclophosphamide per cycle) for 43 weeks on IRS-IV compared to 83% with VA for 54 weeks on IRS-III. ARST0331 sought to maintain the improved outcome with the addition of a modest dose of cyclophosphamide while decreasing the late effects due to the IRS-IV cumulative dose of cyclophosphamide (26.4 mg/m²). Subset 1 patients on ARST0331 received four cycles of VAC (1.2 g/m² cyclophosphamide per cycle) followed by four cycles of VA, for total treatment duration of 24 weeks, resulting in cumulative cyclophosphamide dose of 4.8 g/m². Data from European RMS clinical trials with patients similar to Subset 1 supports the shorter duration of therapy [27,28]. For example, patients...
with paratesticular SIOP stage 1, group I RMS had a 5-year FFS of 88% and 5-year OS of 99% with 22 weeks of VA chemotherapy on German and Italian cooperative group studies (CWS 96 and RMS-96) [29]. Preliminary data from ARST0331 show an estimated 2-year FFS of 88% for Subset 1, which is statistically at least as good as D9602 [30].

The aim of ARST0331 for Subset 2 patients is also to maintain excellent outcomes while minimizing long-term effects. Outcome improved for these patients from IRS-III (5-year FFS 70%) with VA therapy to IRS-IV (5-year FFS 84%) with the addition of intensive cyclophosphamide (2.2 g/m² per dose and 26.4 g/m² cumulative dose) [4,6]. It is unclear whether such high doses are essential to achieve the benefit of cyclophosphamide. High-dose cyclophosphamide causes severe myelosuppression, infectious complications, and infertility in virtually all males and many females [31]. Therefore, on ARST0331, patients in Subset 2 received a modest dose of cyclophosphamide with four cycles of VAC (1.2 g/m² cyclophosphamide per cycle) followed by 12 cycles of VA for a total of 48 weeks. Outcome data for Subset 2 are not yet available.

Intermediate-Risk RMS

Recent studies have failed to show an improvement in outcome for patients with intermediate-risk RMS. The addition of doxorubicin, ifosfamide, and ifosfamide/etoposide to VAC did not improve outcome on IRS-I through IRS-IV [4]. In addition, increased dose of alkylator from 0.9 to 2.2 g/m² cyclophosphamide per cycle did not provide any benefit for patients on IRS-IV compared to IRS-III, and the addition of VTC to VAC failed to show improvement in FFS on D9803 [22].

Beginning with an IRS-IV pilot study, IRSG and the COG-STS committee have conducted a series of phase II window studies to determine which novel agents or drug combinations would be most compelling for evaluation in a randomized study [32]. Rationale for inclusion of VTC on D9803 was based on a previous phase II window [33]. Among the seven regimens evaluated the best response rate was seen with VI (Table IV), with a combined CR + PR rate of 70% [23,32]. The activity of this chemotherapy combination provides rationale for the current COG study (ARST0531) for intermediate-risk RMS.

Despite lack of benefit to the addition of VTC on D9803, the evaluation of another camptothecan in the VI combination is supported by preclinical and clinical data. While irinotecan is active in preclinical models of RMS, the combination of VI is synergistic [34,35]. Irinotecan enhances the cytotoxic activity of the microtubule inhibitor, vincristine, by stabilizing the topoisomerase I–DNA complex during mitosis. Patients on ARST0531 are randomized to receive VAC versus VAC alternating with VI cycles for 43 weeks. As dose intensification of cyclophosphamide did not improve outcome on IRS-IV or D9803, the COG-STS studies now uses a uniform dose of 1.2 g/m² cyclophosphamide per cycle across all studies. ARST0531 opened to accrual in December 2006 and is ongoing.

High-Risk RMS

Based on the tolerability and early outcome data from ARST0431, the successor COG study for high-risk RMS, ARST08P1, uses the same backbone with the addition of novel therapeutic agents. The principal aims of the study are to evaluate the feasibility of adding
Cixutumumab and/or temozolomide to the ARST0431 chemotherapy backbone in a series of three sequential pilot studies. Cixutumumab is a monoclonal antibody against the insulin-like growth factor-I receptor (IGF-IR) that has anti-tumor activity in RMS preclinical models and was well tolerated as a single-agent in children with refractory solid tumors [36–38]. Temozolomide is an alkylating agent that has shown synergy with irinotecan in preclinical models as well as clinical activity in pediatric sarcomas [39–41]. The study opened to enrollment in January 2010.

Recurrent RMS

Patients with progressive or recurrent RMS have a poor prognosis, with a 5-year survival of 17% [42]. A previous COG study for recurrent RMS evaluated an upfront window of VI as well as the addition of tirapazamine to doxorubicin and cyclophosphamide [43]. The OS observed on this study appeared similar to that seen for recurrence after treatment on IRS-III and IRS-IV. The current COG study for first recurrence or progression (ARST0921) is a randomized phase II study to assess the feasibility and activity of bevacizumab or temsirolimus in combination with vinorelbine/cyclophosphamide. The combination of vinorelbine with oral cyclophosphamide has shown activity with a reasonable toxicity profile in patients with recurrent sarcomas and is being evaluated as maintenance therapy in a randomized trial for high-risk RMS patients by the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) [44]. Bevacizumab, a monoclonal antibody to all five isoforms of human vascular endothelial growth factor (VEGF) [45], decreases tumor growth by inhibiting angiogenesis and has shown activity in RMS xenograft models [46]. Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) [47]. Activation of the mTOR signaling pathway has been reported in RMS and mTOR inhibitors, such as rapamycin and temsirolimus, are active against RMS cell lines and xenografts [48,49].

ARST0921 will directly compare the toxicities and activity of two novel agents in combination with a vinca alkaloid and cyclophosphamide. This will allow prioritization of agents to be studied in future upfront trials for intermediate-risk or high-risk RMS.

RATIONALE FOR CURRENT COG STUDIES: LOCAL THERAPY

Successful treatment of RMS requires local therapy in addition to systemic chemotherapy. Due to challenging anatomic primary sites and local invasiveness, surgery is often difficult as the primary means of local control [19]. Within COG-STS studies, RT is a mainstay of treatment for all patients with Group II–IV RMS and can provide effective local control. In contrast, the SIOP MMT 89 study omitted RT for patients who attained a complete response to chemotherapy with or without surgery [50]. The 5-year EFS of 57% for nonmetastatic patients in that study is lower than the EFS for similar patients on IRS-IV. However, many of the patients who recurred on MMT 89 were cured with second-line therapy, resulting in less dramatic differences in OS [51].
**Low-Risk RMS**

The recent COG ARST0331 study treated all patients with group II or III RMS with RT at week 13. The previous study, D9602 evaluated whether radiation dose could safely be reduced from 41.4 to 36 Gy for patients with Group IIA tumors and from 50.4 to 45 Gy for patients with group III orbital tumors [21]. Local therapy aims of ARST0331 are to evaluate local control rates continuing these dose reductions along with decreased doses after delayed resection to 36 Gy or to 41.4 Gy for regional nodal involvement.

Female patients with RMS involving the GU tract present a dilemma regarding the most appropriate local therapy. Despite an excellent prognosis, patients are generally very young and local RT can lead to significant long-term morbidity [52]. In an attempt to minimize morbidity, both D9602 and ARST0331 permitted a treatment approach similar to MMT 89 and allowed delay or omission of RT for Group II and III female GU primary sites if serial biopsies demonstrate response to chemotherapy. However, this approach was associated with a high rate of local recurrence (43% at 2 years) and an inferior outcome (2-year FFS of 42%) on ARST0331 [53]. The increased local failure rate when RT is omitted illustrates the challenge of balancing optimal oncology treatment while attempting to minimize long-term complications.

**Intermediate-Risk RMS**

Each of the last three trials for intermediate-risk RMS has examined a different strategy to improve local control. IRS-IV compared hyperfractionated (twice daily) RT to standard (daily) radiation, but found no difference in outcome [54]. D9803 encouraged second look operation (SLO) for initially unresected tumors and evaluated dose reduced RT after SLO (36 Gy after delayed complete resection instead of 50.4 Gy). Only selected anatomic sites were considered candidates for SLO, including extremity, dome of the bladder, and trunk. Nearly half of potential SLO candidates underwent SLO with 84% of these patients having complete resections and receiving reduced RT [55]. ARST0531 aims to evaluate the benefit of earlier onset of RT (at week 4). The rationale for early RT is the reduced local failure rate for patients with parameningeal tumors and intracranial extension who receive RT within 2 weeks of starting systemic therapy (18% vs. 33% for delay beyond 2 weeks) [56]. However, no statistical difference in FFS was seen by timing of RT. By applying a uniform timing of early RT (at week 4) for all patients, ARST0531 will address the question of RT timing more directly.

**RATIONALE FOR IMAGING QUESTIONS ON CURRENT COG STUDIES**

Response evaluation by standard imaging is typically accomplished by measuring change in tumor size with computed tomography (CT) or magnetic resonance imaging (MRI). In RMS, early response to therapy by imaging does not predict long-term FFS [57]. However, CT and MRI are often unable to distinguish residual viable tumor from necrotic tumor or scar tissue, and change in tumor size may be an inadequate indication of response. Functional imaging, such as with [F-18]-fluorodeoxy-D-glucose (FDG) positron emission tomography (PET), has the potential to differentiate benign residual tissue from viable tumor and may demonstrate changes in tumors sooner than morphologic imaging [58].
changes in FDG PET are predictive of histologic response and correlate with long-term outcome in many cancers [59,60]. In one study for soft-tissue sarcomas, early response by FDG PET, defined as a 40% reduction in the maximum standardized uptake value (SUV$_{\text{max}}$), correlated with better long-term outcome [61].

Both ARST0531 and ARST08P1 are collecting FDG PET imaging data at baseline and during therapy to correlate with radiographic response by standard techniques. In addition, the ability of FDG PET to detect metastases will be assessed in comparison to standard imaging. A recent prospective trial in pediatric sarcomas suggests that FDG PET may improve on the ability of conventional imaging to detect metastases to bone and lymph nodes [62].

**FUTURE DIRECTIONS**

As current COG studies for RMS proceed, strategies for future clinical trials require discussion and planning. For low-risk RMS, current treatment results in an excellent FFS (>90%). If results from ARST0331 provide the same favorable results with reduced cyclophosphamide dose, RT dose, and duration of therapy, it is unlikely that the COG-STS committee will be able to ask another research question for this patient population.

Several studies have failed to improve outcome with the addition of chemotherapeutic agents to VAC. Future trials will likely evaluate incorporation of novel biologic agents with chemotherapy. Current trials for metastatic RMS and relapsed RMS will provide pilot data with which to prioritize drugs for future study in intermediate-risk RMS. Ongoing research using human tumor specimens and animal models will guide development of additional novel agents for RMS.

Finally, future research may require a redefinition of risk groups to include biologic characteristics (such as PAX:FOXO1 fusion gene status) along with clinical features in risk stratification. Evaluation of response by novel imaging techniques may provide further data to be used in risk stratification.

**References**


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<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Group I</td>
<td>Localized disease, completely resected</td>
</tr>
<tr>
<td>Group II</td>
<td>Total gross resection, with evidence of regional spread</td>
</tr>
<tr>
<td>A</td>
<td>Grossly resected tumor with microscopic residual disease</td>
</tr>
<tr>
<td>B</td>
<td>Involved regional nodes completely resected with no microscopic residual disease</td>
</tr>
<tr>
<td>C</td>
<td>Involved regional nodes grossly resected with evidence of microscopic residual disease</td>
</tr>
<tr>
<td>Group III</td>
<td>Biopsy only or incomplete resection with gross residual disease</td>
</tr>
<tr>
<td>Group IV</td>
<td>Distant metastatic disease (excludes regional nodes and adjacent organ infiltration)</td>
</tr>
<tr>
<td>Stage</td>
<td>Sites</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Orbit, head and neck (non-PM), GU (non-B/P), biliary tract</td>
</tr>
<tr>
<td>2</td>
<td>B/P, extremity, PM, other (includes trunk, retroperitoneum, etc.)</td>
</tr>
<tr>
<td>3</td>
<td>B/P, extremity, PM, other (includes trunk, retroperitoneum, etc.)</td>
</tr>
<tr>
<td>4</td>
<td>Any</td>
</tr>
</tbody>
</table>

PM, parameningeal; B/P, bladder/prostate.

<sup>a</sup>T: T1, confined to anatomic site of origin, T2, extension and/or fixative to surrounding tissue;

<sup>b</sup>Size: a, ≤5 cm in diameter; b, >5 cm in diameter;

<sup>c</sup>Nodes: N0, regional nodes not involved; N1, regional nodes involved; Nx, regional node status unknown;

<sup>d</sup>Metastases: M0, no distant metastases; M1, metastases present (includes positive cytology in CSF, pleural, or peritoneal fluid).
TABLE III

Current COG-STS Risk Stratification

<table>
<thead>
<tr>
<th>Risk</th>
<th>5 year FFS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Stage</th>
<th>Group</th>
<th>Histology</th>
<th>Current study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low, subset 1</td>
<td>90%</td>
<td>1 or 2</td>
<td>I or II</td>
<td>EMB</td>
<td>ARST0331</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>III orbit</td>
<td>EMB</td>
<td></td>
</tr>
<tr>
<td>Low, subset 2</td>
<td>87%</td>
<td>1</td>
<td>III nonorbit</td>
<td>EMB</td>
<td>ARST0331</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>I or II</td>
<td>EMB</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>65–73%</td>
<td>2 or 3</td>
<td>III</td>
<td>EMB</td>
<td>ARST0531</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1, 2, or 3</td>
<td>I, II, or III</td>
<td>ALV</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>&lt;30%</td>
<td>4</td>
<td>4</td>
<td>EMB or ALV</td>
<td>ARST08P1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data from IRS-III and IRS-IV. EMB, embryonal; ALV, alveolar.
TABLE IV
Phase II Window Responses From IRS-IV Pilot, IRS-IV, D9501, and D9802

<table>
<thead>
<tr>
<th>Window</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>PD (%)</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifosfamide/doxorubicin</td>
<td>11</td>
<td>41</td>
<td>7</td>
<td>52</td>
</tr>
<tr>
<td>Vincristine/melphalan</td>
<td>4</td>
<td>51</td>
<td>8</td>
<td>55</td>
</tr>
<tr>
<td>Ifosfamide/etoposide</td>
<td>5</td>
<td>36</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>Topotecan</td>
<td>3</td>
<td>46</td>
<td>31</td>
<td>49</td>
</tr>
<tr>
<td>Topotecan/cyclophosphamide</td>
<td>4</td>
<td>46</td>
<td>19</td>
<td>50</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>0</td>
<td>45</td>
<td>32</td>
<td>45</td>
</tr>
<tr>
<td>Vincristine/irinotecan</td>
<td>2</td>
<td>68</td>
<td>8</td>
<td>70</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; PD, progressive disease.