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### **Prognostic Utility of the 21-Gene Assay in Hormone Receptor (HR) Positive Operable Breast Cancer and 0-3 Positive Axillary Nodes Treated with Adjuvant Chemohormonal Therapy (CHT): An Analysis of Intergroup Trial E2197**

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**Background:** Evidence suggests modern chemotherapy (CT) regimens are only marginally more effective in HR-pos breast cancer (Berry et al. JAMA 2006: 295: 1658). Genomic classifiers may be useful for selection of high-risk subjects for more aggressive CHT.

**Methods:** A case-cohort sample of 776 patients enrolled on E2197 who did (N=179) or did not have a recurrence after CT (if HR-neg) or CHT (if HR-pos) and had available tissue were evaluated for Oncotype DX™ Recurrence Score (RS). E2197 included 2885 evaluable patients with 0-3 positive nodes treated with four 3-week cycles of doxorubicin (60 mg/m<sup>2</sup>) plus cyclophosphamide 600 mg/m<sup>2</sup> (AC) or docetaxel 60 mg/m<sup>2</sup> (AT) and hormonal therapy (if HR pos). Median follow-up was 76 months.

**Results:** There was no difference in DFS between treatment arms. In multivariate analysis, RS was a significant predictor of recurrence in HR-pos disease (p=0.0007, recurrence risk 21% lower for each 10 point drop in RS, 95% confidence intervals 9% to 31%). Recurrence risk was significantly elevated for an intermediate RS 18-30 (n=138, hazard ratio [HR] 2.96 [p=0.0002]) or a high RS ≥ 31 (n=108, HR 4.00, p=0.0001) compared with low RS < 18 (n=196), but not for high compared with intermediate RS (HR 1.34, [p=0.32]); results were similar if only HER2-neg disease was included. The 5-year relapse free interval (RFI), breast cancer free survival (BCFS), disease-free survival (DFS), and overall survival (OS) for patients with HR-pos, HER2-neg disease are shown below (%); patients with both node-neg or node-pos breast cancers whose RS was < 18 had excellent outcomes.

<b>Nodal Status</b>	<b>RS</b>	<b>N</b>	<b>RFI</b>	<b>BCFS</b>	<b>DFS</b>	<b>OS</b>
<b>Negative</b>	<b>&lt;18</b>	<b>79</b>	<b>96</b>	<b>94</b>	<b>94</b>	<b>96</b>
<b>Positive</b>	<b>&lt;18</b>	<b>109</b>	<b>95</b>	<b>91</b>	<b>90</b>	<b>97</b>
<b>Negative</b>	<b>18-30</b>	<b>69</b>	<b>85</b>	<b>86</b>	<b>86</b>	<b>97</b>
<b>Positive</b>	<b>18-30</b>	<b>65</b>	<b>87</b>	<b>81</b>	<b>80</b>	<b>86</b>
<b>Negative</b>	<b>≥ 31</b>	<b>41</b>	<b>89</b>	<b>83</b>	<b>83</b>	<b>94</b>
<b>Positive</b>	<b>≥ 31</b>	<b>24</b>	<b>73</b>	<b>62</b>	<b>56</b>	<b>73</b>

**Conclusions:** Oncotype DX™ RS identifies individuals with HR-pos, HER2-neg breast cancer with 0-3 positive axillary lymph nodes at 3-4-fold increased risk of relapse despite standard CHT, and may serve as a means to distinguish between those who do well with standard CHT (RS <18) from those who may be suitable candidates for clinical trials evaluating alternative CT regimens or other strategies (RS > 18).