Detection of NRG1 Gene Fusions in Solid Tumors

Sushma Jonna1, Rebecca A. Feldman2, Jeffrey Swensen2, Zoran Gatalica2, Wolfgang M. Korn2, Hossein Borghaei3, Patrick C. Ma4, Jorge J. Nieva5, Alexander I. Spira6, Ari M. Vanderwalde7, Antoinette J. Wozniak8, Edward S. Kim9, and Stephen V. Liu1

Abstract

Purpose: NRG1 gene fusions are rare but potentially actionable oncogenic drivers that are present in some solid tumors. Details regarding the incidence of these gene rearrangements are lacking. Here, we assessed the incidence of NRG1 fusions across multiple tumor types and described fusion partners.

Experimental Design: Tumor specimens submitted for molecular profiling at a Clinical Laboratory Improvement Amendments (CLIA)–certified genomics laboratory and that underwent fusion testing by anchored multiplex PCR for targeted RNA sequencing were retrospectively identified. The overall and tumor-specific incidence was noted, as was the specific fusion partner.

Results: Out of 21,858 tumor specimens profiled from September 2015 to December 2018, 41 cases (0.2%) harbored an NRG1 fusion. Multiple fusion partners were identified. Fusion events were seen across tumor types. The greatest incidence was in non–small cell lung cancer (NSCLC, 25), though this represented only 0.3% of NSCLC cases tested. Other tumor types harboring an NRG1 fusion included gallbladder cancer, renal cell carcinoma, bladder cancer, ovarian cancer, pancreatic cancer, breast cancer, neuroendocrine tumor, sarcoma, and colorectal cancer.

Conclusions: NRG1 fusions can be detected at a low incidence across multiple tumor types with significant heterogeneity in fusion partner.

See related commentary by Dimou and Camidge, p. 4865

Introduction

Appropriate management of advanced non–small cell lung cancer (NSCLC) is guided by the presence or absence of specific molecular drivers. The identification of activating genomic alterations in EGFR, ALK, ROS1, or BRAF not only provides insight into the underlying biology but also directs initial and subsequent therapeutic decisions (1–5). It is now standard-of-care to search for these mutations and fusions in all patients with nonsquamous NSCLC (6). It has also become clear that some molecular drivers will serve as therapeutic targets across multiple tumor types (7), including the tumor agnostic approval of larotrectinib for tumors with a gene fusion in NTRK1, NTRK2, or NTRK3 (8). As our understanding of cancer grows increasingly sophisticated, additional drivers have surfaced that may have a similar impact on evolving treatment paradigms.

Neuregulin-1 (NRG1) gene fusions are an emerging, potentially actionable oncogenic driver (9). NRG1 fusions can promote pathologic signaling via MAPK and other canonical pathways (10). When NRG1 fusions are present, targeting ERBB2 and ERBB3 has been an effective treatment strategy in vitro. Recently, clinical responses to tyrosine kinase inhibitors and mAbs have also been reported (9, 11–13).

The interest in evaluating the prevalence of NRG1 fusions has increased given the potential therapeutic implications of this genetic alteration. Because the original description of the CD74–NRG1 gene fusion in invasive mucinous lung adenocarcinoma, detection has been noted in other tumor types, both de novo and as a resistance mechanism in ALK-rearranged NSCLC (9, 14–16). Here, we report the incidence and characteristics of NRG1 fusions across a variety of tumor types based on a large molecular profiling experience.

Materials and Methods

Patient cohort

An institutional review board (IRB)–approved, retrospective assessment of a deidentified molecular profiling database was surveyed for solid tumors that underwent fusion testing. From a cohort including all cases submitted to a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory (Caris Life Sciences) for comprehensive genomic profiling from September 2015 to December 2018, all unique cases that underwent successful fusion testing for targeted RNA sequencing were identified. In addition, all histologic characteristics were reviewed by a board-certified pathologist (Z. Gatalica).

Gene fusion detection

Prior to any molecular analysis, H&E-stained sections of formalin-fixed paraffin-embedded (FFPE) tumor tissue were manually assessed by board-certified pathologists for tumor
**NRG1 Fusions in Solid Tumors**

**Translational Relevance**

NRG1 fusions are potentially actionable genomic events seen in various tumor types. While there are reports of therapeutic efficacy with agents that target Erb-B2/Erb-B3, little is known about the characteristics of these fusions. Here, we report the incidence of NRG1 fusions in a large cohort of solid tumors that underwent RNA sequencing. NRG1 fusions were detected at a low incidence across many solid tumor types. Multiple fusion partners were identified, which will influence the development of strategies to detect these events on a large scale.

NRG1 fusions are potential actionable genomic events seen in various tumor types. While there are reports of therapeutic efficacy with agents that target Erb-B2/Erb-B3, little is known about the characteristics of these fusions. Here, we report the incidence of NRG1 fusions in a large cohort of solid tumors that underwent RNA sequencing. NRG1 fusions were detected at a low incidence across many solid tumor types. Multiple fusion partners were identified, which will influence the development of strategies to detect these events on a large scale.

**Results**

**Sample population**

From September 2015 to December 2018, a total of 21,858 tumor specimens from unique patients were successfully evaluated. The tumor types included NSCLC (n = 9,592), glioma (n = 1,997), colorectal cancer (n = 1,690), breast cancer (n = 1,106), bladder cancer (n = 945), ovarian cancer (n = 686), sarcoma (n = 627), pancreatic adenocarcinoma (n = 623), gallbladder cancer (n = 580), other gynecologic malignancies (e.g., uterine, cervical, vulvar; n = 524), melanoma (n = 360), prostate cancer (n = 261), gastric adenocarcinoma (n = 239), head and neck squamous cell carcinoma (n = 236), thyroid cancer (n = 219), renal cell carcinoma (n = 211), neuroendocrine tumors (n = 203), esophageal cancer (n = 202), small-cell lung cancer (n = 187), extracellular bile duct cancer (n = 98), small bowel cancer (n = 98), gastrointestinal stromal tumor (n = 83), hepatocellular carcinoma (n = 83), thymic cancer (n = 31), testicular cancer (n = 25), and other malignancies (n = 1,032).

**Incidence**

The incidence of NRG1 fusions in the entire tested population was 0.2% (41/21,858). Incidence varied by tumor type (Fig. 1): 0.5% gallbladder cancer (3/580), 0.5% pancreatic cancer (3/623), 0.5% renal cell carcinoma (1/211), 0.4% ovarian cancer (3/686), 0.3% NSCLC (25/9,592), 0.2% breast cancer (2/1,106), 0.2% sarcoma (1/627), 0.1% bladder cancer (1/945), and 0.1% colorectal cancer (1/690). The remaining identified NRG1 fusion was in a patient with a neuroendocrine tumor of the nasopharynx. Table 1 describes the characteristics of the 41 patients found to have an NRG1 fusion. The most common histologic subtype was adenocarcinoma (70%), of which 24% were classified as mucinous adenocarcinoma and another 8% had a mixed histology with a mucinous component (Supplementary Fig. S1). The majority of cases were stage IV at the time of fusion detection. NRG1 fusion events were more frequently identified in females (66%) versus males, and most specimens were procured from the primary site (68%) compared with a distant metastasis (32%). In the total cohort, 51% (11,228/21,858) of patients were females and 59% (10,730/21,858) of specimens profiled were from primary sites.

**Fusion partners**

The specific fusion partners were also diverse within and across malignancies (Supplementary Table S1; Figs. 2–5; Supplementary Fig. S2). In NSCLC, CD74 was the most common fusion partner (n = 12), but other detected partners in NSCLC cases included SDCC4 (n = 3), SLC3A2 (n = 1), TNC (n = 1), MDK (n = 1), ATP1B1, and other oncogenic isoforms (Quiver database, ArcherDx), as well as those novel isoforms or fusions with high reads (>1%) were used to enrich target regions, followed by next-generation sequencing (NGS; Illumina MiSeq platform). Targets included 52 genes, and the full list can be found at http://archerdx.com/fusionplex/assays/solid-tumor (accessed 12/27/18). Reads that matched to a database of known fusions and other oncogenic isoforms (Quiver database, ArcherDx), as well as those novel isoforms or fusions with high reads (>10% of total reads) and high confidence after bioinformatic filtering, were analyzed. Samples with less than 4,000 unique RNA reads were reported as indeterminate and excluded from analysis. All NRG1 transcript variants were investigated whereby splice junctions were analyzed using the UCSC Genome Browser to predict the likelihood of the mRNA transcript to encode a functional protein (17). The detection sensitivity of the assay allows for detection of a fusion that is present in at least 10% of the cells in the samples tested.

**Frame retention prediction**

NRG1 fusions were predicted to be (i) in-frame variants, (ii) out of frame variants of unknown significance, or (iii) translated variants where exon 2 of NRG1 is spliced to upstream noncoding exons with confirmed presence of internal initiation sites, (e.g., methionine codon; refs. 17, 18). Inclusion of these variants was based on the retention of the EGF-like domain of NRG1, the functional domain which facilitates its oncogenic potential (19).

**NGS**

NGS was performed on isolated genomic DNA using the Illumina NextSeq platform. A custom-designed SureSelect XT assay was used to enrich 592 whole-gene targets (Agilent Technologies). All variants were detected with >99% confidence based on allele frequency and amplicon coverage, with an average sequencing depth of coverage of >500 and an analytic sensitivity of 5%. For variant classification, variants of genes that were predetermined for their cancer-related and clinical significance were interpreted by board-certified molecular geneticists and categorized as pathogenic, presumed pathogenic, variant of unknown significance, presumed benign, or benign according to American College of Medical Genetics and Genomics (ACMG) standards. Only pathogenic or presumed pathogenic mutations were considered deleterious and included for assessment of comutation patterns with NRG1 fusion–positive cases.

**IHC**

IHC was performed using commercially available detection kits and automated staining techniques (Benchmark XT, Ventana; and AutostainerLink 48, Dako). Primary antibodies tested were as follows: Her2/neu (4B5, Ventana), pan-TRK (C17F1, Cell Signaling Technology), and ALK (D5F3, Ventana). Cutoffs for positive staining: (3) pan-TRK (≥1+ and ≥1% of cells), (4) Her2, ≥3+ and ≥10%, and (5) ALK, ≥3+ and ≥10%.

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In the other malignancies, the identified fusion partners were as follows: SETD4, TSHZ2, and ZMYM2 in ovarian cancer; ADAM9 and COX10-AS1 in breast cancer; ATP1B1, CDH1, and VTCN1 in pancreatic cancer; NOTCH2 and ATP1B1 (n = 2) in gall bladder cancer; POMK in colorectal cancer; RBPMS in renal cell carcinoma; GDF15 in urothelial bladder cancer; WHSC1L1 in sarcoma; and HMBOX1 in neuroendocrine tumor of the nasopharynx.

Of the 41 NRG1 fusions identified, 34 were in-frame, three were out-of-frame variants of unknown significance, and four were translated variants.

Co-occurrence with other genetic aberrations
NRG1 fusions were mutually exclusive with oncogenic alterations in EGFR, KRAS, ALK, ROS1, and RET (Fig. 2). One case co-occurred with a BRAF G466A mutation, one with a KRAS G12D mutation, and three with NF1 or NF2 mutations (NF1, Q616fs, NSCLC and c.204+1G>T, ovarian; NF2 H242fs, NSCLC). Most cases (n = 30) also demonstrated concurrent mutations in tumor suppressor genes, including TP53.

Survival
Limited survival analysis is shown in Supplementary Fig. S3 for patients with full annotation (n = 7). Median survival for

Table 1. Patient and tumor characteristics for NRG1 fusion-positive cases

<table>
<thead>
<tr>
<th>NSCLC</th>
<th>Ovarian cancer</th>
<th>Breast cancer</th>
<th>GI cancers*</th>
<th>GU cancers*</th>
<th>Other†</th>
<th>Overall</th>
</tr>
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<tbody>
<tr>
<td>Total, n</td>
<td>25</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Median age, range</td>
<td>71 (52-90)</td>
<td>53 (47-69)</td>
<td>44 (38-49)</td>
<td>46 (37-68)</td>
<td>61 (58-63)</td>
<td>59 (38-61)</td>
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<tr>
<td>Sex, n, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (32%)</td>
<td>—</td>
<td>—</td>
<td>3 (43%)</td>
<td>1 (50%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (68%)</td>
<td>3 (100%)</td>
<td>2 (100%)</td>
<td>4 (57%)</td>
<td>1 (50%)</td>
<td>—</td>
</tr>
<tr>
<td>Group stage, time of biopsy, n, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (5%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>II</td>
<td>3 (14%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>III</td>
<td>6 (27%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IV</td>
<td>12 (54%)</td>
<td>3 (100%)</td>
<td>2 (100%)</td>
<td>7 (100%)</td>
<td>2 (100%)</td>
<td>—</td>
</tr>
<tr>
<td>Histology, n, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (4%)</td>
<td>—</td>
<td>—</td>
<td>1 (34%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Papillary</td>
<td>6 (24%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mucinous</td>
<td>2 (8%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Acinar</td>
<td>3 (12%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mixed*</td>
<td>2 (8%)</td>
<td>—</td>
<td>—</td>
<td>1 (50%)</td>
<td>—</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>8 (32%)</td>
<td>—</td>
<td>1 (50%)</td>
<td>6 (86%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NOS</td>
<td>2 (8%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>2 (8%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serous carcinoma</td>
<td>—</td>
<td>2 (67%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Other†</td>
<td>1 (4%)</td>
<td>1 (33%)</td>
<td>—</td>
<td>—</td>
<td>1 (50%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Specimen site, n, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>20 (80%)</td>
<td>3 (100%)</td>
<td>—</td>
<td>3 (43%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>5 (20%)</td>
<td>—</td>
<td>2 (100%)</td>
<td>4 (57%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastrointestinal; GU, genitourinary; NOS, not otherwise specified.
*Pancreatic ductal adenocarcinoma, gallbladder cancer (cholangiocarcinoma), and colorectal cancer.
†Renal cell carcinoma and urothelial bladder cancer.
*Soft tissue sarcoma of the extremity/trunk and neuroendocrine tumor of the nasopharynx.
*Mixed histology (2 patients with acinar, clear cell, and mucinous components and 1 patient with adenosquamous features).
*Other, pleomorphic carcinoma or sarcoma, carcinosarcoma, clear cell carcinoma, or neuroendocrine tumor.
the entire cohort was 638 days and varied by tumor type, although analysis is limited by the small sample size.

Discussion

NRG1 gene fusions represent a novel oncogenic driver across cancer types. These rare genomic events can generate proteins that retain the extracellular EGF-like domain of NRG1 and the transmembrane domain of the specific fusion partner. These proteins then serve as ligands for ERBB3 (HER3) and ERBB4 (HER4) receptors (10). ERBB3 can then be activated through juxtacrine signaling from the EGF-like domain and autocrine signaling of secreted NRG1 (19). Subsequent heterodimerization of ERBB3 with ERBB2 activates downstream signaling important in tumorigenesis mediated by pathways including ERK, PI3K, AKT, and NFκB, described in cell models (9, 19).

In this report, we retrospectively analyzed over 21,000 specimens after RNA sequencing using the ArcherDx platform to detect NRG1 fusions. As previously reported, our study confirmed the occurrence of NRG1 fusions in NSCLC, breast cancer, cholangiocarcinoma, ovarian cancer, and pancreatic cancer with a low overall incidence. Here, we also detected NRG1 fusions in colorectal cancer, sarcoma, and a neuroendocrine tumor of the nasopharynx, which had not been previously reported. In this report, the majority of these tumors (70%) were adenocarcinoma. NRG1 fusions in NSCLC had been described more frequently in the invasive mucinous adenocarcinoma subtype; in this series, 32% (8/25) of the NRG1+ NSCLC cases had a mucinous histology or a mucinous component (Table 1). The use of broad molecular profiling in this series was based on clinician discretion and may be influenced by patient and tumor characteristics. Thus, the actual incidence may not be entirely representative of the general population. Despite these shortcomings, the detection of such rare genetic alterations across different tumor types supports broader use of NGS.

The specific NRG1 fusion partners are variable within and across tumor types (11–15, 20). Several novel fusion partners detected in this report include TNC, MRPL13, MDK, and DIP2B in NSCLC. Previous reports suggest fusion partners may influence localization of NRG1 to the plasma membrane (20), although the exact significance remains unclear, and the variety of partners observed may introduce challenges for widespread detection efforts. Splice junctions of all candidate NRG1 fusions were analyzed to predict likelihood to encode functional proteins. Most were predicted to be in-frame; however, a recurrent novel fusion class was identified whereby exon 2 of NRG1 is spliced to upstream
noncoding exons of fusion partner genes. In each of these cases \((n = 4; \text{Supplementary Table S1})\), a codon encoding for methionine is present a short distance into exon 2 of \(NRG1\) that could potentially act as a translation initiation codon; if functional, the fusion partner could be providing the promoter for a likely N-terminal truncated version of \(NRG1\). These observations are consistent with similar studies where \(NRG1\) fusion variants included chimeric proteins and cases where expression of \(NRG1\) is controlled by the promoter of the 5' partner \((21)\). Alternative methodologies are needed to confirm expression of the transcripts identified in this study to determine their significance.

Additional studies describing \(NRG1\) fusions suggest these events are mutually exclusive with other known molecular drivers \((14)\). This was consistent with the findings in this report. Specifically, all NSCLC cases were ALK, ROS, RET fusion–negative, and KRAS wild-type, and all pancreatic adenocarcinomas were KRAS wild-type. The exception was one colorectal cancer case that also harbored a KRAS G12D mutation. The remainder of the cases studied harbored several pathogenic variants in tumor suppressor genes including TP53 and DNA damage and response genes \((CHEK2, BRCA2, WRN)\).

\(NRG1\) fusions are detected in a variety of tumor types. In 2014, Fernandez-Cuesta and colleagues first described the \(CD74–NRG1\) fusion partners. Pie chart showing the proportion and variety of fusion partners for \(NRG1\).

Figure 3.

Circos plot depicting \(NRG1\) fusion genes and partners from Supplementary Table S1. \(NRG1\) and partners in NSCLC \((A)\) and all other tumors \((B)\). chr, chromosome.

Figure 4.
gene fusion in five female never-smokers whose tumors lacked known activating mutations (10). As comprehensive molecular profiling and RNA sequencing has become more prevalent, NRG1 fusions have been detected in a variety of other tumor types, including breast, ovarian, and pancreatic cancer (14, 15). Analysis of MSK-IMPACT dataset including NGS and the MSK solid fusion assay identified 10 patients with NRG1 fusions (out of 17,485 tested): seven in lung adenocarcinoma, two in pancreatic cancer, and one in breast cancer. Further analysis with RNA sequencing revealed additional fusions in other tumor types including ovarian cancer, uterine carcinosarcoma, renal clear cell carcinoma, prostate cancer, and head and neck cancer (9).

As NRG1 alterations activate the ERBB2/ERBB3 signaling pathway, targeted treatment with inhibitors of this pathway is an appealing therapeutic strategy. Dual targeting of ERBB2 and ERBB3 has also been evaluated in preclinical models (22, 23). Afatinib, a pan-ERBB inhibitor, was successfully utilized in this manner, and several patients with tumor harboring an NRG1 fusion achieved durable benefit with afatinib (11–13). Response to an ERBB3 mAb, GSK2849330, has also been reported (9). Combining an ERBB3 mAb and an EGFR tyrosine kinase inhibitor was also effective in a small case series (24). Prospective studies are needed to define the role of targeted therapy for patients with tumors harboring NRG1 fusions, but these data suggest that NRG1 fusions represent a novel potential target across many tumor types that warrant further study.

Disclosure of Potential Conflicts of Interest

W. M. Korn is a consultant/advisory board member for Merck Sharp & Dohme. H. Bonghari reports receiving commercial research grants from Bristol-Myers Squibb and Lilly, and is a consultant/advisory board member for Bristol-Myers Squibb, Lilly, AstraZeneca, Merck, Genentech, Regeneron, Celgene, Genmab, Amgen, EMD Serono, Boehringer Ingelheim, and Takeda. P. C. Ma reports receiving speakers bureau honoraria from AstraZeneca.
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Merck, Bristol-Myers Squibb, Bayer, and Takeda, and is a consultant/advisory board member for AstraZeneca, Apollomics, and Caris Life Sciences. A.J. Spira is a consultant/advisory board member for Foundation Medicine. A.M. Vanderwalde reports receiving commercial research grants from Arogen and Caris Life Sciences, and is a consultant/advisory board member for Apollomics, Bristol-Myers Squibb, Genentech, CompuGen, and Immunocore. A.J. Wozniak reports receiving commercial research grants from Boehringer Ingelheim and Genentech, and is a consultant/advisory board member for AstraZeneca, Boehringer Ingelheim, Takeda, Coherus, Karyopharm, Premier, HIYIA Bioscience, and BeyondSpring. S.V. Liu reports receiving commercial research grants from AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Clovis, ExaneX, Genentech/Roche, Ignyta, Lilly, Lyceer, Merck, Molecular Partners, OncoMed, Pfizer, Rain Therapeutics, and Threshold, and is a consultant/advisory board member for Apollomics, AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech/Roche, Heron, Ignyta, Janssen, Lilly, Merck, Pfizer, Regeneron, Taiho, Takeda, and G1 Therapeutics. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: S. Jonna, R.A. Feldman, Z. Gatalica, A.M. Vanderwalde, S.V. Liu


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Jonna, R.A. Feldman, Z. Gatalica, H. Borphaci, P.C. Ma, J.I. Nieva, A.M. Vanderwalde, A.J. Wozniak, S.V. Liu


Writing, review, and/or revision of the manuscript: S. Jonna, R.A. Feldman, Z. Gatalica, W.M. Korn, H. Borphaci, P.C. Ma, J.I. Nieva, A.I. Spira, A.M. Vanderwalde, A.J. Wozniak, E.S. Kim, S.V. Liu

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Jonna, R.A. Feldman, J. Swensen, S.V. Liu

Study supervision: A.M. Vanderwalde, S.V. Liu

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