Review

RET Gene Fusions in Malignancies of the Thyroid and Other Tissues

Massimo Santoro 1,*, Marialuisa Moccia 1, Giorgia Federico 1 and Francesca Carlomagno 1,2

1 Department of Molecular Medicine and Medical Biotechnology, University of Naples “Federico II”,
80131 Naples, Italy; lisa.moccia@hotmail.it (M.M.); giorgia.federico@libero.it (G.F.);
francesca.carlomagno@unina.it (E.C.)
2 Institute of Endocrinology and Experimental Oncology of the CNR, 80131 Naples, Italy
* Correspondence: massimo.santoro@unina.it

Received: 10 March 2020; Accepted: 12 April 2020; Published: 15 April 2020

Abstract: Following the identification of the BCR-ABL1 (Breakpoint Cluster Region-ABelson murine
Leukemia) fusion in chronic myelogenous leukemia, gene fusions generating chimeric oncoproteins
have been recognized as common genomic structural variations in human malignancies. This is,
in particular, a frequent mechanism in the oncogenic conversion of protein kinases. Gene fusion
was the first mechanism identified for the oncogenic activation of the receptor tyrosine kinase
RET (REarranged during Transfection), initially discovered in papillary thyroid carcinoma (PTC).
More recently, the advent of highly sensitive massive parallel (next generation sequencing, NGS)
sequencing of tumor DNA or cell-free (cfDNA) circulating tumor DNA, allowed for the detection of
RET fusions in many other solid and hematopoietic malignancies. This review summarizes the role
of RET fusions in the pathogenesis of human cancer.

Keywords: kinase; tyrosine kinase inhibitor; targeted therapy; thyroid cancer

1. The RET Receptor

RET (REarranged during Transfection) was initially isolated as a rearranged oncoprotein upon
the transfection of a human lymphoma DNA [1]. The RET gene maps on human chromosome
10 (at q11.21) [2] and codes for the functional tyrosine-kinase receptor (RTK) of GDNF (glial cell
line-derived neurotrophic factor), Neurturin (NRT), Artemin (ART), and Persephin (PSF) growth
factors [3–7]. These growth factors bind to auxiliary membrane-bound co-receptors, named GFR-
s (GDNF family receptor- [1–4]), thereby forming a bipartite complex that, in turn, mediates RET
dimerization and activation [8]. In humans, mutations of this ligand-receptor system cause intestinal
aganglionosis with congenital megacolon (Hirschsprung disease) and congenital defects of kidney and
urinary tract [9].

Structurally, the RET protein is composed by an extracellular (EC), a transmembrane (TM), and
an intracellular (IC) portion (Figure 1). RET-EC contains 4 cadherin-like (CLD) and one cysteine-rich
(CRD) domains, that are involved in binding to the bipartite ligand [8]. RET-IC contains the tyrosine
kinase domain (TKD) that is split into two subdomains [7,10]. This is followed by a C-terminal tail
that is subject to alternative splicing generating different isoforms, the most abundant being RET9 and
RET51 (depending whether they contain 9 or 51 residues starting from glycine 1063 in exon 19) [3].
Figure 1. Representative scheme of RET and its fusion partners. (A) Representation of RET fusion protein partners. Arrows indicate the most frequent breakpoint sites in partner proteins. The number under each protein domain refers to the protein domain legend (Table 1). Coiled-coil domains are very numerous and, therefore, are represented as light green boxes without number. (B) Representation of the RET protein. Arrow indicates the most frequent breakpoint site in RET.

Upon activation, several tyrosine residues of RET-IC undergo phosphorylation and mediate intracellular signal transduction. Thus, tyrosines Y900, Y905, Y981, Y1015, Y1062, and Y1096 (this one is specific for RET51) have been involved in functional RET signaling. Phosphorylated tyrosine 1062 (Y1062), in particular, recruits a multitude of adaptors such as SHC1/3, FRS2, IRS1/2, and DOK1/4/5 that, in turn, mediate the activation of RAS (Rat Sarcoma)-MAPK (Mitogen-Activated Protein Kinases) and PI3K (Phosphatidylinositol-3 Kinase)-AKT (Protein Kinase B) pathways [3–7].

2. RET Oncogenic Conversion in Human Neoplasms

Different RET molecular lesions have been described in tumors at either germline or somatic levels. These include gene amplification, fusion, as well as single base substitutions/small insertions/deletions either in sequences encoding RET-EC or -IC. Germline or somatic single base substitutions/small
insertions/deletions in RET are characteristic of sporadic or familial (MEN2—multiple endocrine neoplasia type 2 associated) medullary thyroid carcinoma (MTC), respectively. Instead, RET fusions, occurring at the somatic level, are typical of papillary thyroid carcinoma, lung adenocarcinoma, and few other cancers. This notion has made RET an attractive molecular target for small molecule tyrosine kinase inhibitors (TKI) [11–14]. In this frame, novel selective RET TKIs have featured promising results in clinical investigation [14,15].

For a fully comprehensive description of the role played by RET in cancer, the reader is referred to other Reviews published on the topic (see References [4–7,16–18]). Moreover, comprehensive annotation of RET genetic lesions in cancer are provided by TCGA PanCancer, AACR GENIE, and MSKCC projects [19–21].

This review addresses, in particular, the role of RET gene fusions in cancer. Table 1 lists RET fusions so far described and Figure 1 depicts the protein structure of RET and its fusion partners.

| Fusion 1 (Alternative Name) | Features of the 5'-Terminal Fusion Partner | Neoplasm 3 | Reference |
|----------------------------|-------------------------------------------|-----------|-----------|
| ACBD5-RET                  | ABCD5 ABCP (1), TM (2), CC                | PTC       | [22]      |
| AFAPI12-RET                | AFAPI12 (XI130) PH (3), CC                | PTC       | [23]      |
| AKAP13-RET                 | RII binding (4), Rho GEF (5), PH (3), CC | PTC       | [24]      |
| ANKRD26-RET                | ANK (6), CCDC144C (7), CC                | PTC       | [25]      |
| BCR-RET                    | BcR-Abl oligo (8), Rho GEF (5), C2 (9), Rho GAP (10), TM (2), CC | 22q11.23 | CMML [26] |
| CDC123-RET                 | D123 (11)                                | LADC      | [27]      |
| CCDC6-RET (RET/PTC1)       | CCDC6 (H4) DUF (12), CC                 | 10q21.2   | PTC, PTC, LADC, BRCA, SCT, CRC, STAD [21,28–35] |
| CLIP2-RET                  | CLIP2 CAP-Gly (13), CC                  | 7q11.23   | SCT, LPF  [31,36] |
| CUX1-RET                   | CUX1 CUT/CUT (14), Homeobox (15), CC    | 7q22.1    | LADC      [37] |
| DLG5-RET                   | DLG5 Takusan (16), PDZ (17), dbPDZ (18), GuKc (19), CC | 10q22.3 | PTC [38] |
| EPHA5-RET                  | -                                         | 4q13.1/2  | LADC [39] |
| ERC1-RET                   | ERC1 (ELKS) Cast (20), RBD FIP (21), CC | 12p13.33  | PTC, BRCA [38,40,41] |
| ETL4-RET                   | KIAA1217 AIP (22), CC                   | 10p12.1/2 | SCT, LPF, IC [36] |
| ETV6-RET                   | ETV6 (TEL) SAM PNT (23), ETS (24)       | 12p13.2   | SC [42] |
| FGFR1OP-RET                | FGFR1OP (FOP) FOP dimer (25)            | 6q27      | CMML, PMF [26] |
| FKBP15-RET                 | FKBP15 FKBP (26), CC                    | 9q22      | PTC [24] |
| FRMD4A-RET                 | FRMD4A FERM (27), DEF (12), CC          | 10p13     | LADC [43] |
| GEMIN5-RET                 | GEMIN5 WD40 (28), ANAPC4 WD40 (29), CC  | 5q33.2    | CRC [35] |
| GOLG5-RET (RET/PTC5)       | GOLG5 (RFC5) Golgin A5 (30), TM (2), CC | 14q32.12  | PTC, SN [44,45] |
| HOOK3-RET                  | HOOK3 HOOK (31), CC                    | 8p11.21   | PTC       [46] |
| KHDBRBS1-RET               | -                                         | 1p35.2    | IPS-like  [36] |
| KIAA1468-RET               | KIAA1468 (RELCH) LisH (32), HEAT (33), CC | 18q21.33 | IMA, PTC [25,47,48] |

Table 1. RET (REarranged during Transfection) gene fusions in human neoplasms.
| Fusion 1 (Alternative Name) | Features of the 5’-Terminal Fusion Partner | Neoplasm 3 | Reference |
|-----------------------------|-------------------------------------------|-----------|-----------|
| KIF13A-RET KIF13A Kinesin (34), Kinesin-eng (35), FHA (36), KIF1B (37) GuKc (19), CC | KIF13A | 6p22.3 | LADC [49] |
| KIF5B-RET KIF5B Kinesin (34), CC | KIF5B | 10p11.22 | LADC, AS, SN [29,44,50–52] |
| KTNI-RET (RET/PTC8) KTNI (RFG8) CC | KTNI | 14q22.3 | PTC [53] |
| MYH10-RET MYH10 Myosin N (38), Myosin head (39), IQ (40), Myosin tail (41), CC | MYH10 | 17p13.1 | IM, SCT [31,36,54] |
| MYH13-RET MYH13 Myosin N (38), Myosin head (39), Myosin tail (41), CC | MYH13 | 17p13.1 | MTC [55] |
| MYO5A-RET MYO5A Myosin head (39), IQ (40), DUF (12), CC | MYO5A | 15q21.2 | PSCN [56] |
| MYO5C-RET MYO5C Myosin head (39), IQ (40), TM (2), DUF (12), CC | MYO5C | 15q21.2 | LADC [57] |
| NCOA4-RET (RET/PTC3) NCOA4 (RFG, ELE1, ARA70) ARA70 (42), CC | NCOA4 | 10q11.22 | PTC, PDTC, LADC, BCRA, IC, SCT, CRC [27,30–35, 52,58–63] |
| PCM1-RET PCM1 PCM1 C (43), CC | PCM1 | 8p22 | PTC [64] |
| PDCD10-RET PDCD10 - | PDCD10 | 3q26.1 | PDTC [21] |
| PICAM-RET PICAM - | PICAM | 11q14.2 | LADC [39] |
| PPTF2-RET PPTF2 SAM PNT (23), CC | PPTF2 | 11p15.4 | PTC [23] |
| PRKAR1A-RET (RET/PTC2) PRKAR1A Rfia (44), cNMP (45), CC | PRKAR1A | 17q24.2 | PTC [65] |
| RASGEF1A-RET (ARRET) 2 RASGEF1A RAS GEF N (46), RAS GEF (47), CC | RASGEF1A | 10q11.21 | BRCA [32] |
| RASSF4-RET RASSF4 RA (48), Norel-SARA (49), CC | RASSF4 | 10q11.21 | LADC [21] |
| RET-RET 3 RET CLD1-4 (50), TM (2), TK (51) | RET | 10q11.21 | BRCA [32] |
| RRBP1-RET RRBP1 TM (2), Rib recep KP reg (52), CC | RRBP1 | 20p12.1 | CRC [66] |
| RUFY2-RET RUFY2 RUN (53), FYVE (54), CC | RUFY2 | 10q21.3 | LADC, PTC [67,68] |
| SNRP70-RET SNRP70 U1snRNP70 N (55), RRM 1 (56), CC | SNRP70 | 19q13.33 | CRC [34] |
| SPECC1L-RET SPECC1L CH (57), CC | SPECC1L | 22q11.23 | PTC, LPF, LPF-NT [24,31] |
| SQSTM1-RET SQSTM1 - | SQSTM1 | 5q35.3 | PTC [69] |
| TBC1D32-RET TBC1D32 BROMI (58), TM (2), CC | TBC1D32 | 6q22.31 | LADC [70] |
| TBL1XR1-RET TBL1XR LeSH (32), WD40 (28) | TBL1XR | 3q26.32 | PTC [24] |
| TFG-RET TFG PB1 (59), CC | TFG | 3q12.2 | PDTC, SCT, LPF [21,71] |
| TNIP1-RET TNIP1 UBD (60), CC | TNIP1 | 5q33.1 | CRC [34] |
| TRIM24-RET (RET/PTC6) TRIM24 zf-B box (61), PHD (62), Bromodomain (63), CC | TRIM24 | 7q32-34 | PTC, LADC, CRC [34,67,72] |
| TRIM27-RET TRIM27 (RFP) zf-C3HC4 4 (64), zf-B box (61), PRY (65), SPRY (66), CC | TRIM27 | 6p22.1 | PTC, IC [24,59,60] |
Table 1. Cont.

| Fusion (Alternative Name) | Features of the 5'-Terminal Fusion Partner | Neoplasm | Reference |
|---------------------------|---------------------------------------------|----------|-----------|
| TRIM33-RET (RET/PTC7)     | TRIM33 zf-RING UBOX (67), zf-B box (61), PHD finger (62), Bromodomain (63), CC | PTC, LADC | [72,73] |
| UEVLD-RET                 | UEVLD UEVLD (68), LDH1 (69)                 | 11p15.1  | PTC       | [74] |
| VCL-RET                   | VCL VINC (70), CC                          | 10q22.2  | LPF       | [75] |
| WAC-RET                   | WAC WW (71), CC                            | 10p12.1  | LADC      | [76] |
| ZNF485-RET                | ZNF485 KRAB (72), ZF-C2H2 (73)              | 10q11.21 | BRCA      | [32] |

1. Some RET fusions (EPHAS-RET, KHDDB51-RET, PICALM-RET, SQSTM1-RET) are listed here but not reported in Figure 1 because of the lack of information about the involved exon. Moreover, additional RET fusion partners have been recently listed but without molecular details: CLIP1 and PRKG1 (15) and EML4 and PARD3 (14). 2. The involved R2 variants (Rat Sarcoma GTPase Exchange Factor) portion (5'-UTR) in; thus, this fusion generates a truncated RET (AR) protein starting at a cryptic ATG site in RET exon 11. 3. These rearrangements result in tandem duplications fusing one copy of RET (exons 1–20) to a second copy of RET starting from exon 7, 9, or 12. 4. Protein domains legend (PFAM, https://pfam.xfam.org/) (domains are numbered as in Figure 1): (1) ACBP: Acyl CoA binding protein; (2) TM: transmembrane domain; (3) PH: PH domain; (4) MTHK: methyl-thio-ketone; (5) RIK: RIK binding domain; (6) RhoGEF: Guanine nucleotide exchange factor for Rho/Rac/Cdc42-like GTPases; (7) ANK: ankryin repeat domain; (8) Bcr-Ab1 oligo Bcr-Ab1 oligomerization domain; (9) C2: C2 domain; (10) Rho GAP: GTPase activator proteins towards Rho/Rac/Cdc42-like small GTPases; (11) D123; (12) DUF: Domain of unknown function; (13) CAP-Gly: Calponin-like domain of cytoskeleton-associated proteins (CAPs); (14) CUT-CUT (also known as ONECUT domain), DNA-binding motif; (15) Homeobox: homeobox domain or homeodomain; (16) Trans: in Japanese ‘many’, found in protein regulating synaptic activity; (17) PDZ: Post synaptic density protein, Drosophila disc large tumor suppressor, and zona occludens-1 protein domain; (18) dbPDZ: PDZ-associated domain; (19) CuPc: Guanlylate kinase homology domain; (20) Cast: Ram-binding protein of the cytofemix active zone; (21) RBD-FIP: Rab11-binding domain (RBD) at the C-terminus of a family of Rab11-interacting proteins (FIPs); (22) AIP: Actin-interacting protein; (23) SAM: Sterile alpha motif (SAM)/Pointed domain; (24) ETS: erythroblast transformation specific domain; (25) FOP: Dimers. 7. 70 kDa MW N terminal domain; (26) FKB: FKB-type peptidyl-prolyl cis-trans isomerase domain; (27) FERM: FERM domain (4.1 protein, Ezrin, Radixin and Moesin); (28) WD40: WD40 repeat (also known as the WD and beta-transducin repeat); (29) ANAPC: Anaphase-promoting complex subunit 4 WD40 domain; (30) Golgin A5: Golgin subfamily A member 5 domain; (31) HOOK: HOOK domain; (32) LissH: Lissencephaly type-1 like homology motif; (33) HEAT: HEAT repeat tandem repeat structural motif (Huntingtin, Elongation factor 3, Phosphatase 2A, and the yeast kinase TOR); (34) Kinesin: Kinesin motor domain; (35) Kinesin-as: Kinesin-associated domain; (36) FHA: Forkhead associated domain; (37) KIF1B: Kinesin protein 1B domain; (38) Myosin N: Myosin N-terminal SH3-like domain; (39) Myosin head: motor domain; (40) IQ: IQ calmodulin-binding motif; (41) Myosin tail: Myosin tail domain; (42) ARA70: Androgen Receptor Activator 70; (43) PCMI C: Pericentriolar material 1 C terminus domain; (44) RIIa: Regulatory subunit of type II PKA R-subunit; (45) cNMP: Cyclic nucleotide-binding domain; (46) RAS GEF: Guanine nucleotide exchange factor for Rho/Rac/Cdc42-like GTPases; (47) TCF: Transcription factor for Rho family Pleckstrin homology (PH) domain; (48) RII Binding domain; (49) RhoGEF: Guanine nucleotide exchange factor for Rho/Rac/Cdc42-like GTPases; (50) ANK: ankyrin repeat domain; (51) Myosin head: motor domain; (52) Myosin head: motor domain; (53) Myosin head: motor domain; (54) Myosin head: motor domain; (55) Myosin head: motor domain; (56) RRM 1: RNA recognition motif; (57) CH: Calponin homology domain; (58) zf-B box (61), PHD finger (62), Bromodomain (63), CC |
3. Functional Consequence of RET Gene Fusions

RTK fusions in cancer may either result in the juxtaposition of a N-terminal partner to the C-terminal portion of the RTK, including its catalytic domain (so called 3’ kinase fusion), or, vice versa, of the N-terminal portion of the RTK, with its catalytic domain, to the C-terminal of a fusion partner (5’ kinase fusion) [77]. In both cases, the retention of an intact kinase domain in the fusion product is essential to distinguish cancer-driving RTK fusions from random chimeric products secondary to genetic instability [77]. 3’ kinase fusions are the most common; however, examples of 5’ kinase fusions have also been described, such as FGFR2 and FGFR3 (fibroblast growth factor receptors) fusions in cholangiocarcinoma and other malignancies [78] as well as the EGFR (epidermal growth factor receptor)-RAD51 (Radiation-sensitive 51) and -PURB (Purin Rich Beta) fusions in lung cancer [79]. One argument supporting the selection of 3’ kinase fusions in cancer may be that this type of fusion is able to move the kinase domain under the control of the transcriptional promoter of the fusion partners, thus fostering aberrant kinase overexpression (see also below) [77]. The cancer-associated RET fusions described so far are of the 3’ kinase fusion type, involving a 5’-terminal partner coding sequence fused to the 3’-terminal RET kinase domain coding sequence. Breakpoints in RET and its fusion partners typically occur in intronic regions and are able to preserve, upon mRNA splicing, an open reading frame. Most commonly, secondary to a breakpoint in RET intron 11, the RET coding sequence from exon 12 to the STOP codon is included in the fusion. However, in rare instances, the fusion product starts from RET alternative exons, such as exon 3, 7, 9 (EC portion), 10 (TM: transmembrane segment), or 11 (IC portion).

RET gene fusions lead to kinase activation, in turn augmenting signal transduction along classical pathways such as the MAPK and the PI3K/AKT ones [4,5,80]. This causes gain of RET oncogenic activity, as shown for the most frequent fusions (CCDC6-RET, NCOA4-RET, KIF5B-RET) using cell-based assays as well as constitutive or conditional transgenic mouse models [28,29,50,51,81–84]. Various mechanisms may contribute to fusion-mediated RET activation, including: (i) as mentioned above, the increased kinase expression, due to the replacement of the 5’-upstream RET promoter, that is normally active mainly in neuronal cell lineages, with that of the fusion partners [85], and (ii) the dimerization/oligomerization of the RET kinase domain mediated by protein–protein interaction motifs, typically coiled-coil domains, present in the fusion partners, that leads to ligand-independent kinase activation [65,86]. In addition, loss of autoinhibitory N-terminal portions and the altered conformation of the rearranged kinase may also contribute to RET kinase activation [87].

Besides the aberrant expression and the gain of intrinsic RET kinase activity, it is possible that other mechanisms contribute to the oncogenic role of RET fusions. First, the altered intracellular localization, due to the loss of the RET signal peptide and TM, may participate to RET transforming ability, for example by facilitating rearranged RET coupling to intracellular signal transducers. In addition, the RET fusion partner may act as a protein–protein interaction platform able to modify RET kinase-substrate(s) binding. Accordingly, in the KIF5B (Kinesin-1 heavy chain)-RET fusion, commonly found in lung carcinoma (see below), the N-terminal KIF5B backbone, containing the kinesin motor domain, was demonstrated to activate, through RAB GTPase vesicles, multiple RTKs, including EGFR and FGFR, and their downstream signaling [88]. Furthermore, the interaction of the chimeric RET kinase with another RTK may potentiate signaling and reduce efficacy of RET-targeted TKIs. In this frame, it has been shown that the physical interaction between CCDC6-RET and the EGFR facilitates signaling and reduces efficacy of RET kinase inhibition in a lung cancer cell line [89]. Finally, the concurrent altered function of the RET fusion partner may also contribute to neoplastic transformation. Accordingly, several RET fusion partners have been shown to exert relevant homeostatic functions (Table 1). PRKAR1A, one of the RET fusion partners, is the tumor suppressor protein involved in inheritance of Carney complex, a tumor-prone syndrome [90]. Similarly, another RET fusion partner, NCOA4, is a multifunctional protein that is involved in the regulation of DNA synthesis by inhibiting replication origin activation. Alteration of such a function in tumors harboring the NCOA4-RET fusion may contribute to its oncogenic activity [91]. Finally, CCDC6 exerts proapoptotic and DNA damage response activities.
Genes 2020, 11, 424

and perturbation of these functions may participate to the oncogenic role of the corresponding RET fusion [92].

4. Genomic Mechanism of RET Gene Fusions

Different inter-chromosomal (translocations) or intra-chromosomal (inversions, tandem duplications, and interstitial deletions) structural variations can result in gene fusion events [87,93]. As discussed below, the most common RET fusions, in papillary thyroid carcinoma (PTC) and in lung adenocarcinoma (LADC) are CCDC6-RET and NCOA4-RET (primarily in PTC) and KIF5B-RET (primarily in LADC). CCDC6 and NCOA4 genes both map on the long arm of chromosome 10, at 10q21.2 or 10q11.22, respectively (Table 1). RET (that maps at 10q11.21) is transcribed in an opposite orientation with respect to CCDC6 and NCOA4. Thus, a 10q paracentric (not including the centromere, e.g., with both breakpoints in the same chromosome arm) inversion is the plausible genomic mechanism underlying CCDC6-RET and NCOA4-RET fusions [94]. Instead, KIF5B maps at 10p11.22; therefore, a pericentric (including the centromere, e.g., with a breakpoint in each chromosome arm) inversion of chromosome 10 is the mechanism of KIF5B-RET fusion (Table 1) [29,50,51,95]. In principle, inversions may be reciprocal (both fusion products) or nonreciprocal (only one fusion product). While in PTC, the majority of the inversions were reciprocal, in LADC, nonreciprocal inversions have also been documented [95].

RET gene fusions are thought to occur secondary to DNA double-strand breaks (DSB) followed by illegitimate repair of the two unrelated genes [13,18,95,96]. DNA repair mechanisms that can be responsible include NHEJ (nonhomologous end joining), which requires no homology or just very short homology sequences and inserts a few nucleotides at the fusion point, and BIR (break-induced replication), that instead requires long homology DNA stretches [95,96]. Sequencing of RET breakpoints in LADC suggested that both mechanisms can be involved, while, at least in radiation-associated PTC, NHEJ was the prevalent one [95,97].

In turn, DSBs can be induced by endogenous sources of DNA damage, such as reactive oxygen species (ROS) and replication stress, or exogenous sources, such as ionizing radiation (IR), see also below [98,99]. Chromosomal fragile sites are DSB-prone genome regions, in particular, under conditions that reduce DNA replication or upon the exposure to several chemical agents. It is worth noting that RET and NCOA4 are located within the fragile site FRA10G, and CCDC6 is located within the fragile site FRA10C, a fact that may facilitate their rearrangement [100–103]. Moreover, breakpoints in RET intron 11 map close to DNA topoisomerase 1/2 predicted cleavage sites, suggesting that DNA topoisomerases may play a role in RET fusion events [102]. Accordingly, during replication and transcription, DNA is unwound by DNA helicase, resulting in torsion that can be removed by topoisomerases through transient introduction of DNA breakage, thus potentially favoring gene rearrangements in cancer cells [102]. Finally, tissue-specific organization of chromatin territories may affect the frequency as well as the specificity of RET fusion with specific gene partners. In this frame, the overlap in thyrocyte interphase chromatin of CCDC6, NCOA4, and RET loci is important to favor their fusion [100].

Chromoplexy occurs when several DSBs are generated at the same time in different chromosomes. This is followed by chains of rearrangements, resulting in the simultaneous shuffling of several chromosomal fragments. Chromoplexy is typically found in prostate carcinoma and lymphoid malignancies [93]. However, in the recent pan-cancer analysis of whole genomes, it was found that 4 of the 13 fusion genes identified in thyroid carcinoma, including 2 RET fusions, were caused by chromoplexy [93].

5. RET Gene Fusions in Thyroid Carcinoma

Papillary thyroid carcinoma (PTC) is the most common (~80%) malignancy of the thyroid gland. PTC was the first human cancer to be consistently associated to RET fusions (so called RET/PTC rearrangements) (Table 1) [28,104]. Overall, gene fusion is a common genomic structural variation in PTC, targeting, besides RET, several other kinases, such as NTRK1, NTRK3 (N Tropomyosin Receptor
Kinase), ALK (Anaplastic Lymphoma Kinase), HGFR (Hepatocyte Growth Factor Receptor), and BRAF (B Rapidly Accelerated Fibrosarcoma) [19,77].

The most common RET fusions in PTC are CCDC6-RET (also named RET/PTC1) and NCOA4-RET (also named RET/PTC3), accounting for about 90% of RET fusion-positive cases [80]. CCDC6 (coiled-coil domain containing 6) was formerly known as H4 or D10S170 and NCOA4 (nuclear coactivator 4) was formerly known as ELE1, RFG, or ARA70 (Table 1). Although alternative breakpoints have been described, the breakpoint cluster region typically maps in RET intron 11, in CCDC6 intron 1, and in NCOA4 intron 8 (Figure 1) [24].

PTC is typically associated with lesions in genes causing unscheduled activation of the MAPK (mitogen-activated protein kinase) cascade. Indeed, besides RET and other RTKs, common PTC-driver events are represented by gain-of-function mutations of RAS small GTPases, and, most commonly, BRAF kinase. The mutually exclusive nature of these lesions supports the notion they act along a common signaling mechanism [104]. In the TCGA study, RET-, similarly to BRAF-positive samples, were “classic” papillary cases, whereas RAS-positive samples typically featured the follicular variant phenotype [24].

RET fusions occur in ~10%–20% of sporadic PTCs [15,18]. In the TCGA study, enrolling almost 500 PTC samples, ~6.8% of cases harbored a RET fusion [24]. RET fusions are more common in radiation-associated than in “sporadic” cases. Several evidences support the possibility that both internal (to 131I and other isotopes) and external irradiation may favor these genomic events [105]. In 1986, large amounts of 131I and other isotopes, released by the Chernobyl nuclear power plant, contaminated regions of Belarus, Russia, and Ukraine, thus resulting in a sharp PTC incidence increase in children and adolescents. In one study, ~58% of post-Chernobyl PTCs in patients who were <10 years old at the time of the accident harbored a RET fusion [106]. Prevalence of RET fusions tended to decline after a longer interval from the nuclear accident [16,107]. Moreover, as many as 50% of PTCs in atomic bomb survivors, who were exposed to high radiation doses (>0.5 Gy), harbored RET fusions [108]. Accordingly, RET fusions occur dose-dependently upon irradiation with or X-ray thyrocytes in culture [24,98,109].

RET fusions have been reported more commonly (and the BRAFV600E mutation more rarely) in pediatric than in adult thyroid cancer patients [16,110,111]. In young patients, the NCOA4-RET fusion occurred more commonly in radiation-associated, particularly in early cases, while CCDC6-RET was more common in “sporadic” cases [112].

RET fusions are uncommon in thyroid cancer subtypes other than PTC [104]. FTC (follicular thyroid carcinoma), the other major type of differentiated thyroid cancer, is generally negative for RET fusions [80]. PDTC (poorly differentiated thyroid carcinoma) and ATC (anaplastic thyroid carcinoma) may derive from pre-existing differentiated carcinomas, including PTC. In the analysis of large databases (more than 60,000 tumor samples), RET fusions were found in 13/560 (2.32%) and 36/500 (7.2%) PTC cases, 1/107 (0.93%) ATC cases, and 6/134 (4.47%) PDTC cases [18]. Similarly, in a recent study, 5.9% of PDTC but no ATC harbored RET rearrangements, suggesting that RET fusion-positive PTCs rarely progress to ATC [30].

As mentioned above, the most typical oncogenic drivers of MTC, a thyroid carcinoma arising from C-cells, are RET point mutations, both in sporadic and familial cases [4–7,16–18]. It is worth noting that RET is normally expressed in C-cells and therefore, its oncogenic conversion does not need the acquisition of a novel transcriptional promoter caused by a gene fusion. However, one MTC case harboring a RET fusion, MYH13-RET, has been recently reported [55].

In terms of the clinical relevance of RET fusions in thyroid cancer, besides the possible therapeutic use of RET TKIs, it should be noted that fine-needle aspiration cytology is commonly used for pre-operative assessment of thyroid nodules, though it is unable to reach a definitive diagnosis in up to 25% of the cases. In these cases, molecular diagnostic methods have been developed to help diagnosis by determining the presence of different oncogenic mutations, including RET fusions [113].
6. RET Gene Fusions in Non-Small Cell Lung Cancer

RET fusions occur in 1%–2% of lung carcinoma, predominantly in adenocarcinoma (LADC) but also in rare types such as adenosquamous carcinoma [13,17,18,29,50–52,114–116]. In the same analysis of large databases described above, RET fusions were found in 0.35%–0.88% of LADC (n = 9088) [18]. The most common RET fusions in NSCLC are KIF5B-RET, NCOA4-RET, and CCDC6-RET. KIF5B (Kinesin-1 heavy chain) is by far the most common RET fusion partner in NSCLC, being detected in up to 70%–90% of the cases (Figure 1, Table 1) [17]. The breakpoint cluster region in KIF5B may occur in several introns, most commonly in intron 15 [95]. In NSCLC, RET fusions are mutually exclusive with other driver mutations, such as ALK or ROS1 rearrangements or EGFR or KRAS mutations, once again suggesting common signaling mechanisms [13,116].

In LADC, RET fusions are reported to be associated with young age (<60 years), female gender, Asian ethnicity, and minimal tobacco exposure [17]. RET fusions were also associated with poor differentiation, solid subtype, presence of signet ring cells, small tumor size, early lymph node metastases, low levels of PD-L1 expression, and poor response to immunotherapy [13,15,17]. In vitro irradiation with -rays generated KIF5B-RET fusion in lung cells, thus pointing, similar to thyroid cancer, to radiation as a possible risk factor for RET fusion in lung cancer [117].

Clinically, there is strong interest in RET TKIs for the targeted treatment of NSCLC [11–15,114]. Interestingly, RET fusions (CCDC6-RET, NCOA4-RET, and the newly described CDC123-RET) have been reported as an acquired resistance mechanism of LADC to EGFR or ALK tyrosine kinase inhibitors [118–120].

7. RET Gene Fusions in Other Malignancies

In the metaanalysis reported by Kohno [18], RET fusions were found in 0.7% of total samples, including cancers other than thyroid and lung ones, such as breast (0.00%–0.21%), colon (0.00%–0.26%), esophageal (0.00%–0.17%), ovarian (0.00%–0.17%), prostate (0.08%), and stomach (0.81%) carcinoma, as well as acute myeloid leukemia (0.00%–0.50%) and very rare cancers such as anaplastic ganglioglioma (a rare CNS tumor of children and young adults), and Erdheim–Chester Disease (a rare form of non-Langerhans cells histiocytosis). In another study, RET fusions were found in 0.6% (27 out of 4871) patients with different malignancies (besides thyroid and lung carcinoma), including ovarian and salivary gland carcinomas [69]. In a further study of nearly 33,000 cases of circulating free tumor DNA (cfDNA) from metastatic patients, RET fusion events were identified in NSCLC and in colorectal, breast, and thyroid carcinomas [121].

Spitz tumors and Spitzoid melanomas frequently harbor kinase, including RET (3% of cases), fusions [44,56]. Moreover, translocations t(10;22)(q11;q11) and t(6;10)(q27;q11) generating BCR-RET and FGFR1OP-RET fusions have been identified in single cases of chronic myelomonocytic leukemia (CMM), and primary myelofibrosis (PMF) with secondary acute myeloid leukemia (AML) [26,122]. Finally, pediatric spindle mesenchymal tumors are a heterogeneous group of rare soft tissue neoplasms with fibroblastic or neural-like differentiation, that include infantile fibrosarcoma and others [31,36]. These tumors typically feature rearrangements involving ALK, BRAF, NTRK1, NTRK2, NTRK3, and MET kinases [36]. A significant fraction of them has been discovered to harbor RET fusions, including the rare MYH10-, CLIP2-, KIAA1217-SPECC1L-, KHDRBS1-, VCL-, and TFG-RET fusions [13,31,36,54,58,71,75,123]. MYH10-RET fusion, in particular, is, thus far, the most common RET lesion in spindle mesenchymal tumor and it was also identified in a case of infantile myofibromatosis [36,54]. The morphology of RET fusion-positive spindle mesenchymal samples largely overlaps that of NTRK-positive ones [31,36].

RET is a transcriptional target of estrogen receptor alpha (ESR1) and several studies have reported its overexpression, particularly in ER+ breast cancer as well as its association with endocrine resistance [124]. In a recent study based on targeted genomic profiling of 9693 cases, RET genomic alterations, including 16 rearrangements, were observed in 1.2% of breast cancers. These rearrangements featured the classical CCDC6-RET and NCOA4-RET fusions, the new uncharacterized RASGEF1A-RET
and ZNF485-RET fusions, and rearrangements resulting in tandem duplications that involve exons 12–19 of RET [32].

RET fusions have been identified in <1% of colorectal carcinomas (CRC) [33,34,66]. The most common fusions in CRC are CCDC6-RET and NCOA4-RET. More rare fusions involving TNIP1-, SNRNP70-, GEMIN5- and RRBP1 as N-terminal partners were also described (Table 1) [34,35]. In CRC, RET fusions were more frequent in old patients, right-sided, RAS/BRAF wild-type, and MSI (microsatellite instable)-high tumors and were associated with negative prognosis. Accordingly, as many as 26% of patients with right-sided RAS and BRAF wild-type tumors harbored a RET rearrangement. This fraction significantly increased when only MSI-high CRCs were considered [34].

Salivary gland carcinomas are rare and heterogeneous tumors with several different subtypes. Secretory carcinoma, originally described as mammary analogue secretory carcinoma (MASC), is a salivary gland low-grade carcinoma typically associated with ETV6-NTRK3 fusion [42]. Recently, some secretory carcinomas, affecting the parotid or the submandibular gland, and negative for ETV6-NTRK3, were found to harbor ETV6- or NCOA4-RET fusions [42]. Recurrent rearrangements involving the RET gene were also identified in a subset of intraductal carcinoma (IC), another salivary duct carcinoma that shares some morphologic and immunophenotypical features with secretory carcinoma. Specifically, more than 40% of the IC cases harbored RET fusions, including NCOA4-RET, TRIM27-RET, and KIAA1217-RET [59,60,125].

8. Conclusions

Though initially believed to be PTC-specific, RET gene fusions have more recently been identified in several cancer types, including lung, colon, and breast carcinoma. In terms of clinical translation, this has significantly raised the interest for RET as far as the possibility of developing molecular diagnostic methods as well as targeted treatments with RET TKIs. On the other hand, from a mechanistic point-of-view, RET fusion was revealed to be an interesting model to study the mechanism of gene rearrangement and the role of radiation in cancer.

Author Contributions: Conceptualization, M.S. and F.C.; picture drawing, M.M. and G.F.; data base analysis, M.M. and G.F.; writing—original draft preparation, M.S.; writing—review and editing, M.S. and F.C.; supervision, F.C.; funding acquisition, M.S and F.C. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC) IG 20793, by the POR Campania FESR 2014–2020 “SATIN” grant and by the NIH 1R01CA197178-01A1R grant.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Takahashi, M.; Ritz, J.; Cooper, G.M. Activation of a novel human transforming gene, ret, by DNA rearrangement. Cell 1985, 42, 581–588. [CrossRef]
2. Pasini, B.; Hofstra, R.M.; Yin, L.; Bocciardi, R.; Santamaria, G.; Grootscholten, P.M.; Ceccherini, I.; Patrone, G.; Priolo, M.; Buys, C.H.; et al. The physical map of the human RET proto-oncogene. Oncogene 1995, 11, 1737–1743. [PubMed]
3. Ibáñez, C.F. Structure and physiology of the RET receptor tyrosine kinase. Cold Spring Harb. Perspect. Biol. 2013, 5, a009134. [CrossRef]
4. Mulligan, L.M. RET revisited: Expanding the oncogenic portfolio. Nat. Rev. Cancer 2014, 14, 173–186. [CrossRef]
5. Plaza-Menacho, I.; Mologni, L.; McDonald, N.Q. Mechanisms of RET signaling in cancer: Current and future implications for targeted therapy. Cell Signal. 2014, 26, 1743–1752. [CrossRef]
6. Mulligan, L.M. 65 Years of the double helix: Exploiting insights on the RET receptor for personalized cancer medicine. Endocr. Relat. Cancer 2018, 25, T189–T200. [CrossRef]
7. Plaza-Menacho, I. Structure and function of RET in multiple endocrine neoplasia type 2. Endocr. Relat. Cancer 2018, 25, T79–T90. [CrossRef]
8. Goodman, K.M.; Kjaer, S.; Beuron, F.; Knowles, P.P.; Nawrotek, A.; Burns, E.M.; Purkiss, A.G.; George, R.; Santoro, M.; Morris, E.P.; et al. RET recognition of GDNF-GFRα1 ligand by a composite binding site promotes membrane-proximal self-association. Cell Rep. 2014, 8, 1894–1904. [CrossRef]

9. Amiel, J.; Sproat-Emison, E.; Garcia-Barcelo, M.; Lantieri, F.; Burzynski, G.; Borrego, S.; Pelet, A.; Arnold, S.; Miao, X.; Griseri, P.; et al. Hirschsprung disease consortium. Hirschsprung disease, associated syndromes and genetics: A review. J. Med. Genet. 2008, 45, 1–14. [CrossRef]

10. Knowles, P.P.; Murray-Rust, J.; Kjaer, S.; Scott, R.P.; Hanrahan, S.; Santoro, M.; Ibáñez, C.F.; McDonald, N.Q. Structure and chemical inhibition of the RET tyrosine kinase domain. J. Biol. Chem. 2006, 281, 33577–33587. [CrossRef]

11. De Falco, V.; Carломagno, F.; Li, H.Y.; Santoro, M. The molecular basis for RET tyrosine-kinase inhibitors in thyroid cancer. Best Pract. Res. Clin. Endocrinol. Metab. 2017, 31, 307–318. [CrossRef]

12. Redaelli, S.; Plaza-Menacho, I.; Mologni, L. Novel targeted therapeutics for MEN2. Endocr. Relat. Cancer 2018, 25, T53–T68. [CrossRef]

13. Drilon, A.; Hu, Z.I.; Lai, G.G.Y.; Tan, D.S.W. Targeting RET-driven cancers: Lessons from evolving preclinical and clinical landscapes. Nat. Rev. Clin. Oncol. 2018, 15, 151–167. [CrossRef] [PubMed]

14. Iams, W.T.; Lovly, C.M. Stop fRETting the target: Next-generation RET inhibitors have arrived. Cancer Discov. 2018, 8, 797–799. [CrossRef] [PubMed]

15. Subbiah, V.; Yang, D.; Velcheti, V.; Drilon, A.; Meric-Bernstam, F. State-of-the-art strategies for targeting RET-dependent cancers. J. Clin. Oncol. 2020, 38, 1209–1221. [CrossRef] [PubMed]

16. Romei, C.; Ciampi, R.; Elisei, R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. Nat. Rev. Endocrinol. 2016, 12, 192–202. [CrossRef]

17. Li, A.Y.; McCusker, M.G.; Russo, A.; Scilla, K.A.; Gittens, A.; Arensmeyer, K.; Mehra, R.; Adamo, V.; Rolfo, C. RET fusions in solid tumors. Cancer Treat. Rev. 2019, 81, 101911. [CrossRef]

18. Kohno, T.; Tabata, J.; Nakaoku, T. REToma: A cancer subtype with a shared driver oncogene. Carcinogenesis 2019, 11, bgz184. [CrossRef]

19. Cancer Genome Atlas Research Network; Weinstein, J.N.; Collisson, E.A.; Mills, G.B.; Shaw, K.R.; Ozenberger, B.A.; Ellrott, K.; Shmulevich, I.; Sander, C.; Stuart, J.M. The cancer genome atlas pan-cancer analysis project. Nat. Genet. 2013, 45, 1113–1120. [CrossRef]

20. AACR Project GENIE Consortium. AACR project GENIE: Powering precision medicine through an international consortium. Cancer Discov. 2017, 7, 818–831. [CrossRef]

21. Zehir, A.; Benayed, R.; Shah, R.H.; Syed, A.; Middha, S.; Kim, H.R.; Srinivasan, P.; Gao, J.; Chakravarty, D.; Devlin, S.M.; et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat. Med. 2017, 23, 703–713. [CrossRef] [PubMed]

22. Hamatani, K.; Eguchi, H.; Koyama, K.; Mukai, M.; Nakachi, K.; Kusunoki, Y. A novel RET rearrangement (ACBD5/RET) by pericentric inversion, inv(10)(p12.1;q11.2), in papillary thyroid cancer from an atomic bomb survivor exposed to high-dose radiation. Oncol. Rep. 2014, 32, 1809–1814. [CrossRef] [PubMed]

23. Iyama, K.; Matsuse, M.; Mitsutake, N.; Rogounovitch, T.; Saenko, V.; Suzuki, K.; Ashizawa, M.; Ookuski, C.; Suzuki, S.; Mizunuma, H.; et al. Identification of three novel fusion oncogenes, SQSTM1/NTRK3, AFAP1L2/RET, and PPFIBP2/RET, in thyroid cancers of young patients in fukushima. Thyroid 2017, 27, 811–818. [CrossRef] [PubMed]

24. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014, 159, 676–690. [CrossRef] [PubMed]

25. Staubitz, J.I.; Musholt, T.J.; Schad, A.; Springer, E.; Lang, H.; Rajalingam, K.; Roth, W.; Hartmann, N. ANKR26—A novel gene fusion involving RET in papillary thyroid carcinoma. Cancer Genet. 2019, 238, 10–17. [CrossRef] [PubMed]

26. Ballerini, P.; Strussi, S.; Cresson, C.; Prade, N.; Toujani, S.; Deswarte, C.; Dobbelstein, S.; Petit, A.; Lapillorne, H.; Gautier, E.F.; et al. RET fusion genes are associated with chronic myelomonocytic leukemia and enhance monocytic differentiation. Leukemia 2012, 26, 2384–2389. [CrossRef] [PubMed]

27. Xu, H.; Shen, J.; Jiang, J.; Li, H.; Li, B.; Zhang, T.; Zhang, L.; Mao, X.; Jian, H.; Shu, Y. Characterization of acquired receptor tyrosine-kinase fusions as mechanisms of resistance to EGFR tyrosine-kinase inhibitors. Cancer Manag. Res. 2019, 11, 6343–6351. [CrossRef]
28. Grieco, M.; Santoro, M.; Berlingieri, M.T.; Melillo, R.M.; Donghi, R.; Bongarzone, I.; Pierotti, M.A.; Della Porta, G.; Fusco, A.; Vecchio, G. PTC is a novel rearranged form of the ret proto-oncogene and is frequently detected in vivo in human thyroid papillary carcinomas. Cell 1990, 60, 557–563. [CrossRef]

29. Takeuchi, K.; Soda, M.; Togashi, Y.; Suzuki, R.; Sakata, S.; Hatano, S.; Asaka, R.; Hamanaka, W.; Ninomiya, H.; Uehara, H.; et al. RET, ROS1 and ALK fusions in lung cancer. Nat. Med. 2012, 18, 378–381. [CrossRef]

30. Landa, I.; Ibrahimipasic, T.; Boucai, L.; Sinha, R.; Knauf, J.A.; Shah, R.H.; Dogan, S.; Ricarte-Filho, J.C.; Krishnamoorthy, G.P.; Xu, B.; et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. J. Clin. Investig. 2016, 126, 1052–1066. [CrossRef]

31. Antonescu, C.R.; Dickson, B.C.; Swanson, D.; Zhang, L.; Sung, Y.S.; Kao, Y.C.; Chang, W.C.; Ran, L.; Pappo, A.; Bahrami, A.; et al. Spindle cell tumors with RET gene fusions exhibit a morphologic spectrum akin to tumors with NTRK gene fusions. Am. J. Surg. Pathol. 2019, 43, 1384–1391. [CrossRef] [PubMed]

32. Paratala, B.S.; Chung, J.H.; Williams, C.B.; Yilmazel, B.; Petrovsy, W.; Williams, K.; Schrock, A.B.; Gay, L.M.; Lee, E.; Dolfi, S.C.; et al. RET rearrangements are actionable alterations in breast cancer. Nat. Commun. 2018, 9, 4821. [CrossRef] [PubMed]

33. Le Rolle, A.F.; Klempner, S.J.; Garrett, C.R.; Seery, T.; Sanford, E.M.; Balasubramanian, S.; Ross, J.S.; Stephens, P.J.; Miller, V.A.; Ali, S.M.; et al. Identification and characterization of RET fusions in advanced colorectal cancer. Oncotarget 2015, 6, 28929–28937. [CrossRef] [PubMed]

34. Pietrantonio, F.; Di Nicolantonio, F.; Schrock, A.B.; Lee, J.; Morano, F.; Fuca, G.; Nikolakos, P.; Drilon, A.; Hechtman, J.F.; Christiansen, J.; et al. RET fusions in a small subset of advanced colorectal cancers at risk of being neglected. Ann. Oncol. 2018, 29, 1394–1401. [CrossRef] [PubMed]

35. Cocco, E.; Benhamida, J.; Middha, S.; Zehir, A.; Mullaney, K.; Shia, J.; Yaeger, R.; Zhang, L.; Wong, D.; Villafania, L.; et al. Colorectal carcinomas containing hypermethylated MLH1 promoter and wild-type BRAF/KRAS are enriched for targetable kinase fusions. Cancer Res. 2019, 79, 1047–1053. [CrossRef] [PubMed]

36. Davis, J.L.; Vargas, S.O.; Rudzinski, E.R.; López Marti, J.M.; Janeway, K.; Forrest, S.; Winsnes, K.; Pinto, N.; Yang, S.E.; VanSandt, M.; et al. Recurrent RET gene fusions in pediatric spindle mesenchymal neoplasms. Histopathology 2020. [CrossRef]

37. Lira, M.E.; Choi, Y.L.; Lim, S.M.; Deng, S.; Huang, D.; Ozeck, M.; Han, J.; Jeong, J.Y.; Shim, H.S.; Cho, B.C.; et al. A single-tube multiplexed assay for detecting ALK, ROS1, and RET fusions in lung cancer. J. Mol. Diagn. 2014, 16, 229–243. [CrossRef]

38. Gao, Q.; Liang, W.W.; Foltz, S.M.; Mutharasu, G.; Jayasinghe, R.G.; Cao, S.; Liao, W.W.; Reynolds, S.M.; Wyczalkowski, M.A.; Yao, L.; et al. Driver fusions and their implications in the development and treatment of human cancers. Cell Rep. 2018, 23, 227–238. [CrossRef]

39. Gautschi, O.; Milia, J.; Filleron, T.; Wolf, J.; Carbone, D.P.; Olsen, D.; Camidge, R.; Narayan, V.; Doebele, R.C.; Besse, B.; et al. Targeting RET in patients with RET-rearranged lung cancers: Results from the global, multicenter RET registry. J. Clin. Oncol. 2017, 35, 1403–1410. [CrossRef]

40. Nakata, T.; Kitamura, Y.; Shimizu, K.; Tanaka, S.; Fujimori, M.; Yokoyama, S.; Ito, K.; Emi, M. Fusion of a novel gene, ELKS, to RET due to translocation t(10;12)(q11;pl3) in a papillary thyroid carcinoma. Genes Chromosomes Cancer. 1999, 25, 97–103. [CrossRef]

41. Liu, R.T.; Chou, F.F.; Wang, C.H.; Lin, C.L.; Chao, F.P.; Chung, J.C.; Huang, C.C.; Wang, P.W.; Cheng, J.T. Low prevalence of RET rearrangements (RET/PTC1, RET/PTC2, RET/PTC3, and ELKS-RET) in sporadic papillary thyroid carcinomas in Taiwan Chinese. Thyroid 2005, 15, 326–335. [CrossRef] [PubMed]

42. Guilmette, J.; Dias-Santagata, D.; Nosè, V.; Lennerz, J.K.; Sadow, P.M. Novel gene fusions in secretory carcinoma of the salivary glands: Enlarging the ETV6 family. Hum. Pathol. 2019, 83, 50–58. [CrossRef] [PubMed]

43. Velcheti, V.; Thawani, R.; Khunger, M.; Mukhopadhyay, S.; Chute, D.J.; Schrock, A.B.; Ali, S.M. FRMD4A/RET: A novel ret oncogenic fusion variant in non-small cell lung carcinoma. J. Thorac. Oncol. 2017, 12, e15–e16. [CrossRef] [PubMed]

44. Wiesner, T.; He, J.; Yelensky, R.; Esteve-Puig, R.; Botton, T.; Yeh, I.; Lipson, D.; Otto, G.; Brennan, K.; Murali, R.; et al. Kinase fusions are frequent in spitz tumours and spitzoid melanomas. Nat. Commun. 2014, 5, 3116. [CrossRef] [PubMed]

45. Klugbauer, S.; Demidchik, E.P.; Lengfelder, E.; Rabes, H.M. Detection of a novel type of RET rearrangement (PTC5) in thyroid carcinomas after Chernobyl and analysis of the involved RET-fused gene RFG5. Cancer Res. 1999, 58, 198–203. [PubMed]
46. Ciampi, R.; Giordano, T.J.; Wikenheimer-Brokamp, K.; Koenig, R.J.; Nikiforov, Y.E. HOOK3-RET: A novel type of RET/PTC rearrangement in papillary thyroid carcinoma. *Endocr. Relat. Cancer* **2007**, *14*, 445–452. [CrossRef]

47. Nakaoku, T.; Tsuta, K.; Ichikawa, H.; Shiraishi, K.; Sakamoto, H.; Enari, M.; Furuta, K.; Shimada, Y.; Ogiwara, H.; Watanabe, S.; et al. Druggable oncogene fusions in invasive mucinous lung adenocarcinoma. *Clin. Cancer Res.* **2014**, *20*, 3078–3093. [CrossRef]

48. Klugbauer, S.; Jauch, A.; Lengfelder, E.; Demidchik, E.; Rabes, H.M. A novel type of RET rearrangement (PTC8) in childhood papillary thyroid carcinomas and characterization of the involved gene (RFG8). *Cancer Res.* **2000**, *60*, 7028–7032.

49. Zhang, X.; Li, Y.; Liu, C.; Wang, W.; Li, M.; Lv, D.; Sun, G.; Chen, H.; Dong, X.; Miao, Z.; et al. Identification of a novel KIF13A-RET fusion in lung adenocarcinoma by next-generation sequencing. *Lung Cancer* **2018**, *118*, 27–29. [CrossRef]

50. Kohno, T.; Ichikawa, H.; Totoki, Y.; Yasuda, K.; Hiramoto, M.; Nammo, T.; Sakamoto, H.; Tsuta, K.; Furuta, K.; Shimada, Y.; et al. KIF5B-RET fusions in lung adenocarcinoma. *Nat. Med.* **2012**, *18*, 375–377. [CrossRef] [PubMed]

51. Lipson, D.; Capelletti, M.; Yelensky, R.; Otto, G.; Parker, A.; Jarosz, M.; Curran, J.A.; Balasubramanian, S.; Bloom, T.; Brennan, K.W.; et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat. Med.* **2012**, *18*, 382–384. [CrossRef] [PubMed]

52. Wang, R.; Hu, H.; Pan, Y.; Li, Y.; Ye, T.; Li, C.; Luo, X.; Wang, L.; Li, H.; Zhang, Y.; et al. RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. *J. Clin. Oncol.* **2012**, *30*, 4352–4359. [CrossRef] [PubMed]

53. Salassidis, K.; Bruch, J.; Zitzelsberger, H.; Lengfelder, E.; Kellerer, A.M.; Bauchinger, M. Translocation t(10;14)(q11.2:q22.1) fusing the kinetin to the RET gene creates a novel rearranged form (PTC8) of the RET proto-oncogene in radiation-induced childhood papillary thyroid carcinoma. *Cancer Res.* **2000**, *60*, 2786–2789. [PubMed]

54. Rosenzweig, M.; Ali, S.M.; Wong, V.; Schrock, A.B.; Laetsch, T.W.; Ahrens, W.; Heilmann, A.; Morley, S.; Chudnovsky, Y.; Erlich, R.L.; et al. A case of advanced infantile myofibromatosis harboring a novel MYH10-RET fusion. *Pediatr. Blood Cancer* **2017**, *64*, [CrossRef] [PubMed]

55. Grubbs, E.G.; Ng, P.K.; Bui, J.; Busaidy, N.L.; Chen, K.; Lee, J.E.; Lu, X.; Lu, H.; Meric-Bernstam, F.; Mills, G.B.; et al. RET fusion as a novel driver of medullary thyroid carcinoma. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 788–793. [CrossRef] [PubMed]

56. VandenBoom, T.; Quan, V.L.; Zhang, B.; Garfield, E.M.; Kong, B.Y.; Isales, M.C.; Panah, E.; Igaruca, C.; Taxter, T.; Beaubier, N.; et al. Genomic fusions in pigmented spindle cell nevus of reed. *Am. J. Surg. Pathol.* **2018**, *42*, 1042–1051. [CrossRef] [PubMed]

57. Lee, S.H.; Lee, J.K.; Ahn, M.J.; Kim, D.W.; Sun, J.M.; Keam, B.; Kim, T.M.; Heo, D.S.; Ahn, J.S.; Choi, Y.L.; et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: A phase II clinical trial. *Ann. Oncol.* **2017**, *28*, 292–297. [CrossRef]

58. Michal, M.; Pátková, N.; Martiník, P.; Gatalica, Z.; Kazakov, D.V.; Michalová, K.; Stoláriková, L.; Švajdler, M.; Michal, M. S100 and CD34 positive spindle cell tumor with prominent perivascular hyalinization and a novel NCOA4-RET fusion. *Genes Chrom. Cancer* **2019**, *58*, 680–685. [CrossRef]

59. Skálová, A.; Vanecek, T.; Uro-Coste, E.; Bishop, J.A.; Weinreb, I.; Thompson, L.D.R.; de Sanctis, S.; Schiavo-Lena, M.; Laco, J.; Badoual, C.; et al. Molecular profiling of salivary gland intraductal carcinoma revealed a subset of tumors harboring NCOA4-RET and novel TRIM27-RET fusions: A report of 17 cases. *Am. J. Surg. Pathol.* **2018**, *42*, 1445–1455. [CrossRef]

60. Skálová, A.; Pátková, N.; Santana, T.; Agaimy, A.; Ihrler, S.; Uro-Coste, E.; Thompson, L.D.R.; Bishop, J.A.; Baněčkova, M.; Rupp, N.J.; et al. NCOA4-RET and TRIM27-RET are characteristic gene fusions in salivary intraductal carcinoma, including invasive and metastatic tumors: Is ‘intraductal’ correct? *Am. J. Surg. Pathol.* **2019**, *43*, 1303–1313. [CrossRef]

61. Bongarzone, I.; Butti, M.G.; Coronelli, S.; Borrello, M.G.; Santoro, M.; Mondellini, P.; Pilotti, S.; Fusco, A.; Della Porta, G.; Pierotti, M.A. Frequent activation of ret protooncogene by fusion with a new activating gene in papillary thyroid carcinomas. *Cancer Res.* **1994**, *54*, 2979–2985.
62. Santoro, M.; Dathan, N.A.; Berlingieri, M.T.; Bongarzone, I.; Paulin, C.; Grieco, M.; Pierotti, M.A.; Vecchio, G.; Fusco, A. Molecular characterization of RET/PTC3; a novel rearranged version of the RET proto-oncogene in a human thyroid papillary carcinoma. *Oncogene* **1994**, *9*, 509–516. [PubMed]

63. Fugazzola, L.; Pierotti, M.A.; Vigano, E.; Pacini, F.; Vorontsova, T.V.; Bongarzone, I. Molecular and biochemical analysis of RET/PTC4, a novel oncogenic rearrangement between RET and ELE1 genes, in a post-Chernobyl papillary thyroid cancer. *Oncogene* **1996**, *13*, 1093–1097. [PubMed]

64. Corvi, R.; Berger, N.; Balcacz, R.; Romeo, G. RET/PCM-1: A novel fusion gene in papillary thyroid carcinoma. *Oncogene* **2000**, *19*, 4236–4242. [CrossRef] [PubMed]

65. Bongarzone, I.; Monzini, N.; Borrello, M.G.; Carcano, C.; Ferraresi, G.; Arighi, E.; Mondellini, P.; Della Porta, G.; Pierotti, M.A. Molecular characterization of a thyroid tumor-specific transforming sequence formed by the fusion of ret tyrosine kinase and the regulatory subunit RI alpha of cyclic AMP-dependent protein kinase A. *Mol. Cell. Biol.* **1993**, *13*, 358–366. [CrossRef] [PubMed]

66. Kloosterman, W.P.; Coebergh van den Braak, R.R.J.; Pieterse, M.; van Roosmalen, M.J.; Sieuwerts, A.M.; Stangl, C.; Brunekreef, R.; Lalmahomed, Z.S.; Oost, S.; van Galen, A.; et al. A systematic analysis of oncogenic gene fusions in primary colon cancer. *Cancer Res.* **2017**, *77*, 3814–3822. [CrossRef] [PubMed]

67. Zheng, Z.; Liebers, M.; Zhelyazkova, B.; Cao, Y.; Panditi, D.; Lynch, K.D.; Chen, J.; Robinson, H.E.; Shim, H.S.; Chmielecki, J.; et al. Anchored multiplex PCR for targeted next-generation sequencing. *Nat. Med.* **2014**, *20*, 1479–1484. [CrossRef]

68. Staubitz, J.I.; Schad, A.; Springer, E.; Rajalingam, K.; Lang, H.; Roth, W.; Hartmann, N.; Musholt, T.J. Novel rearrangements involving the RET gene in papillary thyroid carcinoma. *Cancer Genet.* **2019**, *230*, 13–20. [CrossRef]

69. Kato, S.; Subbiah, V.; Marchlik, E.; Elkin, S.K.; Carter, J.L.; Kurzrock, R. RET aberrations in diverse cancers: Next-generation sequencing of 4,871 patients. *Clin. Cancer Res.* **2017**, *23*, 1988–1997. [CrossRef]

70. Peng, P.; Zheng, Y.; Lv, J. TBC1D32-RET: A Novel RET oncogenic fusion in lung adenocarcinoma. *J. Thorac. Oncol.* **2019**, *14*, e7–e9. [CrossRef]

71. Loong, S.; Lian, D.W.Q.; Kuick, C.H.; Lim, T.H.; Nah, S.A.; Wong, K.P.L.; Chang, K.T.E. Novel TFG-RET fusion rearrangements involving the RET gene in papillary thyroid carcinoma. *Cancer Genet.* **2019**, *2018*, *333–336. [CrossRef] [PubMed]

72. Klugbauer, S.; Rabes, H.M. The transcription coactivator HTIF1 and a related protein are fused to the RET receptor tyrosine kinase in childhood papillary thyroid carcinomas. *Oncogene* **1999**, *18*, 4388–4393. [CrossRef] [PubMed]

73. Drilon, A.; Wang, L.; Hasanovic, A.; Suehara, Y.; Lipson, D.; Stephens, P.; Ross, J.; Miller, V.; Ginsberg, M.; Zakowski, M.F.; et al. Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov.* **2013**, *3*, 630–635. [CrossRef] [PubMed]

74. Lu, Z.; Zhang, Y.; Feng, D.; Sheng, J.; Yang, W.; Liu, B. Targeted next generation sequencing identifies somatic mutations and gene fusions in papillary thyroid carcinoma. *Oncotarget* **2017**, *8*, 45784–45792. [CrossRef] [PubMed]

75. Al-Ibraheemi, A.; Folpe, A.L.; Perez-Atayde, A.R.; Perry, K.; Hofvander, J.; Arbajian, E.; Magnusson, L.; Nilsson, J.; Mertens, F. Aberrant receptor tyrosine kinase signaling in lipofibromatosis: A clinicopathological and molecular genetic study of 20 cases. *Mod. Pathol.* **2019**, *32*, 423–434. [CrossRef]

76. Velchetti, V.; Madison, R.; Ali, S.M.; Schnick, A.B. WAC/RET: A Novel RET oncogenic fusion variant in non-small cell lung carcinoma. *J. Thorac. Oncol.* **2018**, *13*, e122–e123. [CrossRef]

77. Kim, P.; Jia, P.; Zhao, Z. Kinase impact assessment in the landscape of fusion genes that retain kinase domains: A pan-cancer study. *Brief Bioinform.* **2018**, *19*, 450–460. [CrossRef]

78. Wu, Y.M.; Su, F.; Kalyana-Sundaram, S.; Khazanov, N.; Ateeq, B.; Cao, X.; Lonigro, R.J.; Vats, P.; Wang, R.; Lin, S.F.; et al. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov.* **2013**, *3*, 636–647. [CrossRef]

79. Konduri, K.; Gallant, J.N.; Chae, Y.K.; Giles, F.J.; Gitlitz, B.J.; Gowen, K.; Ichihara, E.; Owonikoko, T.K.; Peddareddigari, V.; Ramalingam, S.S.; et al. EGFR fusions as novel therapeutic targets in lung cancer. *Cancer Discov.* **2016**, *6*, 601–611. [CrossRef]

80. Yakushina, V.D.; Lerner, L.V.; Lavrov, A.V. Gene fusions in thyroid cancer. *Thyroid* **2018**, *28*, 158–167. [CrossRef]
81. Jhiang, S.M.; Sagartz, J.E.; Tong, Q.; Parker-Thornburg, J.; Capen, C.C.; Cho, J.Y.; Xing, S.; Ledent, C. Targeted expression of the ret/PTC1 oncogene induces papillary thyroid carcinomas. Endocrinology 1996, 137, 375–378. [CrossRef] [PubMed]

82. Powell, D.J.; Jr; Russell, J.; Nibu, K.; Li, G.; Rhee, E.; Liao, M.; Goldstein, M.; Keane, W.M.; Santoro, M.; Fusco, A.; et al. The RET/PTC3 oncogene: Metastatic solid-type papillary carcinomas in murine thyroids. Cancer Res. 1998, 58, 5523–5528. [PubMed]

83. Huang, Q.; Schneeberger, V.E.; Luetteke, N.; Jin, C.; Afzal, R.; Budzevich, M.M.; Makanji, R.J.; Martinez, G.V.; Shen, T.; Zhao, L.; et al. Preclinical modeling of KIF5B-RET fusion lung adenocarcinoma. Mol. Cancer Ther. 2016, 15, 2521–2529. [CrossRef] [PubMed]

84. Bellelli, R.; Vitagliano, D.; Federico, G.; Marotta, P.; Tamburrino, A.; Salerno, P.; Piciello, O.; Papparella, S.; Knauf, J.A.; Fagin, J.A.; et al. Oncogene-induced senescence and its evasion in a mouse model of thyroid neoplasia. Mol. Cell. Endocrinol. 2018, 460, 24–35. [CrossRef] [PubMed]

85. Attié-Bitach, T.; Abitbol, M.; Gérard, M.; Delezoide, A.L.; Augé, J.; Pelet, A.; Amiel, J.; Pachnis, V.; Munnich, A.; Lyonnet, S.; et al. Expression of the RET proto-oncogene in human embryos. Am. J. Med. Genet. 1998, 80, 481–486. [CrossRef]

86. Monaco, C.; Visconti, R.; Barone, M.V.; Pierantoni, G.M.; Berlingieri, M.T.; De Lorenzo, C.; Mineo, A.; Vecchio, G.; Fusco, A.; Santoro, M. The RFG oligomerization domain mediates kinase activation and re-localization of the RET/PTC3 oncoprotein to the plasma membrane. Oncogene 2001, 20, 599–608. [CrossRef]

87. Schram, A.M.; Chang, M.T.; Jonsson, P.; Drilon, A. Fusions in solid tumours: Diagnostic strategies, targeted therapy, and acquired resistance. Nat. Rev. Clin. Oncol. 2017, 14, 735–748. [CrossRef]

88. Das, T.K.; Cagan, R.L. KIF5B-RET oncoprotein signals through a multi-kinase signaling hub. Cell Rep. 2017, 20, 2368–2383. [CrossRef]

89. Vaiashnavi, A.; Schubert, L.; Rix, U.; Marek, L.A.; Pelet, A.; Amiel, J.; Pachnis, V.; Munnich, A.; Lyonnet, S.; et al. EGFR mediates responses to small-molecule drugs targeting oncogenic fusion kinases. Cancer Res. 2017, 77, 3551–3563. [CrossRef]

90. Wang, S.; Cheng, Y.; Zheng, Y.; He, Z.; Chen, W.; Zhou, W.; Duan, C.; Zhang, C. PRKAR1A is a functional tumor suppressor inhibiting ERK/Snail/E-cadherin pathway in lung adenocarcinoma. Sci. Rep. 2016, 6, 39630. [CrossRef]

91. Bellelli, R.; Castellone, M.D.; Guida, T.; Limongello, R.; Marek, L.A.; Le, A.T.; Keysar, S.B.; Glogowska, M.J.; Smith, M.A.; Kako, S.; Sumi, N.J.; et al. NCOA4 transcriptional coactivator inhibits activation of DNA replication origins. Mol. Cell 2014, 55, 123–137. [CrossRef] [PubMed]

92. Morra, F.; Luise, C.; Visconti, R.; Staibano, S.; Merolla, F.; Ilardi, G.; Guggino, G.; Paladino, S.; Sarnataro, D.; Franco, R.; et al. New therapeutic perspectives in CCDC6 deficient lung cancer cells. Int. J. Cancer 2015, 136, 2146–2157. [CrossRef] [PubMed]

93. ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes. Nature 2020, 580, 82–93. [CrossRef] [PubMed]

94. Pierotti, M.A.; Santoro, M.; Jenkins, R.B.; Sozzi, G.; Bongarzone, I.; Greco, M.; Monzini, N.; Miozzo, M.; Herrmann, M.A.; Fusco, A.; et al. Characterization of an inversion on the long arm of chromosome 10 juxtaposing D10S170 and RET and creating the oncogenic sequence RET/PTC3. Proc. Natl. Acad. Sci. USA 1992, 89, 1616–1620. [CrossRef]

95. Mizukami, T.; Shiraiishi, K.; Shimada, Y.; Ogiwara, H.; Tsuta, K.; Ichikawa, H.; Sakamoto, H.; Kato, M.; Shibata, T.; Nakano, M.; et al. Molecular mechanisms underlying oncogenic RET fusion in lung adenocarcinoma. J. Thorac. Oncol. 2014, 9, 622–630. [CrossRef]

96. Seki, Y.; Mizukami, T.; Kohno, T. Molecular process producing oncogene fusion in lung cancer cells by illegitimate repair of DNA double-strand breaks. Biomolecules 2015, 5, 2464–2476. [CrossRef]

97. Klugbauer, S.; Pfeiffer, P.; Gassenhuber, H.; Beimfohr, C.; Rabes, H.M. RET rearrangements in radiation-induced papillary thyroid carcinomas: High prevalence of topoisomerase I sites at breakpoints and microhomology-mediated end joining in ELE1 and RET chimeric genes. Genomics 2001, 73, 149–160. [CrossRef]

98. Ameziane-El-Hassani, R.; Boufraqueh, M.; Lagente-Chevallier, O.; Weyemi, U.; Talbot, M.; Métivier, D.; Courtin, F.; Bidart, J.M.; El Mzibri, M.; Schlumberger, M.; et al. Role of H2O2 in RET/PTC1 chromosomal rearrangement produced by ionizing radiation in human thyroid cells. Cancer Res. 2010, 70, 4123–4132. [CrossRef]
99. Kramara, J.; Osia, B.; Malkova, A. Break-induced replication: The where, the why, and the how. Trends Genet. 2018, 34, 518–531. [CrossRef]
100. Gandhi, M.; Medvedovic, M.; Stringer, J.R.; Nikiforov, Y.E. Interphase chromosome folding determines spatial proximity of genes participating in carcinogenic RET/PTC rearrangements. Oncogene 2006, 25, 2360–2366. [CrossRef]
101. Lehman, C.E.; Dillon, L.W.; Nikiforov, Y.E.; Wang, Y.H. DNA fragile site breakage as a measure of chemical exposure and predictor of individual susceptibility to form oncogenic rearrangements. Carcinogenesis 2017, 38, 293–301. [CrossRef] [PubMed]
102. Fagin, J.A.; Wells, S.A., Jr. Biologic and clinical perspectives on thyroid cancer. N. Engl. J. Med. 2016, 375, 1054–1067. [CrossRef] [PubMed]
103. Fagin, J.A.; Wells, S.A., Jr. Biologic and clinical perspectives on thyroid cancer. J. Clin. Endocrinol. Metab. 2000, 85, 1170–1175. [CrossRef] [PubMed]
104. Cordioli, M.I.; Moraes, L.; Bastos, A.U.; Besson, P.; Alves, M.T.; Delcelo, R.; Monte, O.; Longui, C.; Cury, A.N.; Cerutti, J.M. Fusion oncogenes are the main genetic events found in sporadic papillary thyroid carcinomas from children. Thyroid 2017, 27, 182–188. [CrossRef] [PubMed]
105. Nikiforov, Y.E.; Rowland, J.M.; Bove, K.E.; Monforte-Munoz, H.; Fagin, J.A. Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. Cancer Res. 1993, 53, 2940–2943. [CrossRef]
106. Fenton, C.L.; Lukes, Y.; Nicholson, D.; Dinauer, C.A.; Francis, G.L.; Tuttle, R.M. The ret/PTC mutations are common in sporadic papillary thyroid carcinoma of children and young adults. J. Clin. Endocrinol. Metab. 2000, 85, 1170–1175. [CrossRef]
107. Bronte, G.; Ulivi, P.; Verlicchi, A.; Cravero, P.; Delmonte, A.; Crinò, L. Targeting RET-rearranged non-small-cell lung cancer: Future prospects. Lung Cancer (Auckl) 2019, 10, 27–36. [CrossRef] [PubMed]
108. O’Leary, C.; Xu, W.; Pavlakis, N.; Richard, D.; O’Byrne, K. Rearranged during transfection fusions in non-small-cell lung cancer. Cancers 2019, 11, 620. [CrossRef]
109. Guo, Y.; Cao, R.; Zhang, X.; Huang, L.; Sun, L.; Zhao, J.; Ma, J.; Han, C. Recent progress in rare oncogenic drivers and targeted therapy for non-small cell lung cancer. Oncol. Targets Ther. 2019, 12, 10343–10360. [CrossRef]
110. Dacic, S.; Luvision, A.; Evdokimova, V.; Kelly, L.; Siegfried, J.M.; Villaruz, L.C.; Socinski, M.A.; Nikiforov, Y.E. RET rearrangements in lung adenocarcinoma and radiation. J. Thorac. Oncol. 2014, 9, 118–120. [CrossRef]
118. Klempner, S.J.; Bazhenova, L.A.; Braiteh, F.S.; Nikolinakos, P.G.; Gowen, K.; Cervantes, C.M.; Chmielecki, J.; Greenbowe, J.R.; Ross, J.S.; Stephens, P.I.; et al. Emergence of RET rearrangement co-existing with activated EGFR mutation in EGFR-mutated NSCLC patients who had progressed on first-or second-generation EGFR TKI. Lung Cancer 2015, 89, 357–359. [CrossRef]

119. Piotrowska, Z.; Isozaki, H.; Lennerz, J.K.; Gainor, J.F.; Lennes, I.T.; Zhu, V.W.; Marcoux, N.; Banwait, M.K.; Digumarthy, S.R.; Su, W.; et al. Landscape of acquired resistance to osimertinib in EGFR-mutant NSCLC and clinical validation of combined EGFR and RET inhibition with osimertinib and BLU-667 for acquired RET fusion. Cancer Discov. 2018, 8, 1529–1539. [CrossRef]

120. McCoach, C.E.; Le, A.T.; Gowen, K.; Jones, K.; Schubert, L.; Doak, A.; Estrada-Bernal, A.; Davies, K.D.; Merrick, D.T.; Bunn, P.A., Jr.; et al. Resistance mechanisms to targeted therapies in ROS1+ and ALK+ non-small cell lung cancer. Clin. Cancer Res. 2018, 24, 3334–3347. [CrossRef]

121. Rich, T.A.; Reckamp, K.L.; Chae, Y.K.; Doebbe, R.C.; Iams, W.T.; Oh, M.; Raymond, V.M.; Lanman, R.B.; Riess, J.W.; Stinchcombe, T.E.; et al. Analysis of cell-free DNA from 32,989 advanced cancers reveals novel co-occurring activating RET alterations and oncogenic signaling pathway aberrations. Clin. Cancer Res. 2019, 25, 5832–5842. [CrossRef] [PubMed]

122. Bossi, D.; Carlomagno, F.; Pallavicini, I.; Pruneri, G.; Trubia, M.; Raviele, P.R.; Marinelli, A.; Anaganti, S.; Cox, M.C.; Viale, G.; et al. Functional characterization of a novel FGFR1OP-RET rearrangement in hematopoietic malignancies. Mol. Oncol. 2014, 8, 221–231. [CrossRef] [PubMed]

123. Gerdemann, U.; Lee, Y.A.; Henry, D.; Smith, S.; Ortiz, M.V.; Rothenberg, S.M.; Raju, S.G.; Craig Cox, M.; Glade Bender, J.L.; Pappo, A.S.; et al. First experience of LOXO-292 in the management of pediatric patients with RET-altered cancers. J. Clin. Oncol. 2019, 37, 10045. [CrossRef]

124. Gattelli, A.; Hynes, N.E.; Schor, I.E.; Vallone, S.A. Ret receptor has distinct alterations and functions in breast cancer. J. Mammary Gland Biol. Neoplasia 2020, 25, 13–26. [CrossRef] [PubMed]

125. Palicelli, A. Intraductal carcinomas of the salivary glands: Systematic review and classification of 93 published cases. APMIS 2019. [CrossRef] [PubMed]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).