Ontologies Classes Object Properties Data Properties Annotation Properties Individuals Datatypes Clouds

Class: Smokers_NSCLC

Annotations (3)

- rdfs:comment "Among the validated 173 somatic rearrangements detected by whole genome sequencing data were 59 inter-chromosomal translocations, 7 tandem duplications, 74 deletions, and 33 inversions (Supplemental Table S16). The majority of the inter-chromosomal events were clustered in four samples: three from smokers and one from a never-smoker (Supplemental Data S2). The never-smoker (LUC7) tumor genome is characterized by widespread chromosomal disruption consistent with chromothripsis (Stephens et al. 2011). We identified 15 validated inter-chromosomal translocation events between chromosome 5 and other chromosomes across the LUC7 tumor genome, with most events connecting the distal end of chromosome 5q with various locations on chromosomes 10, 12, 17, and 20. Copy number alterations often co-occur with translocation breakpoints, consistent with previously described chromothripsis events. We did not identify any TP53 mutations in this tumor though mutations involving the TP53 gene have been reported to be associated with chromothripsis (Rausch et al., 2012). We also analyzed the tumor genomes for novel fusion genes, an area of great interest therapeutically with the recent discovery of novel fusions involving kinase genes ALK, ROS and RET in NSCLC (Takeuchi et al., 2012). With combined whole genome and transcriptome sequencing, we were able to systematically identify and validate fusion genes. Three different algorithms, ChimeraScan (Iyer et al., 2011), defuse (McPherson et al., 2011) and BreakFusion (Chen et al., 2012), were used to identify fusion genes from the transcriptome sequencing data. High confidence fusions then were orthogonally validated by analysis of the whole genome DNA sequencing data. Based on this analysis, we identified 14 high-confidence fusions (Supplemental Table S17 and Supplemental Methods), including an in-frame novel fusion KDELR2-ROS1 in LUC11 and an EML4-ALK fusion in LUC16. Even though ROS1 kinase fusions have been previously reported in patients diagnosed with NSCLC and cholangiocarcinoma (Bergethon et al., 2012; Gu et al., 2011; Rikova et al., 2007), we identified a novel 5′ partner (KDELR2) in our never-smoker sample. A variety of genes have been reported to be 5′ partners in ROS1 fusions and it is not known whether the 5′ partner plays a role in the oncogenic activity of the fusion kinase (Rikova et al., 2007; Takeuchi et al., 2012). Apart from fusion kinases, an in-frame fusion was detected between the RASSF1A (RAS association domain family protein 1) and TTYH2 (Tweety, Drosophila Homolog of 2) genes. Another novel fusion consisted of a transcription factor in the 3′ end; FZR1-NFIC. NFIC (nuclear factor I/C) is a dimeric DNA-binding protein and functions as a cellular transcription factor. FZR1 in association with the APC gene is involved in the regulation of mitosis and meiosis. Integrated analyses of the whole genome and transcriptome data One of the major strengths of our study is the integration of whole genome and transcriptome sequencing. Starting with 3,726 tier 1 variants (point mutations only) from all samples identified by WGS, we characterized the expression of each gene by digital (NGS-based) RNA-sequencing (Supplemental Methods). The median read coverage from RNA sequencing for all tier 1 variant positions was 24×, but in expressed genes, the median read coverage reached, 129×. We observed significant concordance in variant identification between genome and transcriptome sequencing. Transcriptome sequencing confirmed the presence of 40% of the variants identified by WGS (at least one RNA-seq read) despite the observation that 34% of variants identified in WGS data were from a non-expressed allele and 3% of variants from highly expressed genes were not sufficiently covered at the variant positions. We utilized the RNA-seq data to further classify variants into four categories according to their expression patterns: expressed, mutant-biased, wild type-biased, and silent gene (Figure 3A, 3B, Supplemental Table S18 and Supplemental Methods). The genomes of lung cancer from never-smokers had a higher proportion of expressed variants (49.4%) than tobacco smokers (29.1% or 27.0% if the hyper-mutated LUC9 is excluded). The number of expressed variants that are biased towards the mutant allele is a small proportion of all variants (9.6%) (Figure 3B). For these variants, the mutant allele had a significantly higher variant allele frequency (> 20% higher) in the RNA compared to the DNA. Notably, a few genes (KRAS, TP53, GTF3C1, PLEKHA6, and SGOL2) showed mutant biased over-expression relative to the wild type allele in more than one sample. For example, KRAS mutations were detected in five of the 17 samples and in all of these the mutant allele was preferentially expressed (Supplemental Table S19). We did not identify copy number amplification in the mutant-biased expression of the KRAS gene. KRAS and TP53 were highly expressed (above the 75th percentile) in all 17 cases and eight of nine KRAS/TP53 mutations occurred in smokers. KRAS and TP53 mutations were mutually exclusive in our 17 cases (Figure 3C) although previous studies showed they could be present in the same samples (Ding et al., 2008). While the VAFs observed in WGS and RNA-seq are generally correlated (Figure 3D), rare cases such as KRAS and TP53 deviate from the expected VAF considerably. The mechanism underlying the observed difference in VAFs at the DNA and RNA level for these genes remains unknown."
- rdfs:comment "Lung cancer is a molecularly heterogeneous disease. The tumor genomic landscape is markedly distinct in never smokers compared to smokers in several respects: 1) significantly higher mutation frequencies observed in smokers; 2) different mutation spectrum between smokers (C:G->A:T predominant) and never smokers (C:G->T:A predominant); and 3) distinctive sets of mutations identified in never smokers

(EGFR mutations and ROS1 and ALK fusions) and smokers (KRAS, TP53, BRAF, JAK2, JAK3, and mismatch repair gene mutations). Apart from point mutations, we identified a significant number of structural variations and fusion genes. Going forward, comprehensive genomic analyses of whole genomes and transcriptomes of a large number of lung cancer samples from life-long never smokers will be needed to better understand molecular genetics and guide therapy in this unique subset of patients. Aberrations in DNA repair pathway, chromatin modification genes and novel fusions involving metabolic pathways identified in our study present novel therapeutic opportunities. It is possible that these previously poorly characterized molecular lesions in lung cancer may represent the proverbial Achilles' heel for targeted treatment. For example, certain DNA repair pathway lesions may confer unusual susceptibility of cancer cells to PARP inhibitors much like those seen in BRCA deficient cancer types. The role of epigenetic therapy in general and histone deacetylase (HDAC) inhibitors in particular, should be studied in lung cancer given the number of events in chromatin modifier genes we identified in this study. Deep digital sequencing provides large number of events that can be used to precisely estimate clonal size and mutational evolution over time during the natural course of disease progression and in response to selection pressure exerted by therapy. It is unlikely that current therapies would produce lasting remission or cure in advanced lung cancer unless dominant genetic alterations in the founder clone and emerging secondary clones are targeted specifically for therapy. A systematic approach to collect tissue samples not only at the time of diagnosis but serially at the times of relapse to chronicle the dynamic clonal evolution that occurs over time and possibly at different metastatic sites is absolutely critical to make major advances in therapy. Only through a comprehensive assessment of whole genome sequences and transcriptomes in large numbers of carefully curated and well-annotated samples, we will able to catalogue potentially significant point mutations and structural variations that led to critical perturbations in the cellular homeostasis. Moreover, the cancer research community should radically overhaul the current approach to drug development and initiate a series of steps to study comprehensively genomic evolution over time in well-defined cohorts of patients enrolled in clinical trials. Comprehensive genomic characterization efforts to catalogue somatically altered pathways will improve our understanding of the molecular genetics of lung cancer and identify novel therapeutic targets. Functional studies in the laboratory and thoughtfully designed clinical studies will be need to fully harness the data from genomic studies such as ours."

- rdfs:comment "Substantial differences in the mutational burden, spectrum, and affected genes were found between smokers and never-smokers (Figure 1). Of the 12 samples from tobacco smokers (including the former light smoker), we observed one cancer genome (LUC9) with a significantly higher number of point mutations (tier 1: 1,363) when compared to the other tumor samples (Figure 1). This sample meets our criterion for "hypermutation", defined as having a total number of tier 1 mutations at least 2 standard deviations greater (1 standard deviation = 329) than the rest of the samples. The total number of point mutations (tiers 1–3) was much higher in tobacco smokers (median 15,659, range 7,424 to 26,202, LUC9 not included) relative to never smokers (median 888, range 842 to 1,268). Similarly, the total number of point mutations involving coding regions (tier 1) also was much higher in smokers (median 209, range 104 to 1363) compared to never smokers (median 18, range 10 to 22). The total number of point mutations in the former light smoker was 403 in tiers 1–3, with only 10 in tier 1 (Supplemental Table S8). Consistent with previous reports (Ding et al., 2008; Lee et al., 2010), lung cancer due to tobacco smoking is associated with significantly higher number of mutations per Mb (mutations per Mb: median 10.5 range 4.9 to 17.6, LUC9 not included) compared to never-smokers with lung cancer (mutations per Mb: median 0.6, range 0.6 to 0.9) and a single former light smoker with lung cancer (0.3 mutations per Mb) in our study. Figure 1 illustrates the different characteristics of mutations in patients according to their smoking status. In particular, C:G→A:T transversions were noted predominantly in tobacco smokers whereas C:G→T:A transitions were the most frequent type of point mutations in never- smokers with lung cancer and the former light smoker, consistent with previously reported studies (Ding et al., 2008; Lee et al., 2010). The mutational spectrum of the single large cell carcinoma sample was not different from those of lung adenocarcinoma associated with tobacco smoking. Overall the number of point mutations in the lung cancer genome appears to be closely related to the patient's tobacco smoking status and the landscape of the former light smoker genome suggests a possible dose-response relationship between the amount and duration of tobacco smoke exposure and the extent of mutational burden. The hypermutated tumor (LUC9) was found to have point mutations involving several DNA repair genes including PRKDC, TP53, MSH3, POLK, MSH4, FANCM, FBXW7, TOP2B, MLH1, RPA2, BUB1, FANCB and TOP1 (Wood et al., 2001) (http://www.genesilico.pl/index.php/home.html). It is possible that these mutations in DNA repair genes resulted in an impaired ability to repair sustained DNA damage induced by chronic tobacco smoke. Somatically mutated genes in lung cancer Recurrent mutations (previously reported in lung cancer) Given the limited sample size of our study, to prioritize additional important mutations, we used an alternative analysis focusing on tier 1 mutations previously reported in lung cancer as reported in the Catalogue of Somatic Mutations in Cancer (COSMIC) (http://www.sanger.ac.uk/genetics/CGP/cosmic/). In addition to the well-known mutations involving KRAS, EGFR, and TP53 genes, this approach revealed several other recurrent point mutations in lung cancer (Figure 1) including kinase genes that may serve as potential therapeutic targets including BRAF (D594N and V413L), JAK2 (V615L and M532V), JAK3 (A1090S), EPHA3 (M320I, G187R, T393K, and R728L), EPHA4 (E670D), STK11 (D327fs), LTK (R669*), MET (Q99L and Y1003N) and ITK (Y588*) (Supplemental Table S3). Significantly mutated genes (not reported previously in lung cancer) We previously developed the

significantly mutated gene (SMG) algorithm to detect, in an unbiased manner, biologically significant variants from cancer genome sequencing data (Dees et al., 2012) (Figure 1). The statistical significance of mutations in each gene is determined by comparing the mutation frequency of each gene with the background mutation rate across all samples. The algorithm identified 9 genes that were highly significant (Supplemental Table S9, false discovery rate q≤0.05 for two tests, See Supplemental Methods). We did not find any correlations between gender and mutations (Supplemental Table S10). Of the nine significantly mutated genes, mutations involving DACH1, RELN and ABCB5 genes have not been previously reported in lung cancer. Low DACH1 expression levels were associated with poor prognosis in patients with breast cancer (Wu et al., 2006). DACH1 has been reported to have a tumor suppressor role in prostate cancer and in gliomas (Watanabe et al., 2011; Wu et al., 2009). In our study, two frame shift mutations (LUC9: K636fs and LUC13: A656fs) in the coiled coil domain (CCD) of the DACH1 gene were identified. Analysis of RNA-seq data for DACH1 from the hypermutated sample pair revealed an FPKM (fragments per kilobase of exon per million fragments mapped, Supplemental Methods) expression level of 2.257 in the normal sample, while the tumor sample had an expression level of 0.962. This result is corroborated in the WGS data, where three samples (LUC9, LUC15, and LUC20) show a DACH1 copy number loss in the tumor sample (Supplemental Table S11). Lastly our recurrent screening (n = 96) for mutations in DACH1 identified two more non-silent mutations including one missense mutation (D584G) and one nonsense mutation (G430*). Recurrent point mutations in the RELN gene were identified in three samples (LUC13: A1189D, LUC18: Y3301*, and LUC9: H3224N, I1228N, and R301I). Mutations in the RELN gene have been identified in pediatric early T-cell precursor acute lymphoblastic leukemia (Zhang et al., 2012). We also discovered three samples with nonsynonymous point mutations (LUC11: G347R, LUC12: M521L, and LUC9: P580S and A687S) in the ABCB5 gene, which encodes a membrane transporter protein belonging to the ATP binding cassette (ABC) protein family.. There were other genes that did not meet the threshold for significance on the SMG test but were included for testing for recurrence in our extension set (n = 96). Three candidate genes HGF, CFTR, and MICAL3 were chosen for various reasons including the possibility of being a therapeutic target for lung cancer (HGF), their association with other lung diseases (CFTR-cystic fibrosis) or were ssociated with never-smokers (MICAL3). The overall prevalence of these mutations in the combined set of 17 samples used for lung cancer whole genome analysis and 96 samples used for validation was 4.4% (HGF), 4.4% (CFTR), and 0.9% (MICAL3) (Supplemental Table S12). We identified five point mutations involving the CFTR gene in four samples; these included four missense (LUC18: M82V, LUC9: R170L, and F354I and A309S from panel screening) and one nonsense (LUC18: S478*) mutations. Two of the five point mutations involving CFTR (M82V & S478*) have been previously reported in patients with cystic fibrosis (Koukourakis et al., 2003). Recently drugs that target specific CFTR point mutations (G551D and other nonsense mutations) have shown therapeutic benefit in patients with cystic fibrosis (Ramsey et al., 2011).. Chromatin associated genes are found to be mutated in tumor samples from both never smokers and smokers. We identified 73 non-synonymous point mutations in 66 chromatin-associated genes including mutations involving SETD2, ARID1A, and ARID2 (Supplemental Table S13). A nonsense mutation (Q1977*) in SETD2 was identified in LUC11 from a never smoker and two missense mutations (E1735K in ARID1A and V465L in ARID2) were identified in two smokers (LUC14 and LUC18). Exome sequencing of hepatocellular carcinomas have reported recurrent mutations involving the ARID2 gene (Li et al., 2011) and frequent mutations in ARID1A have been reported in ovarian clear cell carcinoma (Jones et al., 2010a) and endometriosis-associated ovarian cancer (Wiegand et al., 2010). Several point mutations in histone methyltransferase genes (MLL3, MLL4, WHSC1L1 and ASH1L) were identified as well. Tumor heterogeneity analysis using deep digital sequencing data By performing targeted sequencing with high read coverage (mean depth of 381 reads) to validate variants detected by WGS, we were able to accurately estimate the variant allele frequencies (VAFs) for somatic mutations identified in each tumor sample. Based on the VAF distribution, we were able to estimate the number and size of the clonal populations in each tumor sample. Recent studies have shown the importance of clonal evolution in tumor progression and development of metastasis (Ding et al., 2012; Gerlinger et al., 2012) Using mutations from copy number neutral regions, we found that 10 tumors had a multi-clonal signature while seven tumors were largely monoclonal (Table 1 and Figure 2). We did not find any correlation between smoking status and tumor clonality. Based on the VAFs of mutations, we were able to identify mutations that were present in the founding clone and/or the subclone(s). All EFGR and KRAS mutations validated in our cohort were present in the founder clones of the associated tumor samples (for example, the EGFR mutation in LUC15 at 19% VAF, Figure 2D, and the KRAS mutation in LUC10 at 48% VAF, Figure 2F). The clonal distributions of other mutations involving genes such as HGF were varied between samples. In the LUC9 tumor in particular, which exhibits two distinct mutation clusters at median VAFs 41.1% and 20.4%, an HGF mutation exists in both subclones (Figure 2E). We extended the subclonality analyses to copy number alterations (in particular, deletions) for LUC9, using an algorithm that compare the observed read counts with the expected diploid read counts in the affected intervals. We found a biclonal pattern in the deletions similar to what we observed with SNV analysis described above (Supplemental Table S14, Supplemental Figure S1). In LUC10, an HGF mutation exists in the secondary clone at 17% VAF (Figure 2F). It is likely that EGFR and KRAS mutations are initiating events for lung cancer and other mutations such as HGF mutations are acquired later and perhaps are important for tumor maintenance and progression."

Superclasses (1)

- Non-Small_Cell_Lung_Cancer

Disjoints (690)

'\'Abraxane_(Paclitaxel_Albumin-stabilized_Nanoparticle_Formulation)_\'', '\'Afinitor_(Everolimus)\'', '\'Afinitor_Disperz_(Everolimus)_\'', '\'Alecensa_(Alectinib)_\'', '\'Alimta_(Pemetrexed_Disodium)_\'', '\'Alunbrig_(Brigatinib)_\'', '\'Alymsys_(Bevacizumab)_\'', '\'Avastin_(Bevacizumab)_\'', '\'Cyramza_(Ramucirumab)_\'', '\'Enhertu_(Fam-Trastuzumab_Deruxtecan-nxki)_\'', '\'Etopophos_(Etoposide_Phosphate)_\'', '\'Exkivity_(Mobocertinib_Succinate)_\'', '\'Gavreto_(Pralsetinib)_\'', '\'Gemzar_(Gemcitabine_Hydrochloride)_\'', '\'Gilotrif_(Afatinib_Dimaleate)_\'', '\'Hycamtin_(Topotecan_Hydrochloride)_\'', '\'Imfinzi_(Durvalumab)_\'', '\'Imjudo_(Tremelimumab-actl)_\'', '\'Infugem_(Gemcitabine_Hydrochloride)_\'', '\'Iressa_(Gefitinib)_\'', '\'Keytruda_(Pembrolizumab)_\'', '\'Krazati_(Adagrasib)_\'', '\'Libtayo_(Cemiplimab-rwlc)_\'', '\'Lorbrena_(Lorlatinib)_\'', '\'Lumakras_(Sotorasib)_\'', '\'Mekinist_(Trametinib_Dimethyl_Sulfoxide)_\'', '\'Mvasi_(Bevacizumab)_\'', '\'Opdivo_(Nivolumab)_\'', '\'Portrazza_(Necitumumab)_\'', '\'Retevmo_(Selpercatinib)_\'', '\'Rozlytrek_(Entrectinib)_\'', '\'Rybrevant_(Amivantamab-vmjw)_\'', '\'Tabrecta_(Capmatinib_Hydrochloride)_\'', '\'Tafinlar_(Dabrafenib_Mesylate)_\'', '\'Tagrisso_(Osimertinib_Mesylate)_\'', '\'Taxotere_(Docetaxel)_\'', '\'Tecentriq_(Atezolizumab)_\'', '\'Tepmetko_(Tepotinib_Hydrochloride)_\'', '\'Trexall_(Methotrexate_Sodium)_\'', '\'Vizimpro_(Dacomitinib)_\'', '\'Xalkori_(Crizotinib)_\'', '\'Yervoy_(Ipilimumab)_\'', '\'Zirabev_(Bevacizumab)_\'', '\'Zykadia_(Ceritinib)_\'', 4A_NSCLC, 4B_NSCLC, Adagrasib_, Adherence_Based_on_Socioeconomics_LC, Adherence_Factors_LC, Adverse_Reactions_ABRAX, Adverse_Reactions_ADAGR, Adverse_Reactions_AFATI, Adverse_Reactions_AFINI, Adverse_Reactions_AFINIT, Adverse_Reactions_ALECE, Adverse_Reactions_ALIMT, Adverse_Reactions_ALUNB, Adverse_Reactions_ALYMS, Adverse_Reactions_AMIVA, Adverse_Reactions_ATEZO, Adverse_Reactions_AVAST, Adverse_Reactions_BRIGA, Adverse_Reactions_CAPMA, Adverse_Reactions_CEMIP, Adverse_Reactions_CYRAM, Adverse_Reactions_DOXOR, Adverse_Reactions_DURVA, Adverse_Reactions_ENHER, Adverse_Reactions_ENTRE, Adverse_Reactions_ERLOT, Adverse_Reactions_ETOP, Adverse_Reactions_ETOPO, Adverse_Reactions_EXKIV, Adverse_Reactions_GAVRE, Adverse_Reactions_GEFIT, Adverse_Reactions_GEMZA, Adverse_Reactions_GILOT, Adverse_Reactions_HYCAM, Adverse_Reactions_IMFIN, Adverse_Reactions_IMJUD, Adverse_Reactions_INFUG, Adverse_Reactions_IRESS, Adverse_Reactions_KEYTR, Adverse_Reactions_KRAZA, Adverse_Reactions_LIBTA, Adverse_Reactions_LORBR, Adverse_Reactions_LUMAK, Adverse_Reactions_LURB, Adverse_Reactions_MEKIN, Adverse_Reactions_METH, Adverse_Reactions_MVASI, Adverse_Reactions_OPDIV, Adverse_Reactions_PORTR, Adverse_Reactions_RAMUC, Adverse_Reactions_RETEV, Adverse_Reactions_ROZLY, Adverse_Reactions_RYBRE, Adverse_Reactions_SELPE, Adverse_Reactions_SOTOR, Adverse_Reactions_TABRE, Adverse_Reactions_TAFIN, Adverse_Reactions_TAGRIS, Adverse_Reactions_TAXOT, Adverse_Reactions_TECEN, Adverse_Reactions_TEPME, Adverse_Reactions_TOPO, Adverse_Reactions_TRAME, Adverse_Reactions_TREME, Adverse_Reactions_TREXA, Adverse_Reactions_VINOR, Adverse_Reactions_VIZIM, Adverse_Reactions_XALKO, Adverse_Reactions_YERVO, Adverse_Reactions_ZIRAB, Adverse_Reactions_ZYKAD, Afatinib_Dimaleate_, Age, Air_Pollution, Amivantamab-vmjw_, Atezolizumab_, Behavioral_Factors_LC, Beta_Carotene_Supplements_LC, Bio_Sensors_LC, Biological_Effects_LC, Breathalyzer_LC, Breathing_LC, Brigatinib_, Capmatinib_Hydrochloride_, Causes_and_Risks_LC, Cemiplimab-rwlc_, Chemical_Sensors_LC, Choosing_Quality_of_Life_-_Reasons_People_Forego_Treatment, Choosing_Survival_-_Deciding_to_Undergo_Treatment, Complications_LC, Contraindications_ABRAX, Contraindications_ADAGR, Contraindications_AFATI, Contraindications_AFINI, Contraindications_AFINIT, Contraindications_ALECE, Contraindications_ALIMT, Contraindications_ALUNB, Contraindications_ALYMS, Contraindications_AMIVA, Contraindications_ATEZO, Contraindications_AVAST, Contraindications_BRIGA, Contraindications_CAPMA, Contraindications_CEMIP, Contraindications_CYRAM, Contraindications_DOXOR, Contraindications_DURVA, Contraindications_ENHER, Contraindications_ENTRE, Contraindications_ERLOT, Contraindications_ETOP, Contraindications_ETOPO, Contraindications_EXKIV, Contraindications_GAVRE, Contraindications_GEFIT, Contraindications_GEMZA, Contraindications_GILOT, Contraindications_HYCAM, Contraindications_IMFIN, Contraindications_IMJUD, Contraindications_INFUG, Contraindications_IRESS, Contraindications_KEYTR, Contraindications_KRAZA, Contraindications_LIBTA, Contraindications_LORBR, Contraindications_LUMAK, Contraindications_LURB, Contraindications_MEKIN, Contraindications_METH, Contraindications_MVASI, Contraindications_OPDIV, Contraindications_PORTR, Contraindications_RAMUC, Contraindications_RETEV, Contraindications_ROZLY, Contraindications_RYBRE, Contraindications_SELPE, Contraindications_SOTOR, Contraindications_TABRE, Contraindications_TAFIN, Contraindications_TAGRIS, Contraindications_TAXOT, Contraindications_TECEN, Contraindications_TEPME, Contraindications_TOPO, Contraindications_TRAME, Contraindications_TREME, Contraindications_TREXA, Contraindications_VINOR, Contraindications_VIZIM, Contraindications_XALKO, Contraindications_YERVO, Contraindications_ZIRAB, Contraindications_ZYKAD, Cultural_Beliefs_and_Perceptions, Cultural_LC, Degrees_of_Smoking_LC, Demographic_Factors_LC, Diet_LC, Disparities_in_Incidence, Dosage_and_Administration_ABRAX, Dosage_and_Administration_ADAGR,

Dosage_and_Administration_AFATI, Dosage_and_Administration_AFINI, Dosage_and_Administration_AFINIT, Dosage_and_Administration_ALECE, Dosage_and_Administration_ALIMT, Dosage_and_Administration_ALUNB, Dosage_and_Administration_ALYMS, Dosage_and_Administration_AMIVA, Dosage_and_Administration_ATEZO, Dosage_and_Administration_AVAST, Dosage_and_Administration_BRIGA, Dosage_and_Administration_CAPMA, Dosage_and_Administration_CEMIP, Dosage_and_Administration_CYRAM, Dosage_and_Administration_DOXOR, Dosage_and_Administration_DURVA, Dosage_and_Administration_ENHER, Dosage_and_Administration_ENTRE, Dosage_and_Administration_ERLOT, Dosage_and_Administration_ETOP, Dosage_and_Administration_ETOPO, Dosage_and_Administration_EXKIV, Dosage_and_Administration_GAVRE, Dosage_and_Administration_GEFIT, Dosage_and_Administration_GEMZA, Dosage_and_Administration_GILOT, Dosage_and_Administration_HYCAM, Dosage_and_Administration_IMFIN, Dosage_and_Administration_IMJUD, Dosage_and_Administration_INFUG, 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Dosage_and_Administration_XALKO, Dosage_and_Administration_YERVO, Dosage_and_Administration_ZIRAB, Dosage_and_Administration_ZYKAD, Dosage_Forms_and_Strengths_ABRAX, Dosage_Forms_and_Strengths_ADAGR, Dosage_Forms_and_Strengths_AFATI, Dosage_Forms_and_Strengths_AFINI, Dosage_Forms_and_Strengths_AFINIT, Dosage_Forms_and_Strengths_ALECE, Dosage_Forms_and_Strengths_ALIMT, Dosage_Forms_and_Strengths_ALUNB, Dosage_Forms_and_Strengths_ALYMS, Dosage_Forms_and_Strengths_AMIVA, Dosage_Forms_and_Strengths_ATEZO, Dosage_Forms_and_Strengths_AVAST, Dosage_Forms_and_Strengths_BRIGA, Dosage_Forms_and_Strengths_CAPMA, Dosage_Forms_and_Strengths_CEMIP, Dosage_Forms_and_Strengths_CYRAM, Dosage_Forms_and_Strengths_DOXOR, Dosage_Forms_and_Strengths_DURVA, Dosage_Forms_and_Strengths_ENHER, Dosage_Forms_and_Strengths_ENTRE, Dosage_Forms_and_Strengths_ERLOT, Dosage_Forms_and_Strengths_ETOP, Dosage_Forms_and_Strengths_ETOPO, Dosage_Forms_and_Strengths_EXKIV, Dosage_Forms_and_Strengths_GAVRE, Dosage_Forms_and_Strengths_GEFIT, Dosage_Forms_and_Strengths_GEMZA, Dosage_Forms_and_Strengths_GILOT, Dosage_Forms_and_Strengths_HYCAM, Dosage_Forms_and_Strengths_IMFIN, Dosage_Forms_and_Strengths_IMJUD, Dosage_Forms_and_Strengths_INFUG, Dosage_Forms_and_Strengths_IRESS, Dosage_Forms_and_Strengths_KEYTR, Dosage_Forms_and_Strengths_KRAZA, Dosage_Forms_and_Strengths_LIBTA, Dosage_Forms_and_Strengths_LORBR, Dosage_Forms_and_Strengths_LUMAK, Dosage_Forms_and_Strengths_LURB, Dosage_Forms_and_Strengths_MEKIN, Dosage_Forms_and_Strengths_METH, Dosage_Forms_and_Strengths_MVASI, Dosage_Forms_and_Strengths_OPDIV, Dosage_Forms_and_Strengths_PORTR, Dosage_Forms_and_Strengths_RAMUC, Dosage_Forms_and_Strengths_RETEV, Dosage_Forms_and_Strengths_ROZLY, Dosage_Forms_and_Strengths_RYBRE, Dosage_Forms_and_Strengths_SELPE, Dosage_Forms_and_Strengths_SOTOR, Dosage_Forms_and_Strengths_TABRE, Dosage_Forms_and_Strengths_TAFIN, Dosage_Forms_and_Strengths_TAGRIS, Dosage_Forms_and_Strengths_TAXOT, Dosage_Forms_and_Strengths_TECEN, Dosage_Forms_and_Strengths_TEPME, Dosage_Forms_and_Strengths_TOPO, Dosage_Forms_and_Strengths_TRAME, Dosage_Forms_and_Strengths_TREME, Dosage_Forms_and_Strengths_TREXA, Dosage_Forms_and_Strengths_VINOR, Dosage_Forms_and_Strengths_VIZIM, Dosage_Forms_and_Strengths_XALKO, Dosage_Forms_and_Strengths_YERVO, Dosage_Forms_and_Strengths_ZIRAB, Dosage_Forms_and_Strengths_ZYKAD, Doxorubicin_Hydrochloride_, Drug_Interactions_ABRAX, Drug_Interactions_ADAGR, Drug_Interactions_AFATI, Drug_Interactions_AFINI, Drug_Interactions_AFINIT, Drug_Interactions_ALECE, Drug_Interactions_ALIMT, Drug_Interactions_ALUNB, Drug_Interactions_ALYMS, Drug_Interactions_AMIVA, Drug_Interactions_ATEZO, Drug_Interactions_AVAST, Drug_Interactions_BRIGA, Drug_Interactions_CAPMA, Drug_Interactions_CEMIP, Drug_Interactions_CYRAM, Drug_Interactions_DOXOR, Drug_Interactions_DURVA, Drug_Interactions_ENHER, Drug_Interactions_ENTRE, Drug_Interactions_ERLOT, Drug_Interactions_ETOP, Drug_Interactions_ETOPO, Drug_Interactions_EXKIV, Drug_Interactions_GAVRE, Drug_Interactions_GEFIT, Drug_Interactions_GEMZA, Drug_Interactions_GILOT, Drug_Interactions_HYCAM, Drug_Interactions_IMFIN, Drug_Interactions_IMJUD, Drug_Interactions_INFUG, Drug_Interactions_IRESS, Drug_Interactions_KEYTR, Drug_Interactions_KRAZA, Drug_Interactions_LIBTA, Drug_Interactions_LORBR, Drug_Interactions_LUMAK, Drug_Interactions_LURB, Drug_Interactions_MEKIN, Drug_Interactions_METH,

Drug_Interactions_MVASI, Drug_Interactions_OPDIV, Drug_Interactions_PORTR, Drug_Interactions_RAMUC, Drug_Interactions_RETEV, Drug_Interactions_ROZLY, Drug_Interactions_RYBRE, Drug_Interactions_SELPE, Drug_Interactions_SOTOR, Drug_Interactions_TABRE, Drug_Interactions_TAFIN, Drug_Interactions_TAGRIS, Drug_Interactions_TAXOT, Drug_Interactions_TECEN, Drug_Interactions_TEPME, Drug_Interactions_TOPO, Drug_Interactions_TRAME, Drug_Interactions_TREME, Drug_Interactions_TREXA, Drug_Interactions_VINOR, Drug_Interactions_VIZIM, Drug_Interactions_XALKO, Drug_Interactions_YERVO, Drug_Interactions_ZIRAB, Drug_Interactions_ZYKAD, Durvalumab_, E-Cigarettes_LC, Electronic_Sensors_LC, Emotions_LC, End_of_Life_Decisions, Entrectinib_, Environmental_Factors_LC, Enzymatic_Sensors_LC, Erlotinib_Hydrochloride_, Etoposide_, Exercise_LC, Extensive_Stage_SCLC, Family_History_LC, Gefitinib_, Geographical_Location, Habits_LC, HIV_Infection_LC, Immunosensors_LC, Increased_Susceptibility_LC, Indications_and_Usage_ABRAX, Indications_and_Usage_ADAGR, Indications_and_Usage_AFATI, Indications_and_Usage_AFINI, Indications_and_Usage_AFINIT, Indications_and_Usage_ALECE, Indications_and_Usage_ALIMT, Indications_and_Usage_ALUNB, Indications_and_Usage_ALYMS, Indications_and_Usage_AMIVA, Indications_and_Usage_ATEZO, Indications_and_Usage_AVAST, Indications_and_Usage_BRIGA, Indications_and_Usage_CAPMA, Indications_and_Usage_CEMIP, Indications_and_Usage_CYRAM, Indications_and_Usage_DOXOR, Indications_and_Usage_DURVA, Indications_and_Usage_ENHER, Indications_and_Usage_ENTRE, Indications_and_Usage_ERLOT, Indications_and_Usage_ETOP, Indications_and_Usage_ETOPO, Indications_and_Usage_EXKIV, Indications_and_Usage_GAVRE, Indications_and_Usage_GEFIT, Indications_and_Usage_GEMZA, Indications_and_Usage_GILOT, Indications_and_Usage_HYCAM, Indications_and_Usage_IMFIN, Indications_and_Usage_IMJUD, Indications_and_Usage_INFUG, Indications_and_Usage_IRESS, Indications_and_Usage_KEYTR, Indications_and_Usage_KRAZA, Indications_and_Usage_LIBTA, Indications_and_Usage_LORBR, Indications_and_Usage_LUMAK, Indications_and_Usage_LURB, Indications_and_Usage_MEKIN, Indications_and_Usage_METH, Indications_and_Usage_MVASI, Indications_and_Usage_OPDIV, Indications_and_Usage_PORTR, Indications_and_Usage_RAMUC, Indications_and_Usage_RETEV, Indications_and_Usage_ROZLY, Indications_and_Usage_RYBRE, Indications_and_Usage_SELPE, Indications_and_Usage_SOTOR, Indications_and_Usage_TABRE, Indications_and_Usage_TAFIN, Indications_and_Usage_TAGRIS, Indications_and_Usage_TAXOT, Indications_and_Usage_TECEN, Indications_and_Usage_TEPME, Indications_and_Usage_TOPO, Indications_and_Usage_TRAME, Indications_and_Usage_TREME, Indications_and_Usage_TREXA, Indications_and_Usage_VINOR, Indications_and_Usage_VIZIM, Indications_and_Usage_XALKO, Indications_and_Usage_YERVO, Indications_and_Usage_ZIRAB, Indications_and_Usage_ZYKAD, Limited_Stage_SCLC, Living_with_LC_LC, Location_LC, Lurbinectedin_, Marijuna_Smoking_LC, Medications_LC, Methotrexate_Sodium_, Never-Smokers_LC, Non-Small_Cell_LC, Non-Small_Cell_LC_NSCLC, Non-Small_Cell_Medication_LC_, Non-Smokers_LC, Non-Smokers_NSCLC, Non-Smokers_SCLC, Nutrition_LC, Occupational_Exposure, Physical_Activity_For_Mitigation_of__LC, Physical_Activity_For_Prevention_Of_LC, Preventative_habits_LC, Quitting/Not_Smoking_LC, Racial/Ethnic, Radiation_Exposure_LC, Ramucirumab_, Recurring_LC_NSCLC, Recurring_LC_SCLC, Rural_LC, Second-hand_Smoke_LC, Secondhand_Smoke_LC, Selpercatinib_, Sensor_Factors_LC, Size_of_the_community_LC, Sleep_LC, Small_Cell_LC, Small_Cell_LC_SCLC, Small_Cell_Lung_Cancer, Small_Cell_Medication_LC_, Smoke_LC, Smokers_LC, **Smokers_NSCLC**, Smokers_SCLC, Smoking_LC, Smoking_Marijuana_LC, Smoking_Other_Drugs_LC, Smoking_Tobacco_LC, Socioeconomics_LC, Sotorasib_, Stage_0_NSCLC, Stage_1_NSCLC, Stage_1_SCLC, Stage_2_NSCLC, Stage_3A_NSCLC, Stage_3B_NSCLC, Stage_4_NSCLC, Support_Groups_LC, Symptoms_and_Tests_LC, Symptoms_NSC, Symptoms_SC, Tests_NSC, Tests_SC, Tobacco_Smoking, Tobacco_Smoking_LC, Topotecan_Hydrochloride_, Tramentinib_Dimethyl_Sulfoxide, Treatment_Regimens_LC, Treatments_LC, Tremelimumab-actl_, Urban_LC, Use_in_Specific_Populations_ABRAX, Use_in_Specific_Populations_ADAGR, Use_in_Specific_Populations_AFATI, Use_in_Specific_Populations_AFINI, Use_in_Specific_Populations_AFINIT, Use_in_Specific_Populations_ALECE, Use_in_Specific_Populations_ALIMT, Use_in_Specific_Populations_ALUNB, Use_in_Specific_Populations_ALYMS, Use_in_Specific_Populations_AMIVA, Use_in_Specific_Populations_ATEZO, Use_in_Specific_Populations_AVAST, Use_in_Specific_Populations_BRIGA, Use_in_Specific_Populations_CAPMA, Use_in_Specific_Populations_CEMIP, Use_in_Specific_Populations_CYRAM, Use_in_Specific_Populations_DOXOR, Use_in_Specific_Populations_DURVA, Use_in_Specific_Populations_ENHER, Use_in_Specific_Populations_ENTRE, Use_in_Specific_Populations_ERLOT, Use_in_Specific_Populations_ETOP, 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Use_in_Specific_Populations_TRAME, Use_in_Specific_Populations_TREME, Use_in_Specific_Populations_TREXA, Use_in_Specific_Populations_VINOR, Use_in_Specific_Populations_VIZIM, Use_in_Specific_Populations_XALKO, Use_in_Specific_Populations_YERVO, Use_in_Specific_Populations_ZIRAB, Use_in_Specific_Populations_ZYKAD, Vinorelbine_Tartrate_, Warnings_and_Precautions_ABRAX, Warnings_and_Precautions_ADAGR, Warnings_and_Precautions_AFATI, Warnings_and_Precautions_AFINI, Warnings_and_Precautions_AFINIT, Warnings_and_Precautions_ALECE, Warnings_and_Precautions_ALIMT, Warnings_and_Precautions_ALUNB, Warnings_and_Precautions_ALYMS, Warnings_and_Precautions_AMIVA, Warnings_and_Precautions_ATEZO, Warnings_and_Precautions_AVAST, Warnings_and_Precautions_BRIGA, Warnings_and_Precautions_CAPMA, Warnings_and_Precautions_CEMIP, Warnings_and_Precautions_CYRAM, Warnings_and_Precautions_DOXOR, Warnings_and_Precautions_DURVA, Warnings_and_Precautions_ENHER, Warnings_and_Precautions_ENTRE, Warnings_and_Precautions_ERLOT, Warnings_and_Precautions_ETOP, Warnings_and_Precautions_ETOPO, Warnings_and_Precautions_EXKIV, Warnings_and_Precautions_GAVRE, Warnings_and_Precautions_GEFIT, Warnings_and_Precautions_GEMZA, Warnings_and_Precautions_GILOT, Warnings_and_Precautions_HYCAM, Warnings_and_Precautions_IMFIN, Warnings_and_Precautions_IMJUD, Warnings_and_Precautions_INFUG, Warnings_and_Precautions_IRESS, Warnings_and_Precautions_KEYTR, Warnings_and_Precautions_KRAZA, Warnings_and_Precautions_LIBTA, Warnings_and_Precautions_LORBR, Warnings_and_Precautions_LUMAK, Warnings_and_Precautions_LURB, Warnings_and_Precautions_MEKIN, Warnings_and_Precautions_METH, Warnings_and_Precautions_MVASI, Warnings_and_Precautions_OPDIV, Warnings_and_Precautions_PORTR, Warnings_and_Precautions_RAMUC, Warnings_and_Precautions_RETEV, Warnings_and_Precautions_ROZLY, Warnings_and_Precautions_RYBRE, Warnings_and_Precautions_SELPE, Warnings_and_Precautions_SOTOR, Warnings_and_Precautions_TABRE, Warnings_and_Precautions_TAFIN, Warnings_and_Precautions_TAGRIS, Warnings_and_Precautions_TAXOT, Warnings_and_Precautions_TECEN, Warnings_and_Precautions_TEPME, Warnings_and_Precautions_TOPO, Warnings_and_Precautions_TRAME, Warnings_and_Precautions_TREME, Warnings_and_Precautions_TREXA, Warnings_and_Precautions_VINOR, Warnings_and_Precautions_VIZIM, Warnings_and_Precautions_XALKO, Warnings_and_Precautions_YERVO, Warnings_and_Precautions_ZIRAB, Warnings_and_Precautions_ZYKAD

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