tarceva® Tarceva®

erlotinibi

1. aRweriloba

1.1 medikamentis Terapiul/farmakologiuri klasi:

antoneoplasturi saSualeba**.**

1.2. dozirebis formi tipebi:

tarcevas Semogarsuli tabletebi 25mg, 100mg, 150mg.

Semogarsuli, moTeTro moyviTalo feris, mrgvali, ormxrivad gamozneqili tabletebi, sxvadasva SeferilobiT tabletebis dozebis Sesabamisad.

an Semogarsuli, moTeTro moyviTalo, mrgvali, ormxrivad gamozneqili tabletebi, cal mxares datanili ’T25, T100 an T150’ gravirebiT tabletebis dozebis Sesabamisad.

1.3 miRebis gza:

peroraluri.

1.4 steriloba/radioaqtivoba:

monacemebi ar aris.

1.5. Tvisobrivi da raodenobrivi Semadgenloba

aqtiuri nivTiereba: erlotinibis hidroqloridi

TiToeuli dozirebuli Semogarsuli tabletSi Seicavs erlotinibis hidroqlorids, rac Seesabameba 25mg, 100mg da 150mg erlotinibis Semcvelobas.

Semasveblebis CamonaTvali

tabletis birTvi

laqtozas monohidrati	Ph. Eur./ USP/ JP
celuloza, mikrokristaluri	Ph. Eur./ USP/ JP
natriumis saxameblis glikolati	Ph. Eur./ USP/ JPE
natriumis laurilsulfati	Ph. Eur./ USP/ JP
magniumis stearati	Ph. Eur./ USP/ JP

tabletis garsi

hidroqsipropil celuloza	Ph. Eur./USP/JP
titanis dioqsidi	Ph. Eur./ USP/ JP
polieTilenglikoli	Ph. Eur./ NF/ JP
hidroqsipropil meTilceluloza	Ph. Eur./ USP/ JP

2. klinikuri maxasiaTeblebi

2.1 Terapiuli Cvenebebi

filtvis arawvrilujredovani kibo:

tarceva naCvenebia filtvis lokalurad ganviTarebuli an metastazuri arawvrilujredovani kibos samkurnalod manamde Catarebuli minimum erTi qimioTerapiuli reJimis araefeqturobis Semdeg.

pankreasis kibo:

tarcevasa da gemcitabinis kombinacia naCvenebia, rogorc pankreasis lokalurad ganviTarebuli, ararezeqcirebadi an metastazuri kibos pirveli rigis mkurnaloba.

2.2 dozireba da gamoyenebis meTodebi

standartuli dozireba

filtvis arawvrilujredovani kibo:

tarcevas rekomendebuli dRiuri doza aris 150mg, sakvebis miRebamde minimum 1 saaTiT adre, an sakvebis miRebidan 2 sT-is Semdeg.

pankreasis kibo:

tarcevas rekomendebuli sadReRamiso doza aris 100mg sakvebis miRebamde minimum 1 saaTiT adre, an sakvebis miRebidan 2 sT-is Semdeg gemcitabinTan kombinaciaSi (gemcitabinis Cveneba pankreasis kibos mkurnalobisTvis ixileT mis instruqciaSi).

2.2.1 specialuri dozirebis instruqciebi

CYP 3A4 substratebis da modulatorebis erTdroulma gamoyenebam SesaZloa saWiro gaxados dozis modificireba (ix. seqcia 2.4.3 sxva medikamentebTan urTierTqmedeba da urTierTqmedebis sxva formebi).

rodesac saWiroa dozis modificireba, rekomendebulia misi Semcireba 50mg-iani safexurebiT (ix. seqcia 2.4 gafrTxileba da sifrTxilis zomebi, agreTve seqcia 2.4.3 sxva medikamentebTan urTierTqmedeba da urTierTqmedebis sxva formebi).

RviZlis ukmarisoba: erlotinibis eliminacia xdeba RviZlSi metabolizmis da biliaruli eqskreciis gziT. miuxedavad imisa, rom erlotinibis eqspozicia RviZlis normaluri funqciebis da RviZlis zomieri ukmarisobis SemTxvevebSi (Child-Pugh 7-9 qula) iyo analogiuri, mainc aucilebelia sifrTxile tarcevas gamoyenebisas RviZlis ukmarisobis mqone pacientebSi. mZime gverdiTi reaqciebis gamovlenisas rekomendebulia tarcevas dozis Semcireba an mkurnalobis Sewyveta. tarcevas usafrTxoeba da efeqturoba RviZlis mZime ukmarisobis mqone pacientebSi ar Seswavlila (ix. seqcia 2.4.1 zogadi gafrTxileba da sifrTxilis zomebi [*hepatiti, RviZlis ukmarisoba*], agreTve seqcia 3.2.5 farmakokinetika specialur populaciaSi).

Tirkmlis ukmarisoba: tarcevas usafrTxoeba da efeqturoba Tirkmlis ukmarisobis mqone pacientebSi ar Seswavlila (ix. seqcia 3.2.5 farmakokinetika specialur populaciaSi).

pediatriuli gamoyeneba: tarcevas usafrTxoeba da efeqturoba 18 wlamde asakis pacientebSi ar Seswvlila.

mweveloba: sigaretis mweveloba amcirebs erlotinibis eqspozicias 50-60%-iT. tarcevas maqsimaluri tolerabeluri doza aqtiur mwevelebSi arawvrilujredovani kibos (NSCLC) dros Seadgens 300mg-s. rekomendebulze meti sawyisi dozebis efeqturoba da grZelvadiani usafrTxoeba pacientebSi, romelnic agrZeleben Tambaqos moxmarebas dadgenili ar aris (ix. seqcia 2.4.3 sxva medikamentebTan urTierTqmedeba da urTierTqmedebis sxva formebi, agreTve seqcia 3.2.5 farmakokinetika specialur populaciaSi).

2.3 winaaRmdegCvenebebi:

tarceva winaaRmdegnaCvenebia ernotinibis an tarcevas SemadgenlobaSi Semavali sxva romelime komponentis mimarT mZime formis hipersensitiulobis arsebobisas.

2.4. gafrTxileba da sifrTxilis zomebi

2.4.1 zogadi

filtvebis intersticiuli daavadeba: tarcevas gamoyenebisas filtvis arawvrilujredovani kibos (NSCLC), pankreasis kibos an sxva Sorswasuli soliduri simsivneebis samkurnalod, filtvebis intersticiuli daavadebis ILD-magvari, maT Soris fataluri SemTxvevebi aRiniSna iSviaTad. sabaziso kvlevaSi BR.21 filtvis arawvrilujredovani kibos dros seriozuli ILD-magvari movlenebis incidentobam placebosa da tarcevas jgufebSi Seadgina 0.8%. pankreasis kibos kvlevis farglebSi gemcitabinisa da tarcevas kombinaciiT mkunalobisas ILD-magvari movlenebis incidentobam gemcitabinis da tarcevas jgufSi Seadgina 2.5%, xolo gemcitabinisa da placebos jgufSi - 0.4%. zogadma incidentobam tarcevas gamoyenebisas yvela Catarebul kvlevaSi (arakontrolirebadi kvlevebis da paraleluri qimioTerapiiT mimdinare kvlevebis CaTvliT) Seadgina daaxloebiT 0.6%. ILD-magvari movlenebis dafiqsirebisas angariSebSi figurirebs Semdegi diagnozebi: pnevmoniti, radiaciuli pnevmoniti, hipersensitiuri pnevmoniti, intersticiuli pnevmonia, filtvis intersticiuli daavadeba, obliteraciuli bronqioliti, filtvis fibrozi, mwvave respiratoruli distres sindromi, filtvis infiltracia da alveoliti. aRniSnuli ILD-magvari mdgomareobebi iwyeboda tarcevas iniciaciis Semdeg ramdenime dRidan ramdenime TveSi. SemTxvevaTa umetesoba asocirdeboda xelSemwyobi an mamodificirebeli faqtorebis arsebobasTan, rogoricaa paraleluri an manamde Catarebuli qimioTerapia, manamde Catarebuli radiaciuli Terapia, manamde arsebuli filtvis parenqimuli daavadeba, filtvis metastazuri daavadeba, an respiratoruli infeqciebi.

pacientebs, romlebsac ganuviTarda mwvave da/an progresirebadi auxsneli pulmonaluri simptomebi, rogoricaa dispnea, xvela da cxeleba, tarcevas gamoyeneba unda SeuCerdes diagnostikuri Sefasebis Catarebamde. Tu diagnostirebulia filtvis intersticiuli daavadeba, tarcevas gamoyeneba unda Sewydes da saWiroebisamebr inicirdes Sesabamisi mkurnaloba (ix. seqcia 2.6 arasasurveli efeqtebi).

diarea, dehidratacia, eleqtrolituri disbalansi da Tirkmlis ukamrisoba: tarcevas miRebisas zog pacients aReniSna diarea, romlis zomieri da mZime formebi saWiroebs loperamidiT mkurnalobas. zogierT SemTxvevaSi SesaZlebelia saWiro gaxdes dozis Semcireba. mZime an persistiuli diareis, gulisrevis, anoreqsiis an Rebinebis SemTxvevaSi, romelic iwvevs dehidratacias, tarcevas miReba unda SeCerdes da miRebuli iqnas Sesabamisi zomebi dehidrataciis samkurnalod (ix. seqcia 2.6 arasasurveli efeqtebi). cnobilia hipokalemiisa da Tirkmlis ukmarisobis (maT Soris fataluri ukmarisobis) ganviTarebis iSviaTi SemTxvevebi, romelTagan nawili meoradad aris gamowveuli diareasTan, Rebinebasa da/an anoreqisiasTan dakavSirebuli dehidrataciis gamo, rac zogjer Rrmavdeba paraleluri qimioTerapiis zegavleniT. gansakuTrebiT mZime an persistuli daireis SemTxvevebSi, an dehidratacis sxva xelSemwyobi risk-faqtorebis arsebobisas (sxva medikamentebis paraleluri miReba, Tanmxlebi daavadebebi, simptomebi an sxva xelSemwyobi faqtorebi, mag. xandazmuli asaki), rekomendebulia tarcevas miRebis Sewyveta da intensiuri intravenuri dehidrataciis zomebis uzrunvelyofa. garda amisa, dehidrataciis riskis mqone pacientebSi saWiroa eleqtrolitebis, maT Soris kaliumis donis mudmivi monitoringi.

hepatiti, RviZlis ukmarisoba: tarcevas gamoyenebisas dafiqsirebulia RviZlis ukmarisobis (maT Soris fataluri ukmarisobis) iSviaTi SemTxvevebi. RviZlis ukamrisobis ganviTarebis xelSemwyob faqtorebs miekuTvneba RviZlis manamde arebuliDdaavadeba, an hepatotoqsiuri preparatebis miReba. aqedan gamomdinare, aseT SemTxvevebSi rekomendebulia RviZlis funqciuri testebis perioduli monitoringi. RviZlis mZime funqciuri dazianebis SemTxvevaSi rekomendebulia tarcevas miRebis Sewyveta (ix. seqcia 2.6 arasasurveli efeqtebi).

gastro-intestinuri traqtis perforacia: tarcevas miRebisas izrdeba gastro-intestinuri traqtis organoebis perforaciis riski, rac dafiqsirebulia iSviaT SemTxvevebSi (maT Soris fataluri perforaciis ramdenime SemTxveva). antiangiogenezuri medikamentebis, kortikosteroidebis, anTebis sawinaaRmdego arasteroiduli saSualebebis (NSAID) paraleluri gamoyenebis da/an taqsanis Semcveli qimioTerapiis SemTxvevebSi, agreTve anamnesturad peftiuri wylulebis da divertikulozis arsebobisas aRniSnuli riski matulobs. gastrointestinuri perforaciis ganviTarebis SemTxvevebSi aucilebelia tarcevas miRebis permanenturi Sewyveta. (ix. seqcia 2.6 arasasurveli efeqtebi).

kanis bulozuri da eqsfoliatiuri dazianeba: tarcevas miRebisas SesaZlebelia kanis bulozuri, blisteruli da eqsfoliatiuri dazianebis ganviTareba, stevens-jonsonis sindromis/toqsiuri epidermuli nekrolizis Zalian iSviaTi (zogjer fataluri) SemTxvevebis CaTvliT (ix. seqcia 2.6 arasasurveli efeqtebi). mZime formis bulozuri, blisteruli an eqsfoliatiuri dazianebis ganviTarebis SemTxvevebSi aucilebelia tarcevas miRebis SeCereba an Sewyveta.

ofTalmologiuri garTulebebi: tarcevas gamoyenebisas Zalian iSviaTad SesaZlebelia ganviTardes rqovanas perforacia an dawyluleba. sxva ofTalmologiur garTulebebs, romlebic aRiniSna tarcevas miRebisas, miekuTvneba quTuToebis zomaSi paTologiuri zrda, mSrali keratokoniuqtiviti an keratiti, rac Tavis mxriv warmoadgens rqovanas perforaciis/ulceraciis risk-faqtors. Sesabamisad, oftalmologiuri garTulebebis (mag. Tvalis tkivilis) wvave ganviTarebis an progresirebadi gauaresebis SemTxvevebSi aucilebelia tarcevas miRebis SeCereba an Sewyveta. (ix. seqcia 2.6 arasasurveli efeqtebi).

sxva medikamentebTan urTierTqmedeba: tarcevas gaaCnia sxva medikamentebTan klinikurad mniSvnelovani urTierTqmedebis potenciali (ix. seqcia 2.4.3 sxva samedicino produqtTan urTierTqmedeba da urTierTqmedebis sxva formebi).

2.4.2 avtomanqanebisa da manqana-danadgarebis marTvis unari

erlotinibis avtomanqanebisa da manqana-danadgarebis marTvis unarze zegavlenis Semswavleli kvlevebi ar Catarebula. Tumca, mentaluri unarebis darRvevebi erlotinibTan asocirebuli ar aris.

2.4.3 sxva medikamentebTan urTierTqmedeba da urTqmedebis sxva formebi

adamianebis sxeulSi erlotinibi metabolizdeba RviZlSi, RviZlis citoqromebis meSveobiT, ZiriTadad CYP3A4-iT, ufro naklebad CYP1A2-iT da pulmonaluri izoformiT CYP1A1.

Sesabamisad, SesaZlebelia Tavi iCinos urTierTqmedebebma im medikamentebis gamoyenebisas, romelTa metabolimzi xorcieldeba aRniSnuli fermentebiT, an romelnic am fermentebis inhibitorebi an inuqtorebi arian.

CYP3A4-is potenturi inhibitorebi aqveiTeben erlotinibis metabloizms da zrdian mis koncentracias plazmaSi. CYP3A4 metabolizmis ketonokonazoliT inhibirebis Sedegad (200mg, p/o, orjer dreSi 5 dRis ganmavlobaSi) erlotinibis eqspozicia gaizarda (86%-mde erlotinibis medianur eqspoziciaSi [AUC]), xolo maqsimalurma koncentraciam (C_{max}) imata 69%-iT mxolod erlotinibis gamoyenebasTan SedarebiT. tarcevas erTdrouli gamoyenebisas CYP3A4 da CYP1A2-is kidev erT inhibitorTan – ciprofloqsacinTan erTan, erlotinibis eqspozicia [AUC] da maqsimaluri koncentracia (C_{max}) gaizarda Sesabamisad 39%-iT da 17%-iT. aqedan gamomdinare, sifrTxilea saWiro tarcevas da CYP3A4-is potenturi inhibitoris, an CYP3A4/CYP1A2-is kombinirebuli inhibitoris erTdrouli gamoyenebisas. aseT situaciebSi, toqsiurobis niSnebis gamovlenisas, aucilebelia tarcevas dozis Semcireba.

CYP34A-is aqtivobis potenturi induqtorebi zrdian erlotinibis metabolizms da mniSvnelovnad amcireben mis koncentracias plazmaSi. CYP34A-is metabolizmis rifampiciniT inducirebis Sedegad (600mg, p/o dReSi oTxjer 7 dRis ganmavlobaSi) tarcevas 150mg dozis miRebisas erlotinibis medianuri AUC Semcirda 69%-iT mxolod tarcevas gamoyenebasTan SedarebiT.

rifampiciniT winaswari mkurnalobis, an paraleluri TanadaniSnvisas 450mg tarcevas erTjerad dozasTan erTad erlotinibis medianurma eqspoziciam (AUC) Seadgina rifampicinis gareSe daniSnuli 150mg tarcevas erTjeradi dozis 57.5%.Aamdenad, rodesac SesaZlebelia, rekomendebulia alternatiuli mkurnalobis gaTvaliswineba medikamentebiT, romelTac ar gaaCniaT CYP3A4-is induqciis Tviseba. Tu pacients esaWiroeba tarcevas da CYP3A4-is induqciis unaris mqone medikamentis, mag. rifampicinis, erTdrouli gamoyeneba, gasaTvaliswinebelia tarcevas dozis gazrda 300mg-mde misi usafrTxoebis profilis (ix. seqcia 2.4.1 zogadi gafrTxileba da sifrTxilis zomebi) zedmiwevniT monitoringis pirobebSi. 2 kviris ganmavlobaSi medikamentis kargi amtanobis SemTxvevaSi dasaSvebia dozis Semdgomi gazrda 450mg-mde usafrTxoebis profilis zedmiwevniT monitoringiT. ufro maRali dozebis gamoyeneba aRniSnul viTarebisTvis Seswavlili ar aris.

tarcevas winaswari mkurnaloba, an paraleluri TanadaniSnva ar axdens gavlenas CYP3A4-is prototipuri substratebis – midazolamis da eriTromicinis klirensze. Sesabamisad, ar aris mosalodneli mniSvnelovani gavlena sxva CYP3A4-is prototipuri substratebis klirensze.Mmidazolamis oraluri gamoyenebisas bioSeRwevadoba 24%-iT mcirdeboda, Tumca es ar iyo damokidebuli CYP3A4-is aqtivobaze.

erlotinibis xsnadoba pH-damokidebulia. pH-is matebisas erlotinibis xsnadoba mcirdeba. medikamentebi, romlebic moqmedeben gastro-intestinuri traqtis pH-ze, SesaZloa gavlenas axdendnen erlotinibis xsnadobasa da bioSeRwevadobaze. tarcevas erTdrouli gamoyenebisas omeprazolTan, romelic warmoadgens protonuli tumbos inhibitors, erlotinibis eqspozicia [AUC] da C_{max} mcirdeba Sesabamisad 46%-iT da 61%-iT. T_{max} da naxevraddaSlis periodis cvlilebebi ar gamovlenila. tarcevas erdrouli miRebisas 300mg

ranitidinTan, romelic warmoadgens H_2-receptorebis antagonists, erlotinibis eqspozicia [AUC] da C_{max} mcirdeba Sesabamisad 33%-iT da 54%-iT. amdenad, kuWis mJavianobaze moqmedi medikamentebis miReba tarcevasTan erTad sasurveli ar aris. aseT SemTxvevebSi tarcevas dozis gazrda savaraudod naklebad axdens misi eqspoziciis danakargis kompensirebas. Tumca, ranitidinis 150mg dozis orjeradad miRebisas tarcevas danawilebuli wesiT daniSvna ranitidinis miRebamde 2 sT-iT adre, an 10 sT-is Semdeg, iwvevda erlotinibis eqspoziciis [AUC] da C_{max} Semcirebas Sesabamisad mxolod 15%-iT da 17%-iT. amdenad, H_2-receptorebis antagonistebis gamoyenebis aucileblobis SemTxvevaSi mizanSewonilia ranitidinis gaTvaliswineba da gamoyeneba danawilebuli wesiT. tarcevas miReba saWiroa ranitidinis miRebamde 2 sT-iT adre, an 10 sT-is Semdeg.

klinikur kvlevebSi dafiqsirebulia tarcevas urTierTqmedeba kumarinul antikoagulantebTan, kerZod varfarinTan, romelTa Tanagamoyenebas Tan axlavs saerTaSoriso normalizebuli Tanafardobis (INR) mateba da sisxldenis SemTxvevebi (maT Soris fataluri). tarcevasa da kumarinuli antikoagulantebis Tanagamoyenebisas aucilebelia proTrombinis drois an INR-is nebismieri cvlilebis regularuli monitoringi.

tarcevas kombinirebuli gamoyeneba statinebTan SesaZloa zrdides statinebiT inducirebuli miopaTiis (maT Soris rabdomiolizis) ganviTarebis potencials, rac dafiqsirda kidec iSviaT SemTxvevebSi.

mwevelebs unda erCioT Tambaqos Tavis danebeba, radgan mas gaaCnia CYP1A1-is da CYP1A2-is induqciis efeqti, rac amcirebs erlotinibis eqspozicias 50-60%-iT (ix. seqcia 2.2.1 specialuri dozirebis instruqciebi, agreTve seqcia 3.2.5 farmakokinetika gansakuTrebul populaciebSi).

Ib fazis kvlevaSi gemcitabinisa da erlotinibis erTad miRebisas erTmaneTis farmakokinetikaze mniSvnelovani gavlena ar gamovlinda.

2.5 gamoyeneba gansakuTrebul populaciebSi

2.5.1 orsulebi

adeqvaturad kontrolirebadi kvlevebi tarcevas orsul qalebSi gamoyenebis Sesaswavlad Catarebuli ar aris. cxovelebSi Catarebul kvlevebSi naCvenebia garkveuli reproduqciuli toqsiuroba (ix. seqcia 3.3.3 fertilobis darRveva, agreTve seqcia 3.3.4 teratogenuroba). adamianebisTvis potenciuri riskis SesaZlebloba ucnobia. reproduqciuli asakis qalebs unda erCios, Tavidan aicilon orsuloba tarcevas miRebis periodSi. unda iyos gamoyenebuli adeqvaturi kontracefciuli saSualebebi mkurnalobis ganmavlobaSi da misi dasrulebidan minimum 2 kviris manZilze. mkurnalobis gagrZeleba orsulobis SemTxvevaSi dasaSvebia mxolod maSin, Tu orsulisaTvis mosalodneli sargebeli aWarbebs nayofisTvis SesaZlo risks.

2.5.2 meZuZuri dedebi

ar aris cnobili, gamoiyofa Tu ara erlotinibi dedis rZiT. axalSobilisTvis SesaZlo safrTxis gamo dedebma Tavi unda Seikavon ZuZuTi kvebisagan tarcevas gamoyenebis periodSi.

2.5.3 RviZlis ukmarisoba

erlotinibis eqspozicia RviZlis zomieri xarisxis ukmarisobis dros (Child-Pugh 7-9 qula) ar gansxvavdeboda RviZlis adeqvaturi funqciebis mqone pacientebisagan, RviZlis pirveldi kibos an metastazuri dazianebis SemTxvevebis CaTvliT (ix. seqcia 2.4.1 zogadi gafrTxileba da sifrTxilis zomebi). tarcevas usafrTxoeba da efeqturoba RviZlis mZime ukmarisobis mqone pacientebSi ar Seswavlila.

2.6 arasasurveli efeqtebi

2.6.1 klinikuri kvlevebi

arawvrilujredovani kibo (BR.21 kvlevaSi tarceva iniSneboda monoTerapiis saxiT)

erT randomizebul ormag brma kvlevaSi (BR.21), romelmac moicva 17 qveyana, filtvis lokalurad gavrcelebuli an metastazuri arawvrilujredovani kibos (NSCLC) mqone 731 pacients manadme Catarebuli minimum erTi qimioTerapiuli reJimis arafeqturobis Semdeg randomulad eniSneboda tarceva (150mg) an placebo TanafardobiT 2:1. pacientebi sacdel preparats Rebulobdnen peroralurad dReSi erTxel daavadebis progresirebis an SeuTavsebeli toqisiurobis ganviTarebamde.

yvelaze xSir gverdiT movlenas warmoadgenda gamonayari (75%) da faRaraTi (54%), mizezobriv-Sedegobrivi damokidebulebis miuxedavad. SemTxvevebis umravlesoba simZimis 1-l an me-2 xarisxs Seesabameboda da ar saWiroebda damatebiT intervencias. me-3/4 xarisxis gamonayari da faRaraTi ganuviTarda tarcevas mimRebi pacientebis Sesabamisad 9%-s da 6%-s, rac gaxda kvlevis Sewyvetis mizezi pacientebis 1%-Si. dozis Semcireba gamonayaris da faRaraTis gamo dasWirda pacientebis Sesabamisad 6%-s da 1%-s. BR.21 kvlevaSi gamonayaris ganviTarebamde gasuli drois mediana Seesabameboda 8 dRes, xolo faRaraTis ganviTarebamde – 12 dRes.

gverdiTi movlenebi, romlebic sabaziso BR.21 kvlevaSi ufro xSirad (≥ 3%) vlindeboda tarcevas jgufSi placebos jgufTan SedarebiT da moicavda tarcevas jgufis pacientebis minimum 10%-s, Sejamebulia onkologiur daavadebaTa nacionaluri institutis toqsiurobis gavrcelebuli kriteriumebis (NCI-CTC) xarisxebis mixedviT **cxrilSi 1**. CamoTvlili movlenebi sponsoris SefasebiT Seesabameba medikamentis gamoyenebis gverdiT reaqciebs da ukavSirdeba tarcevas gamoyenebas.

cxrili #1: gverdiTi movlenebi, romlebic sabaziso BR.21 kvlevaSi ufro xSirad (≥ 3%) vlindeboda tarcevas jgufSi placebos jgufTan SedarebiT da moicavda tarcevas jgufis pacientebis minimum 10%-s

	erlotinibi N=485	**placebo N=242**

NCI-CTC xarisxi	**nebismieri xarisxis**	**3**	**4**	**nebismieri xarisxis**	**3**	**4**
MedDRA termini	**%**	**%**	**%**	**%**	**%**	**%**
pacientebis saerTo ricxvi						
nebismieri gverdiTi efeqtiT	99	40	22	96	36	22
infeqciebi da infestaciebi						
infeqcia*	24	4	0	15	2	0
kvebisa da metabolizmis moSla						
umadoba	52	8	1	38	5	<1
mxedvelobis darRvevebi						
koniuqtiviti	12	<1	0	2	<1	0
mSrali keratokoniuqtiviti	12	0	0	3	0	0
respiratoruli, Torakaluri da Suasayris paTologiebi						
dispnea	41	17	11	35	15	11
xvela	33	4	0	29	2	0
gastrointestinuri traqtis aSlilobebi						
faRaraTi	54	6	<1	18	<1	0
gulisreva	33	3	0	24	2	0
Rebineba	23	2	<1	19	2	0
stomatiti	17	<1	0	3	0	0
muclis tkivili	11	2	<1	7	1	<1
kanisa da kanqveSa qsovilis paTologiebi						
	75	8	<1	17	0	0
gamonayari	13	<1	0	5	0	0
qavili kanis simSrale	12	0	0	4	0	0
zogadi paTologiebi da Seyvanis adgilis reaqciebi						
daRliloba	52	14	4	45	16	4

* neitropeniiT an neitropeniis gareSe mimdinare mZime infeqciebi pnevmoniis, sefsisis, celulitis CaTvliT.

pankreasis kibo (PA.3 kvlevaSi tarceva iniSneboda gemcitabinTan kombinaciaSi)

PA.3 sabaziso kvlevaSi, romlis drosac 100mg tarceva iniSneboda gemcitabinTan kombinaciaSi, yvelaze xSiri gverdiTi movlena iyo sisuste, gamonayari da faRaraTi. tarcevasa da gemcitabinis kombinciis StoSi me-3/4 xarisxis gamonayari da faRaraTi

gamovlinda pacientTa 5%-Si. gamonayarisa da faRaraTis ganviTarebis medianuri periodi Seadgenda Sesabamisad 10 da 15 dRes. gamonayarisa da faRaraTs gamo dozis Semcirebis saWiroeba gamovlinda pacientTa 2%-Si, kombinirebuli Terapiis Sewyveta ki aucilebeli gaxda pacientTa 1%-Si.

150 mg tarcevasa da gemcitabinis kohorta (23 pacienti) asocirebuli iyo specifiuri gverdiTi efeqtebis, maT Soris gamonayaris, momatebul maCveneblebTan da ufro xSirad saWiroebda dozis Semcirebas an Sewyvetas.

gverdiTi movlenebi, romlebic sabaziso PA.3 kvlevaSi ufro xSirad (≥ 3%) vlindeboda 100mg tarcevas da gemcitabinis jgufSi placebos da gemcitabinis jgufTan SedarebiT da moicavda 100mg tarcevas da gemcitabinis jgufis pacientebis minimum 10%-s, Sejamebulia onkologiur daavadebaTa nacionaluri institutis toqsiurobis gavrcelebuli kriteriumebis (NCI-CTC) xarisxebis mixedviT **cxrilSi 2**. CamoTvlili movlenebi sponsoris SefasebiT Seesabameba medikamentis gamoyenebis gverdiT reaqciebs da ukavSirdeba tarcevas gamoyenebas.

cxrili #2: gverdiTi movlenebi, romlebic sabaziso PA.3 kvlevaSi ufro xSirad (≥ 3%) vlindeboda 100mg tarcevas da gemcitabinis jgufSi placebos da gemcitabinis jgufTan SedarebiT da moicavda 100mg tarcevas da gemcitabinis jgufis pacientebis minimum 10%-s

	erlotinibi N=259			**placebo N=256**		
NCI-CTC xarisxi	**nebismieri xarisxis**	**3**	**4**	**nebismieri xarisxis**	**3**	**4**
MedDRA termini	**%**	**%**	**%**	**%**	**%**	**%**
pacientebis saerTo ricxvi nebismieri gverdiTi efeqtiT	99	48	22	97	48	16
infeqciebi da infestaciebi						
infeqcia*	31	3	<1	24	6	<1
kvebisa da metabolizmis moSla						
wonaSi kleba	39	2	0	29	<1	0
fsiqiatriuli aSlilobebi						
depresia	19	2	0	14	<1	0
cns aSlilobebi						
Tavis tkivili	15	<1	0	10	0	0
neiropaTia	13	1	<1	10	<1	0

respiratoruli, Torakaluri da Suasayris paTologiebi xvela	16	0	0	11	0	0
gastrointestinuri traqtis aSlilobebi diarea stomatiti dispefsia meteorizmi	48 22 17 13	5 <1 <1 0	<1 0 0 0	36 12 13 9	2 0 <1 <1	0 0 0 0
kanisa da kanqveSa qsovilis paTologiebi gamonayari, alopecia	69 14	5 0	0 0	30 11	1 0	0 0
zogadi paTologiebi da Seyvanis adgilis reaqciebi cxeleba daRliloba Semcivneba	36 73 12	3 14 0	0 2 0	30 70 9	4 13 0	0 2 0

* neitropeniiT an neitropeniis gareSe mimdinare mZime infeqciebi pnevmoniis, sefsisis, celulitis CaTvliT

<u>sxva dakvirvebebi (yvela klinikuri kvlevis monacemebis analizi)</u>

usafrTxoebis Sefaseba xdeboda 800-ze meti pacientis SeswavliT, romelTac utardeboda tarcevas monoTerapia minimum erTi 150mg-iani dozis saxiT, agreTve 300-ze meti pacientis SeswavliT, romelTac utardeboda mkurnaloba 100mg an 150mg tarcevas da gemcitabinis kombinaciiT.

150mg tarcevas monoTerapiis an 100mg an 150mg tarcevas da gemcitabinis kombinirebuli gamoyenebisass adgili hqonda Semdeg gverdiT efeqtebs.

gansazRvrebebi gverdiTi efeqtebis gamovlenis sixSiris dasaxarisxeblad: Zalian xSiri (>1/10); xSiri (>1/100, <1/10); araxSiri (>1/1,000, <1/100); iSviaTi (>1/10,000, <1/1000); Zalian iSviaTi (<1/10,000) maT Soris calkeuli SemTxvevebi.

Zalian xSirad gamovlenili gverdiTi efeqtebis CamonaTvali mocemulia **cxrilebSi 1 da 2.** sxva sixSireTa kategoriebis gverdiTi efeqtebi Sejamebulia qvemoT.

gastrointestinuri traqtis aSlilobebi:

tarcevas miRebisas gastrointestinuri perforacia, zogierT SemTxvevaSi fataluri gamosavliT, aRiniSna araxSirad (pacientTa <1%) (ix. seqcia 2.4.1 zogadi gafrTxileba da sifrTxilis zomebi).

gastrointestinuri sisxldena, zogierT SemTxvevaSi fataluri gamosavliT, aRiniSna xSirad da iyo asocirebuli varfarinis (ix. seqcia 2.4.3 sxva medikamentebTan urTierTqmedeba da urTierTqmedebis sxva formebi) da arasteroiduli anTebis sawinaaRmdego preparatebis paralelur gamoyenebasTan.

hepatobiliaruli darRvevebi:

RviZlis funqciuri testebis cvlilebebi (maT Soris ALT, AST da bilirubinis momateba) tarcevas klinikuri kvlevisas xSirad vlindeboda. PA.3kvlevaSi aRniSnuli disfunqcia Zalian xSiri iyo. es movlenebi, rogorc wesi, msubuqi an zomieri simZimis iyo da gardamaval xasiaTs atarebda an dakavSirebuli iyo RviZlSi metastazebis ganviTarebasTan. tarcevas gamoyenebisas dafiqsirda RviZlis ukmarisobis iSviaTi SemTxvevebi (maT Soris fataluri gamosavliT). RviZlis ukmarisobis xelisSemwyob faqtorebs warmoadgenda RviZlis fonuri daavadebebis arseboba an hepatotoqsiuri medikamentebis zegavlena (ix. seqcia 2.4 zogadi gafrTxileba da sifrTxilis zomebi).

Tvalis dazianeba:

tarcevas gamoyenebisas rqovanas dawylulebis da perforaciis SemTxveevebi dafiqsirda Zalian iSviaTad (ix. seqcia 2.4 zogadi gafrTxileba da sifrTxilis zomebi). xSiri iyo keratitisa da koniuqtivitis SemTxvevebi. vlindeboda agreTve quTuToebis paTologiuri zrda, gasqeleba da Cazrda (ix. seqcia 2.4 zogadi gafrTxileba da sifrTxilis zomebi).

respiratoruli, Torakaluri da Suasayris paTologiebi:

tarcevas gamoyenebisas filtvis arawvrilujredovani kibos, an sxva Sorswasuli soliduri simsivnis samkurnalod dafiqsirebulia filtvis seriozuli intersticiuli daavadebis ILD-magvari araxSiri SemTxvevebi (maT Soris fataluri gamosavliT) (ix. seqcia 2.4 zogadi gafrTxileba da sifrTxilis zomebi). rogorc filtvis arawvrilujredovani kibos, ise pankreasis kibos kvlevebSi xSiri iyo agreTve epistaqsisis SemTxvevebic.

kanisa da kanqveSa qsovilebis dazianeba:

tarcevas gamoyenebisas Zalian xSiria kanis gamonayaris SemTxvevebi, rac vlindeba ZiriTadad msubuqi an saSualo intensivobis eriTematozuli da papulo-pustozuri gamonayris saxiT, romelic SesaZloa gaCndes an gaZlierdes mzis eqspoziciis gavleniT. amdenad, aRniSnuli eqspoziciis arsebobisas rekomendebulia damcavi tansacmelis da/an mzis maekranirebeli (mag. mineralebis Semcveli) saSualebebis gamoyeneba. xSirad vlindeboda akne, akneiformuli dermatiti da folikuliti, Tumca SemTxvevaTa umravlesoba iyo msubuqi an zomieri intensivobis da ar warmoadgenda seriozul safrTxes. aseve xSiri iyo kanis bzarebis ganviTareba (naklebseriozuli, ZiriTadad asocirebuli gamonayaris da kanis simSralis TanaarsebobasTan). kanis sxva msubuqi reaqciebi, rogoricaa hiperpigmentacia, vlindeboda SedarebiT araxSirad (pacientTa <1%).

tarcevas gamoyenebisas dafiqsirebulia kanis bulozuri, blisteruli da eqsfoliatiuri dazianebis SemTxvevebi, stevens-jonsonis sindromis/toqsiuri epidermuli nekrolizis Zalian iSviaTi (zogjer fataluri) SemTxvevebis CaTvliT (ix. seqcia 2.4 zogadi gafrTxileba da sifrTxilis zomebi).

klinikur kvlevebSi dafiqsirebulia Tmisa da frCxilebis naklebseriozuli cvlilebebis ganviTarebac, magaliTad, xSiri iyo paroniqia, xolo hirsutizmis, quTuToebis cvlilebebis, frCxilebis mtvrevisa da gafaSrebis SemTxvevebi ki araxSirad vlindeboda.

2.6.2 postmarketingi

kanisa da kanqveSa qsovilis dazianeba:

Tmisa da frCxilebis naklebseriozuli cvlilebebi hirsutizmis, quTuToebis cvlilebebis, frCxilebis mtvrevisa da gafaSrebis saxiT araxSirad vlindeboda postmarketinguli zedamxedvelobis pirobebSic.

2.7 dozis gadaWarbeba

tarcevas 1000mg-mde erTjeradi peroraluri doza janmrTel pirebSi da1600mg-mde kviraSi erT miRebaze onkologiuri daavadebebis mqone pirebSi xasiaTdeboda misaRebi amtanobiT. ganmeorebiTi dozireba dReSi 200 mg orjer janmrTel pirebSi xasiaTdeboda cudi amtanobiT ukve ramodenime dReSi. aRniSnul kvlevebSi miRebul monacemebze dayrdnobiT, rekomendebulze maRali dozebis gamoyenebisas SesaZlebelia ganviTardes mZime gverdiTi movlenebi, rogoricaa faRaraTi, gamonayari da SesaZloa RviZlis transaminazebis momateba. dozis gadaWarbebaze eWvis mitanisas tarcevas miReba unda Sewydes da dianiSnos simptomuri mkurnaloba.

3.farmakologiuri Tvisebebi da efeqtebi

3.1farmakodinamikuri Tvisebebi

3.1.1. **moqmedebis meqanizmi**

erlotinibi HER1/EGFR-s ujredSida fosfolirebis Zlieri inhibitoria. HER1/EGFR eqspresirdeba rogorc normaluri, aseve kibos ujredebis zedapirze. araklinikur modelebSi, EGFR-is fosfoTirozinis inhibicia iwvevs ujredis stazs da/an sikvdils.

3.1.2 efeqturoba/klinikuri kvlevebi

filtvis arawvrilujredovani kibo (tarceva iniSneboda monoTerapiis saxiT):

tarcevas efeqturoba da usafrTxoeba iyo demonstrirebuli randomizebuli, ormagad brma, placebo-kontrolirebadi kvleviT (BR.21), romelic Catarda 17 qveynaSi da moicva 731

pacienti lokalurad gavrcelebuli da metastazuri filtvis arawvrilujredovani filtvis kiboTi, romlebTanac manamde Catarebuli minimum erTi qimioTerapiuli mkurnaloba arafeqturi aRmoCnda. pacientebi iyvnen randomizebuli TanafardobiT 2:1, dReSi erTxel peroraluri 150mg tarcevas da placebos jgufebad. kvlevis endpointebi moicavda saerTo gadarCenis maCvenebels, filtvis kibosTan dakavSirebuli simtomebis (xvela, dispnea da tkivili) gauaresebamde saWiro drois periods, mopasuxeobis maCvenebels, mopasuxeobis xangrZlivobas, progresirebis gareSe gadarCenis maCvenebels (PFS) da usafrTxoebis maCveneblebs. pirvelad endpoints warmoadgenda gadarCenis maCvenebeli.

randomizaciis 2:1 Tanafardobis gamo, 488 pacienti Rebulobda tarcevas, xolo 243 pacienti – placebos. pacientebi ar yofilan SerCeuli HER1/EGFR statusis, sqesis, rasis, Tambaqos moxmarebis da histologiuri klasifikaciis mixeviT.

demografiuli maxasiaTeblebi jgufebs Soris kargad iyo dabalansebuli. pacientebis daaxloebiT ori mesamedi mamakaci iyo, daaxloebiT erT mesamedSi sawyisi ECOG Sromisunarianobis statusi (PS) Seadgenda 2-s, xolo 9%-Si sawyisi ECOG PS Seadgenda 3-s. pacientebis Sesabamisad 93%-s da 92%-s tarcevas da placebos jgufebSi manamde miRebuli hqondaT platinis Semcveli reJimi, xolo Sesabamisad 36%-s da 37%-s miRebuli hqonda taqsanebi. pacientebis 50%-s manamde miRebuli hqonda mxolod erTi qimioTerapiuli reJimi.

gadarCenis maCveneblis Sefaseba xdeboda kvlevis mTlian/sawyis populaciaSi. saerTo gadarCenis maCveneblis mediana gaumjobesda 42.4%-iT da tarcevas jgufSi Seadgina 6.7 Tve (95% CI, 5.5–dan 7.8 Tvemde), placebos jgufSi 4.7 TvesTan SedarebiT (95% CI, 4.1–dan 6.3 Tvemde). gadarCenis pirveladi (ZiriTadi) analizi koreqtirebuli iyo randomizaciis momentisaTvis arsebuli stratifikaciis faqtorebTan (ECOG PS statusi, saukeTeso mopasuxeoba wina qimioTerapiaze, miRebuli reJimebis raodenoba, platinis eqspozicia) da HER1/EGFR statusTan mimarTebaSi. pirvelad (ZiriTad) analizSi sikvdilis koreqtirebuli riskis Tanafardoba tarcevas jgufSi placebos jgufTan mimarTebaSi iyo 0.73 (95% CI, 0.60 – 0.87) (p=0.001). gadarCenili pacientebis procentulma Tanafardbam me-12 TvisTvis Sesabamisad Seadgina 31.2% da 21.5%.

tarcevas upiratesoba gadarCenis maCveneblis gaumjobesebis TvalsazrisiT SesamCnevi iyo qvejgufebis umravlebosaSi. randomizaciis momentisaTvis da sabaziso doneze arsebuli stratifikaciis faqtorebis, HER1/EGFR statusis, taqsanebis eqspoziciis, Tambaqos moxmarebis, sqesis, asakis, histologiis, wonaSi klebis, diagnostirebidan randomizaciamde gasuli drois periodis da geografiuli adgilmdebareobis gaTvaliswinebiT SerCeuli pacientbis qvejgufebi Seswavlili iqna univariaciuli analiziT, raTa Sefasebuliyo gadarCenis saerTo Sedegis simtkice/simyare. riskebis Tanafardobis (HR) TiTqmis yvela maCvenebeli tarcevas jgufSi placebos jgufTan SedarebiT 1.0-ze naklebi iyo, rac imis mimaniSnebelia, rom tarcevas upiratesoba gadarCenis maCveneblis gaumjobesebis TvalsazrisiT inarCunebda simyares yvela qvejgufSi. aRsaniSnavia, rom tarcevas upiratesoba gadarCenis maCveneblis gaumjobesebis TvalsazrisiT Sedarebadi iyo rogorc pacientebSi sawyisi ECOG PS statusiT 2-3 (HR = 0.77), agreTve PS statusiT 0-1 (HR = 0.73) da pacientebSi, romelTac miRebuli hqondaT erTi qimioTerapiuli reJimi (HR= 0.76) an ori an meti reJimi (HR=0.76).

tarcevas upiratesoba gadarCenis maCveneblis gaumjobesebis TvalsazrisiT agreTve aRiniSna im pacientebSi, romelTac ver miaRwies simsivnis obieqtur mopasuxeobas (RECISTkriteriumebis mixedviT). es dadasturda sikvdilis riskis Tanafardobis maCvenebliT 0.83 pacientebSi, romelTac ukeTes SemTxvevaSi aReniSna daavadebis stabilizacia da 0.85 pacientebSi, romelTac aReniSna daavadebis progresireba.

cxrilSi 3 Sejamebulia kvlevis Sedegebi, maT Soris gadarCenis maCveneblebi, dro filtvis kibosTan dakavSirebuli simptomebis gauaresebamde, agreTve progresirebis gareSe gadarCenis maCveneblebi (PFS).

cxrili #3: kvleva BR.21 efeqturobis monacemebi

	tarceva (N=488)	placebo (N=243)	**p-value**
gadarCenis maCveneblis mediana 95% CI	6.7 Tve (5.5 - 7.8)	4.7 Tve (4.1 - 6.3)	
gadarCenis maCveneblis mrudebs Soris sxvaoba			0.001
riskebis Tanafardoba*, sikvdiloba (erlotinibi: placebo) 95% CI (riskebis Tanafardoba)	0.73 0.60 - 0.87		
medianuri dro xvelis gauaresebamde *** 95% CI	28.1 kvira (16.1 – 40.0)	15.7 kvira (9.3 – 24.3)	0.041
medianuri dro dispneas gauaresebamde *** 95% CI	20.4 kvira (16.3 – 28.3)	12.1 kvira (9.3 – 20.9)	0.031**
medianuri dro tkivilis gauaresebamde *** 95% CI	12.1 kvira (10.1 – 14.1)	8.1 kvira (7.7 – 12.3)	0.040**
progresirebis gareSe gadarCenis maCveneblis mediana 95% CI	9.7 kvira (8.4 - 12.4)	8.0 kvira (7.9 - 8.0)	<0.001

* koreqtirebulia stratifikaciis faqtorebis da HER1/EGFR statusis mixedviT, 1.00-ze naklebi maCvenebeli metyvelebs tarcevas sasargeblod (pirveladi analizi).
** p maCveneblebi koreqtirebulia mravlobiTi testirebisaTvis.
*** EORTC QLQ-C30 da QLQ-LC13 sicoxlis xarisxis kiTxvarebidan.

simtomebis gauareseba ganisazRvreboda EORTC QLQ-C30 da QLQ-LC13 sicocxlis xarisxis kiTxvarebis meSveobiT. xvelis, dispneas da tkivilis sawyisi maCveneblebi msgavsi iyo orive jgufSi. tarceva aRmoCnda upiratesi placebosTan SedarebiT simptomebis gauaresebis drois mniSvnelovani gaxangrZlivebis TvalsazrisiT: xvela (HR=0.75), dispnea (HR=0.72) da tkivili (HR=0.77). aRniSnuli upiratesoba tarcevas jgufSi ar iyo dakavSirebuli paliatiuri sxivuri Terapiis, an paraleluri qimioTerapiis erTdrouli gamoyenebis efeqtTan.

progresirebis gareSe gadarCenis maCveneblis medianam Seadgina 9.7 kvira tarcevas jgufSi (95 CI, 8.4–dan 12.4 kviramde), xolo placebos jgufSi – 8.0 kvira (95% CI, 7.9–dan 8.1 kviramde). stratifikaciis faqtorebze da HER1/EGFR statusze koreqtirebuli daavadebis progresirebis HR iyo 0.61 (95% CI, 0.51 – 0.73) (p<0.001). progresirebis gareSe gadarCenis maCveneblis procentulma maCvenebelma me-6 TvisTvis Seadgina Sesabamisad 24.7% da 9.3% tarcevasa da placebos jgufebisaTvis.

obieqturi mopasuxeobis maCvenebelma RECIST kriteriumebis mixedviT tarcevas jgufSi Seadgina 8.9% (95% CI, 6.4 – 12.0%). pasuxis medianurma xangrZlivobam Seadgina 34.3 kvira, diapazoniT 9.7–dan 57.6+ kviramde. mopasuxeobis ori SemTxveva (0.9%, 95% CI, 0.1 – 3.4) aRiniSna placebos jgufSic. pacientebis proporcia, romlebsac aReniSna sruli mopasuxeoba, nawilobrivi mopasuxeoba an daavadebis stabilizacia, Sesabamisad Seadgina 44.0% da 27.5% tarcevasa da placebos jgufebSi (p=0.004).

pankreasis kibo (tarceva iniSneboda gemcitabinTan kombinaciaSi):

tarcevas gemcitabinTan kombinaciis, rogorc pirveli rigis Terapiis efeqturoba da usafrTxoeba Seswavlil iqna randomizebuli, ormagad brma, placebo-kontrolirebadi kvleviT, romelSic monawileobda 569 pacienti lokalurad gavrcelebuli, ararezeqcirebadi an metastazuri pankreasis kibos diagnoziT. pacientebi iyvnen randomizebuli 2 jgufad, TanafardobiT 1:1, erTi iRebda 100mg an 150mg tarcevas, meore - placebos, dReSi erTxel, gaxangrZlivebuli sqemiT. orive jgufi damatebiT Rebulobda i/v gemcitabins (1000 mg/m^2, I cikli - 8 kviriani ciklis 1, 8, 15, 22, 29, 36 da 43 dRes. II da momdevno ciklebi: 4 kviriani ciklis 1, 8 da 15 dRes [pankreasis kibos samkurnalod mowodebuli dozebi da ganrigi - ix. gemcitabini SPC]). tarceva an placebo iniSneboda erTjeradi oraluri dozis saxiT daavadebis progresirebis an Zlieri toqsiurobis ganviTarebamde. kvlevis endpointebi moicavdnen zogadad gadarCenas, mopasuxeobis maCvenebels da progresirebis gareSe gadarCenis (PFS) maCvenebels. ganisazRvra aseve mopasuxeobis xangrZlivoba. pirvelad endpoints warmoadgenda gadarCena.

285 pacienti daiyo 2 jgufad, romlebic iRebdnen gemcitabins da 100mg an 150mg tarcevas (261 pacienti 100mg tarcevas kohortaSi, 24 pacienti - 150mg tarcevas kohortaSi). 284 pacienti iRebda gemcitabins da placebos (260 pacienti 100mg-is kohortaSi, 24 pacienti 150mg-is kohortaSi). daskvnebis gamosatanad 150mg-ian kohortaSi Zalian mcire raodenobis observacia Catarda.

sawyisi demografiuli da klinikuri maxasiaTeblebi 100mg tarcevas da gemcitabinis da placebos da gemcitabinis jgufebs Soris erTnairi iyo, mxolod tarcevas jgufSi qalTa procentuli maCvenebeli odnav meti iyo (51%) placebos jgufTan SedarebiT (44%). winaswari diagnozis gamotanidan randomizaciamde drois mediana 1.0 Tves Seadgenda. pacientTa daaxloebiT naxevars hqonda sawyisi ECOG PS statusi-1, xolo daaxloebiT 17%-s sawyisi ECOG PS statusi-2. kvlevaSi CarTvamde pacientTa umetesobas aReniSneboda metastazuri daavadeba, rogorc pankreasis kibos sawyisi gamovlineba (77% tarcevas jggufSi da 76% placebos jgufSi).

gadarCenis maCvenebeli fasdeboda kvlevis mTlian/sawyis populaciaSi gadarCenaze zedamxedvelobis monacemebis safuZvelze, letalobis 551 SemTxvevis CaTvliT. Sedegebi warmodgenilia 100mg tarcevas kohortuli jgufisTvis (letalobis 504 SemTxveva). letalobis riskis korigirebuli Tanafardoba tarcevasa da placebos jgufebSi warmoadgenda 0.82-s (95 % CI, 0.69 - 0.98) (p = 0.028). gadarCenili pacientebis procentoba 12 Tvis Semdeg tarcevas jgufSi Seadgenda 23.8%-s, placebos jgufSi – 19.4%-s. saerTo gadarCenis maCveneblis mediana tarcevas jgufSi Seadgenda 6.4 Tves, xolo placebos jgufSi – 6 Tves.

cxrilSi 4 Sejamebulia PA.3 kvlevis Sedegebi.

cxrili 4: kvleva PA.3 efeqturobis monacemebi

	100mg tarceva da gemcitabinis jgufi (N = 261)	**placebosa da gemcitabinis jgufi (N=260)**	**p-value**
gadarCenis maCveneblis mediana	6.4 Tve	6 Tve	
riskebis Tanafardoba, sikvdiloba (erlotinibi:placebo) (95 % CI)	0.82 (0.69 - 0.98)		p = 0.028
gadarCenili pacientebis % 12 Tvis Semdeg	23.8	19.4	

progresirebis gareSe sicocxlis medianuri xangrZlivoba tarcevas jgufSi Seadgenda 3.81 Tves (16.5 kviras), (95 % CI, 3.58 -dan 4.93 Tvemde) palacebos jgufSi - 3.55 Tves (16 kviras) (95 % CI, 3.29 -dan 3.75Tvemde) (p = 0.006).

mopasuxeobis medianuri xangrZlivoba Seadgenda 23.9 kviras (3.71-56+ kviramde diapazonSi). obieqturi mopasuxeobis maCvenebeli (sruli da nawilobrivi mopasuxeoba) tarcevas jgufSi iyo 8.6%, placebos jgufSi - 7.9%. pacientTa Tanafardoba sruli an nawilobrivi pasuxis an daavadebis stabilizaciis mixedviT tarcevas da palcebos jgufebisaTvis Seadgenda Sesabamisad 59%-s da 49.4%-s (p = 0.036).

3.2 farmakokinetikuri Tvisebebi

eqspozicia:

150mg tarcevas peroraluri miRebisas platos fazis dros maqsimaluri plazmuri koncentraciis miRwevis medianuri dro Seadgens 4sT-s, xolo maqsimaluri plazmuri koncentraciis medianuri maCvenebeli Seadgens 1.995ng/ml-s. Semdegi dozis miRebamde 24sT-Si tarcevas minimaluri koncentraciis medianuri maCvenebeli Sadgens 1.238ng/ml-s. medianuri AUC, romelic miiRweva dozirebis intervalisas stabilur mdgomareobaSi, Seadgens 41.300mkg*sT/ml.

3.2.1.absorbcia

perorulad miRebuli erlotinibi kargad Seiwoveba da aqvs absorbciis gafarToebuli faza, rodesac plazmaSi saSualo pikuri koncentracia miiRweva peroruli dozis miRebidan 4 saaTSi. janmrTel moxaliseebSi Catarebuli kvlevis mixedviT, bioSeRwevadoba Seadgens 59%-s. peroruli miRebis Semdeg eqspoziciis gazrda SesaZlebelia sakvebiT.

erlotinibs maRali SekavSirebadoba axasiaTebs, absorbciis Semdeg 95% ukavSirdeba sisxlis komponentebs, ZiriTadad plazmis cilebs (mag., albumins da alfa-1 mJava glikoproteini [AAG]), Tavisufali fraqcia daaxloebiT 5%-s Seadgens.

3.2.2.ganawileba

erloTinibis saSualo xiluli ganawilebis moculobaa 232l, romelic nawildeba adamianis simsivnur qsovilSi. 4 pacientisgan Semdgar kvlevaSi (3 filtvis arawvrilujredovani kibo da 1 xorxis kibo), romlebic peroralurad Rebulobdnen 150mg tarcevas yoveldRiurad, mkurnalobis me-9 dReze amokveTil qirurgiul masalaSi tarcevas konecentraciam simsivneSi Seadgina 1.185ng/g. es Seesabameboda stabilur mdgomareobaSi dafiqsirebul plazmaSi pikuri koncentraciis saerTo saSualo 63%-ian maCvenebels. ZiriTadi aqtiuri metabolitebis koncentracia simsivnur qsovilSi aRwevda 160ng/g, rac Seesabameboda stabilur mdgomareobaSi dafiqsirebul plazmaSi pikuri koncentraciis saerTo saSualo 113%-ian maCvenebels. qsovilebSi ganawilebis Semswavlel kvlevebSi gamoyenebuli iyo mTliani sxeulis autiradiografiis meTodi HN5 simsivnis qsenograftis mqone uTimuso TagvebSi [^{14}C] moniSnuli erlotinibis peroraluri gamoyenebis Semdeg. naCvenebi iyos swrafi da srulyofili ganawileba qsovilebSi, rodesac moniSnuli preparatis maqsimaluri koncentracia (plazmuri koncentraciis daaxloebiT 73%) aRiniSna 1 saaTSi.

3.2.3. metabolizmi

adamianis sxeulSi erlotinibi metabolizdeba RviZlSi RviZlis P450 citoqromuli fermentebis, ZiriTadad CYP3A4 -is da naklebi moculobiT - CYP1A2-is mier. Eeqstrahepaturi metabolizmi xorcieldeba nawlavuri CYP3A4-is, filtvis CYP1A1-is da simsivnuri qsovilis CYP1B1-is meSveobiT, rac potenciurad agreTve monawileobs erlotinibis metabolur klirensSi. *In vitro* kvlevebSi naCvenebi iyo, rom erlotinibis 80-95% metabolizdeba CYP3A4 fermentiT. gamovlenilia metabolizmis sami ZiriTadi gza: 1) O-demeTilireba jaWvis romlelime an orive mxaris, rasac mohyveba daJangva karboqsilis mJavebiT; 2) acetilenis nawilis daJangvas mohyveba hidrolizi aril karboqsilis mJavamde; 3) fenil acetilenis nawilis aromatuli hidroqsilireba. jaWvis romelime mxaris O-demeTilirebiT miRebul pirvelad metabolitebs erlotinibis msgavsi potenciali gaaCnia, rogorc es naCvenebi iyo preklinikur *In vitro* eqsperimentebSi da simsivnis *in vivo* modelebze. plazmaSi maTi koncentracia erlotinibis <10% Seadgens da erlotinibis msgavsi farmakokinetikiT xasiaTdeba.

3.2.4. gamoyofa:

metabolitebi da erlotinibis umniSvnelo raodenoba ZiriTadad gamoiyofa fekaliebiT (>90%), peroraluri dozis mxolod mcire nawili gamoiyofa TirkmlebiT.

klirensi

populaciuri farmakokinetikuli kvlevis analiziT, romelSic 591 pacientma miiRo tarcevas erTjeradi doza, naCvenebi iyo saSualo xiluli klirensis maCvenebeli 4.47l/sT da naxevrad gamoyofis saSualo maCvenebeli 36.2sT. aqedan gamomdinare, plazmaSi mdgradi koncentraciis misaRwevad saWiro dro savaraudod Seadgens 7-8 dRes. mniSvnelovani kavSiri klirensis prognozirebad maCvenebelsa da pacientis asaks, sxeulis wonas, sqess da eTnikur wrmomavlobas Soris ar aRniSnula.

pacientze damokidebuli faqtorebs, romlebic korelaciaSia elrotinibis farmakokinetikasTan, miekuTvneba Sratis saerTo bilirubini, AAG koncentraciebi da Tambaqos mimdinare moxmareba. saerTo bilirubinis da AAG koncentraciis momateba asocirebulia erlotinibis klirensis siCqaris daqveiTebasTan. mwevelebSi elrotinibis klirensis maCvenebeli ufro maRalia (ix. seqcia 2.4.3 sxva medikamentebTan urTierTqmedeba da urTierTqmedebis sxva formebi).

meore farmakokinetikuri populaciuri kvlevis analizi Catarda 204 pankreasis kibos mqone pacientSi, romelTac utardeboda kombinaciuri Terapia erlotinibiTa da gemcitabiniT. gamovlinda, rom erlotinibis da gemcitabinTan erTad miRebisas erlotinibis klirensze moqmedebs analoguri faqtorebi, romlebic gamovlinda erlotinibis monoTerapiis farmakokinetikuri analiziT. erlotinibis miReba gemcitabinTan erTad araviTar gavlenas ar axdens erlotinibis plazmur klirensze.

3.2.5.farmakokinetika specialur populaciaSi

specialuri kvlevebi pediatriul an xandazmul kontingentze ar Catarebula.

RviZlis funqciis darRvevebi: elrotinibis gamoyofa ZiriTadad xorcieldeba RviZlis mier. erlotinibis eqspozicia RviZlis zomieri xarisxis ukmarisobis dros (Child-Pugh 7-9 qula) ar gansxvavdeboda RviZlis adeqvaturi funqciebis mqone pacientebisagan, RviZlis pirveldi kibos an metastazuri dazianebis SemTxvevebis CaTvliT.

Tirkmlis funqciis darRvevebi: erlotinibis da misi metabolitebis gamoyofa TirkmlebiT umniSvneloa, dozis mxolod 9% gamoiyofa SardiT. Tirkmlis funqciis darRvevebis mqone pacientebSi klinikuri kvlevebi ar Catarebula.

mwevelebi: mwevel da aramwevel janmrTel individebSi Catarebulma farmakokinetikurma kvlevam aCvena, rom mwevelebSi aRiniSneba erlotinibis klirensis zrda da eqspoziciis Semcireba. $AUC_{0\text{-infinity}}$ mwevelebSi aramwevelebis (arasdros/yofili mwevelebis) maCveneblis 1/3-s Seadgenda (pacientebis n=16 TiToeul sakvlev jgufSi). mwevelebSi aRniSnuli eqspoziciis Semcireba savaudod ganpirobebulia RviZlis CYP1A1-is da filtvis CYP1A2-is induqciiT.

filtvis arawvrilujredovani (NSCLC) kibos III fazis sabaziso kvlevaSi mwevelebisTvis erlotinibis stabiluri plazmuri koncentraciia Seadgenda 0.65 µg/ml (n=16), rac daaxloebiT 2-jer naklebi iyo yofil mwevelebTan da anamnezSi mwevelobis armqone pacientebTan

SedarebiT (1.28 µg/ml, n=108). aRniSnuli efeqti iyo Tanxlebuli plazmuri klirensis 24%-iani gaZlierebiT.

filtvis arawvrilujredovani (NSCLC) kibos I fazis dozis eskalaciis kvlevaSi mwevelebisTvis tarcevas dozis 150mg-dan maqsimalurad asatan 300mg-mde gazrdisas stabiluri mdgomareobis farmakokinetikuri analizebiT gamovlinda erlotinibis doza-proporciuli eqspoziciis zrda. 300mg tarcevas miRebisas stabiluri mdgomareobis narCeni plazmuri koncentracia Seadgenda 1.22µg/ml-s (n=17) (ix. seqia 2.2.1 specialuri dozirebis instruqciebi da seqcia sxva medikamentebTan urTierTqmedeba da urTierTqmedebis sxva formebi).

3.3 preklinikuri usafrTxoeba

3.3.1.kancerogenoba

preklinikuri kvlevebiT tarcevas kancerogenuli potencialis mtkicebuleba ar gamovlenila. dawyebulia kancerogenulobis grZelvadiani kvlevebi virTagvebsa da TagvebSi; Tumca pre-malignanturi proliferaciuli dazianebis kerebi 6 Tvis ganmavlobaSi mimdinare qronikuli toqsiurobis kvlevebSi jer nanaxi ar yofila.

3.3.2 mutagenoba

erlotinibi aRmoCnda negatiuri genotoqsiurobis testirebis standartuli batareis gamoyenebisas.

3.3.3 fertilobis darRveva

mdedr da mamr virTagvebze Catarebuli kvlevebiT fertilobis daRveva ar gamovlenila dozebis MTD-sTan miaxlovebul doneebzec.

3.3.4. teratogenoba

virTagvebsa da bocvrebSi Catarebuli reproduqciuli toqsiurobis eqsperimentebSi erlotinibis dozebis MTD-sTan miaxlovebul doneebze da/an maternalurad toqsiuri dozebis gamoyenebis Semdeg dafiqsirda embriotoqsiuroba, magram teratogenobis an pre- da postnataluri fizikuri da qceviTi ganviTarebis darRvevis niSnebi ar aRniSnula. mocemul kvlevebSi maternaluri toqsiuroba virTagvebsa da bocvrebSi aRiniSna plazmuri eqspoziciis iseT doneebze, romelic msgavsia adamianebSi erloTinibis 150mg gamoyenebis Semdeg miRebuli koncentraciisa.

3.3.5. sxva

qronikuli dozirebis efeqtebi, romelic aRiniSna minimum cxovelebis erT jiSSi an kvlevaSi, moicavda efeqtebs rqovanaze (atrofia, dawyluleba), kanze (flokuluri degeneracia da anTeba, siwiTle da alopecia), sakvercxeze (atrofia), RviZlze (RviZlis nekrozi), Tirkmlebze (Tirkmlis papilaruli nekrozi da tubularuli dilatacia), da

gastrointestinur traqtze (kuWis dagvianebuli dacla da faRaraTi). adgili hqonda eriTrocitebis (RBC) raodenobis, hematokritis da hemoglobinis donis Semcirebas da retikulocitebis zrdas. leikocitebis (WBC), gansakuTrebiT neitrofilebis raodenoba izrdeboda. aRiniSna alananin aminotransferazas (ALT), aspartat aminotransferazas (ALT) da bilirubinis doneebis mkurnalobasTan dakavSirebuli momateba.

erlotinibis *in vitro* kvlevebSi nanaxia hERG arxebis inhibitoruli moqmedeba koncentraciebiT, romlebic minimum 20-jer aRemata Tavisufali medikamentis koncentracias adamianis Terapiuli dozebis miRebisas. ZaRlebze Catarebul kvlevebSi QT-intervalis gaxangrZliveba nanaxi ar iyo. 152 individze Catarebuli janmrTeli moxaliseebis Svidi kvlevis ECG monacemebis sistematizebuli centralizebuli reviziiT QT-intervalis gaxangrZlivebis aranairi mtkicebuleba nanaxi ar iyo, xolo klinikuri kvlevebiT ar iyo nanaxi QT-intervalis gaxangrZlivebasTan asocirebuli ariTmiebis ganviTarebis mtkicebuleba.

4. farmacevtuli maxasiaTeblebi

4.1.Senaxvis pirobebi

stabiluroba

SefuTvaze miTiTebuli Senaxvis vadis (EXP) gasvlis Semdeg tarcevas gamoyeneba ar SeiZleba. pirvelad SefuTvaSi tabletebi inrCunebs stabilurobas 4 wlis ganmavlobaSi.

Senaxvis gansakuTrebuli pirobebi:

nu SeinaxavT 30ºC-ze meti temperaturis pirobebSi.

4.2. eqspluataciis, moxmarebis da gauvnebelyofis specialuri instruqciebi

gamouyenebeli/vadagasuli medikamentebis gauvnebelyofa

farmacevtuli produqtebis garemoSi moxvedra minimalizebuli unda iyos. dauSvebelia medikamentebis moxvedra Camonarecx wylebSi da gadayra sayofacxovrebo narCenebTan erTad. Tu SesaZlebelia, gamoiyeneT specialuri “koleqtoruli sistemebi”.

4.3. SefuTva

25mg tabletebi	30
100mg tabletebi	30
150mg tabletebi	30

medikamenti: ar SeinaxoT bavSvebisaTvis xelmisawvdom adgilze.

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